BRE 212

A Phase II Open Label Study of Everolimus in Combination with Anti-estrogen Therapy in Hormone Receptor-Positive HER2-Negative Advanced Breast Cancer

SCRI INNOVATIONS STUDY NUMBER:	BRE 212
STUDY DRUG(S):	Everolimus
SPONSOR:	SCRI Development Innovations, LLC (SCRI Innovations) 3322 West End Avenue , Suite 900 Nashville, TN 37203 1-877-MY-1-SCRI asksarah@sarahcannon.com
STUDY CHAIR:	Denise A. Yardley, M.D. Sarah Cannon Research Institute 3322 West End Avenue , Suite 900 Nashville, TN 37203 615-329-7274 asksarah@sarahcannon.com
DATE FINAL:	19 June 2014

SCRI DEVELOPMENT℠ INNOVATIONS

Clinical Study Statement of Compliance

A Phase II Open Label Study of Everolimus in Combination with Anti-estrogen Therapy in Hormone Receptor-Positive HER2-Negative Advanced Breast Cancer

This clinical study shall be conducted in compliance with the protocol, as referenced herein, and all applicable local, national, and international regulatory requirements to include, but not be limited to:

- **International Conference on Harmonisation (ICH) Guidelines on Good Clinical Practice (GCP)**
- **Ethical principles that have their origins in the Declaration of Helsinki**
- **Food and Drug Administration (FDA) Code of Federal Regulation (CFR):**
  - **Title 21CFR Part 50 & 45 CFR Part 46, Protection of Human Subjects**
  - **Title 21CFR Part 54, Financial Disclosure by Clinical Investigators**
  - **Title 21CFR Part 56, Institutional Review Boards**
  - **Title 21CFR Part 312, Investigational New Drug Application**
  - **Title 45 CFR Parts 160, 162, and 164, Health Insurance Portability and Accountability Act (HIPAA)**

As the Study Chair and/or Principal Investigator, I understand that my signature on the protocol constitutes my agreement and understanding of my responsibilities to conduct the clinical study in accordance to the protocol and applicable regulations. Furthermore, it constitutes my understanding and agreement that any changes initiated by myself, without prior agreement in writing from the Sponsor, shall be defined as a deviation from the protocol, and shall be formally documented as such.

SCRI DEVELOPMENT℠
INNOVATIONS

Clinical Study Signature Approval Page

A Phase II Open Label Study of Everolimus in Combination with Anti-estrogen Therapy in Hormone Receptor-Positive HER2-Negative Advanced Breast Cancer

SCRI INNOVATIONS STUDY NUMBER:	BRE 212
STUDY DRUG(S):	Everolimus
DATE FINAL:	19 June 2014

Denise A Yardley, M.D. **Study Chair** Denise A Yardley, M.D. Sarah Cannon Research Institute	**Study Chair Signature**	July 31, 2014 **Date**
Sheetal Khedkar **SCRI Development Innovations, LLC** Sheetal Khedkar, Director	**SCRI Development Innovations, LLC Representative Signature**	6 August 2014 **Date**

SCRI DEVELOPMENT℠ INNOVATIONS

Clinical Study Principal Investigator Signature Form

A Phase II Open Label Study of Everolimus in Combination with Anti-estrogen Therapy in Hormone Receptor-Positive HER2-Negative Advanced Breast Cancer

SCRI INNOVATIONS STUDY NUMBER:	BRE 212
DATE FINAL:	19 June 2014

By signing this protocol acceptance page, I confirm I have read, understand, and agree to conduct the study in accordance with the current protocol.

Principal Investigator Name (Please Print)	**Principal Investigator Signature**	**Date**

Please retain a copy of this page for your study files and return the original signed and dated form to:

SCRI Development Innovations, LLC
3322 West End Avenue, Suite 900
Attn: BRE 212 Study Team
Nashville, TN 37203

BRE 212 PROTOCOL SYNOPSIS

Title of Study:	A Phase II Open Label Study of Everolimus in Combination with Anti-estrogen Therapy in Hormone Receptor-Positive HER2-Negative Advanced Breast Cancer	
SCRI Innovations Study Number:	BRE 212	
Sponsor:	SCRI Development Innovations, LLC – Nashville - TN	
Study Duration:	The duration of the study is approximately 30 months (enrollment + treatment)	**Phase of Study:** II
Study Centers:	This study will be conducted by 9 participating sites.	
Number of Patients:	46 patients will be enrolled in the study.	
Objectives:	**Primary Objective** The primary objective of this study is: • To determine the efficacy of everolimus in combination with anti-estrogen therapy in patients with ER and/or PR-positive, HER2-negative advanced breast cancer demonstrating disease progression on prior hormonal therapy as measured by PFS. **Secondary Objective** The secondary objective of this study is: • To determine the safety and tolerability of everolimus with an anti-estrogen therapy in patients with ER and/or PR-positive, HER2-negative advanced breast cancer. **Exploratory Objective** The exploratory objective of this study is: • To evaluate the VeriStrat assay in this HR-positive patient population treated with everolimus in combination with anti-estrogen therapy.	
Study Design:	This is a multi-centered, open-labeled, Phase II study in MBC. The patient population includes locally recurrent or MBC patients with cytologically or histologically confirmed hormone receptor-positive breast cancer who have demonstrated disease progression on prior anti-estrogen therapy or therapies. Eligible patients must have evaluable or measurable disease per RECIST v1.1. Everolimus will be administered at a dose of 10 mg PO daily combined with the last anti-estrogen therapy (tamoxifen, fulvestrant, anastrozole, letrozole, exemestane, toremifine, or LHRH agonists in conjunction with anti-estrogen therapy) to which they demonstrated disease progression. Anti-estrogen therapy will be administered at the US Food and Drug Administration (FDA) prescribed doses. A treatment cycle will be defined as 4 weeks, with radiological evaluations every 2 cycles. Patients will be treated until disease progression, toxicity or intercurrent illness requiring cessation of treatment, withdrawal of consent, or other reasons outlined in Section 3.3.	

BRE 212 PROTOCOL SYNOPSIS

Study Drugs, Doses, and Modes of Administration:	**PHASE II** N = 46 **Everolimus** 10mg PO once daily **Anti-estrogen Therapy** Treatment cycle = 4 weeks **Restaging:** every 2 cycles Patients will continue on treatment until disease progression, intolerance to side effects or withdrawal of consent.
Inclusion Criteria:	Patients must meet all of the following criteria in order to be included in the research study: 1. Histologic diagnosis of unresectable, locally recurrent or MBC. 2. ER and/or PR-positive tumors with staining by immunohistochemistry (IHC) based on the most recent biopsy. 3. Only 1 previous chemotherapy regimen for MBC. Patients progressing while receiving adjuvant endocrine therapy or progressing <12 months from completion of adjuvant endocrine therapy are eligible. 4. Progressed on anti-estrogen therapy (tamoxifen, fulvestrant, anastrozole, letrozole, exemestane, toremifine, or LHRH agonists in conjunction with anti-estrogen therapy) defined as: • Recurrence while on, or within 12 months of end of anti-estrogen therapy for early stage breast cancer, or • Progression while on, or within one month of anti-estrogen therapy for locally advanced or metastatic breast cancer. Note: No washout for anti-estrogen therapy required. Anti-estrogen therapy does not have to be the last treatment prior to study entry. 5. Post-menopausal or pre/peri-menopausal women on tamoxifen. LHRH agonists may be used to render ovarian suppression with postmenopausal ranges of estradiol or FSH per institutional guidelines. 6. HER2-negative breast cancer, defined as follows: • Fluorescent In Situ Hybridization (FISH)-negative (FISH ratio <2.0), or • IHC 0-1+, or • IHC 2-3+ AND FISH-negative (FISH ratio <2.0). 7. Measureable disease as measured by Response Evaluation Criteria in Solid Tumors (RECIST) criteria version 1.1 (See Appendix E) or evaluable bone lesions, lytic or mixed, in absence of measureable disease by RECIST criteria. 8. Adequate hematologic function, defined by: • Absolute neutrophil count (ANC) $\geq 1.5 \times 10^9$/L • Platelet count $\geq 100 \times 10^9$/L • Hemoglobin >9 g/dL.

Inclusion Criteria:	9. Adequate liver function, defined by: • Aspartate aminotransferase (AST) and alanine aminotransferase (ALT) ≤2.5 x the upper limit of normal (ULN) or ≤5 x ULN in presence of liver metastases) • Total bilirubin ≤1.5 x ULN. 10. Adequate renal function, defined by: • Serum creatinine ≤1.5 x ULN or calculated creatinine clearance of ≥40 ml/min. 11. International normalized ratio (INR) ≤1.5 or prothrombin time (PT)/partial thromboplastin time (PTT) within normal limits (WNL) of the institution (if patient is not on anti-coagulation therapy). Note: Patients receiving anti-coagulation treatment with an agent such as warfarin or heparin are eligible if the INR is stable and within the therapeutic range prior to first dose of everolimus. 12. Adequate lipid profile, defined by: • Fasting serum cholesterol ≤300 mg/dL OR ≤7.75 mmol/L, AND • Fasting triglyceride ≤ 2.5 x ULN. Note: In case one or both of these thresholds are exceeded, the patient can only be included after initiation of appropriate lipid lowering medication. 13. Age ≥ 18 years. 14. ECOG Performance Status score of 0-2 (See Appendix A). 15. Life expectancy of ≥ 12 weeks. 16. Willingness and ability to comply with study and follow-up procedures. 17. Ability to understand the nature of this study and give written informed consent.
Exclusion Criteria:	Patients who meet any of the following criteria will be excluded from study entry: 1. Previous therapy or known intolerance/hypersensitivity with any approved or investigational mTOR inhibitor (e.g., temsirolimus, everolimus, sirolimus). 2. Patients who are ≤21 days after their most recent chemotherapy and have not recovered from side effects. 3. Use of an investigational drug ≤21 days or 5 half-lives (whichever is shorter) prior to the first dose of everolimus. For investigational drugs for which 5 half-lives is ≤21 days, a minimum of 10 days between termination of the investigational drug and administration of everolimus is required. 4. Wide field radiotherapy (including therapeutic radioisotopes such as strontium 89) administered ≤28 days or limited field radiation for palliation ≤7 days for metastatic disease prior to first dose of everolimus or has not recovered from side effects of such therapy.

Exclusion Criteria:	5. Previously untreated brain metastases. Patients who have received radiation or surgery for brain metastases are eligible if there is no evidence of central nervous system (CNS) disease progression, and at least 2 weeks have elapsed since treatment. Patients are not permitted to receive enzyme inducing anti-epileptic drugs (EIAEDs) during the study and should not be receiving chronic corticosteroid therapy for CNS metastases. 6. Cardiac disease, including: congestive heart failure (CHF) > Class II per New York Heart Association (NYHA,See Appendix B) classification; unstable angina (anginal symptoms at rest) or new-onset angina (i.e., began within the last 3 months), or myocardial infarction within the past 6 months; symptomatic CHF, unstable angina pectoris, or cardiac ventricular arrhythmias requiring anti-arrhythmic therapy. 7. Patients who have any severe and/or uncontrolled medical conditions or other conditions that could affect their participation such as: • Severe impaired lung functions as defined as spirometry and diffusing capacity of the lung for carbon monoxide (DLCO) that is 50% of the normal predicted value and/or O2 saturation that is 88% or less at rest on room air • Uncontrolled diabetes as defined by HbA1c >8% despite adequate therapy. • Liver disease such as cirrhosis or severe hepatic impairment (Child-Pugh class C) • Any history of a bleeding diathesis. 8. Impairment of gastrointestinal function or gastrointestinal (GI) disease that may significantly alter absorption of everolimus (e.g., ulcerative disease, uncontrolled nausea, vomiting, diarrhea, malabsorption syndrome, or small bowel resection). 9. Patients with known active hepatitis B (HBV) or hepatitis C (HCV) infection. Patients with risk factors for hepatitis (See Section 7.1) must have HBV DNA and HCV RNA testing by PCR, and are ineligible if these tests are positive. 10. Concurrent use of strong CYP3A4 inhibitors or inducers from 72 hours prior to initiation of study treatment until the end of treatment with everolimus (See Section 5.5). 11. Chronic treatment with systemic steroids or other immunosuppressive agents. Note: Topical or inhaled corticosteroids are allowed. 12. Patients receiving immunization with attenuated live vaccines within 1 week of study entry or during study period (See Section 5.4). 13. Pregnant or lactating women or women of childbearing potential without a negative serum pregnancy test, ≤7 days prior to date of first treatment, regardless of the method of contraception used. 14. Patients with known human immunodeficiency virus (HIV) seropositivity. 15. History of other malignancy ≤ 5 years of study entry which could affect compliance with the protocol or interpretation of results. Note: History of curatively treated basal or squamous cell carcinoma of the skin or in situ carcinoma of the cervix, or ductal carcinoma in situ (DCIS) of the breast treated with lumpectomy alone with curative intent, are generally eligible. 16. Significant concurrent, uncontrolled medical condition which, in the opinion of the investigator, may interfere with patient participation in the study.

BRE 212 PROTOCOL SYNOPSIS

Correlative Testing:	For patients who participate in the exploratory biomarker research component of this study, archival tumor tissue will be collected and assayed for selected biomarkers. **VeriStrat Assay** Serum samples will be collected from all patients at baseline and subsequent selected time points, for performing the VeriStrat assay. Treatment options for this study will not be based on the results of this testing. For details regarding the assay and sample collection, refer to Section 7.3.4and Appendix F.
Statistical Methodology:	Results from the recently published BOLERO-2 study reported a median PFS of 2.8 months (as assessed by the treating investigator) that improved to 6.9 months as a result of the addition of everolimus in patients treated with exemestane after failing the NSAI therapy (Baselga J.et al. 2012). A similar median PFS is predicted in this study's study population that is based on similar inclusion criteria. It is anticipated that everolimus in combination with the last anti-estrogen therapy that the patient demonstrated disease progression to, will result in an increase in median PFS from 2.8 months to 5 months in this refractory population. Based on the above assumptions, given a follow-up period of 12 months after the completion of enrollment (18 months), with a 5% alpha and a one-sided test of hypothesis, a sample size of 42 will provide 80% power to detect an improvement in median PFS from 2.8 months to 5 months in the patients treated with the combination of everolimus with anti-estrogen therapy. Allowing for 8-10% inevaluable patients, the total number of patients to be enrolled is 46 patients.

BRE 212 CONTACT INFORMATION

SCRI Innovations **Contact Information:**	SCRI Innovations 3322 West End Avenue, Suite 900 Nashville, TN 37203 1-877-MY-1-SCRI asksarah@sarahcannon.com
Study Chair:	Denise A. Yardley, M.D. Sarah Cannon Research Institute 3322 West End Avenue, Suite 900 Nashville, TN 37203 1-877-MY-1-SCRI asksarah@sarahcannon.com
Safety Dept. Fax #: **Safety Dept. Email:**	1-866-807-4325 CANN.SAE@SCRI-Innovations.com
Regulatory Phone # **Regulatory Email:**	1-877-MY-1-SCRI SCRIRegulatory@SCRI-Innovations.com

LIST OF ABBREVIATIONS

AE	Adverse event
AI	Aromatase inhibitor
ALP	Alkaline phosphatase
ALT	Alanine aminotransferase
ANC	Absolute neutrophil count
AST	Aspartate aminotransferase
BSA	Body surface area
CBC	Complete blood count
CFR	Code of Federal Regulations
CHF	Congestive heart failure
CI	Confidence interval
CMP	Comprehensive metabolic profile
CR	Complete response
CT	Computerized tomography
CYP3A4	Cytochrome P450 3A4
ECOG	Eastern Cooperative Oncology Group
eCRF	electronic Case Report Form
ER	Estrogen receptor
FDA	Food and Drug Administration
FISH	Fluorescent In Situ Hybridization
GCP	Good Clinical Practice
HbA1c	Hemoglobin A1c
HBcAb	Hepatitis B core antibody
HbsAb	Hepatitis B surface antibody
HbsAg	Hepatitis B surface antigen
HBV	Hepatitis B virus
HCV	Hepatitis C virus
HER2	Human epidermal growth factor receptor 2
HIPAA	Health Insurance Portability and Accountability Act
IB	Investigator Brochure
ICF	Informed consent form
ICH	International Conference on Harmonization
INR	International Normalized Ratio
IRB	Institutional Review Board
MBC	Metastatic breast cancer
NCI CTCAE	National Cancer Institute Common Terminology Criteria for Adverse Events
PgP	P-glycoprotein
PFS	Progression-free survival
PR	Partial response
PT	Prothrombin time
PTT	Partial thromboplastin time
RECIST	Response Evaluation Criteria in Solid Tumors
SAE	Serious adverse event

LIST OF ABBREVIATIONS (continued)

SAR	Suspected adverse reaction
SCRI	Sarah Cannon Research Institute
SD	Stable disease
UAE	Unexpected adverse event
SUSAR	Suspected unexpected serious adverse reaction
ULN	Upper limit of normal

TABLE OF CONTENTS

LIST OF TABLES

LIST OF FIGURES

LIST OF APPENDICES

1. INTRODUCTION

In the United States (US) it is estimated that approximately 226,870 women were diagnosed with breast cancer in 2012. Many breast cancer patients are hormone receptor (estrogen receptor [ER] and/or progesterone receptor [PR])-positive and are usually treated with endocrine therapy. While most of the ER/PR-positive tumors initially respond to hormonal therapy, many patients experience disease progression. Treatment opportunities for these patients do not offer a cure. However, the reinstitution of anti-estrogen therapy could be useful.

1.1 Background

The mammalian target of rapamycin (mTOR) pathway is an intracellular convergence point for numerous cellular signaling pathways involved in cell growth, protein synthesis, autophagy and metabolism. The mTOR complex performs its regulatory function in response to activating or inhibiting signals transmitted through these pathways.

Abundant evidence has linked hormone resistance to crosstalk between cell signaling pathways and signal transduction pathways and ER signaling. Evidence of the PI3 kinase/Akt/mTOR pathway activation in aromatase inhibitor-resistant and in long-term estrogen deprived breast cancer cells has been demonstrated (Campbell R. A. et al. 2001, Santen R. J. et al. 2005, Tokunaga E. et al. 2006). mTOR inhibitors have the potential to provide critical pathway blockade, irrespective of the nature of the upstream activating oncogenic event. Early preclinical data for mTOR inhibitors in combination with tamoxifen or letrozole have been encouraging (Boulay A. et al. 2005).

1.2 Everolimus

Everolimus, a rapamycin analog, is a signal transduction inhibitor that acts by selectively inhibiting mTOR. mTOR is a key serine-threonine kinase in the PI3K/AKT signaling cascade, which is known to be dysregulated in a wide spectrum of human cancers (Boulay A. et al. 2005). There is growing evidence for a close interaction between the mTOR pathway and ER signaling. A substrate of the mTOR complex 1 (mTORC1) called S6 kinase 1, phosphorylates the activation function domain 1 of the ER, which is responsible for ligand independent receptor activation (Yamnik R. L. et al. 2009, Yamnik R. L. et al. 2010).

