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SWOG

FULVESTRANT ALONE VERSUS FULVESTRANT AND EVEROLIMUS VERSUS FULVESTRANT, EVEROLIMUS AND ANASTROZOLE: A PHASE III RANDOMIZED PLACEBO-CONTROLLED TRIAL IN POSTMENOPAUSAL PATIENTS WITH HORMONE-RECEPTOR-POSITIVE STAGE IV BREAST CANCER

NCT #02137837

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AGENTS:

SWOG-Held IND Agents:
Anastrozole/Placebo (NSC-719344) (IND-120404)
Everolimus/Placebo (NSC-733504) (IND-120404)
Fulvestrant (NSC-719276) (IND-120404)

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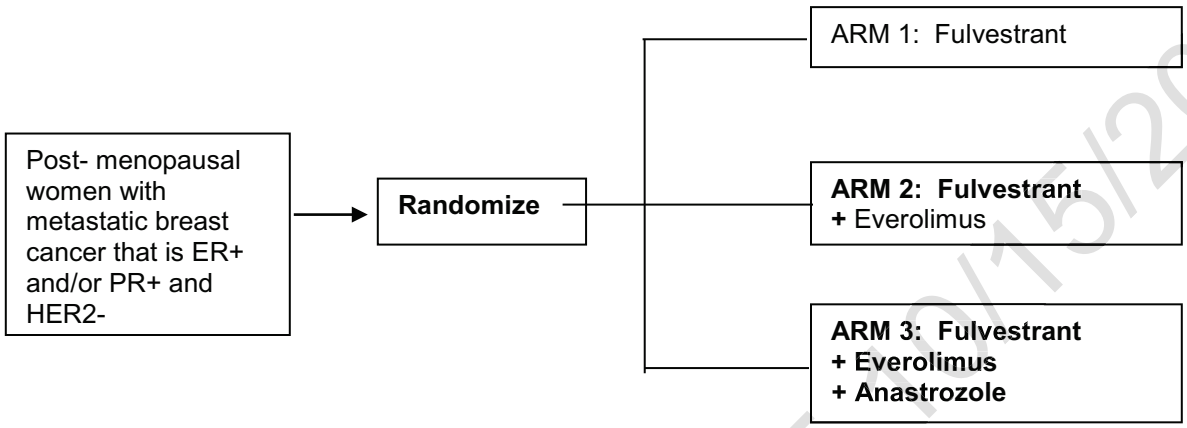
SCHEMA



1.0 OBJECTIVES

1.1 Primary Objectives

a. To test the benefit of interfering with the function of the estrogen receptor (ER) and providing downstream target inhibition (PI3K/AKT/mTOR) with a combination of optimal dose fulvestrant and everolimus (Arm 2) to improve progression-free survival compared to the optimal dose fulvestrant alone (Arm 1).

b. To test the benefit of adding the non-steroidal aromatase inhibitor anastrozole to optimal dose fulvestrant and everolimus (Arm 3) in order to improve progression-free survival over optimal dose fulvestrant (Arm 1).

1.2 Secondary Objectives

a. To compare progression-free survival among those receiving fulvestrant + everolimus + anastrozole (Arm 3) versus fulvestrant + everolimus (Arm 2).

b. To compare overall survival among the treatment arms in post-menopausal patients with hormone-receptor positive (HR+) Stage IV breast cancer.

c. To assess and compare toxicities, feasibility and compliance among the study regimens.

d. To compare response rates and clinical benefit rates among the study regimens.

e. To test molecular determinants of response to endocrine therapy and everolimus in circulating tumor cells:

1. CTC-Endocrine Therapy Index (CTC ETI) on the CellSearch® platform.

2. CTC-Next Generation Sequencing Analysis (CTC-NGS) of single cells captured on the HD-CTC® platform.

1.3 Tertiary Objectives

To collect and bank the following specimens for future research:

a. Circulating Cell-Free DNA

b. Cancer Tissue

c. Germline DNA

2.0 BACKGROUND

Stage IV metastatic breast cancer (MBC) remains largely incurable, regardless of the biological characteristics. Due to recent progress in target-specific therapies, patients with HER2+ and hormone receptor-positive Stage IV metastatic breast cancer have been experiencing incremental but significant improvements in median progression-free and overall survivals, while those diagnosed with triple-negative Stage IV breast cancer are in great and urgent need of advancement. *(1)* The median overall survival exceeds 3 years for HER2+ Stage IV breast cancer, and is approximately 3.5 years for patients presenting with estrogen (ER) and/or progesterone receptor (PgR)-positive (hormone receptor-positive [HR+]) Stage IV disease, although progression-free and overall survival vary greatly by numerous biological characteristics

including the degree of HR+ expression, age, extent of disease and visceral organ involvement, genetic, and by socio-economic and environmental differences. *(2,3,4,5)*

2.1 Treatment of Estrogen Receptor Positive Metastatic Breast Cancer:

Selecting the optimal treatment strategy for patients with HR+ MBC remains a challenge. One of the oldest and most widely used endocrine therapies (ETs) is tamoxifen, a selective estrogen receptor modulator (SERM). Over the last two decades, several studies have demonstrated that aromatase inhibition is slightly more effective than tamoxifen in regards to prolonging progression-free and even overall survival (PFS, OS) in patients with HR+ MBC. *(6)*

In the second line setting, fulvestrant, a selective ER downregulator (SERD), when given at 500 mg intramuscularly (IM) followed by 250 mg IM two and four weeks later, and then at a dose of 250 mg IM monthly, was equivalent to the aromatase inhibitor (AI) exemestane and yielded a 3.7-month median progression-free survival. *(7)* Of importance, patients were eligible if they progressed on a non-steroidal AI or relapsed within 6 months after completing a non-steroidal AI given adjuvantly. In the first line setting, randomized comparison of high-dose fulvestrant (three doses of 500 mg IM, given every 2 weeks, followed by 500 mg monthly) versus anastrozole in HR+ MBC, favored the use of fulvestrant. The median PFS was 23.4 months for patients treated with fulvestrant versus 13.1 months for those treated with anastrozole, at the time of publication. *(8)* Of importance, patients were eligible for enrollment on this (FIRST) trial only if prior anti-HR therapy had been completed at least 12 months prior to enrollment. Recent data from our prospective randomized Phase III SWOG trial (**S0226**) suggest that the combination of agents targeting both the estrogen receptor (fulvestrant) for degradation, and generation of estrogen via the administration of the non-steroidal aromatase inhibitor anastrozole, may benefit patients with HR+ Stage IV breast cancer. When such a strategy was applied in the first line setting, as it was done in **S0226**, a progression-free survival (PFS) of 15 months vs. 13.5 months was observed favoring the combination with a hazard ratio of 0.80. The combination also resulted in a decreased hazard ratio of 0.81 for overall survival (p-value of 0.05) versus single agent therapy. *(9)* Similarly to the above mentioned FIRST trial, anti-HR therapy had to be completed at least 12 months prior to enrollment onto **S0226**. However, neither **S0226**, nor a second, negative randomized trial (FACT NCT00253422) testing fulvestrant and anastrozole versus anastrozole, prescribed the optimal high dose of fulvestrant. It is worth mentioning that the difference in outcome between the two trials: **S0226** and FACT may be partly due to the fact that a greater portion of patients treated on **S0226** received no prior adjuvant anti-HR therapy. *(10)*

2.2 Inhibitors of mTOR in ER positive MBC:

Abnormalities of the PI3K/AKT/mTOR signaling pathway represent the most common molecular anomalies in breast cancer; the frequency of such abnormalities is highest in HR-positive tumors. It has been hypothesized that activation of the PI3K/AKT/mTOR pathway is associated with endocrine resistance, and as a corollary, that inhibition of the pathway may prevent or reverse resistance to ET. *(11)* Recently, Baselga et al. have reported the results of a prospective randomized placebo-controlled trial (BOLERO-2) in which patients with ER positive MBC who were refractory to non-steroidal AI therapy were randomly assigned to the steroidal AI exemestane with or without the mTOR inhibitor everolimus (10 mg dosing). The combination resulted in doubling of PFS to 6.9 months versus 2.9 months by investigator assessment, and 10.6 months versus 4.6 months by central assessment. *(12)* Likewise, in a Phase II randomized trial, the addition of everolimus to tamoxifen in patients who progressed through aromatase inhibitor therapy resulted in a significant time to progression benefit of 8.6 months versus 4.5 months. *(13)*

Analyses of predictors of benefit to combined ET and mTOR are ongoing. *(14,15)* Preliminary data combining fulvestrant and everolimus is also encouraging, with a median time to progression of 7.4 months in patients who progressed within 6 months of aromatase inhibitor therapy, and with observing a 55% clinical benefit rate, including 3% complete and 10% partial response rates. *(16)* Of importance, that in all of the above-mentioned combination trials, the prescribed dose of fulvestrant was suboptimal in comparison to the currently recommended 500 mg loading dose, which is to be repeated every two weeks twice, with subsequent dosing of 500 mg, all given intramuscularly (IM).

2.3 Rationale for this clinical trial (**S1222**)

It should be noted that in all of the above-mentioned combination trials, the prescribed dose of fulvestrant was suboptimal, at 250 mg/month after an initial loading dose, and that subsequent trials have demonstrated that a higher monthly dose (500 mg/month) is more efficacious. Thus, it has been suggested that the advantage of the combination of anastrozole and fulvestrant observed in **S0226** might be even greater using the higher dose of fulvestrant. Alternatively, since **S0226** did not contain a fulvestrant only arm, it is possible that the higher dose of fulvestrant might be as effective as the combination of anastrozole and the lower fulvestrant dose.

Further, eligibility for BOLERO-2 was restricted to patients who were already refractory to a non-steroidal AI, such as anastrozole.

No prospective randomized placebo-controlled trials have been conducted testing fulvestrant alone versus first line fulvestrant plus everolimus or first line fulvestrant and everolimus and anastrozole. Thus, **S1222** is a natural extension of the **S0226** trial, the BOLERO-2 trial and higher dose fulvestrant trials.

While there are many potentially promising agents in development, including antibodies and small molecules targeting specific ER-associated receptors and signal transduction pathways, such as insulin-like growth factor-receptor and insulin receptor inhibitors and Src inhibitors, clinical confirmation of their roles is still lacking. *(17,18,19)* Similarly encouraging but so far only preliminary data are available to support further testing of CDK 4/6 inhibitors, and histone deacetylase inhibitors, based on small randomized Phase II trials. *(20,21)*

In the United States, approximately 26,000 women die of hormone receptor-positive metastatic breast cancer each year. *(22)* Therefore, therapeutic improvements leading to prolongation of PFS and overall survival (OS) for patients with metastatic breast cancer and, in parallel, prevention of recurrence from high-risk primary breast cancer are urgently needed. This proposal will focus on the HR+ patient population with either *de novo* or recurrent Stage IV MBC. The significance of this project will only increase in view of the fact that the incidence of *de novo* Stage IV breast cancer is on the rise, especially in younger women. *(23)* While multiple strategies can and should be tested in the second and frontline metastatic settings, the 6-month centrally assessed clinically significant progression-free survival difference in BOLERO-2 patients who developed progressive disease despite prior anti-HR therapies, makes the approach of testing mTOR inhibition in combination with the best anti-HR partner drug/s in the first-line metastatic setting a high priority. *(24)* Identifying patients who may benefit the most based on their tumor biology is of utmost importance, underscoring the need to incorporate biomarker substudies in order to personalize therapy.

2.4 Translational Medicine:

a. Predictors of Resistance to ET and Response to mTOR inhibition

Prediction of benefit from endocrine therapies (ET) is defined by the presence or absence of hormone receptor (HR). Patients with HR-negative cancers do not benefit from ET, and therefore are not eligible for this study. However, in many previously conducted trials, at most 50% of women with HR-positive breast cancer benefited from ET. There are no known biomarkers that identify those women with HR-positive breast cancer who will not benefit from ET, although, in the adjuvant setting, the 21-gene recurrence score (RS) divides HR-positive women treated with ET alone into 3 prognostic groups – low, intermediate, and high and as such, it has been applied as an adjunctive tool for selecting patients who are less likely to do well with anti-ET alone. *(25,26)* This assay is strongly driven by relative expression of genes within the HR (including BCL2), HER2, and proliferative (including Ki67) pathways.

Efforts are ongoing to identify subsets of patients whose cancers, either due to multiple mutations and copy number alterations in addition to the PI3K and PTEN-dependent pathways, or alternative pathway activations independent of PI3K and mTOR may be affected differently when exposed to everolimus. *(27,28)* However, at this time, there are no known and validated biomarkers that predict sensitivity or resistance to everolimus or other mTOR inhibitors.

Recent data have suggested that whole genome copy number alterations can determine the amplification status at the genome-wide level, which is expected to provide a predictive profile of response and/or resistance to a number of drugs, including ET and mTOR inhibitors. A direct correlation between hormone receptor expression and single cell genomics will identify such a profile with high precision.

A fundamental key to this clinical trial is to perform correlative studies to determine if patients with HR-positive MBC who are refractory to ET alone, yet sensitive to ET plus everolimus, can be identified. Presumably, such patients would be better treated with chemotherapy, or more relevant to this study, they may be the patients for whom the addition of everolimus may be most effective. Therefore, we will conduct translational studies in circulating tumor cells that may provide insight into future selection of patients for and perhaps mechanisms of resistance to these treatments. We will also collect and bank archived tissue (primary or metastatic previously collected for routine clinical purposes) and serum for circulating DNA studies in the future.

b. Circulating Tumor Cells

Ideally, one would like to collect serial metastatic tissue biopsies from patients at baseline and during treatment to investigate genetic and expression markers associated with resistance to therapy. However, serial collection of metastatic biopsies is impractical, since they are invasive, costly, limited to a small patient population, and potentially dangerous.

Capture, enumeration, and characterization of circulating tumor cells (CTC) might serve as a “liquid biopsy”. Enumeration of CTC at baseline, and during the course of treatment has been shown to be prognostic in patients with MBC starting a new treatment. *(29,30)* There are several already completed or ongoing clinical trials evaluating the potential roles for treatment decisions based on numerical changes and actionable biological differences between tumors and CTCs including a recently closed study (**S0500**), which is designed to determine if changing chemotherapy regimens in patients who fail to clear CTC after one cycle of first line chemotherapy improves outcomes. *(31)*

There are more than 35 reported devices that can be used to capture and characterize CTCs. *(32,33,34)* Of these, we have chosen to use two separate platforms. We will study expression of several markers related to endocrine sensitivity (ER, BCL2, HER2, and Ki-67) using the only currently FDA-approved detection system: CellSearch® (Veridex LLC, Raritan, NJ). We will also use a newer platform, the HD-CTC® system (EPIC Sciences and Scripps Research, San Diego, CA) to isolate single CTCs and profile them for genome-wide copy number variations (an assay we designate as "CTC-NGS"). *(35)*

c. CellSearch®-CTC-Endocrine Therapy Index:

CellSearch® is an FDA-cleared automated immunomagnetic-based system to capture and enumerate CTCs in patients with metastatic breast, colorectal, and prostate cancers. Baseline CTCs, as determined by CellSearch®, and perhaps more importantly first-follow-up levels, predict progression-free and overall survival. *(36)* Moreover, CTC reductions are better predictors of long term outcome than are clinical or radiographic analyses of response. *(37)* Therefore, the study team hypothesizes that reduction of CTC in patients with metastatic breast cancer will provide evidence of benefit from either fulvestrant alone or fulvestrant plus everolimus (with or without anastrozole).

The CellSearch® assay can be modified to perform molecular characterization of CTCs. The Hayes Laboratory has recently reported that four markers associated with endocrine sensitivity (ER and BCL-2) or resistance (HER2 and Ki67) can technically be reliably and reproducibly analyzed on CTC using CellSearch®. From this, a "CTC-endocrine therapy index" (CTC-ETI) has been generated. *(38,39,40,41)* The study team hypothesizes that women with high CTC-ETI (elevated CTC number, and low ER, low BCL2, high HER2 and high Ki67) will derive reduced benefit from ET in the metastatic setting compared to those women with low CTC-ETI values. The control arm of this study will be used to generate preliminary evidence relevant to this hypothesis that will support development of future, more definitive trials.

Moreover, the BOLERO2 trial demonstrated activity of everolimus in patients who were refractory to at least one prior endocrine therapy (non-steroidal AIs). Therefore, we further hypothesize that CTC-ETI high patients, who may have endocrine refractory, albeit ER positive disease, may be more likely to benefit from the addition of everolimus.

d. HD-CTC®

HD-CTC® is a next generation fluid biopsy representing an enrichment-free rare cell characterization platform that has completed its technical and clinical validation processes with broad application in carcinomas. Its success rate as a fluid biopsy is defined by greater than 4 cells per test, which is applicable to approximately 70% of metastatic breast cancer patients. Its main utility is the single cell characterization at the protein and molecular levels with diagnostic pathology quality. It has demonstrated concordance with the primary solid tumor biopsy in prostate cancer for both PTEN loss by FISH and whole genome copy number variation using single cell next generation sequencing.

The HD-CTC Fluid Biopsy blood preparation provides for the use of a single blood collection tube to prepare four independent fluid biopsy samples. These pre-analytically validated samples are permanently stored in a biorepository and retrieved for specific assay execution. Assays are tailored to each product goal. Specifically, quantitative single cell characterization includes i) cellular morphology, ii) subcellular localization of each biomarker, iii) multi-color FISH

assays, iv) whole genome analysis of copy number alterations using next generation sequencing.

In the context of this trial, samples will be subjected to an initial candidate cell identification assay followed by a next generation sequencing assay for genome wide copy number alteration analysis-CTC NGS assay. Details are located in Section 18.4.

e. Other Translational Medicine/Correlative Studies:

We anticipate that this clinical trial will take approximately 3 years to accrue and another 2-3 years to achieve appropriate follow up. During that time, we anticipate that biological and technical advances will be made regarding both mechanisms of ET resistance and prediction of everolimus activity. Thus, we will collect and store formalin-fixed, paraffin-embedded (FFPE) tissue collected for routine clinical purposes (primary and metastatic), and these tissues will be available for future correlative studies using these new technologies. At that time, separate translational/correlative study concepts will be prepared and reviewed, and those that are approved by SWOG will be submitted to the appropriate IRB for review.

Recently, several investigators have reported exciting advances in the ability to determine mutations and copy number variations in circulating, somatic DNA. *(42)* We hypothesize that such abnormalities might be associated with resistance to fulvestrant and/or response to everolimus. Thus, we will collect and store plasma specimens in a manner that will permit future correlative studies of circulating DNA.

2.5 Inclusion of Women and Minorities

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

TARGETED/PLANNED ENROLLMENT: Number of Subjects			
Ethnic category	**Sex/Gender**		
	Females	**Males**	**Total**
Hispanic or Latino	25	0	25
Not Hispanic or Latino	800	0	800
Ethnic Category Total	825	0	825
TARGETED/PLANNED ENROLLMENT: Number of Subjects			
	Sex/Gender		
Racial Categories	**Females**	**Males**	**Total**
American Indian /Alaska Native	1	0	1
Asian	14	0	14
Black or African American	92	0	92
Native Hawaiian or Other Pacific Islander	1	0	1
White	717	0	717
Racial Categories: Total of all Subjects	825	0	825

3.0 DRUG INFORMATION

For information regarding Investigator's Brochures, please refer to SWOG Policy #15 (www.swog.org). For this study everolimus, anastrozole and fulvestrant are investigational and are being provided under an IND held by SWOG. For INDs filed by SWOG, the protocol serves as the Investigator Brochure for the performance of the protocol. In such instances submission of the protocol to the IRB should suffice for providing the IRB with information about the drug. However, in cases where the IRB insists on having the official Investigator Brochure from the company, further information may be requested by contacting the SWOG Operations Office at 210/614-8808.

