NCT02236572
Neoadj ph 2 AI Plus Everolimus in Postmenopausal Women w/ ER Pos/HER2 Neg, Low Risk Score

Protocol and SAP

Last Approved: 9/16/2016

A neoadjuvant phase II trial of aromatase inhibitors in combination with everolimus in postmenopausal women with hormone receptor positive/HER2 negative breast cancers with low and intermediate risk (≤ 25) Oncotype Dx Recurrence Scores

CRAD001JUS228T

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Title of Trial:	A phase II clinical trial evaluating neoadjuvant endocrine therapy with everolimus in postmenopausal women with hormone receptor positive/HER 2negative breast cancers with low and intermediate risk (≤25) Oncotype Dx Recurrence Scores	
Protocol Number:	CRAD001JUS228T	
Sponsor:	Thomas Jefferson University	
Trial Duration:	24 months	**Phase of Trial:** II
Trial Centers:	Thomas Jefferson University: Sidney Kimmel Cancer Cener Yale University: Smilow Cancer Hospital-Main Campus, Smilow Hospital Care Centers	
Patient Population	This study will enroll postmenopausal women with hormone receptor positive/HER-2 negative Stage II-III breast cancer with low to intermediate risk (≤ 25) Oncotype Dx Recurrence Scores, who have not had surgical resection of their breast cancer.	
Objectives:	Primary objectives • The primary objective of the study is to determine the percent of postmenopausal patients with stage II-III hormone receptor positive/ HER2 negative breast cancers and an Oncotype Dx recurrence score ≤ 25, who achieve a PEPI score of 0 following neoadjuvant treatment with everolimus and an aromatase inhibitor Secondary objectives 1) To assess the tolerability and side effect profile of neoadjuvant aromatase inhibitor therapy and everolimus 2) To identify biologic markers predictive of clinical and pathologic response (pathologic complete response or PEPI 0) to neoadjuvant aromatase inhibitor therapy and everolimus in postmenopausal hormone receptor positive/HER2 negative breast cancer patients selected by Oncotype Dx Recurrence Score ≤ 25, on tissue biopsies obtained at baseline and at end of treatment	
Number of Patients:	Up to 33 patients will be enrolled on the clinical trial.	
Trial Design:	This is an open label, non-randomized phase II clinical trial evaluating the efficacy and safety of neoadjuvant endocrine therapy with everolimus in postmenopausal women with hormone receptor positive/HER2 negative breast cancers with low and intermediate risk (≤ 25) Oncotype Dx Recurrence Scores	
Trial Drug(s), Dose, and Mode of Administration	Eligible patients will receive daily aromatase inhibitor therapy (anastrozole 1 mg, or letrozole 2.5 mg or exemestane 25 mg) in combination with everolimus 10 mg daily. Both study agents will be administered orally for a total of 26 weeks.	

Inclusion Criteria:	1. Patients must have a histologically confirmed diagnosis of hormone receptor positive, HER2 negative invasive breast carcinoma. 2. Tumors must be estrogen and/or progesterone receptor positive according to ASCO/CAP 2010 guidelines as either ER or PR ≥ 1% positive nuclear staining by immunohistochemistry. Estrogen and/or progesterone receptor results by Oncotype Dx will not be accepted. 3. Tumors must be HER2 negative as defined according to ASCO/CAP 2013, as HER2 0 – 1+ by IHC or non-amplified FISH or CISH. If HER2 IHC is 2+, FISH/CISH must be performed and must not be positive (must be a ratio of < 2), but otherwise FISH/CISH is not required if IHC is 0 or 1+ by institutional standards. 4. Patients must not have had prior ipsilateral breast-conserving surgery or total mastectomy and be eligible for neoadjuvant treatment. 5. Clinical Stage II-IIIC (T2-4 N0-3 M0) by mammogram, ultrasound or MRI 6. Baseline Oncotpye Dx recurrence score ≤ 25. 7. Staging studies with a CT scan of the chest and abdomen and bone scan, or a PET/CT is required for clinical stage III, and are considered optional for stage II breast cancers. 8. Patients with multifocal, multicentric and synchronous bilateral breast cancers are allowed: • Multifocal disease is defined as more than one invasive cancer < 2 cm from the largest lesion within the same breast quadrant. • Multicentric disease is defined as more than one invasive cancer ≥ 2 cm from the largest lesion within the same breast quadrant or more than one lesion in different quadrants. • Synchronous bilateral disease is defined as invasive breast cancer in both breasts, diagnosed within 30 days of each other. • In patients with multicentric or bilateral invasive breast cancers, all sampled lesions must be hormone receptor-positive and HER2-negative. Any lesion measuring ≥ 1 cm must have an Oncotype Dx and the score must be ≤ 25. Lesions less than 1 cm in size are not required to have an Oncotype Dx. One lesion (typically the largest) should be designated as the target lesion for which clinical and radiographic response to the neoadjuvant therapy will be judged. • Patients with a hormone receptor-positive, HER2-negative invasive cancer that meets study criteria may have ductal carcinoma in situ in another quadrant of the same breast or in the contralateral breast even if the DCIS is hormone receptor-negative. 9. Patients must have adequate bone marrow function, as defined by peripheral granulocyte count of ≥ 1,500/mL, hemoglobin ≥ 9 g/dL and a platelet count ≥ 100,000/ mL within 28 days prior to registration. 10. Patients must have adequate hepatic function obtained within 28 days prior to registration and documented by all of the following: • Bilirubin ≤ 1.5 mg/dL (or ≤ 3.0 mg/dL if due to Gilbert's Syndrome) • ALT and AST ≤ 1.5 x Institutional Upper Limit of Normal (IULN)