Everolimus is being investigated as an anticancer agent based on its potential to act:

- directly on the tumor cells by inhibiting tumor cell growth and proliferation;
- indirectly by inhibiting angiogenesis leading to reduced tumor vascularity (via potent inhibition of tumor cell [vascular endothelial growth factor {VEGF}] production and VEGF-induced proliferation of endothelial cells).

Everolimus has been in clinical development since 1996 as an immunosuppressant in solid organ transplantation. It is marketed in the US for oncology indications under the trade name Afinitor®. It is approved in Europe and other global markets (trade name: Certican®) for cardiac

and renal transplantation, and in the US (trade name: Zortress®) for the prevention of organ rejection of kidney transplantation.

Everolimus is approved in the United States for various conditions:

- Advanced kidney cancer (approved in March 2009)
- Prevention of organ rejection after renal transplant (April 2010)
- Subependymal giant cell astrocytoma (SEGA) associated with tuberous sclerosis (TS) in patients who are not suitable for surgical intervention (October 2010)
- Progressive or metastatic pancreatic neuroendocrine tumors not surgically removable (May 2011)
- Breast cancer in post-menopausal women with advanced hormone-receptor positive, HER2-negative type cancer, in conjunction with exemestane (July 2012)
- Prevention of organ rejection after liver transplant(Feb 2013)

A randomized Phase II study with single agent everolimus compared two schedules, daily versus weekly dosing in minimally pretreated metastatic breast cancer (MBC) patients. The results suggested that daily dosing at 10 mg everolimus was beneficial relative to weekly dosing in this setting, with a trend favoring benefit in ER-positive and human epidermal growth factor receptor 2 (HER2)-negative MBC (Ellard S. L. et al. 2009); however, the single agent activity was modest. Reports from preclinical studies on the potential ability of everolimus to inhibit cell proliferation and re-establish sensitivity to anti-hormonal therapy have prompted its evaluation in combination with endocrine therapy in ER-positive MBC. One of the first studies to report results evaluating this approach was the TAMRAD trial. This randomized phase II trial in hormone receptor (HR)-positive MBC patients progressing on an aromatase inhibitor (AI), demonstrated that the addition of everolimus to tamoxifen improved the clinical benefit rate (CBR) from 42% to 61% and lengthened median time to progression (TTP) from 4.5 months to 8.6 months. In the subset of patients who demonstrated sensitivity to the preceding AI as defined by a response to or a late relapse following a 6 month AI treatment interval, the CBR increased from 45% to 78% with median TTP improving from 5 months to 17.4 months (Bachelot T. et al. 2010). In a small, Phase II single arm study, the addition of everolimus to fulvestrant in ER-positive MBC after AI failure revealed a median TTP of 8.6 months with a clinical benefit rate of 55% (Badin F. et al. 2010). Further support for the activity of everolimus in ER-positive MBC comes from the results of the Phase III, randomized, placebo controlled, BOLERO-2 study (Baselga J. et al. 2012). Hormone receptor-positive advanced breast cancer patients (N=724) who had recurrence or progression while receiving previous therapy with a nonsteroidal aromatase inhibitors (NSAI) were randomized in a 2:1 ratio to receive everolimus and exemestane or exemestane and placebo. This study reported a 6 month improvement in median progression-free survival (PFS) with the addition of everolimus to exemestane of 10.6 months relative to 4.2 months on the exemestane/placebo arm (HR 0.36, 95% CI, 0.27-0.47, $p<0.001$) based on central assessment. The most common Grade 3 or 4 adverse events (AEs) were

stomatitis (8% in the combination-therapy group vs. 1% in the exemestane-alone group), anemia (6% vs. <1%), dyspnea (4% vs. 1%), hyperglycemia (4% vs. <1%), fatigue (4% vs. 1%), and pneumonitis (3% vs. 0%). The time to deterioration of Eastern Cooperative Oncology Group (ECOG) performance status (PS) and time to deterioration of quality of life (≥5%) were not statistically different between the two treatment groups.

Most recently, data from the BOLERO-3 trial presented at ASCO 2013 reported that addition of everolimus to trastuzumab and vinorelbine in HER2+ MBC resulted in a 22% decrease in risk of disease progression or death (median PFS 7.0 months vs 5.78 months, P=0.0067, HR=0.78) in patients with HR- positive, HER2-positive advanced breast cancer (O'Regan R, et al. 2013).

Approximately 35,982 cancer patients have been treated with everolimus as of 31-Mar-2014:

- 19,668 patients in Novartis-sponsored clinical trials
- 2,394 patients in the individual patient supply program
- More than 13,930 patients in investigator-sponsored studies.

In 2012 Afinitor® received FDA approval for the treatment of postmenopausal women with advanced hormone receptor-positive, HER2- negative breast cancer (advanced HR+ BC) in combination with exemestane, after failure of treatment with letrozole or anastrozole. Furthermore in 2012, Afinitor® received approval for the treatment of patients with TSC who have renal angiomyolipoma not requiring immediate surgery.

Further details can be found in the Everolimus Investigator's Brochure (IB).

1.3 Rationale for the Study

Based on the activity of everolimus in previous studies investigating endocrine resistant disease, we propose to evaluate the efficacy of everolimus in patients with ER-positive metastatic breast cancer who have progressed on anti-estrogen therapy. It is hypothesized that in this group of endocrine resistant patients, resistance to anti-estrogen therapy is driven by the activation of the PI3K/Akt/mTOR pathways and hence the addition of the mTOR inhibitor to the failing anti-estrogen therapy may result in reversing the resistance established by these cellular mechanisms in these patients.

2. STUDY OBJECTIVES

2.1 Primary Objective

The primary objective of this study is:

- To determine the efficacy of everolimus in combination with anti-estrogen therapy in patients with ER and/or PR-positive, HER2-negative advanced breast cancer demonstrating disease progression on prior hormonal therapy as measured by PFS.

2.2 Secondary Objectives

The secondary objective of this study is:

- To determine the safety and tolerability of everolimus with an anti-estrogen therapy in patients with ER and/or PR-positive, HER2-negative advanced breast cancer.

2.3 Primary Endpoint

The primary endpoint of this study is:

- Median PFS.

2.4 Secondary Endpoints

The secondary endpoints of this study are:

- Overall response rate in the subset of patients with measurable disease.
- Clinical benefit rate (Complete response (CR) + Partial response (PR) + Stable disease (SD) x 6 months).
- Duration of response (DOR).
- Percentage of patients progression-free at 4 and 6 months.
- Overall survival (OS).
- Safety and tolerability of everolimus with an anti-estrogen therapy.

2.5 Exploratory Objectives

The exploratory objective of this study is:

- To evaluate the VeriStrat assay in this HR-positive patient population treated with everolimus in combination with anti-estrogen therapy.

3. STUDY PATIENT POPULATION AND DISCONTINUATION

3.1 Inclusion Criteria

Patients must meet all of the following criteria in order to be included in the research study:

1. Histologic diagnosis of unresectable, locally recurrent or MBC.
2. ER and/or PR-positive tumors with staining by immunohistochemistry (IHC) based on the most recent biopsy.
3. Only 1 previous chemotherapy regimen for MBC. Patients progressing while receiving adjuvant endocrine therapy or progressing <12 months from completion of adjuvant endocrine therapy are eligible.

4. Progressed on anti-estrogen therapy (tamoxifen, fulvestrant, anastrozole, letrozole, exemestane, toremifine, or LHRH agonists in conjunction with anti-estrogen therapy) defined as:

    - Recurrence while on, or within 12 months of end of anti-estrogen therapy for early stage breast cancer, or
    - Progression while on, or within one month of anti-estrogen therapy for locally advanced or metastatic breast cancer.

    Note: No washout for anti-estrogen therapy required.

    Anti-estrogen therapy does not have to be the last treatment prior to study entry.

5. Post- menopausal or pre/peri-menopausal women on tamoxifen. LHRH agonists may be used to render ovarian suppression with postmenopausal ranges of estradiol or FSH per institutional guidelines.

6. HER2-negative breast cancer, defined as follows:

    - Fluorescent In Situ Hybridization (FISH)-negative (FISH ratio <2.0), or
    - IHC 0-1+, or
    - IHC 2-3+ AND FISH-negative (FISH ratio <2.0).

7. Measureable disease as measured by Response Evaluation Criteria in Solid Tumors (RECIST) criteria version 1.1 (See Appendix E) or evaluable bone lesions, lytic or mixed, in absence of measureable disease by RECIST criteria.

8. Adequate hematologic function, defined by:

    - Absolute neutrophil count (ANC) $\geq 1.5 \times 10^9$/L
    - Platelet count $\geq 100 \times 10^9$/L
    - Hemoglobin >9 g/dL.

9. Adequate liver function, defined by:

    - Aspartate aminotransferase (AST) and alanine aminotransferase (ALT) ≤2.5 x the upper limit of normal (ULN) or ≤5 x ULN in presence of liver metastases)
    - Total bilirubin ≤1.5 x ULN.

10. Adequate renal function, defined by:

    - Serum creatinine ≤1.5 x ULN or calculated creatinine clearance of ≥40 ml/min.

11. International normalized ratio (INR) ≤1.5 or prothrombin time (PT)/partial thromboplastin time (PTT) within normal limits (WNL) of the institution (if patient is not on anti-coagulation therapy).

    Note: Patients receiving anti-coagulation treatment with an agent such as warfarin or heparin are eligible if the INR is stable and within the therapeutic range prior to first dose of everolimus.

12. Adequate lipid profile, defined by:

    - Fasting serum cholesterol ≤300 mg/dL OR ≤7.75 mmol/L, AND
    - Fasting triglyceride ≤ 2.5 x ULN.

    Note: In case one or both of these thresholds are exceeded, the patient can only be included after initiation of appropriate lipid lowering medication.

13. Age ≥ 18 years.

14. ECOG Performance Status score of 0-2 (See Appendix A).

15. Life expectancy of ≥ 12 weeks.

16. Willingness and ability to comply with study and follow-up procedures.

17. Ability to understand the nature of this study and give written informed consent.

3.2 Exclusion Criteria

Patients who meet any of the following criteria will be excluded from study entry:

1. Previous therapy or known intolerance/hypersensitivity with any approved or investigational mTOR inhibitor (e.g., temsirolimus, everolimus, sirolimus).

2. Patients who are ≤21 days after their most recent chemotherapy and have not recovered from side effects.

3. Use of an investigational drug ≤21 days or 5 half-lives (whichever is shorter) prior to the first dose of everolimus. For investigational drugs for which 5 half-lives is ≤21 days, a minimum of 10 days between termination of the investigational drug and administration of everolimus is required.

4. Wide field radiotherapy (including therapeutic radioisotopes such as strontium 89) administered ≤28 days or limited field radiation for palliation ≤7 days for metastatic disease prior to first dose of everolimus or has not recovered from side effects of such therapy.

5. Previously untreated brain metastases. Patients who have received radiation or surgery for brain metastases are eligible if there is no evidence of central nervous system (CNS) disease progression, and at least 2 weeks have elapsed since treatment. Patients are not permitted to receive enzyme inducing anti-epileptic drugs (EIAEDs) during the study and should not be receiving chronic corticosteroid therapy for CNS metastases.

6. Cardiac disease, including: congestive heart failure (CHF) > Class II per New York Heart Association (NYHA, Appendix B) classification; unstable angina (anginal symptoms at rest) or new-onset angina (i.e., began within the last 3 months), or myocardial infarction within the past 6 months; symptomatic CHF, unstable angina pectoris, or cardiac ventricular arrhythmias requiring anti-arrhythmic therapy.

7. Patients who have any severe and/or uncontrolled medical conditions or other conditions that could affect their participation such as:

    - Severe impaired lung functions as defined as spirometry and diffusing capacity of the lung for carbon monoxide (DLCO) that is 50% of the normal predicted value and/or O_2 saturation that is 88% or less at rest on room air
    - Uncontrolled diabetes as defined by HbA1c >8% despite adequate therapy.
    - Liver disease such as cirrhosis or severe hepatic impairment (Child-Pugh class C)
    - Any history of a bleeding diathesis.

8. Impairment of gastrointestinal function or gastrointestinal (GI) disease that may significantly alter absorption of everolimus (e.g., ulcerative disease, uncontrolled nausea, vomiting, diarrhea, malabsorption syndrome, or small bowel resection).

9. Patients with known active hepatitis B (HBV) or hepatitis C (HCV) infection. Patients with risk factors for hepatitis (See Section 7.1) must have HBV DNA and HCV RNA testing by PCR, and are ineligible if these tests are positive.

10. Concurrent use of strong CYP3A4 inhibitors or inducers from 72 hours prior to initiation of study treatment until the end of treatment with everolimus (See Section 5.5).

11. Chronic treatment with systemic steroids or other immunosuppressive agents. Note: Topical or inhaled corticosteroids are allowed.

12. Patients receiving immunization with attenuated live vaccines within 1 week of study entry or during study period (See Section 5.4).

13. Pregnant or lactating women or women of childbearing potential without a negative serum pregnancy test, ≤7 days prior to date of first treatment, regardless of the method of contraception used.

14. Patients with known human immunodeficiency virus (HIV) seropositivity.

15. History of other malignancy ≤ 5 years of study entry which could affect compliance with the protocol or interpretation of results. Note: History of curatively treated basal or squamous cell carcinoma of the skin or in situ carcinoma of the cervix, or ductal carcinoma in situ (DCIS) of the breast treated with lumpectomy alone with curative intent, are generally eligible.

16. Significant concurrent, uncontrolled medical condition which, in the opinion of the investigator, may interfere with patient participation in the study.

3.3 Discontinuation from Study Treatment

Patients will be discontinued from study treatment for any of the following reasons:

- Disease progression.
- Irreversible or intolerable toxicity or abnormal laboratory values.
- Patient requests to withdraw from the study and discontinue treatment.
- Inability of the patient to comply with study requirements.
- Conditions requiring therapeutic intervention not permitted by the protocol.
- Intercurrent illness (this will be at the investigator's discretion).
- Non-compliance or lost to follow-up.

After discontinuation from protocol treatment, patients must be followed for AEs for 30 calendar days after their last dose of study drug. All new AEs occurring during this period must be reported and followed until resolution, unless, in the opinion of the investigator, these values are not likely to improve because of the underlying disease. In this case, the investigator must record his or her reasoning for this decision in the patients' medical records and as a comment on the electronic Case Report Form (eCRF).

All patients who have Grade 3 or 4 laboratory abnormalities (Common Terminology Criteria for Adverse Events [CTCAE] v4.0 (http://evs.nci.nih.gov/ftp1/CTCAE/CTCAE) at the time of discontinuation must be followed until the laboratory values have returned to Grade 1 or 2, unless it is, in the opinion of the investigator, not likely that these values are to improve. In this case, the investigator must record his or her reasoning for making this decision in the patients' medical records and as a comment on the CRF.

3.4 Pregnancy

Patients, even if surgically sterilized, must:

- Agree to practice effective barrier contraception during the entire study treatment period and for 6 months after the last dose of study drug, or
- Agree to completely abstain from heterosexual intercourse.

During the course of the study, all female patients of childbearing potential (the definitions of "women of childbearing potential" are listed in Appendix C) must contact the treating investigator immediately if they suspect that they may be pregnant (a missed or late menstrual period should be reported to the treating investigator), despite following the precautions listed above.

If an investigator suspects that a patient may be pregnant prior to administration of study drug(s), the study drug(s) must be withheld until the result of the pregnancy test is confirmed. If a pregnancy is confirmed, the patient must not receive any study drug(s), and must be discontinued from the study.

If an investigator suspects that a patient may be pregnant after the patient has been receiving study drug(s), the study drug(s) must immediately be withheld until the result of the pregnancy test is confirmed. If a pregnancy is confirmed, the study drug(s) must be immediately and permanently stopped, the patient must be discontinued from the study, and the investigator must notify the Sarah Cannon Research Institute (SCRI) study chair as soon as possible. If a patient becomes pregnant while enrolled in the study, a Pregnancy Form (a paper report form) should be completed and faxed to SCRI Safety Department. For more details regarding handling and reporting of pregnancies that occur during treatment, see Section 11.2.

4. STUDY REGISTRATION

The patient must willingly consent after being informed of the procedures to be followed, the experimental nature of the treatment, potential benefits, alternatives, side-effects, risks and discomforts. Institutional Review Board (IRB) approval of this protocol and consent form is required. Eligible patients who wish to participate in the study will be enrolled into the study.

Registration must occur prior to the initiation of protocol therapy. Patients eligible to participate in the study may be enrolled through the SCRI Development Innovations, LLC (SCRI Innovations) Central Enrollment Desk. Registration may be done via email (CANN.SCRIInnovationsEnr@scri-innovations.com) or fax (1-866-346-1062 or 615-524-4012). Patient registration will be confirmed via email within 24 hours, or by the next business day.

5. STUDY DESIGN

This is a multi-centered, open-labeled, Phase II study in MBC. The patient population includes locally recurrent or MBC patients with cytologically or histologically confirmed hormone receptor-positive breast cancer who have demonstrated disease progression on prior anti-estrogen therapy or therapies. Eligible patients must have evaluable or measurable disease per RECIST v1.1.

Everolimus will be administered at a dose of 10 mg PO daily combined with the last anti-estrogen therapy (tamoxifen, fulvestrant, anastrozole, letrozole, exemestane, toremifine, or LHRH agonists in conjunction with anti-estrogen therapy) to which they demonstrated disease progression. Anti-estrogen therapy will be administered at the US Food and Drug Administration (FDA) prescribed doses.

A treatment cycle will be defined as 4 weeks, with radiological evaluations every 2 cycles. Patients will be treated until disease progression, toxicity or intercurrent illness requiring cessation of treatment, withdrawal of consent, or other reasons outlined in Section 3.3.

The primary objective of this study is to determine efficacy as measured by progression-free survival. This study will be conducted by approximately 9 participating sites. A total of 46 patients will be enrolled.

Figure 1 Study Schema

PHASE II **N = 46**

Everolimus 10mg PO once daily

Anti-estrogen Therapy

Treatment cycle = 4 weeks

Restaging: every 2 cycles

Patients will continue on treatment until disease progression, intolerance to side effects or withdrawal of consent.

5.1 Treatment Plan

5.1.1 Everolimus

Patients entering this study will receive everolimus in combination with the last anti-estrogen therapy on which they experienced disease progression at the FDA prescribed dose.

Everolimus 10 mg PO continuous daily dosing

Medication labels will comply with US legal requirement and be printed in English. They will supply no information about the patient. The storage conditions for everolimus will be described on the medication label.

The extent of absorption of everolimus through topical exposure is not known. Therefore, caregivers are advised to avoid contact with suspensions of everolimus tablets. Wash hands thoroughly before and after preparation of either suspension.