3.1 Anastrozole (Arimidex®) (NSC-719344) (SWOG IND-120404)

a. PHARMACOLOGY

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

b. PHARMACOKINETICS

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

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

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

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

c. ADVERSE EFFECTS

1. Possible Adverse Reactions of Anastrozole:

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

Adverse Events with Possible Relationship to Anastrozole		
Likely (> 20%)	**Less Likely (≤ 20%)**	**Rare but Serious (< 3%)**
	Diarrhea	
	Nausea	
	Vomiting	
GENERAL DISORDERS AND ADMINISTRATION SITE CONDITIONS		
	Asthenia	
HEPATOBILIARY DISORDERS		
		Increase in alkaline phosphatase
		Increase in ALT
		Increase in AST
METABOLISM AND NUTRITION DISORDERS		
	Hypercholesterolemia	Anorexia
MUSCULOSKELETAL AND CONNECTIVE TISSURE DISORDERS		
Arthralgia/Joint stiffness	Myalgia	
	Bone pain	
	Arthritis	
NERVOUS SYSTEM DISORDERS		
	Headache	Somnolence
	Sensory disturbances (paresthesia, taste disturbances and taste perversion)	Carpal Tunnel Syndrome
RENAL AND URINARY DISORDERS		
	Vaginal bleeding	
	Vaginal dryness	
SKIN AND SUBCUTANEOUS TISSUE DISORDERS		
	Rash	Allergic reactions
	Alopecia	
VASCULAR DISORDERS		
Hot flashes		

< 1%, postmarketing, and case reports: hepatitis, increase in gamma-GT, bilirubinemia, hypercalcemia (with or without an increase in parathyroid hormone), trigger finger, urticaria, angioedema, anaphylaxis, cutaneous vasculitis (including Henoch-Schönlein purpura), erythema multiforme, Stevens-Johnson syndrome.

Refer to the current FDA-approved package insert for the most comprehensive and up to date information on adverse reactions.

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

3. Drug Interactions: Per the manufacturer, it is unlikely that anastrozole will inhibit the metabolism of cytochrome P450-mediated drugs given concomitantly. Tamoxifen should not be administered with anastrozole. Estrogen containing therapies should not be used with anastrozole as they may diminish its pharmacological effect.

d. DOSING & ADMINISTRATION

1. Dosing – See Section 7.0 Treatment Plan

2. Anastrozole or placebo may be administered with or without food.

e. STORAGE & STABILITY

Store at controlled room temperature, 20-25°C (68-77°F).

f. How Supplied

1. Anastrozole will be supplied in HDPE bottles of 112 tablets.

Anastrozole 1 mg tablets are film coated tablets.

2. Anastrozole is commercially available; however, it is considered investigational for this study. Anastrozole 1 mg tablets will be supplied by AstraZeneca **until June 30, 2019.** Anastrazole will be distributed by the Department of Veterans Affairs Cooperative Studies Program Clinical Research Pharmacy Coordinating Center (PCC). **For patients still receiving study treatment as of December 2018, remaining drug supply** for the duration of 2019 (supplied until June 30, 2019) **will be shipped to participating sites no later than December 28, 2018.** Each participating Institution must have a Pharmacy ID Number, in addition to their Institution Number, before randomization of subjects can begin. SWOG institutions already have a pharmacy associated with them, so they do not need to report a Pharmacy ID number since that information is already linked in the SWOG database. However, non-SWOG institutions must be assigned a pharmacy ID number by the PCC. With the initial and each subsequent randomization, the non-SWOG institution will be required to provide its Institution's Pharmacy ID Number. No randomizations can be completed without a Pharmacy ID Number.

For participating non-SWOG institutions, each Institution must call the PCC at (505) 248-3203 to register its Institution with the PCC and receive a Pharmacy ID Number. This registration by non-SWOG Participating Institutions with the PCC must be completed at least 1 working day prior to the randomization of the first subject at the site or randomization of the first subject will have to be postponed. When calling the PCC, the caller will be asked which study they are calling in regards to. To facilitate the caller being transferred to the correct PCC staff, the caller should indicate the "SWOG protocol **S1222**". To register an Institution, the PCC will require:

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

Anastrozole will be packaged by AstraZeneca, labeled by the PCC and supplied to the Institutions in HDPE bottles containing 112 tablets sufficient drug for three cycles of treatment. No supply of unassigned anastrozole will be maintained at the Institutions. Rather anastrozole will be supplied to the site in a "just in time" manner. Upon notification of a randomization by the SWOG Statistics and Data Management Center, the PCC will ship the first patient-specific bottle to an Institution to arrive within four working days. Each bottle will be labeled specifically for an individual subject with the subject's SWOG Patient Number.

Subsequent patient-specific bottles will automatically be shipped to the Institution approximately two weeks prior to the needed cycle. The bottle labels will be permanently attached. The site will write down the bottle

numbers on the Drug Accountability Record Form when the bottle is dispensed.

If a subject requires a replacement kit (Emergency Kit) for lost (etc.) medication prior to December 28, 2018, an Emergency Kit should be supplied by calling the PCC at (505) 248-3203.

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

3. Drug Handling and Accountability

   a. Drug accountability: The investigator, or a responsible party designated by the investigator, must maintain a careful record of the receipt, dispensing, and return of all study drugs received from the distributor using the NCI Drug Accountability Record Form for oral agents. A separate record must be maintained for each patient on this protocol. Expiration dates will be centrally monitored by PCC and sites will be notified of any drug that should not be dispensed.

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

4. Drug Return and/or Disposition Instruction

   a. Drug Returns: All unused drug, unopened and unused bottles remaining when a subject goes off treatment, and expired bottles should be destroyed on-site in accordance with institutional policy. Opened bottles with remaining tablets should be documented in the patient-specific accountability record (i.e., logged in as "# of tablets returned") and destroyed on-site in accordance with institutional policy.

   b. Drug Transfers: Bottles MAY NOT be transferred from one patient to another patient or from one protocol to another protocol.

5. Contact Information: Questions about drug orders, transfers, returns or accountability should be addressed to the PCC at (505) 248-3203 until December 31, 2018, then question about drug accountability should be addressed to protocols@swog.org.

3.2 Everolimus (Afinitor®, Zortress®) (NSC-733504) (SWOG IND-120404)

a. PHARMACOLOGY

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

b. PHARMACOKINETICS

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

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

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

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

c. ADVERSE EFFECTS

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

Adverse Events with Possible Relationship to Everolimus		
Likely (>20%)	**Less Likely (≤20%)**	**Rare but Serious (<3%)**
BLOOD AND LYMPHATIC SYSTEM DISORDERS		
Anemia	Leukopenia	Pancytopenia
	Lymphopenia	Pure red cell aplasia
	Neutropenia	
	Thrombocytopenia	
CARDIAC DISORDERS		
		Congestive cardiac failure
GASTROINTESTINAL DISORDERS		
Stomatitis	Abdominal pain	
Diarrhea	Dry mouth	
Nausea	Dyspepsia	
	Dysphagia	
	Oral pain	
	Vomiting	
GENERAL DISORDERS AND ADMINISTRATION SITE CONDITIONS		
Asthenia	Mucosal inflammation	Impaired wound healing
Fatigue	Pyrexia	
Peripheral edema	Non-cardiac chest pain	
IMMUNE SYSTEM DISORDERS		
		Hypersensitivity
INFECTIONS AND INFESTATIONS		
Infections	Pneumonia	
INVESTIGATIONS		
Weight decreased	ALT increased	
	AST increased	

Adverse Events with Possible Relationship to Everolimus		
Likely (>20%)	**Less Likely (≤20%)**	**Rare but Serious (<3%)**
	Blood creatinine increased	
METABOLISM AND NUTRITION DISORDERS		
Decreased appetite	Dehydration	
Hypercholesterolemia	Diabetes mellitus	
Hyperglycemia	Hypokalemia	
	Hyperlipidemia	
	Hypophosphatemia	
	Hypertriglyceridemia	
MUSCULOSKELETAL AND CONNECTIVE TISSURE DISORDERS		
	Arthralgia	
NERVOUS SYSTEM DISORDERS		
Dysgeusia	Ageusia	
Headache		
PSYCHIATRIC DISORDERS		
	Insomnia	
RENAL AND URINARY DISORDERS		
	Proteinuria	Acute renal failure
	Renal failure	
	Increased daytime urination	
REPRODUCTIVE AND BREAST DISORDERS		
	Menstruation irregular	
	Amenorrhea	
RESPIRATORY, THORACIC AND MEDIASTINAL DISORDERS		
Epistaxis	Cough	Acute respiratory distress syndrome
Pneumonitis	Dyspnea	Hemoptysis
		Pulmonary embolism
SKIN AND SUBCUTANEOUS TISSUE DISORDERS		
Rash	Acne	Angioedema
Pruritus	Dry skin	
	Erythema	
	Hand-foot syndrome	
	Nail disorder	
VASCULAR DISORDERS		
	Hemorrhage	Deep vein thrombosis
	Hypertension	

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

3. Drug Interactions: Everolimus is a substrate of cytochrome P450 3A4 (CYP3A4) and also a substrate and moderate inhibitor of the multidrug efflex pump P-glycoprotein (PgP). In vitro, everolimus is a competitive inhibitor of CYP3A4 and a mixed inhibitor of CYP2D6. Drugs or

substances known to be strong inhibitors or inducers of the isoenzyme CYP3A4 must be avoided as these can alter metabolism.

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

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

d. DOSING & ADMINISTRATION

1. Dosing – See Treatment Plan

2. Everolimus should be administered orally, once daily preferably in the morning with a glass of water and no more than a light fat-free meal. Tablets should be swallowed whole with a glass of water. Grapefruit or grapefruit juice should be avoided. The tablets must not be chewed and crushed. If unable to swallow whole tablet, may disperse tablet completely in 30 mL water and drink immediately; rinse container with additional 30 mL water and swallow. If vomiting occurs, the dose is replaced only if the tablets can actually be seen and counted. Missed doses must not be made up.

e. STORAGE & STABILITY

The intact blister packs should be stored at controlled room temperature (15°-30°C) and protected from light. Current stability data permit shelf life of 24 months for 5 mg tablet variant based on solid dispersion dried by paddle dryer and 36 months for 5 mg tablet variant based on solid dispersion dried by evaporation/drying oven if stored below 30° C in the original double-sided aluminum blister and protected from light and moisture.

f. HOW SUPPLIED

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

Everolimus 5 mg tablets are white to slightly yellow, elongated tablets with a beveled edge and no score, engraved with "5" on one side and "NVR" on the other.

Everolimus is commercially available, however it is considered investigational for this study. Everolimus 5 mg tablets will be supplied by Novartis Pharmaceuticals Corporation **until December 31, 2019.** Everolimus will be distributed by the Department of Veterans Affairs Cooperative Studies Program Clinical Research Pharmacy Coordinating Center (PCC). **For patients still receiving study treatment as of December 2018, remaining drug supply** for the duration of 2019 (supplied until December 31, 2019) **will be shipped to participating sites no later than December 28, 2018.** Each participating Institution must have a Pharmacy ID Number, in addition to their Institution Number, before randomization of subjects can begin. SWOG institutions already have a pharmacy associated with them, so they do not need to

report a Pharmacy ID number since that information is already linked in the SWOG database. However, non-SWOG institutions must be assigned a pharmacy ID number by the PCC. With the initial and each subsequent randomization, the non-SWOG institution will be required to provide their Institution's Pharmacy ID Number. No randomizations can be completed without a Pharmacy ID Number. For participating non-SWOG institutions, each Institution must call the PCC at (505) 248-3203 to register their Institution with the PCC and receive a Pharmacy ID Number. This registration by non-SWOG Participating Institutions with the PCC must be completed **at least 1 working day prior to the randomization of the first subject** at the site or randomization of the first subject will have to be postponed. When calling the PCC, the caller will be asked which study they are calling in regards to. To facilitate the caller being transferred to the correct PCC staff, the caller should indicate the "SWOG protocol **S1222**". To register an Institution, the PCC will require:

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

2. Everolimus will be packaged by Novartis, labeled by the PCC and supplied to the Institutions in kits of 20 blister cards, with each kit containing sufficient drug for three cycles of treatment. No supply of unassigned everolimus will be maintained at the Institutions. Rather everolimus will be supplied to the site in a "just in time" manner. **Upon notification of a randomization by the SWOG Statistics and Data Management Center, the PCC will ship the first patient-specific kit to an Institution to arrive within four working days.** Each kit will be labeled specifically for an individual subject with the subject's SWOG Patient Number.

   Subsequent patient-specific kits will automatically be shipped to the Institution approximately two weeks prior to the needed cycle.

   If a subject requires a replacement kit (Emergency Kit) for lost (etc.) medication prior to December 28, 2018, an Emergency Kit should be supplied by calling the PCC at 505/248-3203.

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

3. Drug Handling and Accountability

   Drug accountability: The investigator, or a responsible party designated by the investigator, must maintain a careful record of the receipt, dispensing, and return of all study drugs received from the distributor using the NCI Drug Accountability Record Form for oral agents. Each kit should be logged sequentially (Kit #1, Kit #2, etc.) and the five-digit number on the upper left-hand corner of the box recorded as the Lot #. A separate record must be maintained for each patient on this protocol. Expiration dates will be centrally monitored by PCC and sites will be notified of any drug that should not be dispensed.

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

4. Drug Return and/or Disposition Instruction

a. Drug Returns: All unused drug, unopened and unused blister cards remaining when a subject goes off treatment, and expired blister cards should be destroyed on-site in accordance with institutional policy. Partially used blister cards with remaining tablets should be documented in the patient-specific accountability record (i.e., logged in as "# of tablets returned") and destroyed on-site in accordance with institutional policy.

b. Drug Transfers: Blister cards MAY NOT be transferred from one patient to another patient or from one protocol to another protocol.

5. Contact Information: Questions about drug orders, transfers, returns or accountability should be addressed to the PCC at (505) 248-3203 until December 31, 2018, then question about drug accountability should be addressed to protocols@swog.org.

3.3 Fulvestrant (Faslodex®) (NSC-719276) (SWOG IND-120404)

a. PHARMACOLOGY

Mechanism of Action: Fulvestrant, a 7-alph alkylamide estrogen analogue, is an estrogen receptor down regulator (ERD). One of its main differences from tamoxifen and the other SERMs is its lack of estrogen-agonist activity. Compared to tamoxifen and toremifene (Fareston®), fulvestrant appears uterine-sparing, and may inhibit endometrial cancer. ERDs can bind to the ER with high affinity, similar to that of estradiol. Two activation functions, AF-1 and AF-2, are involved in activation of transcription. ERD is able to render both AF-1 and AF-2 inactive, thus eliminating estrogenic activity. ERD triggers rapid degradation of the ER, which can, therefore, no longer contribute to cell growth. Thus, not only is ER blocked functionally, but cellular levels of ER are significantly reduced.

b. PHARMACOKINETICS

1. Absorption: When given, steady state concentrations are reached within the first month, when administered with an additional dose given 2 weeks following the initial dose; plasma levels were maintained for at least 1 month. After administration of 250 mg of fulvestrant intramuscularly every month, plasma levels approach steady-state after 3 to 6 doses, with an average 2.5-fold increase in plasma AUC compared to single dose AUC and trough levels about equal to the single dose Cmax.

2. Distribution: Fulvestrant is highly bound (99%) to plasma proteins. VLDL, LDL, and HDL appear to be the major binding components. The role of sex hormone-binding globulin, if any, could not be determined. Fulvestrant is subject to extensive and rapid distribution. Volume of distribution is 3-5 L/kg. This suggests that distribution is largely extravascular.

Metabolism: Fulvestrant appears to undergo multiple hepatic biotransformation pathways such as oxidation, hydroxylation, and conjugation with glucuronic acid and/or sulphate. Metabolites formed are either less active or have similar activity to the parent compound.

3. Elimination: Following intravenous administration, fulvestrant is rapidly cleared at a rate approximating hepatic blood flow (10.5 mL plasma/min/Kg). The apparent half-life is approximately 40 days. Elimination occurs through the feces (90%) and urine (1%).

c. ADVERSE EFFECTS

1. Refer to the current FDA-approved package insert for the most comprehensive and up to date information on adverse reactions.

Adverse Events with Possible Relationship to Fulvestrant		
Likely (≥ 10%)	**Less Likely (≥/+= 10%)**	**Rare but Serious (≥ 0.1% and 1%)**
BLOOD AND LYMPHATIC SYSTEM		
	Reduced platelet count	
GASTROINTESTINAL DISORDERS		
Nausea	Diarrhea	
	Vomiting	
GENERAL DISORDERS AND ADMINISTRATION SITE CONDITIONS		
Asthenia		
Injection Site Reactions		
HEPATOBILIARY DISORDERS		
Elevated liver enzymes (ALT, AST and ALP)	Elevated bilirubin	Hepatic failure
		Hepatitis
		Elevated gamma-GT
IMMUNE SYSTEM DISORDERS		
Hypersensitivity reactions		
INFECTIONS AND INFESTATIONS		
	Urinary tract infections	
METABOLISM AND NUTRITION DISORDERS		
	Anorexia	
MUSCULOSKELETAL AND CONNECTIVE TISSUE DISORDERS		
Joint and musculoskeletal pain		
NERVOUS SYSTEM DISORDERS		
Headache		
SKIN AND SUBCUTANEOUS TISSUE DISORDERS		
Rash		
VASCULAR DISORDERS		
Hot flashes		

ALT: Alanine aminotransferase; AST: Aspartate aminotransferase; ALP: alkaline phosphatase; gamma-GT: gamma-glutamyltransferase

2. Pregnancy and Lactation: Category D. Excretion in breast milk unknown/not recommended.

3. Drug Interactions: There are no known significant interactions.

d. DOSING & ADMINISTRATION

Dosing – See Section 7.0 Treatment Plan

e. HOW SUPPLIED

1. Fulvestrant will be supplied as a 500 mg dose kit containing two fulvestrant 50 mg/ml LA IM prefilled syringes + 2 safety glide needles and a safety glide application leaflet.

2. Fulvestrant is commercially available and will be supplied by AstraZeneca **until December 31, 2019.** Fulvestrant will be distributed by the Department of Veterans Affairs Cooperative Studies Program Clinical Research Pharmacy Coordinating Center (PCC). **For patients still receiving study treatment as of December 2018, remaining drug supply** for the duration of 2019 (supplied until December 31, 2019) **will be shipped to participating sites no later than December 28, 2018.** Each participating Institution must have a Pharmacy ID Number, in addition to its Institution Number, before randomization of subjects can begin. SWOG institutions already have a pharmacy associated with them, so they do not need to report a Pharmacy ID number since that information is already linked in the SWOG database. However, non-SWOG institutions must be assigned a pharmacy ID number by the PCC. With the initial and each subsequent randomization, the non-SWOG institution will be required to provide its Institution's Pharmacy ID Number. No randomizations can be completed without a Pharmacy ID Number. For participating non-SWOG institutions, each Institution must call the PCC at (505) 248-3203 to register with the PCC and receive a Pharmacy ID Number. This registration by non-SWOG Participating Institutions with the PCC must be completed **at least 1 working day prior to the randomization of the first subject** at the site or randomization of the first subject will have to be postponed. When calling the PCC, the caller will be asked which study they are calling in regards to. To facilitate the caller being transferred to the correct PCC staff, the caller should indicate the "SWOG protocol **S1222**". To register an Institution, the PCC will require:

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

   Fulvestrant will be packaged by AstraZeneca, labeled by the PCC and supplied to the Institutions in kits of 2 syringes, with each kit containing sufficient drug for one cycle of treatment. A supply of sufficient drug for up to three months (four kits for the initial supply and three kits for subsequent treatments) may be sent in a single shipment. Unused fulvestrant kits will be stored at sites in accordance with storage requirements (above) until the patient returns for the next treatment cycle. **Upon notification of a randomization by the SWOG Statistics and Data Management Center, the PCC will ship the first set of patient-specific kits to an Institution to arrive within four working days.** Each kit will be labeled specifically for an individual subject with the subject's SWOG Patient Number.

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

If a subject requires a replacement kit (Emergency Kit) for damaged (etc.) medication prior to December 28, 2018, an Emergency Kit should be supplied by calling the PCC at (505) 248-3203.

3. Drug Handling and Accountability

   a. Drug accountability: The investigator, or a responsible party designated by the investigator, must maintain a careful record of the receipt, dispensing, and return of all study drugs received from the distributor using the NCI DARF. A separate record must be maintained for each patient on this protocol. Expiration dates will be centrally monitored by PCC and sites will be notified of any drug that should not be dispensed.

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

4. Drug Return and/or Disposition Instruction

   a. Drug Returns: All unused drug, unopened and unused kits remaining when a subject goes off treatment, and expired kits should be destroyed on-site in accordance with institutional policy.

   b. Drug Transfers: Kits **MAY NOT** be transferred from one patient to another patient or from one protocol to another protocol.

5. Contact Information: Questions about drug orders, transfers, returns or accountability should be addressed to the PCC at 505/248-3203 until December 31, 2018, then question about drug accountability should be addressed to protocols@swog.org.

