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Distribution Date: December 1, 2016
E-mailed Date: November 22, 2016
Version Date: November 9, 2016

TO: ALL NATIONAL CLINICAL TRIALS NETWORK (NCTN) MEMBERS (U.S. Institutions Only); INCAN (Mexico)

FROM: SWOG Operations Office (E-mail: protocols@swog.org)

RE: **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." Study Chairs: Drs. M. Chavez-MacGregor, P Rastogi and L. Pusztai.

**REVISION #7**

Study Chair: Mariana Chavez-MacGregor, M.D., M.Sc.
Phone Number: 713/792-2817
E-mail: **S1207**medicalquery@swog.org

**IRB Review Requirements**
( ) Full board review required
(√) Expedited review allowed
( ) No review required

**Status Change**
( ) IRB Review only
( ) Activation
( ) Closure
( ) Reactivation

**Protocol changes**
( ) Eligibility changes
( ) Treatment / Dose Modification / Study Calendar changes
(√) Informed Consent changes
  ( ) Patient notification not required
  (√) Patient notification required: see below for details.
( ) Scientific / Statistical Consideration changes
( ) Specimen Submission changes
( ) Data Submission / Forms changes
( ) Editorial / Administrative changes
(√) Other

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**REVISION #7**

The above-referenced study has been updated as follows:

This revision has been prepared in response to the Request for Rapid Amendment (RRA) for Everolimus (NSC- 733504) (IND-115643) from Dr. Austin Doyle (doylela@mail.nih.gov), Dr. James Zwiebel (zwiebelj@ctep.nci.nih.gov), and Dr. Meg

Mooney (mooneym@ctep.nci.nih.gov) on October 12, 2016. The associated action letter is attached.

1. The Version Dates of the protocol and Model Consent Form have been updated.

2. Table of Contents: The page numbers have been updated.

3. Section 3.1c, the CAEPR for Everolimus, Version 2.2, March 21, 2016, has been replaced with Version 2.3, June 30, 2016. The section has been updated as follows:

- Added New Risk:
  - Reported but with Insufficient Evidence for Attribution: Ascites; Blood and lymphatic system disorders - Other (thrombotic microangiopathy); Bronchopulmonary hemorrhage; Cardiac disorders - Other (myocardial abnormality); Chest wall pain; Colitis; Delirium; Edema trunk; Encephalopathy; Endocrine disorders - Other (low testosterone); Flu like symptoms; Gastroesophageal reflux disease; Gastrointestinal disorders - Other (Dieulafoy's lesion); Generalized muscle weakness; Genital edema; Glucose intolerance; Hematuria; Hepatobiliary disorders - Other (hepatomegaly); Hydrocephalus; Hypomagnesemia; Hypothyroidism; INR increased; Intra-abdominal hemorrhage; Investigations - Other (low density lipoprotein raised); Investigations - Other (thrombocythemia); Keratitis; Left ventricular systolic dysfunction; Lethargy; Mania; Metabolism and nutrition disorders - Other (high ammonia); Muscle weakness lower limb; Myalgia; Pancreatitis; Respiratory, thoracic and mediastinal disorders - Other (rales); Sinus bradycardia; Supraventricular tachycardia; Toothache; Vascular disorders - Other (acute bowel ischemia); Voice alteration.
- Increase in Risk Attribution:
  - Changed to Less Likely from Reported with Insufficient Evidence for Attribution: Constipation
- Decrease in Risk Attribution:
  - Changed to Less Likely from Likely: Aspartate aminotransferase increased; Cholesterol high; Hyperglycemia; Hypertriglyceridemia Lymphocyte count decreased; Platelet count decreased
  - Changed to Reported with Insufficient Evidence for Attribution from Less Likely: Activated partial thromboplastin time prolonged; Dizziness; Dry mouth; Hypoalbuminemia; Hypocalcemia; Hypokalemia; Insomnia; Investigations - Other (bicarbonate decreased); Rash acneiform; Skin and subcutaneous tissue disorders - Other (nail disorder)
- Deleted Risk:
  - Reported But With Insufficient Evidence for Attribution: Hypernatremia
- Provided Further Clarification:
  - Nasal congestion (under Also Reported But With Insufficient Evidence for Attribution) is now reported as Respiratory, thoracic and mediastinal disorders - Other (rhinorrhea).

Model Consent Form Changes

Patients currently receiving everolimus and patients who sign a consent form prior to local implementation of the consent form changes must be informed of the bolded changes below. The manner by which this notification takes place is at the discretion of the local institution. At a minimum, the patient must be notified by the next visit and this notification must be documented in the patient chart. Patients need not be informed of the non-bolded changes unless required by the local IRB.

1. The following changes have been made to the risk tables for Everolimus in the Model Consent Form:
    - Increase in Risk Attribution:
        - Added to Occasional: **Constipation**
    - Decrease In Risk Attribution:
        - Changed to Occasional from Common: Bruising, Bleeding
        - Removed from risk tables: Acne; Change in or loss of some or all of the finger or toenails; Difficulty sleeping; Dizziness; Dry mouth

This memorandum serves to notify the NCI and the SWOG Statistical Center.

cc: PROTOCOL & INFORMATION OFFICE
Jeffrey Huminik – PCC
Emily Tabinski – PCC
Meredith Lavin - Novartis
Katie Von Derau - WPC

DEPARTMENT OF HEALTH & HUMAN SERVICES
Public Health Service

National Institutes of Health
National Cancer Institute
Bethesda, Maryland 20892

# Action Letter

**DATE:** **November 21, 2016**

**FROM:** L. Austin Doyle, MD, Medical Officer, IDB, CTEP, DCTD, NCI
James Zwiebel, MD, Branch Chief, IDB, CTEP, DCTD, NCI
Meg Mooney, MD, Branch Chief, CIB, CTEP, DCTD, NCI

**SUBJECT:** **CONFIDENTIAL COMMUNICATION** – Action Letter for Everolimus (RAD-001, NSC 733504)

**TO:** Investigators for CTEP-supported Studies Involving Everolimus (RAD-001, NSC 733504)

The purpose of this Action Letter is to alert patients and investigators in studies conducted by the Cancer Therapy Evaluation Program (CTEP), National Cancer Institute (NCI), of new and/or modified risk information associated with everolimus, and to request all trials with everolimus be amended to reflect these changes. You are receiving this letter because you are conducting a CTEP-sponsored trial that includes everolimus. See the accompanying list of CTEP trials with everolimus.

**Although there is modified risk information for everolimus, the added risks are very similar to risks that were already included in the previous version of the CAEPR and would have been communicated to patients in the informed consent document (ICD).** In this case, (1) constipation is associated with previously identified risks, abdominal pain and vomiting; and (2) a decrease in the frequency of aspartate aminotransferase increased, cholesterol high, lymphocyte count decreased, platelet count decreased, hyperglycemia and hypertriglyceridemia resulted in the risks being moved from likely to less likely in the CAEPR.

**When changes such as these are made to the ICD (i.e., changes as to how risk information is presented and/or additional clarifying information), it is not necessary to suspend enrollment of new subjects until a revised ICD is reviewed and approved by the IRB**. For this requested amendment, patient enrollment may continue before the IRB reviews and approves such changes to the ICD; however, changes to the ICDs cannot be implemented until they are approved by the IRB. An amendment that includes the new version of the CAEPR for everolimus and this additional clarification of risks in the ICD must be included in a protocol amendment as outlined in this Action Letter and per the time-lines specified.

In response to the new/modified risk information CTEP is requiring that all trials with everolimus be amended to reflect this new information. Detailed description of the new/modified risk(s) as well as detailed instructions regarding amendment requirements are described in this Action Letter. **Amendments are due to the Protocol and Information Office (PIO) at PIO@CTEP.NCI.NIH.GOV by 5 PM ET on December 2, 2016** or as required based on protocol status (see the *General Actions Required Based on Protocol Status* section). The cover letter for the submitted amendment should state that it is being submitted in response to an Action Letter from Dr. L. Austin Doyle (doylela@mail.nih.gov). Failure to respond in a timely fashion may result in suspension of the Principal Investigator or permanent study closure.

# Action Letter

After review of all the available data, CTEP believes that the new and/or modified risk information does **NOT** significantly alter the risk-benefit profile for patients in the study since everolimus is already known to cause serious adverse events and this new risk information does not change the overall weight given to risks versus benefits for patients in the study. CTEP considers all the proposed protocol and informed consent changes for studies affected by this Action Letter to be minor. Therefore, under the provisions of Department of Health and Human Services regulations for the protection of human subjects at 45 CFR 46.110, a protocol amendment that includes this new information can undergo expedited review if the Institutional Review Board (IRB) Chair (or other experienced IRB member designated to conduct expedited review by the Chair) concurs that the changes are minor. Additional information from the Office of Human Research Protections (OHRP) regarding this process is available at: http://www.hhs.gov/ohrp/policy/Correspondence/nci200870929.html.

The following section, *Specific Instruction*, includes background information on the risk(s), any risk mitigation strategies, and amendment requirements. The revised Comprehensive Adverse Events and Potential Risks (CAEPR) list (Attachment 1) and Informed Consent Document (ICD) risk information (Attachment 2) are also attached. Action Letter general instructions as well as instructions regarding amendment preparation (if a CTEP-approved amendment does not already accompany this Action Letter) are included in Attachment 3. **You MUST follow the instructions outlined in Attachment 3.**

# Action Letter

**SPECIFIC INSTRUCTION**

**Background**

As part of Good Clinical Practice, CTEP reviews each CAEPR list on an annual basis. The review includes literature search, CTEP-AERS submission review, and comparison to the latest agent Investigator's Brochure. After review of all the available data, CTEP has identified new and/or modified risk information associated with everolimus.

**Detailed Description of Required Protocol Changes for the Amendment/ Sample Change Memo Template**

1) New Protocol Amendment/Version Date Included on the Title/Cover Page per Operations Office Policy:

   Protocol Cover Page: Page Number(s): _____
   Version Date: _____

2) Revision of the Protocol CAEPR:

   Protocol Section(s) for Insertion of Revised CAEPR (Version 2.3, June 30, 2016): ___
   Page Number(s): ____

- Added New Risk:
  - Also Reported on Everolimus Trials But With Insufficient Evidence for Attribution: Ascites; Blood and lymphatic system disorders - Other (thrombotic microangiopathy); Bronchopulmonary hemorrhage; Cardiac disorders - Other (myocardial abnormality); Chest wall pain; Colitis; Delirium; Edema trunk; Encephalopathy; Endocrine disorders - Other (low testosterone); Flu like symptoms; Gastroesophageal reflux disease; Gastrointestinal disorders - Other (Dieulafoy's lesion); Generalized muscle weakness; Genital edema; Glucose intolerance; Hematuria; Hepatobiliary disorders - Other (hepatomegaly); Hydrocephalus; Hypomagnesemia; Hypothyroidism; INR increased; Intra-abdominal hemorrhage; Investigations - Other (low density lipoprotein raised); Investigations - Other (thrombocythemia); Keratitis; Left ventricular systolic dysfunction; Lethargy; Mania; Metabolism and nutrition disorders - Other (high ammonia); Muscle weakness lower limb; Myalgia; Pancreatitis; Respiratory, thoracic and mediastinal disorders - Other (rales); Sinus bradycardia; Supraventricular tachycardia; Toothache; Vascular disorders - Other (acute bowel ischemia); Voice alteration

- Increase in Risk Attribution:
  - Changed to Less Likely from Also Reported on Everolimus Trials But With Insufficient Evidence for Attribution: Constipation

- Decrease in Risk Attribution:
  - Changed to Less Likely from Likely: Aspartate aminotransferase increased; Cholesterol high; Hyperglycemia; Hypertriglyceridemia; Lymphocyte count decreased; Platelet count decreased
  - Changed to Also Reported on Everolimus Trials But With Insufficient Evidence for Attribution from Less Likely: Activated partial thromboplastin time prolonged; Dizziness; Dry mouth; Hypoalbuminemia; Hypocalcemia; Hypokalemia; Insomnia; Investigations - Other (bicarbonate decreased); Rash acneiform; Skin and subcutaneous tissue disorders - Other (nail disorder)

- Deleted Risk:
  - Also Reported on Everolimus Trials But With Insufficient Evidence for Attribution: Hypernatremia

- Provided Further Clarification:
  - Nasal congestion (under Also Reported But With Insufficient Evidence for Attribution) is now reported as Respiratory, thoracic and mediastinal disorders - Other (rhinorrhea).

PLEASE NOTE: The specific detailed changes listed here compare the new revised CAEPR Version 2.3, and associated risk information for the ICD, to the most recent CAEPR Version 2.2. If your trial contains an older CAEPR version (i.e., does **NOT** currently contain CAEPR Version 2.2), you **MUST** include a description of any additional changes resulting from migration from the older CAEPR version.

3) Revision of the ICD as Specified Below:

The terminology for CTEP's suggested lay terms may change periodically. The condensed risk profile represents CAEPR risks in lay terms in a "patient-friendly" condensed form. It is provided as a guide and its use is completely optional; however, all risks listed in the current CAEPR must be reflected in the ICD. Expanding or condensing similar terms is acceptable. If you have chosen to reformat and/or reword the condensed risk profile in any way, please state, "The condensed risk profile has been modified" in the cover memo.

- Increase in Risk Attribution:
  - Changed to Occasional from Also Reported on Everolimus Trials But With Insufficient Evidence for Attribution (i.e., added to the Risk Profile): Constipation

- Decrease in Risk Attribution:
  - Changed to Occasional from Common: Bruising, bleeding
  - Changed to Also Reported on Everolimus Trials But With Insufficient Evidence for Attribution from Occasional (i.e., deleted from the Risk Profile): Acne; Change in or loss of some or all of the finger or toenails; Difficulty sleeping; Dizziness; Dry mouth

PLEASE NOTE: The potential risks listed in the CAEPR whose relationship to everolimus is still undetermined are not required by CTEP to be described in the ICD; however, they may be communicated to patients according to local IRB requirements.

# Action Letter

**Attachment 1: Revised Everolimus CAEPR – Version 2.3, June 30, 2016**

## Comprehensive Adverse Events and Potential Risks list (CAEPR) for Everolimus (RAD-001, NSC 733504)

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. In addition to the comprehensive list, a subset, the Specific Protocol Exceptions to Expedited Reporting (SPEER), appears in a separate column and is identified with bold and italicized text. This subset of AEs (SPEER) is a list of events that are protocol specific exceptions to expedited reporting to NCI (except as noted below). 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).

**NOTE**: Report AEs on the SPEER **ONLY IF** they exceed the grade noted in parentheses next to the AE in the SPEER. If this CAEPR is part of a combination protocol using multiple investigational agents and has an AE listed on different SPEERs, use the lower of the grades to determine if expedited reporting is required.

**Version 2.3, June 30, 2016[1]**

| **Adverse Events with Possible Relationship to Everolimus (RAD-001) (CTCAE 4.0 Term) [n= 3033]** | | | **Specific Protocol Exceptions to Expedited Reporting (SPEER)** |
|---|---|---|---|
| **Likely (>20%)** | **Less Likely (<=20%)** | **Rare but Serious (<3%)** | |
| BLOOD AND LYMPHATIC SYSTEM DISORDERS | | | |
| Anemia | | | ***Anemia (Gr 2)*** |
| GASTROINTESTINAL DISORDERS | | | |
| | Abdominal pain | | |
| | Constipation | | |
| Diarrhea[2] | | | ***Diarrhea[2] (Gr 2)*** |
| Mucositis oral[3] | | | ***Mucositis oral[3] (Gr 2)*** |
| | Nausea | | ***Nausea (Gr 2)*** |
| | Vomiting | | ***Vomiting (Gr 2)*** |
| GENERAL DISORDERS AND ADMINISTRATION SITE CONDITIONS | | | |
| | Edema limbs | | ***Edema limbs (Gr 2)*** |
| Fatigue | | | ***Fatigue (Gr 2)*** |
| | Fever | | ***Fever (Gr 2)*** |
| INFECTIONS AND INFESTATIONS | | | |
| | Infection[4] | | ***Infection[4] (Gr 2)*** |
| INJURY, POISONING AND PROCEDURAL COMPLICATIONS | | | |
| | | Wound complication[5] | |
| INVESTIGATIONS | | | |
| | Alanine aminotransferase increased | | ***Alanine aminotransferase increased (Gr 2)*** |
| | Alkaline phosphatase increased | | ***Alkaline phosphatase increased (Gr 2)*** |
| | Aspartate aminotransferase increased | | ***Aspartate aminotransferase increased (Gr 2)*** |
| | Cholesterol high | | ***Cholesterol high (Gr 2)*** |
| | Creatinine increased | | ***Creatinine increased (Gr 2)*** |
| | Lymphocyte count decreased | | ***Lymphocyte count decreased (Gr 2)*** |
| | Neutrophil count decreased | | ***Neutrophil count decreased (Gr 2)*** |
| | Platelet count decreased | | ***Platelet count decreased (Gr 2)*** |
| | Weight loss | | |

# Action Letter

| Adverse Events with Possible Relationship to Everolimus (RAD-001) (CTCAE 4.0 Term) [n= 3033] | | | Specific Protocol Exceptions to Expedited Reporting (SPEER) |
|---|---|---|---|
| **Likely (>20%)** | **Less Likely (<=20%)** | **Rare but Serious (<3%)** | |
| | White blood cell decreased | | ***White blood cell decreased (Gr 2)*** |
| METABOLISM AND NUTRITION DISORDERS | | | |
| | Anorexia | | ***Anorexia (Gr 2)*** |
| | Hyperglycemia[6] | | ***Hyperglycemia[6] (Gr 2)*** |
| | Hypertriglyceridemia | | ***Hypertriglyceridemia (Gr 2)*** |
| | Hypophosphatemia | | ***Hypophosphatemia (Gr 2)*** |
| MUSCULOSKELETAL AND CONNECTIVE TISSUE DISORDERS | | | |
| | Arthralgia | | |
| | Back pain | | |
| | Pain in extremity | | |
| NERVOUS SYSTEM DISORDERS | | | |
| | Dysgeusia | | |
| | Headache | | ***Headache (Gr 2)*** |
| RENAL AND URINARY DISORDERS | | | |
| | | Acute kidney injury | |
| RESPIRATORY, THORACIC AND MEDIASTINAL DISORDERS | | | |
| | Cough | | ***Cough (Gr 2)*** |
| | Dyspnea | | ***Dyspnea (Gr 2)*** |
| | Epistaxis | | ***Epistaxis (Gr 2)*** |
| | Pneumonitis[7] | | |
| SKIN AND SUBCUTANEOUS TISSUE DISORDERS | | | |
| | Dry skin | | |
| | Pruritus | | |
| Rash maculo-papular | | | ***Rash maculo-papular (Gr 2)*** |

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

[9]Patients taking concomitant ACE inhibitor therapy may be at increased risk for angioedema.

# Action Letter

**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** - Blood and lymphatic system disorders - Other (thrombotic microangiopathy)
**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); Endocrine disorders - Other (low testosterone); Hypothyroidism
**EYE DISORDERS** - Blurred vision; Conjunctivitis; 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; Irritability; Non-cardiac chest pain; Pain
**HEPATOBILIARY DISORDERS** - Hepatic failure; Hepatobiliary disorders - Other (hepatomegaly)
**IMMUNE SYSTEM DISORDERS** - Allergic reaction
**INVESTIGATIONS** - Activated partial thromboplastin time prolonged; Blood bilirubin increased; CPK increased; GGT increased; INR increased; Investigations - Other (bicarbonate decreased); Investigations - Other (increased lactate dehydrogenase); Investigations - Other (low density lipoprotein raised); Investigations - Other (thrombocythemia)
**METABOLISM AND NUTRITION DISORDERS** - Dehydration; Glucose intolerance; Hypercalcemia; Hyperkalemia; Hypoalbuminemia; Hypocalcemia; Hypokalemia; Hypomagnesemia; Hyponatremia; Metabolism and nutrition disorders - Other (high ammonia); Metabolism and nutrition disorders - Other (hyperlipidemia)
**MUSCULOSKELETAL AND CONNECTIVE TISSUE DISORDERS** - Bone pain; Chest wall pain; Generalized muscle weakness; Muscle weakness lower limb; Musculoskeletal and connective tissue disorder - Other (muscle spasms); 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[8]; Delirium; Depression; Insomnia; 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); Respiratory, thoracic and mediastinal disorders - Other (rhinorrhea); Sore throat; Voice alteration
**SKIN AND SUBCUTANEOUS TISSUE DISORDERS** - Nail loss; Palmar-plantar erythrodysesthesia syndrome; Rash acneiform; Skin and subcutaneous tissue disorders - Other (angioedema)[9]; 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.

# Action Letter

**Attachment 2: Revised ICD Section(s) for Everolimus**

Please note that the terminology for CTEP's suggested lay terms may change periodically. The condensed risk profile represents CAEPR risks in lay terms in a "patient-friendly" condensed format. It is provided as a guide and its use is completely optional; however, all risks listed in the current CAEPR must be reflected in the ICD. Expanding or condensing similar terms is acceptable. If you have chosen to reformat and/or reword the condensed risk profile in any way, please state, "The condensed risk profile has been modified" in the cover memo. Please insert this condensed risk profile as the Table of Possible Side Effects for everolimus in your ICD.

**Risk Profile for Everolimus (CAEPR Version 2.3, June 30, 2016)**

**NOTE:** The risk list section in the new NCI Consent Form Template (latest version: May 2013) will include the wording below:

"If you choose to take part in this study, there is a risk that:

- You may lose time at work or home and spend more time in the hospital or doctor's office than usual
- You may be asked sensitive or private questions which you normally do not discuss

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 who 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 serious and may even result in death.

Here are important points about how you and the study doctor can make side effects less of a problem:

- Tell the study doctor if you notice or feel anything different so they can see if you are having a side effect.
- The study doctor may be able to treat some side effects.
- The 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."

Please insert this condensed risk profile as the Table of Possible Side Effects for Everolimus in your ICD.

# Action Letter

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

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

| **RARE, AND SERIOUS**<br>In 100 people receiving everolimus, 3 or fewer may have: |
|---|
| • Non-healing surgical site<br>• Kidney damage which may require dialysis |

# Action Letter

**Attachment 3: Action Letter GENERAL INSTRUCTIONS**

1. **Distribute this Action Letter (and any accompanying CTEP-approved amendment) to all participating investigators and IRBs within 2 working days.** For National Clinical Trials Network (NCTN) studies, please follow instructions from your Operations office. For sites participating in the NCI Central-IRB (CIRB) Initiative, CTEP has provided a copy of this Action Letter to the CIRB if the Action Letter affects any studies under CIRB review.

2. **Patients currently on study may continue on study provided they are informed of the new and/or modified risk information.** This information should be communicated to patients already enrolled on study without waiting for IRB review/approval since this information represents a significant new finding(s) that developed during the course of the research that may relate to a patient's willingness to continue participation and per the Office for Human Research Protections, the regulations do not require IRB review and approval of statements describing such significant new findings before they are provided to already enrolled patients. Documentation of their informed consent should be carried out according to local IRB requirements.

3. **Save a copy of the Action Letter (and any CTEP approval letter for an accompanying amendment) for your records.**

**INSTRUCTIONS FOR PREPARATION OF AN AMENDMENT IN RESPONSE TO THIS Action Letter (if a CTEP-Approved amendment for your trial does not already accompany the Action Letter)**

**General Instructions on Amendment Preparation:**

1. Instructions regarding the due date for an amendment and where to send it are included on the first page of this Action Letter. The Clinical Trials Operations Offices may use the *Detailed Description of Required Protocol Changes* section in this Action Letter as the template for their Change Memo; however, it is not required if an Operations Office prefers to use its own Change Memo.
2. If any of the NCI-required changes are not applicable for your trial (i.e., already appear in your protocol), note this in your Change Memo.
3. **The ICD changes include CTEP's suggested lay terms for each adverse event identified in the CAEPR. You may substitute different lay terms for each concept if appropriate for your patient population. If you have chosen to reformat and/or reword the risk profile in any way, please state, "The risk profile has been modified" in the cover memo.**

**Specific Instructions on Amendment Preparation Based on Protocol Status:**

A. Trials with a current CTEP status of **"Active"**
   - Review and follow **ALL** the instructions outlined in this Action Letter.
   - The information provided in this memo outlines the **ONLY** changes that can be made in response to the Action Letter, except for changes that are consistent with CTEP's editorial and administrative update policy.