	• Alkaline phosphatase ≤ 1.5 x IULN 11. Patients must have adequate renal function with serum creatinine level ≤ IULN within 28 days prior to registration. 12. Patients must have a fasting cholesterol ≤ 300 mg/dl OR ≤7.75 mmol/L and triglycerides ≤ 2.5 x IULN obtained within 28 days prior to registration. Patients may be on lipid lowering agents to reach these values. 13. Patients must have a ECOG performance status of 0-2. 14. Patients must be able to take oral medications. 15. Postmenopausal women (women are considered post-menopausal and not of child-bearing potential if they are > 18 years of age and have had 12 months of natural (spontaneous) amenorrhea with an appropriate clinical profile (e.g. age appropriate, history of vasomotor symptoms or biochemically postmenopausal by estradiol and FSH levels) prior to enrollment, or have had surgical bilateral oophorectomy (with or without hysterectomy) prior to registration. Medical ovarian suppression with LHRH agonists to render a patient postmenopausal will not be acceptable. 16. Patients or their legally authorized representative must be informed of the investigational nature of this study and must sign and give written informed consent prior to any screening procedures in accordance with institutional and federal guidelines.
Exclusion Criteria:	1. Patients must not have inflammatory breast cancer (T4d) and must not have metastatic breast cancer (Stage IV disease). 2. Patients must not have prior exposure to mTOR inhibitors (e.g. rapamycin, everolimus, sirolimus, temsirolimus, deforolimus). 3. Patients must not have prior treatment with any investigational drug within the preceding 28 days and must not be planning to receive any other investigational drug for the duration of the study. 4. Patient may not have any impairment of gastrointestinal function or gastrointestinal disease that may significantly alter the absorption of the drug (e.g. ulcerative disease, uncontrolled nausea, vomiting, diarrhea, malabsorption syndrome or small bowel resection). 5. Uncontrolled diabetes mellitus as defined by HbA1c >8% within 28 days prior to registration despite adequate therapy. 6. Patients who have any severe and/or uncontrolled cardiac disease within ≤ 6 months prior to start of everolimus, including: unstable angina pectoris, Symptomatic congestive heart failure of New York heart Association Class III or IV, myocardial infarction, serious uncontrolled cardiac arrhythmia, or any other clinically significant cardiac disease 7. Patients must not have an organ allograft or other history of immune compromise. 8. Patients must not be receiving chronic, systemic treatment with corticosteroids or other immunosuppressive agent. Topical or inhaled corticosteroids are allowed. 9. Patients must not have a known history of HIV seropositivity

	10. Patients must not have a known diagnosis of hepatitis B or C. Patients with the following risk factors must 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 • History of jaundice. 11. Patients must not have any known uncontrolled underlying pulmonary disease or severely impaired lung function (spirometry and DLCO 50% or less of normal and O2 saturation 88% or less at rest on room air), 12. Active (acute or chronic) or uncontrolled severe infection. 13. Patients who have received live attenuated vaccines within 1 week of start of Everolimus, or have plans to receive such vaccination while on protocol treatment. Patient should also avoid close contact with others who have received live attenuated vaccines. Examples of live attenuated vaccines include intranasal influenza, measles, mumps, rubella, oral polio, BCG, yellow fever, varicella and TY21a typhoid vaccines; 14. , Patients who are currently part of or have participated in any clinical investigation with an investigational drug within 1 month prior to dosing; 15. 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. 16. Patients with active bleeding diathysis.
Statistical Methodology:	This is a single arm phase II study to evaluate neoadjuvant endocrine therapy with everolimus in postmenopausal women with hormone receptor positive/HER2 negative breast cancers with low and intermediate risk ($\leq$ 25) Oncotype Dx recurrence score. The primary endpoint is response defined as a PEPI-0 rate. A treatment with minimal activity would be expected to have PEPI-0 rate of 25%. Alternatively, a treatment will be considered worthy of further study if its true PEPI-0 rate is 45% or better. Simon's optimal two-stage design is employed for this single-arm phase II trial. The sample size is 27. Assuming 10-20% ineligibility rate, we plan to enroll up to 33 patients totally.

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SIGNATURE PAGE FOR PRINCIPAL INVESTIGATOR

Title: A phase II clinical trial evaluating neoadjuvant endocrine therapy with everolimus in postmenopausal women with ER+/HER2- breast cancers with low and intermediate risk (≤ 25) Oncotype Dx Recurrence Scores

I have read this protocol and agree to conduct this trial in accordance with all stipulations of the protocol and in accordance with Good Clinical Practices (GCP) as well as applicable legal and regulatory requirements. I will make all reasonable efforts to complete the study within the designated time.

I will provide copies of the protocol and access to all necessary information to study personnel under my supervision. I will discuss this material with them to ensure that they are fully informed about the drug and the study.

I understand that the study may be terminated or enrollment suspended at any time by the Principal Investigator with or without cause, or by me if it becomes necessary to protect the best interests of the study subjects.

_____ _____

Principal Investigator Date

1.0 Background

1.1 Neoadjuvant therapy for hormone receptor positive breast cancer

Endocrine therapy is the cornerstone of treatment for patients with hormone-receptor (HR)–positive breast cancer. The presence of hormone receptors, especially estrogen receptor (ER), is a clear positive predictor of efficacy of adjuvant hormone therapy (HT) [1] [2]. Chemotherapy is less effective in the genomically and immunohistochemically defined (ER+/HER2−) luminal subtype when compared with the HER2-enriched and basal-like subtypes[3, 4]. Oncotype DX, developed by Genomic Health, is a diagnostic test that quantifies the likelihood of disease recurrence in women with early-stage hormone receptor positive breast cancer and assesses the likely benefit from certain types of chemotherapy. A prospective analysis of archived tissue from 367 postmenopausal, hormone receptor–positive, node-positive patients with invasive breast cancer treated on Southwest Oncology Group (SWOG) 8814 with tamoxifen or tamoxifen plus chemotherapy, suggests that only the subset of patients with intrinsically more biologically aggressive cancers, as defined by a high Oncotype Dx Recurrence Score (RS), appears to benefit from the addition of chemotherapy, whereas patients with low-intermediate RS may not have a significant benefit from chemotherapy. Further analysis incorporating determination of recurrence score by RT-PCR showed that after adjusting for number of lymph nodes involved, patients with high recurrence score had worse outcomes [5]. Patients treated with chemotherapy followed by tamoxifen had a 10-year disease free survival (DFS) of 55% and a 10-year overall survival (OS) of 68% [6]. An ongoing large randomized phase III clinical trial (SWOG 1007) is designed to evaluate the benefit from chemotherapy for ER positive breast cancer with 1-3 positive lymph nodes and an Oncotype Dx recurrence score of < 25 (low-intermediate recurrence scores).

In recent years, neoadjuvant therapy has been increasingly offered to breast cancer patients to facilitate tumor down-staging and to better understand tumor response to therapy [7]. Although neoadjuvant endocrine therapy has not been studied as extensively as neoadjuvant chemotherapy, neoadjuvant hormonal therapy is, in general, considered to be a suitable option for hormone receptor (HR)-positive patients who are unfit for chemotherapy or surgery with mild toxicity profile [8-10]. In the European Cooperative Trial in Operable Breast Cancer, pathologic complete response (pCR) after neoadjuvant chemotherapy was observed in 42% of patients with ER-negative tumors, compared with 12% in the ER-positive group [11-13]. In four phase III trials, differences in neoadjuvant treatment outcomes between aromatase inhibitors (AIs) and tamoxifen were studied. Clinical response rates ranged from 38% to 70% for AIs and from 36% to 51% for tamoxifen. Overall AIs have demonstrated superior results when compared with tamoxifen in postmenopausal patients [14-17].