4.0 STAGING CRITERIA

Note: All staging will be based on the American Joint Committee on Cancer 2002 Staging System, 7th Edition.

M1 Distant metastases as determined by classical clinical and radiographic means and/or histologically proven larger than 0.2 mm.

5.0 ELIGIBILITY CRITERIA

Each of the criteria in the following section must be met in order for a patient to be considered eligible for registration. Use the spaces provided to confirm a patient's eligibility. For each criterion requiring test results and dates, please record this information on the **S1222** On Study Form and submit via Medidata Rave® (see Section 14.0). Any potential eligibility issues should be addressed to the SWOG Statistics and Data Management Center in Seattle at 206/652-2267 prior to registration.

In calculating days of tests and measurements, the day a test or measurement is done is considered Day 1. Therefore, if a test is done on a Monday, the Monday 2 weeks later would be considered Day 15. This allows for efficient patient scheduling without exceeding the guidelines. If Day 15, 29, 43, or 85 falls on a weekend or holiday, the limit may be extended to the next working day.

5.1 Disease Related Criteria

a. Patients must have a histologically confirmed diagnosis of invasive breast carcinoma with positive estrogen and/or progesterone receptor status, and negative HER-2, for whom endocrine therapy is planned. Cytology-based diagnosis is allowed only if morphology, hormone-receptor and HER2 status can be assessed on such specimen. The HER-2 test result is negative (and should be reported as such), if a single test (or all tests) performed in a tumor specimen show: a) IHC 1+ negative or IHC 0 negative or b) ISH negative using a single probe ISH or dual probe ISH. Estrogen receptor (ER) and progesterone receptor (PgR) positivity must be assessed according to ASCO/CAP guidelines as either ER or PR ≥ 1% positive nuclear staining. If HER2 IHC is 2+, an evaluation for gene amplification must be performed and the gene must not be amplified. Gene amplification evaluation is not required if evaluation by IHC is 0 or 1+ by institutional standards. NOTE: In cases where the HER2 status of metastases (particularly in bone) is inconclusive (i.e. HER2 testing is 2+ by immunohistochemistry) the primary tumor must be HER2 negative by ASCO/CAP guidelines.

b. Patients must be post-menopausal women with a confirmed diagnosis of metastatic breast cancer (M1-see Section 4.0). Pathologic confirmation of histology is preferable. In the case of bone metastases only, biopsy-proven metastatic disease of solitary site, or multiple sites of involvement are required. Post-menopausal is defined by at least one of the following criteria:

- Prior bilateral oophorectomy OR
- Amenorrheic for ≥ 12 months (if ≤ 55 years of age and prior chemotherapy in the past 5 years and/or tamoxifen within the past year, then FSH and estradiol must be in the post-menopausal range and obtained within 28 days prior to registration) OR
- Previous hysterectomy with one or both ovaries left in place (or previous hysterectomy in which documentation of bilateral oophorectomy is unavailable AND FSH values consistent with the institutional normal values for the post-menopausal state. FSH levels must be obtained within 28 days prior to registration.

5.2 Clinical/Laboratory Criteria

a. Patients must have measurable or non-measurable disease (see Section 10.1). Patients must have a chest/abdominal CT scan (PET/CT of diagnostic quality, conventional or spiral) and bone scan within 28 days prior to registration. All scans needed for assessment of measurable disease must be performed within 28 days prior to registration. Non-measurable disease must be assessed within 42 days prior to registration. All disease must be assessed and documented on the Baseline Tumor Assessment Form.

b. Patients with a history of prior chemotherapy or hormone therapy or immunotherapy for recurrent or metastatic disease are NOT eligible. Prior adjuvant or neoadjuvant chemotherapy if completed more than 12 months prior to registration is acceptable. Any number of prior hormonal therapy regimens for the adjuvant setting but not for metastatic or recurrent disease is allowed; prior adjuvant or neoadjuvant treatment with an aromatase inhibitor (e.g. anastrozole, letrozole, exemestane) is allowed, if completed more than 12 months prior to randomization. Radiation therapy to any site must be completed at least 7 days prior to registration.

c. Patients who have taken luteinizing hormone-releasing hormone (LHRH) analogue as adjuvant therapy are eligible provided they have a) discontinued such therapy at least 12 months prior to registration AND b) have not resumed their menstrual periods.

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

e. Patients must have an International Normalized Ratio (INR) ≤ 1.6 within 28 days prior to registration.

f. Patients must have adequate bone marrow function, as defined by Absolute Neutrophil Count (ANC) of ≥ 1,500/mL, hemoglobin ≥ 9 g/dL and a peripheral platelet count ≥ 100,000/ mL, all within 28 days prior to registration.

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

- Bilirubin ≤ 1.5 mg/dL (or ≤ 3.0 mg/dL if due to Gilbert's Syndrome)
- ALT (SGPT) and AST (SGOT) ≤ 2.5 x Institutional Upper Limit of Normal (IULN), or ≤ 5 x IULN if hepatic metastases are present.

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

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

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

k. Patients with bleeding diathesis (i.e., disseminated intravascular coagulation [DIC], clotting factor deficiency) or long-term anti-coagulant therapy (other than antiplatelet therapy) are NOT eligible.

l. Patients with presence of life-threatening metastatic visceral disease, defined as extensive hepatic involvement, or any degree of brain or leptomeningeal involvement (past or present), or symptomatic pulmonary lymphangitic spread are not eligible. Patients with discrete pulmonary parenchymal metastases are eligible, provided their respiratory function is not significantly compromised as a result of disease in the opinion of the investigator.

m. Patients must have a performance status of 0 - 2 by Zubrod criteria (see Section 10.4).

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

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

p. Patients must not have an organ allograft or other history of immune compromise. Patients must not be receiving chronic, systemic treatment with corticosteroids or other immunosuppressive agent. Topical or inhaled corticosteroids are allowed.

q. Patients known to be HIV positive may be enrolled if baseline CD4 count is > 500 cells/mm3 AND not taking anti-retroviral therapy. Patients with known chronic or active hepatitis are not eligible. Patients must not have any known uncontrolled underlying pulmonary disease.

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

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

t. Patients must not have taken within 14 days prior to registration, be taking, nor plan to take while on protocol treatment, strong CYP3A4 inhibitors, and/or CYP3A4 inducers. (See Section 7.3 and Section 18.3.)

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

5.2 Specimen Submission

a. Patients must have consented to a baseline blood draw for analysis of CTC-ETI, CTC-NGS and germline DNA sequencing as outlined in Section 15.2.

b. Patients must be offered participation in banking of specimens for future research. With the patient's consent, specimens (tissue from primary tumor and/or metastatic biopsy) must be submitted to the repository. Patient consent must be obtained before specimens are submitted. See Section 15.1 for further information, including specimen submission timepoints.

5.3 Regulatory Criteria

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

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

6.0 STRATIFICATION FACTORS

Patients will be stratified according to the following factors:

- Measurable versus evaluable non-measurable disease
- Prior adjuvant hormonal therapy completed more than 5 years ago vs. prior adjuvant hormonal therapy completed 1-5 years ago vs. de novo presentation of metastatic disease or no prior adjuvant hormonal therapy.

7.0 TREATMENT PLAN

For treatment or dose modification related questions, please contact Dr. Halle Moore at 216/445-4624 (S1222question@swog.org). For dosing principles or questions, please consult the SWOG Policy #38 "Dosing Principles for Patients on Clinical Trials" at at https://www.swog.org/sites/default/files/docs/2017-11/Policy38.pdf.

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

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

7.1 Treatment Schedule

Patients will be randomized to one of the following arms:

- Arm 1: fulvestrant
- Arm 2: fulvestrant + everolimus
- Arm 3: fulvestrant + everolimus + anastrozole

Treatment will be continued until patient has met any of the criteria outlined in Section 7.7.

Arm 1: Cycle 2 and Subsequent Doses:

AGENT	DOSE	ROUTE	DAYS	RE-TX
Fulvestrant	500 mg (2 x 5 ml)	IM *	1	q 28 days **

* Administer one (250 mg [50 mg/ml:5 ml vial]) injection into EACH buttock (total dose 500 mg).

** One cycle equals 28 days, or the interval between fulvestrant if greater than 28 days (in the event of a treatment delay).

Arm 2: Cycle 2 and Subsequent Doses:

AGENT	DOSE	ROUTE	DAYS	RE-TX
Fulvestrant	500 mg (2 x 5 ml)	IM *	1	q 28 days **

Everolimus ***	10 mg (2 [5mg] tablets)	PO	Every day

* Administer one (250 mg [50 mg/ml:5 ml vial]) injection into EACH buttock (total dose 500 mg).
** One cycle equals 28 days, or the interval between fulvestrant if greater than 28 days (in the event of a treatment delay).
*** Everolimus must be administered orally, once daily preferably in the morning with a glass of water and no more than a light fat-free meal. Tablets must be swallowed whole with a glass of water. The tablets must not be chewed or crushed, and grapefruit or grapefruit juice should be avoided (see Section 3.2d.2 for more details).

Arm 3: Cycle 2 and Subsequent Doses:

AGENT	DOSE	ROUTE	DAYS	RE-TX
Fulvestrant	500 mg (2 x 5 ml)	IM *	1	q 28 days **
Everolimus ***	10 mg (2 [5mg] tablets)	PO	Every day	
Anastrozole	1 mg	PO	Every day	

* Administer one (250 mg [50 mg/ml:5 ml vial]) injection into EACH buttock (total dose 500 mg).
** One cycle equals 28 days, or the interval between fulvestrant if greater than 28 days (in the event of a treatment delay).
*** Everolimus must be administered orally, once daily preferably in the morning with a glass of water and no more than a light fat-free meal. Tablets must be swallowed whole with a glass of water. The tablets must not be chewed or crushed, and grapefruit or grapefruit juice should be avoided (see Section 3.2d.2 for more details).

7.2 Fulvestrant Administration

Fulvestrant will be administered by two 250 mg IM injections, one into each buttock using aseptic parenteral technique. The injection is not to be administered into any other site, nor is it to be split. The injection must be administered slowly. On Cycle 1 Day 1 the patient will receive (2) 250 mg injections, one into each buttock. The patient will return on Day 15 for two 250 mg injections, one into each buttock. All subsequent injections of 500 mg total dose (two 250 mg injections, one into each buttock) will be given on Day 1 of each cycle. NOTE: There is a three day window for fulvestrant administration.

Following administration the injection sites should be assessed by the investigator for any local reaction. The patient should be instructed to report complications to the investigator. Appropriate measures such as the application of heat or cold should be instituted according to basic nursing intervention and institutional policy. Any severe local site reaction should be treated with appropriate medical intervention.

7.3 Concomitant Therapy

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

- No other investigational therapy must be given to patients.
- No chronic treatment with systemic steroids (unless for the treatment of pneumonitis as described in Section 8.4d) or another immunosuppressive agent. Topical or inhaled corticosteroids are allowed.
- No anticancer agents other than the study medications administered as part of this study protocol must be given to patients. If such agents are required for a patient then the patient must be removed from protocol treatment.
- Growth factors (e.g. G-CSF, G-GM-CSF) are not to be administered prophylactically but may be prescribed by the treating physician for rescue from severe hematologic events.
- Live vaccines must not be administered to patient due to immunosuppressant potential of everolimus.
- Drugs or substances known to be strong inhibitors or inducers of the isoenzyme CYP3A4 (as indicated in Section 3.2c.3 and Section 18.5) must be avoided in association with everolimus as these can alter metabolism. Strong inhibitors or inducers of the isoenzyme CYP3A4 must not be administered as systemic therapy.

7.4 Intake Calendar

Drug adherence will be recorded by patients in the Intake Calendar (see Appendix 18.1). Do not submit Intake Calendars to the SWOG Statistics and Data Management Center. Institutional CRAs will review and ascertain patient adherence with protocol therapy at the end of treatment for each reporting period. Summarized information from the daily intake calendars will be reported on the **S1222** Treatment Form and submitted per Section 14.4.

7.5 Criteria for Removal from Protocol Treatment

a. Progression of disease or symptomatic deterioration as defined in Section 10.2.

b. Unacceptable toxicity (as defined in Section 8.0).

c. Delay of treatment ≥ 4 weeks for any reason.

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

e. Drug interactions with anti-retroviral therapy are likely, and if the patient requires the initiation of such therapy due to a drop in CD4 count < 500 cells/mm^3, study medication must be permanently discontinued.

NOTE: Removal due to Stable Disease is NOT acceptable. All patients should be followed for objective progression and survival irrespective of whether they are removed from study treatment

7.6 Discontinuation of Treatment

All reasons for discontinuation of treatment must be documented in the Off Treatment Notice

7.7 Follow-Up Period

All patients will be followed until death, a minimum of 2 years or until December 31, 2019.

8.0 TOXICITIES TO BE MONITORED AND DOSE MODIFICATIONS

8.1 NCI Common Terminology Criteria for Adverse Events

This study will utilize the CTCAE (NCI Common Terminology Criteria for Adverse Events) Version 4.0 for toxicity and Serious Adverse Event reporting. A copy of the CTCAE Version 4.0 can be downloaded from the CTEP home page (http://ctep.cancer.gov). All appropriate treatment areas should have access to a copy of the CTCAE Version 4.0.

8.2 General Considerations

a. Missed doses for the oral drugs are to be omitted rather than made up.

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

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

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

e. There are no dose modifications for fulvestrant.

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

8.3 Dose Levels for Everolimus

Dose Levels	Dose
Full	2 tablets daily (5 mg x 2 for a total dose of 10 mg)
-1 Level	1 tablet daily (5 mg)
-2 Level	1 tablet every other day (5 mg)
-3 Level	Discontinue everolimus

8.4 Dose Modifications for Everolimus

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

Toxicity	Actions
Stomatitis (Oral Mucositis)	
Grade 2	Interrupt everolimus until recovery to Grade ≤ 1, then reintroduce everolimus at one lower dose level. If event returns to Grade ≥ 2, then interrupt everolimus until recovery to Grade ≤ 1. Then reintroduce everolimus at one

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

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

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

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

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

Any other non-hematological toxicities not previously described	
Grade 4 Anemia	Discontinue everolimus.
Grade 3 Lymphopenia	Interrupt everolimus until recovery to Grade ≤ 1. Then resume everolimus at one lower dose level. If Grade 3 lymphopenia recurs, interrupt everolimus until recovery to Grade ≤ 1. Then reintroduce everolimus at one lower dose level. If the event returns to Grade 3, then discontinue everolimus.
Grade 4 Lymphopenia	Discontinue everolimus.
Grade 2 Hyperglycemia	Treat diabetes according to current guidelines, with particular emphasis on diet modification. When medical therapy is initiated try to give priority to metformin or other non-insulin methods. No dose change.
Grade 3 Hyperglycemia	Stop the everolimus and treat diabetes according to current guidelines, with particular emphasis on diet modification. Priority should be given to metformin or other non-insulin methods. Restart the everolimus at one lower dose level. If despite optimal therapy, the event returns to Grade ≥ 3, interrupt everolimus until recovery to Grade ≤ 1. Then reintroduce everolimus at one lower dose level. If the event returns again to Grade ≥ 3, discontinue everolimus.
Grade 4 Hyperglycemia	Discontinue everolimus.
Hematological toxicity	**Actions**
Grade 2 Hypercholesterolemia	Treat according to guidelines with emphasis on diet modifications. No dose reduction.
Grade 3 Hypercholesterolemia	Stop the everolimus and treat according to current guidelines, with particular emphasis on diet modification, and medical therapy with statins. Restart the everolimus at one lower dose level. If despite optimal therapy, the event returns to Grade ≥ 3, interrupt everolimus until recovery to Grade ≤ 1. Then reintroduce everolimus at one lower dose level. If the event returns again to Grade ≥ 3, discontinuer everolimus.
Grade 4 Hypercholesterolemia	Discontinue everolimus.

a. Hematological Toxicity

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

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

b. Hyperlipidemia

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

c. Hyperglycemia

Grade 3 hyperglycemia has been observed in patients receiving everolimus therapy. The fasting state of patients should be verified when interpreting results. It is suggested that optimal glucose control should be achieved before starting a patient on everolimus and should be monitored during everolimus therapy. Should hyperglycemia develop during protocol therapy, standard glucose control interventions should be implemented.

d. Pneumonitis

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

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

e. Oral Mucositis

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

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

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

aminobenzoate, tetracaine hydrochloride, menthol, or phenol) with or without topical corticosteroids, such as triamcinolone oral paste 0.1% (Kenalog in Orabase®).

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

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

f. Nausea

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

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

g. Diarrhea

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

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

8.5 Fulvestrant Related Toxicity

Toxicity potentially associated with fulvestrant will be monitored and recorded on the S1222 Adverse Event Form for all patients during therapy. Toxicities that persist after the patient has been removed from protocol treatment will be recorded on the Follow-Up Form at each follow-up visit. This will include hot flashes, vaginitis, vaginal bleeding, tumor flare, nausea, vomiting, constipation, diarrhea, abdominal pain, xerostomia. Others include weight gain, anxiety, confusion, dizziness, insomnia, paresthesia, thrombo-embolism, fatigue, UTI, arthralgia and injection site reaction.

8.6 Anastrozole Related Toxicity

Patients experiencing apparent anastrozole related toxicity will be first treated with appropriate agents to ameliorate the toxicity. When this strategy is not effective and the patient is experiencing Grade 3 or 4 toxicity that appears to be related to anastrozole treatment, all protocol related therapy will be held up to 4 weeks, or until the toxicity returns to a Grade 2 or less (whichever is shorter). For patients for whom toxicity resolves within four weeks, anastrozole will be restarted at the same dose level. For

patients for whom Grade 3 or 4 toxicity does not resolve within four weeks or recurs, the patient will be taken off protocol treatment.

8.7 Treatment for Hot Flashes

Avoid hormone treatment for hot flashes. Use hormone alternatives, example; clonidine, analgin, fluoxetine or venlafaxine while continuing with treatment. For patients with severe vaginal dryness, estrogen creams are discouraged.

8.8 Dose Modification Contacts

For treatment or dose modification related questions, please contact Halle Moore, M.D. at 216/445-4624 (S1222question@swog.org).

8.9 Adverse Event Reporting

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

9.0 STUDY CALENDAR

		Cycle 1				Cycle 2				Cycle 3 @				Off Treatment F/U Prior to Progression £	Off Treatment F/U After Progression √
REQUIRED STUDIES	PRE STUDY	W 1	W 2	W 3	W 4	W 5	W 6	W 7	W 8	W 9	W 10	W 11	W 12		
PHYSICAL															
History & Physical Exam	X	XЯ				X				X				X	X
Height, Weight and Performance Status	X	XЯ				X				X					
Disease Assessment **						X				X				X	
Toxicity Notation Ω		X	X	X	X	X				X				X	X
Review Intake Calendar & Pill Count						X				X					
LABORATORY															
CBC, differential, platelets	X					X				X					
Serum Creatinine	X					X				X					
Bilirubin	X					X				X					
ALT/AST	X					X				X					
Hbg A1c	X					X				X					
Fasting Cholesterol and Triglycerides	X					X				X					
INR	X														
FSH and estradiol levels ◇	X														
SCANS/IMAGE SUBMISSION															
CT scan chest abd/bone scan for tumor measurement **	X												X	X	
SPECIMEN SUBMISSION															
Tissue for Banking	X														X
Blood for CTC-ETI and CTC-NGS *	X					X									X
TREATMENT (see Section 7.0 for details)															
Arm 1: Fulvestrant ∑		X		X		X				X					
Arm 2: Fulvestrant and Everolimus ∑ †		X	X	X	X	X	X	X	X	X	X	X	X		
Arm 3: Fulvestrant, anastrozole and everolimus ∑ †		X	X	X	X	X	X	X	X	X	X	X	X		

(CORRESPONDING FOOTNOTES ARE CONTINUED ON THE NEXT PAGE.)

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

Footnotes:

√ After progression, follow-up will occur (with lab tests and scans performed at the discretion of the treating physician) every 6 months for two years or until death, whichever occurs first.

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

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

* Blood for the CTC-ETI and CTC-NGS studies will be collected prior to starting treatment and at Cycle 2, Day 1 and at progression (see Section 15.2 for further instructions).

† Everolimus and anastrozole is taken daily for all cycles with drug supply dispensed as per Section 3.2f.2 for everolimus and 3.1f.2 for anastrozole.

∑ See Section 7.2 for fulvestrant loading instructions.