B. Trials with a current status of **"Approved", "Temporarily Closed to Accrual and Treatment", or "Temporarily Closed to Accrual"**
   - The protocol and ICD must be revised as per the instructions outlined in the Action Letter in the next revised protocol draft submitted to CTEP. The protocol amendment must be submitted and approved by CTEP before the trial can be activated or re-opened.
   - You may include additional non-Action Letter related changes (any type) in your amendment response.

# Action Letter

C. Trials with a current CTEP status of **"In Review"**
- The protocol and ICD must be revised as per the instructions outlined in the Action Letter. These changes must be included in the next revised protocol draft submitted to and approved by CTEP before the trial can be activated.
- You may include additional non-Action Letter related changes (any type) in your revision response. Note the inclusion of non-Action Letter related changes may delay approval of your trial.

D. Trials with a current CTEP status of **"Closed to Accrual"**

*If your trial is under a CTEP-held IND:*
- Review and follow **ALL** the instructions outlined in this Action Letter.
- The information provided in this memo outlines the **ONLY** changes that can be made in response to the Action Letter, except for changes that are consistent with CTEP's amendment request submission policy.

*If your trial is NOT under a CTEP-held IND:*
- If Action Letter INCLUDES information that impacts patient care (e.g., new/adjusted dose modifications or special monitoring for patient population at risk) - An amendment is required. Review and follow **ALL** the instructions outlined in this Action Letter. The information provided in this memo outlines the **ONLY** changes that can be made in response to the Action Letter, except for changes that are consistent with CTEP's amendment request submission policy.
  - **If Action Letter does NOT INCLUDE information that impacts patient care - Amendment is typically NOT required.**

E. Trials with a current CTEP status of **"Closed to Accrual and Treatment"** or **"Complete"**
- Amendment is not required. This information is being sent for informational purposes only. You may follow local IRB or Operations Office procedures and requirements.

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swog.org

November 1, 2016

TO: ALL NATIONAL CLINICAL TRIALS NETWORK (NCTN) MEMBERS

FROM: SWOG Operations Office

RE: IND Safety Reports for Everolimus

**MEMORANDUM**

**IRB Review Requirements**
( ) Full board review required
(X) Expedited review allowed
( ) No review required

**Status Change**
( ) IRB Review only
( ) Activation
( ) Closure
( ) Reactivation

**Protocol changes**
( ) Eligibility changes
( ) Treatment / Dose Modification / Study Calendar changes
( ) Informed Consent changes
  ( ) Patient notification not required
  ( ) Patient notification required
( ) Scientific / Statistical Consideration changes
( ) Specimen Submission changes
( ) Data Submission / Forms changes
( ) Editorial / Administrative changes
( ) Other:

---

**MEMORANDUM**

The following new safety report has been posted regarding an adverse event that occurred in association with the drug everolimus. Please access this safety report via the study's abstract page or the safety report link on the SWOG website (https://swog.org/safetyreports/safetyreports.asp).

| This safety report pertains to the following studies: | Reports: |
|---|---|
| **S0528** Early Therapeutics<br>**S0931** Genitourinary<br>**S1207** Breast<br>**S1222** Breast | Sep. 21, 2016 Mfr Rpt #PHHO2016US012541 |

Protocol amendments are not necessary at this time, but your consent form may be revised to include the information provided in this report if it is deemed necessary by your institution. Please append this notice and this report to your copy of the protocol and forward copies to your Institutional Review Board (IRB) as required by your local policies and procedures. Should any further information regarding these adverse events be made available, it will be forwarded to you.

This memorandum serves to notify the NCI and the SWOG Statistical Center.

cc: PROTOCOL & INFORMATION OFFICE
Carol French – AstraZeneca
John Parnell – AstraZeneca
Jean Sowa – AstraZeneca
Meredith Lavin – Novartis
Kristin White – Novartis
Rebecca DeLos Rios - Novartis
Heather Campbell, PharmD – VACSP/PCC
Anne Davis – VACSP/PCC
Sharon Jenkins – VACSP/PCC
James Rasp – VACSP/PCC
Emily Tabinski – VACSP/PCC
Jason Koury – VACSP/PCC
Jeffrey Huminik – VACSP/PCC

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November 1, 2016

TO: ALL NATIONAL CLINICAL TRIALS NETWORK (NCTN) MEMBERS (U.S. Institutions Only); INCAN (Mexico)

FROM: SWOG Operations Office (E-mail: protocols@swog.org)

RE: **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." Study Chairs: Drs. M. Chavez-MacGregor, P Rastogi and L. Pusztai.

**MEMORANDUM**

Study Chair: Mariana Chavez-MacGregor, M.D., M.Sc.
Phone Number: 713/792-2817
E-mail: **S1207**medicalquery@swog.org

**IRB Review Requirements**
( ) Full board review required
( ) Expedited review allowed
(X) No review required

**Status Change**
( ) IRB Review only
( ) Activation
( ) Closure
( ) Reactivation

**Protocol changes**
( ) Eligibility changes
( ) Treatment / Dose Modification / Study Calendar changes
( ) Informed Consent changes
  ( ) Patient notification not required
  ( ) Patient notification required: see below for details.
( ) Scientific / Statistical Consideration changes
( ) Specimen Submission changes
( ) Data Submission / Forms changes
( ) Editorial / Administrative changes
(X) Other: Clarification of specimen submission requirements (Section 15.1)

---

**MEMORANDUM**

The purpose of this memorandum is to clarify the specimen submission requirements and to inform sites of an update to the Master Forms Set for the above-referenced study.

Specimen Submission Requirements: Please note that the whole blood submitted for pharmacogenomics studies (Section 15.1b) and the BAHO substudy (Section 15.1c) must be submitted unprocessed and at ambient temperature (no processing and/or freezing is required). This will be clarified further in the next available protocol revision.

Master Forms Set: The Onstudy Form has been updated to include additional spaces in the "Requisition Number" field. The Form Version has been updated to 1.4; the form number has not changed.

This memorandum serves to notify the NCI and the SWOG Statistical Center.

cc: PROTOCOL & INFORMATION OFFICE
Jeffrey Huminik – PCC
Emily Tabinski – PCC
Meredith Lavin - Novartis
Katie Von Derau - WPC

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Distribution Date: September 1, 2016
CIRB Submission Date: August 17, 2016


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TO: ALL NATIONAL CLINICAL TRIALS NETWORK (NCTN) MEMBERS (U.S. and Canadian Institutions Only); INCAN (Mexico)

FROM: Megan M. Hardin, Protocol Coordinator (E-mail: mhardin@swog.org)

RE: **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." Study Chairs: Drs. M. Chavez-MacGregor and L. Pusztai.

**MEMORANDUM**

Study Chair: Mariana Chavez-MacGregor, M.D., M.Sc.
Phone Number: 713/792-2817
E-mail: **S1207**medicalquery@swog.org

**IRB Review Requirements**
( ) Full board review required
(X) Expedited review allowed
( ) No review required

**Status Change**
( ) IRB Review only
( ) Activation
( ) Closure
( ) Reactivation

**Protocol changes**
( ) Eligibility changes
( ) Treatment / Dose Modification / Study Calendar changes
( ) Informed Consent changes
  ( ) Patient notification not required
  ( ) Patient notification required
( ) Scientific / Statistical Consideration changes
( ) Specimen Submission changes
( ) Data Submission / Forms changes
( ) Editorial / Administrative changes
( ) Other:

---

**MEMORANDUM**

The purpose of this memorandum is to inform the CIRB and sites of a correction in the Revision #6 cover memo that was distributed on July 1st. That memo indicated that patients need not be notified of the changes. It has come to our attention that, despite the assessment that patients need not be notified of the changes in this revision, CTEP's Action Letter **does** require patient notification.

Therefore, patients currently receiving everolimus and patients who sign a consent form prior to the revised consent being implemented must be informed of the new and modified risk information outlined in Revision #6.

The manner by which the notification takes place is at the discretion of the local institution. At a minimum, the patient must be notified by the next visit and this notification process must be documented in the patient chart.

Also, SWOG distributed a memo to sites 5/1/15 indicating that there would be two changes made to the model consent form in a forthcoming revision. Upon further review, SWOG will not be adding "/placebo" in the header of each risk table for everolimus as this information in the headers is based off of everolimus only, not the placebo.

Finally, Revision #6 didn't include the following change: "Change in or loss of some or all of the fingers or toenails" corrected to "Change in or loss of some or all of the fingernails or toenails." CTEP has recently agreed to this change and therefore sites can make this change to their local consent forms. SWOG will make this correction to the consent form in a forthcoming revision.

SWOG considers that these Model Consent Form changes **do not** represent an alteration in risk/benefit ratio. Therefore, local accrual does **not** need to be suspended pending implementation of these changes. Patients need not be informed of these two changes unless required by the local IRB.

This memorandum serves to notify the NCI and the SWOG Statistical Center.

cc: PROTOCOL & INFORMATION OFFICE

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swog.org

Distribution Date: July 1, 2016
CTEP Submission Date: June 6, 2016

TO: ALL NATIONAL CLINICAL TRIALS NETWORK (NCTN) MEMBERS (U.S. Institutions Only); INCAN (Mexico)

FROM: Megan M. Hardin, Protocol Coordinator (E-mail: mhardin@swog.org)

RE: **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." Study Chairs: Drs. M. Chavez-MacGregor, P Rastogi and L. Pusztai.

**REVISION #6**

Study Chair: Mariana Chavez-MacGregor, M.D., M.Sc.
Phone Number: 713/792-2817
E-mail: **S1207**medicalquery@swog.org

**IRB Review Requirements**
( ) Full board review required
(√) Expedited review allowed
( ) No review required

**Status Change**
( ) IRB Review only
( ) Activation
( ) Closure
( ) Reactivation

**Protocol changes**
( ) Eligibility changes
( ) Treatment / Dose Modification / Study Calendar changes
(√) Informed Consent changes
  (√) Patient notification not required
  ( ) Patient notification required
( ) Scientific / Statistical Consideration changes
( ) Specimen Submission changes
( ) Data Submission / Forms changes
( ) Editorial / Administrative changes
( ) Other:

---

**REVISION #6**

The changes in Section 3.1c and the Model Consent Form noted below are in response to a Request for Rapid Amendment (RRA) from Dr. L. Austin Doyle (doylela@mail.nih.gov) received on May 6, 2016. The associated Action Letter is attached.

1. Title Page, Page 1: The Version Date of the protocol and model consent form has been updated.

2. Section 3.1c, Pages 10-13: The everolimus adverse event (AE) table has been replaced with a CAEPR Version 2.2 (March 21, 2016). The section has been updated as follows:

   - Increase in Risk Attribution:
     - Changed to Likely from Less Likely: Aspartate aminotransferase increased
     - Changed to Less Likely from Reported but With Insufficient Evidence for Attribution: Hypoalbuminemia

   - Decrease in Risk Attribution:
     - Changed to Reported but With Insufficient Evidence for Attribution from Less Likely: Constipation; Hypertension; Pharyngolaryngeal pain

   - Provided Further Clarification:
     - Respiratory, thoracic and mediastinal disorders - Other (pulmonary toxicity) (under Less Likely) is now reported as Pneumonitis (under Less Likely), and footnote #7 now states "Includes pneumonitis, interstitial lung disease, lung infiltration, pulmonary alveolar hemorrhage, pulmonary toxicity, alveolitis, pulmonary fibrosis, and restrictive pulmonary disease."
     - The following footnote #9, "Patients taking concomitant ACE inhibitor therapy may be at increased risk for angioedema," was added.

   - Modified Specific Protocol Exceptions to Expedited Reporting (SPEER) reporting requirements:
     - Added: Infection

**Model Consent Form Changes:**

3. Model Consent Form, Pages 6-7: The following changes have been made to the risk tables for everolimus/placebo:

   - Decrease in Risk Attribution:
     - Changed to Reported but With Insufficient Evidence for Attribution from Occasional (i.e., removed from the Risk Profile): Constipation; High blood pressure which may cause blurred vision

   - Provided Further Clarification:
     - Damage to the lungs which may cause difficulty breathing (under Occasional) is now reported as Swelling of the lungs which may cause shortness of breath (under Occasional).

This memorandum serves to notify the NCI and the SWOG Statistical Center.

cc: PROTOCOL & INFORMATION OFFICE
Jeffrey Huminik – PCC
Emily Tabinski – PCC
Meredith Lavin - Novartis
Katie Von Derau - WPC

DEPARTMENT OF HEALTH & HUMAN SERVICES
Public Health Service

National Institutes of Health
National Cancer Institute
Bethesda, Maryland 20892

# Action Letter

**DATE:** **June 30, 2016**

**FROM:** L. Austin Doyle, MD, Medical Officer, IDB, CTEP, DCTD, NCI
James Zwiebel, MD, Branch Chief, IDB, CTEP, DCTD, NCI
Meg Mooney, MD, Branch Chief, CIB, CTEP, DCTD, NCI

**SUBJECT:** **CONFIDENTIAL COMMUNICATION** – Action Letter for Everolimus (RAD-001, NSC 733504)

**TO:** Investigators for CTEP-supported Studies Involving Everolimus (RAD-001, NSC 733504)

The purpose of this Action Letter is to alert patients and investigators in studies conducted by the Cancer Therapy Evaluation Program (CTEP), National Cancer Institute (NCI), of new and/or modified risk information associated with everolimus, and to request all trials with everolimus be amended to reflect these changes. You are receiving this letter because you are conducting a CTEP-sponsored trial that includes everolimus. See the accompanying list of CTEP trials with everolimus.

**Although there is modified risk information for everolimus, the added risks are very similar to risks that were already included in the previous version of the CAEPR and would have been communicated to patients in the informed consent document (ICD).** In this case, (1) an increase in the frequency of aspartate aminotransferase increased resulted in the risk being moved from less likely to likely in the CAEPR, and (2) hypoalbuminemia is an abnormal laboratory value that is not included in the ICD, as it is felt that patients would not perceive that they are experiencing this adverse event; also, the consent states that the study intervention may affect how different parts of the body work and that the study doctor will be testing blood and will let patients know if changes occur that may affect their health.

**When changes such as these are made to the ICD (i.e., changes as to how risk information is presented and/or additional clarifying information), it is not necessary to suspend enrollment of new subjects until a revised ICD is reviewed and approved by the IRB.** For this requested amendment, patient enrollment may continue before the IRB reviews and approves such changes to the ICD; however, changes to the ICDs cannot be implemented until they are approved by the IRB. An amendment that includes the new version of the CAEPR for everolimus and this additional clarification of risks in the ICD must be included in a protocol amendment as outlined in this RRA and per the time-lines specified.

In response to the new/modified risk information CTEP is requiring that all trials with everolimus be amended to reflect this new information. Detailed description of the new/modified risk(s) as well as detailed instructions regarding amendment requirements are described in this Action Letter. **Amendments are due to the Protocol and Information Office (PIO) at PIO@CTEP.NCI.NIH.GOV by 5 PM ET on July 14, 2016** or as required based on protocol status (see the *General Actions Required Based on Protocol Status* section). The cover letter for the submitted amendment should state that it is being submitted in response to an Action Letter from Dr. L. Austin Doyle (doylela@mail.nih.gov). Failure to respond in a timely fashion may result in suspension of the Principal Investigator or permanent study closure.

# Action Letter

After review of all the available data, CTEP believes that the new and/or modified risk information does **NOT** significantly alter the risk-benefit profile for patients in the study since everolimus is already known to cause serious adverse events and this new risk information does not change the overall weight given to risks versus benefits for patients in the study. CTEP considers all the proposed protocol and informed consent changes for studies affected by this Action Letter to be minor. Therefore, under the provisions of Department of Health and Human Services regulations for the protection of human subjects at 45 CFR 46.110, a protocol amendment that includes this new information can undergo expedited review if the Institutional Review Board (IRB) Chair (or other experienced IRB member designated to conduct expedited review by the Chair) concurs that the changes are minor. Additional information from the Office of Human Research Protections (OHRP) regarding this process is available at: http://www.hhs.gov/ohrp/policy/Correspondence/nci200870929.html.

The following section, *Specific Instruction*, includes background information on the risk(s), any risk mitigation strategies, and amendment requirements. The revised Comprehensive Adverse Events and Potential Risks (CAEPR) list (Attachment 1) and Informed Consent Document (ICD) risk information (Attachment 2) are also attached. Action Letter general instructions as well as instructions regarding amendment preparation (if a CTEP-approved amendment does not already accompany this Action Letter) are included in Attachment 3. **You MUST follow the instructions outlined in Attachment 3.**

# Action Letter

**SPECIFIC INSTRUCTION**

**Background**

As part of Good Clinical Practice, CTEP reviews each CAEPR list on an annual basis. The review includes literature search, CTEP-AERS submission review, and comparison to the latest agent Investigator's Brochure. After review of all the available data, CTEP has identified new and/or modified risk information associated with everolimus.

**Detailed Description of Required Protocol Changes for the Amendment/ Sample Change Memo Template**

1) New Protocol Amendment/Version Date Included on the Title/Cover Page per Operations Office Policy:

   Protocol Cover Page: Page Number(s): _____
   Version Date: _____

2) Revision of the Protocol CAEPR:

   Protocol Section(s) for Insertion of Revised CAEPR (Version 2.2, March 21, 2016): ___
   Page Number(s): ____

   - Increase in Risk Attribution:
     - Changed to Likely from Less Likely: Aspartate aminotransferase increased
     - Changed to Less Likely from Reported but With Insufficient Evidence for Attribution: Hypoalbuminemia

   - Decrease in Risk Attribution:
     - Changed to Reported but With Insufficient Evidence for Attribution from Less Likely: Constipation; Hypertension; Pharyngolaryngeal pain

   - Provided Further Clarification:
     - Respiratory, thoracic and mediastinal disorders - Other (pulmonary toxicity) (under Less Likely) is now reported as Pneumonitis (under Less Likely), and footnote #7 now states "Includes pneumonitis, interstitial lung disease, lung infiltration, pulmonary alveolar hemorrhage, pulmonary toxicity, alveolitis, pulmonary fibrosis, and restrictive pulmonary disease."
     - The following footnote #9, "Patients taking concomitant ACE inhibitor therapy may be at increased risk for angioedema," was added.

   - Modified Specific Protocol Exceptions to Expedited Reporting (SPEER) reporting requirements:
     - Added: Infection

   PLEASE NOTE: The specific detailed changes listed here compare the new revised CAEPR Version 2.2, and associated risk information for the Informed Consent Document (ICD), to the most recent CAEPR Version 2.1. If your trial contains an older CAEPR version (i.e., does **NOT** currently contain CAEPR Version 2.1), you **MUST** include a description of any additional changes resulting from migration from the older CAEPR version.

3) Revision of the ICD as Specified Below:

# Action Letter

The terminology for CTEP's suggested lay terms may change periodically. The condensed risk profile represents CAEPR risks in lay terms in a "patient-friendly" condensed form. It is provided as a guide and its use is completely optional; however, all risks listed in the current CAEPR must be reflected in the ICD. Expanding or condensing similar terms is acceptable. If you have chosen to reformat and/or reword the condensed risk profile in any way, please state, "The condensed risk profile has been modified" in the cover memo.

- Decrease in Risk Attribution:
  - Changed to Reported but With Insufficient Evidence for Attribution from Occasional (i.e., removed from the Risk Profile): Constipation; High blood pressure which may cause blurred vision

- Provided Further Clarification:
  - Damage to the lungs which may cause difficulty breathing (under Occasional) is now reported as Swelling of the lungs which may cause shortness of breath (under Occasional).

PLEASE NOTE: The potential risks listed in the CAEPR whose relationship to everolimus is still undetermined are not required by CTEP to be described in the ICD; however, they may be communicated to patients according to local IRB requirements.

# Action Letter

**Attachment 1: Revised Everolimus CAEPR – Version 2.2, March 21, 2016**

## Comprehensive Adverse Events and Potential Risks list (CAEPR) for Everolimus (RAD-001, NSC 733504)

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. In addition to the comprehensive list, a subset, the Specific Protocol Exceptions to Expedited Reporting (SPEER), appears in a separate column and is identified with bold and italicized text. This subset of AEs (SPEER) is a list of events that are protocol specific exceptions to expedited reporting to NCI (except as noted below). 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 1423 patients.* Below is the CAEPR for Everolimus (RAD-001).

**NOTE**: Report AEs on the SPEER **ONLY IF** they exceed the grade noted in parentheses next to the AE in the SPEER. If this CAEPR is part of a combination protocol using multiple investigational agents and has an AE listed on different SPEERs, use the lower of the grades to determine if expedited reporting is required.

**Version 2.2, March 21, 2016[1]**

| **Adverse Events with Possible Relationship to Everolimus (RAD-001) (CTCAE 4.0 Term) [n= 1423]** | | | **Specific Protocol Exceptions to Expedited Reporting (SPEER)** |
|---|---|---|---|
| **Likely (>20%)** | **Less Likely (<=20%)** | **Rare but Serious (<3%)** | |
| BLOOD AND LYMPHATIC SYSTEM DISORDERS | | | |
| Anemia | | | ***Anemia (Gr 2)*** |
| GASTROINTESTINAL DISORDERS | | | |
| | Abdominal pain | | |
| Diarrhea[2] | Dry mouth | | ***Diarrhea[2] (Gr 2)*** |
| Mucositis oral[3] | | | ***Mucositis oral[3] (Gr 2)*** |
| | Nausea | | ***Nausea (Gr 2)*** |
| | Vomiting | | ***Vomiting (Gr 2)*** |
| GENERAL DISORDERS AND ADMINISTRATION SITE CONDITIONS | | | |
| | Edema limbs | | ***Edema limbs (Gr 2)*** |
| Fatigue | | | ***Fatigue (Gr 2)*** |
| | Fever | | ***Fever (Gr 2)*** |
| INFECTIONS AND INFESTATIONS | | | |
| | Infection[4] | | ***Infection[4] (Gr 2)*** |
| INJURY, POISONING AND PROCEDURAL COMPLICATIONS | | | |
| | | Wound complication[5] | |
| INVESTIGATIONS | | | |
| | Activated partial thromboplastin time prolonged | | |
| | Alanine aminotransferase increased | | ***Alanine aminotransferase increased (Gr 2)*** |
| | Alkaline phosphatase increased | | ***Alkaline phosphatase increased (Gr 2)*** |
| Aspartate aminotransferase increased | | | ***Aspartate aminotransferase increased (Gr 2)*** |
| Cholesterol high | | | ***Cholesterol high (Gr 2)*** |
| | Creatinine increased | | ***Creatinine increased (Gr 2)*** |
| | Investigations - Other (bicarbonate decreased) | | |

# Action Letter

| Adverse Events with Possible Relationship to Everolimus (RAD-001) (CTCAE 4.0 Term) [n= 1423] | | | Specific Protocol Exceptions to Expedited Reporting (SPEER) |
|---|---|---|---|
| **Likely (>20%)** | **Less Likely (<=20%)** | **Rare but Serious (<3%)** | |
| Lymphocyte count decreased | | | ***Lymphocyte count decreased (Gr 2)*** |
| | Neutrophil count decreased | | ***Neutrophil count decreased (Gr 2)*** |
| Platelet count decreased | | | ***Platelet count decreased (Gr 2)*** |
| | Weight loss | | |
| | White blood cell decreased | | ***White blood cell decreased (Gr 2)*** |
| METABOLISM AND NUTRITION DISORDERS | | | |
| | Anorexia | | ***Anorexia (Gr 2)*** |
| Hyperglycemia[6] | | | ***Hyperglycemia[6] (Gr 2)*** |
| Hypertriglyceridemia | | | ***Hypertriglyceridemia (Gr 2)*** |
| | Hypoalbuminemia | | |
| | Hypocalcemia | | |
| | Hypokalemia | | |
| | Hypophosphatemia | | ***Hypophosphatemia (Gr 2)*** |
| MUSCULOSKELETAL AND CONNECTIVE TISSUE DISORDERS | | | |
| | Arthralgia | | |
| | Back pain | | |
| | Pain in extremity | | |
| NERVOUS SYSTEM DISORDERS | | | |
| | Dizziness | | |
| | Dysgeusia | | |
| | Headache | | ***Headache (Gr 2)*** |
| PSYCHIATRIC DISORDERS | | | |
| | Insomnia | | |
| RENAL AND URINARY DISORDERS | | | |
| | | Acute kidney injury | |
| RESPIRATORY, THORACIC AND MEDIASTINAL DISORDERS | | | |
| | Cough | | ***Cough (Gr 2)*** |
| | Dyspnea | | ***Dyspnea (Gr 2)*** |
| | Epistaxis | | ***Epistaxis (Gr 2)*** |
| | Pneumonitis[7] | | |
| SKIN AND SUBCUTANEOUS TISSUE DISORDERS | | | |
| | Dry skin | | |
| | Pruritus | | |
| | Rash acneiform | | |
| Rash maculo-papular | | | ***Rash maculo-papular (Gr 2)*** |
| | Skin and subcutaneous tissue disorders - Other (nail disorder) | | |

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

[9]Patients taking concomitant ACE inhibitor therapy may be at increased risk for angioedema.