More recently, attempts have been made to quantitate response to neoadjuvant endocrine therapy. Post-treatment Ki67 can be of prognostic value, as shown by Ellis et al., who developed a preoperative endocrine prognostic index (PEPI) score for the prediction of recurrence free survival (RFS). The PEPI score incorporates post-treatment pathological

tumor size, pathological node status, level of ER expression and the proliferative rate (defined by the percent of cells expressing Ki67) [8].

1.2 PI3kinase/AKT/mTOR signaling pathway in hormone receptor positive breast tumors.

The phosphatidylinositol 3-kinase (PI3K)/AKT/mTOR signaling pathway plays an important role in cell survival, proliferation, angiogenesis and metabolism [18, 19]. mTOR, a serine/threonine protein kinase that belongs to the PI3kinase protein family, is frequently activated during carcinogenesis via genetic and epigenetic alterations. Abnormalities of the PI3kinase/AKT/mTOR signaling pathway are some of the most common molecular anomalies in breast cancer, and many of these abnormalities are detected in HR-positive tumors [1]. Activation of mTOR pathway leads to PI3K gene activation, phosphatase and tensin homolog (PTEN) loss and high levels of AKT expression in 16-48% of breast cancer patients [20-22]. A substrate of mTOR complex 1 (mTORC1), called S6 kinase 1, phosphorylates the activation function domain 1 of the ER, which is responsible for ligand-independent receptor activation[23, 24]. High levels of phosphorylated mTOR were correlated with nodal metastasis and poor prognosis in breast cancer patients [25]. Preclinical studies have shown that upregulation of the PI3K-mTOR pathway is a mechanism of resistance to endocrine therapy, and sensitivity to endocrine therapy can be restored by treatment with everolimus or other mTOR inhibitors [26, 27]. Interestingly, the rate of PI3K mutations is highest in low/intermediate grade and Luminal A breast cancers [28, 29]. This tumor subset is also thought to be less likely to benefit from chemotherapy.

Everolimus (Afinitor, Novartis) is an oral sirolimus (formerly called rapamycin) derivative that inhibits its mTOR through allosteric binding to mTORC1 potently [23, 30]. Everolimus has been recently approved for use in patients with advanced breast cancer progressing on a nonsteroidal aromatase inhibitors in combination with the steroidal aromatase inhibitor exemestane based on the results of BOLERO-2 which showed a PFS benefit in favor of the exemestane and everolimus combination arm compared to exemestane alone[31]. The BOLERO-2 study randomized 724 patients with metastatic hormone receptor positive breast cancer who had progressed on prior estrogen-deprivation therapy to receive exemestane or exemestane in combination with everolimus. The initial analysis, based on investigator assessment, demonstrated a significant improvement in progression-free survival (hazard ratio 0.43; 95% CI 0.35-0.54). On central review, the median time to progression was 4.1 months in the exemestane arm and 10.6 months in the combination arm. In addition, response rate and clinical benefit rate were both significantly superior with the combination, and while there was some increase in toxicity, there was no difference in quality of life during treatment in the two arms of the study [32]. The most common Grade 3 or 4 adverse events were stomatitis, anemia, hyperglycemia, fatigue and pneumonitis. Therefore, the combination of endocrine therapy and everolimus resulted in an increased antitumor effect in groups of patients without prior therapy, limited prior therapy and even extensive prior endocrine treatment suggesting that targeting mTOR activation may be implicated in restoring endocrine resistance.

1.3 Everolimus

Everolimus is a novel derivative of rapamycin. It has been in clinical development since 1996 as an immunosuppressant in solid organ transplantation. Everolimus is approved in Europe and other global markets (trade name: Certican®) for cardiac and renal transplantation, and in the United States (trade name: Zortress®) for the prevention of organ rejection of kidney transplantation. Afinitor® and was approved for adults with advanced renal cell carcinoma (RCC) after failure of treatment with sunitinib or sorafinib in 2009. In 2010, Afinitor® received United States (US) approval for patients with subependymal giant cell astrocytoma (SEGA) associated with tuberous sclerosis complex (TSC). Everolimus is also available as Votubia® in the European Union (EU) for patients with SEGA associated with TSC who require therapeutic intervention but are not candidates for curative surgical resection. Afinitor® was approved for "progressive pancreatic neuroendocrine tumor (PNET) in patients with unresectable, locally advanced, or metastatic disease" in 2011 in various countries, including the US and Europe. In 2012 Afinitor® received approval for the treatment of postmenopausal women with advanced hormone receptor-positive, HER2-negative breast cancer (advanced HR+ BC) in combination with exemestane, after failure of treatment with letrozole or anastrozole. Furthermore in 2012, Afinitor® received approval for the treatment of patients with TSC who have renal angiomyolipoma not requiring immediate surgery. In the US, Afinitor® was approved in 2016 for advanced non-functional NET of gastrointestinal (GI) or lung origin.

Approximately 44,060 cancer patients (excluding those patients who received marketed Afinitor® , those on planned and roll over studies as well as excluding investigator-sponsored studies) have been treated with everolimus as of 31-Mar-2016

- 25,356 patients in Novartis-sponsored clinical trials
- 2,043 patients in the individual patient supply program

1.3.1 Everolimus mechanism of action

Everolimus is a derivative of rapamycin which acts as a signal transduction inhibitor (Table 1, Figure 1). Everolimus selectively inhibits mTOR (mammalian target of rapamycin), specifically targeting the mTOR-raptor signal transduction complex. mTOR is a key serine-threonine kinase in the PI3K/AKT signaling cascade, which is known to be dysregulated in a wide spectrum of human cancers [33].

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

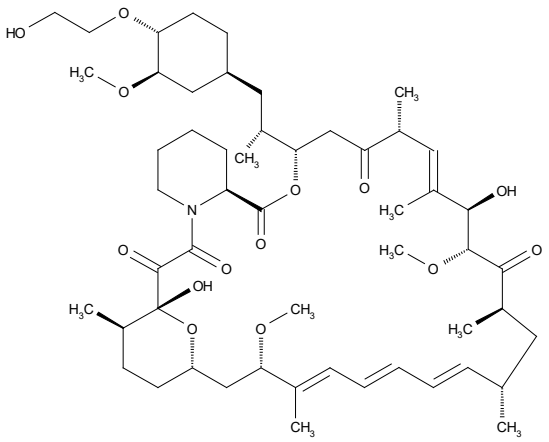
- directly on the tumor cells by inhibiting tumor cell growth and proliferation;

- indirectly by inhibiting angiogenesis leading to reduced tumor vascularity (via potent inhibition of tumor cell VEGF (vascular endothelial growth factor) production and VEGF-induced proliferation of endothelial cells).