@ Protocol treatment and parameters will continue at these intervals until patient has met any of the criteria outlined in Section 7.3. Scans must be completed every 12 weeks for 2 years from registration until progression.

** Disease will be assessed clinically at each visit. Scans for disease assessment will be repeated after every 3rd cycle using the same methods used at baseline. All sites of disease that existed at baseline must be evaluated at each assessment. Measurements must be provided for target measurable lesions, while presence or absence must be noted for non-target measurable and non-measurable disease.

£ If patient is taken off protocol treatment due to toxicity, he/she must continue to be followed every 12 weeks for progression for 2 years until progression.

◇ Patients < 60 years of age and amenorrheic for ≥ 12 months in the absence of chemotherapy, tamoxifen, etc. or patients < 60 years of age taking tamoxifen or toremifene must have FSH and estradiol levels in the post-menopausal range (see Section 5.1b).

10.0 CRITERIA FOR EVALUATION AND ENDPOINT DEFINITIONS

10.1 Measurability of lesions

a. **Measurable disease**: Measurable disease is defined differently for lymph nodes compared with other disease and will be addressed in a separate section below.

1. Lesions that can be accurately measured in at least one dimension (longest diameter to be recorded) as ≥ 2.0 cm by chest x-ray, by ≥ 1.0 cm with CT or MRI scans, or ≥ 1.0 cm with calipers by clinical exam. All tumor measurements must be recorded in decimal fractions of centimeters (or millimeters).

   The defined measurability of lesions on CT scan is based on the assumption that CT slice thickness is 0.5 cm or less. If CT scans have slice thickness greater than 0.5 cm, the minimum size for a measurable lesion should be twice the slice thickness.

2. Malignant lymph nodes are to be considered pathologically enlarged and measurable if it measures ≥ 1.5 cm in SHORT AXIS (greatest diameter perpendicular to the long axis of the lymph node) when assessed by scan (CT scan slice recommended being no greater than 0.5 cm).

b. **Non-measurable disease**: All other lesions (or sites of disease), including small lesions (longest diameter < 1.0 cm or pathologic lymph nodes with ≥ 1.0 cm to < 1.5 cm short axis), are considered non-measurable disease. Bone lesions, leptomeningeal disease, ascites, pleural/pericardial effusions, lymphangitis cutis/pulmonitis, inflammatory breast disease, and abdominal masses (not followed by CT or MRI), are considered non-measurable as are previously radiated lesions that have not progressed.

c. **Notes on measurability**

1. For CT and MRIs, the same type of scanner should be used and the image acquisition protocol should be followed as closely as possible to prior scans. Body scans should by performed with breath-hold scanning techniques, if possible.

2. PET-CT: At present, the low dose or attenuation correction CT portion of a PET-CT is not always of optimal diagnostic CT quality for use with RECIST measurements. However, if the site can document that the CT performed as part of a PET-CT is of identical diagnostic quality to a diagnostic CT, then the CT portion of the PET-CT can be used for RECIST measurements and can be used interchangeably with conventional CT.

3. Ultrasound: Ultrasound is not useful in assessment of lesion size and should not be used as a method of measurement.

4. Cystic lesions that meet the criteria for radiographically defined simple cysts should not be considered as malignant lesions (neither measurable nor non-measurable) since they are, by definition simple cysts.

5. If a target lesion becomes very small some radiologists indicate that it is too small to measure. If the lesion is actually still present, a default measurement of 0.5 cm should be applied. If the radiologist believes the lesion has gone, a default measurement of 0.0cm should be recorded.

10.2 Objective Status at Each Disease Evaluation

Objective Status is to be recorded at each evaluation. All measurable lesions up to a maximum of 2 lesions per organ 5 lesions in total, representative of all involved organs, should be identified as *target* lesions at baseline. All other lesions (or sites of disease) including any measurable lesions over and above the 5 target lesions should be identified as *non-target* lesions. Measurements must be provided for target measurable lesions, while presence or absence must be noted for non-target measurable and non-measurable disease.

For studies that use disease progression as an endpoint, whole body scanning at specific intervals is necessary to determine that progression is NOT present outside of the "target" areas. Therefore, in these studies it is not acceptable to image only the "target" areas of the body in follow-up scans. For study-specific imaging requirements, see the Study Calendar in Section 9.0.

a. **Complete Response (CR):** Complete disappearance of all target and non-target lesions (with the exception of lymph nodes mentioned below). No new lesions. No disease related symptoms. Any lymph nodes (whether target or non-target) must have reduction in short axis to < 1.0 cm. All disease must be assessed using the same technique as baseline.

b. **Partial Response (PR):** Applies only to patients with at least one measurable lesion. Greater than or equal to 30% decrease under baseline of the sum of appropriate diameters of all target measurable lesions. No unequivocal progression of non-measurable disease. No new lesions. All target measurable lesions must be assessed using the same techniques as baseline.

c. **Stable:** Does not qualify for CR, PR, Progression or Symptomatic Deterioration. All target measurable lesions must be assessed using the same techniques as baseline.

d. **Progression**: One or more of the following must occur: 20% increase in the sum of appropriate diameters of target measurable lesions over smallest sum observed (over baseline if no decrease during therapy) using the same techniques as baseline, as well as an absolute increase of at least 0.5 cm. Unequivocal progression of non-measurable disease in the opinion of the treating physician (an explanation must be provided). Appearance of any new lesion/site. Death due to disease without prior documentation of progression and without symptomatic deterioration (see Section 10.2e).

Notes regarding new lesions: FDG-PET imaging can complement regular scans in identifying new lesions according to the following algorithm.

1. Negative FDG-PET at baseline, with a positive FDG-PET at follow-up is a sign of progression based on a new lesion.

2. No FDG-PET at baseline and a positive FDG-PET at follow-up corresponding to a potential new site of disease must have a confirmation by anatomical assessment (e.g. CT, MRI, x-ray) as new site of disease to be considered progressive disease. In such a case, the

date of progressive disease will be the date of the initial abnormal FDG-PET.

e. **Assessment inadequate, objective status unknown**. Progression has not been documented, and one or more target measurable lesions have not been assessed or inconsistent assessment methods were used.

f. Objective status notes:

1. Non-measurable and non-target measurable disease do not affect Objective Status in determination of CR (must be absent--a patient who otherwise has a CR, but who has non-measurable or non-target measurable disease present or not assessed, will be classified as having a PR). However, non-measurable and non-target lesions are included in determination of progression (if new sites of disease develop or if unequivocal progression occurs in the opinion of the treating physician).

2. An objective status of PR or stable cannot follow one of CR. Stable can follow PR only in the rare case that tumor increases too little to qualify as progression, but enough that a previously documented 30% decrease no longer holds.

3. In cases for which initial flare reaction is possible (hypercalcemia, increased bone pain, erythema of skin lesions), objective status is not progression unless either symptoms persist beyond 4 weeks or there is additional evidence of progression.

4. Lesions that appear to increase in size due to presence of necrotic tissue will not be considered to have progressed.

5. For bone disease documented on bone scan only, increased uptake does not constitute unequivocal progression. However, increase in the soft tissue component of a lesion as measured by CT or MRI would constitute progression.

6. Appearance of new pleural effusions does not constitute unequivocal progression unless cytologically proven of neoplastic origin, since some effusions are a toxicity related to therapy or other medical conditions. Increase in the size of an existing effusion does not constitute unequivocal progression, since the fluid status of the patient could alter the size of the effusion.

7. CR determination depends on a lesion for which the status is unclear by the required tests, it is recommended the residual lesion be investigated with biopsy or fine needle aspirate.

10.3 Best Response. This is calculated from the sequence of objective statuses.

a. CR: Two or more objective statuses of CR a minimum of four weeks apart documented before progression.

b. PR: Two or more objective statuses of PR or better a minimum of four weeks apart documented before progression, but not qualifying as CR.

c. Unconfirmed CR: One objective status of CR documented before progression but not qualifying as CR or PR.

d. Unconfirmed PR: One objective status of PR documented before progression but not qualifying as CR, PR or unconfirmed CR.

e. Stable/no response: At least one objective status of stable/no response documented at least 6 weeks after registration and before progression, but not qualifying as anything else above.

f. Increasing disease: Objective status of progression within 12 weeks of registration, not qualifying as anything else above.

g. Inadequate assessment, response unknown: Progression greater than 12 weeks after registration and no other response category applies.

10.4 Performance Status

Patients will be graded according to the Zubrod Performance Status Scale.

POINT	DESCRIPTION
0	Fully active, able to carry on all pre-disease performance without restriction.
1	Restricted in physically strenuous activity but ambulatory and able to carry out work of a light or sedentary nature, e.g., light housework, office work.
2	Ambulatory and capable of self-care but unable to carry out any work activities; up and about more than 50% of waking hours.
3	Capable of limited self-care, confined to bed or chair more than 50% of waking hours.
4	Completely disabled; cannot carry on any self-care; totally confined to bed or chair.

10.5 Progression-Free Survival

From date of registration to date of first documentation of progression (as defined above), or death due to any cause. Patients last known to be alive without report of progression are censored at date of last contact.

10.6 Time to Death

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

10.7 Time to Treatment Failure

From date of registration to date of first documentation of progression (as defined above), early discontinuation of treatment or death due to any cause. Patients last known not to have failed treatment are censored at the date of last contact.

10.8 Response Rate and Clinical Benefit Rate

Response rate will be calculated for patients with measurable disease. The numerator includes the patients whose best response is Complete Response or Partial Response, while the denominator includes all patients with measurable disease in that treatment group (including those with inevaluable status). Clinical benefit rate will be computed for both measurable and nonmeasurable patients together. The numerator includes patients with CR, PR or Stable Disease (or Non-CR/Non-PD for nonmeasurable with all patients in that treatment group included in the denominator.

11.0 STATISTICAL CONSIDERATIONS

11.1 Design Overview

This is a parallel randomized design with equal allocation to the three arms: (1) fulvestrant + placebo for everolimus + placebo for anastrozole; (2) fulvestrant and everolimus plus placebo for anastrozole; and (3) fulvestrant, everolimus, and anastrozole. All patients take fulvestrant as the backbone therapy. The primary outcome is progression-free survival (PFS) and overall survival (OS) is the secondary survival outcome. There are two co-primary hypotheses: (1) Arm 2 versus Arm 1; and (2) Arm 3 versus Arm 1. Arm 2 versus Arm 3 is a secondary comparison. All analyses are intent-to-treat including all eligible patients.

11.2 Randomization

Patients are randomized in a 1:1:1 allocation within the appropriate stratum. There are two stratification factors described in Section 6.0.

11.3 Basis for Sample Size

There are two co-primary hypotheses each to be tested at $\alpha = 0.025$ (2-sided) so that the overall trial $\alpha = 0.05$ (2-sided). Arm 2 will be compared to Arm 1 in the first comparison and Arm 3 compared to Arm 1 in the second comparison. Both comparisons use PFS as the primary outcome. Sample size computations are based on accrual of 33 patients per month for 24 months resulting in a computed accrual total of 792. However, this number has been increased by 4% to allow for loss to follow-up so that the final accrual goal is 825. We assume that the final analysis will occur about 24 months after the last patient is accrued so length of follow-up will be 24-48 months with an average of 36 months at the time of the final analysis. Power is based on the following assumptions:

Treatment Arms	HR relative to Arm 1	Median PFS in months
1: Fulvestrant	1.0	15 months
2: Fulvestrant + Everolimus	0.70	21.5 months
3: Fulvestrant + Everolimus + Anastrozole	0.60	25 months

Under these assumptions, the comparison of Arm 2 versus Arm 1 has 90% power. The comparison of Arm 3 versus Arm 1 has 99.7% power. If exactly one of the primary comparisons is significant, then we can perform a secondary analysis of Arm 2 vs. Arm 3 at $\alpha = 0.025$ (2-sided). If both are significant, then the secondary analysis of Arm 2 vs.

Arm 3 is performed at α = 0.05 (2-sided). Power for this analysis is only 28%, but the comparison should give an indication of the degree of benefit of adding anastrozole. Under the design assumptions, there would be 264 patients with follow-up in each of the three arms. The expected number of events would be 211, 180 and 164 (total of 555 events) under the assumed hazard rates. However, the timing of the analyses is determined by the number of events in Arm 1 (control arm) only.

11.4 Accrual

Accrual is assumed to be 33 patients per month on the basis of **S0226** accrual at its maximum. However, accrual may ramp up before it reaches the expected monthly goal so this may extend the accrual period. Power would increase slightly under that scenario since the average duration of follow-up would increase.

11.5 Interim Analyses

There would be two interim analyses performed at 50% and 75% of the expected events in Arm 1 (211 events among 264 patients). The interim analyses would occur approximately at 25 months and 33 months with the final analysis at 100% of the expected events in Arm 1 (211 events). So, full publication if the trial went to 100% events on the expected schedule would lead to an expected date of 5/1/2018. If the number of events in Arm 1 is less than the target of 211 more than three years after the last accrual, then the final analysis will proceed since the expected hazard rates are less than expected.

A truncated O'Brien-Fleming rule is used for testing efficacy in the interim analyses so the 1-sided p-values are 0.001, and 0.00345 at the interim analyses and 0.0112 at the final analysis so that the cumulative 1-sided alpha is 0.0125 for the test of each hypothesis. P-values are obtained from the Lan-DeMets software (http://www.biostat.wisc.edu/Software/landemets/index.html). Accrual should be complete by the time of the first interim analysis, but if the interim analysis occurs prior to completion of accrual the following guidelines apply. If an interim analysis is significant for one of the two comparisons, then a recommendation to stop accrual to that experimental arm (Arm 2 or 3) could be made if accrual is not yet complete. If the other co-primary analysis is not significant, then accrual would continue for the two remaining arms. Upon completion of accrual, the trial would be declared positive given a significant interim analysis. Follow-up would continue in the remaining comparison if not yet significant according to the pre-specified conditions.

Futility will be assessed at each interim analysis by construction of 99.9% likelihood-ratio based confidence intervals (CI) at each interim analysis. If the CI excludes the alternative hypothesis, then futility will be suggested. Using likelihood-ratio based CI's for futility is equivalent to testing the alternative hypothesis directly. If futility is found prior to completion of accrual, a recommendation will be made that randomization for that experimental arm should stop. If futility is found after completion of accrual, a recommendation will be made that follow-up will continue until the planned end of the trial unless both comparisons show futility.

In all cases only recommendations are made to the DSMC (see Section 11.1). The DSMC will weigh the totality of the evidence including efficacy, toxicity, adverse events, and the broader context of other clinical trial results. The DSMC would then make a recommendation to the SWOG Group Chair with regard to stopping accrual, reporting trial results, or continuing the trial.

11.6 Follow-Up Time for Each Patient

The minimum follow-up time for each patient is 5 years from registration to allow assessment of overall survival. Though the analysis of PFS is planned for 2 years after the last patient is accrued, all patients will continue to be followed for progression and overall survival until at least 5 years from registration or death whichever comes first. Continued monitoring of survival beyond five years is at patient and institutional discretion.

11.7 Primary Analysis

The primary analysis is stratified log-rank testing of the comparison of the two arms in each analysis with stratification on the two factors in Section 6.0. Cox regression will be used to estimate the hazard ratio and its 95% confidence interval for the comparison. The stratification factors are also included as main effects in the Cox regression analysis regardless of statistical significance. Interactions of the treatment factors with each stratification variable will be tested to assess whether the treatment effect varies across strata. The assumption of proportional hazards will be tested for the treatment effect. The hazard ratio for the treatment comparison within each stratification factor and select demographic and disease characteristics will be estimated with 95% confidence intervals and displayed in a forest plot. This is to assess consistency of the hazard ratio across population subsets. Interaction tests of treatment with the stratification variables and other covariates will be tested using Cox regression.

11.8 Secondary Survival Analyses

Regardless of the significance of the primary analyses, overall survival will also be compared since presentation of OS is expected for all cooperative group trials. The two primary comparisons will be performed at $\alpha = 0.025$ (2-sided). The comparison of Arms 2 versus 3 for both PFS and OS will be performed at $\alpha = 0.05$ (2-sided) since power is low for these comparisons. Stratified log-tests are the primary analytic methods, but Cox regression will be used to estimate the hazard ratios and confidence intervals.

For powering the OS comparisons we assume that median OS in Arm 1 will be 4.0 years based on **S0226**. Power is only 40% to detect an increase in OS of 12 months for comparing either Arm 2 or Arm 3 to Arm 1 five years after the last patient accrual. This illustrates why PFS is a better outcome for assessing treatment efficacy in this patient population.

11.9 Other Secondary Analyses

Response rates (measurable disease only) and clinical benefit rates (all patients) will be compared across all three groups simultaneously using $\alpha = 0.05$ (2-sided). Fisher's exact test for three proportions will be used for these tests. Subsequently, logistic regression will be used to adjust for stratification variables, test individual pairwise differences between arms, and to test for effect modification of treatment on outcome by the stratification variables and other covariates.

11.10 Toxicity Analyses

For each toxicity category we will compare Grades 3-5 to Grades 0-2. There would be 90% power to detect a 15% difference in toxicities for a very common toxicity (e.g. 50%), a 12% difference in moderate toxicities (e.g. 20%), and a 7% difference in rare toxicities (e.g. 5%).

11.11 Monitoring of Compliance

Compliance with oral medications and fulvestrant will be assessed during the first two years of treatment. The expectation is that more than 80% of the planned doses would be taken by a minimum of 60% of the patients in each arm. Noncompliant patients would be those going off treatment permanently within two years of registration and before progression had occurred. If the percentage of noncompliant patients exceeded 30% on any arm, then non-compliance and its effect on the study would be discussed with the DSMC.

11.12 Likelihood of Early Reporting and/or a Positive Clinical Trial

We have simulated the study under both the null and alternative hypotheses. While the futility rules are conservative, there can be slight loss of power if early stopping for futility occurs. This is minimal under the strong alternative hypotheses used here but can be a factor for alternatives closer to the null. It can also decrease test size under the null hypothesis making the design more conservative than the design specifications.

Under the alternative hypothesis (hazard ratios of 0.70 and 0.60), power is 89.3% to conclude Arm 2 differs from Arm 1 and 99.7% Arm 3 differs from Arm 1). There is 52.9% chance that the analysis for Arm 3 vs. Arm 1 will be statistically significant in the first interim analysis and 90.8% probability after the second interim analysis if the true hazard ratio is 0.60. We would have definitive answers for both primary comparisons after each interim analysis with probability 13% and 52% respectively.

If the hazard ratio is 0.73 for both Arm 2 vs. Arm 1 and Arm 3 vs. Arm1, then power is still 80% to detect a significant difference between each pair of arms by the end of the trial and 91.8% that at least one of the comparisons is statistically significant.

Finally, under the null hypothesis of no difference among the three arms, then the overall test size is 2.5% to find a significant difference in either comparison. This is below the nominal level due to the futility comparisons. The likelihood of declaring both comparisons futile is 21.1% at the first interim analysis and 44.1% after the second interim analysis under the null hypothesis.

11.13 Data Safety and Monitoring Committee

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

The statistics for Translational Medicine are in Section 18.4.

12.0 DISCIPLINE REVIEW

There will be no discipline review for this study.

13.0 REGISTRATION GUIDELINES

13.1 Registration Timing

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

13.2 Investigator/Site Registration

Prior to the recruitment of a patient for this study, investigators must be registered members of a Cooperative Group. Each investigator must have an NCI investigator number and must maintain an "active" investigator registration status through the annual submission of a complete investigator registration packet (FDA Form 1572 with original signature, current CV, Supplemental Investigator Data Form with signature and Financial Disclosure Form with original signature) to the Pharmaceutical Management Branch, CTEP, DCTD, NCI. These forms are available on the CTSU Web site (enter credentials at https://www.ctsu.org; then click on the Register tab) or by calling the PMB at 301/496-5725 Monday through Friday between 8:30 a.m. and 4:30 p.m. Eastern time.

Each investigator or group of investigators at a clinic site must obtain IRB approval for this protocol and submit IRB approval and supporting documentation including a list of all enrolling sites covered by the IRB approval to the SWOG Operations Office only:

SWOG Operations Office
4201 Medical Dr., Suite 250
San Antonio, TX 78229
FAX: 210/614-0006
E-mail: IRBapprovals@swog.org

Do **not** submit IRB approvals to the CTSU Central Regulatory Office in Philadelphia, PA. You will only need to submit the initial approval, annual re-approvals, and any amendments that require submission of IRB approval to the SWOG Operations Office. You will not need to submit other version approvals or copies of consent forms.