Everolimus is supplied by Novartis. Everolimus is formulated as tablets for oral administration of 1mg, 2.5mg, 5mg, and 10mg strength. Tablets are blister-packed under aluminum foil, which should be opened only at the time of administration as drug is both hygroscopic and light-sensitive. Refer to label for expiration date and storage conditions.

Everolimus will be self-administered (by the patient). Everolimus will be administered as two 5mg tablets on a continuous daily dosing schedule. Everolimus should be taken at the same time every day either consistently with food or without food. Everolimus tablets should be swallowed whole with a glass of water. Patients should not chew or crush them. For patients unable to swallow tablets, everolimus tablet(s) should be dispersed completely in a 1 oz glass of water by gently stirring until the tablet(s) is fully disintegrated (approximately 7 minutes), immediately prior to drinking. The glass should be rinsed with 1 oz of water and the rinse should be completely swallowed to ensure that the entire dose is administered. Grapefruit juice should be avoided.

If vomiting occurs, no attempt should be made to replace the vomited dose.

If the patient forgets to take his dose before 6:00 pm, then the dose should be withheld that day and the everolimus should be restarted the following day.

Everolimus drug compliance will be reviewed on Day 1 of each cycle. The research staff will document the amount of everolimus taken and missed by the patient.

Anti-estrogen Therapy (tamoxifen, fulvestrant, anastrozole, letrozole, exemestane, toremifine, or LHRH agonist in conjunction with anti-estrogen therapy)

The patient will be prescribed the last anti-estrogen therapy to which they demonstrated disease progression. Anti-estrogen therapy (tamoxifen, fulvestrant, anastrozole, letrozole, exemestane, toremifine, or LHRH agonist in conjunction with anti-estrogen therapy) will be administered according to the directions in the FDA approved labeling. Consult the appropriate package insert for specific information and instructions.

Restaging

A treatment cycle will be defined as 4 weeks, with radiological evaluations every 2 cycles (8 weeks). Patients will be evaluated for response to treatment before every odd numbered cycle with imaging and chemistry. Patients will be treated until disease progression, toxicity requiring cessation of treatment or withdrawal of consent.

5.2 Correlative Studies

Archival tumor tissue blocks, if available, will be collected and assayed for selected biomarkers. Details regarding sample submission will be provided in a separate lab manual.

5.3 VeriStrat® Assay

Serum samples will be collected from all patients at baseline and subsequent selected time points, for performing the VeriStrat assay. Treatment options for this study will not be based on the results of this testing. For details regarding the assay and sample collection, refer to Section 7.3.4 and Appendix F.

5.4 Concomitant Medications

Patients may receive full supportive care, including transfusion of blood products, anti-emetics, antimicrobials, etc., when appropriate, per institutional or ASCO guidelines, at the discretion of investigator. Bisphosphonates and RANK ligand inhibitors like XGEVA will be allowed for treating osteoporosis or bone metastases.

All concomitant medications and other significant drug therapies taken ≤30 days prior to start of study treatment and after start of study treatment, including blood transfusions, should be recorded.

Patients should be instructed not to take any additional medications (including over-the-counter products) during the course of the study without prior consultation with the investigator.

Antineoplastic Therapies

Treatment with systemic anticancer agents (chemotherapy, hormone therapy, targeted or biologic agents) other than the protocol treatment is not permitted until disease progression is documented per RECIST v1.1. Palliative radiotherapy or surgery may be allowed and should be discussed with the Study Chair prior to administration.

Vaccinations

The use of live vaccines and close contact with those who have received live vaccines should be avoided one week before and during treatment with everolimus. Examples of live vaccines include intranasal influenza, measles, mumps, rubella, oral polio, BCG, yellow fever, varicella and TY21a typhoid vaccines.

5.5 CYP3A4 and/or PgP Inhibitors/Inducers/Substrates

Everolimus is metabolized by CYP3A4 in the liver and to some extent in the intestinal wall. Therefore, the following are recommended:

- Co-administration with strong inhibitors of CYP3A4 (e.g., ketoconazole, itraconazole, ritonavir) or P-glycoprotein (PgP) inhibitor should be avoided.
- Co-administration with moderate CYP3A4 inhibitors (e.g. erythromycin, fluconazole) or PgP inhibitors should be used with caution. If a patient requires co-administration of moderate CYP3A4 inhibitors or PgP inhibitors, reduce the dose of everolimus by approximately 50%. Additional dose reductions to every other day may be required to manage toxicities. If the inhibitor is discontinued, the everolimus dose should be returned to the dose used prior to initiation of the moderate CYP3A4/PgP inhibitor after a washout period of 2 to 3 days.
- Grapefruit or citrus juices affect P450 and PgP activity; therefore, concomitant use should be avoided.
- If patients require co-administration of a strong CYP3A4 inducer, consider doubling the daily dose of everolimus (based on pharmacokinetic data), using increments of 5 mg or less. This dose of everolimus is predicted to adjust the AUC to the range observed without inducers. However, there are no clinical data with this dose adjustment in patients receiving strong CYP3A4 inducers. If the strong inducer is discontinued, consider a washout period of at least 3 to 5 days (reasonable time for significant enzyme de-induction), before the everolimus dose is returned to the dose used prior to initiation of the strong CYP3A4 inducer.
- This dose adjustment of everolimus is intended to achieve similar AUC to the range observed without inducers. However, there are no clinical data with this dose adjustment in patients receiving strong CYP3A4 inducers. If the strong inducer is discontinued the everolimus dose should be returned to the dose used prior to initiation of the strong CYP3A4/PgP inducer.
- Oral contraceptives in preclinical and clinical data have shown everolimus to have CYP3A4 inhibitory activity rather than induction activity; induction of metabolism of contraceptive hormones by everolimus is unlikely. Consequently, administration of everolimus should not reduce the efficacy of oral contraceptives.

Refer to the listing of relevant inducers and inhibitors of CYP3A4 and the list of relevant substrates, inducers and inhibitors of PgP in Appendix E.

Everolimus and drugs influencing CYP3A4 enzyme

Everolimus is a substrate of CYP3A4, and a substrate and moderate inhibitor of the multidrug efflux pump, PgP (PgP, MDR1, and ABCB1). Therefore, extent of absorption and subsequent elimination of systemically absorbed everolimus may be influenced by products that are

substrates, inhibitors, or inducers of CYP3A4 and/or PgP. Concurrent treatment with strong CYP3A4-inhibitors should be avoided. Refer to Appendix E for a comprehensive list of inducers and inhibitors of CYP3A4 and for a list of relevant substrates, inducers and inhibitors of PgP. Inhibitors of PgP may decrease the efflux of everolimus from brain or tumor and therefore increase everolimus concentrations in these tissues. In vitro studies showed that everolimus is a competitive inhibitor of CYP3A4 and of CYP2D6, potentially increasing the concentrations of products eliminated by these enzymes. Thus, caution should be exercised when co-administering everolimus with CYP3A4 and CYP2D6 substrates with a narrow therapeutic index. Clinical studies have been conducted in healthy subjects to assess pharmacokinetic drug interactions between everolimus and potential CYP3A modifiers (ketoconazole, verapamil, erythromycin, rifampin, midazolam, and HMGCoA reductase inhibitors (statins).

6. DOSE MODIFICATIONS

All toxicities will be graded utilizing the NCI CTCAE v 4.0 (http://evs.nci.nih.gov/ftp1/CTCAE/CTCAE). If toxicity occurs, the toxicity will be graded, and appropriate supportive care treatment will be administered to decrease the signs and symptoms thereof. Dose adjustments will be based on the organ system exhibiting the greatest degree of toxicity.

Adverse events most frequently observed with everolimus are rash, stomatitis/oral mucositis, non-infectious pneumonitis, fatigue, headache, anorexia, nausea, vomiting, diarrhea, and infections. Overall, the most frequently observed laboratory abnormalities include neutropenia, thrombocytopenia, hyperglycemia, hypercholesterolemia, and/or hypertriglyceridemia. The majority of these AEs have been of mild to moderate severity (NCI CTCAE Grade 1-2).

The dose level reductions for everolimus to be used in this study are shown in Table 1.

If everolimus is interrupted for any reason, and the patient has no toxicity related to anti-estrogen therapy, the patient should continue anti-estrogen therapy per schedule. If the patient discontinues everolimus for any reason, they should continue to receive anti-estrogen therapy if patient is deriving clinical benefit from the therapy.

Table 1 Everolimus Dose Level for Toxicity

Dose Level	Everolimus
Starting Dose	10 mg daily
Dose Level -1	5 mg daily
Dose Level -2	5 mg every other day

No more than 2 dose reductions for everolimus are permitted. Patients who need an additional dose reduction will be required to discontinue everolimus.

Table 2 lists the dosing guidelines for everolimus-related hematologic toxicities, Table 3 and Table 4 list the dosing guidelines for everolimus-related non-hematologic toxicities.

6.1 Dose Modifications Due to Hematologic Toxicity

Dose modifications on Day 1 of each cycle will be based on blood counts determined on the day of scheduled treatment. Nadir blood counts will not be used to determine dose modifications. Treatment on Day 1 of any cycle will proceed if blood counts demonstrate ANC $\geq 1.5 \times 10^9$/L and platelets $\geq 100 \times 10^9$/L (See Table 2).

Table 2 Everolimus Dose Modifications Due to Hematologic Toxicities

Toxicity	Actions
Grade 3 thrombocytopenia (platelets <50, ≥ 25 x10^9/L)	Interrupt everolimus until resolution to ≤ Grade 1. If AE resolution occurs ≤ 7 days, reintroduce everolimus at the dose level prior to interruption. If AE resolution occurs > 7 days, or event recurs within 28 days, reintroduce everolimus at one dose level lower, if available.
Grade 4 thrombocytopenia (platelets < 25 x10^9/L)	Interrupt everolimus until recovery to ≤ Grade 1. Then reintroduce everolimus at one dose level lower, if available.
Grade 3 Neutropenia (neutrophils <1, ≥ 0.5 x 10^9/L) **or Grade 3 anemia** (Hgb <8.0-6.5g/dL; <4.9-4.0 mmol/L; <80-65 g/L; transfusion indicated.	Interrupt everolimus until resolution to ≤ Grade 1 or baseline value. If AE resolution occurs ≤ 7 days, reintroduce everolimus at the same dose level. If AE resolution occurs > 7 days, or event occurs within 28 days, reintroduce everolimus at one dose level lower, if available.
Grade 4 Neutropenia (neutrophils <0.5 x 10^9/L) **or Grade 4anemia** (Life-threatening consequences; urgent intervention indicated.)	Interrupt everolimus until recovery to ≤ Grade 1 or baseline value. Reintroduce everolimus at one dose level lower, if available.*
Febrile Neutropenia	Interrupt everolimus until resolution to ≤ Grade 1 (or baseline value) and no fever. Reintroduce everolimus at one dose level lower, if available.*
Grade 3 AE recurrence after dose reduction	Interrupt everolimus until resolution to ≤ Grade 1. Reduce dose to the next lower dose level, if available. The lowest possible dose level of everolimus is 5 mg every other day (2.5 mg daily). Below this level, everolimus must be discontinued.

***Grade 4 AE recurrence (including febrile neutropenia) after dose reduction, discontinue everolimus.**

***Any hematologic toxicity requiring everolimus interruption for > 28 days, discontinue everolimus.**

6.2 Everolimus Dose Modifications Due to Non-Hematologic Toxicity

Dose reductions and management of non-hematologic toxicities related to everolimus are defined in Table 3 and Table 4.

Table 3 Everolimus Dose Modifications and Management of Hepatic Toxicity

Toxicity	Actions
AST or ALT elevation Grade 3 (> 5.0 - 20.0 ULN)*	Interrupt everolimus administration until resolution to ≤ Grade 1 (or ≤ Grade 2, if baseline values were within the range of Grade 2). If resolution occurs ≤ 7 days, reintroduce everolimus at the dose level prior to interruption. If resolution occurs > 7 days, or if event recurs within 28 days, hold everolimus until recovery to ≤ Grade 1 or baseline value and reintroduce everolimus at one dose level lower, if available.
AST or ALT elevation Grade 4 (> 20 x ULN)*	Interrupt everolimus administration until resolution to ≤ Grade 1 (or ≤ Grade 2, if baseline values were within the range of Grade 2). If resolution occurs ≤ 7 days, reintroduce everolimus at one dose level lower. If resolution occurs > 7 days, discontinue everolimus.
Recurrence of Grade 4 after dose reduction or toxicity requiring Everolimus interruption for > 28 days	**Discontinue everolimus.**
Grade 3 or 4 clinical liver failure (asterixis or encephalopathy/coma)	**Discontinue everolimus.**

* Should HCV flare be confirmed, the guidelines for flare must take precedence (See Section 6.2.10).

Table 4 Everolimus Dose Modifications and Management of Non-Hematologic Toxicity

Toxicity	Actions
Intolerable Grade 2 mucositis, or Grade 3 AE (except pneumonitis [see Table 5] and except hyperglycemia or hypercholesterolemia [See Section 6.2.5])	Interrupt everolimus administration until resolution to ≤ Grade 1 or baseline value. If resolution occurs within ≤ 7 days, reintroduce everolimus at the dose level prior to interruption. If resolution occurs > 7 days, or if event recurs within 28 days, hold everolimus until recovery to ≤ Grade 1 or baseline value and reintroduce everolimus at one dose level lower, if available. Patients will be withdrawn from the study if they fail to recover to ≤ Grade 1 or baseline value within 28 days.
Recurrence of Grade 2 mucositis or Grade 3 AE after dose reduction	Reduce dose to the next lower dose level, if available. The lowest possible dose level of everolimus is 5 mg every other day (2.5 mg daily). Below this level, everolimus must be discontinued. If toxicity recurs at Grade 3, consider discontinuation.
Grade 4 AE	Hold everolimus until recovery to ≤ Grade 1 or baseline value. Reintroduce everolimus at one dose level lower, if available.
Grade 4 AE recurrence after dose reduction	**Discontinue everolimus.**
Any non-hematologic toxicity requiring interruption for >28 days.	**Discontinue everolimus.**

6.2.1 Management of Infections

Everolimus has immunosuppressive properties and may predispose patients to bacterial, fungal, viral or protozoal infections, including infections with opportunistic pathogens. Localized and systemic infections, including pneumonia, other bacterial infections, invasive fungal infections, such as aspergillosis or candidiasis and viral infections including reactivation of hepatitis B virus, have been described in patients taking everolimus. Some of these infections have been severe (e.g. leading to sepsis, respiratory or hepatic failure) and occasionally have had a fatal outcome.

Physicians and patients should be aware of the increased risk of infection with everolimus and treat pre-existing infections prior to starting treatment with everolimus. While the patient is taking everolimus, the treating investigator should be vigilant for symptoms and signs of infection; if a diagnosis of infection is made, institute appropriate treatment promptly and consider interruption or discontinuation of everolimus.

If a diagnosis of invasive systemic fungal infection is made, discontinue everolimus and treat with appropriate antifungal therapy.

Cases of pneumocystis jirovecii pneumonia (PJP), some with a fatal outcome, have been reported in patients who received everolimus. PJP may be associated with concomitant use of

corticosteroids or other immunosuppressive agents. Prophylaxis for PJP should be considered when concomitant use of corticosteroids or other immunosuppressive agents are required.

6.2.2 Management of Skin Toxicity

For patients with Grade 1 toxicity, no specific supportive care is usually needed or indicated. Rash must be reported as an AE. Patients with Grade 2 or higher toxicity may be treated with the following suggested supportive measures at the discretion of the investigator: oral minocycline, topical tetracycline, topical clindamycin, topical silver sulfadiazine, diphenhydramine, oral prednisolone (short course), topical corticosteroids, or pimecrolimus.

6.2.3 Management of Hypersensitivity reactions

Hypersensitivity reactions manifested by symptoms including, but not limited to, anaphylaxis, dyspnea, flushing, chest pain or angioedema (e.g. swelling of the airways or tongue, with or without respiratory impairment) have been observed with everolimus. Please refer to Table 4 for management of non-hematologic toxicities related to everolimus.

6.2.4 Angioedema with concomitant use of angiotensin-converting enzyme (ACE) inhibitors

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

6.2.5 Renal Failure Events

Cases of renal failure (including acute renal failure), some with fatal outcome, occurred in patients treated with everolimus. Renal function of patients should be monitored particularly where patients have additional risk factors that may further impair renal function.

Elevations of serum creatinine, usually mild, and proteinuria have been reported in patients taking everolimus. Monitoring of renal function, including measurement of blood urea nitrogen (BUN), urinary protein, or serum creatinine, is recommended prior to the start of everolimus therapy and periodically thereafter. Please refer to Table 4 for management of non-hematologic toxicities related to everolimus.

6.2.6 Management of Stomatitis, Oral Mucositis and Mouth Ulcers

Adverse Drug Reaction	Severity	Everolimus Dose Adjustment and Management Recommendations
Stomatitis	Grade 1 (Minimal symptoms, normal diet)	No dose adjustment required. Manage with non-alcoholic or salt water (0.9%) mouth wash several times a day.
	Grade 2 (Symptomatic but can eat and swallow modified diet)	Temporary dose interruption until recovery to grade ≤1. Re-initiate everolimus at the same dose. If stomatitis recurs at grade 2, interrupt dose until recovery to grade ≤1. Re-initiate everolimus at a lower dose. Manage with topical analgesic mouth treatments (e.g. benzocaine,butyl aminobenzoate, tetracaine hydrocholoride, menthol or phenol)with or without topical corticosteroids (i.e. triamcinolone oral paste)*.
	Grade 3 (Symptomatic and unable to adequately eat or hydrate orally)	Temporary dose interruption until recovery to grade ≤1. Re-initiate everolimus at lower dose. Manage with topical analgesic mouth treatments (i.e. benzocaine,butyl aminobenzoate, tetracaine hydrocholoride, menthol or phenol) with or without topical corticosteroids (i.e. triamcinolone oral paste)*
	Grade 4 (Symptoms associated with life-threatening consequences)	Discontinue everolimus and treat with appropriate medical therapy.

* using agents containing alcohol, hydrogen peroxide, iodine, and thyme derivatives in management of stomatitis is not recommended as they may worsen mouth ulcers.

Patients with a clinical history of stomatitis/mucositis/mouth ulcers and those with gastrointestinal morbidity associated with mouth/dental infections, irritation of esophageal mucosa (e.g. gastroesophageal reflux disease [GERD]) must be monitored even more closely. Patients should be instructed to report the first onset of buccal mucosa irritation/reddening to their study physician immediately.

Stomatitis/oral mucositis/mouth ulcers due to everolimus should be treated using local supportive care. Please note that investigators in earlier studies have described the oral toxicities associated with everolimus as mouth ulcers, rather than mucositis or stomatitis. If your examination reveals mouth ulcers rather than a more general inflammation of the mouth, please classify the AE as such. Please follow the paradigm below for treatment of stomatitis/oral mucositis/mouth ulcers:

1. For mild toxicity (Grade 1), 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 pain but are able to maintain adequate oral alimentation, or Grade 3 in which case patients 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 alcohol, hydrogen peroxide, iodine, and thyme derivatives may tend to worsen mouth ulcers. It is preferable to avoid these agents.