Table 1 Everolimus - Drug substance

Chemical name	(1R,9S,12S,15R,16E,18R,19R,21R,23S,24E,26E,28E,30S,32S,35R)-1,18-dihydroxy-12-{(1R)-2-[(1S,3R,4R)-4-(2-hydroxyethoxy)-3-methoxycyclohexyl]-1-methylethyl}-19,30-dimethoxy-15,17,21,23,29,35-hexamethyl-11,36-dioxa-4-aza-tricyclo[30.3.1.$0^{4,9}$]hexatriaconta-16,24, 26,28-tetraene-2,3,10,14,20-pentaone
International non-proprietary name	Everolimus

Figure 1 Chemical structure of Everolimus



At the cellular and molecular level, Everolimus acts as a signal transduction inhibitor. It selectively inhibits mTOR (mammalian target of rapamycin), a key protein kinase which regulates cell growth, proliferation and survival. The mTOR kinase is mainly activated via the phosphatidylinositol 3-kinase (PI3-Kinase) pathway through AKT/PKB and the tuberous sclerosis complex (TSC1/2). Mutations in these components or in PTEN, a negative regulator of PI3-kinase, may result in their dysregulation. Abnormal functioning of various components of the signaling pathways contributes to the pathophysiology of numerous human cancers. Various preclinical models have confirmed the role of this pathway in tumor development [34].

The main known functions of mTOR include the following [35].

- mTOR functions as a sensor of mitogens, growth factors and energy and nutrient levels;
- Facilitating cell-cycle progression from G1-S phase in appropriate growth conditions;
- The PI3K/mTOR pathway itself is frequently dysregulated in many human cancers, and oncogenic transformation may sensitize tumor cells to mTOR inhibitors;
- PI3-kinase mutations have been reported in the primary tumor in 10-20% of human colorectal cancers [36, 37].

- The loss of PTEN protein, either through gene deletion or functional silencing (promoter hypermethylation), is reported in approximately 60% of primary human colorectal cancers [38].
- The mTOR pathway is involved in the production of pro-angiogenic factors (i.e., VEGF) and inhibition of endothelial cell growth and proliferation;
- Through inactivating eukaryotic initiation factor 4E binding proteins and activating the 40S ribosomal S6 kinases (i.e., p70S6K1), mTOR regulates protein translation, including the HIF-1 proteins. Inhibition of mTOR is expected to lead to decreased expression of HIF-1.

1.3.2 Non-clinical experience

Everolimus inhibits the proliferation of a range of human tumor cell lines *in vitro* including lines originating from lung, breast, prostate, colon, melanoma and glioblastoma. IC50s range from sub/low nM to μM. Everolimus also inhibits the proliferation of human umbilical vein endothelial cells (HUVECS) *in vitro*, with particular potency against VEGF-induced proliferation suggesting that Everolimus may also act as an anti-angiogenic agent. The anti-angiogenic activity of Everolimus was confirmed *in vivo*. Everolimus selectively inhibited VEGF-dependent angiogenic response at well tolerated doses. Mice with primary and metastatic tumors treated with Everolimus showed a significant reduction in blood vessel density when compared to controls.

The potential of Everolimus as an anti-cancer agent was shown in rodent models. Everolimus is orally bioavailable, residing longer in tumor tissue than in plasma in a subcutaneous mouse xenograft model, and demonstrating high tumor penetration in a rat pancreatic tumor model. The pharmacokinetic profile of Everolimus indicates sufficient tumor penetration, above that needed to inhibit the proliferation of endothelial cells and tumor cell lines deemed sensitive to Everolimus *in vitro*.

Everolimus administered orally daily was a potent inhibitor of tumor growth, at well tolerated doses, in 11 different mouse xenograft models (including pancreatic, colon, epidermoid, lung and melanoma) and two syngeneic models (rat pancreatic, mouse orthotopic melanoma). These models included tumor lines considered sensitive and “relatively resistant” *in vitro*. In general, Everolimus was better tolerated in mouse xenograft models than standard cytotoxic agents (i.e., doxorubicin and 5-fluorouracil), while possessing similar anti-tumor activity. Additionally, activity in a VEGF-impregnated subcutaneous implant model of angiogenesis and reduced vascularity (vessel density) of Everolimus-treated tumors (murine melanoma) provided evidence of *in vivo* effects of angiogenesis.

It is not clear which molecular determinants predict responsiveness of tumor cells to Everolimus. Molecular analysis has revealed that relative sensitivity to Everolimus *in vitro* correlates with the degree of phosphorylation (activation) of the AKT/PKB protein kinase and the S6 ribosomal protein; in some cases (i.e., glioblastoma) there is also a correlation with PTEN status.

In vivo studies investigating the anti-tumor activity of Everolimus in experimental animal tumor models showed that Everolimus monotherapy typically reduced tumor cell

growth rates rather than produced regressions. These effects occurred within the dose range of 2.5 mg to 10 mg/kg, orally once a day.

In preclinical models, the administration of Everolimus is associated with reduction of protein phosphorylation in target proteins downstream of mTOR, notably phosphorylated S6 (p-S6) and p-4E-BP1, and occasionally with an increase in phosphorylated AKT, a protein upstream of mTOR signaling pathway.

All significant adverse events observed in toxicology studies with Everolimus in mice, rats, monkeys and mini-pigs were consistent with its anticipated pharmacological action as an anti-proliferative and immunosuppressant and at least in part reversible after a 2 or 4-week recovery period with the exception of the changes in male reproductive organs, most notably testes.

In vitro genotoxicity studies covering relevant genotoxicity end-points showed no evidence ofclastogenic or mutagenic activity.

In male fertility studies in rats, testicular morphology was affected at 0.5 mg/kg and above, and sperm motility, sperm head count and plasma testosterone levels were diminished at 5 mg/kg which corresponded to 0.7 times the estimated clinical exposure at 10 mg/day, and caused a decrease in male fertility. There was evidence of reversibility. Female fertility was not affected, but everolimus caused an increase of pre-implantation loss in female rats at doses > 0.1 mg/kg, suggesting it could also potentially impact fertility in females. Everolimus crossed the placenta and was toxic to the conceptus. In rats, everolimus caused embryo/fetotoxicity at systemic exposure below the planned therapeutic level comprising mortality and reduced fetal weight. The incidence of skeletal variations and malformations at 0.3 and 0.9 mg/kg (e.g. sternal cleft) was increased. In rabbits, embryo toxicity was evident by an increase in late resorptions. Effects of everolimus on the pre- and postnatal development of rats were limited to slightly affected body weight and survival in the F1-generation at ≥0.1 mg/kg, and did not indicate a specific toxic potential.