13.3 Medidata Rave® Registration Procedures

a. Enrollments to this study will be conducted via Medidata Rave® (rather than OPEN) at the following url: https://login.imedidata.com/selectlogin

- If prompted, select the 'CTEP-IAM IdP' link.
- Enter your valid and active CTEP-IAM userid and password. This is the same account used for the CTSU member's web site and OPEN.
- Click the link for "Add Subject" located just below subject search.
- Enter each data item required using the SWOG Registration Worksheet and as outlined in Section 13.4.

  Clicking 'Save' will run applicable edit checks. Once a successful submission is made, Rave® will generate a Subject Enrollment Form confirming the registration and displaying treatment information. Please print this confirmation for your records.

b. Prior to accessing Medidata Rave® site staff should verify the following:

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

c. Access requirements for Medidata Rave®

- Site staff will need to be registered with CTEP and have a valid and active CTEP-IAM account. This is the same account (user ID and password) used for the CTSU members' web site.
- To perform registrations, the site user must contact the SWOG Operations Office at member@swog.org for a study invitation.

13.4 Medidata Rave® Registration Requirements

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

The individual registering the patient must be prepared to provide answers to the following questions:

a. Institution CTEP ID

b. Protocol Number

c. Registration Step

d. Treating Investigator

e. Credit Investigator

f. Patient Initials

g. Patient's Date of Birth

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

i. Country of Residence

j. ZIP Code

k. Gender (select one):

- Female Gender
- Male Gender

l. Ethnicity (select one):

- Hispanic or Latino
- Not Hispanic or Latino

- Unknown

m. Method of Payment (select one):

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

n. Race (select all that apply):

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

13.5 Exceptions to SWOG Registration Policies Will Not be Permitted

a. Patients must meet all eligibility requirements.

b. Institutions must be identified as approved for registration.

c. Registrations may not be cancelled.

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

14.0 DATA SUBMISSION SCHEDULE

14.1 Data Submission Requirement

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

14.2 Master Forms

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

14.3 Data Submission Procedures

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

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

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

b. You may also access Rave® via the SWOG CRA Workbench via the SWOG website at (http://swog.org).

For difficulties with the CRA Workbench, please e-mail technicalquestion@crab.org.

14.4 Data Submission Overview and Timepoints

a. WITHIN 7 DAYS OF REGISTRATION:

Submit the following:

S1222 Onstudy Form

Baseline Tumor Assessment Form

Copies of all pre-registration breast cancer pathology reports

Radiology reports for baseline CT and bone scans

Tumor specimen submission per Section 15.1

Blood specimen submission per Section 15.2

b. WITHIN 7 DAYS OF COMPLETION OF EACH CYCLE:

Submit the following:

S1222 Treatment Form

S1222 Adverse Event Form.

c. WITHIN ONE WORKING DAY OF DAY 1 OF CYCLE 2:

Submit blood specimens as per Section 15.2.

d. AFTER EVERY 3 CYCLES FOR TWO AND A HALF YEARS, THEN EVERY SIX MONTHS UNTIL PROGRESSION:

Submit the following:

Follow-Up Tumor Assessment Form

Radiology reports for CT and bone scans

e. AT TIME OF RESOLUTION OF ALL TOXICITIES AFTER OFF TREATMENT:

Submit the **S1222** Adverse Event Form

f. WITHIN 14 DAYS OF DISCONTINUING TREATMENT:

Submit the following:

Off Treatment Notice

Follow-Up Tumor Assessment Form

S1222 Adverse Event Form

S1222 Treatment Summary Form

g. WITHIN 14 DAYS OF PROGRESSION:

Submit the following:

Follow-Up Form

Follow-Up Tumor Assessment Form

Blood specimens per Section 15.2.

h. EVERY 6 MONTHS FOR 2 YEARS AFTER OFF TREATMENT OR UNTIL DEATH WHICHEVER COMES FIRST:

Submit the Follow-Up Form.

i. WITHIN 30 DAYS OF DIAGNOSIS OF SECOND MALIGNANCY (breast or non-breast):

Submit the Follow-Up Form documenting secondary malignancy.

j. WITHIN FOUR WEEKS OF KNOWLEDGE OF DEATH:

Submit the Notice of Death documenting death information.

15.0 SPECIAL INSTRUCTIONS

15.1 Specimens for Banking

Specimens for correlative studies and banking (submitted to the SWOG Specimen Repository – Solid Tissue, Myeloma and Lymphoma Division, Lab #201) (optional for patient):

a. With patient's consent specimens must be submitted at the following times (see Section 9.0:

1. Paraffin block, punch biopsy or 20 unstained slides from the primary tumor and/or metastatic biopsy (prestudy and progression)

b. Specimen collection and submission instructions can be accessed on the SWOG Specimen Submission webpage (https://www.swog.org/member-resources/biospecimen-resources),

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

15.2 Specimens for Circulating Tumor Cell – Endocrine Therapy Index (CTC by CellSearch®) followed by CTC-ETI) and Circulating Tumor Cell-Next Generation Sequencing (CTC-by HD-CTC followed by CTC-NGS) (required for patient):

a. Specimens must be submitted at the timepoints listed below. Collection instructions are outlined in Section 15.2c and submission instructions are outlined in Section 15.2e.

b. Blood draws for both CTC assays will be performed in the same venipuncture but blood is drawn into different tubes that are to be sent to different laboratories, as described below. Specimens must be submitted at the following times (see Section 9.0 and below diagram):

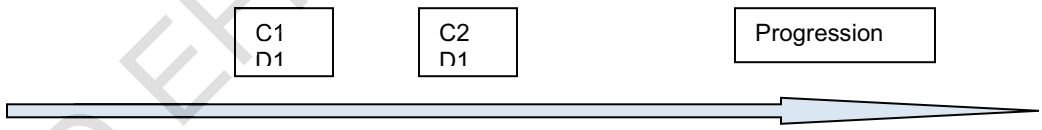
1. 5 tubes of whole blood in CellSave® tubes after registration (prior to treatment), Cycle 2 Day 1 and progression. The specimens must be shipped on the same day as collection.

   The patient will only have the C2D1 blood draws in CellSave® tubes if the C1D1 is elevated (≥ 5 CTC/7.5 mL WB).

2. 1 tube of whole blood in a Streck Cell-Free DNA tube after registration (prior to treatment), Cycle 2 Day 1 and progression regardless of baseline value. The specimens must be shipped on the same day as collection.

NOTE: The five (5) CellSave® tubes will be shipped to the University of Michigan and the Streck Cell-Free DNA tube will be shipped to the Kuhn Laboratory.

S1222: Time-line for Blood Draws



	C1 D1	C2 D1	Whenever Progression Documented
CTC-ETI (5 CellSave® tubes sent to U. Michigan)	√	√ **ONLY if CTC elevated at C1D1** [1]	√
CTC-NGS (1 Streck Cell-Free DNA tube to the Kuhn Laboratory.)	√	√	√

1 The University of Michigan Lab will enter results in the Specimen Assay Results Form in Rave.

c. Specimen Collection Instructions for CTC-ETI and CTC-NGS

ONLY COLLECT AND SHIP SAMPLES TO THE DESIGNATED STUDY LABORATORY MONDAY THROUGH THURSDAY. DO NOT DRAW SAMPLES ON A FRIDAY OR THE DAY BEFORE A HOLIDAY. SAMPLES MUST BE SHIPPED ON THE SAME DAY OF COLLECTION.

- Materials required for blood collections are five (5) 10 mL purple/yellow top CellSave® blood collection tubes, one (1) Streck Cell-Free DNA Tube, Vacutainer® brand adapter, and needles.
- For each patient, perform a venous puncture using a Vacutainer® brand adapter and needle and fill each of the blood collection tubes (minimum blood volume of 8-9 mL for each tube). Alternatively, blood samples may be obtained from a port or other central venous catheter using appropriate access needles and techniques.
- Invert each tube a minimum of eight (8) times to ensure proper mixing of the additives contained in each tube.
- Write the SWOG patient number, visit designation (i.e. baseline, C2D1, progression) and the date of collection on the tubes.
- The filled tubes must be maintained at ambient (15–30°C) temperature, avoiding extremes of heat and cold, at all times.

d. Specimen Collection Kits for CTC-ETI (sent to U. Michigan)

Prior to patient registration, all requests for blood collection tubes must be placed through the Path-Tec Customer Service department. The supplies can be obtained by completing the CTC Supply Form and submitting the form to the e-mail address included on the form.

Note: A Microsoft Word version of the CTC Supply Order Form can be downloaded from the **S1222** abstract page of the SWOG website (www.swog.org). The supply form will allow the user to enter information directly onto the form and should be included as an attachment with the e-mail message.

The hours of operation for Customer Service are Monday–Friday, 8:00 AM – 5:00 PM EST. **Although Path-Tec will attempt to ship supplies out as quickly as possible, please try to place orders approximately one week before supplies are needed.** To facilitate the ordering process, you will need to provide your customer number (if you do not have your customer number it will be provided for you after your first order), study number (e.g. SWOG **S1222**), your contact information, and the items (product code, name, and quantity) you require when placing an order.

e. Specimen Collection Kits for CTC-NGS (sent to Kuhn Laboratory)

Supplies can be obtained by sending an e-mail to info@cansera.com. Please indicate the part number and quantities. To facilitate the ordering process, please provide your study number on the subject line of your e-mail and your site (e.g. SWOG **S1222** – [your site]).

Part Number	Product Description	Quantity
42107	CTC-NGS shipping kit	1

CTC-NGS Shipping kit includes shipping system, Streck Cell-free DNA tube and shipping instructions.

The hours of operation for Customer Service are Monday-Friday, 8:00 AM – 5:00PM PST. Although Cansera, Inc. will attempt to ship supplies out as quickly as possible, orders should be placed approximately one week before supplies are needed.

f. Shipping Instructions

ONLY COLLECT AND SHIP SAMPLES TO THE DESIGNATED STUDY LABORATORY MONDAY THROUGH THURSDAY, DO NOT DRAW SAMPLES ON A FRIDAY OR THE DAY BEFORE A HOLIDAY. SAMPLES MUST BE SHIPPED ON THE SAME DAY OF COLLECTION.

1. SWOG Specimen Tracking System (STS)

All specimen submissions for this study must be entered and tracked using the SWOG online Specimen Tracking system. SWOG members may log on the online system via the CRA Workbench. To access the CRA Workbench, go to the SWOG Web site (http://swog.org). Non-SWOG users may log into SpecTrack using their CTSU UserID and password on the SpecTrack login page located at https://spectrack.crab.org (select the option "SWOG – SWOG – CTSU"). SpecTrack start-up instructions (both written and demo) are available after signing in to SpecTrack.

A copy of the Shipment Packing List produced by the online Specimen Tracking system should be printed and placed in the pocket of the specimen bag if it has one, or in a separate resealable bag.

ALL SPECIMENS MUST BE LOGGED VIA THIS SYSTEM; THERE ARE NO EXCEPTIONS.

To report technical problems with Specimen Tracking, such as database errors or connectivity issues, please send an e-mail to technicalquestion@crab.org. For procedural help with logging and shipping specimens, there is an introduction to the system on the Specimen Tracking main page (http://dnet.crab.org/SpecTrack/Documents/Instructions.pdf); or contact the SWOG Statistics and Data Management Center at 206/667-2267 to be routed to the Data Coordinator for further assistance.

In the online specimen tracking system, the appropriate SWOG laboratory for submission of blood samples for **CTC-ETI** testing (**5 CellSave® tubes**) is identified as follows:

Lab #210: Breast Oncology Tissue Bank
University of Michigan
1500 E. Medical Center Drive
Room 7130 CCC, SPC 5948
Ann Arbor, MI 48109-5948
Phone: 734-615-5224
Contact: Marty Brown

In the online specimen tracking system, the appropriate SWOG laboratory for submission of blood samples **CTC-NGS** testing (**1 Streck Cell-Free DNA tube**) is identified as follows:

Lab #209: Kuhn-Hicks Laboratory
Phone: 213/740-9945
Contact: Xiomara Villasenor
E-mail: kuhnlab@usc.edu

NOTE: SpecTrack will prompt you to enter the CBC results for each of the CTC-NGS collection timepoints.

2. Guidelines for the Shipment of CTC-ETI (sent to U. Michigan):

   a. The tubes must be wrapped in the shipping blanket.

   b. The tubes must then be placed in the AIRTIGHT resealable bag.

   c. Place the Shipment Packing List (generated by SpecTrack) in the pocket of the specimen bag.

   d. Place the bag in the Styrofoam shipping box

   e. Place ROOM TEMPERATURE gel packs in the box to stabilize the temperature at 15-30ºC. Place the styrofoam lid.

   f. Seal the insulated box.

   g. Seal the insulated shipper box and contact your local Fed-Ex representative for pick-up.

   h. Mark the box "Biohazard".

3. Guidelines for the shipment of CTC-NGS (sent to the Kuhn laboratory)

   a. Instructions are available at: http://www.cansera.com/shipping

   b. The filled Streck Cell-Free BCT must be inserted into the inner primary container along with a sachet of absorbent material and place cap on securely to close.

   c. The primary container must be placed into a secondary container and place cap on securely to close.

   d. Place the secondary container containing the primary container and the Streck Cell-Free BCT into the blue cassette.

e. Place the Shipment Packing List (generated by SpecTrack) into the back cavity of the blue cassette of the second half.

f. Place the second half of the blue cassette onto the other half fitting the plugs into the holes.

g. Place the blue cassette into the protective shipping air bag and close the top flap.

h. Place the shipping air bag into the blue standard 71.com shipping box and seal.

i. Verify the provided FedEx label and visibility of Biohazard label, and contact your local Fed-Ex representative for pick-up.

16.0 ETHICAL AND REGULATORY CONSIDERATIONS

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

Informed Consent

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

Institutional Review

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

Drug Accountability

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

Monitoring

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

Confidentiality

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

16.1 Adverse Event Reporting Requirements

a. Purpose

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

b. Reporting method

This study requires that expedited adverse event reporting use the Medidata Rave® System.

c. When to report an event in an expedited manner

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

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

d. Other recipients of adverse event reports

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

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

e. **Expedited reporting for investigational agents**

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

Table 16.1:
Late Phase 2 and Phase 3 Studies: Expedited Reporting Requirements for Adverse Events that Occur on Studies under a SWOG held IND within 30 Days of the Last Administration of the Investigational Agent Intervention (everolimus, anastrozole and fulvestrant).

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

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

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

ALL SERIOUS adverse events that meet the above criteria **MUST** be immediately reported to the Sponsor via Medidata Rave® within the timeframes detailed in the table below.

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

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

Expedited AE reporting timelines are defined as:

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

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

Expedited 24-hour notification followed by complete report within 5 calendar days for:

- All Grade 4, and Grade 5 AEs

Expedited 10 calendar day reports for:

- Grade 2 adverse events resulting in hospitalization or prolongation of hospitalization
- Grade 3 adverse events

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

1. **Group-specific instructions.**

Supporting Documentation Submission - Within **5 calendar days** copies of clinical documentation supporting the event(s) reported should be uploaded into Medidata Rave®. If on-line Medidata Rave® cannot be used or if you have difficulty uploading your documents, please telephone or e-mail the SAE Specialist at the Operations Office, 210/614-8808 or adr@swog.org.

g. **Reporting Secondary Malignancy, including AML/ALL/MDS**

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

SWOG requires all secondary malignancies that occur following treatment with an agent under a SWOG held IND to be reported via Medidata Rave®. Three options are available to describe the event.

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

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

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

2. Supporting documentation should be submitted to SWOG by uploading the documentation in the Medidata Rave® system. Documentation should consist of the following:

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

h. **Reporting Pregnancy, Fetal Death, and Death Neonatal**

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

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

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

   A Pregnancy loss should NOT be reported as a Grade 5 event under the Pregnancy, puerperium and perinatal conditions SOC.

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

   Neonatal death should **NOT** be reported as a Grade 5 event under the General disorders and administration SOC as currently Medidata Rave® recognizes this event as a patient death.

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18.0 APPENDIX

18.1 Intake Calendar

18.2 New York Heart Association Criteria

18.3 Drugs Known to be Metabolized by CYP450 Isoenzyme 3A4

18.4 Translational Medicine Studies

18.1 Intake Calendar

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

If you have questions contact: _____ Telephone: _____

Your next appointment is: _____

Special instructions:

Month: _____ Year: _____

Sunday	Monday	Tuesday	Wednesday	Thursday	Friday	Saturday

Patient Signature:_____

18.2 New York Heart Association Criteria

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

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

** At accustomed occupation or usual tasks.

18.3 Drugs Known to be Metabolized by CYP450 Isoenzyme 3A4

Because the lists of these agents are constantly changing, it is important to regularly consult a frequently-updated list such as http://www.fda.gov/Drugs/DevelopmentApprovalProcess/DevelopmentResources/DrugInteractionsLabeling/ucm093664.htm; medical reference texts such as the Physicians' Desk Reference may also provide this information.

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

18.4 Translational Medicine Studies

The overall goal of the translational medicine project is to identify patients treated with endocrine treatment (ET) alone, or ET plus everolimus, who are refractory to these therapies, and to identify potential mechanisms of resistance that might be targeted in the future. This section will only address the CTC portion. The other portions (tissue, circulating DNA, other), will be addressed in separate, specific analytical plans as they are developed.

Overall design of circulating marker studies

The overall design of this trial is to test whether adding everolimus to anti-estrogen therapy (fulvestrant at 500 mg/month, or fulvestrant (500 mg/month) plus anastrozole) will improve outcomes. However, important secondary aims are to determine whether baseline or serial circulating tumor cells (CTC) can identify factors that predict resistance to endocrine therapy and/or benefit from mTOR inhibition by everolimus. We have two hypotheses:

- That enumeration and characterization of selected markers (ER, BCL2, HER2, Ki67) of CTC using the CellSearch platform will identify patients with endocrine resistant therapy.
- That isolation of individual CTC and genetic characterization of CNV (amplification and deletions) will identify distinct genetic markers of both endocrine resistance and prediction of activity/resistance of everolimus.

They will also include exploratory studies of these hypotheses in archived FFPE cancer tissue that has been collected for routine clinical care but that will be collected and stored in the SWOG repository, as well as in circulating free DNA and in germline DNA that will be collected from patients prior to and during therapy (for cell free DNA) and stored in the SWOG repository.

The latter exploratory studies will be designed after the clinical trial is complete, using advanced technologies that will be available at that time. However, the CTC studies will be performed in “real time” during the trial itself. Therefore, the remainder of this section will focus on the two CTC approaches.

CTCs will be analyzed in two laboratories:

- Hayes laboratory (University of Michigan), CTC will be enumerated using the CellSearch® platform (Veridex LLC), and the CTC-endocrine therapy index (CTC-ETI) will be determined as described below. This assay permits semi-quantitative measurement of ER, BCL2 (indicators of endocrine sensitivity) and HER2 and Ki67 (indicators of endocrine resistance).

- Kuhn-Hicks laboratories (San Diego, CA), CTCs will be identified using the HD-CTC® platform (The Scripps Research Institute), and CTC-genome wide copy number alterations (CTC-NGS) will be performed in the Kuhn-Hicks Laboratory.