4. Antifungal agents should 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 everolimus metabolism, therefore leading to higher everolimus exposures. Therefore, topical antifungal agents are preferred if an infection is diagnosed.

6.2.7 Management of Diarrhea

Appearance of Grade 1-2 diarrhea attributed to study drug toxicity may be treated with supportive care such as loperamide, initiated at the earliest onset (for example 4 mg orally followed by 2 mg orally every 2 hours until resolution of diarrhea).

6.2.8 Management of Hyperlipidemia and Hyperglycemia

Treatment of hyperlipidemia should take into account the pre-treatment status and dietary habits of the patient. Blood test to monitor hyperlipidemia must be taken in the fasting state. Grade 2 hypercholesterolemia (>300 mg/dL or 7.75 mmol/L) or Grade 2 hypertriglyceridemia (>2.5 x ULN) 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.

Note: Concomitant therapy with fibrates and an HMG-CoA reductase inhibitor is associated with an increased risk of a rare but serious skeletal muscle toxicity manifested by rhabdomyolysis, markedly elevated creatine kinase (CPK) levels and myoglobinuria, acute renal failure and sometimes death. The risk versus benefit of using this therapy should be determined for individual patients based on their risk of cardiovascular complications of hyperlipidemia.

Dyslipidemia (including hypercholesterolemia and hypertriglyceridemia) has been reported in patients taking everolimus. Monitoring of blood cholesterol and triglycerides prior to the start of everolimus therapy and periodically thereafter as well as management with appropriate medical therapy is recommended.

Hyperglycemia has been reported in patients taking everolimus. Monitoring of fasting serum glucose is recommended prior to the start of everolimus and periodically thereafter. More frequent monitoring is recommended when everolimus is co-administered with other drugs that may induce hyperglycemia. Optimal glycemic control should be achieved before starting a patient on everolimus.

6.2.9 Management of Non-Infectious Pneumonitis

Non-infectious pneumonitis is a class effect of rapamycin derivatives. Cases of non-infectious pneumonitis (including interstitial lung disease) have also been described in patients taking

everolimus. Some of these have been severe and on rare occasions, a fatal outcome was observed.

- 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-medicinal causes have been excluded by means of appropriate investigations. Opportunistic infections such as PJP should be ruled out in the differential diagnosis of non-infectious pneumonitis. Patients should be advised to report promptly any new or worsening respiratory symptoms.

Patients who develop radiological changes suggestive of non-infectious pneumonitis and have few or no symptoms may continue everolimus therapy without dose alteration.

If symptoms are moderate (grade 2), consideration should be given to interruption of therapy until symptoms improve. The use of corticosteroids may be indicated. Everolimus may be reintroduced at a daily dose approximately 50% lower than the dose previously administered.

For cases of grade 3 non-infectious pneumonitis, interrupt everolimus until resolution to less than or equal to grade 1. Everolimus may be re-initiated at a daily dose approximately 50% lower than the dose previously administered depending on the individual clinical circumstances. If toxicity recurs at grade 3, consider discontinuation of everolimus. For cases of grade 4 non-infectious pneumonitis, everolimus therapy should be discontinued. Corticosteroids may be indicated until clinical symptoms resolve.

For patients who require use of corticosteroids for treatment of non-infectious pneumonititis, prophylaxis for pneumocystis jirovecii pneumonia (PJP) may be considered. The two compounds studied most extensively for prophylaxis against PJP have been trimethoprim-sulfamethoxazole, given orally, and pentamidine, given as an aerosol.

Patients in this study will be routinely questioned as to the presence of new or changed pulmonary symptoms consistent with pneumonitis. Moreover, potential lung radiological changes can be detected by the chest CT/MRI scans that are performed on all patients every 2 cycles for tumor assessment according to the schedule of events (Appendix D). Pulmonary function tests (PFTs) will be conducted, if clinically indicated, to monitor for pneumonitis. If non-infectious pneumonitis develops, the guidelines in Table 5 should be followed. Consultation with a pulmonologist is recommended for any case of pneumonitis that develops during the study.

Table 5 Management of Non-Infectious Pneumonitis Due to Everolimus

Worst Grade Pneumonitis	Required Investigations	Management of Pneumonitis	Everolimus Dose Adjustment
Grade 1 (Asymptomatic, radiographic findings only)	CT scans with lung windows. Consider room air O_2 saturation at rest	No specific therapy is required	Administer 100% of everolimus dose. Initiate appropriate monitoring.
Grade 2 (Symptomatic, not interfering with Activities of Daily Living)	CT scan with lung windows. Consider pulmonary function testing including: spirometry, DLCO, and room air O_2 saturation at rest. Consider a bronchoscopy with biopsy and/or BAL. Monitor at each visit until return to ≤ Grade 1. Return to initial monitoring frequency if no recurrence.	Symptomatic only. Consider corticosteroids and/or other supportive therapy if symptoms are troublesome.	Rule out infection and consider interruption of everolimus until symptoms improve to ≤ Grade 1. Re-introduce everolimus at one dose level lower. Discontinue everolimus if failure to recover within ≤ 28 days.
Grade 3 (Symptomatic, Interfering with Activities of Daily Living. O2 indicated	CT scan with lung windows and pulmonary function testing including: spirometry, DLCO, and room air O2 saturation at rest. Consider a bronchoscopy with biopsy and/or BAL. Monitor at each visit until return to ≤ Grade 1. Return to initial monitoring frequency if no recurrence.	Consider corticosteroids if infective origin is ruled out. Taper as medically indicated.	Rule out infection and interrupt everolimus until symptoms improve to ≤ Grade 1. Consider reintroducing everolimus at one dose level lower. Discontinue everolimus if failure to recover within ≤ 28 days. If toxicity recurs at Grade 3, consider discontinuation.
Grade 4 (Life-threatening, ventilatory support indicated)	CT scan with lung windows and required pulmonary function testing, if possible, including: spirometry, DLCO, and room air O2 saturation at rest. Bronchoscopy with biopsy and/or BAL is recommended if possible. Monitor at each visit until return to ≤ Grade 1. Return to initial monitoring frequency if no recurrence.	Consider corticosteroids if infective origin is ruled out. Taper as medically indicated.	Rule out infection and discontinue everolimus.

6.2.10 Management of Hepatitis Reactivation/Flare

Reactivation of hepatitis B (HBV) has been observed in patients with cancer receiving chemotherapy (Yeo W. et al. 2004). Sporadic cases of hepatitis B reactivation have also been seen in this setting with everolimus. In cancer patients with hepatitis B, whether carriers or in chronic state, use of antivirals during anti-cancer therapy has been shown to reduce the risk of hepatitis B virus reactivation and associated morbidity and mortality (Loomba R. et al. 2008). A detailed assessment of hepatitis B or C medical history and risk factors must be done for all patients at screening, with testing performed prior to the first dose of everolimus.

Patients with known hepatitis, or positive hepatitis serology, are ineligible to enroll in this study.

Patients found to have positive hepatitis serology while on study may continue treatment but must receive appropriate hepatitis prophylaxis during the remainder of their treatment with everolimus and for 4 weeks after everolimus is discontinued.

Monitoring and prophylactic treatment for Hepatitis B reactivation

Table 6 provides details of monitoring and prophylactic therapy according to the baseline results of viral load and serologic markers testing.

Table 6 Action Required for Positive Hepatitis B Results While Receiving Everolimus

Test	Result	Result	Result	Result	Result
HBV-DNA	+	+ or -	-	-	-
HBsAg	+ or -	+	-	-	-
HBsAb	+ or -	+ or -	+	+ or -	-
HBcAb	+ or -	+ or -	+ or -	+	-
Recommendation	Prophylaxis treatment should be started 1-2 weeks prior to first dose of everolimus Monitor HBV-DNA every 4 - 8 weeks.		No prophylaxis treatment. Monitor HBV-DNA every 3-4 weeks.		No specific action.

Antiviral prophylaxis therapy should continue for at least 4 weeks after last dose of everolimus. Hepatitis B reactivation definition and management guidelines are defined below in Table 7.

Table 7 Guidelines for Management of Hepatitis B

HBV reactivation (with or without clinical signs and symptoms)*	
Baseline Results	**Actions**
Positive HBV-DNA OR Positive HBsAg **Reactivation is defined as:** Increase of 1 log in HBV-DNA relative to baseline HBV-DNA value OR New appearance of measurable HBV-DNA	Start a second antiviral medication AND Interrupt everolimus administration until resolution: • ≤ baseline HBV-DNA levels **If resolution occurs within ≤ 28 days, e**verolimus should be re-started at one dose lower, if available. (See Table 1 for dose levels available) If the patient is already receiving the lowest dose of everolimus according to the protocol, the patient should restart at the same dose after resolution. Both antiviral therapies should continue at least 4 weeks after last dose of everolimus. **If resolution occurs > 28 days,** Patients should discontinue everolimus but continue both antiviral therapies at least 4 weeks after last dose of everolimus.
Negative HBV-DNA and HBsAg AND Positive HBsAb (with no prior history of vaccination against HBV), OR Positive HBcAb **Reactivation is defined as: New appearance of measurable HBV-DNA**	Start first antiviral medication AND Interrupt everolimus administration until resolution: • ≤ undetectable (negative) HBV-DNA levels **If resolution occurs within ≤ 28 days, e**verolimus should be re-started at one dose lower, if available (See Table 1 for dose levels available). If the patient is already receiving the lowest dose of everolimus according to the protocol, the patient should restart at the same dose after resolution. Antiviral therapy should continue at least 4 weeks after last dose of everolimus. **If resolution occurs > 28 days**, discontinue everolimus but continue antiviral therapy at least 4 weeks after last dose of everolimus.

* All reactivations of HBV are to be recorded as Grade 3 (e.g. CTCAE Version 4.0 - Investigations/Other: Viral Reactivation) (http://evs.nci.nih.gov/ftp1/CTCAE/CTCAE), unless considered life threatening by the investigator, in which case they should be recorded as Grade 4. Date of viral reactivation is the date on which the rise or reappearance of HBV-DNA was recorded.

Monitoring and Management of Hepatitis C

Two groups of patients will require monitoring every 4 -8 weeks for HCV flare during this study:

- Patients with detectable HCV RNA-PCR test at baseline.
- Patients known to have a history of HCV infection, despite a negative viral load test at baseline (including those that were treated and considered "cured").

Definitions and management guidelines of hepatitis C flare are Table 8.

Table 8 Guidelines for Management of Hepatitis C Flare

Baseline Results	HCV Flare Definition*	HCV Flare Management
Detectable HCV-RNA	> 2 $\log_{10}$ IU/mL increase in HCV-RNA AND ALT elevation > 5 x ULN or 3 x baseline level, whichever is higher.	Discontinue everolimus
Knowledge of past hepatitis C infection with no detectable HCV-RNA	New appearance of detectable HCV-RNA AND ALT elevation > 5 x ULN or 3 x baseline level, whichever is higher.	Discontinue everolimus

* All flares of HCV are to be recorded as Grade 3 (e.g. CTCAE Version 3.0 - Investigations - Other: Viral Flare), unless considered life threatening by the investigator; in which case they should be recorded as Grade 4. Date of viral flare is the date on which both the clinical criteria described above were met (e.g., for a patient whose HCV-RNA increased by 2 logs on 01 JAN 2014 and whose ALT reached > 5 x ULN on 22 JAN 2014, the date of viral flare is 22 JAN 2014).

6.3 Other Grade 3 or 4 Non-Hematologic Toxicity

Adverse events associated with anti-estrogen therapy will vary by medication. The treating investigator should consult the currently approved package insert and watch for signs and symptoms of expected and possible AEs. There are no dose reduction sections for these therapies. If Grade 3 (or chronic Grade 2) toxicity attributed to anti-estrogen therapy occurs, the drug may be stopped for up to 2 weeks and then restarted. Patients may continue everolimus treatment if anti-estrogen therapy is held. If toxicity does not improve or resolve with a treatment break, or recurs and is intolerable to the patient, the anti-estrogen therapy should be discontinued.

7. STUDY ASSESSMENTS AND EVALUATIONS

7.1 Overview

All patients must visit the study center on the days specified within this protocol. The complete Schedule of Assessments for this study is shown in Appendix D. The baseline physical examination, medical history, ECOG PS, complete blood counts (CBCs), comprehensive metabolic profile (CMP), serum pregnancy test for pre/peri menopausal women (regardless of ovarian suppression), and urinalysis must be done ≤ 7 days prior to initiation of treatment. However, if these initial examinations are obtained within 72 hours of Cycle 1 Day 1 they do not have to be repeated. CT Scans and MRIs to document measureable disease must be performed ≤ 4 weeks prior to initiation of treatment.

Review medical history to determine if patient requires hepatitis B and/or hepatitis C testing. Hepatitis serology (See Appendix D) will be required at screening if the patient is in the following risk categories:

- Currently lives in (or has lived in) Asia, Africa, Central and South America, Eastern Europe, Spain, Portugal, or Greece.
- Has any of the following risk factors:
  - known or suspected past hepatitis B infection,
  - known or suspected past hepatitis C infection (including past interferon 'curative' treatment)
  - blood transfusion(s) prior to 1990,
  - current or prior IV drug use,
  - current or prior dialysis,
  - household contact with hepatitis B or hepatitis C infected person(s)
  - current or prior high-risk sexual activity,
  - body piercing or tattoos,
  - biological mother known to have hepatitis B infection
  - history suggestive of hepatitis B infection (e.g., dark urine, jaundice, right upper quadrant pain)or
  - any other risk factors as determined

Positive hepatitis serology at screening will make the patient ineligible for this study.

7.2 Baseline Study Assessments

The following information will be collected and procedures will be performed for each patient at screening:

- Informed consent form prior to performing any study related procedures
- Medical history
- Physical examination (PE), including measurements of height (baseline visit only), weight, and vital signs (resting heart rate, blood pressure, respiratory rate, oral temperature)
- ECOG PS (See Appendix A)
- Single ECG
- Concomitant medication review
- CBC including 3-part differential and platelets
- CMP to include: glucose, BUN, creatinine, sodium, potassium, chloride, calcium, CO2, alkaline phosphatase, AST, ALT, total bilirubin, total protein, and albumin (may be done up to 72 hours prior to treatment)

- Fasting serum glucose
- Fasting cholesterol, HDL, LDL, and triglycerides
- HBV-DNA, HBsAg, HBc-Ab, and HBs-Ab serologic markers (applies only to patients with risk factors)
- HCV RNA testing (applies only to patients with risk factors)
- PT or INR, and PTT (if abnormal, repeat as clinically indicated)
- Serum pregnancy test for all pre/peri menopausal women (regardless of ovarian suppression)
- Urinalysis
- Blood sample for the VeriStrat® assay (See Appendix F)
- Block of archived tumor tissue if available (slides acceptable, see lab manual for details)
- CT scan of chest
- CT scan of abdomen and pelvis
- Bone scan (if abnormal, must be repeated at restaging)

7.3 Study Treatment Assessments

7.3.1 Cycles 1 and 2, Day 1

- Update of medical history
- PE including measurement of weight and vital signs
- ECOG PS (See Appendix A)
- AE assessment
- Concomitant medication review
- Study drug compliance assessment (Cycle 2, Day1)
- CBC, including 3-part differential and platelets
- CMP
- Fasting serum glucose
- Cholesterol, HDL, LDL, and triglycerides (Repeat only if abnormal at baseline)

7.3.2 Cycle 3, Day 1

- Update of medical history
- PE including measurement of weight and vital signs
- ECOG PS (See Appendix A)

- AE assessment
- Concomitant medication review
- Study drug compliance assessment
- CBC, including 3-part differential and platelets
- CMP
- Fasting serum glucose
- Cholesterol, HDL, LDL, and triglycerides – every odd treatment cycle
- Serum or urine pregnancy test for all pre/peri menopausal women (regardless of ovarian suppression) every 2 cycles (8 weeks). If a urine pregnancy test is positive, it must be followed by a serum pregnancy test.
- CT scan of chest, abdomen and pelvis (See Section 7.4)
- Blood sample for the VeriStrat® assay (See Appendix F)

7.3.3 Cycle 4 +

- Update of medical history
- PE including measurement of weight and vital signs
- ECOG PS (See Appendix A)
- AE assessment
- Concomitant medication review
- Study drug compliance assessment
- CBC, including 3-part differential and platelets
- CMP
- Fasting serum glucose
- Cholesterol, HDL, LDL, and triglycerides-every odd treatment cycle (Repeat only if abnormal at baseline)
- Serum or urine pregnancy test for all pre/peri menopausal women (regardless of ovarian suppression) every 2 cycles (8 weeks). If a urine pregnancy test is positive, it must be followed by a serum pregnancy test.

7.3.4 Veri Strat® Assay Schedule

- Baseline visit (pre-treatment)
- Cycle 3 Day 1 visit (prior to treatment)
- At disease progression

- At the first Follow-Up visit after disease progression

7.4 Response Assessment Every 2 Cycles

Patients will be reevaluated for response to treatment after every 2 cycles of treatment, prior to the start of odd-numbered cycles. The following assessments will be performed:

- CT scans of chest
- CT of abdomen and pelvis
- Bone scan (if abnormal at baseline)

7.5 End of Study Treatment

The follow-up evaluations required after treatment ends (due to disease progression, or once the patient is discontinued due to unacceptable toxicity or decision to discontinue treatment by the patient or the study physician) are specified in Appendix D. **A blood sample for the VeriStrat® assay will be collected from patients at the time of disease progression.**

After withdrawal from protocol treatment, patients must be followed for adverse events for 30 calendar days after the last dose of study drug. The following assessments will be performed for the End of Study Treatment Visit:

- Update of medical history
- PE including measurement of weight and vital signs
- ECOG PS (See Appendix A)
- AE assessment
- Concomitant medication review
- Study drug compliance assessment
- CBC, including 3-part differential and platelets
- CMP
- Fasting serum glucose
- Cholesterol, HDL, LDL, and triglycerides
- Serum or urine pregnancy test for all pre/peri menopausal women (regardless of ovarian suppression). If a urine pregnancy test is positive, it must be followed by a serum pregnancy test.
- CT scan of chest, abdomen and pelvis
- Blood sample for the VeriStrat® assay (only if patient is discontinued due to disease progression)

7.6 Follow-up

7.6.1 Follow-up for Patients Who Discontinue Prior to Disease Progression

Patients who discontinue study treatment prior to the occurrence of disease progression will be followed every 3 months (± 1 month) from the date of last dose of study drug until disease progression or for up to 3 years from the start of treatment whichever comes first. Assessments at these visits will be performed as described in Appendix D. **A VeriStrat serum sample will be collected from all patients at the time of disease progression**.

7.6.2 Survival Follow-Up

After disease progression is documented, patients will be followed every 3 months (± 1 month) for survival (e.g., date and cause of death) for up to 3 years from the start of treatment or death whichever comes first. **A VeriStrat serum sample will be collected from all patients at the first Follow-Up Visit after disease progression**. For subsequent follow up, patients may be contacted during outpatient visits or by telephone.