**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:**

**CARDIAC DISORDERS** - Atrial fibrillation; Chest pain - cardiac; Heart failure; Myocardial infarction; Sinus tachycardia
**ENDOCRINE DISORDERS** - Endocrine disorders - Other (increased blood follicle stimulating hormone [FSH] levels); Endocrine disorders - Other (increased blood luteinizing hormone [LH] levels)
**EYE DISORDERS** - Blurred vision; Conjunctivitis
**GASTROINTESTINAL DISORDERS** - Constipation; Dyspepsia; Dysphagia; Flatulence; Hemorrhoids; Oral pain; Periodontal disease
**GENERAL DISORDERS AND ADMINISTRATION SITE CONDITIONS** - Chills; Edema face; Irritability; Non-cardiac chest pain; Pain
**HEPATOBILIARY DISORDERS** - Hepatic failure
**IMMUNE SYSTEM DISORDERS** - Allergic reaction
**INVESTIGATIONS** - Blood bilirubin increased; CPK increased; GGT increased; Investigations - Other (increased lactate dehydrogenase)
**METABOLISM AND NUTRITION DISORDERS** - Dehydration; Hypercalcemia; Hyperkalemia; Hypernatremia; Hyponatremia; Metabolism and nutrition disorders - Other (hyperlipidemia)
**MUSCULOSKELETAL AND CONNECTIVE TISSUE DISORDERS** - Bone pain; Musculoskeletal and connective tissue disorder - Other (muscle spasms)
**NEOPLASMS BENIGN, MALIGNANT AND UNSPECIFIED (INCL CYSTS AND POLYPS)** - Neoplasms benign, malignant and unspecified (incl cysts and polyps) - Other (ovarian cysts)
**NERVOUS SYSTEM DISORDERS** - Paresthesia
**PSYCHIATRIC DISORDERS** - Agitation; Anxiety[8]; Depression
**RENAL AND URINARY DISORDERS** - Proteinuria; Urinary frequency
**REPRODUCTIVE SYSTEM AND BREAST DISORDERS** - Dysmenorrhea; Irregular menstruation; Menorrhagia; Vaginal hemorrhage
**RESPIRATORY, THORACIC AND MEDIASTINAL DISORDERS** - Nasal congestion; Pharyngolaryngeal pain; Pleural effusion; Respiratory failure; Sore throat
**SKIN AND SUBCUTANEOUS TISSUE DISORDERS** - Nail loss; Palmar-plantar erythrodysesthesia syndrome; Skin and subcutaneous tissue disorders - Other (angioedema)[9]; Skin and subcutaneous tissue disorders - Other (skin lesion); Skin ulceration
**VASCULAR DISORDERS** - Flushing; Hypertension; Lymphedema; Phlebitis; Thromboembolic event; 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.

# Action Letter

**Attachment 2: Revised ICD Section(s) for Everolimus**

Please note that the terminology for CTEP's suggested lay terms may change periodically. The condensed risk profile represents CAEPR risks in a "patient-friendly" condensed form. It is provided as a guide and its use is completely optional; however, all risks listed in the current CAEPR must be reflected in the ICD. Expanding or condensing similar terms is acceptable. If you have chosen to reformat and/or reword the condensed risk profile in any way, please state, "The condensed risk profile has been modified" in the cover memo. Please insert this condensed risk profile as the Table of Possible Side Effects for everolimus in your ICD.

**Risk Profile for Everolimus (CAEPR Version 2.2, March 21, 2016)**

**NOTE:** The risk list section in the new NCI Consent Form Template (latest version: May 2013) will include the wording below:

"If you choose to take part in this study, there is a risk that:

- You may lose time at work or home and spend more time in the hospital or doctor's office than usual
- You may be asked sensitive or private questions which you normally do not discuss

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 who 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 serious and may even result in death.

Here are important points about how you and the study doctor can make side effects less of a problem:

- Tell the study doctor if you notice or feel anything different so they can see if you are having a side effect.
- The study doctor may be able to treat some side effects.
- The 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."

Please insert this condensed risk profile as the Table of Possible Side Effects for Everolimus in your ICD.

| **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
- Bruising, bleeding
- Rash

**OCCASIONAL, SOME MAY BE SERIOUS**
In 100 people receiving everolimus, from 4 to 20 may have:

- Pain
- Dry mouth, skin
- Nausea, vomiting
- Swelling of the arms, legs
- Fever
- Infection, especially when white blood cell count is low
- Weight loss, loss of appetite
- Dizziness, headache
- Changes in taste
- Difficulty sleeping
- Cough, shortness of breath
- Nose bleed
- Swelling of the lungs which may cause shortness of breath
- Itching, acne
- Change in or loss of some or all of the finger or toenails

**RARE, AND SERIOUS**
In 100 people receiving everolimus, 3 or fewer may have:

- Non-healing surgical site
- Kidney damage which may require dialysis

# Action Letter

**Attachment 3: Action Letter GENERAL INSTRUCTIONS**

1. **Distribute this Action Letter (and any accompanying CTEP-approved amendment) to all participating investigators and IRBs within 2 working days.** For National Clinical Trials Network (NCTN) studies, please follow instructions from your Operations office. For sites participating in the NCI Central-IRB (CIRB) Initiative, CTEP has provided a copy of this Action Letter to the CIRB if the Action Letter affects any studies under CIRB review.

2. **Patients currently on study may continue on study provided they are informed of the new and/or modified risk information.** This information should be communicated to patients already enrolled on study without waiting for IRB review/approval since this information represents a significant new finding(s) that developed during the course of the research that may relate to a patient's willingness to continue participation and per the Office for Human Research Protections, the regulations do not require IRB review and approval of statements describing such significant new findings before they are provided to already enrolled patients. Documentation of their informed consent should be carried out according to local IRB requirements.

3. **Save a copy of the Action Letter (and any CTEP approval letter for an accompanying amendment) for your records.**

**INSTRUCTIONS FOR PREPARATION OF AN AMENDMENT IN RESPONSE TO THIS Action Letter (if a CTEP-Approved amendment for your trial does not already accompany the Action Letter)**

**General Instructions on Amendment Preparation:**

1. Instructions regarding the due date for an amendment and where to send it are included on the first page of this Action Letter. The Clinical Trials Operations Offices may use the *Detailed Description of Required Protocol Changes* section in this Action Letter as the template for their Change Memo; however, it is not required if an Operations Office prefers to use its own Change Memo.
2. If any of the NCI-required changes are not applicable for your trial (i.e., already appear in your protocol), note this in your Change Memo.
3. **The ICD changes include CTEP's suggested lay terms for each adverse event identified in the CAEPR. You may substitute different lay terms for each concept if appropriate for your patient population. If you have chosen to reformat and/or reword the risk profile in any way, please state, "The risk profile has been modified" in the cover memo.**

**Specific Instructions on Amendment Preparation Based on Protocol Status:**

A. Trials with a current CTEP status of **"Active"**
   - Review and follow **ALL** the instructions outlined in this Action Letter.
   - The information provided in this memo outlines the **ONLY** changes that can be made in response to the Action Letter, except for changes that are consistent with CTEP's editorial and administrative update policy (http://ctep.cancer.gov/protocolDevelopment/docs/requestsubmissionpolicyfinal.pdf).

B. Trials with a current status of **"Approved", "Temporarily Closed to Accrual and Treatment", or "Temporarily Closed to Accrual"**
   - The protocol and ICD must be revised as per the instructions outlined in the Action Letter in the next revised protocol draft submitted to CTEP. The protocol amendment must be submitted and approved by CTEP before the trial can be activated or re-opened.
   - You may include additional non-Action Letter related changes (any type) in your amendment response.

# Action Letter

C. Trials with a current CTEP status of **"In Review"**
- The protocol and ICD must be revised as per the instructions outlined in the Action Letter. These changes must be included in the next revised protocol draft submitted to and approved by CTEP before the trial can be activated.
- You may include additional non-Action Letter related changes (any type) in your revision response. Note the inclusion of non-Action Letter related changes may delay approval of your trial.

D. Trials with a current CTEP status of **"Closed to Accrual"**

*If your trial is under a CTEP-held IND:*
- Review and follow **ALL** the instructions outlined in this Action Letter.
- The information provided in this memo outlines the **ONLY** changes that can be made in response to the Action Letter, except for changes that are consistent with CTEP's amendment request submission policy (http://ctep.cancer.gov/protocolDevelopment/amendments.htm).

*If your trial is NOT under a CTEP-held IND:*
- If Action Letter INCLUDES information that impacts patient care (e.g., new/adjusted dose modifications or special monitoring for patient population at risk) - An amendment is required. Review and follow **ALL** the instructions outlined in this Action Letter. The information provided in this memo outlines the **ONLY** changes that can be made in response to the Action Letter, except for changes that are consistent with CTEP's amendment request submission policy (http://ctep.cancer.gov/protocolDevelopment/amendments.htm).
  - **If Action Letter does NOT INCLUDE information that impacts patient care - Amendment is typically NOT required.**

E. Trials with a current CTEP status of **"Closed to Accrual and Treatment"** or **"Complete"**
- Amendment is not required. This information is being sent for informational purposes only. You may follow local IRB or Operations Office procedures and requirements.

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May 15, 2016

TO: ALL NATIONAL CLINICAL TRIALS NETWORK (NCTN) MEMBERS (U.S. and Canadian Institutions Only); INCAN (Mexico)

FROM: Megan M. Hardin, Protocol Coordinator (E-mail: mhardin@swog.org)

RE: **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." Study Chairs: Drs. M. Chavez-MacGregor and L. Pusztai.

**MEMORANDUM**

Study Chair: Mariana Chavez-MacGregor, M.D., M.Sc.
Phone Number: 713/792-2817
E-mail: **S1207**medicalquery@swog.org

**IRB Review Requirements**
( ) Full board review required
( ) Expedited review allowed
(☒) No review required

**Status Change**
( ) IRB Review only
( ) Activation
( ) Closure
( ) Reactivation

**Protocol changes**
( ) Eligibility changes
( ) Treatment / Dose Modification / Study Calendar changes
( ) Informed Consent changes
  ( ) Patient notification not required
  ( ) Patient notification required
( ) Scientific / Statistical Consideration changes
( ) Specimen Submission changes
( ) Data Submission / Forms changes
( ) Editorial / Administrative changes
( ) Other:

---

**MEMORANDUM**

The following form has been updated and replaced in the **S1207** forms packet, which is accessible through the **S1207** abstract page (www.swog.org):

Breast Radiation Therapy Form: A field has been added to capture laterality (left versus right versus bilateral). For patients who have received different radiation doses and/or schedules for each side, two separate forms (one for the left side and one for the right side) must be submitted. For patients who receive the same radiation treatment to both sides, select "bilateral" on the form and submit only one form.

This memorandum serves to notify the NCI and the SWOG Statistical Center.

cc: PROTOCOL & INFORMATION OFFICE

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Distribution Date: May 1, 2016
CIRB Submission Date: April 13, 2016

TO: ALL NATIONAL CLINICAL TRIALS NETWORK (NCTN) MEMBERS (U.S. and Canadian Institutions Only); INCAN (Mexico)

FROM: Megan M. Hardin, Protocol Coordinator (E-mail: mhardin@swog.org)

RE: **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." Study Chairs: Drs. M. Chavez-MacGregor and L. Pusztai.

**MEMORANDUM**

Study Chair: Mariana Chavez-MacGregor, M.D., M.Sc.
Phone Number: 713/792-2817
E-mail: **S1207**medicalquery@swog.org

**IRB Review Requirements**
( ) Full board review required
( ) Expedited review allowed
(X) No review required

**Status Change**
( ) IRB Review only
( ) Activation
( ) Closure
( ) Reactivation

**Protocol changes**
( ) Eligibility changes
( ) Treatment / Dose Modification / Study Calendar changes
( ) Informed Consent changes
  ( ) Patient notification not required
  ( ) Patient notification required
( ) Scientific / Statistical Consideration changes
( ) Specimen Submission changes
( ) Data Submission / Forms changes
( ) Editorial / Administrative changes
( ) Other:

---

**MEMORANDUM**

The purpose of this memorandum is to inform the CIRB and sites of two corrections in the **S1207** Model Consent Form that will be corrected in a forthcoming revision:

1. "/placebo" was errantly omitted in the header of each risk table for everolimus.

2. "Change in or loss of some or all of the fingers or toenails" must be corrected to "Change in or loss of some or all of the fingernails or toenails."

In the meantime, Institutions may update their local consent forms to include this change.

SWOG considers that the Model Consent Form change does not represent an alteration in risk/benefit ratio. Therefore, local accrual does not need to be suspended pending implementation of this change.

Patients need not be informed of the preceding change unless required by the local IRB.

This memorandum serves to notify the NCI and the SWOG Statistical Center.

cc: PROTOCOL & INFORMATION OFFICE

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May 1, 2016

TO: ALL NATIONAL CLINICAL TRIALS NETWORK (NCTN) MEMBERS (U.S. and Canadian Institutions Only); INCAN (Mexico)

FROM: Megan M. Hardin, Protocol Coordinator (E-mail: mhardin@swog.org)

RE: **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." Study Chairs: Drs. M. Chavez-MacGregor and L. Pusztai.

**MEMORANDUM**

Study Chair: Mariana Chavez-MacGregor, M.D., M.Sc.
Phone Number: 713/792-2817
E-mail: **S1207**medicalquery@swog.org

**IRB Review Requirements**
( ) Full board review required
( ) Expedited review allowed
(X) No review required

**Status Change**
( ) IRB Review only
( ) Activation
( ) Closure
( ) Reactivation

**Protocol changes**
( ) Eligibility changes
( ) Treatment / Dose Modification / Study Calendar changes
( ) Informed Consent changes
  ( ) Patient notification not required
  ( ) Patient notification required
( ) Scientific / Statistical Consideration changes
( ) Specimen Submission changes
( ) Data Submission / Forms changes
( ) Editorial / Administrative changes
( ) Other:

---

**MEMORANDUM**

The following forms have been updated and replaced in the **S1207E01** BAHO forms packet which are accessible through the **S1207** abstract page (www.swog.org). The specific form changes include the following:

1. **S1207E01** Form SQ: The time point box has changed from “Baseline (within 7 days after registration)” to “Prior to randomization (after the consent form is signed)”.

2. **S1207E01** Form MCL-B: The instructions to the institution in bullet 2 changed to, “This form should be completed prior to randomization, after the consent form is signed.”

This memorandum serves to notify the NCI and the SWOG Statistical Center.

cc: PROTOCOL & INFORMATION OFFICE

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April 1, 2016

TO: ALL NATIONAL CLINICAL TRIALS NETWORK (NCTN) MEMBERS (U.S. Institutions Only); INCAN (Mexico)

FROM: Megan M. Hardin, Protocol Coordinator (E-mail: mhardin@swog.org)

RE: **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." Study Chairs: Drs. M. Chavez-MacGregor and L. Pusztai.

**MEMORANDUM**

Study Chair: Mariana Chavez-MacGregor, M.D., M.Sc.
Phone Number: 713/792-2817
E-mail: **S1207**medicalquery@swog.org

**IRB Review Requirements**

( ) Full board review required. Reason:
- ( ) Initial activation (should your institution choose to participate)
- ( ) Increased risk to patient
- ( ) Complete study redesign
- ( ) Addition of tissue banking requirements
- ( ) Study closure due to new risk information

( ) Expedited review allowed

( √ ) No review required

---

**MEMORANDUM**

The following forms have been updated and replaced in the forms packet and **S1207E01** BAHO forms packet which are accessible through the **S1207** abstract page (www.swog.org). The specific form changes include the following:

1. **S1207** Registration Worksheet: The stratification questions have been revised to be consistent with Section 6 of the protocol.

2. **S1207E01** Form MED: The first submission time point has changed from "Baseline (within 7 days after registration)" to "Prior to randomization (after the consent form is signed)".

This memorandum serves to notify the NCI and the SWOG Statistical Center.

cc:
PROTOCOL & INFORMATION OFFICE
William Barlow, Ph.D.
Danika Lew, M.A.
Iris Syquia
Jeffrey Huminik – PCC
Emily Tabinski – PCC
Meredith Lavin - Novartis
Katie Von Derau - WPC

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Distribution Date: April 1, 2016
CTEP Submission Date: February 10, 2016

TO: ALL NATIONAL CLINICAL TRIALS NETWORK (NCTN) MEMBERS (U.S. Institutions Only); INCAN (Mexico)

FROM: Megan M. Hardin, Protocol Coordinator (E-mail: mhardin@swog.org)

RE: **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." Study Chairs: Drs. M. Chavez-MacGregor, P Rastogi and L. Pusztai.

**REVISION #5**

Study Chair: Mariana Chavez-MacGregor, M.D., M.Sc.
Phone Number: 713/792-2817
E-mail: **S1207**medicalquery@swog.org

**IRB Review Requirements**

( ) Full board review required. Reason:
- ( ) Initial activation (should your institution choose to participate)
- ( ) Increased risk to patient
- ( ) Complete study redesign
- ( ) Addition of tissue banking requirements
- ( ) Study closure due to new risk information

( √ ) Expedited review allowed

( ) No review required

---

**REVISION #5**

The changes in Section 3.1c and the Model Consent Form noted below are in response to a Request for Amendment (RA) from Dr. L. Austin Doyle (doylela@mail.nih.gov) received on December 16, 2015. There is not an Action Letter associated with this RA.

1. Title Page, Page 1: The Version Date of the protocol and model consent form has been updated. Jieling Miao has been added to the list of Biostatisticians.

2. Section 1.3, Page 7: The two "Other Objectives" have been added to this section. These were previously listed as secondary objectives.

3. Section 3.1c, Pages 10-13: CTEP now requires all protocols involving everolimus to include a Comprehensive Adverse Events and Potential Risks (CAEPR) list. Therefore, the adverse event (AE) table has been replaced with a CAEPR Version 2.1 (July 29, 2015). Information has been displaced through Page 13 and subsequent sections/pages have been renumbered.

4. Section 3.1f.2, Page 14: The following sentences have been added to this section

> "(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.)"

The following paragraph has been added below the 2nd paragraph of this section:

> "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)."

5. Section 5.0, Page 37: "breastquestion@crab.org" has been added to this section as an alternative contact method to the Data Operations Center for eligibility issues.

6. Section 6.0, Page 41: The words "prior to or" have been added to the 4th stratification factor.

7. Section 7.5, Pages 44-45: A new section, "Unblinding Procedures" has been added. Subsequent sections have been renumbered.

8. Section 9.0, Study Calendar, Pages 54-55: The "&" footnote has been added to Weeks 7, 13, 25, 37, 49 and 55. The footnote reads as follows: "Study visits may be scheduled within +/- 7 days of Weeks 7, 13, 25, 37, 49 and 55."

Institutions should update their local consent forms to include the changes to the Model Consent Form. SWOG considers that the Model Consent Form changes **do not** represent an alteration in risk/benefit ratio. Therefore, local accrual does **not** need to be suspended pending implementation of these changes. Patients currently on treatment and patients who sign a consent form prior to local implementation of the consent form changes **must** be informed of the following changes in bold. The manner by which this notification takes place is at the discretion of the local institution. At a minimum, the patient must be notified by the next visit and this notification process must be documented in the patient chart.

9. Model Consent Form, Pages 6-7: The following changes have been made to the risk tables for everolimus/placebo:

**Added New Risk:**
- **Common: bruising**
- **Occasional: constipation; dizziness; shortness of breath**

**Increase in Risk Attribution:**
- **Changed to Common from Occasional: bleeding**

Decrease in Risk Attribution:
- Changed to Occasional from Common: Nausea; itching; headache; nosebleed; weight loss; loss of appetite; swelling of the hands and/or feet (now referred to as swelling of arms and legs); altered taste (now referred to as changes in taste); infection ("especially when blood count is low" has been added to this risk)

Provided Further Clarification:
- Common: "Mouth or lip sores" has been changed to "Sores in the mouth which may cause difficulty swallowing", "Lack or loss of strength, fatigue" is now referred to as "Tiredness"
- Occasional: "Difficult or labored breathing" is now referred to as "Damage to the lungs which may cause difficulty breathing"; "dry skin" and "dry mouth" are now in the same section; "-chest, oral, joint, abdominal" has been removed from the pain risk; "which may cause blurred vision" has been added to the high blood pressure risk; "inability to sleep" is now referred to as "difficulty sleeping"; "Nail disorder" is now referred to as "change in or loss of some or all of the fingernails or toenails"
- Rare: Lengthy wound healing" is now referred to as "non-healing surgical site"; "kidney damage which may cause swelling, may require dialysis" is now referred to as "kidney damage which may require dialysis"

Deleted Risk:
- Common: inflammation of the lungs
- Occasional: indigestion; dehydration; flushing, reddening of skin; pneumonia; kidney failure; frequent urination; abnormal or loss of menstrual period; diabetes; Hand-foot syndrome: reddening, swelling, numbness, and peeling on palms of the hands and soles of the feet.
- Rare: Blood clot which may cause swelling, pain, shortness of breath; heart failure which may cause shortness of breath, swelling of ankles and tiredness; coughing or spitting up blood from the lungs or respiratory tract; allergic reaction; angioedema-swelling under the skin

cc: PROTOCOL & INFORMATION OFFICE
Jeffrey Huminik – PCC
Emily Tabinski – PCC
Meredith Lavin - Novartis
Katie Von Derau - WPC

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swog.org

February 15, 2016

TO: ALL NATIONAL CLINICAL TRIALS NETWORK (NCTN) MEMBERS

FROM: SWOG Operations Office

RE: IND Safety Reports for Everolimus

**MEMORANDUM**

**IRB Review Requirements**

( ) Full board review required. Reason:
- ( ) Initial activation (should your institution choose to participate)
- ( ) Increased risk to patient
- ( ) Complete study redesign
- ( ) Addition of tissue banking requirements
- ( ) Study closure due to new risk information

( ☒ ) Expedited review allowed

( ) No review required

---

**MEMORANDUM**

The following new safety reports have been posted regarding adverse events that occurred in association with the drug everolimus. Please access these safety reports via the safety report link in the member section of the SWOG website (https://swog.org/SafetyReports/SafetyReports.asp).

| These safety reports pertain to the following studies: | Reports: |
|---|---|
| **S0931** Genitourinary | Nov. 12, 2015 Mfr Rpt #PHHO2015AR018401 FU |
| **S1207** Breast | Nov. 23, 2015 Mfr Rpt #PHHO2015DE014592 |
| **S1222** Breast | Nov. 26, 2015 Mfr Rpt #PHHO2014US015000 |
| | Dec. 9, 2015 Mfr Rpt #PHH02014FR016631 FU |
| | Dec. 21, 2015 Mfr Rpt #PHHO2015ES020063 |

Protocol amendments are not necessary at this time, but your consent form may be revised to include the information provided in these reports if it is deemed necessary by your institution. Please append this notice and these reports to your copy of the protocol and forward copies to your Institutional Review Board (IRB) as required by your local policies and procedures. Should any further information regarding these adverse events be made available, it will be forwarded to you.

This memorandum serves to notify the NCI and the SWOG Statistical Center.

cc: PROTOCOL & INFORMATION OFFICE
Cathy M. Tangen, Dr.P.H.
William Barlow, Ph.D.
Danika Lew, M.S.
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February 15, 2016

TO: ALL NATIONAL CLINICAL TRIALS NETWORK (NCTN) MEMBERS (U.S. Institutions Only); INCAN (Mexico)

FROM: Megan M. Hardin, Protocol Coordinator (E-mail: mhardin@swog.org)

RE: **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." Study Chairs: Drs. M. Chavez-MacGregor and L. Pusztai.