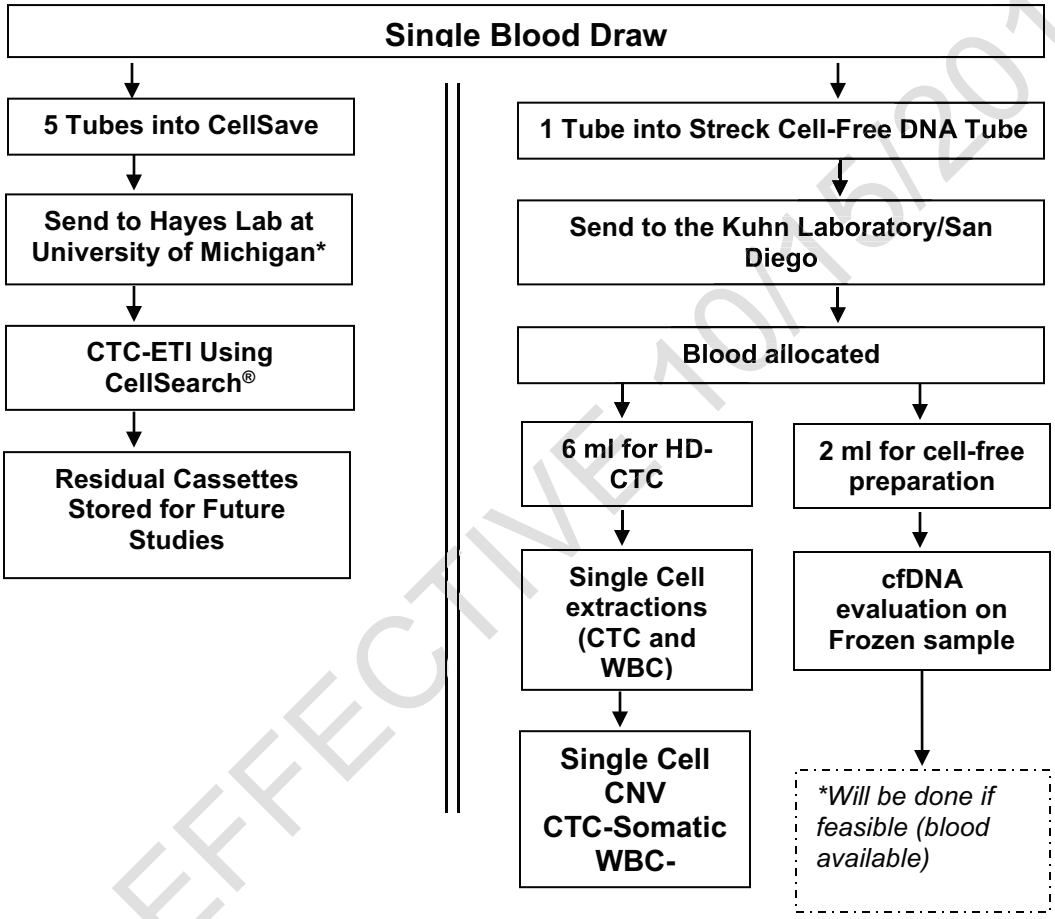
Five tubes of blood, drawn into CellSave Tubes, will be sent to the Hayes laboratory for CTC enumeration and CTC-ETI determination.

One tube of blood, drawn into a Streck Cell-free DNA tube, will be sent to the Kuhn-Hicks lab (San Diego, CA) for divisions into aliquots for CTC identification and extraction for CNV analysis, as well as for plasma for circulating DNA analysis, and WBC for germ line DNA analysis (exploratory and when sufficient sample is available as not all blood samples will have the required 8 ml of blood). Thus, the Kuhn-Hicks laboratory will

process the blood they receive for both cell analysis and cell-free DNA isolation. Copy number alteration profiles will be developed from both CTCs and normal white blood cells.

These considerations are summarized in the following diagram:

S1222: Circulating Marker Schema



A single blood draw will be collected at baseline, Cycle 2 Day 1, and at progression. Six (6) tubes of blood (approximately 48-54 ml) will be collected at each time point as per Section 15.2.

CTC enumeration and CTC-ETI analysis by CellSearch system at UM:

Samples shipped to the Hayes laboratory will be processed according to the manufacturer's instructions for CTC enumeration using the Cellsearch© system. These same specimens will be analyzed for expression of ER, BCL2, HER2, and Ki67.

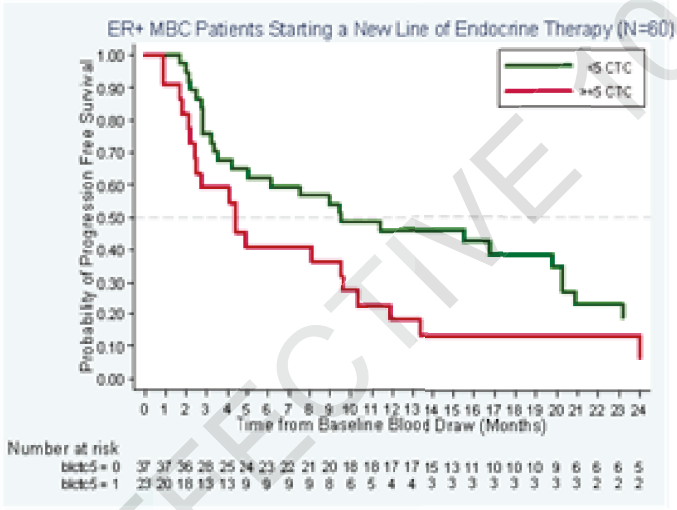
Background for CTC-ETI

Multiple previous studies have demonstrated that pre-treatment CTC enumeration performed using the CellSearch© system is associated with worse prognosis in metastatic breast cancer (MBC). (*1)* Approximately 50% of patients with MBC have

elevated CTC prior to treatment. Furthermore, failure to clear CTC is associated with even worse prognosis and very short time to progression. We have performed a subgroup analysis of patients who participated in the original Cristofanilli et al study and who had ER positive MBC and were starting a new endocrine therapy.

ER+ MBC Pts Starting a New Line of ET

	Baseline CTC Counts	
	< 5 CTC	≥ 5CTC
ER + Patients, Hormone Tx Only (N)	37	23
Median PFS_BL (95% CI)	9.5 (4.2 - 20.3)	4.4 (2.2 - 9.6)



From IMM01 *Modified from Cristofanilli M, et al. NEJM 2004*

Figure 1. PFS according to CTC levels in 60 patients with ER positive breast cancer starting an endocrine therapy (first line or later). *(2)*

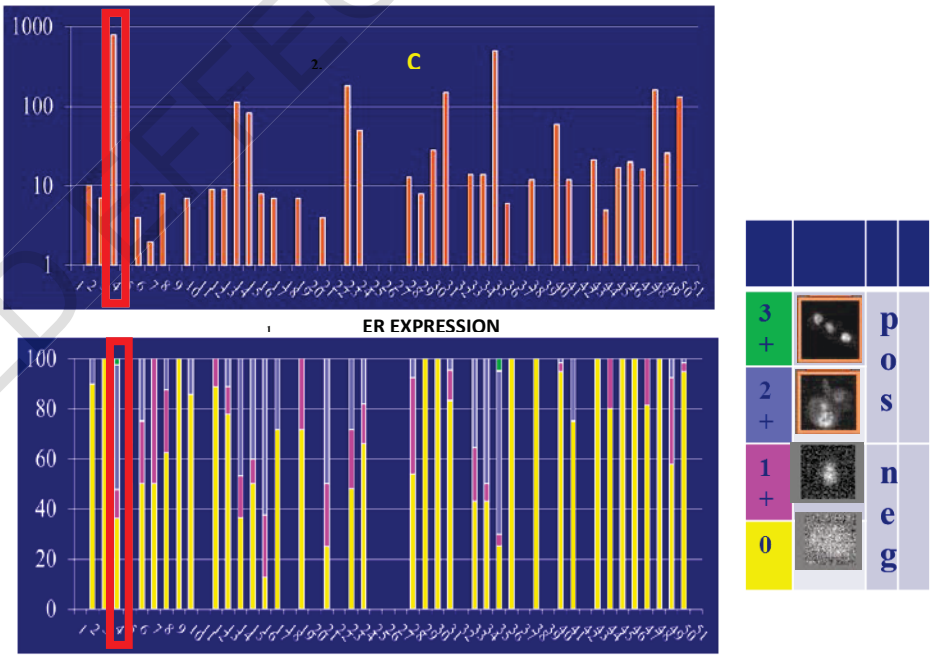
Therefore, we hypothesize that pre-treatment CTC levels will be associated with worse prognosis for patients who are treated with fulvestrant alone.

Recently, the Hayes' laboratory has developed a CTC-ETI, which we hypothesize will predict resistance to ET in patients with ER positive breast cancer. This index incorporates the number of CTC/7.5 ml whole blood and the relative expression of ER and BCL2 (favorable) and HER2 and Ki67 (unfavorable) by the CTC. The following figure is an example of CTC-ETI for a single patient with MBC whose primary tumor was positive for ER, but who had become refractory to ET. This patient had median 13 CTC/7.5 ml whole blood and note that all of these CTC were negative for ER.

Markers					Total bio-points
	Composite	*Marker PE*	*% CTC positive*	*Assigned Bio-Points*	
ER			0%	6	*8*
Bcl-2			60%	0	
HER-2			0%	0	
Ki-67			14%	2	

The CTC-ETI is calculated by assigning "points" based on the number of CTC/7.5 mL whole blood and the relative expression. Points are assigned according to the number of CTC/7.5 ml whole blood, and according to each "bioscore" with more points for ER and BCL2 negativity and HER2 and Ki67 positivity. Therefore, a high score (elevated CTC with low ER, BCL2 and high HER2 and Ki67) results in a high CTC-ETI, while a low score (no CTC, or elevated CTC with high ER, BCL2 and low HER2 and Ki67) results in a low CTC-ETI, in a manner similar to tumor grade.

We have now completed a pilot analytical study at U. Michigan and demonstrated highly reproducible analytical validity between separate reviewers. The following diagram demonstrates the number of CTC/7.5 ml whole blood (top box) and the relative expression of ER (%) (bottom box) according to a scale of relative fluorescence (see side box).



This figure, which illustrates CTC-ER for each of 51 patients, is representative of what we have also observed with CTC-BCL2, CTC-HER2, and CTC-Ki67. We observed enormous inter- and intrapatient heterogeneity for each of the markers. For example, the highlighted patient (Patient #4), had nearly 1,000 CTC/7.5 mL whole blood. 36% and 11% of these cells had CTC-ER of 0 and 1+, respectively, while 50% and 3% had CTC-ER of 2+ and 3+. We hypothesize that the CTC-ETI will predict resistance to ET (fulvestrant, anastrozole) and perhaps sensitivity to everolimus.

CTC-ETI Assay/Device Descriptions
All assays performed on the blood collected specifically for the purposes of this study are for research use only and the results may not be used for patient management. The RUO CellSearch® CXC Kit enables the immunomagnetic selection of CTC of epithelial origin from WB and the characterization of user-defined markers with low antigen density (~50,000 antigens/cell). CTCs are isolated from a 7.5mL sample of WB using the reagents in the CellSearch® CXC Kit and a CellTracks® AutoPrep® System and subsequently identified using the CellTracks Analyzer II® System. CTCs are defined as Epithelial Cell Adhesion Molecule (EpCAM) positive, cytokeratin positive, 4', 6-diamidino-2-phenylindole dihydrochloride (DAPI) positive, CD45 negative events with a cellular morphology including an intact cytoplasmic diameter of at least 4µm containing a nucleus.

Before placing samples on the CellTracks® AutoPrep® System for processing, blood is pooled, aliquoted into separate CellTracks® AutoPrep® sample tubes, buffer is added, and the samples are centrifuged (see CXC Kit Instructions for Use [IFU] for detailed procedure). After incubation and magnetic separation with magnetic nano-particles (ferrofluid) labeled with antibodies specific for EpCAM, the cell suspension enriched for cells expressing EpCAM is incubated with fluorescein isothiocyanate (FLU) labeled monoclonal antibodies recognizing cytokeratins 8, 18 and/or 19 (markers of epithelial cells) [CK-FLU], allophycocyanin (APC) labeled monoclonal antibodies specific for CD45 (a broad-spectrum leukocyte marker) [CD45-APC], the nucleic acid dye DAPI, and the selected PE conjugated tumor profiling antibody in the presence of the staining buffer. Excess fluorescent material is removed by repeated magnetic washes, and the fluorescently labeled cells are resuspended in a cellular preservative to a final volume of 320 mL and transferred to a CellTracks® cell presentation chamber (cartridge). This cartridge is held in a magnetic device called a MagNest® which orients the magnetically labeled cells for fluorescence microscopic examination in the CellTracks Analyzer II®. This semi-automated image analysis system identifies and captures images of the fluorescently labeled cells and presents them to the operator for classification and enumeration. One CXC control is run on the instrument each day. Positive and negative controls for each marker will be run with each batch of samples.

CXC Assay
The CellSearch® CXC Kit contains EpCAM labeled ferrofluid, CK-FLU, CD45-APC, DAPI and a staining buffer. The following tumor profiling antibodies, conjugated to PE, will be used to characterize the isolated CTC: ER, HER2, Bcl-2, Ki67.

CXC Assay Controls
The CellSearch® CXC Control Cell Kit contains 24 single-use bottles containing a fixed breast cancer cell line (SK-BR-3) pre-labeled with fluorescent dyes. A CellSearch® CXC Control Cell bottle is used to verify the performance of the CellSearch® CXC Kit reagents, sample processing by the CellTracks® AutoPrep® System, and cell analysis by the CellTracks Analyzer II®. The fixed SK-BR-3 cells are a single level population and differentiated as control cells by the detection of fluorescence in the dihexyloxacarboeyanine iodide (DIOC) control channel of the CellTracks Analyzer II®. The number of SK-BR-3 cells isolated is automatically tallied by the system and must fall

within a pre-determined range specific to that particular lot of control cells. One CXC control is run per instrument per day.

Marker Controls
Positive and negative controls for the tumor profiling antibodies consist of normal blood spiked with the appropriate cell line(s) positive and/or negative for the marker being evaluated. Normal blood spiked with the negative cell lines and processed in the presence of the marker reagent (negative control) is used to establish the background signal in the PE channel. The normal blood spiked with the cell lines and processed in the presence of the marker reagent (positive control) is used to control the marker reagent. Each cell will be evaluated for positive staining of the marker (i.e. staining above the negative control), and the proportion of cells positive for each of the markers will be determined. The table below indicates the cell lines and the marker reactivity.

Control Cell Line	Marker Positive	Marker Negative
MCF-7	**ER**, Bcl-2, Ki67	**HER2**
SK-BR-3	**HER2**, Ki67	**ER**, **Bcl-2**
BT-474	ER, **Bcl-2**, HER2, Ki67	---

To reduce the number of marker controls that have to be run, it may be possible to spike two cell lines into a single aliquot of blood to control for two different markers at once. For example, the MCF-7 and SK-BR-3 cell lines can be combined into a single 7.5mL aliquot of blood to act as the positive and negative controls, respectively for ER (nuclear localization) and the negative and positive controls, respectively, for HER2 (cytoplasmic localization). Similarly, the SK-BR-3 and BT-474 cell lines can be combined into a single 7.5mL aliquot of blood to act as the negative and positive controls, respectively, for Bcl-2 (cytoplasmic localization). All of the cell lines are positive at some level for Ki67 (nuclear localization), however, there should always be a population of cells that are not undergoing proliferation and thus you will always have a population of cells that will be negative for Ki67.

BioMarQ Software
We have also developed RUO software for the CellTracks Analyzer II® that allows quantitation of the marker expressions. The software, called BioMarQ, is an enhancement to the CellTracks Analyzer II® platform that allows for quantitative analysis of Tumor Profile Reagents (i.e. markers). BioMarQ is for research use only and consists of a new standardization cartridge (called a BioMarker Cartridge, or BMC) and an external hard drive loaded with a modified version of the CellTracks® software. Before scanning the samples or controls on the CellTracks Analyzer II®, the BMC is scanned and the images are analyzed. Next, the blood samples and positive/negative controls are loaded and a test definition is selected with the associated marker definition. Immediately prior to scanning the sample or control, camera settings for the marker channels are adjusted using the BMC test results. After the images captured from the samples and/or controls are classified in the browser, image clips are generated from the collected raw images. These image clips are used for segmentation of the CTC; images of selected CTC can be either saved to disk or printed. A series of features, including marker intensity, are extracted from the segmented cells and these features are saved to a disk. The extracted features can be analyzed using scatter plots and histograms and the results and CTC image related to selected data points can be visualized on the screen.

Primary correlation with rapid progression and PFS in this trial will be made using CTC-ETI calculation derived from the visual determination of the biomarker expression on the CTC and not from the BioMarQ data. We will use the data collected from the BioMarQ software in conjunction with the operator's visual interpretations of the markers to help

determine marker intensity thresholds that could possibly be used in future studies to classify CTC images as marker positive or marker negative.

Calculation of CTC-ETI

For each blood draw (five tubes of WB, ~40-50 mL total), the WB collected will be pooled and four separate 7.5mL aliquots will be prepared. The remaining WB will be saved to be used as a backup for retesting if necessary. Upon completion of the testing, all used and unused WB (and tubes) will be appropriately disposed of.

Each marker will be evaluated in a separate 7.5 mL aliquot of WB. CTC will be enumerated in each of the four different 7.5 mL aliquots of WB, and the average CTC count of the four tubes will be calculated. Table 1 below provides the CTC Assigned Points for each category of average CTC levels.

Table 1. CTC Assigned Points: Prognosis Based on Average CTC Number Only

	Low (Good)	Intermediate		High (Bad)
Number of CTC/7.5 mL (average of 4 aliquots)	0-4	5-10	11-100	> 100
Assigned Points	0	1	3	4

Next, for those subjects who have an average of 5 or more CTC/7.5 mL of WB (average of CTC values from the 4 aliquots), we assign "Biologic Points" (or Bio-Points) based on the percentage of CTC that are positive for the respective marker (Table 2). Note that we have weighed low or negative ER expression more heavily than HER2, Ki67, or Bcl-2 due to its fundamental role in endocrine responsiveness. These Bio-Points are added to calculate a final CTC Bio-Score (NOTE: this score is currently for informational purposes only and may not be used in the management of patients).

Table 2. CTC Assigned Biologic Points: Prediction of Endocrine Sensitivity Based on Relative Expression of Each Biological Marker Within CTC (elevated CTC ≥ 5/7.5 mL of WB only).

Response Prediction to ET	Favorable		Intermediate		Unfavorable	
	% CTC positive	*Assigned Bio-Points*	*% CTC positive*	*Assigned Bio-Points*	*% CTC positive*	*Assigned Bio-Points*
ER	>10%	0	1-10%*	2	0%*	6
Bcl-2	>10%	0	1-10%	1	0%	2
HER2	0%	0	1-10%	1	>10%	2
Ki67	0%	0	1-10%	1	>10%	2

* NOTE: we have weighed low or negative ER expression more than HER2, Ki67, or Bcl-2, due to its fundamental role in endocrine responsiveness. Thus final CTC Bio-Score can range from 0 (ER and Bcl-2 high; HER2 and Ki67neg) to 12 (ER and Bcl-2 neg; HER2 and Ki67 high). Abbreviation: ET= Endocrine Therapy

Finally, we add the CTC Assigned Points and CTC Bio-Score (defined as the combination of CTC Assigned Biologic Points for each marker) to derive the CTC-ETI Score (Table 3).

Table 3. CTC-ETI Scores

Average CTC Counts	CTC Assigned Points	Marker	CTC Assigned Biologic Points			Potential CTC-ETI Score (sum of CTC Assigned and Bio- Points)
			Low	*Intermediate*	*High*	
CTC 0-4	0	N/A	0	0	0	0
CTC 5-10	1	ER	0	2	6	1-13
		Bcl-2	0	1	2	
		HER2	0	1	2	
		Ki67	0	1	2	
CTC 11-100	3	ER	0	2	6	3-15
		Bcl-2	0	1	2	
		HER2	0	1	2	
		Ki67	0	1	2	
CTC > 100	4	ER	0	2	6	4-16
		Bcl-2	0	1	2	
		HER2	0	1	2	
		Ki67	0	1	2	

Each of the factors (CTC, ER, HER2, Ki67, and Bcl-2) were placed into categories to develop the CTC-ETI by combining the number of CTC (CTC Assigned Points) and the Biologic Points of these CTC (CTC Bio-Score), as determined using the CellSearch® CXC assay and marker reagents. A subject can have a CTC-ETI Score ranging from 0 (0-4 CTC/7.5mL WB), or 1 (5-10 CTC/7.5 mL WB, but all Bio-Scores are 0) to 16 (> 100 CTC/7.5mL WB, 0% of these cells are positive for ER and Bcl-2, and > 10% of CTC are positive for HER2 and Ki67).

To make the CTC-ETI Score clinically applicable, the scores are placed into 3 categories, much as histologic grading is categorized. We hypothesize that a Low CTC-ETI will predict a favorable outcome (response, long time to progression) for subjects with ER positive MBC starting a new ET, while a High CTC-ETI will predict rapid progression. Intermediate CTC-ETI scores should fall in between the other two. These proposed categories are provided in Table 4.

Table 4. Proposed CTC-ETI Categories

CTC-ETI Category	CTC-ETI Score	Predictive clinical outcomes	Treatment strategy
Low	0-3	Favorable; respond to ET and/or indolent disease; long time to progression	Treat with ET*
Intermediate	4-6	Probably respond or moderately indolent disease; modest time to progression	Treat with ET*
High	7-16	Poor; Resistant to ET, rapid progression	Treat as ER neg with chemotherapy

Abbreviations: *ET= Endocrine Therapy.