8. DRUG FORMULATION, AVAILABILITY, ADMINISTRATION, AND TOXICITY INFORMATION

8.1 Everolimus

Investigational Product	Dosage Form and Strength	Manufacturer
Everolimus	5 mg	Novartis

8.1.1 Labeling, Packaging, and Supply

Everolimus will be supplied in 5mg tablets by Novartis Pharmaceuticals as individual patient packs.

At the beginning of every cycle, patients will be dispensed sufficient supplies until the next visit. Study drug compliance will be assessed at each patient visit. The research staff will count and document the amount of study drug taken and returned by the patient.

All study drugs must be kept in a secure place under appropriate storage conditions. Storage conditions for everolimus are included on the product label.

SCRI Innovations must be granted access on reasonable request to check drug storage, dispensing procedures, and accountability records.

8.1.2 Preparation and Administration of Everolimus

Everolimus is administered orally by the patients themselves, on an outpatient basis.

Everolimus should be taken by the patient once daily, at the same time every day, either consistently with food or consistently without food. Dietary habits around the time of everolimus intake should be as consistent as possible throughout the study. Each dose of everolimus should be taken with a whole glass of water. Everolimus pills should be swallowed whole, and not chewed or crushed.

For patients unable to swallow tablets, everolimus should be dispersed completely in 1oz of water by gently stirring. The glass should then be rinsed completely with another ounce of water and swallowed to ensure the entire dose is administered.

If vomiting occurs, no attempt should be made to replace the vomited dose.

8.1.3 Precautions and Risks Associated with Everolimus

Precautions and risks are located in the everolimus IB.

8.2 Anti-estrogen Therapy

Patients will be prescribed the last anti-estrogen therapy received prior to study entry. This medication (tamoxifen, fulvestrant, anastrozole, letrozole, exemestane, toremifine, or LHRH agonists in conjunction with anti-estrogen therapy) is to be administered in accordance with the directions on the label. Please refer to the US Package Insert for detailed information on how to administer medication.

8.2.1 Labeling, Packaging, and Supply of Anti-estrogen Therapy

See the appropriate anti-estrogen package insert or product information.

SCRI Innovations or its representatives must be granted access on reasonable request to check drug storage, dispensing procedures, and accountability records.

8.2.2 Preparation and Administration of Anti-estrogen Therapy

Refer to the appropriate anti-estrogen package insert or product information for detailed information on the preparation and administration associated with the use of the medication.

8.2.3 Precautions and Risks Associated with Anti-estrogen Therapy

Please refer to the appropriate package insert for detailed information on related risks.

8.3 Accountability for All Study drugs

The Principal Investigator (PI) or designee is responsible for accountability of all used and unused study drug supplies at the site.

All study drug inventories must be made available for inspection by the monitor, Sponsor or representatives of the aforementioned and regulatory agency inspectors upon request.

At the end of the study, all SCRI Innovations Drug Accountability Record Form(s) will be completed by the site and copies will be sent to the SCRI Innovations Regulatory Department. Study drug supplies must not be destroyed unless prior approval has been granted by the Sponsor or its representative. Please contact SCRI Innovations regarding disposal of any study drug.

9. RESPONSE EVALUATIONS AND MEASUREMENTS

Response and progression will be evaluated in this study using the Response Evaluation Criteria in Solid Tumors (RECIST) Version 1.1 (see Appendix E). Lesions are either measurable or non-measurable according to the criteria. The term "evaluable" in reference to measurability will not be used, as it does not provide additional meaning or accuracy.

10. STATISTICAL CONSIDERATIONS

10.1 Statistical Design

This is a multi-centered, open-labeled, Phase II study in MBC. The patient population includes locally recurrent or MBC patients with cytologically or histologically confirmed hormone receptor-positive breast cancer who have demonstrated disease progression on prior anti-estrogen therapy or therapies. Eligible patients must have evaluable or measurable disease per RECIST v1.1.

10.2 Sample Size Considerations

Results from the recently published BOLERO-2 study reported a median PFS of 2.8 months (as assessed by the treating investigator) that improved to 6.9 months as a result of the addition of everolimus in patients treated with exemestane after failing the NSAI therapy (Baselga J. et al. 2012). A similar median PFS is predicted in this study's patient population that is based on similar inclusion criteria. It is anticipated that everolimus in combination with the last anti-estrogen therapy on which the patient demonstrated disease progression, will result in an increase in median PFS from 2.8 months to 5 months in this refractory population.

Based on the above assumptions, given a follow-up period of 12 months after the completion of enrollment (18 months), with a 5% alpha and a one-sided test of hypothesis, a sample size of 42 will provide 80% power to detect an improvement in median PFS from 2.8 months to 5 months in the patients treated with the combination of everolimus with anti-estrogen therapy. Allowing for 8-10% inevaluable patients, the total number of patients to be enrolled is 46 patients.

Sample size calculations are based on SWOGSTAT online sample size calculator for one-arm non-parametric survival endpoints (http://www.swogstat.org/stat/public/one_nonparametric_survival.htm).

10.3 Analysis Population

The following analysis populations will be used:

- Efficacy Evaluable Population is defined as all patients who receive at least 1 cycle of study treatment and have at least one post-baseline assessment. (Patients who discontinue treatment during Cycle 1 will not be replaced in the study.)
- Safety Population is defined as all patients who have received any dose of study treatment.

10.4 Data Analysis

Descriptive statistics, including mean, median, standard deviations and ranges for all continuous measures will be tabulated and reported. Percentages and frequencies for all categorical measures will also be presented. Time to events endpoints will be reported using Kaplan-Meier estimates, with 95% confidence intervals (CI) for median time to event.

All statistical analyses will be performed using SAS v9.3 or higher.

10.4.1 Demographics and Baseline Characteristics

Demographic and baseline disease characteristics will be summarized. Data to be tabulated will include demographic features such as age, sex and race, as well as disease-specific characteristics.

The number and percentages of patients enrolled, treated, completed the treatment/study and withdrawn from treatment/study for any reasons will be presented overall.

10.4.2 Efficacy Analysis

All efficacy analyses will be performed using the Efficacy Evaluable Population.

- Overall Response Rate (ORR) is defined as the proportion of patients with observed complete response (CR) or partial response (PR) according to the RECIST v1.1 criteria.

- Clinical Benefit Rate (CBR) is defined as the proportion of patients with CR, PR or SD x 6 months according to the RECIST v1.1 criteria.

    - For ORR and CBR, patients without a post-baseline tumor assessment will be classed as not evaluable (NE) and considered as non-responder.

- Progression Free Survival (PFS), defined as the time from the first day of study drug administration (Day 1) to disease progression (event) as defined by the RECIST v1.1 criteria, or death (event) on study. Patients who are alive and free from disease progression will be censored at the date of last tumor assessment. Patients who receive non-protocol therapy (subsequent therapy) prior to incurring an event will be censored at the date of last tumor assessment prior to the start of subsequent therapy. Patients who do not have a post-baseline tumor assessment will be censored at the date of first treatment (Day 1).

- Overall Survival (OS), defined as the time from the first day of study drug administration (Day 1) or death on study. Patients who are alive will be censored at the date of last known date alive.

- Duration of Response (DOR), is defined as the time from the first date of CR or PR to disease progression or death as defined by the RECIST v1.1 criteria. Patients who are alive and free from disease progression will be censored at the date of last tumor

assessment. Patients who receive non-protocol therapy (subsequent therapy) prior to incurring an event will be censored at the date of last tumor assessment prior to the start of subsequent therapy. Only those patients who achieved CR or PR will be included in the summaries of DOR.

- Percentage of patients progression-free at 4 and 6 months, defined as the proportion of patients who are progression-free as defined by the RECIST v1.1 starting from the date of their first treatment.

For ORR and CBR, the estimates and the associated 95% CI (based on both asymptotic normal approximation and exact binomial methods) will be calculated.

Best overall response will be tabulated: CR, PR, SD, PD and not evaluable (NE).

For PFS, DOR and OS, Kaplan-Meier curves will be generated and the median time to event and the associated 95% CI will be provided.

The number and percentage of patients progression-free at 4 and 6 months will be provided.

10.4.3 Safety Analysis

Safety will be assessed through the analysis of the reported incidence of treatment-emergent AEs. Treatment-emergent AEs are those with an onset on or after the initiation of therapy, and will be graded according to NCI CTCAE v 4.03. A copy of CTCAE scoring system may be downloaded from: http://evs.nci.nih.gov/ftp1/CTCAE/CTCAE_4.03_2010-06-14_QuickReference_8.5x11.pdf.

The AEs will be coded using Medical Dictionary for Regulatory Activities (MedDRA), and summarized using system organ class and preferred term for all patients in the Safety Population. In addition, summaries of SAEs, AEs leading to treatment discontinuation, AEs by maximum NCI CTCAE grade, and AEs related to study treatment will also be presented.

Other safety endpoints including laboratory results, vital signs and ECG findings will be summarized for all patients in the Safety Population.

10.4.4 Pharmacokinetics/Pharmcodynamics

PK/PD analyses will not be provided for this study.

10.5 Analysis Time Points

10.5.1 Final Analysis

The final analysis of the study will occur when 42 patients have discontinued treatment, progressed, died or are still on treatment but have at least 12 months of follow up (time from first treatment until last tumor assessment).

10.5.2 Planned Interim Analysis

No interim analyses are planned for this study.

10.5.3 Safety Review

No early safety reviews are planned for this study.

10.5.4 Efficacy Review

No early efficacy reviews are planned for this study.

10.6 Data Monitoring Committee

A Data Monitoring Committee (DMC) will not be utilized for this study.

10.7 Steering Committee

A Steering Committee will not be utilized for this study.

11. SAFETY REPORTING AND ANALYSES

Safety assessments will consist of monitoring and recording protocol-defined AEs and Serious Adverse Events (SAEs), measurement of protocol-specified hematology, clinical chemistry, and urinalysis variables, measurement of protocol-specified vital signs, and other protocol-specified tests that are deemed critical to the safety evaluation of the study drug.

The Principal Investigator is responsible for recognizing and reporting SAEs to the SCRI Innovations Safety Department (SD) (see Section 11.2). It is the Sponsor's responsibility to report relevant SAEs to the applicable local, national, or international regulatory bodies. In addition, Investigators must report SAEs and follow-up information to their responsible IRB/EC according to the policies of that IRB/EC.

The Principal Investigator is also responsible for ensuring that every staff member involved in the study is familiar with the content of this section.

11.1 Definitions

11.1.1 Adverse Events

Adverse event means any untoward medical occurrence associated with the use of a drug in humans, whether or not considered drug related. An adverse event (also known as adverse experience) can be any unfavorable and unintended sign (e.g., an abnormal laboratory finding), symptom, or disease temporarily associated with the use of a drug, without any judgement about causality. An adverse event can arise with any use of the drug (e.g., off-label use, use in combination with another drug) and with any route of administration, formulation, dose or including overdose.

11.1.2 Serious Adverse Event

An AE or a suspected adverse reaction (SAR) is considered "serious" if it results in any of the following outcomes:

- **Death**
- **A life-threatening AE**
- **Inpatient hospitalization of at least 24-hours or prolongation of existing hospitalization**
- **A persistent or significant incapacity or substantial disruption of the ability to conduct normal life functions**
- **A congenital anomaly/birth defect**

Important medical events that may not result in death, be life-threatening, or require hospitalization may be considered serious when, based upon appropriate 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. Examples of such medical events include allergic bronchospasm requiring intensive treatment in an emergency room or at home, blood dyscrasias or convulsions that do not result in hospitalization, or development of drug dependency or drug abuse.

It is important to distinguish between "serious" and "severe" AE, as the terms are not synonymous. Severity is a measure of intensity; however, an AE of severe intensity need not necessarily be considered serious. Seriousness serves as the guide for defining regulatory reporting obligations. "Serious" is a regulatory definition and is based on patient/event outcome or action usually associated with events that pose a threat to a patient's life or vital functions. For example, nausea which persists for several hours may be considered severe nausea, but may not be considered an SAE. On the other hand, a stroke which results in only a limited degree of disability may be considered only a mild stroke, but would be considered an SAE. Severity and seriousness should be independently assessed when recording AEs on the eCRF and SAEs on the SAE Report Form.

11.1.3 Adverse Reaction

An adverse reaction means any adverse event caused by a drug. Adverse reactions are a subset of all suspected adverse reactions where there is a reason to conclude that the drug caused the event.

11.1.4 Suspected Adverse Reaction

Suspected adverse reaction means any adverse event for which there is a reasonable possibility that the drug caused the adverse event. Reasonable possibility means that there is evidence to suggest a causal relationship between the drug and the adverse event. A suspected adverse reaction implies a lesser degree of certainty about causality than adverse reaction, which means any adverse event caused by a drug.

11.1.5 Recording and Reporting of Adverse Events

Recording of Adverse Events

All AEs of any patient during the course of the research study will be recorded in the eCRF, and the investigator will give his or her opinion as to the relationship of the AE to the study drug treatment (i.e., whether the event is related or unrelated to study drug administration).

All AEs should be documented. A description of the event, including its date of onset and resolution, whether it constitutes a serious adverse event (SAE) or not, any action taken (e.g., changes to study treatment), and outcome, should be provided, along with the investigator's assessment of causality (i.e., the relationship to the study treatment[s]). For an AE to be a suspected treatment-related event there should be at least a reasonable possibility of a causal relationship between the protocol treatment and the AE. Adverse events will be graded according to the NCI CTCAE v4.0, and changes will be documented.

If the AE is serious, it should be reported immediately to SCRI Innovations SD. Other untoward events occurring in the framework of a clinical study are to be recorded as AEs (i.e., AEs that occur prior to assignment of study treatment that are related to a protocol-mandated intervention, including invasive procedures such as biopsies, medication washout, or no treatment run-in).

Any clinically significant signs and symptoms; abnormal test findings; changes in physical examination; hypersensitivity; and other measurements that occur will be reported as an AE, and collected on the relevant eCRF screen.

Test findings will be reported as an AE if: the test result requires an adjustment in the study drug(s) or discontinuation of treatment, and/ or test findings require additional testing or surgical intervention, a test result or finding is associated with accompanying symptoms, or a test result is considered to be an AE by the investigator.

Reporting Period for Adverse Events

All AEs regardless of seriousness or relationship to everolimus treatment (called study treatment), spanning from the the start of study treatment, until 30 calendar days after discontinuation or completion of study treatment as defined by the clinical study for that patient, are to be recorded on the corresponding screen(s) included in the eCRF.

All AEs resulting in discontinuation from the study should be followed until resolution or stabilization. All new AEs occurring during this period must be reported and followed until resolution unless, in the opinion of the investigator, the AE or laboratory abnormality/ies are not likely to improve because of the underlying disease. In this case, the investigators must record his or her reasoning for this decision in the patient's medical record and as a comment on the eCRF screen.

After 30 days of completion of protocol-specific treatment or discontinuation, only AEs, SAEs, or deaths assessed by the investigator as treatment related are to be reported.

11.1.6 Assessment of Adverse Events

All AEs and SAEs whether volunteered by the patient, discovered by study personnel during questioning, or detected through physical examination, laboratory test, or other means will be

reported appropriately. Each reported AE or SAE will be described by its duration (i.e., start and end dates), regulatory seriousness criteria if applicable, suspected relationship to the study drug (see following guidance), and actions taken.

To ensure consistency of AE and SAE causality assessments, investigators should apply the following general guideline:

> **YES:** There is a plausible temporal relationship between the onset of the AE and administration of the study medication, and the AE cannot be readily explained by the patient's clinical state, intercurrent illness, or concomitant therapies, and/or the AE follows a known pattern of response to the study drug, and/or the AE abates or resolves upon discontinuation of the study drug or dose reduction and, if applicable, reappears upon re-challenge.
>
> **NO:** Evidence exists that the AE has an etiology other than the study drug (e.g., pre-existing medical condition, underlying disease, intercurrent illness, or concomitant medication), and/or the AE has no plausible temporal relationship to study drug administration (e.g., cancer diagnosed 2 days after first dose of study drug).

11.2 Serious Adverse Event Reporting by Investigators

Adverse events classified by the treating investigator as serious require expeditious handling and reporting to SCRI Innovations Safety Department in order to comply with regulatory requirements. Determination of life-threatening or serious is based on the opinion of either the Sponsor or the Investigator.

Serious AEs may occur at any time from the start of study treatment through the 30 day follow-up period after the last study treatment. **The SCRI Innovations Safety Department must be notified of all SAEs, regardless of causality, within 24 hours of the first knowledge of the event by the treating physician or research personnel.**

To report a SAE, the SAE Report Form should be completed with the necessary information.

The SAE report should be sent to SCRI Innovations Safety Department via fax or e-mail using the using the following contact information (during both business and non-business hours):

SCRI Innovations Safety Department

Safety Dept. Fax #: 1-866-807-4325

Safety Dept. Email: CANN.SAE@SCRI-Innovations.com

Transmission of the SAE report should be confirmed by the site personnel submitting the report.

Follow-up information for SAEs and information on non-serious AEs that become serious should also be reported to SCRI Innovations Safety Department as soon as it is available; these reports should be submitted using the SCRI Innovations SAE Report Form. The detailed SAE reporting process will be provided to the sites in the SAE reporting guidelines contained in the study reference manual.

Investigators must report SAEs and follow-up information to their responsible IRB according to the policies of the responsible IRB.

11.3 Recording of Adverse Events and Serious Adverse Events

11.3.1 Diagnosis versus Signs and Symptoms

All AEs should be recorded individually in the patient's own words (verbatim) unless, in the opinion of the Principal Investigator or designated physician, the AEs constitute components of a recognized condition, disease, or syndrome. In the latter case, the condition, disease, or syndrome should be named rather than each individual sign or symptom. If a constellation of signs and/or symptoms cannot be medically characterized as a single diagnosis or syndrome at the time of reporting, each individual event should be recorded as an AE or SAE as appropriate on the relevant form(s) (SAE Report Form and/or AE eCRF screen). If a diagnosis is subsequently established, it should be reported as follow-up information is available. If a diagnosis is determined subsequent to the reporting of the constellation of symptoms, the signs/symptoms should be updated to reflect the diagnosis.

Progression of malignancy (including fatal outcomes), if documented by use of appropriate method (for example, as per RECIST criteria for solid tumors), should not be reported as an SAE.

11.3.2 Persistent or Recurrent Adverse Events

A persistent AE is one that extends continuously, without resolution, between patient evaluation time points. Such events should only be recorded once on the SAE Report Form and/or the AE eCRF screen. If a persistent AE becomes more severe or lessens in severity, it should be recorded on a separate SAE Report Form and/or AE eCRF screen.

A recurrent AE is one that occurs and resolves between patient evaluation time points, and subsequently recurs. All recurrent AEs should be recorded on an SAE Report Form and/or AE eCRF screen.