The potential reproductive risk for humans is unknown. However, due to the observed malformations in rats, everolimus should be considered potentially teratogenic. Everolimus should not be given to pregnant women unless the potential benefit outweighs the potential risk for the fetus. Women of childbearing potential should be advised to use highly effective contraception methods while they are receiving everolimus and up to 8 weeks after treatment has been stopped. It is not known whether everolimus is excreted in human milk. In animal studies, everolimus and/or its metabolites were readily transferred into the milk of lactating rats. Therefore women who are taking everolimus should not breastfeed.

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

2.0 RATIONALE

A phase II randomized study of neoadjuvant letrozole and everolimus vs. letrozole alone enrolled 270 postmenopausal patients with tumors larger than 2 cm, and showed improvements in clinical and radiographic responses [7]. However, this study did not select

patients by proliferation rate or recurrence score and thus likely included a broad mix of ER+ cancers. We propose a single arm phase II trial evaluating the combination of everolimus and an aromatase inhibitor in postmenopausal women with hormone receptor positive/HER2 negative breast cancers with low and intermediate risk (≤ 25) Recurrence Scores by Oncotype Dx. The type of aromatase inhibitor administered during this trial will be at the physician's choice, since they all can be considered equivalent in activity based on the results of the ACOSOG Z1031 trial [1]. Our study eligibility will be limited to patients with 'low to moderately aggressive', hormone-responsive tumors, identified by recurrence score ≤ 25, similar to the group of patients in whom the omission of adjuvant chemotherapy is being tested by the TAILORx and SWOG 1007 studies. Therefore, we propose to use pretreatment recurrence score to identify patients most likely to benefit from neoadjuvant endocrine therapy, and determine if the addition of the mTOR inhibitor everolimus enhances that response.

Our primary endpoint will be to evaluate response defined as a PEPI -0. Results from ACOSOG Z1031 demonstrated no difference in clinical response or surgical outcomes between luminal A vs luminal B tumors in postmenopausal patients treated with three different aromatase inhibitors, however, there were significantly higher responses defined by a Preoperative Endocrine Prognostic Index (PEPI) score of 0 in luminal A vs luminal B tumors (27.1% v 10.7 %; P=.0004) [1]. A PEPI score 0 was also highest in tumors with Ki67 levels <10% at baseline. Kelly et al compared risk assignment by PAM 50 Breast cancer intrinsic classifier and Oncotype DX recurrence score in 151 hormone receptor positive stage I-II breast cancers [2]. The majority (83%) of low recurrence score cases were found to be luminal A subtype by PAM 50. Additionally, half of the intermediate recurrence scores were re-categorized as low risk luminal A subtypes by PAM 50. While there are no available reports of the incidence of PEPI-0 following neoadjuvant AI therapy in hormone receptor positive breast cancer patients with an Oncotype of ≤ 25, Ellis et al did report a PEPI-0 of 27% in the Luminal A subset in ACOSOG Z1031. Therefore this will be used as our benchmark. Patients with clinical stage I –III (just like ACOSOG Z1031) hormone receptor tumors and RS <25 will be eligible for the study.

An ongoing large randomized phase III clinical trial (SWOG 1007) is designed to evaluate the benefit from chemotherapy for ER positive breast cancer with 1-3 positive lymph nodes and an Oncotype Dx recurrence score of ≤ 25 (low-intermediate recurrence scores). It is likely that this tumor subset is more sensitive to a combination of an mTOR inhibitor and endocrine therapy. Our proposed neoadjuvant trial will provide rapid and complementary information to assess whether everolimus might improve the efficacy of endocrine therapy in breast cancers with low to intermediate recurrence scores.

3.0 STUDY OBJECTIVES

Primary objectives:

- The primary objective of the study is to determine the percent of postmenopausal patients with stage II-III hormone receptor positive/ HER2 negative breast cancer and an Oncotype Dx recurrence score ≤ 25 who achieve a PEPI score of 0 following neoadjuvant treatment with everolimus and an aromatase inhibitor

Secondary objectives:

1) To assess the tolerability and side effect profile of neoadjuvant aromatase inhibitor therapy and everolimus
2) To identify biologic markers predictive of clinical and pathologic response (pathologic complete response or PEPI 0) to neoadjuvant aromatase inhibitor therapy and everolimus in postmenopausal hormone receptor positive/HER2 negative breast cancer patients selected by Oncotype Dx Recurrence Score ≤ 25, on tissue biopsies obtained at baseline and after completion of study treatment

4.0 TRIAL PATIENT POPULATION AND ELIGIBILITY

This trial which will enroll postmenopausal women with hormone receptor positive /HER2 negative breast cancers with low and intermediate risk (≤ 25) Recurrence Scores by Oncotype Dx. The sample size for this study is 27 patients. Assuming that 10% of enrolled patients will be inevaluable , we plan to enroll up to 33 in total. Patients must have required baseline evaluations performed prior to the first dose of study drug and must meet all inclusion and exclusion criteria. The written informed consent must be obtained from the patient prior to enrollment. The following criteria apply to all patients enrolled onto the study unless otherwise specified.

4.1 Inclusion criteria

1. Patients must have a histologically confirmed diagnosis of hormone receptor positive, HER2 negative invasive breast carcinoma.
2. Tumors must be estrogen and/or progesterone receptor positive according to ASCO/CAP 2010 guidelines as either ER or PR $\geq 1\%$ positive nuclear staining by immunohistochemistry. Estrogen and/or progesterone receptor results by Oncotype Dx will not be accepted.
3. Tumors must be HER2 negative as defined according to ASCO/CAP 2013, as HER2 0 – 1+ by IHC or non-amplified FISH or CISH. If HER2 IHC is 2+, FISH/CISH must be performed and must not be positive (must be a ratio of < 2), but otherwise FISH/CISH is not required if IHC is 0 or 1+ by institutional standards.
4. Patients must not have had prior ipsilateral breast-conserving surgery or total mastectomy and be eligible for neoadjuvant treatment.
5. Clinical Stage II-IIIC (T2-4 N0-3 M0) by mammogram, ultrasound or MRI