**MEMORANDUM**

Study Chair: Mariana Chavez-MacGregor, M.D., M.Sc.
Phone Number: 713/792-2817
E-mail: **S1207**medicalquery@swog.org

**IRB Review Requirements**

( ) Full board review required. Reason:
- ( ) Initial activation (should your institution choose to participate)
- ( ) Increased risk to patient
- ( ) Complete study redesign
- ( ) Addition of tissue banking requirements
- ( ) Study closure due to new risk information

( ) Expedited review allowed

( √ ) No review required

---

**MEMORANDUM**

The following form has been updated and replaced in the forms packet which is accessible through the **S1207** abstract page (www.swog.org). The specific form change includes the following:

1. **S1207** Adverse Event Form: "Skin infection" has been added to the list of CTC adverse event terms.

This memorandum serves to notify the NCI and the SWOG Statistical Center.

cc:
PROTOCOL & INFORMATION OFFICE
William Barlow, Ph.D.
Danika Lew, M.A.
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swog.org

November 15, 2015

TO: ALL NATIONAL CLINICAL TRIALS NETWORK (NCTN) MEMBERS

FROM: SWOG Operations Office

RE: IND Safety Reports for Everolimus

**MEMORANDUM**

**IRB Review Requirements**

( ) Full board review required. Reason:
- ( ) Initial activation (should your institution choose to participate)
- ( ) Increased risk to patient
- ( ) Complete study redesign
- ( ) Addition of tissue banking requirements
- ( ) Study closure due to new risk information

( ☒ ) Expedited review allowed

( ) No review required

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**MEMORANDUM**

The following new safety reports have been posted regarding adverse events that occurred in association with the drug everolimus. Please access these safety reports via the safety report link in the member section of the SWOG website (https://swog.org/SafetyReports/SafetyReports.asp).

| These safety reports pertain to the following studies: | Reports: |
|---|---|
| **S0931** Genitourinary | Aug. 5, 2015 Mfr Rpt # PHHO2015DE011077 |
| **S1207** Breast | Aug. 14, 2015 Mfr Rpt # PHHO2015DE12647 |
| **S1222** Breast | Aug. 28, 2015 Mfr Rpt # PHJP2015JP013606 |
| | Oct. 9, 2015 Mfr Rpt # PHHO2015US014557 |
| | Nov. 2, 2015 Mfr Rpt # PHHO2015AR018401 |

Protocol amendments are not necessary at this time, but your consent form may be revised to include the information provided in these reports if it is deemed necessary by your institution. Please append this notice and these reports to your copy of the protocol and forward copies to your Institutional Review Board (IRB) as required by your local policies and procedures. Should any further information regarding these adverse events be made available, it will be forwarded to you.

This memorandum serves to notify the NCI and the SWOG Statistical Center.

cc: PROTOCOL & INFORMATION OFFICE
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Distribution Date: October 15, 2015
CTEP Submission Date: September 14, 2015

TO: ALL NATIONAL CLINICAL TRIALS NETWORK (NCTN) MEMBERS (U.S. Institutions Only); INCAN (Mexico)

FROM: Megan M. Hardin, Protocol Coordinator (E-mail: mhardin@swog.org)

RE: **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." Study Chairs: Drs. M. Chavez-MacGregor, P Rastogi and L. Pusztai.

**REVISION #4**

Study Chair: Mariana Chavez-MacGregor, M.D., M.Sc.
Phone Number: 713/792-2817
E-mail: **S1207**medicalquery@swog.org

**IRB Review Requirements**

( ) Full board review required. Reason:
- ( ) Initial activation (should your institution choose to participate)
- ( ) Increased risk to patient
- ( ) Complete study redesign
- ( ) Addition of tissue banking requirements
- ( ) Study closure due to new risk information

( √ ) Expedited review allowed

( ) No review required

---

**REVISION #4**

The above-referenced protocol has been revised as follows:

1. Pages 1-2, Title Page: The Version Date of the protocol has been updated. The Activation Date (9/13/13) and "**S1207**/NSABP B-53" have been added to Page 1. "NSABP" has been replaced with "NRG Oncology" as part of Dr. Paik's contact information on Page 2. INCan-Instituto Nacional de Cancerologia has been removed from the Participants Table on Page 2 as they are a SWOG Institution and therefore not necessary to list here.

2. Page 9, Section 2.0: The Racial and Ethnic Table has been revised to reflect a decreased sample size of 1,900 patients.

3. Page 11, Section 3.1c.1: A paragraph regarding pneumocystis jirovecii pneumonia (PJP) has been added to the end of this section.

4. Pages 11-12, Section 3.1c.3: Instructions regarding obtaining a complete patient medication list along with information for patients who may be taking ACE inhibitor therapy have been added to this section.

5. Pages 35-36, Section 5.1c: The following sentence has been added to the end of the first bullet of this section:

   > "Patients with micrometastases as the only nodal involvement (pN1mi) are eligible, and will be categorized as node-negative."

   The following phrase has been removed from the third bullet of this section: "…independent of the Oncotype DX® Recurrence Score in the primary tumor."

   The NOTE at the end of this section has been revised for clarity and now reads, "In the lymph node positive groups, at least one metastasis ≥ 2.0mm must be present. Patients with micrometastases as the only nodal involvement (pN1mi) are eligible and will be categorized as node-negative."

6. Page 36, Section 5.2b.1: "2cm" has been revised to "5cm".

7. Page 36, Section 5.2c: This section has been revised to indicate that patients have 42 weeks from their last dose of chemotherapy to be registered rather than 21 weeks.

8. Page 37, Section 5.2e: "peripheral granulocyte count" has been revised to "ANC" for clarity.

9. Page 37, Section 5.2n: "…unless there is a known negative hepatitis panel" has been added to the end of the second sentence of this section.

10. Page 38, Section 5.2q: The reference to Appendix 18.5 has been revised to Appendix 18.4. This change has also been made to Section 7.3.

11. Page 38, Section 5.3b: This section has been revised to indicate that patients who have already started endocrine therapy are eligible for the BAHO study.

12. Page 39, Section 6.0: "(any RS value)" has been removed from the 3rd stratification factor and "(any RS value) prior to or" has been removed the 4th stratification factor.

13. Page 39, Section 7.1: The following sentence has been added to this section: "NOTE: Mouth washes/rinses commonly used in practice to prevent the development of everolimus-associated mucositis can be used at the discretion of the treating physician."

14. Page 40, Section 7.2: A new endocrine therapy regimen for premenopausal women has been added to the table: Tamoxifen 20 mg daily for 10 years. The "*" footnote has been revised to indicate that aromatase inhibitor (AI) combined with ovarian suppression or ablation is also a choice for high risk premenopausal patients based on data from the SOFT/TEXT trials.

15. Page 41, Section 7.4: The reference to Appendix 18.6 has been revised to Appendix 18.5.

16. Page 42, Section 7.5c: The following sentence has been added to the end of this section, "If the patient is undergoing a surgical procedure, study drug can be delayed ≤ 28 days at the discretion of the treating physician."

17. Pages 47-48, Section 8.4: The dose modifications for Grade 2 Anemia and Grade 3 lymphopenia have been removed and the Grade 3 Anemia and Grade 4 lymphopenia modifications have been revised.

18. Page 51, Section 9.0, Study Calendar: "CBC, differential" has been revised to "ANC, hemoglobin" in the LABORATORY section to be consistent with eligibility.

19. Pages 54-58, Section 11.0: The statistical section has been revised to outline the rationale for a decreased sample size from 3,800 patients to 1,900 patients and a decrease in power by 10%.

20. Page 63, Section 14.4g: The instructions have been revised to indicate that the Endocrine and Concomitant Therapies Form should be submitted until progression or discontinuation of both endocrine therapy and blinded protocol treatment (if prior to progression).

21. Page 64, Section 14.4i: "Final **S1207** Endocrine and Concomitant Therapies Form" has been added to the list of items to be submitted in the "If patient was still on protocol treatment" section.

22. Page 66, Section 15.1c: "NSABP Biostatistical Center" has been replaced with "NRG Oncology Statistics and Data Management Center".

23. Page 67, Section 16.1a: The last sentence of this section has been removed as Appendix 18.4 has been removed from the protocol because it is no longer deemed necessary.

24. Page 75, Section 18.0: Appendix 18.4 has been deleted from this list and the subsequent sections have been renumbered.

25. Page 77, Appendix 18.1, **S1207-EO1** Behavioral and Health Outcome (BAHO): The following phrase has been added to the 2nd sentence of this page: "…as well as time on endocrine therapy prior to enrollment". The following sentences have replaced the second sentence of the 3rd paragraph on this page: "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."

26. Page 81, Appendix 18.1: The phrase "and time on endocrine therapy prior to enrollment" has been added to the 3rd paragraph of this page.

27. Pages 88-89, Appendix 18.4: The Determination of Expedited Adverse Event Reporting Requirements Appendix has been removed from the protocol. The subsequent appendices have been renumbered.

Institutions should update their local consent forms to include the changes to the Model Consent Form within 90 days of distribution of this notice. SWOG considers that the Model Consent Form changes do not represent an alteration in risk/benefit ratio. Therefore, local accrual does not need to be suspended pending implementation of these changes. Patients need not be informed of the following changes unless required by the local IRB.

1. The Version Date has been updated.

2. Page 1, “Notes for Local Institution Informed Consent Authors”: “additions” has been added to the 5th sentence of the first paragraph of this page.

3. Page 3, “How many people will take part in the study?”: This section has been revised to indicate that the new sample size is 1900 patients instead of 3500 patients as originally indicated.

4. Page 10, “Will my medical information be kept private?”: ECOG-ACRIN and Alliance have added to the list of organizations that may review medical records.

5. Page 12, “What are the costs of taking part in this study?”: The url for obtaining information on clinical trials and insurance coverage has been revised.

6. Page 13, Behavioral and Health Outcomes (BAHO) Study: The following instructions have been added to this section:

   *“(Non-NCORP Institutions must remove the BAHO study from their consent form)”.*

Please attach this memorandum to your copy of the protocol.

This memorandum serves to notify the NCI and the SWOG Statistical Center.

cc: PROTOCOL & INFORMATION OFFICE
William Barlow, Ph.D.
Danika Lew, M.A.
Jean Barce
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Larry Kaye
Iris Syquia
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swog.org

Distribution Date: October 15, 2015
E-mailed Date: October 6, 2015

TO: ALL NATIONAL CLINICAL TRIALS NETWORK (NCTN) MEMBERS (U.S. and Canadian Institutions Only); INCAN (Mexico)

FROM: Megan M. Hardin, Protocol Coordinator (E-mail: mhardin@swog.org)

RE: **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." Study Chairs: Drs. M. Chavez-MacGregor and L. Pusztai.

**MEMORANDUM**

Study Chair: Mariana Chavez-MacGregor, M.D., M.Sc.
Phone Number: 713/792-2817
E-mail: **S1207**medicalquery@swog.org

**IRB Review Requirements**

( ) Full board review required. Reason:
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- ( ) Complete study redesign
- ( ) Addition of tissue banking requirements
- ( ) Study closure due to new risk information

( ) Expedited review allowed

( √ ) No review required

---

**MEMORANDUM**

The purpose of this memorandum is to inform all NCORP institutions to stop collecting and submitting the blood specimens for the BAHO substudy as outlined in Section 15 until further notice. All other specimens should continue to be submitted.

This memorandum serves to notify the NCI and the SWOG Statistical Center.

cc:
PROTOCOL & INFORMATION OFFICE
William Barlow, Ph.D.
Danika Lew, M.A.
Jean Barce
Jennie Barrett
Larry Kaye
Iris Syquia
Michael Moody – PCC
Emily Tabinski – PCC
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swog.org

August 1, 2015

TO: ALL NATIONAL CLINICAL TRIALS NETWORK (NCTN) MEMBERS

FROM: SWOG Operations Office

RE: IND Safety Reports for Everolimus

**MEMORANDUM**

**IRB Review Requirements**

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**MEMORANDUM**

The following new safety reports have been posted regarding adverse events that occurred in association with the drug everolimus. Please access these safety reports via the safety report link in the member section of the SWOG website (https://swog.org/SafetyReports/SafetyReports.asp).

| These safety reports pertain to the following studies: | Reports: |
|---|---|
| **S0931** Genitourinary | May 13, 2015 Mfr Rpt #PHHO2015IT008256 |
| **S1207** Breast | May 13, 2015 Mfr Rpt #PHHO2015IT008257 |
| **S1222** Breast | May 13, 2015 Mfr Rpt #PHHO2015IT008272 |
| | May 26, 2015 Mfr Rpt #PHHO2015US009217 |
| | May 27, 2015 Mfr Rpt #PHHO2015US009213 |
| | June 16, 2015 Mfr Rpt #PHHO2014US008515 |
| | June 16, 2015 Mfr Rpt #PHHO2013US012889 |
| | June 19, 2015 Mfr Rpt #PHHO2015US006784 FU |
| | July 2, 2015 Mfr Rpt #PHHO2015FR010015 |
| | July 6, 2015 Mfr Rpt #PHHO2015FR010935 |
| | July 8, 2015 Mfr Rpt #PHHO2013BE001444 |
| | July 8, 2015 Mfr Rpt #PHHO2015SK002702 |
| | July 13, 2015 Mfr Rpt #PHHO2015DE009757 |

Protocol amendments are not necessary at this time, but your consent form may be revised to include the information provided in these reports if it is deemed necessary by your institution. Please append this notice and these reports to your copy of the protocol and forward copies to your Institutional Review Board (IRB) as required by your local policies and procedures. Should any further information regarding these adverse events be made available, it will be forwarded to you.

This memorandum serves to notify the NCI and the SWOG Statistical Center.

cc: PROTOCOL & INFORMATION OFFICE
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swog.org

July 1, 2015

TO: ALL NATIONAL CLINICAL TRIALS NETWORK (NCTN) MEMBERS

FROM: SWOG Operations Office

RE: IND Safety Report for Everolimus

**MEMORANDUM**

**IRB Review Requirements**

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(X) Expedited review allowed

( ) No review required

---

**MEMORANDUM**

The following safety report was inadvertently posted for the drug everolimus. In actuality, the event that occurred was in association with the drug LEE011 and should be disregarded. The safety report has been removed from the SWOG website (https://swog.org/safetyreports/safetyreports.asp).

| This safety report pertains to the following studies: | Report: |
|---|---|
| **S0528** Early Therapeutics<br>**S0931** Genitourinary<br>**S1207** Breast<br>**S1222** Breast | Apr. 29, 2015 Mfr Rpt #PHHO2015US006628 |

Please append this notice and this report to your copy of the protocol and forward a copy to your Institutional Review Board (IRB) as required by your local policies and procedures.

This memorandum serves to notify the NCI and the SWOG Statistical Center.

cc: PROTOCOL & INFORMATION OFFICE
Megan Othus, Ph.D.
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swog.org

May 15, 2015

TO: ALL NATIONAL CLINICAL TRIALS NETWORK (NCTN) MEMBERS

FROM: SWOG Operations Office

RE: IND Safety Reports for Everolimus

**MEMORANDUM**

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| These safety reports pertain to the following studies: | Reports: | |
|---|---|---|
| **S0528** Early Therapeutics | Mar. 5, 2015 | Mfr Rpt #PHHO2015FR003167 |
| **S0931** Genitourinary | Mar. 5, 2015 | Mfr Rpt #PHHO2010FR14815 |
| **S1207** Breast | Apr. 8, 2015 | Mfr Rpt #PHHO2015DE003225 |
| **S1222** Breast | Apr. 16, 2015 | Mfr Rpt #PHHY2013BR124787 |
| | Apr. 20, 2015 | Mfr Rpt #PHHO2015BR006547 |
| | Apr. 21, 2015 | Mfr Rpt #PHHO2015BR006547 FU |
| | Apr. 21, 2015 | Mfr Rpt #PHHO2013BR017080 |
| | Apr. 21, 2015 | Mfr Rpt #PHHO2012BR009857 |
| | Apr. 24, 2015 | Mfr Rpt #PHHO2013BR017080 FU |
| | Apr. 29, 2015 | Mfr Rpt #PHHO2015US006628 |
| | Apr. 29, 2015 | Mfr Rpt #PHHO2015US007003 |
| | Apr. 30, 2015 | Mfr Rpt #PHHO2015US006784 |
| | Apr. 30, 2015 | Mfr Rpt #PHHO2015US007456 |
| | Apr. 30, 2015 | Mfr Rpt #PHHO2015US007463 |
| | May 5, 2015 | Mfr Rpt #PHHY2015MX052874 |
| | May 6, 2015 | Mfr Rpt #PHHO2015DE003225 FU |
| | May 6, 2015 | Mfr Rpt #PHHO2015FR007310 |

Protocol amendments are not necessary at this time, but your consent form may be revised to include the information provided in these reports if it is deemed necessary by your institution. Please append this notice and these reports to your copy of the protocol and forward copies to your Institutional Review Board (IRB) as required by your local

policies and procedures. Should any further information regarding these adverse events be made available, it will be forwarded to you.

This memorandum serves to notify the NCI and the SWOG Statistical Center.

cc:

| | |
|---|---|
| PROTOCOL & INFORMATION OFFICE | Carol French – AstraZeneca |
| Megan Othus, Ph.D. | William Turnbull – AstraZeneca |
| Cathy M. Tangen, Dr.P.H. | Jean Sowa – AstraZeneca |
| William Barlow, Ph.D. | Kathleen DeRose – GSK |
| Danika Lew, M.S. | Royce Ann Adkins – Path-tec |
| Melissa Plets, M.S. | Meredith Lavin – Novartis |
| Jean Barce | Kristin White – Novartis |
| Jennie Barrett | Heather Campbell, PharmD – VACSP/PCC |
| Austin Hamm | Anne Davis – VACSP/PCC |
| Louise Highleyman | Michael Moody – VACSP/PCC |
| Amy Johnson | Sharon Jenkins – VACSP/PCC |
| Larry Kaye | James Rasp – VACSP/PCC |
| Laura Kingsbury, M.R.T. | Emily Tabinski – VACSP/PCC |
| Christine McLeod | Katie VonDerau – WPC |
| Iris Syquia | |

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Distribution Date: April 1, 2015
CIRB Submission Date: March 24, 2015

TO: ALL NATIONAL CLINICAL TRIALS NETWORK (NCTN) MEMBERS (U.S. and Canadian Institutions Only); INCAN (Mexico)

FROM: Megan M. Hardin, Protocol Coordinator (E-mail: mhardin@swog.org)

RE: **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." Study Chairs: Drs. M. Chavez-MacGregor and L. Pusztai.

**MEMORANDUM**

Study Chair: Mariana Chavez-MacGregor, M.D., M.Sc.
Phone Number: 713/792-2817
E-mail: **S1207**medicalquery@swog.org

**IRB Review Requirements**

( ) Full board review required. Reason:
- ( ) Initial activation (should your institution choose to participate)
- ( ) Increased risk to patient
- ( ) Complete study redesign
- ( ) Addition of tissue banking requirements
- ( ) Study closure due to new risk information

( ) Expedited review allowed

( √ ) No review required

---

**MEMORANDUM**

The purpose of this memorandum is to inform the CIRB and non-NCORP sites of a correction in the **S1207** Model Consent Form.

The following sentence will be added to Page 13 of the Model Consent Form in a forthcoming revision:

"Non-NCORP Institutions must remove the BAHO study from their consent form."

In the meantime, Non-NCORP Institutions may update their local consent forms to include this change.

SWOG considers that the Model Consent Form change does not represent an alteration in risk/benefit ratio. Therefore, local accrual does not need to be suspended pending implementation of this change.

Patients need not be informed of the following change unless required by the local IRB.

This memorandum serves to notify the NCI and the SWOG Statistical Center.

cc: PROTOCOL & INFORMATION OFFICE
William Barlow, Ph.D.
Danika Lew, M.A.
Jean Barce
Jennie Barrett
Louise Highleyman
Larry Kaye
Iris Syquia
Michael Moody – PCC
Emily Tabinski – PCC
Meredith Lavin - Novartis
Katie Von Derau - WPC

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March 15, 2015

TO: ALL NATIONAL CLINICAL TRIALS NETWORK (NCTN) MEMBERS

FROM: SWOG Operations Office

RE: IND Safety Reports for Everolimus

**MEMORANDUM**

**IRB Review Requirements**

( ) Full board review required. Reason:
- ( ) Initial activation (should your institution choose to participate)
- ( ) Increased risk to patient
- ( ) Complete study redesign
- ( ) Addition of tissue banking requirements
- ( ) Study closure due to new risk information

( ) Expedited review allowed

( ) No review required

---

**MEMORANDUM**

The following new safety reports have been posted regarding adverse events that occurred in association with the drug everolimus. Please access these safety reports via the study's abstract page or the safety report link on the SWOG website (https://swog.org/safetyreports/safetyreports.asp).

| These safety reports pertain to the following studies: | Reports: | |
|---|---|---|
| **S0528** Early Therapeutics | Feb. 5, 2015 | Mfr Rpt #PHHO2015DE001378 |
| **S0931** Genitourinary | Feb. 23, 2015 | Mfr Rpt #PHHO2014DE012547 |
| **S1207** Breast | | |
| **S1222** Breast | | |

Protocol amendments are not necessary at this time, but your consent form may be revised to include the information provided in these reports if it is deemed necessary by your institution. Please append this notice and these reports to your copy of the protocol and forward copies to your Institutional Review Board (IRB) as required by your local policies and procedures. Should any further information regarding these adverse events be made available, it will be forwarded to you.

This memorandum serves to notify the NCI and the SWOG Statistical Center.

cc:
PROTOCOL & INFORMATION OFFICE
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Cathy M. Tangen, Dr.P.H.
William Barlow, Ph.D.
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February 15, 2015

TO: ALL NATIONAL CLINICAL TRIALS NETWORK (NCTN) MEMBERS (U.S. and Canadian Institutions Only); INCAN (Mexico)

FROM: Megan M. Hardin, Protocol Coordinator (E-mail: mhardin@swog.org)

RE: **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." Study Chairs: Drs. M. Chavez-MacGregor and L. Pusztai.

**MEMORANDUM**

Study Chair: Mariana Chavez-MacGregor, M.D., M.Sc.
Phone Number: 713/792-2817
E-mail: **S1207**medicalquery@swog.org

**IRB Review Requirements**

( ) Full board review required. Reason:
- ( ) Initial activation (should your institution choose to participate)
- ( ) Increased risk to patient
- ( ) Complete study redesign
- ( ) Addition of tissue banking requirements
- ( ) Study closure due to new risk information

( ) Expedited review allowed

( √ ) No review required

---

**MEMORANDUM**

The following form has been updated and replaced in the forms packet which is accessible through the **S1207** abstract page (www.swog.org). The specific form change includes the following:

1. **S1207** Registration Worksheet: The stratification questions have been revised to be consistent with Revision #3. "NA" has been added next to the two consent form questions as options for sites that are not participating in the BAHO study.

This memorandum serves to notify the NCI and the SWOG Statistical Center.

cc:
PROTOCOL & INFORMATION OFFICE
William Barlow, Ph.D.
Danika Lew, M.A.
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swog.org

February 1, 2015

TO: ALL NATIONAL CLINICAL TRIALS NETWORK (NCTN) MEMBERS

FROM: SWOG Operations Office

RE: IND Safety Reports for Everolimus

**MEMORANDUM**

**IRB Review Requirements**

( ) Full board review required. Reason:
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**MEMORANDUM**

The following new safety reports have been posted regarding adverse events that occurred in association with the drug everolimus. Please access these safety reports via the study's abstract page or the safety report link on the SWOG website (https://swog.org/safetyreports/safetyreports.asp).

| These safety reports pertain to the following studies: | Reports: | |
|---|---|---|
| **S0528** Early Therapeutics | Aug. 28, 2014 | Mfr Rpt #PHHY2014BE103661 |
| **S0931** Genitourinary | Sep. 5, 2014 | Mfr Rpt #PHHO2014JP009849 |
| **S1207** Breast | Jan. 9, 2015 | Mfr Rpt #PHHO2014DE017192 |
| **S1222** Breast | Jan. 12, 2015 | Mfr Rpt #PHHO2014ES017327 |

Protocol amendments are not necessary at this time, but your consent form may be revised to include the information provided in these reports if it is deemed necessary by your institution. Please append this notice and these reports to your copy of the protocol and forward copies to your Institutional Review Board (IRB) as required by your local policies and procedures. Should any further information regarding these adverse events be made available, it will be forwarded to you.