11.3.3 Abnormal Laboratory Values

If an abnormal laboratory value or vital sign is associated with clinical signs and/or symptoms, the sign or symptom should be reported as an AE or SAE, and the associated laboratory value or vital sign should be considered additional information that must be collected on the relevant eCRF screen. If the laboratory abnormality is a sign of a disease or syndrome, only the diagnosis needs to be recorded on the SAE Report Form or AE eCRF screen.

Abnormal laboratory values will be reported as an AE if: the laboratory result requires an adjustment in the study drug(s) or discontinuation of treatment, and/ or laboratory findings require additional testing or surgical intervention, a laboratory result or finding is associated with accompanying symptoms, or a laboratory result is considered to be an AE by the investigator.

11.3.4 Deaths

Deaths that occur during the protocol-specified AE reporting period that are attributed by the Investigator solely to progression of disease will be recorded on the "Study Discontinuation" eCRF screen. All other on study deaths, regardless of attribution, will be recorded on an SAE Report Form and expeditiously reported to the SCRI Innovations Safety Department.

When recording a SAE with an outcome of death, the event or condition that caused or contributed to the fatal outcome should be recorded as the single medical concept on the SAE Report Form and Adverse Event screen of the eCRF. If the cause of death is unknown and cannot be ascertained at the time of reporting, record "Death NOS" on the eCRF Adverse Event screen. During post-study survival follow-up, deaths attributed to progression of disease will be recorded only on the "After Progressive Disease Follow-Up" eCRF screen.

11.3.5 Hospitalization, Prolonged Hospitalization, or Surgery

Any AE that results in hospitalization of >24 hours or prolongation of pre-existing hospitalization should be documented and reported as an SAE unless specifically instructed otherwise in this protocol. There are some hospitalizations that do not require reporting as an SAE.

Treatment within or admission to the following facilities is not considered to meet the criteria of "inpatient hospitalization" (although if any other SAE criteria are met, the event must still be treated as an SAE and immediately reported):

- Emergency Department or Emergency Room
- Outpatient or same-day surgery units
- Observation or short-stay unit
- Rehabilitation facility
- Hospice or skilled nursing facility
- Nursing homes, Custodial care or Respite care facility

Hospitalization during the study for a pre-planned surgical or medical procedure (one which was planned prior to entry in the study), does not require reporting as an SAE to the SCRI Innovations Safety Department.

11.3.6 Pre-Existing Medical Conditions

A pre-existing medical condition is one that is present at the start of the study. Such conditions should be recorded on the General Medical History eCRF screen. A pre-existing medical condition should be recorded as an AE or SAE only if the frequency, severity, or character of the condition worsens during the study. When recording such events on an SAE Report Form and/or AE eCRF screen, it is important to convey the concept that the pre-existing condition has changed by including applicable descriptors.

11.3.7 New Cancers

The development of a new primary cancer should be regarded as an AE and will generally meet at least one of the seriousness criteria (see Section 11.2). New primary cancers are those that are not the primary reason for the administration of the study treatment and have developed after the inclusion of the patient into the study. They do not include metastases of the original cancer. Symptoms of metastasis or the metastasis itself should not be reported as an AE/SAE, as they are considered to be disease progression.

11.3.8 Pregnancy, Abortion, Birth Defects/Congenital Anomalies

Pregnancy, abortion, birth defects, and congenital anomalies are events of special interest. Please refer to Section 11.4 for specific instructions.

11.3.9 Everolimus Overdose

Symptomatic and non-symptomatic overdose must be reported in the eCRF. Any accidental or intentional overdose with the study treatment that is symptomatic, even if not fulfilling a seriousness criterion, is to be reported to the SCRI Innovations Safety Department no greater than 24 hours from first knowledge of the event using the corresponding screens in the eCRF and following the same process described for SAE reporting (see Section 11.2) if the overdose is symptomatic.

For information on how to manage an overdose of everolimus, see the Investigator's Brochure.

11.4 Protocol-Defined Events of Special Interest

The following are events of special interest, and will need to be reported expeditiously (see Section 11.2). These events include the following:

Pregnancy, Abortion, Birth Defects/Congenital Anomalies:

If a patient becomes pregnant while enrolled in the study, a Pregnancy Form (a paper report form) should be completed and faxed to SCRI Innovations Safety Department. SCRI Innovations Safety Department should be notified expeditiously, irrespective of whether or not it meets the criteria for expedited reporting. Abortions (spontaneous, accidental, or therapeutic) must also be reported to SCRI Innovations Safety Department.

Congenital anomalies/birth defects always meet SAE criteria, and should therefore be expeditiously reported as an SAE, using the previously described process for SAE reporting. A Pregnancy Form should also have been previously completed, and will need to be updated to reflect the outcome of the pregnancy.

Sexually active males must use a condom during intercourse while taking the drug and for 8 weeks after stopping treatment and should not father a child in this period.

A condom is required to be used also by vasectomized men in order to prevent delivery of the drug via seminal fluid.

Female partners of male patients must also be advised to use one of the following contraception methods: Use of (1) oral, injected, implanted or other hormonal methods of contraception, or (2) intrauterine device (IUD) or intrauterine system (IUS), or (3) prior male/female sterilization.

11.5 Sponsor Serious Adverse Event Reporting Requirements

SCRI Innovations Safety Department will forward SAE information to Novartis Pharmaceuticals Clinical Safety and Epidemiology Department (CS&E) at Fax #: (877) 778-9739 within 24 hours of SCRI Innovations Safety Department personnel becoming aware of the SAE.

SCRI Innovations is responsible for reporting relevant SAEs to the competent authority, other applicable regulatory authorities, and participating investigators, in accordance with International Conference on Harmonisation (ICH) guidelines, FDA regulations.

11.5.1 SCRI Innovations Safety Department Assessment of Unexpected

SCRI Innovations SD is responsible for assessing an adverse event or suspected adverse event as "unexpected."

An adverse event or suspected adverse reaction is considered "unexpected" when the following conditions occur:

- Event(s) is not mentioned in the IB (or current US Package Insert)
- Event(s) is not listed at the specificity or severity that has been observed
- An event(s) is not consistent with the General Investigative Plan or in the current application
- Includes AEs or SAR that may be anticipated from the pharmacological properties of the study drug, or that occur with members of the drug class, but that have previously been observed under investigation

When applicable, an unexpected adverse event may also apply to an event that is not listed in the current US Package Insert (USPI) or an event that may be mentioned in the USPI, but differs from the event because of greater severity or specificity.

Known as Suspected Unexpected Serious Adverse Reactions (SUSAR), these events suspected (by the Investigator or Sponsor) to be related to the study drug, are unexpected (not listed in the Investigator's Brochure or USPI), and are serious (as defined by the protocol) and require expedient submission to relevant health authorities within 7 days (fatal or life-threatening event) or 15 days (all serious events), or as defined by law. The term SUSAR is used primarily in the reporting of events to regulatory authorities.

Expected AEs are those events that are listed or characterized in the Package Insert or current IB.

11.5.2 Sponsor Reporting for Clinical Studies Under an Investigational New Drug Application

All written IND Safety Reports submitted to the FDA by the SCRI Innovations Safety Department must also be faxed to pharmaceutical company(ies) that are supporting the study with either funding or drug supply:

Novartis Pharmaceuticals
Clinical Safety and Epidemiology Department (CS&E)
Fax #: (877) 778-9739

12. QUALITY ASSURANCE AND QUALITY CONTROL

12.1 Study Monitoring, Auditing, and Inspecting

The investigator will permit study-related monitoring, quality audits, and inspections by SCRI Innovations or its representative(s), government regulatory authorities, and the IRB of all study-related documents (e.g., source documents, regulatory documents, data collection instruments, case report forms). The investigator will ensure the capability for inspections of applicable study-related facilities. The investigator will ensure that the study monitor or any other compliance or Quality Assurance reviewer is given access to all study-related documents and study-related facilities.

At SCRI Innovations discretion, Source Document Verification (SDV) may be performed on all data items or a percentage thereof.

Participation as an investigator in this study implies the acceptance of potential inspection by government regulatory authorities, SCRI Innovations or its representative(s).

13. ETHICAL, FINANCIAL, AND REGULATORY CONSIDERATIONS

This research study will be conducted according to the standards of Good Clinical Practice outlined in the ICH E6 Tripartite Guideline and CFR Title 21 part 312, applicable government regulations, institutional research policies and procedures and any other local applicable regulatory requirement(s).

13.1 Institutional Review Board Approval

The clinical study protocol, informed consent form (ICF), IB, available safety information, patient documents (e.g., study diary), patient recruitment procedures (e.g., advertisements), information about payments (i.e., Principal Investigator payments) and compensation available to the patients and documentation evidencing the Principal Investigator's qualifications should be submitted to the IRB for ethical review and approval if required by local regulations, prior to the study start.

The Principal Investigator will follow all necessary regulations to ensure appropriate, initial, and on-going, IRB study review. The Principal Investigator (as appropriate) must submit and, where necessary, obtain approval from the IRB for all subsequent protocol amendments and changes to the informed consent document. Investigators will be advised by SCRI Innovations or designee whether an amendment is considered substantial or non-substantial and whether it requires submission for approval or notification only to an IRB.

Safety updates for everolimus, will be prepared by SCRI Innovations or its representative as required, for distribution to the Investigator(s) and submission to the relevant IRB.

13.2 Regulatory Approval

SCRI Innovations will be responsible for compliance with FDA regulations and guidance documents, including Good Clinical Practice. Clinical investigators are responsible for understanding and complying with regulations and guidance documents pertaining to obligations of Investigators, including assurance of initial and ongoing review and approval by a cognizant IRB. Furthermore, investigators must adhere to all regulations and guidance documents regarding informed consent of participating patients.

13.3 Informed Consent

Informed consent is a process by which a patient voluntarily confirms his or her willingness to participate in a particular study after having been informed of all aspects of the study that are relevant to the patient's decision to participate. Informed consent is documented by means of a written, signed, and dated informed consent form (ICF).

The ICF will be submitted for approval to the IRB that is responsible for review and approval of the study. Each consent form must include all of the relevant elements currently required by the FDA, as well as local county authority or state regulations and national requirements.

Before recruitment and enrollment into the study, each prospective candidate will be given a full explanation of the research study. Once the essential information has been provided to the prospective candidate, and the Investigator is sure that the individual candidate understands the implications of participating in this research study, the candidate will be asked to give consent to participate in the study by signing an ICF. A notation that written informed consent has been obtained will be made in the patient's medical record. A copy of the ICF, to include the patient's signature, will be provided by the investigator to the patient.

If an amendment to the protocol substantially alters the study design or the potential risks to the patients, the patient's consent to continue participation in the study should be obtained.

13.3.1 Confidentiality

13.3.1.1 Patient Confidentiality

Confidentiality of patient's personal data will be protected in accordance with the Health Insurance Portability and Accountability Act of 1996 (HIPAA). HIPAA regulations require that, in order to participate in the study, a patient must sign an authorization form for the study that he or she has been informed of following:

- What protected health information (PHI) will be collected from patients in this study
- Who will have access to that information and why
- Who will use or disclose that information
- That health information may be further disclosed by the recipients of the information, and that if the information is disclosed the information may no longer be protected by federal or state privacy laws

- The information collected about the research study will be kept separate from the patient's medical records, but the patient will be able to obtain the research records after the conclusion of the study
- Whether the authorization contains an expiration date
- The rights of a research patient to revoke his or her authorization

In the event that a patient revokes authorization to collect or use his or her PHI, the investigator, by regulation, retains the ability to use all information collected prior to the revocation of patient authorization. For patients that have revoked authorization to collect or use PHI, attempts should be made to obtain permission to collect at least vital status (i.e., that the patient is alive) at the end of their scheduled study period.

In compliance with ICH GCP guidelines and applicable parts of 21 CFR it is a requirement that the investigator and institution permit authorized representatives of the Sponsor, the regulatory authorities and the IRB direct access to review the patient's original medical records at the site for verification of study-related procedures and data.

Measures to protect confidentiality include: only a unique study number and initials will identify patients in the eCRF or other documents submitted to SCRI Innovations. This information, together with the patient's date of birth, will be used in the database for patient identification. Patient names or addresses will not be entered in the eCRF. No material bearing a patient's name will be kept on file by SCRI Innovations. Patients will be informed of their rights within the ICF.

13.3.1.2 Investigator and Staff Information

Personal data of the investigators and sub-investigators may be included in the SCRI Innovations database, and shall be treated in compliance with all applicable laws and regulations. When archiving or processing personal data pertaining to the investigator or sub investigator, SCRI Innovations shall take all appropriate measures to safeguard and prevent access to this data by any unauthorized party.

13.4 Financial Information

SCRI Innovations is the sponsor of the clinical study. Novartis Pharmaceuticals Corp. will provide funding to SCRI Innovations for this study and will also provide the study drug everolimus for all study participants. The physicians participating in this study will receive compensation from SCRI Innovations.

The finances for this clinical study will be subject to a separate written agreement between SCRI Development Innovations, LLC and applicable parties. Any Investigator financial disclosures as applicable to 21CFR Part 54 shall be appropriately provided.

14. RESEARCH RETENTION AND DOCUMENTATION OF THE STUDY

14.1 Amendments to the Protocol

Amendments to the protocol shall be planned, documented, signature authorized, and submitted to the FDA if required prior to implementation.

If an amendment to the protocol is required, the amendment will be originated and documented by SCRI Innovations. All amendments require review and approval of all pharmaceutical companies and the Principal Investigator supporting the study. The written amendment must be reviewed and approved by SCRI Innovations, and submitted to the IRB at the investigator's facility for the board's approval.

Amendments specifically involving change to study design, risk to patient, increase to dosing or exposure, patient number increase, addition or removal of new tests or procedures, shall be reviewed and approved by the IRB of record for the Investigator's facility.

The amendment will be submitted formally to the FDA or other regulatory authorities by the Sponsor as applicable and IRB approval obtained, and specifically when an increase to dosing or patient exposure and/or patient number has been proposed; or, when the addition or removal of an Investigator is necessitated.

Protocol amendments requiring IRB approval which include but are not limited to the following:

- Change to study design
- Risk to patient
- Increase to dose or patient exposure to drug
- Patient number increase
- Addition or removal of tests and / or procedures
- Addition/removal of a new Investigator

It should be further noted that, if an amendment to the protocol substantially alters the study design or the potential risks to the patients, their consent to continue participation in the study should be obtained.

14.2 Documentation Required to Initiate the Study

Before the study may begin certain documentation required by FDA regulations and ICH GCP must be provided by the Investigator. The required documentation should be submitted to:

SCRI Innovations
Regulatory Department
3322 West End Avenue, Suite 900
Nashville, TN 37203

Documents at a minimum required to begin a study in the US include, but are not limited to, the following:

- A signature-authorized protocol and contract
- A copy of the official IRB approval of the study and the IRB members list
- Current Curricula Vitae for the principal investigator and any associate investigator(s) who will be involved in the study
- Indication of appropriate accreditation for any laboratories to be used in the study and a copy of the normal ranges for tests to be performed by that laboratory
- Original Form FDA 1572 (Statement of Investigator), appropriately completed and signed
- A copy of the IRB-approved consent form
- Financial disclosure forms for all investigators listed on Form FDA 1572 (if applicable)
- Site qualification reports, where applicable
- Verification of Principal Investigator acceptability from local and/or national debarment list(s)

14.3 Study Documentation and Storage

The Principal Investigator must maintain a list of appropriately qualified persons to whom he/she has delegated study duties and should ensure that all persons assisting in the conduct of the study are informed of their obligations. All persons authorized to make entries and/or corrections on the eCRFs are to be included on this document. All entries in the patient's eCRF are to be supported by source documentation where appropriate.

Source documents are the original documents, data, records, and certified copies of original records of clinical findings, observations, and activities from which the patient's eCRF data are obtained. These can include, but are not limited to, hospital records, clinical and office charts, laboratory, medico-technical department and pharmacy records, diaries, microfiches, ECG traces, copies or transcriptions certified after verification as being accurate and complete, photographic negatives, microfilm or magnetic media, X-rays, and correspondence.

The Principal Investigator and each study staff member is responsible for maintaining a comprehensive and centralized filing system (e.g., regulatory binder or investigator study file [ISF]) of all study-related (essential) documentation, suitable for inspection at any time by representatives from SCRI Innovations and/or applicable regulatory authorities. The ISF must consist of those documents that individually or collectively permit evaluation of the conduct of the study and the quality of the data produced. The ISF should contain as a minimum all relevant documents and correspondence as outlined in ICH GCP Section 8 and 21 CFR Part 312.57, including key documents such as the IB and any amendments, protocol and any amendments, signed ICFs, copies of completed eCRFs, IRB approval documents, Financial Disclosure forms, patient identification lists, enrollment logs, delegation of authority log, staff qualification documents, laboratory normal ranges, records relating to the study drug including accountability records. Drug accountability records should, at a minimum, contain information regarding receipt, shipment, and disposition. Each form of drug accountability record, at a minimum, should contain Principal Investigator name, date drug shipped/received, date, quantity and batch/code, or lot number for identity of each shipment. In addition, all original source documents supporting entries in the eCRF must be maintained and be readily available.

SCRI Innovations shall maintain adequate investigational product records and financial interest records as per 21CFR Part 54.6 and Part 312.57 for no less than 2 years after the last marketing application has been approved by FDA; or, in the event that a marketing application will not be submitted to FDA, for no less than 2 years after the completion of the study.

The IRB shall maintain adequate documentation and records of IRB activities as per 21CFR Part 56.115 for at least 3 years after completion of the research.

The Investigator shall maintain adequate records of drug disposition, case histories, and any other study-related records as per 21 CFR Part 312.62 for no less than 2 years after the last marketing application has been approved by FDA; or, in the event that the marketing application will not be submitted to FDA, for no less than 2 years after the completion of the study.

To enable evaluations and/or audits from regulatory authorities or from SCRI Innovations or its representative, the investigator additionally agrees to keep records, including the identity of all participating patients (sufficient information to link records e.g., eCRF records, and medical records), all original, signed ICFs, and copies of all eCRF records, SAE Reporting forms, source documents, detailed records of treatment disposition, and related essential regulatory documents. The documents listed above must be retained by the investigator for as long as needed to comply with national and international regulations (generally 2 years after discontinuing clinical development or after the last marketing approval). SCRI Innovations will notify the investigator(s)/institutions(s) when the study-related records are no longer required.

If the investigator relocates, retires, or for any reason withdraws from the study, both SCRI Innovations and its representative should be prospectively notified. The study records must be transferred to an acceptable designee, such as another investigator, another institution, or to SCRI Innovations. The investigator must obtain SCRI Innovations written permission before disposing of any records, even if retention requirements have been met. All study files will be maintained by SCRI Innovations throughout the study.

14.4 Data Collection

The study eCRF is the primary data collection instrument for the study. Case report forms will be completed using the English language and should be kept current to enable the Sponsor to review the patients' status throughout the course of the study.