6. Baseline Oncotpye Dx recurrence score $\leq$ 25.
7. Staging studies with a CT scan of the chest and abdomen and bone scan, or a PET/CT is required for clinical stage III, and are considered optional for stage II breast cancers.
8. Patients with multifocal, multicentric and synchronous bilateral breast cancers are allowed:
    - Multifocal disease is defined as more than one invasive cancer < 2 cm from the largest lesion within the same breast quadrant.
    - Multicentric disease is defined as more than one invasive cancer ≥ 2 cmfrom the largest lesion within the same breast quadrant or more than one lesion in different quadrants.
    - Synchronous bilateral disease is defined as invasive breast cancer in both breasts, diagnosed within 30 days of each other.In patients with multicentric or bilateral invasive breast cancers, all sampled lesions must be hormone receptor-positive.. Any lesion measuring $\geq$ 1 cm must have an Oncotype Dx and the score must be $\leq$ 25. Lesions less than 1 cm in size are not required to have an Oncotype Dx.One lesion (typically the largest) should be designated as the target lesion for which clinical and radiographic response to the neoadjuvant therapy will be judged.
    - Patients with a hormone receptor-positive, HER2-negative invasive cancer that meets study criteria may have ductal carcinoma in situ in another quadrant of the same breast or in the contralateral breast even if the DCIS is hormone receptor-negative.
9. Patients must have adequate bone marrow function, as defined by peripheral granulocyte count of ≥ 1,500/mL, hemoglobin ≥ 9 g/dL and a platelet count ≥ 100,000/ mL within 28 days prior to registration.
10. Patients must have adequate hepatic function obtained within 28 days prior to registration and documented by all of the following:
    - Bilirubin ≤ 1.5 mg/dL (or ≤ 3.0 mg/dL if due to Gilbert's Syndrome)
    - ALT and AST ≤ 1.5 x Institutional Upper Limit of Normal (IULN)
    - Alkaline phosphatase ≤ 1.5 x IULN
11. Patients must have adequate renal function with serum creatinine level ≤ IULN within 28 days prior to registration.
12. Patients must have a fasting cholesterol ≤ 300 mg/dl OR ≤7.75 mmol/L and triglycerides ≤ 2.5 x IULN obtained within 28 days prior to registration. Patients may be on lipid lowering agents to reach these values.
13. Patients must have a ECOG performance status of 0-2.
14. Patients must be able to take oral medications.

15. Postmenopausal women (women are considered post-menopausal and not of child-bearing potential if they are > 18 years of age and have had 12 months of natural (spontaneous) amenorrhea with an appropriate clinical profile (e.g. age appropriate, history of vasomotor symptoms or biochemically postmenopausal by estradiol and FSH levels)) prior to enrollment or have had surgical bilateral oophorectomy (with or without hysterectomy) prior to registration. Medical ovarian suppression with LHRH agonists to render a patient postmenopausal will not be acceptable.
16. Patients or their legally authorized representative must be informed of the investigational nature of this study and must sign and give written informed consent prior to any screening procedures in accordance with institutional and federal guidelines.

4.2 Exclusion criteria

1. Patients must not have inflammatory breast cancer (T4d) and must not have metastatic breast cancer (Stage IV disease).
2. Patients must not have prior exposure to mTOR inhibitors (e.g. rapamycin, everolimus, sirolimus, temsirolimus, deforolimus).
3. Patients must not have prior treatment with any investigational drug within the preceding 28 days and must not be planning to receive any other investigational drug for the duration of the study.
4. Patient may not have any impairment of gastrointestinal function or gastrointestinal disease that may significantly alter the absorption of the drug (e.g. ulcerative disease, uncontrolled nausea, vomiting, diarrhea, malabsorption syndrome or small bowel resection).
5. Uncontrolled diabetes mellitus as defined by HbA1c >8% within 28 days prior to registration despite adequate therapy.
6. Patients who have any severe and/or uncontrolled cardiac disease within ≤6 months prior to start of Everolimus, including: unstable angina pectoris, Symptomatic congestive heart failure of New York heart Association Class III or IV, myocardial infarction, serious uncontrolled cardiac arrhythmia, or any other clinically significant cardiac disease
7. Patients must not have an organ allograft or other history of immune compromise.
8. Patients must not be receiving chronic, systemic treatment with corticosteroids or other immunosuppressive agent. Topical or inhaled corticosteroids are allowed.
9. Patients must not have a known history of HIV seropositivity
10. Patients must not have a known diagnosis of hepatitis B or C. Patients with the following risk factors must 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
- History of jaundice.

11. Patients must not have any known uncontrolled underlying pulmonary disease or severely impaired lung function (spirometry and DLCO 50% or less of normal and O2 saturation 88% or less at rest on room air),
12. Active (acute or chronic) or uncontrolled severe infection.
13. Patients who have received live attenuated vaccines within 1 week of start of Everolimus, or have plans to receive such vaccination while on protocol treatment. Patient should also avoid close contact with others who have received live attenuated vaccines. Examples of live attenuated vaccines include intranasal influenza, measles, mumps, rubella, oral polio, BCG, yellow fever, varicella and TY21a typhoid vaccines;
14. Patients who are currently part of or have participated in any clinical investigation with an investigational drug within 1 month prior to dosing;
15. 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.
16. Patients with active bleeding diathysis.

5.0 STUDY DESIGN

This is a single arm open-lableled, multicenter neoadjuvant phase II clinical trial evaluating everolimus in combination with an aromatase inhibitor in postmenopausal women with hormone receptor positive/HER2 negative breast cancers with low and intermediate risk ($\leq$ 25) Recurrence Scores by Oncotype Dx.

5.1 Pre-registration

- Postemnopausal patients who have a hormone receptor positive, HER2 negative breast cancer appropropriate for neoadjuvant therapy and who have not undergone prior Oncotype Dx testing, will be consented and pre-registered prior to submission of tissue from their diagnostic biopsy for Oncotype Dx analysis for the purpose of clinical trial screening.
- Patients with a RS $\leq$ 25 will be offered the opportunity to participate in this clinical trial, and will be enrolled on the trial once consent is obtained.

- Patients with a non-diagnostic Oncotype Dx analysis from their initial biopsy will be offered the opportunity to undergo a repeat biopsy for Oncotype Dx testing to determine if they are eligible to participate in the study.
- Patients with a Recurrence Score (RS) >25 cannot proceed to the treatment phase of the study, but may be offered the opportunity to participate in other neoadjuvant trials or be treated off study.