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swog.org

January 15, 2015

TO: ALL NATIONAL CLINICAL TRIALS NETWORK (NCTN) MEMBERS

FROM: SWOG Operations Office

RE: IND Safety Reports for Everolimus

**MEMORANDUM**

**IRB Review Requirements**

( ) Full board review required. Reason:
- ( ) Initial activation (should your institution choose to participate)
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( ) Expedited review allowed

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**MEMORANDUM**

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| These safety reports pertain to the following studies: | Reports: |
|---|---|
| **S0528** Early Therapeutics | Dec. 17, 2014 Mfr Rpt #PHH02014AR004429 |
| **S0931** Genitourinary | Dec. 19, 2014 Mfr Rpt #PHHO2014FR016631 |
| **S1207** Breast | |
| **S1222** Breast | |

Protocol amendments are not necessary at this time, but your consent form may be revised to include the information provided in these reports if it is deemed necessary by your institution. Please append this notice and these reports to your copy of the protocol and forward copies to your Institutional Review Board (IRB) as required by your local policies and procedures. Should any further information regarding these adverse events be made available, it will be forwarded to you.

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January 1, 2015

TO: ALL NATIONAL CLINICAL TRIALS NETWORK (NCTN) MEMBERS

FROM: SWOG Operations Office

RE: IND Safety Report for Everolimus

**MEMORANDUM**

**IRB Review Requirements**

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( ) Expedited review allowed

( ) No review required

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**MEMORANDUM**

The following new safety report has been posted regarding an adverse event that occurred in association with the drug everolimus. Please access this safety report via the study's abstract page or the safety report link on the SWOG website (https://swog.org/safetyreports/safetyreports.asp).

| This safety report pertains to the following studies: | Report: |
|---|---|
| **S0528** Early Therapeutics<br>**S0931** Genitourinary<br>**S1207** Breast<br>**S1222** Breast | Dec. 15, 2014 AE #2086422 |

Protocol amendments are not necessary at this time, but your consent form may be revised to include the information provided in this report if it is deemed necessary by your institution. Please append this notice and this report to your copy of the protocol and forward a copy to your Institutional Review Board (IRB) as required by your local policies and procedures. Should any further information regarding this adverse event be made available, it will be forwarded to you.

This memorandum serves to notify the NCI and the SWOG Statistical Center.

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Distribution Date: January 1, 2015
CTEP Submission Date: November 13, 2014

TO: ALL NATIONAL CLINICAL TRIALS NETWORK (NCTN) MEMBERS (U.S. and Canadian Institutions Only); INCAN (Mexico)

FROM: Megan M. Hardin, Protocol Coordinator (E-mail: mhardin@swog.org)

RE: **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." Study Chairs: Drs. M. Chavez-MacGregor and L. Pusztai.

**REVISION #3**

Study Chair: Mariana Chavez-MacGregor, M.D., M.Sc.
Phone Number: 713/792-2817
E-mail: **S1207**medicalquery@swog.org

**IRB Review Requirements**

( ) Full board review required. Reason:
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(√) Expedited review allowed

( ) No review required

---

**REVISION #3**

Due to the changes to the eligibility criteria, institutions **must** receive IRB approval to include the changes in this revision within 60 days of distribution of this notice, or must locally close the study to accrual until approval is obtained.

The above-referenced protocol has been revised as follows:

1. Page 1, Title Page: The version date of the protocol has been updated.

2. Page 2, Participants: Per the new NCTN guidelines, ECOG-ACRIN has been added to the participants list.

3. Pages 3-4, Table of Contents: The page numbering has been updated.

4. Pages 7-8, Section 2.0: Additional background has been added to the first paragraph of this section which explains the rationale of adding high-grade tumors to eligibility. Two references were added to this section and subsequent references have been renumbered throughout the protocol. As a result of this change, information has been displaced to Page 8.

5. Pages 10-11, Section 3.1c.1: The Adverse Event table has been revised to be consistent with the most recent everolimus Investigator Brochure (Edition 13).

   Specifically, the risk attribution that increased was "Proteinuria" which changed from "Rare but Serious" to "Less Likely". The following risks have been added to the adverse event table:

   - Pneumonia (Less Likely)
   - Angioedema (Rare but Serious)

   The following risk attributions decreased from "Likely" to "Less Likely":

   - Thrombocytopenia
   - Vomiting
   - Cough
   - Dyspnea

6. Page 13, Section 3.1f.2: "or require a dosing decrease" has been removed from the fourth paragraph of this page because sites do not need to notify the PCC of a dosing decrease as the shipment of blister packs will remain the same regardless of the dose.

7. Page 14, Section 3.1f.3a: This section has been revised to instruct sites to use the NCI oral DARF instead of the study specific **S1207** DARF.

8. Pages 35-36, Section 5.1c:

   - The second bullet point of this section has been revised as follows: The word "either" has been added before "…an Oncotype DX®…". At the end of the second bullet point, the following has been added: "…or tumor tissue with pathological Grade III following local practice. If Oncotype DX® is done, then RS must be > 25. If the test is not done, but the patient has Grade III disease then the patient is eligible and Oncotype DX® does not need to be performed.".
   - "4" has been changed to "1" in the fourth bullet point of this section.
   - The following note has been added to the end of this section: "NOTE: Patients with micrometastases as the only nodal involvement (pN1mi) are not eligible."

9. Page 37, Section 5.2l: The words "…previously diagnosed with diabetes…" have been added after "Patients" in this section.

10. Page 38, Section 5.3b: "CCOP" has been changed to "NCORP" in this section. This change has also been made to Sections 9.0 (Page 51), 14.4d (Page 63), 15.1c (Page 65) and Appendix 18.1 (Page 77).

11. Page 39, Section 6.0: The stratification factors have been revised as follows:

    - "or Grade III disease" has been added to the second stratification factor.
    - The number of positive lymph nodes has been changed from 4 to 1 in the fourth stratification factor.

12. Page 48, Section 8.4: "Grade ≥ 2" has been revised to "Grade 3" throughout the Grade 3 Lymphopenia dose modification section.

13. Pages 51-52, Section 9.0: "…is part of the BAHO study and…" has been added to the "Φ" footnote for clarity. The "" footnote has been added to the "Prestudy" column in the "Fasting glucose, Cholesterol and Triglycerides" row. The "" footnote reads as follows: "A fasting glucose is not required at pre-study, only the fasting cholesterol and triglycerides are required." The "¶" footnote has been revised for clarity. "If the patient is taken off protocol treatment due to toxicity, he/she…" has been changed to "All patients (including patients taken off protocol treatment due to toxicity)… ".

14. Page 54, Section 11.2: "…or Grade III disease is present" has been added to the end of the first sentence of the third paragraph. "…or pathological Grade III disease", has been added to the end of the third sentence of the same paragraph.

15. Pages 55-56, Section 11.2: "or Grade III disease" has been added after "RS > 25" in the table. The following paragraphs have been added to the end of this section:

    "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. Given the comparability to the DFS rate for 1-3+ nodes and RS > 25 above (80.8%), we have kept the table above the same. Similarly, we have expanded the last stratum to allow any positive nodes after surgery (previously it was 4+).

    Since the current amendment is intended to increase accrual, we are not changing these values at the current time. Instead, after quarters 5-6, accrual rates will be revisited as required by NCI if accrual is less than 50% of the expected rate. Approximately March 2015, we will submit a new accrual plan based on the percentage in each stratum above. While accrual is lagging, patients entering the trial are much higher risk for recurrence than originally expected. A reduction in the sample size requirement is expected."

    Section 11.3 has been displaced to Page 56, causing the remaining pages to be repaginated.

16. Page 58, Section 11.6: The figure has been revised to be consistent with Section 5.1c.

17. Pages 73-74, Section 17.0: References 7 and 8 have been added to this section and subsequent references have been renumbered.

18. Page 86, Appendix 18.3c: "Dr. Christopher Ryan" has been revised to "Dr. Mariana Chavez-MacGregor".

Institutions **must** update their local consent forms to include the changes to the Model Consent Form within 60 days of distribution of this notice. SWOG considers that the Model Consent Form changes **do not** represent an alteration in risk/benefit ratio. Therefore, local accrual does **not** need to be suspended pending implementation of these changes. Patients currently receiving everolimus/placebo and patients who sign a consent form prior to local implementation of the consent form changes **must** be informed of the following changes. The manner by which this notification takes place is at the discretion of the local institution. At a minimum, the patient must be notified by the next visit and this notification process must be documented in the patient chart.

1. The Version Date has been updated.

2. Pages 6-7, Model Consent Form: The everolimus/placebo risks and side effects list has been revised to be consistent with the most recent version of the Investigator's Brochure. Specifically, risk attributions that have decreased include the following:

   a. Changed from "COMMON, SOME MAY BE SERIOUS" to "OCCASIONAL, SOME MAY BE SERIOUS":

      - **Vomiting**
      - **Cough**
      - **Difficulty or labored breathing**

   b. The following risks have been added to the risk section:

      - **Pneumonia**, (Occasional, Some May Be Serious)
      - **Angioedema – swelling under the skin** (Rare and Serious)

3. Page 13, Model Consent Form: "CCOP" has been changed to "NCORP" in the "Behavioral and Health outcomes (BAHO) Study" section. NCORP sites may continue to register patients without mandatory participation in the BAHO study for 60 days while obtaining approval of the updated consent form.

Please attach this memorandum to your copy of the protocol. Replacement pages are attached for the revised pages referenced above. Please insert these pages into your copy of the protocol and forward to the responsible Institutional Review Board (IRB).

This memorandum serves to notify the NCI and the SWOG Statistical Center.

cc: PROTOCOL & INFORMATION OFFICE
William Barlow, Ph.D.
Danika Lew, M.A.
Jean Barce
Jennie Barrett
Larry Kaye
Iris Syquia
Michael Moody – PCC
Emily Tabinski – PCC
Meredith Lavin - Novartis
Katie Von Derau - WPC

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swog.org

December 15, 2014

TO: ALL NATIONAL CLINICAL TRIALS NETWORK (NCTN) MEMBERS

FROM: SWOG Operations Office

RE: IND Safety Report for Everolimus

**MEMORANDUM**

**IRB Review Requirements**

( ) Full board review required. Reason:
- ( ) Initial activation (should your institution choose to participate)
- ( ) Increased risk to patient
- ( ) Complete study redesign
- ( ) Addition of tissue banking requirements
- ( ) Study closure due to new risk information

( ) Expedited review allowed

( ) No review required

---

**MEMORANDUM**

The following new safety report has been posted regarding an adverse event that occurred in association with the drug everolimus. Please access this safety report via the study's abstract page or the safety report link on the SWOG website (https://swog.org/safetyreports/safetyreports.asp).

| This safety report pertains to the following studies: | Report: |
|---|---|
| **S0528** Early Therapeutics<br>**S0931** Genitourinary<br>**S1207** Breast<br>**S1222** Breast | Nov. 24, 2014 Mfr Rpt #2140561 |

Protocol amendments are not necessary at this time, but your consent form may be revised to include the information provided in this report if it is deemed necessary by your institution. Please append this notice and this report to your copy of the protocol and forward a copy to your Institutional Review Board (IRB) as required by your local policies and procedures. Should any further information regarding this adverse event be made available, it will be forwarded to you.

This memorandum serves to notify the NCI and the SWOG Statistical Center.

cc:
PROTOCOL & INFORMATION OFFICE
Megan Othus, Ph.D.
Cathy M. Tangen, Dr.P.H.
William Barlow, Ph.D.
Danika Lew, M.S.
Melissa Plets, M.S.
Jean Barce
Jennie Barrett
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Jean Sowa – AstraZeneca
Kathleen DeRose – GSK
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Heather Campbell, PharmD – VACSP/PCC
Anne Davis – VACSP/PCC

| | |
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swog.org

December 1, 2014

TO: ALL NATIONAL CLINICAL TRIALS NETWORK (NCTN) MEMBERS

FROM: SWOG Operations Office

RE: IND Safety Report for Everolimus

**MEMORANDUM**

**IRB Review Requirements**

( ) Full board review required. Reason:
- ( ) Initial activation (should your institution choose to participate)
- ( ) Increased risk to patient
- ( ) Complete study redesign
- ( ) Addition of tissue banking requirements
- ( ) Study closure due to new risk information

( ☒ ) Expedited review allowed

( ) No review required

---

**MEMORANDUM**

The following new safety report has been posted regarding an adverse event that occurred in association with the drug everolimus. Please access this safety report via the study's abstract page or the safety report link on the SWOG website (https://swog.org/safetyreports/safetyreports.asp).

| This safety report pertains to the following studies: | Report: |
|---|---|
| **S0528** Early Therapeutics<br>**S0931** Genitourinary<br>**S1207** Breast<br>**S1222** Breast | Nov. 18, 2014 Mfr Rpt #PHHO2014US013821 FU |

Protocol amendments are not necessary at this time, but your consent form may be revised to include the information provided in this report if it is deemed necessary by your institution. Please append this notice and this report to your copy of the protocol and forward a copy to your Institutional Review Board (IRB) as required by your local policies and procedures. Should any further information regarding this adverse event be made available, it will be forwarded to you.

This memorandum serves to notify the NCI and the SWOG Statistical Center.

cc:
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swog.org

November 15, 2014

TO: ALL NATIONAL CLINICAL TRIALS NETWORK (NCTN) MEMBERS

FROM: SWOG Operations Office

RE: IND Safety Report for Everolimus

**MEMORANDUM**

**IRB Review Requirements**

( ) Full board review required. Reason:
- ( ) Initial activation (should your institution choose to participate)
- ( ) Increased risk to patient
- ( ) Complete study redesign
- ( ) Addition of tissue banking requirements
- ( ) Study closure due to new risk information

(X) Expedited review allowed

( ) No review required

---

**MEMORANDUM**

The following new safety report has been posted regarding an adverse event that occurred in association with the drug everolimus. Please access this safety report via the study's abstract page or the safety report link on the SWOG website (https://swog.org/safetyreports/safetyreports.asp).

| This safety report pertains to the following studies: | Reports: | |
|---|---|---|
| **S0528** Early Therapeutics | Nov. 4, 2014 | Mfr Rpt #PHHO2014FR008155 |
| **S0931** Genitourinary | Nov. 4, 2014 | Mfr Rpt #PHHO2014US013821 |
| **S1207** Breast | | |
| **S1222** Breast | | |

Protocol amendments are not necessary at this time, but your consent form may be revised to include the information provided in this report if it is deemed necessary by your institution. Please append this notice and this report to your copy of the protocol and forward a copy to your Institutional Review Board (IRB) as required by your local policies and procedures. Should any further information regarding this adverse event be made available, it will be forwarded to you.

This memorandum serves to notify the NCI and the SWOG Statistical Center.

cc:

| | |
|---|---|
| PROTOCOL & INFORMATION OFFICE | Carol French – AstraZeneca |
| Megan Othus, Ph.D. | John Parnell – AstraZeneca |
| Cathy M. Tangen, Dr.P.H. | Jean Sowa – AstraZeneca |
| William Barlow, Ph.D. | Kathleen DeRose – GSK |
| Danika Lew, M.S. | Royce Ann Adkins – Path-tec |
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swog.org

September 15, 2014

TO: ALL NATIONAL CLINICAL TRIALS NETWORK (NCTN) MEMBERS

FROM: SWOG Operations Office

RE: IND Safety Report for Everolimus

**MEMORANDUM**

**IRB Review Requirements**

( ) Full board review required. Reason:
- ( ) Initial activation (should your institution choose to participate)
- ( ) Increased risk to patient
- ( ) Complete study redesign
- ( ) Addition of tissue banking requirements
- ( ) Study closure due to new risk information

( ☒ ) Expedited review allowed

( ) No review required

---

**MEMORANDUM**

The following new safety report has been posted regarding an adverse event that occurred in association with the drug everolimus. Please access this safety report via the study's abstract page or the safety report link on the SWOG website (https://swog.org/safetyreports/safetyreports.asp).

| This safety report pertains to the following studies: | Reports: | |
|---|---|---|
| **S0528** Early Therapeutics | Aug. 28, 2014 | Mfr Rpt #PHHO2014ES011418 |
| **S0931** Genitourinary | Sep. 4, 2014 | Mfr Rpt #PHHO2014JP009849 |
| **S1207** Breast | | |
| **S1222** Breast | | |

Protocol amendments are not necessary at this time, but your consent form may be revised to include the information provided in this report if it is deemed necessary by your institution. Please append this notice and this report to your copy of the protocol and forward a copy to your Institutional Review Board (IRB) as required by your local policies and procedures. Should any further information regarding this adverse event be made available, it will be forwarded to you.

This memorandum serves to notify the NCI and the SWOG Statistical Center.

cc:
PROTOCOL & INFORMATION OFFICE
Megan Othus, Ph.D.
Cathy M. Tangen, Dr.P.H.
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swog.org

August 15, 2014

TO: ALL NATIONAL CLINICAL TRIALS NETWORK (NCTN) MEMBERS

FROM: SWOG Operations Office

RE: IND Safety Report for Everolimus

**MEMORANDUM**

**IRB Review Requirements**

( ) Full board review required. Reason:
- ( ) Initial activation (should your institution choose to participate)
- ( ) Increased risk to patient
- ( ) Complete study redesign
- ( ) Addition of tissue banking requirements
- ( ) Study closure due to new risk information

( ☒ ) Expedited review allowed

( ) No review required

---

**MEMORANDUM**

The following new safety report has been posted regarding an adverse event that occurred in association with the drug everolimus. Please access this safety report via the study's abstract page or the safety report link on the SWOG website (https://swog.org/safetyreports/safetyreports.asp).

| This safety report pertains to the following studies: | Report: |
|---|---|
| **S0528** Early Therapeutics<br>**S0931** Genitourinary<br>**S1207** Breast<br>**S1222** Breast | Aug. 5, 2014 Mfr Rpt #PHHO2014JP010364 |

Protocol amendments are not necessary at this time, but your consent form may be revised to include the information provided in this report if it is deemed necessary by your institution. Please append this notice and this report to your copy of the protocol and forward a copy to your Institutional Review Board (IRB) as required by your local policies and procedures. Should any further information regarding this adverse event be made available, it will be forwarded to you.

This memorandum serves to notify the NCI and the SWOG Statistical Center.

cc:

| | |
|---|---|
| PROTOCOL & INFORMATION OFFICE | Carol French – AstraZeneca |
| Megan Othus, Ph.D. | John Parnell – AstraZeneca |
| Cathy M. Tangen, Dr.P.H. | Jean Sowa – AstraZeneca |
| William Barlow, Ph.D. | Kathleen DeRose – GSK |
| Danika Lew, M.S. | Scott Adams – Janssen |
| Melissa Plets, M.S. | Meredith Lavin – Novartis |
| Rachel Sexton, M.S. | Kristin White – Novartis |
| Jean Barce | Heather Campbell, PharmD – VACSP/PCC |
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| Iris Syquia | Katie VonDerau – WPC |
| Brian Zeller | |

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swog.org

August 15, 2014

TO: ALL NATIONAL CLINICAL TRIALS NETWORK (NCTN) MEMBERS (U.S. and Canadian Institutions Only), INCAN (Mexico)

FROM: Megan M. Hardin, Protocol Coordinator (E-mail: mhardin@swog.org)

RE: **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." Study Chairs: Drs. M. Chavez-MacGregor and A.M. Gonzalez-Angulo.

**MEMORANDUM**

Study Chair: Mariana Chavez-MacGregor, M.D., M.Sc.
Phone Number: 713/792-2817
E-mail: **S1207**medicalquery@swog.org

**IRB Review Requirements**

( ) Full board review required. Reason:
- ( ) Initial activation (should your institution choose to participate)
- ( ) Increased risk to patient
- ( ) Complete study redesign
- ( ) Addition of tissue banking requirements
- ( ) Study closure due to new risk information

( ) Expedited review allowed

( √ ) No review required

---

**MEMORANDUM**

The following form has been updated and replaced in the forms packet which is accessible through the **S1207** abstract page (www.swog.org). The specific form change includes the following:

1. **S1207** Onstudy Form: "HgA1c" has been added to the "Lab Test" section to be consistent with eligibility.

This memorandum serves to notify the NCI and the SWOG Statistical Center.

cc: PROTOCOL & INFORMATION OFFICE
William Barlow, Ph.D.
Danika Lew, M.S.
Jean Barce
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swog.org

July 1, 2014

TO: ALL NATIONAL CLINICAL TRIALS NETWORK (NCTN) MEMBERS (U.S. and Canadian Institutions Only), INCAN (Mexico)

FROM: Megan M. Hardin, Protocol Coordinator (E-mail: mhardin@swog.org)

RE: **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." Study Chairs: Drs. M. Chavez-MacGregor and A.M. Gonzalez-Angulo.

**MEMORANDUM**

Study Chair: Mariana Chavez-MacGregor, M.D., M.Sc.
Phone Number: 713/792-2817
E-mail: **S1207**medicalquery@swog.org

**IRB Review Requirements**

( ) Full board review required. Reason:
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- ( ) Increased risk to patient
- ( ) Complete study redesign
- ( ) Addition of tissue banking requirements
- ( ) Study closure due to new risk information

( ) Expedited review allowed

( √ ) No review required

---

**MEMORANDUM**

The following form has been removed from the **S1207** BAHO forms packet which is accessible through the **S1207** abstract page (www.swog.org).

1. BAS-Transmittal Form for Blood Specimens: This form is not relevant to this study because these specimens are being sent to the SWOG Repository.

This memorandum serves to notify the NCI and the SWOG Statistical Center.

cc: PROTOCOL & INFORMATION OFFICE
William Barlow, Ph.D.
Danika Lew, M.S.
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swog.org

June 15, 2014

TO: ALL NATIONAL CLINICAL TRIALS NETWORK (NCTN) MEMBERS (U.S. and Canadian Institutions Only), INCAN (Mexico)

FROM: Megan M. Hardin, Protocol Coordinator (E-mail: mhardin@swog.org)

RE: **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." Study Chairs: Drs. M. Chavez-MacGregor and A.M. Gonzalez-Angulo.

**MEMORANDUM**

Study Chair: Mariana Chavez-MacGregor, M.D., M.Sc.
Phone Number: 713/792-2817
E-mail: **S1207**medicalquery@swog.org

**IRB Review Requirements**

( ) Full board review required. Reason:
- ( ) Initial activation (should your institution choose to participate)
- ( ) Increased risk to patient
- ( ) Complete study redesign
- ( ) Addition of tissue banking requirements
- ( ) Study closure due to new risk information

( ) Expedited review allowed

( √ ) No review required

---

**MEMORANDUM**

The following forms have been replaced in the forms packet which is accessible through the **S1207** abstract page (www.swog.org).

1. **S1207** Registration Worksheet Form #16721 (previously Form #50866): The "Auxiliary Question" field has been added to this form. The form date has been revised to 10/30/13.

2. **S1207** Onstudy Form, Form #21218: The "HER2 results" section has been revised to be consistent with the eligibility changes in Revision #2. The form date has been revised to 6/15/14.

This memorandum serves to notify the NCI and the SWOG Statistical Center.

cc:
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swog.org

June 1, 2014

TO: ALL SWOG MEMBER, CCOP AND AFFILIATE MEDICAL ONCOLOGISTS AND SURGEONS

FROM: Megan M. Hardin, Protocol Coordinator (E-mail: mhardin@swog.org)

RE: **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." Study Chairs: Drs. M. Chavez-MacGregor and A.M. Gonzalez-Angulo.

**MEMORANDUM**

Study Chair: Mariana Chavez-MacGregor, M.D., M.Sc.
Phone Number: 713/792-2817
E-mail: **S1207**medicalquery@swog.org

**IRB Review Requirements**

( ) Full board review required. Reason:
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- ( ) Increased risk to patient
- ( ) Complete study redesign
- ( ) Addition of tissue banking requirements
- ( ) Study closure due to new risk information

( ) Expedited review allowed

( √ ) No review required

---

**MEMORANDUM**

This is a reminder to please refer to the Adverse Event management guidelines for everolimus that are available on the **S1207** Trial Support Page. The **S1207** Trial Support Page can be accessed via the CTSU menu and the **S1207** abstract page (www.swog.org).