In order to maintain confidentiality, only study number, patient number, initials and date of birth will identify the patient in the eCRF. If the patient's name appears on any other document (e.g., laboratory report), it must be obliterated on the copy of the document to be supplied to SCRI Innovations and replaced instead with the patient number and patient's initials. The investigator will maintain a personal patient identification list (patient numbers with corresponding patient identifiers) to enable records to be identified and verified as authentic. Patient data/information will be kept confidential, and will be managed according to applicable local, state, and federal regulations.

All data requested in the eCRF must be supported by and be consistent with the patient's source documentation. All missing data must be explained. When a required laboratory test, assessment, or evaluation has not been done or an "Unknown" box is not an option on the eCRF, a note should be created verifying that the field was "Not Done" or "Unknown." For any entry errors made, the error(s) must be corrected, and a note explaining the reason for change should be provided.

The investigator will electronically sign and date the patient eCRF casebook indicating that the data in the eCRF has been assessed. Each completed eCRF will be signed and dated by the Principal Investigator, once all data for that patient is final.

14.5 Disclosure and Publication Policy

All information provided regarding the study, as well as all information collected/documented during the course of the study, will be regarded as confidential. SCRI Innovations reserves the right to release literature publications based on the results of the study. Results from the study will be published/presented as per SCRI Innovations publication process.

Inclusion of the investigator in the authorship of any multicenter publication will be based upon substantial contribution to the design, analysis, interpretation of data, drafting and/or critically revising any manuscript(s) derived from the study. The investigator acknowledges that the study is part of a multicenter study and agrees that any publication by the investigator of the results of the study conducted at research site shall not be made before the first multicenter publication. In the event there is no multicenter publication within fifteen (15) months after the study has been completed or terminated at all study sites, and all data has been received, the investigator shall have the right to publish its results from the study, subject to the notice requirements described herein and subject to acknowledgement of the funding partner as appropriate. Investigator shall provide the funding partner thirty (30) days to review a manuscript, and 1 week (7 days) to review any poster presentation, abstract or other written or oral material which describes the results of the study for the purpose only of determining if any confidential or patentable information is disclosed thereby. If the funding partner requests in writing, the investigator shall withhold any publication or presentation an additional sixty (60) days solely to permit the

funding partner to seek patent protection and to remove any funding partner Confidential Information from all publications.

15. REFERENCES

Bachelot T. et al. 2010

Bachelot, T, Bourgier C., et al (2010). TAMRAD: a GINECO randomized phase II trial of everolimus in combination with tamoxifen vs. tamoxifen alone in patients with hormone receptor positive, HER2-negative metastatic breast cancer with prior exposure to aromatase inhibitors. SABCS- S1-6.

Badin F. et al. 2010

Badin F., Romond, E. et al (2010). A phase II trial of fulvestrant and RAD001 (everolimus) in patients with metastatic estrogen receptor positive breast cancer after aromatase inhibitor failure; A study in progress. SABCS- P4-02-05.

Baselga J. et al. 2012

Baselga J. et al Campone M, Piccart M, Burris HA 3rd,et al. Everolimus in postmenopausal hormone-receptor-positive advanced breast cancer. *N Eng J Med* 2012, 366:520-529.

Boulay A. et al. 2005

Boulay A, Rudolf J, Ye J, et al. Dual inhibition of mTOR pathway and estrogen signaling in vitro induces cell death in models of breast cancer. *Clin Cancer Res*. 2005;11:5319-5328.

Campbell R. A. et al. 2001

Campbell RA, Bhat-Nakshatri P, Patel NM, et al. (2001). Phosphatidylinositol 3-kinase/AKT mediated activation of estrogen receptor alpha: a new model for anti-estrogen resistance. J Biol Chem; 276:9817-9824.

Eisenhauer E. A. et al. 2009

Eisenhauer EA et al. New response evaluation criteria in solid tumours; revised RECIST guideline (version 1.1). Eur J Cancer. 2009; 45 p. 228-47.

Ellard S. L. et al. 2009

Ellard SL et al Randomized Phase II Study Comparing Two Schedules of Everolimus in Patients With Recurrent/Metastatic Breast Cancer: NCIC Clinical Trials Group IND.163 J Clin Oncol 27:4536-4541, 2009

Krishna G. et al. 2009

Krishna G, Moton A, Lei Ma L, Savant I, Martinho M, Seiberling M, McLeod J. Effects of oral posaconazole on the pharmacokinetic properties of oral and intravenous midazolam: A phase I, randomized, open-label, crossover study in healthy volunteers. Clinical Therapeutics, 2009; 31: 286-98

Loomba R. et al. 2008

Loomba R, Rowley A, Wesley R, et al (2008). Systematic review: the effect of preventive lamivudine on hepatitis B reactivation during chemotherapy. *Ann Intern Med* 148(7): 519-28.

O'Regan R, et al. 2013

O'Regan R, Ozguroglu M, Andre F, et al. Phase III, randomized, double-blind, placebo-controlled multicenter trial of daily everolimus plus weekly trastuzumab and vinorelbine in trastuzumab-resistant, advanced breast cancer (BOLERO-3). J Clin Oncol 31, 2013 (suppl; abstr 505)

Santen R. J. et al. 2005

Santen RJ, Song RX, Zhang Z, et al. (2005). Adaptive hypersensitivity to estrogen mechanisms and clinical relevance to aromatase inhibitor therapy in breast cancer treatment. J Steroid Biochem Mol Biol 95:155-165

Tokunaga E. et al. 2006

Tokunaga E, Kimura Y, Oki E, et al. (2006). Akt is frequently activated in HER2/neu-positive breast cancers and associated with poor prognosis among hormone-treated patients. Int J Cancer; 118:284-289.

Yamnik R. L. et al. 2009

Yamnik RL, Digilova A, Davis DC, Brodt ZN, Murphy CJ, Holz MK. S6 kinase 1 regulates estrogen receptor alpha in control of breast cancer cell proliferation. J Biol Chem 2009;284:6361-9.

Yamnik R. L. et al. 2010

Yamnik RL, Holz MK. mTOR/S6K1 and MAPK/RSK signaling pathways coordinately regulate estrogen receptor alpha serine 167 phosphorylation. FEBS Lett 2010;584:124-8.

Yeo W. et al. 2004

Yeo W, Lam KC, Zee B, et al. (2004) Hepatitis B reactivation in patients with hepatocellular carcinoma undergoing systemic chemotherapy. Annals of Oncology 15: 1661-1666

16. APPENDICES

Appendix A: ECOG Performance Status Criteria

ECOG Performance Status Scale		Karnofsky Performance Scale	
Grade	**Descriptions**	**Percent**	**Description**
0	Normal activity. Fully active, able to carry on all pre-disease performance without restriction.	100	Normal, no complaints, no evidence of disease.
		90	Able to carry on normal activity; minor signs or symptoms of disease.
1	Symptoms, but ambulatory. 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).	80	Normal activity with effort; some signs or symptoms of disease.
		70	Cares for self, unable to carry on normal activity or to do active work.
2	In bed <50% of the time. Ambulatory and capable of all self-care, but unable to carry out any work activities. Up and about more than 50% of waking hours.	60	Requires occasional assistance, but is able to care for most of his/her needs.
		50	Requires considerable assistance and frequent medical care.
3	In bed > 50% of the time. Capable of only limited self-care, confined to bed or chair more than 50% of waking hours.	40	Disabled, requires special care and assistance
		30	Severely disabled, hospitalization indicated. Death no imminent.
4	100% bedridden. Completely disabled. Cannot carry on any self-care. Totally confined to bed or chair.	20	Very sick, hospitalization indicated. Death not imminent.
		10	Moribund, fatal processes progressing rapidly.
5	Dead	0	Dead

Appendix B: New York Heart Association (NYHA) Classification of Cardiac Disease

The following table presents the NYHA classification of cardiac disease.

Class	Functional Capacity	Objective Assessment
I	Patients with cardiac disease but without resulting limitations of physical activity. Ordinary physical activity does not cause undue fatigue, palpitation, dyspnea, or anginal pain.	No objective evidence of cardiovascular disease.
II	Patients with cardiac disease resulting in slight limitation of physical activity. They are comfortable at rest. Ordinary physical activity results in fatigue, palpitation, dyspnea, or anginal pain.	Objective evidence of minimal cardiovascular disease.
III	Patients with cardiac disease resulting in marked limitation of physical activity. They are comfortable at rest. Less than ordinary activity causes fatigue, palpitation, dyspnea, or anginal pain.	Objective evidence of moderately severe cardiovascular disease.
IV	Patients with cardiac disease resulting in inability to carry on any physical activity without discomfort. Symptoms of heart failure or the anginal syndrome may be present even at rest. If any physical activity is undertaken, discomfort is increased.	Objective evidence of severe cardiovascular disease.

Source: The Criteria Committee of New York Heart Association. Nomenclature and Criteria for Diagnosis of Diseases of the Heart and Great Vessels. 9th Ed. Boston, MA: Little, Brown & Co; 1994:253-256.

Appendix C: Guidelines for Female Patients of Childbearing Potential and Fertile Male Patients

Acceptable Contraception Methods:

Women of childbearing potential, defined as all women physiologically capable of becoming pregnant, must use highly effective contraception during the study and for 8 weeks after stopping treatment.

Highly effective contraception is defined as either:

True Abstinence When this is in line with the preferred and usual lifestyle of the subject. Periodic abstinence (e.g., calendar, ovulation, symptothermal, post-ovulation methods) and withdrawal are not acceptable methods of contraception.

Sterilization When a woman of childbearing potential has had surgical bilateral oophorectomy (with or without hysterectomy) or tubal ligation at least six weeks prior to study entry. In case of oophorectomy alone, only when the reproductive status of the woman has been confirmed by follow up hormone level assessment.

Male Partner Sterilization When the appropriate post-vasectomy documentation of the absence of sperm in the ejaculate.

Use of a combination of any two of the following (one from a + one from b):

a) Placement of an intrauterine device (IUD) or intrauterine system (IUS).

b) Barrier methods of contraception: Condom or Occlusive cap (diaphragm or cervical/vault caps) with spermicidal foam/gel/film/cream/vaginal suppository.

Fertile male patients, defined as all males physiologically capable of conceiving offspring, with female partners of child-bearing potential must use condoms plus spermicidal agent during the study treatment period and for 8 weeks after the last dose of study drug, and should not father a child during this period.

Male patients must also refrain from donating sperm during their participation in the study.

The following are acceptable forms of barrier contraception:

- Latex condom, diaphragm or cervical/vault cap when used with spermicidal foam/gel/film/cream/suppository

Unacceptable Contraception Methods: for women of childbearing potential include:

- IUD progesterone T
- Female condom

- Natural family planning (rhythm method) or breastfeeding
- Fertility awareness
- Withdrawal
- Cervical shield

Pregnancies

To ensure subject safety, each pregnancy in a subject on study treatment must be reported to the SCRI Innovations Safety Department within 24 hours of learning of its occurrence. The pregnancy should be followed up for 3 months after the termination of the pregnancy to determine outcome, including spontaneous or voluntary termination, details of the birth, and the presence or absence of any birth defects, congenital abnormalities, or maternal and/or newborn complications.

Pregnancy should be recorded on a Clinical Study Pregnancy Form and reported by the investigator to **SCRI Innovations Safety Department**. Pregnancy follow-up should be recorded on the same form and should include an assessment of the possible relationship to the study drug of any pregnancy outcome. Any SAE experienced during pregnancy must be reported on the SAE Report Form.

Pregnancy outcomes must be collected for the female partners of any males who took study treatment in this study. Consent to report information regarding these pregnancy outcomes should be obtained from the mother.

Women Not of Childbearing Potential are defined as Follows:

- Women are considered post-menopausal and not of childbearing potential if they have had 12 months of natural (spontaneous) amenorrhea with an appropriate clinical profile (e.g., age appropriate, history of vasomotor symptoms).
- Women who are permanently sterilized (e.g., tubal occlusion, hysterectomy, bilateral salpingectomy, bilateral oophorectomy).
- Women who are >45 years-of-age, not using hormone-replacement therapy and who have experienced total cessation of menses for at least 12 months OR who have a follicle stimulating hormone (FSH) value >40 mIU/mL and an estradiol value <40 pg/mL (140 pmol/L).
- Women who are >45 years-of-age, using hormone-replacement therapy and who have experienced total cessation of menses for at least 1 year OR who have had documented evidence of menopause based on FSH >40 mIU/mL and estradiol <40 pg/mL prior to initiation of hormone-replacement therapy.

Appendix D: Schedule of Assessments

Assessments	Baseline Study Assessments[a]	Study Treatment				Off-Treatment	Follow-Up	
		Cycles 1 and 2	Cycle 3	Cycle 4 +	Every 2 Cycles	End of Study Treatment[k]	Off Treatment Prior to Disease Progression[l]	Survival Follow-Up[m]
		Day 1	Day 1	Day 1				
Tests and Observations								
Informed consent	X							
Medical history	X	X	X	X		X	X	
Physical exam[b]	X	X	X	X		X	X	
ECOG PS	X	X	X	X		X	X	
ECG (single)	X							
Adverse event evaluation		X	X	X		X		
Concomitant medication review	X	X	X	X		X	X	
Study drug compliance assessment[c]		X	X	X		X		
Survival status								X
Laboratory Observations								
CBC, including 3-part differential, and platelets	X	X	X	X		X	X	
CMP[d]	X	X	X	X		X	X	
Fasting serum glucose	X	X	X	X		X		
Cholesterol/HDL/LDL/triglycerides[e, f]	X	X[f]	X	X[f]		X		
Hepatitis B and C screening	X[o]							
PT or INR, and PTT	X[g]							
Serum (or urine) pregnancy test[h]	X[h]		X[h]	X[h]		X[h]		
Urinalysis	X							
Archived tumor block	X[i]							
Serum sample for VeriStrat® assay	X[n]		X[n]			X[n]		X[n]
Staging								
CT scan of chest	X		X[j]		X[j]	X	X	
CT scan of abdomen and pelvis	X		X[j]		X[j]	X	X	
Bone scan	X[j]							

Appendix D: Schedule of Assessments (continued)

a The physical examination including neurological examination, update of medical history, ECOG PS, CBC, CMP plus uric acid, magnesium, phosphorus, and PT or INR, PTT must be done ≤7 days prior to initiation of treatment. However, if these initial examinations are obtained within 72 hours of Cycle 1 Day 1 they do not have to be repeated. Scans to document measurable or evaluable disease (i.e., tumor measurement) must be performed ≤ 4 weeks prior to initiation of treatment.

b Physical examination will include measurements of height (to calculate body surface area [BSA]), weight, and vital signs (resting heart rate, blood pressure, respiratory rate, oral temperature) at the Pre-Treatment Visit. Physical examinations (PE) done at all other times during the study will include only measurements of vital signs and weight.

c Study drug compliance will be assessed at each patient visit. The study staff will count and document the amount of study drug taken and returned by the patient.

d CMP will include measurements of glucose, BUN, creatinine, sodium, potassium, chloride, calcium, CO2, alkaline phosphatase, AST, ALT, total bilirubin, total protein, and albumin.

e Patients must fast at least 8 hours overnight prior to collection of the blood specimen.

f Cholesterol/HDL/LDL/triglycerides do not need to be repeated on Cycle 1 Day 1 if they are normal at baseline. Repeat on Day 1 of every odd cycle.

g If PT or INR, and PTT are normal at baseline they do not need to be repeated. Patients requiring the initiation of an anti-coagulation therapy during study treatment should have their coagulation test performed as clinically indicated.

h A serum pregnancy test for all pre/peri menopausal women (regardless of ovarian suppression) is required at baseline ≤ 7 days prior to date of first treatment. All pre/peri menopausal women will need a serum or urine pregnancy test every 2 cycles (8 weeks) before receiving study treatment. If a urine pregnancy test is positive, it must be followed by a serum pregnancy test.

i Tumor specimens from the primary site or from metastatic lesions will be collected from all patients with available archived tissue. See lab manual for details.

j Scans are required every 2 cycles, prior to the start of odd-numbered cycles beginning with Cycle 3. Bone scans that are abnormal at baseline must be repeated at restaging.

k After patients complete therapy or are discontinued from the study, they will visit the study center 30 days after finishing treatment for end-of-treatment assessments. CT scans performed within 8 weeks prior to the End of Treatment visit do not need to be repeated. All patients will be followed during the off study period until all treatment related toxicity resolves, and for at least 30 days post-study drug discontinuation.

l Patients who discontinue study treatment prior to the occurrence of disease progression will be followed every 3 months (± 1 month) from the date of last dose of study drug until disease progression or for up to 3 years whichever comes first. A blood sample will be collected for the VeriStrat® assay at disease progression.

m Patients will be followed for survival status after study treatment has ended (including the discontinuation of treatment for any reason prior to the end of the study) every 3 months (± 1 month) for up to 3 years or until patient death whichever comes first. A blood sample will be collected for the VeriStrat® assay at the 1st follow-up visit after disease progression. For subsequent follow-up visits, patients may be contacted during outpatient visits or by telephone.

n Blood samples will be collected from all patients enrolled on the study for the VeriStrat® assay. Samples will be collected at baseline, prior to start of treatment on C3D1, at disease progression and at the 1st follow-up visit after disease progression.

o HBV-DNA, HBsAg, HBcAb, HBsAb and/or HCV RNA testing applies only to patients at risk for hepatitis (Section 7.1)

Appendix E: Response Evaluation Criteria in Solid Tumors (RECIST) Version 1.1

Definitions

Response and progression will be evaluated in this study using the Response Evaluation Criteria in Solid Tumors (RECIST) version 1.1 (Eisenhauer et al 2009). Lesions are either measurable or non-measurable using the criteria provided below. The term "evaluable" in reference to measurability will not be used, as it does not provide additional meaning or accuracy.

Baseline Eligibility

Measurable Disease:	**Tumor lesions:** Must be accurately measured in at least one dimension (longest diameter in the plane of measurement is to be recorded) with a minimum size of: • 10 mm by CT by computerized tomography (CT scan slice thickness no greater than 5 mm). • 10 mm caliper measurement by clinical exam (lesions that cannot be accurately measured with calipers should be recorded as non-measurable). • 20 mm by chest x-ray. **Skin lesions:** Documentation by color photography, including a ruler to estimate the size of the lesion, is recommended. **Malignant lymph nodes:** To be considered pathologically enlarged and measurable, a lymph node must be ≥15 mm in short axis when assessed by CT scan. At baseline and in follow-up, only the short axis will be measured and followed.
Non-Measurable Disease:	All other lesions, including small lesions (longest diameter <<10 mm or pathological lymph nodes with ≥10- to <<15-mm short axis) as well as truly non-measurable lesions. Lesions considered truly non-measurable include: leptomeningeal disease, ascites, pleural or pericardial effusion, inflammatory breast disease, lymphangitic involvement of skin or lung, abdominal masses, abdominal organomegaly identified by physical exam that is not measurable by reproducible imaging techniques.
Target Lesions:	The most reproducible measurable lesions, up to a maximum of 2 lesions per organ and 5 lesions in total, representative of all involved organs should be identified as target lesions and recorded and measured at baseline. Target lesions should be selected on the basis of their size (lesions with the longest diameter), should be representative of all involved organs, and in addition should be those that lend themselves to reproducible repeated measurements. Pathological nodes which are defined as measurable and that may be identified as target lesions must meet the criterion or a short axis of ≥15 mm by CT scan. A sum of the diameters (longest for non-nodal lesions, short axis for nodal lesions) for all target lesions will be calculated and reported as the baseline sum diameters. If lymph nodes are to be included in the sum, then as noted above, only the short axis is added into the sum. The baseline sum diameters will be used as reference to further characterize any objective tumor response.
Non-Target Lesions:	**All other lesions should be identified as non-target lesions at baseline. Measurements of these lesions are not required, but the presence or absence of each should be noted throughout follow-up.**

Guidelines for Evaluation of Measureable Disease

All measurements should be taken and recorded in metric notation, using a ruler or calipers. All baseline evaluations should be performed as closely as possible to the beginning of treatment, as per protocol screening requirements.