(NOTE: The proposed CTC-ETI Score and Categories are for informational purposes only and may not be used in the management of patients).

CTC-ETI BLOOD SAMPLE PROCESSING PROCEDURES

Samples will be shipped to the University of Michigan Breast Oncology Laboratory for processing. Upon receipt in the laboratory, the samples will be accessioned and blinded with a laboratory assigned sample ID, the blood will be pooled, and four separate 7.5 mL aliquots will be created and evaluated for CTC + ER, CTC + Bcl-2, CTC + HER2, and CTC + Ki67 using the CellSearch® CXC assay and marker reagents. Any excess blood will be aliquoted into a separate 7.5mL aliquot and saved for up to 4 days after the time of collection to be used as a backup in case one or more of the assays has a technical failure and needs to be re-run. Remaining blood will be appropriately disposed of upon successful completion of the CTC assays.

Results of the CTC-ETI assay will be recorded on the appropriate CRF(s) by the study laboratory. **As indicated above, the study laboratory will notify SWOG via e-mail of all samples unable to be processed due to a pre-analytical error within 7 days after receipt of the sample and of all samples with an unsuccessful CTC-ETI calculation within 14 days after the receipt of the sample and provide a PDF copy of the CTC requisition and results forms.** The study laboratory will also store and or fix and store all cartridges either in the fridge (containing 1 or more CTC at 4°C) or in the freezer (containing 5 or more CTC at -20°C) for future analyses (i.e. FISH).

Pooling

In the study laboratory, the blood from the five different CellSave® tubes collected from each subject will be pooled, mixed together (total volume of ~40-50 mL), and separated into five different 7.5 mL aliquots (if there is a sufficient volume of blood). A minimum of four 7.5 mL aliquots are required for CTC-ETI testing. Four out of the five aliquots will be used to enumerate CTC and to determine ER, Bcl-2, HER2, or Ki67, expression using the CellSearch® CXC assay and to calculate the final CTC Assigned Points and CTC Biologic Points. The fifth aliquot (if a sufficient volume of blood was available) will be used as backup in case any instrument and/or reagent failures cause a loss of results from one of the first four aliquots. If there are no assay failures, the remaining volume of blood will be properly disposed of.

Statistical Plan: This will be an exploratory correlative study to generate preliminary data to inform development of future studies using CTC as a quantifiable endpoint of future trials, specifically of CTC-ETI (as applicable for target-specific therapies) and CTC-NGS.

Objectives of CTC Studies

CTC-ETI (CellSearch®)

Primary: Does decline in Circulating Tumor Cell (CTC) number at first follow-up (C2D1) predict benefit from fulvestrant vs. fulvestrant and anastrozole, +/- everolimus?

Secondary 1. Does CTC-endocrine therapy index (CTC-ETI) predict rapid progression for patients with ER positive metastatic breast cancer starting a new endocrine therapy?

Secondary 2. Does CTC-ER predict response to fulvestrant and anastrozole +/- everolimus?

Secondary 3. What are the effects of treatment variables on CTC profiling?

Clinical Endpoint(s) to be used in analyses:
The primary outcome in the clinical trial, progression-free survival (PFS), would be the primary outcome here. Response rate would be a secondary endpoint.

Primary Objective*:*
Baseline CTC and Prognosis- This proposal anticipates approximately 50% of patients will have elevated CTCs (≥ 5 CTC/7.5 ml whole blood) at baseline, when determined using the CellSearch© system. From the subgroup analysis of ER positive patients initiating a new endocrine therapy within the original IMMO1 study (Figure 1), we hypothesize that baseline CTC will be associated with a worse prognosis, with the HR for progression of ~ 2.0, or, stated another way, the median PFS for those with elevated baseline CTC (≥ 5 CTC/7.5 ml WB) will be approximately half as long as for those without elevated CTCs.

In each treatment arm (n=264 patients with outcomes) we anticipate that approximately 130 patients will have elevated CTC at baseline. We expect those with high CTC ≥ 5 to have 50%-60% the survival of those with CTC < 5. As stated in Section 11.0, we estimate that the HR for progression of fulvestrant plus everolimus (Arm 2) is reduced by 30% compared to fulvestrant alone (Arm 1) (i.e. HR= 0.7), and that the HR or fulvestrant plus anastrozole plus everolimus (Arm 3) will be reduced by 40% compared to fulvestrant alone (HR-0.6).

First Follow-up CTC and Prognosis- Several studies have now demonstrated that first follow-up CTC levels reflect response or resistance to therapy. (1) Indeed, this observation is the basis for a recently accrued PRCT conducted by SWOG (**S0500**). Therefore, the hypothesis is that failure to clear CTC from baseline to first follow-up will be associated with even worse prognosis than that estimated by baseline CTC and will predict benefit or lack of it from the investigational therapies in this protocol.

The estimation is that for patients with persistently elevated CTC at first follow-up, median PFS will be even shorter than for patients with elevated CTC at baseline (this estimate is based on assumption that persistently elevated CTC = lack of response).

Assuming CTC response is a surrogate for PFS, the anticipation is that twice as many patients would have CTC-response in the investigational arms. If 50% of patients respond in Arm 1 to fulvestrant alone, then 65% will respond in Arm 2 to fulvestrant and everolimus, and 70% will respond to the combination of fulvestrant, anastrozole, and everolimus (Arm 3). In this exploratory correlative study, observing a statistically

significant difference would not be possible, but the results of "CTC response" will provide an estimate of the magnitude of benefit provided by this surrogate measure of benefit. This could serve as evidence that CTC-response may be used as an additional marker of benefit for patients who have non-measurable disease, and are therefore currently not eligible, and thus participate in future Phase II trials of novel agents.

Secondary Objective:
Baseline CTC-ETI- CTC-ETI is based on the number of CTC and for those patients with ≥ 5 CTC/7.5 ml whole blood, the relative expression of each of the relevant markers on the CTC. We hypothesize that that CTC-ETI will identify patients with endocrine resistant disease. Low CTC-ETI will be determined either because the patient does not have elevated CTC (~ 50% of patients) or because patients who do have elevated CTC will have high CTC-ER and BCL2 and low CTC-HER2 and Ki67. Thus, we hypothesize that CTC-ETI will further divide the prognosis of patients who have elevated CTCs, since the hypothesis is that a high CTC-ETI is associated with lack of response to endocrine therapy.

In a pilot study at University of Michigan, the observation was that approximately 20% of enrolled patients with ER-positive metastatic breast cancer have high CTC-ETI levels at baseline. The anticipation is that patients with High CTC-ETI on fulvestrant alone will have median PFS of ≤3 months and that those with low or intermediate CTC-ETI will have median PFS of >8 months, since the hypothesis is that CTC-ETI patients are hormone refractory.

We further hypothesize that the addition of everolimus to fulvestrant, or to fulvestrant and anastrozole will improve PFS in Arms 2 and 3, respectively, and the presence of CTCs will be an adverse predictor for PFS.

Arm	Therapy	Estimated HR for PFS	Estimated PFS for CTC ETI High	Estimated PFS for CTC ETI Intermed/Low
1	Fulvestrant alone	NA	≤ 3 months	9-13 months
2	Fulvestrant + everolimus	0.70	~ 4.0months	12-17 months
3	Fulvestrant + anastrozole + everolimus	0.60	~ 4.1 months	12, 5-22 months

The hypothesis will test that high CTC-ETI predicts rapid progression in the control arm. Since the expected hazard ratio is high (3.0), this test has 84% power even if only 20% are in the high CTC-ETI group since the failure rate is high. Again, this exploratory correlative study will provide preliminary evidence as to whether CTC-ETI does, indeed, identify patients with ER-positive, metastatic breast cancer that is resistant to endocrine treatment, and who might be better treated with chemotherapy or alternative novel treatments, such as the addition of everolimus. Furthermore, within the confines of the sample size, the same analysis can be performed in the experimental arms as a validation exercise. The results of this preliminary study will inform planned, future studies to address this issue definitively.

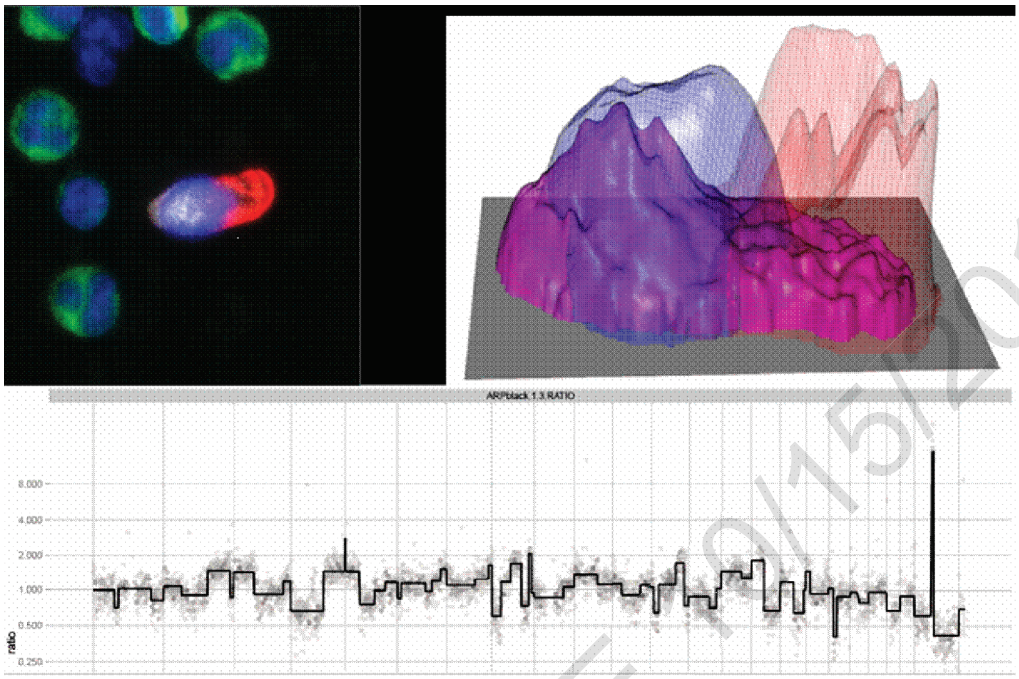
Follow-up CTC-ETI- Fulvestrant works by down-regulating ER. The effects of fulvestrant (or for that matter, everolimus) on CTC-ETI are unknown, and whether patients with resistant disease might be identified by either lack of down-regulation of CTC-ER or changes in CTC-BCL2, HER2, or Ki67 remains to be demonstrated. In an exploratory analysis, the change in CTC-ETI as a whole, and in individual CTC-biomarker results, at first follow-up will be correlated with PFS in each arm.

Data analysis performed by:
CTC analysis will be performed in Dr. Hayes' laboratory at University of Michigan. Laboratory data will be transferred to SWOG Statistical office, to be analyzed by Dr. Barlow.

CTC-Next Generation Sequencing (CTC-NGS)
Assay Description:
For this portion of the translational medicine studies, the CTC will be harvested using the HD-CTC® system (The Scripps Research Institute San Diego, CA). HD-CTC® is a next generation Fluid Biopsy representing an enrichment free rare cell characterization platform that has completed its technical and clinical validation processes with broad application in carcinomas. Its success rate as a fluid biopsy is defined by greater than 4 cells per test, which is applicable to approximately 70% of metastatic breast cancer patients. *(3)* Its main utility is the single cell characterization at the protein and molecular levels with diagnostic pathology quality. It has demonstrated concordance with the primary solid tumor biopsy prostate cancer for both PTEN loss by FISH and whole genome copy number variation using single cell next generation sequencing. The HD-CTC® fluid biopsy is under development at the Kuhn Lab of The Scripps Research Institute and is being commercially developed at Epic Sciences, Inc. Cansera Inc. is providing the logistics and sample handling for the Kuhn-Hicks laboratory that has developed the CTC-NGS. All SWOG interactions will be handled by Cansera.

The HD-CTC® Fluid Biopsy blood preparation provides for the use of a single blood collection tube to prepare independent fluid biopsy samples. These pre-analytically validated samples are permanently stored in a bio-repository and retrieved for specific assay execution. Assays are tailored to each product goal. Specifically, quantitative single cell characterization includes i) cellular morphology, ii) subcellular localization of each biomarker, iii) multi-color FISH assays, iv) whole genome analysis of copy number alterations using next generation sequencing.

In the context of this trial, samples will be first screened for candidate cells using a combination of fluorescent markers including DAPI to identify nuclei, CD45 to identify leukocytes and a mixed preparation of anti-cytokeratin antibodies to identify epithelial cells. Four categories of candidate cells are described in the Analysis section (below). Based on previously collected data, we anticipate that 75% of patients will have a positive HD-CTC fluid biopsy at baseline (defined as > 4 cells/ml). Candidate cells are then morphologically characterized with higher resolution imagery for subcellular analysis of both protein and DNA distributions. Finally, up to 20 candidate cells from each case are then individually extracted from the slide and prepared for single cell genomic analysis using next generation sequencing technologies.



The combined results from the CTC-NGS process are illustrated in the figure above, which shows a single HD-CTC defined as DAPI positive (blue), Cytokeratin positive (red), CD-45 negative (green) cell that is morphologically distinct from its surrounding white blood cells (DAPI positive in blue and CD45 positive in green). It also shows a 3D rendering of the same cell prior to isolation and below the whole genome analysis of copy number alterations (chromosome 1 on the left and chromosomes XY on the right).

In summary, patients will have a single tube of blood drawn and sent to the Kuhn and Hicks laboratories, where the blood will be subjected to the HD-CTC® assay. Single cancer cells will be isolated and processed for NGS analysis.

Upon receipt in the laboratory, the samples will be accessioned, barcoded and blinded. Following standard procedures, 4 aliquots will be prepared from each sample. Aliquot processing will be performed sequentially to maximize single cell workflow productivity. Following the standard HD-CTC® Fluid Biopsy protocols, candidate cells will be characterized morphologically using fluorescent imagery. All protocols will be carried out under academic research standards, using SOP's and documented reagents.

Results of the CTC-NGS assay will be recorded on the appropriate CRF by the study laboratory.

As indicated above, the study laboratory will notify SWOG via e-mail of all samples unable to be processed due to a pre-analytical error within 7 days after receipt of the sample.

CTC-NGS Analysis I:

CTC-NGS candidate cell identification: The HD-CTC® assay identifies a range of rare cell populations that are each defined by specific morphometric parameters. At this point, the below categories will be key focus:

- Category 1 cells: C1 (HD-CTC) cells CTC are defined as DAPI+ with an intact nucleus, CK+ with an intact cytoplasm, and CD45- events that are morphologically distinct from the surrounding leucocytes.
- Category 2 cells: C2 (smallCK) cells are defined as DAPI+ with an intact nucleus, CK+ with an intact cytoplasm, and CD45- events that are not morphologically distinct from the surrounding leucocytes.
- Category 3 cells: C3 (noCK) cells are defined as DAPI+ with an intact nucleus, CK- and CD45- events that are morphologically distinct from the surrounding leucocytes

CTC-NGS Analysis II
Slide coordinates for each candidate cell will be fed into a master spreadsheet in preparation for capture. Cells will be reimaged and relocated using these coordinates. Candidate cells will be extracted and prepared for low pass genomic DNA sequencing. Single cell DNA amplification procedures and preparation for Illumina DNA sequencing have been described in Baslan, et al. *(4)* Samples will be identified and tracked using the barcodes assigned at accession.

Illumina sequencing libraries will then be created for each individual CTC preparation, using 1 ug of amplified DNA and using methods and materials directed by Illumina in their product specifications. Each preparation will carry one of 96 oligonucleotide barcodes synthesized into the Illumina P5 and P7 adaptor molecules. Sequencing will be done using the 150 bp single read flow cell. Output from the sequencing instruments will be fed into a computer cluster and will be processed for QC filtering and base quality scores by standard methods. Sequencing reads passing QC will be processed informatically as described below. Expected yield is 2 million unique mapping reads per cell, with a minimum of 1 million reads to be scored.

CTC-NGS DNA informatics pipeline:
The basic informatics pipeline has been published including the scripts in the R statistics package and additional scripts written in Python and C++. *([5,6])* After read mapping, and normalization, the output is an array of read counts in 50,000 'bins' across the genome. Using segmentation algorithms, the 'bin' data is converted to a genome profile that identifies the copy number of genomic segments with a resolution of ~50 kbp. Gains, losses and amplifications will be scored gene by gene, for each cell and tracked as individual markers. An additional genome-wide analysis of multigene events, such as whole chromosome arm gains and losses will be performed using methods described by Krasnitz, et al using data from the entire patient population of each arm. (7) The latter process reduces the number of genomic markers from 20,000+ individual genes, to less than 100 common events, decreasing the effects of multiple testing.

Statistical plan:

This will be an exploratory correlative study to generate preliminary data to inform development of future studies using CTC as a quantifiable endpoint of future trials, specifically of the extended data available through HD-CTC and CTC-NGS assays.

Objectives of CTC-NGS® phenotype-genotype testing using the HD-CTC® platform:

Primary: Does the specific phenotype-genotype relationship of High-Definition Circulating Tumor Cell (HD-CTC®) prior to treatment predict benefit from fulvestrant vs. fulvestrant and anastrozole +/- everolimus?

Secondary 1. Does genome-wide copy number alteration/genomic stability predict response to fulvestrant +/- anastrozole +/- everolimus?

Secondary 2. Do specific genomic alterations predict resistance to fulvestrant +/- anastrozole +/- everolimus?

Secondary 3. What is the integrated predictive value of a multi-element analysis of both imaging and fluid biopsy modalities?

In each treatment arm (n=264 patients with outcomes) we anticipate that approximately 200 patients (50% of 264) will have a positive HD-CTC fluid biopsy at baseline. Following the selection of candidate cells via the standard HD-CTC protocol, up to 20 cells will be extracted for the CTC-NGS analysis. These cells will have been morphologically characterized with higher resolution imagery taken for subcellular analysis of both protein and DNA distributions.

Scorable markers for Primary and Secondary Objectives:
Quantitative markers will include, but are not limited to:

1. Enumeration of candidate events by Category

2. Morphology of candidate events, including cell shape and protein localization

3. Scoring of gene-specific CNV, including, but not limited to: ER, TP53, MYC, ERBB2, PTEN, P16ARF, CHK1, CHK2, ATM, MDM1, MDM2, TORC1, TORC2.

4. Scoring of large multigene CNV events (chromosome arm gains/losses)

5. Scoring of aggregate CNV genome complexity measured across cell population for each case.

Statistical power for genomic events depends on the number of events available for scoring in each of the categories. The significance of any results will be calculating using methods appropriate to the marker categories, such as permutation tests or standard multiple testing corrections algorithms.

Clinical Endpoint(s) to be used in analyses:
The primary outcome in the clinical trial, progression-free survival (PFS), would be the primary outcome here. Response rate would be a secondary endpoint.

Data analysis performed by:
HD-CTC and CTC-NGS analysis will be performed in the Kuhn and Hicks laboratories. Compiled laboratory data will be transferred to SWOG Statistical office, to be analyzed by

18.4 Bibliography

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4 Baslan T, Kendall J, Rodgers L, et al. Genome-wide copy number analysis of single cells. Nature protocols 7:1024-41, 2012.

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Informed Consent Model for S1222

*NOTES FOR LOCAL INSTITUTION INFORMED CONSENT AUTHORS:

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

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

Readability Statistics:	
Flesch Reading Ease	56.9 (targeted above 55)
Flesch-Kincaid Grade Level	9.6 (targeted below 8.5)

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

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

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

*NOTES FOR LOCAL INVESTIGATORS:

- The goal of the informed consent process is to provide people with sufficient information for making informed choices. The informed consent form provides a summary of the clinical study and the individual's rights as a research participant. It serves as a starting point for the necessary exchange of information between the investigator and potential research participant. This model for the informed consent form is only one part of the larger process of informed consent. For more information about informed consent, review the "Recommendations for the Development of Informed Consent Documents for Cancer Clinical Trials" prepared by the Comprehensive Working Group on Informed Consent in Cancer Clinical Trials for the National Cancer Institute. The Web site address for this document is http://cancer.gov/clinicaltrials/understanding/simplification-of-informed-consent-docs/
- A blank line, _____, indicates that the local investigator should provide the appropriate information before the document is reviewed with the prospective research participant.
- Suggestion for Local Investigators: An NCI pamphlet explaining clinical trials is available for your patients. The pamphlet is titled: "Taking Part in Cancer Treatment Research Studies". This pamphlet may be ordered on the NCI Web site at *https://pubs.cancer.gov/ncipl/detail.aspx?prodid=P105* or call 1-800-4-CANCER (1-800-422-6237) to request a free copy.
- Optional feature for Local Investigators: Reference and attach drug sheets, pharmaceutical information for the public, or other material on risks. Check with your local IRB regarding review of additional materials.