This memorandum serves to notify the NCI and the SWOG Statistical Center.

cc:
PROTOCOL & INFORMATION OFFICE
William Barlow, Ph.D.
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swog.org

Distribution Date: June 1, 2014
17CTEP Submission Date: April 17, 2014

TO: ALL NATIONAL CLINICAL TRIALS NETWORK (NCTN) MEMBERS (U.S. and Canadian Institutions Only), INCAN (Mexico)

FROM: Megan M. Hardin, Protocol Coordinator (E-mail: mhardin@swog.org)

RE: **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." Study Chairs: Drs. M. Chavez-MacGregor and L. Pusztai.

**REVISION #2**

Study Chair: Mariana Chavez-MacGregor, M.D., M.Sc.
Phone Number: 713/792-2817
E-mail: **S1207**medicalquery@swog.org

**IRB Review Requirements**

( ) Full board review required. Reason:
- ( ) Initial activation (should your institution choose to participate)
- ( ) Increased risk to patient
- ( ) Complete study redesign
- ( ) Addition of tissue banking requirements
- ( ) Study closure due to new risk information

( √ ) Expedited review allowed

( ) No review required

---

**REVISION #2**

The above-referenced protocol has been revised as follows:

1. Pages 1-2, Title Page: The version date has been updated. The NCT number has been added to this page. The participants list has been removed from Page 1 and is now revised and located on Page 2 to be consistent with the new NCTN/CTSU guidelines. "NSABP" has been replaced with "NRG Oncology". This change has also been made to Sections 11.7 (Page 57), 14.4d (Page 62), and 15.2 (Page 65). The contact information for Dr. Priya Rastogi and Dr. Soonmyung Paik have been updated. The e-mail address for Hanna Bandos has been updated.

2. Pages 3-4, Table of Contents: The Table of Contents has been updated.

3. Page 9, Section 3.0: "…Physician's Desk Reference (PDR)…" has been removed from the last sentence of this section.

4. Pages 10-11, Section 3.1c.1: The Adverse Event table has been revised to be consistent with the most recent Investigator's Brochure.

   Specifically, risk attributions that have increased include the following:

   a. Changed from "Less Likely" to "Likely"
      -Vomiting
      -Headache
      -Epistaxis
      -Pruritis

   b. Changed from "Rare but Serious" to "Likely"
      -Pneumonitis

   c. The following risks have been added to the adverse event table:
      -Lymphopenia (Less Likely)
      -Abdominal pain (Less Likely)
      -Dyspepsia (Less Likely)
      -Oral Pain (Less Likely)
      -Mucosal inflammation (Less Likely)
      -Non-cardiac chest pain (Less Likely)
      -Dysphagia (Less Likely)
      -Dehydration (Less Likely)
      -Diabetes mellitus (Less Likely)
      -Hyperlipidemia (Less Likely)
      -Ageusia (Less Likely)
      -Renal failure (Less Likely)
      -Increased daytime urination (Less Likely)
      -Menstruation irregular (Less Likely)
      -Amenorrhea (Less Likely)
      -Acne (Less Likely)
      -Dry skin (Less Likely)
      -Erythema (Less Likely)
      -Hand-foot syndrome (Less Likely)
      -Nail disorder (Less Likely)
      -Hemorrhage (Less Likely)
      -Hypertension (Less Likely)
      -Pancytopenia (Rare but Serious)
      -Pure red cell aplaxia (Rare but Serious)
      -Hypersensitivity (Rare but Serious)
      -Pulmonary embolism (Rare but Serious)
      -Deep vein thrombosis (Rare but Serious)
      -Congestive cardiac failure (Rare but Serious)
      -Impaired wound healing (Rare but Serious)
      -Acute renal failure (Rare but Serious)
      -Proteinuria (Rare but Serious)
      -Acute respiratory distress syndrome (Rare but Serious)
      - Hemoptysis (Rare but Serious)

5. Page 11, Section 3.1c.3: The drug interaction section has been revised to be consistent with the most recent Investigator's Brochure. This required the table in this section to be removed.

6. Page 13, Section 3.1f.2: The following sentence in the second paragraph of this page has been revised: “For Reporting Periods 3, 4 and 5, the PCC will package sufficient drug for one reporting period of treatment (twelve weeks) (20 blister cards or 200 tablets).” This sentence now reads, “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).”

7. Page 35, Section 5.1a: The following sentences have been removed from this section: “HER-2 will be determined by IHC or gene amplification. If HER2 IHC is 2+, an evaluation for gene amplification must be performed and must not be amplified, but otherwise gene amplification evaluation is not required if IHC is 0 or 1+ by institutional standards.” The following sentences have been added to the end of this section:

> “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+. HER-2 equivocal is not eligible.”

8. Page 36, Section 5.2c: “completion of” has been replaced with “the last dose of” in the third sentence of this section.

9. Page 37, Section 5.2i: The following section has been added to eligibility: “Patients must have a complete history and physical examination within 28 days prior to registration.” Subsequent sections have been renumbered respectively.

10. Page 38, Section 5.3a: The following section has been added to eligibility: “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.” Subsequent sections have been renumbered respectively.

11. Page 41, Section 7.3: “strong” has been added before “inhibitors” in the first sentence of the sixth bullet point of this section and “in Section 3.1b and” has been removed from the same sentence.

12. Page 50, Section 8.7: References to the Adverse Event Expedited Reporting System (AdEERS) have been changed to CTEP Adverse Event Reporting System (CTEP-AERS) in this section and throughout the protocol (Sections 16.1b, 16.1c, 16.1e, 16.1f, 16.1g and 16.1h [Pages 66-71] and Tables 16.1 and 16.2 [Pages 68 and 70]). Associated url’s have been updated on these pages as well.

13. Page 51, Section 9.0: “(CCOP Sites Only)” has been added after “Health Resource Utilization Form” on the study calendar.

14. Page 57, Section 13.1: “blinded” has been added before treatment in this section. The following sentences were added to the end of this section: “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 Data Operations Center at 206/652-2267.”

15. Page 59, Section 13.4b: The words "…and the affirmation of eligibility on the Registration Worksheet has been signed by the registering investigator or another investigator designate." have been added to the end of the first sentence of this section.

16. Page 66, Section 16.0: The following standard statement has been added to the end of this section:

    "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."

17. Page 67, Section 16.1b: The adverse events website url has been revised. This change has also been made to Section 16.1h.1 (Page 70).

18. Page 70, Section 16.1h.1: The following sentences were added to this section: "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."

19. Pages 71, Section 16.1i: This section has been added on how to report Pregnancy, Fetal Death, and Death Neonatal.

20. Page 86, Appendix 18.3: The E-mail addresses for Dr. Mariana Chavez-MacGregor and Dr. Julie Gralow have been added to this section.

21. Page 89, Appendix 18.5: The table of drugs known to be metabolized by CYP450 Isoenzymes 2D6 and 3A4 has been revised to only include strong CYP 3A4 inhibitors and inducers to be consistent with the protocol. Subsequent pages have been renumbered accordingly.

Institutions **must** update their local consent forms to include the changes to the Model Consent Form within 90 days of distribution of this notice. SWOG considers that the Model Consent Form changes **do not** represent an alteration in risk/benefit ratio. Therefore, local accrual does **not** need to be suspended pending implementation of these changes. As of 9/1/14, patients must be consented under the 4/17/14 version of the consent form. Patients currently receiving everolimus/placebo and patients who sign a consent form prior to local implementation of the consent form changes **must** be informed of the following changes. The manner by which this notification takes place is at the discretion of the local institution. At a minimum, the patient must be notified by the next visit and this notification process must be documented in the patient chart.

1. The Version Date has been updated.

2. Pages 6-7, Model Consent Form: The everolimus/placebo risks and side effects list has been replaced by the new NCI-approved condensed risk profile table to be consistent with the most recent version of the Investigator's Brochure.

Specifically, risk attributions that have increased include the following:

a) Changed from 'Less Likely' to 'Common':
-**Vomiting**
**-Headache**
**-Nosebleed**
**-Itching**

b) Changed from 'Rare but Serious' to 'Likely':
**-Inflammation of the lungs**

c) The following risks have been added to the risk section:
-Abdominal pain (Occasional)
**-Indigestion** (Occasional)
**-Chest and Oral Pain** (Occasional)
**-Difficulty swallowing** (Occasional)
**-Dehydration** (Occasional)
**-Diabetes** (Occasional)
**-Inability to taste** (Occasional)
**-Kidney failure** (Occasional)
**-Frequent urination** (Occasional)
**-Abnormal or loss of menstrual period** (Occasional)
**-Acne, dry skin** (Occasional)
**-Reddening of skin** (Occasional)
**-Bleeding** (Occasional)
**-Nail disorder** (Occasional)
**-Hand-foot syndrome: reddening, swelling, numbness and peeling on palms of the hands and soles of the feet** (Occasional)
**-Blood clot which may cause swelling, pain, shortness of breath** (Rare but serious)
**-Heart failure which may cause shortness of breath, swelling of ankles, and tiredness** (Rare but serious)
**-Lengthy wound healing** (Rare but serious)
**-Kidney damage which may cause swelling, may require dialysis** (Rare but serious)
**-Coughing or spitting up blood from the lungs or respiratory tract** (Rare but serious)
**-Allergic reaction** (Rare but serious)

3. Pages 7-9, Model Consent Form: The risks and side effects related to hormone treatment list has been replaced by the new NCI-approved condensed risk profile table. There have been no actual changes to the drug's risk profile.

   Note: The NCI has created the condensed risk profile tables in an effort to increase patient understanding of protocol treatment-related side effects. Risks which the patient would not otherwise notice such as changes in laboratory values have been removed. In simplifying the risk language, similar risks which may have been listed separately before have now been combined or removed if considered duplicative.

4. Page 10, Model Consent Form, "Will my medical information be kept private?": "NSABP" has been changed to "NRG Oncology" in the list of organizations that may review medical records. The following statement has been added to this section as well: "(This study was originally conducted with the National Surgical Adjuvant 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.)".

5. Page 12, Model Consent Form, “What are my rights if I take part in this study?”: The following sentence has been deleted from this section because it’s considered duplicative: “We will tell you about new information or changes in the study that may affect your health or your willingness to continue in the study.”

Please attach this memorandum to your copy of the protocol. Replacement pages are attached for the revised pages referenced above. Please insert these pages into your copy of the protocol and forward to the responsible Institutional Review Board (IRB).

This memorandum serves to notify the NCI and the SWOG Statistical Center.

cc: PROTOCOL & INFORMATION OFFICE
William Barlow, Ph.D.
Danika Lew, M.A.
Jean Barce
Jennie Barrett
Larry Kaye
Iris Syquia
Michael Moody – PCC
Emily Tabinski – PCC
Patrice Rine - Novartis
Katie Von Derau - WPC

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swog.org

May 15, 2014

TO: ALL NATIONAL CLINICAL TRIALS NETWORK (NCTN) MEMBERS

FROM: SWOG Operations Office

RE: IND Safety Report for Everolimus

**MEMORANDUM**

**IRB Review Requirements**

( ) Full board review required. Reason:
- ( ) Initial activation (should your institution choose to participate)
- ( ) Increased risk to patient
- ( ) Complete study redesign
- ( ) Addition of tissue banking requirements
- ( ) Study closure due to new risk information

( ☒ ) Expedited review allowed

( ) No review required

---

**MEMORANDUM**

The following new safety report has been posted regarding an adverse event that occurred in association with the drug everolimus. Please access this safety report via the study's abstract page or the safety report link on the SWOG website (https://swog.org/safetyreports/safetyreports.asp).

| This safety report pertains to the following studies: | Report: |
|---|---|
| **S0528** Early Therapeutics<br>**S0931** Genitourinary<br>**S1207** Breast<br>**S1222** Breast | Apr. 16, 2014 Mfr Rpt #PHHO2012FR013807 |

Protocol amendments are not necessary at this time, but your consent form may be revised to include the information provided in this report if it is deemed necessary by your institution. Please append this notice and this report to your copy of the protocol and forward a copy to your Institutional Review Board (IRB) as required by your local policies and procedures. Should any further information regarding this adverse event be made available, it will be forwarded to you.

This memorandum serves to notify the NCI and the SWOG Statistical Center.

cc:
PROTOCOL & INFORMATION OFFICE
Megan Othus, Ph.D.
Cathy M. Tangen, Dr.P.H.
William Barlow, Ph.D.
Danika Lew, M.S.
Hongli Li, M.S.
Rachel Sexton, M.S.
Jean Barce
Carol French – AstraZeneca
John Parnell – AstraZeneca
Jean Sowa – AstraZeneca
Kathleen DeRose – GSK
Scott Adams – Janssen
Rebecca De Los Rios – Novartis
Patrice Rine - Novartis
Kristin White – Novartis

| | |
|---|---|
| Jennie Barrett | Heather Campbell, PharmD – VACSP/PCC |
| Austin Hamm | Anne Davis – VACSP/PCC |
| Larry Kaye | Michael Moody – VACSP/PCC |
| Laura Kingsbury, M.R.T. | Sharon Jenkins – VACSP/PCC |
| Christine McLeod | James Rasp – VACSP/PCC |
| Iris Syquia | Emily Tabinski – VACSP/PCC |
| Brian Zeller | Katie VonDerau – WPC |

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swog.org

April 15, 2014

TO: ALL NATIONAL CLINICAL TRIALS NETWORK (NCTN) MEMBERS

FROM: SWOG Operations Office

RE: IND Safety Reports for Everolimus

**MEMORANDUM**

**IRB Review Requirements**

( ) Full board review required. Reason:
- ( ) Initial activation (should your institution choose to participate)
- ( ) Increased risk to patient
- ( ) Complete study redesign
- ( ) Addition of tissue banking requirements
- ( ) Study closure due to new risk information

( ☒ ) Expedited review allowed

( ) No review required

---

**MEMORANDUM**

The following new safety reports have been posted regarding adverse events that occurred in association with the drug everolimus. Please access these safety reports via the study's abstract page or the safety report link on the SWOG website (https://swog.org/safetyreports/safetyreports.asp).

| These safety reports pertain to the following studies: | Reports: | |
|---|---|---|
| **S0528** Early Therapeutics | Mar. 22, 2013 | Mfr Rpt #PHHO2013SE003791 |
| **S0722** Lung | Apr. 10, 2013 | Mfr Rpt #PHHO2013BR004674 |
| **S0931** Genitourinary | Apr. 10, 2013 | Mfr Rpt #PHHO2013BR004675 |
| **S1207** Breast | Apr. 10, 2013 | Mfr Rpt #PHHO2013BR004769 |
| **S1222** Breast | Apr. 22, 2013 | Mfr Rpt #PHHO2013AU000493 |
| | May 7, 2013 | Mfr Rpt #PHHO2013FR005718 |
| | May 8, 2013 | Mfr Rpt #PHHO2013US005955 |
| | May 22, 2013 | Mfr Rpt #PHHO2013DE003478 FU |
| | Jun. 18, 2013 | Mfr Rpt #PHHO2013US007940 |
| | Jun. 18, 2013 | Mfr Rpt #PHHO2013FR005541 |
| | Jun. 19, 2013 | Mfr Rpt #PHHO2012BE001726 |
| | Jun. 28, 2013 | Mfr Rpt #PHHO2013US007122 FU |
| | Jul. 25, 2013 | Mfr Rpt #PHHO2013DE004079 FU |
| | Sep. 11, 2013 | Mfr Rpt #PHHO2013BR008407 |
| | Nov. 5, 2013 | Mfr Rpt #PHHO2013DE008522 |
| | Dec. 6, 2013 | Mfr Rpt #PHHO2013FR015441 |
| | Dec. 27, 2013 | Mfr Rpt #PHHO2013FR016460 FU |
| | Dec. 27, 2013 | Mfr Rpt #PHHO2013FR016402 FU |
| | Mar. 5, 2014 | Mfr Rpt #PHHO2014CN001000 |
| | Mar. 10, 2014 | Mfr Rpt #PHHO2014AT002913 |

Protocol amendments are not necessary at this time, but your consent form may be revised to include the information provided in these reports if it is deemed necessary by your institution. Please append this notice and these reports to your copy of the protocol and forward copies to your Institutional Review Board (IRB) as required by your local policies and procedures. Should any further information regarding these adverse events be made available, it will be forwarded to you.

This memorandum serves to notify the NCI and the SWOG Statistical Center.

cc:

| | |
|---|---|
| PROTOCOL & INFORMATION OFFICE | Iris Syquia |
| Antje Hoering, Ph.D. | Brian Zeller |
| Mary Redman, Ph.D. | Carol French – AstraZeneca |
| Cathy M. Tangen, Dr.P.H. | John Parnell – AstraZeneca |
| William Barlow, Ph.D. | Jean Sowa – AstraZeneca |
| Danika Lew, M.S. | Scott Adams - Janssen |
| Hongli Li, M.S. | Rebecca De Los Rios – Novartis |
| James Moon, M.S. | Patrice Rine - Novartis |
| Rachel Sexton, M.S. | Kristin White – Novartis |
| Jean Barce | Kathleen DeRose – GSK |
| Jennie Barrett | Heather Campbell, PharmD – VACSP/PCC |
| Vicki Green | Anne Davis – VACSP/PCC |
| Austin Hamm | James Rasp – VACSP/PCC |
| Larry Kaye | Sharon Jenkins – VACSP/PCC |
| Laura Kingsbury, M.R.T. | Katie VonDereau - WWPC |
| Christine McLeod | |

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swog.org

September 1, 2013

TO: ALL SWOG MEMBER, CCOP AND AFFILIATE MEDICAL ONCOLOGISTS AND SURGEONS; CTSU (U.S. and Canadian Institutions Only), INCAN (Mexico)

FROM: Megan M. Hardin, Protocol Coordinator

RE: **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." Study Chairs: Drs. M. Chavez-MacGregor and L. Pusztai.

**STATUS NOTICE**

Study Chair: Mariana Chavez-MacGregor, M.D., M.Sc.
Phone Number: 713/792-2817
E-mail: **S1207**medicalquery@swog.org

**IRB Review Requirements**

( √ ) Full board review required. Reason:
- ( √ ) Initial activation (should your institution choose to participate) (for sites that have NOT yet received approval)
- ( ) Increased risk to patient
- ( ) Complete study redesign
- ( √ ) Addition of tissue banking requirements (for sites that have previously received approval)
- ( ) Study closure due to new risk information

( ) Expedited review allowed

( ) No review required

---

**ACTIVATION**

The study referenced above is open for participation **effective September 3, 2013 at 2:00 p.m. Eastern Time.**

Institutions may begin enrolling patients using the approved protocol and consent form with Version Date of 10/8/12. However, upon Institutional Review Board (IRB) approval of Revision #1 (Version Date 8/13/13), the following instructions must be followed:

Patients who are enrolled under the 10/8/12 version of the consent form are not eligible for the BAHO Quality of Life substudy. Therefore, patients enrolled prior to local implementation of the consent form changes made with Revision #1 need not be informed of the addition of this substudy unless required by the local IRB.

Patients who are enrolled under the 10/8/12 version of the consent form **must be informed** of the additional specimen submission (paraffin-embedded core biopsies at recurrence) required for correlative studies that was added with Revision #1 and must be given the opportunity to consent to participation. The manner by which the notification and additional consent (if applicable) take place is at the discretion of the local institution. At minimum, the patient must be notified at the next visit and the notification must be documented in the patient chart.

Please note that the funding memorandum has been revised and the coverage analysis is now available on the **S1207** abstract page (www.swog.org).

This memorandum serves to notify the NCI and SWOG Statistical Center.

cc: PROTOCOL & INFORMATION OFFICE
William Barlow, Ph.D.
Danika Lew, M.A.
Jean Barce
Jennie Barrett
Larry Kaye
Iris Syquia
Sharon Jenkins – PCC
Anne Davis – PCC
Heather Campbell – PCC
Patrice Rine – Novartis
Katie VonDerau - WWPC

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Distribution Date: September 1, 2013
CTEP Submission Date: August 13, 2013

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TO: ALL SWOG MEMBER, CCOP AND AFFILIATE MEDICAL ONCOLOGISTS AND SURGEONS; CTSU (U.S. and Canadian Institutions Only), INCAN (Mexico)

FROM: Megan M. Hardin, Protocol Coordinator

RE: **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." Study Chairs: Drs. M. Chavez-MacGregor and L. Pusztai.

**REVISION #1**

Study Coordinator: Mariana Chavez-MacGregor, M.D., M.Sc.
Phone Number: 713/792-2817
E-mail: **S1207**medicalquery@swog.org

**IRB Review Requirements**

( √ ) Full board review required. Reason:
- ( ) Initial activation (should your institution choose to participate)
- ( ) Increased risk to patient
- ( ) Complete study redesign
- ( √ ) Addition of tissue banking requirements
- ( ) Study closure due to new risk information

( ) Expedited review allowed

( ) No review required

---

**REVISION #1**

Institutions must update their local consent forms to include the changes to the Model Consent Form.

The above-referenced protocol has been revised as follows:

1. Page 1, Title Page: The version date has been updated. The title of the study has been updated to include "**e**$^3$ Breast Cancer Study – **e**valuating **e**verolimus with **e**ndocrine therapy". The Table of Contents has been moved to the end of the Title Page section (Pages 3-4).



2. Page 1 (Previously Page 3), Title Page: Dr. Lajos Pusztai has replaced Dr. Ana M. Gonzalez-Angulo as the Translational Medicine Chair. Therefore, Dr. Pusztai's contact information has been added. All contact information for Danika Lew has been moved from Page 2 (Previously Page 4) to Page 1 (Previously Page 3). "Study Coordinator" has been changed to "Study Chair". This change has been made throughout the protocol (Sections 8.7 [Page 50] and 18.7 [Pages 99 and 100]).

3. Page 2 (Previously Page 4), Title Page: "(NSABP B53)" has been added after "NSABP STUDY CHAIRS". Dr. Patricia A. Ganz and Dr. Eleftherios P. Mamounas' contact information has been revised. The Alliance Study Chair and corresponding contact information have been added.

4. Page 11, Section 3.1c.3: The drug interaction table has been revised. The specific escalation/reduction instructions have been removed.

5. Page 12, Section 3.1d.2: "citrus" has been changed to "grapefruit" to be consistent with Section 3.1c.3. This change has also been made to Page 21 (Previously Page 39), Section 7.1.

6. Page 35, Section 5.1a: This section has been revised as follows:

   - "non-amplified FISH or CISH" has been replaced with "gene amplification" in the third sentence of this section.
   - The fourth sentence of this section previously read as follows: "If HER2 IHC is 2+, FISH/CISH must be performed and must not be positive (must be a ratio of ≤ 2), but otherwise FISH/CISH is not required if IHC is 0 or 1+ by institutional standards." This sentence now reads, "If HER2 IHC is 2+, an evaluation for gene amplification must be performed and must not be amplified, but otherwise gene amplification evaluation is not required if IHC is 0 or 1+ by institutional standards."

7. Page 35, Section 5.1b: "…inflammatory breast cancer and must not have…" has been removed from the first sentence of this section. The second sentence of this section has been revised and now reads, "Patients with multifocal, multicentric, synchronous bilateral, and primary inflammatory breast cancers are allowed." The 3rd bullet of this section previously read as follows: "Synchronous bilateral disease is defined as invasive breast cancer in both breasts, diagnosed within 30 days of each other." It now reads: "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.)"

8. Page 36, Section 5.2c: "taxane and/or anthracycline based" has been added after "adjuvant" in the first sentence of this section.

9. Page 42, Section 7.5a: The following sentence has been added to the end of this section: "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." This sentence has also been added to Section 7.7.

10. Page 44, Section 8.4: A dose modification table for stomatitis (oral mucositis) has been added to the beginning of this section.

    The Grade 1 dose modifications for acute kidney injury have been revised. Previously, this section read as follows: "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, stop the blinded drug." It now reads: “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 blinded drug until recovery and reintroduce blinded drug at one lower dose level. If the event returns at Grade ≥ 1 stop the blinded drug.”

    The Grade 2 dose modifications for worst grade pneumonitis have been displaced to Page 45. The remainder of the protocol has been repaginated.