5.2 Patient registration

The patient must voluntarily consent after being informed of the experimental nature of the treatment, potential benefits, alternatives, side-effects, risks and discomforts. Human protection committee approval of this protocol and the informed consent form are required. Registration must occur prior to the initiation of protocol therapy. All patients will be registered for the trial by a research staff member following the policy of the Clinical Trial Office at Sidney Kimmel Cancer Center.

6.0 STUDY TREATMENT

Eligible patients will be enrolled and will receive treatment with an aromatase inhibitor plus everolimus by mouth daily for 26 weeks. All patients will begin treatment on Cycle 1 Day 1 with both the standard dose of one of the following 3 aromatase inhibitors (physician's choice) plus everolimus 10 mg by mouth daily:

- Anastrozole 1 mg
- Letrozole 2.5 mg
- Exemestane 25 mg

The study drug (everolimus) will be dispensed by the research pharmacy at the participating site. Tablets should be administered orally once daily at the same time every day, either consistently with or consistently without food. The tablets should be swallowed whole with a glass of water and should not be chewed or crushed. If vomiting occurs, no attempt should be made to replace the vomited dose. Patients should be instructed that if they miss a dose on one day, they must not take any extra dose the next day, but instead resume their next dose at the regularly scheduled time. Study drug compliance should be reviewed with the patient during each clinic visit. Missed doses should be documented.

6.1 Study drugs:

6.1.1 Everolimus (Afinitor®)

a. PHARMACOLOGY

Mechanism of Action: Everolimus binds to the cytosolic immunophyllin FKBP12;

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

b. PHARMACOKINETICS

1. Absorption: Everolimus levels peak in 1-3 hours after oral administration. There is rapid but moderate absorption.
2. Distribution: Everolimus is about 74% protein bound in healthy subjects and patients with moderate hepatic impairment.
3. Metabolism: Everolimus is extensively metabolized by CYP3A4 and forms 6 weak metabolites. It is also a P-glycoprotein substrate.
4. Elimination: Everolimus is extensively eliminated via the bile. The elimination half-life of everolimus is about 30 hours and is prolonged in patients with hepatic impairment. Everolimus is primary excreted through the feces.

c. ADVERSE EFFECTS

1. Adverse events with possible relationship to Everolimus:

The most common ADRs, suspected to be related to treatment by the investigator (incidence ≥1/10) from the pooled safety data were (in decreasing order): stomatitis, rash, fatigue, diarrhea, infections, nausea, decreased appetite, anemia, dysgeusia, pneumonitis, edema peripheral, hyperglycemia, asthenia, pruritus, weight decreased, pruritus, asthenia, peripheral edema, hypercholesterolemia, epistaxis, cough and headache.

The most common grade 3/4 ADRs, suspected to be related to treatment by the investigator (incidence ≥1/100 to <1/10) were stomatitis, anemia, hyperglycemia, fatigue, infections, pneumonitis, diarrhea, asthenia, thrombocytopenia, neutropenia, dyspnea, lymphopenia, proteinuria, hemorrhage, hypophosphatemia, rash, hypertension, aspartate aminotransferase (AST) increased, alanine aminotransferase (ALT) increased, and pneumonia and diabetes mellitus.

The below table presents the frequency category of ADRs reported in the pooled safety analysis.

ADRs are listed according to MedDRA system organ class. Within each system organ class, the adverse reactions are ranked by frequency, with the most frequent reactions first. In addition, the corresponding frequency category using the following convention (CIOMS III) is also provided for each adverse reaction: very common (≥1/10); common (≥1/100 to <1/10); uncommon (≥1/1,000 to <1/100); rare (≥1/10,000 to <1/1,000); very rare (<1/10,000); not known (cannot be estimated from the available data).

Infections and infestations
Very common - Infections

Blood and lymphatic system disorders
Very common - Anemia, thrombocytopenia
Common - Neutropenia, leukopenia, lymphopenia
Uncommon - Pancytopenia
Rare -Pure red cell aplasia

Immune system disorders
Uncommon - Hypersensitivity

Metabolism and nutrition disorders
Very common - Decreased appetite, hyperglycemia, hypercholesterolemia
Common - Hypertriglyceridemia, hyperlipidemia, hypophosphatemia, diabetes mellitus, hypokalemia, dehydration

Psychiatric disorders
Common - Insomnia

Nervous system disorders
Very common - Dysgeusia, headache
Uncommon - Ageusia

Cardiac disorders
Uncommon - Congestive cardiac failure

Vascular disorders
Common - Hemorrhage, hypertension
Uncommon - Deep vein thrombosis

Respiratory, thoracic and mediastinal disorders
Very common - Pneumonitis, epistaxis, cough
Common - Dypsnea
Uncommon - Hemoptysis, pulmonary embolism
Rare - Acute respiratory distress syndrome

Gastrointestinal disorders
Very common - Stomatitis, diarrhea, nausea
Common - Vomiting, dry mouth, abdominal pain, oral pain, dyspepsia, dysphagia

Skin and subcutaneous tissue disorders
Very common - Rash, pruritus
Common - Dry skin, nail disorder, acne, erythema, hand-foot syndrome
Rare - Angioedema

Musculoskeletal and connective tissue disorders
Common - Arthralgia

Renal and urinary disorders
Common - Proteinuria, renal failure
Uncommon - Increased daytime urination, acute renal failure

Reproductive system and breast disorders
Common - Menstruation irregular
Uncommon - Amenorrhea

General disorders and administration site conditions
Very common - Fatigue, asthenia, edema peripheral
Common - Pyrexia, mucosal inflammation
Uncommon - Non-cardiac chest pain, impaired wound healing

Investigations
Very common - Weight decreased
Common - Alanine aminotransferase increased, aspartate aminotransferase increased, blood
creatinine increased

a Includes all reactions within the 'infections and infestations' system organ class including common: pneumonia, urinary tract infection
and uncommon: bronchitis, herpes zoster, sepsis, abscess, and isolated cases of opportunistic infections (e.g. aspergillosis, and rare: viral myocarditis, candidiasis and hepatitis B)
b Includes different bleeding events from different sites not listed individually
c Includes very common: pneumonitis and common: interstitial lung disease, lung infiltration, alveolitis, pulmonary
alveolar hemorrhage, and pulmonary toxicity
d Includes very common: stomatitis; common: aphthous stomatitis, mouth and tongue ulceration; uncommon:
glossitis, glossodynia
e reported as palmar-plantar erythrodysaesthesia syndrome

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

3. Drug Interactions: Everolimus is metabolized by CPY3A4 in the liver and to some extent the intestinal wall. Due to the extensive number of everolimus drug interactions, a complete patient medication list,including everolimus, should be screened prior to initiation of everolimus.