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

Testing Fulvestrant with Anastrozole and Everolimus for Postmenopausal Patients with Hormone Receptor Positive Stage IV Breast Cancer

S1222, " Fulvestrant Alone Versus Fulvestrant and Everolimus Versus Fulvestrant, Everolimus and Anastrozole: A Phase III Randomized Placebo-Controlled Trial in Postmenopausal Patients with Hormone-Receptor Positive Stage IV Breast Cancer"

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

You are being asked to take part in this study because you are postmenopausal and have breast cancer that has spread to other parts of your body (metastasized). People who are not in a study are usually treated with surgery, chemotherapy, and radiation therapy.

What is the usual approach to my metastatic breast cancer?

To treat hormone receptor positive metastatic breast cancer doctors usually use the drug fulvestrant, or other anti-estrogen therapeutic agents, including the aromatase inhibitors and tamoxifen. *(5/9/14)*

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

Your other choices may include:

- **You may choose to have the usual approach described above**
- **You may choose to take part in a different study, if one is available**
- **Or may choose not to be treated for cancer but you may want to receive comfort care to relieve symptoms.**

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

Why is this study being done?

The purpose of this study is to find out what effects, good and/or bad, adding the drugs anastrozole and everolimus to regular treatment with fulvestrant has on you and your disease. Anastrozole, everolimus and fulvestrant are all approved by the Food and Drug Administration for the treatment of metastatic breast cancer. However, it is the combination of the three drugs that is considered experimental.

A second purpose of this study is to determine if there are some patients who are more or less likely to benefit from adding either of these drugs to fulvestrant, or even if there are patients with hormone receptor positive breast cancers who will not respond to any of these three drugs. To accomplish this goal, we will collect several tubes of blood from you before you start your assigned treatment. We will also collect blood at the end of the first month of therapy, and then if and whenever your cancer begins to grow.

These blood samples will be sent to investigational laboratories where they will be studied for the presence of certain changes in the genes and proteins of cancer cells that have broken off the metastatic cancers in your body and are floating in your blood. These are called "circulating tumor cells" because they came from the tumors (cancer) in your body and are now "circulating" throughout your body in your blood. We will also study DNA not found in cells but that is also present in your blood because it has been released from the cancers in your body.

The changes that are found in these circulating tumor cells and DNA will be compared to your normal DNA so that we can be sure we are studying changes related to the cancer and not just normal variations in DNA that you inherited from your parents.

At the end of these studies, we hope that we can find many interesting, clinically important observations, such as whether some patients get lots of benefit from adding the extra anti-cancer drugs to fulvestrant while others get none. *(4/3/14)* **In this case, in the future, we can treat those patients likely to benefit with these drugs, while sparing those who will not, the cost and toxicity of taking them.**

How many people will take part in the study?

There will be about 825 people taking part in this study.

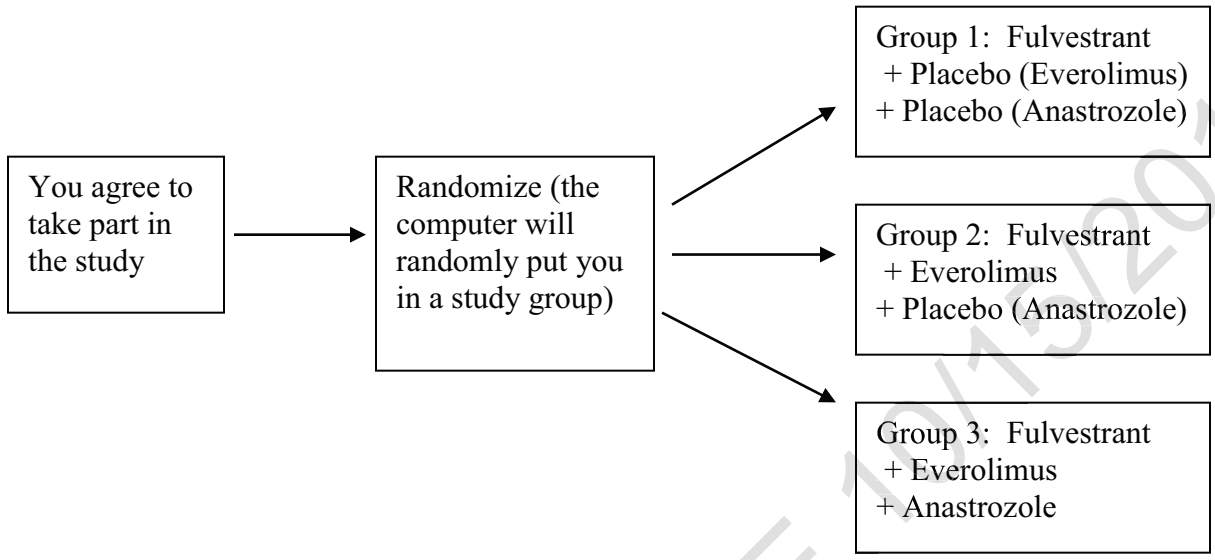
What are the study groups?

This study has three main study groups. Group 1 will get fulvestrant and two different placebos (pills that look like the study drugs but contain no medication) and Group 2 will get fulvestrant with the study drug everolimus and a placebo. Group 3 will get fulvestrant with the study drugs everolimus and anastrozole.

A computer will randomly put you in a study group. This is done because no one knows if one study group is better, the same, or worse than the other groups. Neither you nor your doctor can choose which group you will be in.

One cycle of study treatment lasts 28 days. No matter which group you are in you will get fulvestrant into each buttock on Days 1 and 15 for the first cycle; Day 1 only for subsequent cycles. Then you will take anastrozole/placebo and everolimus/placebo by mouth every day.

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



How long will I be in this study?

You will receive the study drugs as long as your disease does not get worse and the side effects are not too severe. After you finish the study drugs, your doctor will continue to watch you for side effects and follow your condition for up to five years.

What extra tests and procedures will I have if I take part in this study?

Before you start the study:
You will need to have the following extra tests to find out if you can be in the study:

- Blood tests to check your blood sugar and lipids

Additional blood samples are also required in order for you to take part in this study because research that is an important part of the study will be conducted on the samples. The samples will be collected before you start treatment, 4 weeks into the study and if your disease progresses. At each timepoint you will have a single needle stick, but several tubes of blood will be drawn; about 3 and ½ tablespoons.

Neither you nor your health care plan/insurance carrier will be billed for the collection of the samples that will be used for this study. You and your study doctor will not receive the results of any tests done on your samples.

While you are on the study, most of the exams, tests, and procedures you will have are part of the usual approach for your cancer. However, the following are some extra exams and tests that you will need to have if you take part in this study:

- Blood tests to check your blood sugar and lipids

What risks can I expect from taking part in this study?

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

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

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

There is also a risk that you could have side effects.

Here are important points about side effects:

- **The study doctors do not know who will or will not have side effects.**
- **Some side effects may go away soon, some may last a long time, or some may never go away.**
- *(deleted 4/3/14)*
- **Some side effects may be serious and may even result in death.**

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

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

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

(deleted 4/3/14)

Possible Side Effects of Anastrozole

COMMON, SOME MAY BE SERIOUS
In 100 people receiving anastrozole, more than 20 may have:
• **Hot flashes and/or flushing** • **Joint pain**

OCCASSIONAL, SOME MAY BE SERIOUS
In 100 people receiving anastrozole, from 4 to 20 may have:
• **Diarrhea** • **Nausea and/or Vomiting** • **Weakness and/or tiredness** • **Arthritis and/or bone and/or muscle pain** • **Difficulty tasting** • **Headache** • **Rash** • **Thinning hair** • **Vaginal bleeding and/or dryness**

RARE, AND SERIOUS
In 100 people receiving anastrozole, 3 or fewer may have:
• **Loss of appetite** • **Difficulty sleeping and/or sleepiness** • **Carpal Tunnel Syndrome** • **Allergic reactions** • *(deleted 4/3/14)*

Possible Side Effects of Everolimus:

COMMON, SOME MAY BE SERIOUS
In 100 people receiving everolimus, more than 20 may have:
• **Mouth or lip sores** • **Diarrhea** • **Nausea** *(11/15/14)* • **Lack or loss of strength** • **Swelling of the hands and/or feet** • **Infections** • **Weight loss** • **Loss of appetite** • **Altered taste** • **Headache** • *(deleted 11/15/14)* • *(deleted 11/15/14)* • **Nosebleed** • **Inflammation of the lungs** • **Rash** • **Itching**

OCCASIONAL, SOME MAY BE SERIOUS

In 100 people receiving everolimus, from 4 to 20 may have:

- **Pain – abdominal, oral, chest (non-cardiac) and joints**
- **Dry mouth**
- **Indigestion**
- **Difficulty swallowing**
- **Vomiting** *(added 11/15/14)*
- **Swelling of the lining (mucous membranes) of your mouth, throat and stomach**
- **Fever**
- **Pneumonia** *(added 11/15/14)*
- **Dehydration**
- **Diabetes Mellitus**
- **Inability to taste**
- **Inability to sleep**
- **Decreased kidney function**
- **Frequent urination**
- **Cough** *(added 11/15/14)*
- **Difficulty or labored breathing** *(added 11/15/14)*
- **Acne**
- **Dry skin**
- **Flushed or red skin**
- **Hand-foot syndrome-redness swelling and/or pain on palms of hands and soles of feet**
- **Nail disorder**
- **Excessive bleeding**
- **Increased blood pressure**

RARE, AND SERIOUS

In 100 people receiving everolimus, 3 or fewer may have:

- **Heart failure**
- **Difficult wound healing**
- **Allergic reaction** *(4/3/14)*
- **Sudden decrease of kidney function**
- **Respiratory failure**
- **Coughing up blood**
- **Blood clot which may cause swelling, pain, shortness of breath**
- **Swelling around the eyes, lips, hands and feet (angioedema)** *(added 11/15/14)*

Possible Side Effects of Fulvestrant

COMMON, SOME MAY BE SERIOUS *(section added 11/15/14)*
In 100 people receiving fulvestrant, more than 20 may have:
• **Nausea** • **Tiredness or weakness** • **Pain and/or swelling where the shot is given** • **Allergic reaction (moved 11/7/18)** • **Headache (moved 11/7/18)** • **Rash (moved 11/7/18)** • **Hot flashes (moved 11/7/18)** • **Joint, Muscle and bone pain (added 11/7/18)**

OCCASIONAL, SOME MAY BE SERIOUS
In 100 people receiving fulvestrant, from 4 to 20 may have:
• **Loss of appetite** ***(moved 11/7/18)****deleted 4/3/14)* • **Vomiting** *(11/15/14)* • **Diarrhea** • *(5/9/14)* • ***(moved 11/7/18)*** • ***(moved 11/7/18)*** • **Urinary tract infections** ***(moved 11/7/18)*** • **Decreased number of a type of blood cell that helps to clot blood (platelet) (added 11/7/18)** • *(deleted 11/15/14)* • *(deleted 11/15/14)*

RARE, AND SERIOUS
In 100 people receiving fulvestrant, 3 or fewer may have:
• ***(moved 11/7/18)*** • **Liver failure** *(added 11/15/14)* • **Hepatitis** *(added 11/15/14)*

Let your study doctor know of any questions you have about possible side effects. You can ask the study doctor questions about side effects at any time.

(deleted 4/3/14)

What possible benefit, can I expect from taking part in this study?

It is not possible to know at this time if the study drug regimen is better than the usual approach so this study may or may not help you. This study will help researchers learn things that will help people in the future.

Can I stop taking part in this study?

Yes. You can decide to stop at any time. If you decide to stop for any reason, it is important to let the study doctor know as soon as possible so you can stop safely. If you stop, you can decide whether or not to let the study doctor continue to provide your medical information to the organization running the study.

The study doctor will tell you about new information or changes in the study that may affect your health or your willingness to continue in the study.

The study doctor may take you out of the study:

- If your health changes and the study is no longer in your best interest
- If new information becomes available
- If you do not follow the study rules
- If the study is stopped by the sponsor, IRB or FDA

What are my rights in this study?

Taking part in this study is your choice. No matter what decision you make, and even if your decision changes, there will be no penalty to you. You will not lose medical care or any legal rights.

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

What are the costs of taking part in this study?

The anastrozole will be supplied at no charge while you take part in this study until June 30, 2019. The everolimus and fulvestrant will be supplied at no charge while you take part in this study until December 31, 2019. The cost of getting the anastrozole, everolimus and fulvestrant ready and giving it to you is not paid by the study sponsor so you or your insurance company may have to pay for this. It is possible that the anastrozole, everolimus and fulvestrant may not continue to be supplied free while you are on the study. Although not likely, if this occurs, your study doctor will talk to you about your options.

You and/or your health plan/insurance company will need to pay for all of the other costs of treating your cancer while in this study, including the cost of managing any side effects. Before you decide to be in the study, you should check with your health plan or insurance company to find out exactly what they will pay for.

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

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

If you are injured or hurt as a result of taking part in this study and need medical treatment, please tell your study doctor. The study sponsors will not offer to pay for medical treatment for injury. No other form of compensation will be provided by Novartis or AstraZeneca. *(added 11/15/14)* Your insurance company may not be willing to pay for study-related injury. If you have no insurance, you will be responsible for any costs. If you feel this injury was a result of medical error, you keep all your legal rights to receive payment for this even though you are in a study.

Who will see my medical information?

Your privacy is very important to us and the researchers will make every effort to protect it. Your information may be given out if required by law. For example, certain states require doctors to report to health boards if they find a disease like tuberculosis. However, the researchers will do their best to make sure that any information that is released will not identify you. Some of your health information, and information about your specimen, from this study will be kept in a central database for research. Your name or contact information will not be put in the database.

There are organizations that may inspect your records. These organizations are required to make sure your information is kept private, unless required by law to provide information. Some of these organizations are:

- The study sponsor and Novartis Pharmaceuticals (supplier of everolimus), AstraZeneca (supplier of anastrozole and fulvestrant) or any subsequent pharmaceutical collaborator and their authorized agents. *(updated 11/15/14)*
- Your local Institutional Review Board, IRB, a group of people who review the research with the goal of protecting the people who take part in the study.
- The Food and Drug Administration in the U.S., and government agencies in other countries where the study drug may be considered for approval. *(4/3/14) (updated 11/15/14)*
- A qualified representative of AG Mednet (the company providing image transfer of CT scans). *(added 4/3/14)*

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

Where can I get more information?

(paragraph deleted 4/3/14)

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

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

Who can answer my questions about this study?

You can talk to the study doctor about any questions or concerns you have about this study or to report side effects or injuries. Contact the study doctor _____ *(insert name of study doctor[s])* at _____ *(insert telephone number).*

This section is about optional studies you can choose to take part in

This part of the consent form is about optional studies that you can choose to take part in. You will not get health benefits from any of these studies. The researchers leading this optional study hope the results will help other people with cancer in the future.

The results will not be added to your medical records, nor will you or your study doctor know the results.

You will not be billed for these optional studies. You can still take part in the main study even if you say 'no' to any or all of these studies. If you sign up for but cannot complete any of the studies for any reason, you can still take part in the main study.

Circle your choice of "yes" or "no" for each of the following studies.

1. Future Contact

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

Yes No

2. Optional Biobanking for Possible Future Studies

Researchers are trying to learn more about cancer, diabetes, and other health problems. Much of this research is done using samples from your tissue, blood, urine, or other fluids. Through these studies, researchers hope to find new ways to prevent, detect, treat, or cure health problems.

Some of these studies may be about genes. Genes carry information about features that are found in you and in people who are related to you. Researchers are interested in the way that genes affect how your body responds to treatment.

If you choose to take part in this study, the study doctor for the main study would like to collect a sample of tissue from your previous biopsy. Also, if your disease progresses and you and your

physician decide you should have a biopsy as part of your usual cancer care, the study doctor for the main study would like to collect a sample of tissue from that biopsy.

The researchers also ask your permission to store and use your samples and health information for medical research. The research that may be done is unknown at this time. Storing samples for future studies is called "biobanking". The Biobank is being run by SWOG and supported by the National Cancer Institute.

WHAT IS INVOLVED?

If you agree to take part, here is what will happen next:

1) Your tissue will be collected as described above and will be sent to the Biobank.
2) Your sample and some related information may be stored in the Biobank, along with samples and information from other people who take part. The samples will be kept until they are used up.
3) Qualified researchers can submit a request to use the materials stored in the Biobanks. A science committee at the clinical trials organization will review each request. *(4/3/14)* There will also be an ethics review to ensure that the request is necessary and proper. Researchers will not be given your name or any other information that could directly identify you.
4) Neither you nor your study doctor will be notified when research will be conducted or given reports or other information about any research that is done using your samples.
5) Some of your genetic and health information may be placed in central databases that may be public, along with information from many other people. Information that could directly identify you will not be included.

WHAT ARE THE POSSIBLE RISKS?

1) There is a risk that someone could get access to the personal information in your medical records or other information researchers have stored about you.
2) There is a risk that someone could trace the information in a central database back to you. Even without your name or other identifiers, your genetic information is unique to you. The researchers believe the chance that someone will identify you is very small, but the risk may change in the future as people come up with new ways of tracing information.
3) In some cases, this information could be used to make it harder for you to get or keep a job or insurance. There are laws against the misuse of genetic information, but they may not give full protection. There can also be a risk in knowing genetic information. New health information about inherited traits that might affect you or your blood relatives could be found during a study. The researchers believe the chance these things will happen is very small, but cannot promise that they will not occur.

HOW WILL INFORMATION ABOUT ME BE KEPT PRIVATE?

Your privacy is very important to the researchers and they will make every effort to protect it. Here are just a few of the steps they will take:

1) When your samples are sent to the researchers, no information identifying you (such as your name) will be sent. Samples will be identified by a unique code only.
2) The list that links the unique code to your name will be kept separate from your sample and health information. Any Biobank and SWOG staff with access to the list must sign an agreement to keep your identity confidential.
3) Researchers to whom SWOG sends your sample and information will not know who you are. They must also sign an agreement that they will not try to find out who you are.
4) Information that identifies you will not be given to anyone, unless required by law.
5) If research results are published, your name and other personal information will not be used.

WHAT ARE THE POSSIBLE BENEFITS?

You will not benefit from taking part. The researchers, using the samples from you and others, might make discoveries that could help people in the future.

ARE THERE ANY COSTS OR PAYMENTS?

There are no costs to you or your insurance. You will not be paid for taking part. If any of the research leads to new tests, drugs, or other commercial products, you will not share in any profits.

WHAT IF I CHANGE MY MIND?

If you decide you no longer want your samples to be used, you can call the study doctor, _____, *(insert name of study doctor for main trial)* at _____ *(insert telephone number of study doctor for main trial)* who will let the researchers know. Then, any sample that remains in the bank will no longer be used. Samples or related information that have already been given to or used by researchers will not be returned.

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

WHAT IF I HAVE MORE QUESTIONS?

If you have questions about the use of your samples for research, contact the study doctor, _____, *(insert name of study doctor for main trial)*, at _____ *(insert telephone number of study doctor for main trial)*.

Please circle your answer to show whether or not you would like to take part in each option (*include only applicable questions)*:

SAMPLES FOR FUTURE RESEARCH STUDIES:

My samples and related information may be kept in a Biobank for use in future health research.

YES NO

This is the end of the section about optional studies.

My Signature Agreeing to Take Part in the Main Study

I have read this consent form or had it read to me. I have discussed it with the study doctor and my questions have been answered. I will be given a signed copy of this form. I agree to take part in the main study and any additional studies where I circled 'yes'.

Participant's signature (or authorized legal representative) _____

Date of signature_____

Specimen Consent Supplemental Sheets

How are Specimens Used for Research?

Where do specimens come from?

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

Why do people do research with specimens?

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

What type of research will be done with my specimen?

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

How do researchers get the specimen?

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

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

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

Why do you need information from my health records?

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

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

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

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

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

How am I protected?

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

What if I have more questions?

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