11. Page 45, Section 8.4: The first sentence of the ”Blinded drug Dose Adjustment” column for Grade 2 pneumonitis previously read, “Reduce blinded drug to one lower dose level until recovery to ≤ Grade 1.” This sentence now reads, “Hold treatment until recovery to ≤ Grade 1, reduce blinded drug to one lower dose level.” The second sentence of the “Required Investigations” column for Grade 3 pneumonitis has been removed. It read as follows: “Repeat each subsequent reporting period until return to baseline.” The dose modifications for other non-hematological toxicities have been displaced to Page 46.

12. Page 48, Section 8.4: Dose modification tables for lymphopenia, hyperglycemia and hypercholesterolemia have been added to this section. The remainder of the protocol has been repaginated.

13. Page 51 (Previously Page 49), Section 9.0: The Study Calendar has been revised as follows:

    - “√” footnote has been added to the “Off Treatment F/U After Local Recurrence” section. The footnote definition was listed. However, it was errantly left off the calendar in the previous version.
    - “Health Resource Utilization Form” has been added in the “PHYSICAL” section and “X”’s have been added to the respective timepoints (Weeks 7, 13, 25 and 49, and Off Treatment F/U Prior to Local Recurrence).
    - “Correlative Studies and” has been added before “Banking” in the “SPECIMEN SUBMISSION” section.
    - An “X£” has been added in the “Off Treatment F/U Prior to Local Recurrence” column and the “Tissue for Correlative Studies and Banking” row to be consistent with Section 5.1a.

14. Page 52 (Previously Page 50), Section 9.0: The following footnotes to the Study Calendar have been revised:

    - ¶ - “…for local recurrence” has been replaced with “for 55 weeks, then every 6 months for two years, and then annually thereafter until local recurrence, death or 10 years after registration, whichever comes first” to be consistent with Section 7.1.
    - ¥ - “registration” has been changed to “randomization” for consistency.
    - The “Φ” footnote has been added and reads as follows: “The Health Resource Utilization Form should be completed at Weeks 7, 13, 25, and 49, and at 18 months after randomization.”

- The "£" footnote has been added which reads: "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)

15. Page 62 (Previously Page 60), Section 14.4d: The following form has been added to the list of forms in this section to be submitted online: "Health Resource Utilization Form".

16. Page 62 (Previously Page 60), Section 14.4e: "**S1207** Endocrine and Concomitant Therapies Form" has been removed from this section.

17. Page 62 (Previously Page 60), Section 14.4g: The title of this section has been changed from "AFTER OFF BLINDED PROTOCOL TREATMENT, EVERY SIX MONTHS FOR TWO YEARS AND ANNUALLY THEREAFTER UNTIL DISCONTINUATION OF ENDOCRINE THERAPY" to "AFTER EVERY REPORTING PERIOD (WEEKS 7, 13, 25, 37, 49 AND 55) WHETHER OR NOT STILL ON BLINDED PROTOCOL TREATMENT OR ENDOCRINE THERAPY, THEN EVERY SIX MONTHS FOR TWO YEARS AND ANNUALLY THEREAFTER UNTIL DISCONTINUATION OF ENDOCRINE THERAPY".

18. Page 63 (Previously Page 61), Section 14.4h: The title of this section has been changed from "AFTER OFF BLINDED PROTOCOL TREATMENT, EVERY SIX MONTHS FOR TWO YEARS AND ANNUALLY UNTIL TEN YEARS AFTER REGISTRATION OR UNTIL DEATH" to "AFTER WEEK 55 REPORTING PERIOD, EVERY SIX MONTHS FOR TWO YEARS AND ANNUALLY THEREAFTER UNTIL TEN YEARS AFTER REGISTRATION OR UNTIL DEATH". The following sentence was removed from this section: "NOTE: Additionally for patients who go off blinded protocol treatment early due to toxicity, these forms must be submitted after assessment for recurrence every 12 weeks until Week 55 from registration." "Submit copies of the" has been removed from this section.

19. Page 63 (Previously Page 61), Section 14.4i: The following sentence has been added to the end of this section: "Submit tissue specimens as outlined in Section 15.1a."

20. Page 64 (Previously Page 62), Section 15.1a: The following bullet point has been added to this section: "Two (2) paraffin-embedded core biopsies at the time of **disease recurrence**." The following language was errantly missing from the previous version of italicized language in this section, therefore making it an incomplete sentence so has been added: "submission took place must be noted in the patient's medical record.)". The following sentence has been added prior to the last sentence of this section: "Institutions that are unable to submit 20 slides for each tissue sample should contact the SWOG Operations Office (210/614-8808)." The following sentence has been added to the end of this section: "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"."

21. Page 64, (Previously Page 62), Section 15.1b: The following sentence has been added to the end of this section: "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"."

22. Page 65 (Previously Page 63), Section 15.2: The following sentences have been added to the end of the first paragraph to provide instructions in completing the Health Resource Utilization Form for the BAHO Substudy: "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®." Section 16.0 has been displaced to Page 66 and the remainder of the protocol has been repaginated.

23. Page 76 (Previously Page 74), Appendix 18.1: The following paragraph has been added: "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."

24. Page 77 (Previously Page 75), Appendix 18.1: The Health Resource Utilization Form description has been added to this page.

25. Pages 78-79 (Previously Pages 76-78), Appendix 18.1: The first four objectives of this section have been revised to be consistent with the first 4 hypotheses listed subsequently. The following objective has been added to this section: "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.". Subsequent objectives have been renumbered respectively.

26. Page 79 (Previously Page 77), Appendix 18.1: The following hypothesis has been added to this section: "e. There will be greater numbers of health care services used by patients receiving everolimus compared to placebo across the 18 months of observation.". Subsequent hypotheses have been renumbered respectively. Subsequent sections have been repaginated respectively.

27. Page 85 (Previously Page 83), Appendix 18.3: Dr. Anne Schott has been replaced with Dr. Julie Gralow as a resource physician in the emergency unblinding procedures. Her contact information has also been added.

28. Pages 88-91 (Previously Pages 86-89), Appendix 18.5: Anastrozole, exemestane, letrozole and tamoxifen have been removed from this list because they are part of the treatment regimen. Several spelling errors have also been corrected in this list.

29. Page 94 (Previously Page 91), Appendix 18.7: "and two (2) paraffin-embedded core biopsies (at the time of disease recurrence)" has been added before "in all patients" in the first sentence of the "Molecular characterization of node-positive, HR-Positive and HER-2-negative breast cancer and association with patient outcome" section.

30. Page 95 (Previously Page 92), Appendix 18.7: "Two (2) paraffin-embedded core biopsies will be collected at the time of disease recurrence to study mechanisms of resistance," has been added as the second sentence below "Statistical design".

31. Page 96 (Previously Page 93), Appendix 18.7: The first sentence under the "Pharmacogenomic studies of the effects of inherited, germline polymorphisms on toxicity and efficacy of everolimus therapies" section has been revised from "8.5 cc of whole blood will be collected in PAXgene Blood DNA Tubes (Qiagen, Valencia, CA), and 10 cc of whole blood…" to "7.5 mL of whole blood will be collected in a lavender top, EDTA, Vacutainer® tube, and 10 mL of whole blood…". "Dr. Gonzalez-Angulo" has been replaced with "Dr. Pusztai".

32. Model Consent Form, Page 3: The title of the study has been updated to include "**e**$^3$ Breast Cancer Study – **e**valuating **e**verolimus with **e**ndocrine therapy".

33. Model Consent Form, "Why is this study being done?", Page 3: "or breast" has been added after "kidney" in the 3rd sentence of this section. "non-metastatic" has been added before breast in the 4th sentence of this section.

34. Model Consent Form, "What will happen if I take part in this research study?", Page 4: The following language has been added to the list of exams, tests and procedures during the study: "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."

35. Model Consent Form, Pages 7-10 (Previously Pages 7-18): The risk sections for all of the hormone treatments (anastrozole, exemestane, goserelin acetate, letrozole, leuprolide acetate and tamoxifen) have been combined into one risk section. Subsequent pages have been repaginated.

36. Model Consent Form, "Will my medical information be kept private?", Page 11 (Previously Page 19): The following sentences were revised for spacing and punctuation but the content was unchanged: "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." The following sentences have been added to the end of this section:

    *[Note to Informed Consent Authors: The above paragraph complies with the new FDA regulation found at 21 CFR50.25(c) and must be included verbatim in all informed consent documents. The text in this paragraph cannot be revised.]"*

37. Model Consent Form, "What are the costs of taking part in this study?", Page 12 (Previously Page 20): The following sentences of the 4th paragraph in this section have been removed: "If this would occur, other possible options are: 1. You might be able to get the everolimus from your pharmacy but you or your insurance company may have to pay for it. 2. If there is no everolimus or placebo available at all, no one will be able to get more and the study would close." The following sentence has been added to replace these sentences: "If this were to happen the study will close."

38. Model Consent Form, Page 12 (Previously Page 20): The url in the 6th paragraph has been revised to http://cancer.gov/clinicaltrials/learningabout/payingfor/how-insurance-companies-decide.

39. Model Consent Form, "Behavioral and Health Outcomes (BAHO) Study", Page 14 (Previously Page 22): The third sentence of the first paragraph has been revised as follows: "…other symptoms, and quality of life during ..." now reads "…other symptoms, quality of life, and health care utilization during…". The following sentences have been added to the end of this paragraph: "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, hospital admissions during the fist 18 months on the study, so that we can determine if the treatment is influencing your need for various health care services.".

40. Model Consent Form, Pages 14-15 (Previously Page 22): The following paragraph has been added to this page:

"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."

41. Model Consent Form, Page 15 (Previously Page 23): The following sentences were added to the second paragraph of this page:

"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."

42. Model Consent Form, Page 16 (Previously Page 24): The fifth paragraph, which previously read, "Just like in the main study, we will do our best to make sure that your personal information will be kept private.", now reads as follows: "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."

43. Model Consent Form, Page 16 (Previously Page 24): The following question has been added to the consent form:

"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."

Please attach this memorandum to your copy of the protocol. Replacement pages are attached for the revised pages referenced above. Please insert these pages into your copy of the protocol and forward to the responsible Institutional Review Board (IRB). This memorandum serves to notify the NCI and the SWOG Statistical Center.

cc: PROTOCOL & INFORMATION OFFICE
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Distribution Date: December 1, 2012
E-mailed Date: November 19, 2012

TO: ALL SWOG MEMBER, CCOP AND AFFILIATE MEDICAL ONCOLOGISTS AND SURGEONS; CTSU (U.S. and Canadian Institutions Only), INCAN (Mexico)

FROM: Megan M. Hardin, Protocol Coordinator

RE: **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." Study Coordinators: Drs. M. Chavez-MacGregor and A.M. Gonzalez-Angulo.

**MEMORANDUM**

Study Coordinator: Mariana Chavez-MacGregor, M.D., M.Sc.
Phone Number: 713/792-2817
E-mail: **S1207**medicalquery@swog.org

**IRB Review Requirements**

( √ ) Full board review required. Reason:
- ( √ ) Initial activation (should your institution choose to participate)
- ( ) Increased risk to patient
- ( ) Complete study redesign
- ( ) Addition of tissue banking requirements
- ( ) Study closure due to new risk information

( ) Expedited review allowed

( ) No review required

---

**MEMORANDUM**

This protocol is being distributed at this time **for Institutional Review Board (IRB) review only.** Institutions will be notified when the study is activated for patient registrations.

This memorandum serves to notify the NCI and the SWOG Statistical Center.

cc: PROTOCOL & INFORMATION OFFICE
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Anne Davis – PCC
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PRIVILEGED COMMUNICATION
FOR INVESTIGATIONAL USE ONLY

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.
**e**$^3$ Breast Cancer Study- **e**valuating **e**verolimus with **e**ndocrine 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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**NRG**/NRG Oncology
**SWOG**/SWOG

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**CANCER TRIALS SUPPORT UNIT (CTSU) ADDRESS AND CONTACT INFORMATION**

| **To submit site registration documents:** | **For patient enrollments:** | **Submit study data directly to the Lead Cooperative Group unless otherwise specified in the protocol:** |
|---|---|---|
| CTSU Regulatory Office<br>1818 Market Street,<br>Suite 1100<br>Philadelphia, PA 19103<br><br>Fax: 215-569-0206<br><br>E-mail:<br><br>CTSURegulatory@ctsu.coccg.org<br><br>For more information, call the CTSU Help Desk at 888-823-5923 or the Regulatory Help Desk at 866-651-CTSU. | Please refer to the patient enrollment section for instructions on using the OPEN system. | Online Data Submission: This protocol will use Medidata Rave® for electronic data submission. Access Rave® using your active CTEP-IAM userid and password at the following url:<br><br>https://login.imedidata.com/selectlogin<br><br>Other Tools and Reports: Institutions participating through the CTSU continue to have access to other tools and reports available on the SWOG Workbench. Access this by using your active CTEP-IAM userid and password at the following url:<br><br>https://crawb.crab.org/TXWB/ctsulogon.aspx |

The **study protocol and all related forms and documents** must be downloaded from the protocol-specific Web page of the CTSU Member Web site located at https://www.ctsu.org. Sites must use the current form version and adhere to the instructions and submission schedule outlined in the protocol.

CTSU sites should follow procedures outlined in the protocol for Site registration, Patient Enrollment, Adverse Event Reporting, Data Submission (including ancillary studies), and Drug Procurement.

**For patient eligibility questions** contact the SWOG Data Operations Center by phone or email:

206/652-2267.

breastquestion@crab.org

**For treatment or toxicity related questions** contact the Study PI of the Coordinating Group**.**

**For questions unrelated to patient eligibility, treatment, or data submission** contact the CTSU Help Desk by phone or e-mail:

888-823-5923

ctsucontact@westat.com

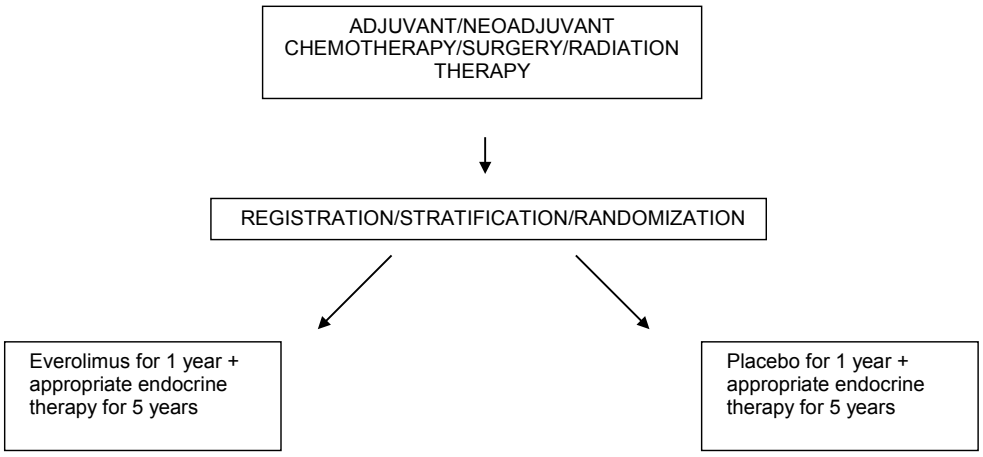
All calls and correspondence will be triaged to the appropriate CTSU representative.

**For detailed information on the regulatory and monitoring procedures for CTSU sites** please review the CTSU Regulatory and Monitoring Procedures policy located on the CTSU members' website

https://www.ctsu.org.

**The CTSU Website is located at** https://www.ctsu.org

**SCHEMA**



## 1.0 OBJECTIVES

1.1 Primary Objective

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 Objectives

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%. *(3)* 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. *(4-8)* 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. *(9)* 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. *(10)* 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. *(10-12)* 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. *(13)*

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. *(14)*

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). *(15)* 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. *(16)* 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. In addition to the comprehensive list, a subset, the Specific Protocol Exceptions to Expedited Reporting (SPEER), appears in a separate column and is identified with bold and italicized text. This subset of AEs (SPEER) is a list of events that are protocol specific exceptions to expedited reporting to NCI (except as noted below). 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).

**NOTE**: Report AEs on the SPEER **ONLY IF** they exceed the grade noted in parentheses next to the AE in the SPEER. If this CAEPR is part of a combination protocol using multiple investigational agents and has an AE listed on different SPEERs, use the lower of the grades to determine if expedited reporting is required.

**Version 2.3, June 30, 2016[1]**

| **Adverse Events with Possible Relationship to Everolimus (RAD-001) (CTCAE 4.0 Term) [n= 3033]** | | | **Specific Protocol Exceptions to Expedited Reporting (SPEER)** |
|---|---|---|---|
| **Likely (>20%)** | **Less Likely (<=20%)** | **Rare but Serious (<3%)** | |
| BLOOD AND LYMPHATIC SYSTEM DISORDERS | | | |
| Anemia | | | ***Anemia (Gr 2)*** |
| GASTROINTESTINAL DISORDERS | | | |
| | Abdominal pain | | |
| | Constipation | | |
| Diarrhea[2] | | | ***Diarrhea[2] (Gr 2)*** |
| Mucositis oral[3] | | | ***Mucositis oral[3] (Gr 2)*** |
| | Nausea | | ***Nausea (Gr 2)*** |
| | Vomiting | | ***Vomiting (Gr 2)*** |

| Adverse Events with Possible Relationship to Everolimus (RAD-001) (CTCAE 4.0 Term) [n= 3033] | | | Specific Protocol Exceptions to Expedited Reporting (SPEER) |
|---|---|---|---|
| **Likely (>20%)** | **Less Likely (<=20%)** | **Rare but Serious (<3%)** | |
| GENERAL DISORDERS AND ADMINISTRATION SITE CONDITIONS | | | |
| | Edema limbs | | ***Edema limbs (Gr 2)*** |
| Fatigue | | | ***Fatigue (Gr 2)*** |
| | Fever | | ***Fever (Gr 2)*** |
| INFECTIONS AND INFESTATIONS | | | |
| | Infection[4] | | ***Infection[4] (Gr 2)*** |
| INJURY, POISONING AND PROCEDURAL COMPLICATIONS | | | |
| | | Wound complication[5] | |
| INVESTIGATIONS | | | |
| | Alanine aminotransferase increased | | ***Alanine aminotransferase increased (Gr 2)*** |
| | Alkaline phosphatase increased | | ***Alkaline phosphatase increased (Gr 2)*** |
| | Aspartate aminotransferase increased | | ***Aspartate aminotransferase increased (Gr 2)*** |
| | Cholesterol high | | ***Cholesterol high (Gr 2)*** |
| | Creatinine increased | | ***Creatinine increased (Gr 2)*** |
| | Lymphocyte count decreased | | ***Lymphocyte count decreased (Gr 2)*** |
| | Neutrophil count decreased | | ***Neutrophil count decreased (Gr 2)*** |
| | Platelet count decreased | | ***Platelet count decreased (Gr 2)*** |
| | Weight loss | | |
| | White blood cell decreased | | ***White blood cell decreased (Gr 2)*** |
| METABOLISM AND NUTRITION DISORDERS | | | |
| | Anorexia | | ***Anorexia (Gr 2)*** |
| | Hyperglycemia[6] | | ***Hyperglycemia[6] (Gr 2)*** |
| | Hypertriglyceri-demia | | ***Hypertriglyceridemia (Gr 2)*** |
| | Hypophosphate-mia | | ***Hypophosphatemia (Gr 2)*** |
| MUSCULOSKELETAL AND CONNECTIVE TISSUE DISORDERS | | | |
| | Arthralgia | | |
| | Back pain | | |
| | Pain in extremity | | |

| Adverse Events with Possible Relationship to Everolimus (RAD-001) (CTCAE 4.0 Term) [n= 3033] | | | Specific Protocol Exceptions to Expedited Reporting (SPEER) |
|---|---|---|---|
| **Likely (>20%)** | **Less Likely (<=20%)** | **Rare but Serious (<3%)** | |
| NERVOUS SYSTEM DISORDERS | | | |
| | Dysgeusia | | |
| | Headache | | ***Headache (Gr 2)*** |
| RENAL AND URINARY DISORDERS | | | |
| | | Acute kidney injury | |
| RESPIRATORY, THORACIC AND MEDIASTINAL DISORDERS | | | |
| | Cough | | ***Cough (Gr 2)*** |
| | Dyspnea<br>Epistaxis | | ***Dyspnea (Gr 2)***<br>***Epistaxis (Gr 2)*** |
| | Pneumonitis[7] | | |
| SKIN AND SUBCUTANEOUS TISSUE DISORDERS | | | |
| | Dry skin | | |
| | Pruritus | | |
| Rash maculo-papular | | | ***Rash maculo-papular (Gr 2)*** |

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

[9] Patients taking concomitant ACE inhibitor therapy may be at increased risk for angioedema.

**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** - Blood and lymphatic system disorders - Other (thrombotic microangiopathy)
**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); Endocrine disorders - Other (low testosterone); Hypothyroidism
**EYE DISORDERS** - Blurred vision; Conjunctivitis; 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; Irritability; Non-cardiac chest pain; Pain
**HEPATOBILIARY DISORDERS** - Hepatic failure; Hepatobiliary disorders - Other (hepatomegaly)
**IMMUNE SYSTEM DISORDERS** - Allergic reaction
**INVESTIGATIONS** - Activated partial thromboplastin time prolonged; Blood bilirubin increased; CPK increased; GGT increased; INR increased; Investigations - Other (bicarbonate decreased); Investigations - Other (increased lactate dehydrogenase); Investigations - Other (low density lipoprotein raised); Investigations - Other (thrombocythemia)
**METABOLISM AND NUTRITION DISORDERS** - Dehydration; Glucose intolerance; Hypercalcemia; Hyperkalemia; Hypoalbuminemia; Hypocalcemia; Hypokalemia; Hypomagnesemia; Hyponatremia; Metabolism and nutrition disorders - Other (high ammonia); Metabolism and nutrition disorders - Other (hyperlipidemia)
**MUSCULOSKELETAL AND CONNECTIVE TISSUE DISORDERS** - Bone pain; Chest wall pain; Generalized muscle weakness; Muscle weakness lower limb; Musculoskeletal and connective tissue disorder - Other (muscle spasms); 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[8]; Delirium; Depression; Insomnia; 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); Respiratory, thoracic and mediastinal disorders - Other (rhinorrhea); Sore throat; Voice alteration
**SKIN AND SUBCUTANEOUS TISSUE DISORDERS** - Nail loss; Palmar-plantar erythrodysesthesia syndrome; Rash acneiform; Skin and subcutaneous tissue disorders - Other (angioedema)[9]; 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.

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.

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 Statistical 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 | |
| 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 | | |
| | | 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 $\alpha_1$-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) |
| | Hypertension | |
| EYE DISORDERS | | |
| | Visual disturbances | |
| GASTROINTESTINAL DISORDERS | | |
| | Abdominal pain | |
| | Anorexia | |
| | Appetite increased | |
| | Constipation | |
| | Diarrhea | |
| GASTROINTESTINAL DISORDERS (contd.) | | |
| | 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 | |
| | 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 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 | |
| | 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 | |
| | 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 | |
| | 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 | | |
| | 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 | |
| | 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 Data Operations Center in Seattle at breastquestion@crab.org or 206/652-2267 prior to registration.

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.**

**SWOG Patient No.** _____

**Patient's Initials (L, F, M)** _____

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+. 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 an Oncotype DX® Recurrence Score > 25 (completed as standard of care). Patients with micrometastases as the only nodal involvement (pN1mi) are eligible, and will be categorized as node-negative.

**SWOG Patient No.** _____

**Patient's Initials (L, F, M)** _____

- Completion of adjuvant chemotherapy, and pathologically 1-3 positive lymph nodes, and either an Oncotype DX® Recurrence Score > 25 (screened via **S1007** or otherwise) or tumor tissue with pathological Grade III following local practice. If Oncotype DX® is done, then RS must be > 25. If the test is not done, but the patient has Grade III disease then the patient is eligible and Oncotype DX® 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 prior to or after chemotherapy.

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) are eligible and 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 no sooner than 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 chemotherapy. Patients may have started endocrine therapy at any time after the diagnosis of the current breast cancer.

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**Patient's Initials (L, F, M)** _____

____ 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 any investigational drug within the preceding 28 days and must not be planning to receive 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. Patients must not have any known uncontrolled underlying pulmonary disease.