The same method of assessment and the same technique should be used to characterize each identified and reported lesion at baseline and during follow-up. Imaging-based evaluation is preferred to evaluation by clinical examination when both methods have been used to assess the anti-tumor effect of a treatment.

Clinical Lesions:	Clinical lesions will only be considered measurable when they are superficial (e.g., skin nodules and palpable lymph nodes) and ≥10 mm in diameter. In the case of skin lesions, documentation by color photography, including a ruler to estimate the size of the lesion, is recommended.
Chest X-ray:	Lesions on chest X-ray are acceptable as measurable lesions when they are clearly defined and surrounded by aerated lung. However, a CT scan is preferable.
Conventional CT and MRI:	CT, MRI: CT is the best currently available and reproducible method to measure lesions selected for response assessment. This guideline has defined measurability of lesions on CT scan based on the assumption that CT slice thickness is 5mm or less. When CT scans have slice thickness greater than 5 mm, the minimum size for a measurable lesion should be twice the slice thickness. MRI is also acceptable in certain situations (e.g. for body scans).
Ultrasound:	When the primary study endpoint is objective response, ultrasound should not be used to measure tumor lesions. It is, however, a possible alternative to clinical measurements of superficial palpable lymph nodes, subcutaneous lesions, and thyroid nodules. Ultrasound may also be useful to confirm the complete disappearance of superficial lesions usually assessed by clinical examination.
Endoscopy and Laparoscopy:	Use of endoscopy and laparoscopy for objective tumor evaluation has not yet been fully and widely validated. Therefore, use of these techniques for objective tumor response should be restricted to validation purposes in specialized centers. Such techniques can be useful in confirming complete pathological response when biopsies are obtained.
Tumor Markers:	Tumor markers alone cannot be used to assess response. If markers are initially above the upper limit of normal, they must normalize for a subject to be considered in complete clinical response when all lesions have disappeared.
Cytology and Histology:	Cytology and histology can be used to differentiate between partial response (PR) and complete response (CR) in rare cases (e.g., after treatment to differentiate between residual benign lesions and residual malignant lesions in tumor types such as germ cell tumors).

Response Criteria

Evaluation of Target Lesions

Complete Response (CR):	Disappearance of all target lesions.
Partial Response (PR):	At least a 30% decrease in the sum of diameters of target lesions, taking as reference the baseline sum diameters..
Stable Disease (SD):	Neither sufficient shrinkage to qualify for PR nor sufficient increase to qualify for PD, taking as reference the smallest (nadir) sum of diameters since the treatment started.
Progressive Disease (PD):	At least a 20% increase in the sum of the diameters of target lesions, taking as reference the smallest (nadir) sum since the treatment started, or the appearance of one or more new lesions. Requires not only 20% increase, but absolute increase of a minimum of 5 mm over sum.

Evaluation of Non-Target Lesions

Complete Response (CR):	Disappearance of all non-target lesions and normalization of tumor markers. All lymph nodes must be non-pathological in size (<<10 mm short axis).
Stable Disease (SD):	Persistence of one or more non-target lesions and/or persistence of tumor marker level above the normal limits.
Progressive Disease (PD):	Appearance of one or more new lesions and/or unequivocal progression of existing non-target lesions. When the subject also has measurable disease, to achieve "unequivocal progression" on the basis of the non-target disease, there must be an overall level of substantial worsening in non-target disease such that, even in presence of SD or PR in the target disease, the overall tumor burden has increased sufficiently to merit discontinuation of therapy.

Evaluation of Best Overall Response

As detailed above, the best overall response is the best response recorded from the start of the treatment until disease progression/recurrence (taking as reference for PD the smallest measurements recorded since the treatment started). In general, the subject's best response assignment will depend on the achievement of both measurement and confirmation criteria.

Confirmation of response (by repeat scans after 4 weeks or as specified in the protocol) is required for studys in which response rate is the primary endpoint, but is not required in randomized studys or studys with primary survival endpoints (i.e., where response is not a primary endpoint).

Target Lesions	Non-Target Lesions	New Lesions	Overall Response
CR	CR	NO	CR
CR	SD	NO	PR
CR	NE	NO	PR
PR	SD OR NE	NO	PR
SD	SD OR NE	NO	SD
PD	ANY	YES OR NO	PD
ANY	PD	YES OR NO	PD
ANY	ANY	YES	PD

In some circumstances, it may be difficult to distinguish residual disease from normal tissue. When the evaluation of a CR depends upon this determination, it is recommended that the residual lesion be investigated by fine needle aspirate or biopsy to confirm the CR status.

When nodal disease is included in the sum of target lesions, and the nodes decrease to "normal" size (<<10 mm), they may still have a measurement reported on scans. This measurement should be recorded even though the nodes are normal in order not to overstate progression, should it be based on increase in size of the nodes. As noted earlier, this means that subjects with CR may not have a total sum of "zero" on the eCRF.

Appendix F: Clinically Relevant Drug Interactions of CYP3A and PgP

Clinically relevant drug interactions: inducers, and inhibitors of isoenzyme CYP3A

Inducers
Strong inducers:
avasimibe, carbamazepine, mitotane, phenobarbital, phenytoin, rifabutin, rifampin (rifampicin), St. John's wort, (hypericum perforatum)
Moderate inducers:
bosentan, efavirenz, etravirine, genistein, modafinil, nafcillin, ritonavir, [talviraline], thioridazine, tipranavir
Weak inducers:
amprenavir, aprepitant, armodafinil (R-modafinil), bexarotene, clobazam, danshen, dexamethasone, Echinacea, garlic (allium sativum), gingko (ginkgo biloba), glycyrrhizin, methylprednisolone, nevirapine, oxcarbazepine, pioglitazone, prednisone, [pleconaril], primidone, raltegravir, rufinamide, sorafenib, telaprevir, terbinafine,

Inhibitors
Strong inhibitors:
boceprevir, clarithromycin, cobicistat, conivaptan, elvitegravir, indinavir, itraconazole, ketoconazole, lopinavir, mibefradil, nefazodone, nelfinavir, posaconazole (Krishna et al 2009), ritonavir, saquinavir, telaprevir, telithromycin, tipranavir, troleandamycin, voriconazole
Moderate inhibitors:
Amprenavir, aprepitant, atazanavir, casopitant, cimetidine, ciprofloxacin, cyclosporine, darunavir, diltiazem, dronedarone, erythromycin, fluconazole, fosamprenavir, grapefruit juice (citrus parasidi fruit juice), imatinib, schisandra sphenanthera, tofisopam, verapam

Clinically relevant drug interactions: substrates, inducers, inhibitors of PgP and PgP/CYP3A dual inhibitors

Substrates
colchicine, digoxin, fexofenadine, indinavir, paclitaxel, talinolol, topotecan, vincristine, everolimus
Inducers
rifampin, St John's wort
PgP Inhibitors and PgP/CYP3A Dual Inhibitors
amiodarone, azithromycin, captopril, carvedilol, clarithromycin, conivaptan, diltiazem, dronedarone, elacridar, erythromycin, felodipine, fexofenadine, fluvoxamine, ginkgo (ginkgo biloba), indinavir, itraconazole, lopinavir, mibefradil, milk thistle (silybum marianum), nelfinavir, nifedipine, nitrendipine, paroxetine, quercetin, quinidine, ranolazine, rifampin, ritonavir, saquinavir, Schisandra chinensis, St John's wort (hypericum perforatum), talinolol, Telaprevir, telmisartan, ticagrelor, tipranavir, tolvaptan, valspodar, verapamil
Reference: Internal Clinical Pharmacology Drug-drug interaction (DDI) memo, updated Oct. 2, 2011,29-Oct-2012 which summarizes DDI data from three sources including the FDA's "Guidance for Industry, Drug Interaction Studies", the University of Washington's Drug Interaction Database, and Indiana University School of Medicine's Drug Interaction Table

Appendix G: VeriStrat® Assay

VeriStrat is a pre-treatment blood-based test correlated with clinical outcome after epidermal growth factor receptor (EGFR)-tyrosine kinase inhibitor (TKI) therapy in patients with NSCLC. VeriStrat was developed in a multi-institutional study of advanced NSCLC patients treated with gefitinib [1]. The VeriStrat algorithm was developed using a training set of pre-treatment serum samples from patients who experienced either long term stable disease or early progression on gefitinib therapy. Mass spectra (MS) from these patients' serum samples were used to define 12 MS features (i.e. peaks), differentiating these two outcome groups. VeriStrat was created by utilizing eight of these features based on a *k*-nearest neighbors (KNN) classification scheme and its parameters optimized using additional spectra from the training cohort. All aspects of the algorithm were permanently frozen after development. VeriStrat assigns patient samples a classification of VeriStrat Good (VS-G) or VeriStrat Poor (VS-P).

VeriStrat was validated in a blinded fashion on the pre-treatment serum of two independent cohorts of patients who were treated with gefitinib or erlotinib (an EGFR-TKI)[1]. These studies confirmed that patients classified as VS-G had better outcomes than patients classified as VS-P (Hazard Ratio [HR] of death=0. 50 P=0.0054 in one cohort, HR of death=0.40 $P \leq 0.001$ in the other). VeriStrat was shown to correlate with clinical outcome following EGFR-TKI therapy, but not following chemotherapy or post-surgery as there was no statistically significant difference seen in the overall survival of patients classified as VS-G or VS-P before second-line chemotherapy (HR=0.74, 95%, P=0.42 in one cohort and HR=0.81, P=0.54 in another). In a third control cohort of patients with resected early-stage NSCLC, the HR for overall survival was 0.90 (P=0.79).

Retrospective analysis of VeriStrat testing performed on available serum samples of a subset of patients from the BR 21 trial (second or third line NSCLC patients randomized to erlotinib or placebo), demonstrated evidence of a significant prognostic component of the VeriStrat test, and indicated a strong statistically significant correlation of the VS-G label with objective response rate (ORR) and disease control rate (DCR) in the treatment arm (Fisher exact test 2-sided p value 0.0022 for ORR and p value <0.001 for DCR)[2]. Importantly, this study also demonstrated the independence of VeriStrat classification from known genetic markers (i.e., *EGFR* mutations, *EGFR* amplification [by FISH], and *KRAS* mutations).

Finally, VeriStrat was prospectively validated in the Randomized Proteomic Stratified Phase III Study of Second Line Erlotinib versus Chemotherapy in Patients with Inoperable Non-Small Cell Lung Cancer (PROSE)[3]. PROSE is the world's first completed prospective biomarker-stratified study in oncology to test treatment and biomarker interaction. This is a multi-center, randomized, Phase 3 study of 285 study patients with advanced NSCLC who have progressed after first line chemotherapy treatment. Patients were randomized 1:1 to receive either standard dose erlotinib or chemotherapy (dealer's choice, pemetrexed or docetaxel), and stratified by ECOG Performance Status, smoking status, and blinded pre-treatment VeriStrat classification. PROSE results show that patients classified as VS-G have similar OS when treated with either

erlotinib or chemotherapy, whereas patients classified as VS-P have better OS on chemotherapy compared with erlotinib. The study reached its primary objective of showing significant interaction between treatment outcome and VeriStrat classification with an interaction p-value of 0.031. The results confirm that VeriStrat status is predictive of differential overall survival benefit for erlotinib versus chemotherapy in a second-line setting.

Further studies demonstrate that VeriStrat may have clinical utility in various solid epithelial tumors treated with a variety of targeted drugs and their combinations [4]. In head and neck squamous cell carcinoma (HNSCC), VeriStrat was correlated with survival of patients treated with gefitinib (HR=0.41, p=0.007), erlotinib/bevacizumab (HR=0.2, p=0.02), and cetuximab (HR=0.26, p=0.06); a chemotherapy cohort showed no statistically significant survival difference. In a cohort of colorectal cancer (CRC) patients treated with cetuximab, the difference in progression free survival between VS-G and VS-P patients was also significant, with HR=0.51 (p=0.0065).

More recent studies evaluated the effect of VeriStrat stratification on the treatment efficacy of letrozole with or without lapatinib in first line metastatic breast cancer patients in a retrospective analysis of the phase III trial EGF30008[5]. Of the 1286 patients randomized (HER2 positive=219; HER2 negative=952; HER2 unknown=115), 1163 patients had serum available for analysis. A VeriStrat label was assigned to 1046 patients (VS-G=961; VS-P=80; VS Indeterminate=5). In the overall population there was no significant difference in PFS between VS-G and VS-P groups within the letrozole + lapatinib arm (p=0.53). In contrast, PFS of the VS-G group was longer than that of the VS-P group within the letrozole only arm (HR=0.36, p<0.001) and comparable with that of Good patients within the letrozole + lapatinib arm (median PFS 10.8 months vs 11.0 months). In multivariate analysis VeriStrat classification was independently significant in the presence of other clinical variables. A significant interaction between VeriStrat classification and treatment (interaction p=0.002) indicate that the test is not merely prognostic, but predictive with respect to benefit from different treatments. This suggests that the VS-P group may represent primary hormone resistance that is overcome by the addition of lapatinib to letrozole.

In this study an exploratory evaluation of VeriStrat will be conducted. Treatment options for this study will not be based on the results of this testing.

Serum samples for VeriStrat testing will be collected as follows; the investigative site will follow standard of care protocols:

- Baseline visit (pre-treatment)
- Cycle 3, Day 1 visit (prior to treatment)
- At disease progression
- At the first Follow-Up visit after disease progression.

Sample Collection and Processing

1. Use a BRE 212 VeriStrat collection kit for each sample collection.

2. Complete 3 BRE 212 study identification labels with BRE 212 Subject ID, visit type and collection date.

3. Place 1 label on each of the following

    a) 3.5 mL SST (gold-top) Vacutainer tube.

    b) Serum Collection Card.

    c) BRE 212 Test Request Form (BRE 212 TRF), upper right corner.

4. Collect venous blood into the 3.5 mL SST Vacutainer.

5. Gently invert the SST 5 times and allow the tube to clot in an upright position for 30 minutes at room temperature (approximately 70°Farenheit or 21°Celcius (C).

6. Spin the SST in a standard clinical centrifuge at a speed of 1000-1300 gravity (g), or equivalent, for 10-15 minutes. Speed should not exceed 1300 g, and time should not exceed 15 minutes or hemolysis may occur.

7. Verify that the serum is light yellow in color. Pink or reddish serum indicates sample has hemolyzed and must be redrawn.

8. Without disturbing the clot layer, use a transfer pipette to transfer 2 drops (0.1 mL) of serum to each of the 2 circles on the Serum Collection Card.

9. Dispose of SST.

10. Close cover of Serum Collection Card and follow shipping instructions. Sample must be shipped within 24 hours, and may be stored at room temperature until shipping.

Sample Shipment

1. Place the Serum Collection Card into the foil bag and seal.

2. Place the foil bag and the completed, signed BRE 212 TRF into the shipping envelope. Save the yellow copy of the TRF for placement in the subject's study records.

3. Complete the required FedEx® air bill fields, and if shipping on a Friday, check the Saturday delivery box. Remove the sender's copy of the air bill for the subject's study records, and place the remainder of the air bill in the pouch of the shipping envelope.

4. Arrange for and confirm FedEx pickup of the package on the same day as the sample is prepared for shipping.

5. Notify Biodesix of pending shipment by emailing a message to lab@biodesix.com Include the following in the notification email:

    a) Subject: BRE 212 sample shipment

    b) Body of message: FedEx tracking number; name and contact information of sender.

Procedures

Upon completion of all serum collection (i.e., all patients have completed the first follow-up visit following end of trial treatment), serum samples will be analyzed using MALDI ToF MS and the VeriStrat results will be sent to SCRI at the completion of the study. Upon unblinding of the clinical data, in accordance with the endpoints described in the trial protocol, statistical analysis will be carried out independently by SCRI and by Biodesix. Biodesix statistical analyses will be performed using SAS 9.2 (Cary, NC) and PRISM (GraphPad, La Jolla, CA).

Statistical Analysis Plan

Since there is no previous information on VeriStrat testing in this population of patients, this study is exploratory in nature. In the retrospective analysis of metastatic breast cancer patients from the EGF30008 study, the VS-P classification was observed in 8-10% of the study population. Assuming a similar rate of occurrence of the VS-P classification, and the planned accrual of 46 subjects, ~4 baseline samples are expected to have a VS-P classification. Based on the lack of previous information on the VeriStrat classification for the patients to be enrolled in this study, no estimation of detectable alternative is provided for the suggested statistical analyses. The feasibility of the statistical analyses will be evaluated after the actual ratio of VS-G/VS-P classification has been determined.

References

1. Taguchi F, Solomon B, Gregorc V, et al. Mass spectrometry to classify non-small-cell lung cancer patients for clinical outcome after treatment with epidermal growth factor receptor tyrosine kinase inhibitors: a multicohort cross-institutional study. *J Natl Cancer Inst* 2007;99(11):838-46.
2. Carbone DP, Ding K, Roder H, et al. Serum proteomic prediction of outcomes in advanced NSCLC patients treated with erlotinib or placebo in the NCIC CTG BR.21 trial. *J Thorac Oncol.* 2012;7(11):1653-60.
3. Gregorc V, Novello S, Lazarri C, et al. Predictive value of a proteomic signature in patients with non-small-cell lung cancer treated with second-line erlotinib or chemotherapy (PROSE): a biomarker-stratified, randomised phase 3 trial. *Lancet Oncol.* 2014, epub ahead of print. doi: 10.1016/S1470-2045(14)70162-7.

4. Chung CH, Seeley EH, Roder H, et al. Detection of tumor epidermal growth factor receptor pathway dependence by serum mass spectrometry in cancer patients. *Cancer Epidemiol Biomarkers Prev.* 2010;19(2):358-65.
5. Roder J, Roder H, Hunsucker S, et al. Retrospective Analysis of Study EGF30008 by Mass-Spectrometry Based Serum Assay (VeriStrat®). *Cancer Research.* 2011;71(24):supp 3.