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**Patient's Initials (L, F, M)** _____

____ 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.

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 Sections 15.1c, 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 RS > 25 in the primary tumor, and a tumor measuring ≥ 2 cm in greatest diameter treated with adjuvant therapy;

(2) 1-3 positive lymph nodes and RS > 25 or Grade III disease treated with adjuvant therapy;

(3) ≥ 4 positive lymph nodes treated with adjuvant therapy;

(4) ≥ 1 positive lymph node prior to or 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 http://swog.org (then click on "Policies and Manuals" under the "Visitors" menu and choose Policy #38).

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: Mouth washes/rinses commonly used in practice to prevent the development of everolimus-associated mucositis can be used at the discretion of the treating physician.

| 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).

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 for two years, and then annually 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.

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 (www.nccn.org/professionals/physicians_gls/pdf/breast.pdf) 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 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 Data Operations 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.

## 7.5 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 should be placed in the patient's chart and also uploaded into Rave.

b. Planned Unblinding Procedures

You may unblind patients at time of disease recurrence from Member, Affiliate, and NCORP institutions to a Therapeutics study using the SWOG planned unblinding program. To access the planned unblinding program go to the SWOG Web site (http://swog.org) and click on the *Logon* link to go to the SWOG Members Area logon page (https://swog.org/members/logon.asp). This Web program is available at any time except for periods listed under *Down Times.* Log on as an Individual User using your SWOG Roster ID Number and individual web user password. Help for the logon process may be found at https://swog.org/members/logonhelp.asp. After you have logged on, click on the *Workbenches* link, then the *CRA Workbench* link, and then the *Planned Unblinding* link. Go to the Entry Page for the Planned Unblinding program. The CRA must have the SWOG ID number, initials, and investigator number available for the unblinding.

To unblind a patient at disease recurrence, you must meet the following criteria (in order):

1. You are entered into the SWOG Roster and issued a SWOG Roster ID Number.

2. You are associated as an investigator or CRA/RN to the institution where a planned unblinding is occurring.

3. You are granted permission to use the Planned Unblinding program at that institution.

For assistance with points 1 and 2 call the SWOG Operations Office at 210/614-8808. For point 3 you must contact your Web User Administrator. Each SWOG institution has one or more Web User Administrators who may set up Web Users at their institution and assign permissions and passwords to these users.

Non-SWOG sites may unblind patients at time of disease recurrence using the following url: https://crawb.crab.org/TXWB/ctsulogon.aspx.

If the Web Planned Unblinding program is not used, the planned unblinding must be done by phone.

Member, Affiliate and NCORP Institutions

Planned unblinding by phone of patients from Member, Affiliate and NCORP institutions must be done through the SWOG Data Operations Center in Seattle by telephoning 206/652-2267, 6:30 a.m. to 4:00 p.m. Pacific Time, Monday through Friday, excluding holidays.

NOTE: When unblinding **S1207** patients in the SWOG Planned Unblinding Program leave "Bottle ID" field blank.

7.6 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.

7.7 Discontinuation of Treatment

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

7.8 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

This study will utilize the CTCAE (NCI Common Terminology Criteria for Adverse Events) Version 4.0 for toxicity and Serious Adverse Event reporting. A copy of the CTCAE Version 4.0 can be downloaded from the CTEP home page (http://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 | 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. |
| 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.<br>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.<br>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.<br>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 | 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. |
| Grade 4 Anemia | 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. |
| 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. 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

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 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.

2. 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®).

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

4. 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 | | | | | | RP 2 | RP 3 | RP 4 | RP 5 | RP 6 | | Off Treatment F/U Prior to Local Recurrence¶ | Off Treatment F/U After Local Recurrence√ |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | | WK 1 | WK 2 | WK 3 | WK 4 | WK 5 | WK 6 | WK 7 & | WK 13 & | WK 25 & | WK 37 & | WK 49 & | WK 55 & | | |
| **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 |
| 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 | | | | | | | | | | | | | | |
| Blood for BAHO study * | X | | | | | | | | X | X | | X | | 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.**

**Footnotes**:

√ After local recurrence, follow-up will occur (with lab tests and scans performed at the discretion of the treating physician) every 6 months for the first two years and then yearly thereafter until 10 years after registration in order to ascertain subsequent distant recurrence.

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 every 12 weeks for 55 weeks, 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.

* Blood for BAHO substudy will be collected prior to starting treatment and at Weeks 13, 25 and 49, and at 18 and 24 months after registration.

† 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.

## 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. *(15)* 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. *(17)* 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. *(18)* 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; RS > 25 | 10% | 83.4% (S8897) | 0.0308 | 85.7% | 89.1% |
| 1-3 pos nodes; RS > 25 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 | 10% | | 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 $\alpha = 0.025$ 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 $\alpha$'s will be 0.0005, 0.00361, and 0.01154, respectively, and the final $\alpha$= 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

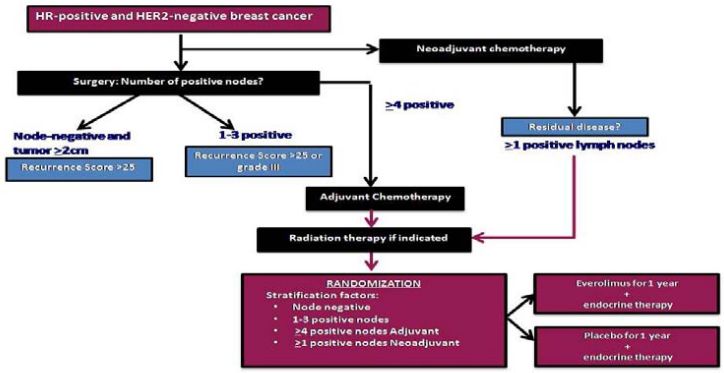
In Section 11.2 we used 0.75 as the effective hazard ratio, i.e. the hazard ratio obtained from the ITT analysis. This incorporates the expectation that patients are more likely to be non-adherent to everolimus than to placebo. Non-adherence moves the observed hazard ratio toward the null hypothesis, 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 Recurrence Scores. Patients not eligible for **S1007** (RxPONDER) trial due to high RS can be enrolled. The two trials are mutually exclusive. The relationship between the two trials is illustrated below.




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 Statistical 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

There will be no formal discipline review done in conjunction with 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 Data Operations Center at 206/652-2267.

13.2 Investigational/Site Registration

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

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 (FDA Form 1572 with original signature, current CV, Supplemental Investigator Data Form with signature and Financial Disclosure Form with original signature) to the Pharmaceutical Management Branch, CTEP, DCTD, NCI. These forms are available on the CTSU Web site (enter credentials at https://www.ctsu.org; then click on the Register tab) or by calling the PMB at 301/496-5725 Monday through Friday between 8:30 a.m. and 4:30 p.m. Eastern time.

Each investigator or group of investigators at a clinic site must obtain IRB approval for this protocol and submit IRB approval and supporting documentation to the CTSU Regulatory Office before they can enroll patients. Study centers can check the status of their registration packets by querying the Regulatory Support System (RSS) site registration status page of the CTSU member web site by entering credentials at https://www.ctsu.org.

Requirements for site registration:

- CTSU IRB Certification
- CTSU IRB/Regulatory Approval Transmittal Sheet

13.3 OPEN Registration Requirements

The individual registering the patient must have completed the appropriate SWOG Registration Worksheet. The completed form must be referred to during the registration but should not be submitted as part of the patient data.

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. Cooperative Group Credit

f. Credit Investigator

g. Patient Initials

h. Patient's Date of Birth

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

j. Country of Residence

k. ZIP Code

l. Gender (select one):

- Female Gender
- Male Gender

m. Ethnicity (select one):

- Hispanic or Latino
- Not Hispanic or Latino
- Unknown

n. 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

o. Race (select all that apply):

- American Indian or Alaska Native
- Asian
- Black or African American
- Native Hawaiian or other Pacific Islander
- White
- Unknown

13.4 Registration Procedures

a. All site staff (SWOG and CTSU Sites) will use OPEN to enroll patients to this study. OPEN is a web-based application and can be accessed at https://open.ctsu.org or from the OPEN tab on the CTSU members' side of the website at https://www.ctsu.org, or from the OPEN Patient Registration link on the SWOG CRA Workbench.

b. Prior to accessing OPEN site staff should verify the following:

- All eligibility criteria have been met 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).
- The study site is listed as "approved" in the CTSU RSS.

c. Access requirements for OPEN:

- Site staff will need to be registered with CTEP and have a valid and active CTEP-IAM account. This is the same account (user ID and password) used for the CTSU members' web site.
- To perform registrations, the site user must have been assigned the 'Registrar' role on the SWOG or CTSU roster:

1. If you are a SWOG member, to perform registrations on SWOG protocols you must have an equivalent 'Registrar' role on the SWOG roster. Role assignments are handled through SWOG.

2. If you are not a SWOG member, to perform registrations on SWOG protocols you must have the role of Registrar on the CTSU roster. Site and/or Data Administrators can manage CTSU roster roles via the new Site Roles maintenance feature under RSS on the CTSU members' web site. This will allow them to assign staff the "Registrar" role.

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

d. Further instructional information is provided on the OPEN tab of the CTSU members' side of the CTSU website at https://www.ctsu.org or at https://open.ctsu.org. For any additional questions contact the CTSU Help Desk at 1-888-823-5923 or ctsucontact@westat.com.

13.5 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 SWOG website (www.swog.org) and (with the exception of the sample consent form and the Registration Worksheet) must be submitted on-line via the Web; see Section 14.3a for details.

14.3 Data Submission Procedures

a. SWOG institutions must submit data electronically via the Web using Medidata Rave® at the following url: https://login.imedidata.com/selectlogin

1. If prompted, select the "CTEP-IAM IdP" link.

2. Enter your valid and active CTEP-IAM userid and password. This is the same account used for the CTSU members website and OPEN.

3. Access **S1207** for the main study and **S1207-E01** for the NSABP BAHO Study.

b. You may also access Rave® via the SWOG CRA Workbench. Go to the SWOG website (http://swog.org) and logon to the Members Area using your SWOG Roster ID number and password. After you have logged on, click on Workbenches, then CRA Workbench to access the home page for the CRA Workbench and follow the link to Rave® provided in the left-hand navigation panel.

To access the CRA Workbench the following must be done (in order):

1. You are entered into the SWOG Roster and issued a SWOG Roster ID Number,

2. You are associated as an investigator or CRA/RN at the institution where the patient is being treated or followed,

3. Your Web User Administrator has added you as a web user and has given you the appropriate system permissions to view data for that institution.

For assistance with points 1 and 2 call the Operations Office at 210/614-8808. For point 3, contact your local Web User Administrator (refer to the "Who is my Web User Administrator?" function on the swog.org Members logon page).

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 on page 3.

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)

Submit blood specimens as outlined in Section 15.1c.

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

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 slides from the primary tumor (in that order of preference)
- Positive lymph node block, punch biopsy or 20 slides (in that order of preference)
- Negative lymph node block, punch biopsy or 20 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.)* Institutions that are unable to submit 20 slides for each tissue sample should contact the SWOG Operations office (210/614-8808). 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. Specimens for **S1207-E01** BAHO Substudy (for patients at NCORP Institutions Only):

1. With patients consent for the **S1207-E01** BAHO study, the following specimens must be submitted at the following times (see Section 9.0)

   (3) 7.5 mL whole blood collected in lavender top, EDTA, Vacutainer® tubes collected prior to starting treatment and at Weeks 13, 25 and 49, and at 18 and 24 months after registration (see Section 9.0).

   - The baseline blood specimen must be collected after **S1207** enrollment before **S1207** study therapy begins.
   - Except for the baseline specimen, blood specimens should be collected within 2 weeks before or 2 weeks after the patient completes the concurrent Form SQ with strong preference for the same day that the questionnaire is completed.
   - Whenever possible, blood specimens should be collected in the morning between 8:00 a.m. and 10:00 a.m. to minimize the effects of diurnal variation in cytokine levels. The date and time of all collections will be noted, and if a morning collection is not possible, it will still be accepted but accounted for by the recorded specimen collection time.

- **Fasting is required** prior to blood specimen collection.

- If the baseline specimen is not collected before **S1207** study therapy begins, subsequent **S1207-E01** study specimens at the additional time points must not be collected and the **S1207-E01** questionnaires should not be completed.

- If a specimen collection time point is missed, complete and submit online a Missing Data Form for Blood Specimen form (Form SMD) to the NRG Oncology Statistics and Data Management Center.

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

d. Specimen collection and submission instructions can be accessed on the SWOG Specimen Submission webpage (https://swog.org/members/clinicaltrials/specimens/STSpecimens.asp) or via the link in the **S1207** protocol abstract page on the SWOG website (www.swog.org).

15.2 **S1207-E01** BAHO Questionnaire Administration Instructions

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 and continue specimen collections (if baseline collected) per protocol schedule. If a blood specimen (other than the baseline specimen) is not collected, patients should continue to complete Form SQ and Form MCL-F.

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.

<table>
<tr><th>Hospitalization</th><th>Grade 1 Timeframes</th><th>Grade 2 Timeframes</th><th>Grade 3 Timeframes</th><th>Grade 4 & 5 Timeframes</th></tr>
<tr><td>Resulting in Hospitalization ≥ 24 hrs</td><td colspan="3">10 Calendar Days</td><td rowspan="2">24-Hour 5 Calendar Days</td></tr>
<tr><td>Not resulting in Hospitalization ≥ 24 hrs</td><td colspan="2">Not required</td><td>10 Calendar Days</td></tr>
</table>

**NOTE:** Protocol specific exceptions to expedited reporting of serious adverse events are found in the Specific Protocol Exceptions to Expedited Reporting (SPEER) portion of the CAEPR or 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

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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 Data Operations 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 <u>commercial</u> 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.** **Fetal Death** Fetal Death defined in CTCAE as "A disorder characterized by death in utero; failure of the product of conception to show evidence of respiration, heartbeat, or definite movement of a voluntary muscle after expulsion from the uterus, without possibility of resuscitation" should be reported expeditiously as **Grade 4 "pregnancy, puerperium and perinatal conditions – Other (pregnancy loss)" under the Pregnancy, puerperium and perinatal conditions** SOC.

**3.** **Death Neonatal** Neonatal death, defined in CTCAE as "A disorder characterized by cessation of life occurring during the first 28 days of life" that is felt by the investigator to be at least possibly due to the investigational agent/intervention should be reported expeditiously.

A neonatal death should be reported expeditiously as **Grade 4 "General disorders and administration – Other (neonatal loss)"** under the **General disorders and administration** SOC.

*Fetal death and neonatal death should **NOT** be reported as a Grade 5 event. If reported as such, the CTEP-AERS interprets this as a death of the patient being treated.*

**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 301-230-0159. 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

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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). *(3-8)* 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. *(1, 13-19)* In addition, since anemia was a prominent adverse event in BOLERO-2 and has been reported in the organ transplant population, additional laboratory correlative studies are proposed below to evaluate this important outcome. *(10,20)*

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 and have blood specimens collected 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. *(12)* 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. *(21-22)* 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. *(23-25)* 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. *(13,26)* Symptoms associated with endocrine therapy will be measured with the BCPT (BESS) symptom checklist. *(14,27)* We will measure mucositis using two items from the *PRO-CTCAE*. *(28)*

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. *(29-30)* 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). *(31)* 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. *(16, 27-33)* These findings are part of the constellation of post-adjuvant treatment fatigue in breast cancer patients. *(7-8)* 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). *(16)* 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.

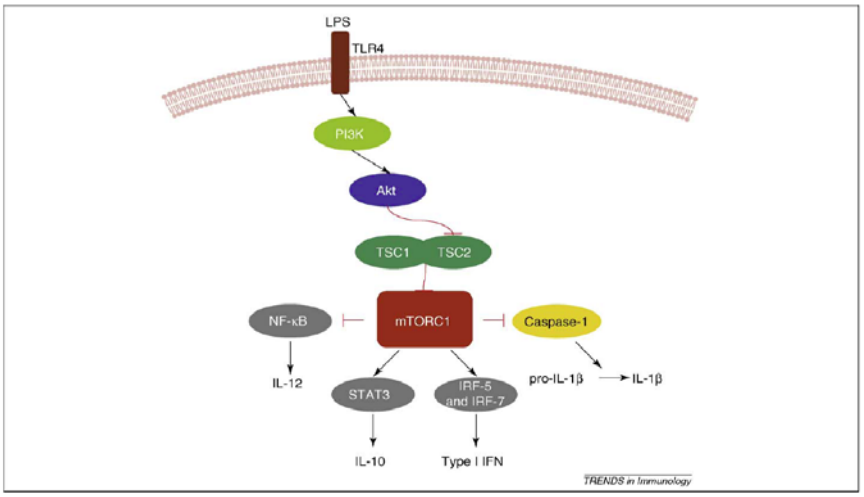


**Figure 4.** mTOR regulates the inflammatory cytokine response in myeloid phagocytes. Stimulation of TLR4 by LPS (lipopolysaccharide) activates PI3K in freshly isolated monocytes and dendritic cells. PI3K transmits a signal to mTORC1 via Akt and the TSC1–TSC2 complex. Activation of mTORC1 limits the 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.

g. To determine if the risk for fatigue and other symptoms in study patients will be associated with specific SNPs in the promoter regions of IL-1, IL-6 and TNF-α.

h. To determine if patients who develop anemia in the course of the study will have greater elevations of proinflammatory cytokines than those who do not.

i. To examine the association between biomarkers of inflammation and patient reported fatigue in relationship to 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.

f. 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.

g. The risk for fatigue and other symptoms in study patients will be associated with specific SNPs in the promoter regions of IL-1, IL-6 and TNF-α.

h. Patients who develop anemia in the course of the study will have greater elevations of proinflammatory cytokines than those who do not.

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 of fatigue (other symptoms) with the presence of specific SNPs in the promoter regions of IL-1, IL-6 and TNF-α will be evaluated by means of linear mixed effects model with fatigue measures (other symptoms) as outcome variable after controlling for treatment with everolimus and other important covariates. Of special interest will be interaction between SNP presence and treatment.

The association of fatigue (and other symptoms) with the levels of cytokines will be evaluated by means of linear mixed effects models with fatigue measures (other symptoms) as outcome variable after controlling for treatment with everolimus and other important covariates. Of special interest will be interaction between cytokines level and treatment.

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.

The biology of anemia that occurs incident to study treatment will be examined through a nested case control design, assessing iron-related measures in the serum of those affected and non-affected, as well as examining the contribution of inflammation to the development of anemia.

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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31. Bower JE, Ganz PA, Irwin MR, et al. Fatigue and gene expression in human leukocytes: Increased NF-κB and decreased glucocorticoid signaling in breast cancer survivors with persistent fatigue. Brain Behav Immun 25(1):147-150, 2011. [PMID 20854893].

32. Collado-Hidalgo A, Bower JE, Ganz PA, et al. Inflammatory biomarkers for persistent fatigue in breast cancer survivors. Clin Cancer Res 12(9):2759-2766, 2006. [PMID 16675568].

33. Collado-Hidalgo A, Bower JE, Ganz PA, et al. Cytokine gene polymorphisms and fatigue in breast cancer survivors: early findings. Brain Behav Immun 22(8):1197-1200, 2008. [PMID 18617366].

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<br>Aprepitant<br>Armodafinil<br>Avasimibe<br>Bosentan<br>Carbamazepine<br>Dexamethasone<br>Efavirenz<br>Etravirine<br>Glucocorticoids<br>Modafinil<br>Nafcillin<br>Nevirapine<br>Oxcarbazepine | Phenobarbital<br>Phenytoin<br>Pioglitazone<br>Prednisone<br>Rifabutin<br>Rifampin<br>Ritonavir<br>Rufinamide<br>St John's Wort<br>Talviraline<br>Topiramate<br>Tipanavir<br>Troglitazone |
| Inhibitors | |
| (Strong) | |
| Clarithromycin<br>Conivaptan<br>Elvitegravir<br>Indinavir<br>Itraconazole<br>Ketoconazole<br>Lopinavir<br>Mibefradil<br>Nefazodone<br>Nelfinavir<br>Posaconazole<br>Ritonavir<br>Saquinavir<br>Telithromycin<br>Tipranavir<br>Troleandamycin<br>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 Statistical 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 statistical 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.

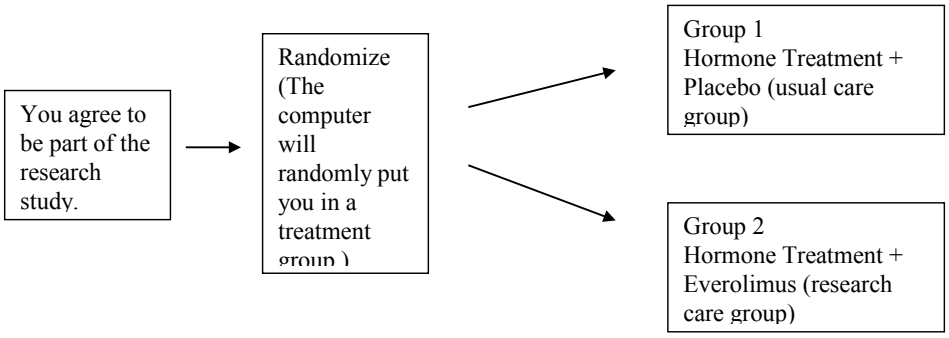
- Physical exam every six weeks for Reporting Periods 1, 2 and 6 and every twelve weeks for Reporting Periods 3-5,
- Blood tests for blood counts and to test your kidney function every six weeks for Reporting Periods 1, 2 and 6 and every twelve weeks for Reporting Periods 3-5,
- Blood tests to check 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. 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?

**You may have side effects while on the study. Everyone taking part in the study will be watched carefully for any side effects. However, doctors don't know all the side effects that may happen. Side effects may be mild or very serious. Your health care team may give you medicines to help lessen side effects. Many side effects go away soon after you stop taking the study drug. In some cases, side effects can be serious, long lasting, or may never go away. There also is a risk of death.**

**You should talk to your study doctor about any side effects that you have while taking part in the study.**

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

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

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

| **RARE, AND SERIOUS**<br>In 100 people receiving everolimus, 3 or fewer may have: |
|---|
| • **Non-healing surgical site**<br>• **Kidney damage which may require dialysis** |

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

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

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

| **RARE, AND SERIOUS**<br>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**<br>• **Vaginal bleeding**<br>• **A new cancer resulting from treatment of earlier cancer**<br>• **Seizure**<br>• **Stroke**<br>• **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. Your personal information may be given out if required by law. If information from this study is published or presented at scientific meetings, your name and other personal information will not be used.

Organizations that may look at and/or copy your medical records for research, quality assurance, and data analysis include:
- 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.]*

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.

### 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. Specifically, the companion study is being done to determine if there are markers in blood cells that can explain why some patients have persistent fatigue after breast cancer treatments. 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.

Researchers also want to know if variations in genes that affect inflammation can determine which patients will experience ongoing fatigue after breast cancer treatment ends. In the companion study, researchers will do tests on blood cells to look for variations in these genes to see if patients who continue to have fatigue after initial breast cancer treatment have a different pattern of gene activity than those who recover their energy.

The researchers will also measure blood levels of inflammation proteins called cytokines to see if their levels are related to the symptoms and quality of life that are reported by patients on the questionnaires. Researchers will also see if the levels of cytokines are higher in patients who have low levels of red blood cells compared to patients who have normal levels of red blood cells.

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.

**Blood sample collections:**

Blood samples will be collected before you start taking the study drug (everolimus or placebo). You will also have blood samples collected at 13 weeks, 25 weeks, 49 weeks, 18 months, and 24 months after you join the study. These blood collections will be at the same visits that you will be having blood samples collected for the main study. This means you should not need to have additional needle sticks for the blood collections in the companion study. About 2 tablespoons of blood (3 tubes) will be taken from a vein for each blood sample collection for the companion study. Each time you have a blood sample collected for the companion study, you will be asked about medications you are taking.

**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.

The information from the questionnaires and the results from the blood sample marker tests 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. The research using your blood samples will not affect your care.

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

You can decide to stop having your blood samples collected, 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 and from tests already done on your samples 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 blood samples and/or questionnaires, and they will no longer be used for research. Otherwise, your blood samples will be kept until used or until the researchers decide to destroy them, and 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 and to have my blood submitted for the specific tests 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**

**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 for this purpose.**

## 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.

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).