Drug	Severity	Recommendation
Strong CYP3A4 inhibitor or P-glycoprotein (PgP) inhibitor	Major	Co-administration should be avoided
Strong CYP3A4 inducers	Major	Co-administration should be avoided; if alternative treatment cannot be administered consider an increase in the everolimus dose up to twice the current dose, in 5 mg increments.
Moderate CYP3A4 or PgP inhibitor	Moderate	Use caution; if alternative treatment cannot be administered reduce everolimus dose to 50% the current dose.
ACE Inhibitors	Moderate	Use caution; everolimus may enhance the adverse effects of ACE inhibitors, specifically the risk of angioedema
Live vaccines	Major	Avoid live vaccines and close contact with those who have received live vaccines; everolimus may enhance adverse effects of live vaccines or diminish their therapeutic effects
Grapefruit and grapefruit juice	Major	Co-administration should be avoided

4. Hepatic Impairment: Dosage adjustment of everolimus is recommended if patients develop hepatic impairment during study treatment. Please refer to Dosage Modification section (section 7.0).

d. ADMINISTRATION

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 citrus juices should be avoided. The tablets must not be chewed orcrushed. If patients are unable to temporarily swallow whole tablet during the duration of the clinical trial, patients may disperse tablet completely in 30 mL water for approximately 7 minutesand drink immediately; rinse container with additional 30 mL water and swallow.

e. STORAGE & STABILITY

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

The 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

Everolimus 10 mg (5 mg tablets will be supplied for dose de-escalation) tablets will be supplied by Novartis Pharmaceuticals Corporation. Everolimus will be supplied as tablets blisterpacked 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.

Refer to label for expiration date and storage conditions. The extent of absorption of everolimus through topical exposure is not known. Therefore, caregivers are advised to avoid contact with suspensions of Afinitor Tablets. Wash hands thoroughly before and after preparation of either suspension.

On Day 1 of each cycle, subject will be dispensed the appropriate amount of study medication and will be instructed to return remaining medication and packaging at the next visit.

3. Drug Handling and 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.

4. Drug Return and/or Disposition Instruction

All unused drug, unopened and unused blister cards remaining when a subject goes off treatment, and expired blister cards should be returned to research pharmacy.

6.1.2 Anastrazole

a. PHARMACOLOGY

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

b. PHARMACOKINETICS

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

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

3. Metabolism: Anastrozole is extensively (85%) hepatically metabolized viaN-dealkylation, hydroxylation, and glucuronidation. Three metaboliteshave 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. Adverse Events with Possible Relationship to Anastrozole

Likely (>20%)

- Vasodilatation
- Hotflashes

.

Less likely (< 20%)

- Anemia
- Leukopenia
- Edema
- Hypertention
- Cataracts
- Abdominal pain
- Constipation
- Diarrhea
- Dyspepsia
- Nausea
- Vomiting
- Xerostomia
- Fever
- Pain
- Malaise
- Thrombophlebitis
- Flu-like syndrome
- Weight gain or loss

- Hypercholesteremia
- Arthralgia
- Arthritis
- Back pain
- Breast painm
- Carpal tunnel syndrome
- Myalgia
- Neck pain
- Osteoporosis
- Paresthesia
- Weakness Confusion
- Dizziness
- Fatigue
- Headache
- Somnolence
- Anxiety
- Depression
- Insomnia
- Mood disturbance
- Nervousness
- Pelvic pain
- Urinary tract infection
- Vaginal bleeding
- Vaginal discharge
- Vaginitis
- Rhinitis
- Pharyngitis
- Sinusitis
- Alopecia
- Pruritis
- Rash
- Lymphedema

Rare but serious (<3%)

- Angina
- Ischemic cerebrovascular event
- Myocardial infarction
- Venous thromboembolic event.
- Alkaline phosphatase increased
- Liver function tests increased
- Fracture
- Bronchitis
- Dyspnea

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

2. Pregnancy and Lactation: Pregnancy category X. Fetal toxicity was observed in animal studies. It is not known if anastrozole is excreted intobreast milk.
3. Drug Interactions: Anastrozole is a weak CYP3A4 inhibitor. Due topotential drug interactions, a complete patient medication list, including anastrozole, should be screened prior to initiation of anastrozole.

d. DOSING & ADMINISTRATION
Anastrozole should be administered orally, with or without food.

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

f. HOW SUPPLIED
1. Anastrozole is commercially available in 1 mg tablets., and will not be supplied.

6.1.2 Exemestane

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

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

2. Distribution: Exemestane is distributed extensively into tissues. Exemestane is 90% bound to plasma proteins and the fraction bound is independent of the total concentration. Albumin and α1-acid glycoprotein both contribute to the binding. The distribution of exemestane and its metabolites into blood cells is negligible.

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

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

c. ADVERSE EFFECTS

1. Adverse Events with Possible Relationship to Exemestane

Likely (>20%)

- Vasodilatation
- Arthralgia

Less likely (< 20%)

- Edema
- Chest pain
- Visual disturbances
- Abdominal pain
- Anorexia
- Appetite increased
- Constipation
- Diarrhea
- Dyspepsia
- Nausea
- Vomiting
- Endometrial hyperplasia
- Endometrial polyps
- Hypoesthesia
- Fever
- Pain
- Serum creatinine increased
- Weakness
- Flu-like syndrome
- Weight gain
- Back pain

- Cramping
- Limb pain
- Carpal tunnel syndrome
- Osteoarthritsis
- Osteoporosis
- Paresthesia
- Confusion
- Dizziness
- Fatigue
- Headache
- Anxiety
- Depression
- Insomnia
- Urinary tract infection
- Upper respiratory tract infections
- Cough
- Rhinitis
- Pharyngitis
- Sinusitis
- Alopecia
- Pruritis
- Rash
- Hyperhidosis

Rare but serious (<3%)

- Angina
- Cardiac failure
- Myocardial infarction
- Trigger finger
- Infection
- Alkaline phosphatase increased
- Bilirubin increased
- Transaminases increased
- Fracture
- Neuropathy
- Osteochindrosis
- Bronchitis
- Dyspnea
- Lymphedema
- Thromboembolism

2. Pregnancy and Lactation: Pregnancy Category X. Exemestane is notindicated for premenopausal women and should not be given to women who are breast-feeding their

infants. It is not known if exemestane isexcreted into human breast milk; however, it has been detected in the breast milk of animals.
3. Drug Interactions: Exemestane is an inducer of CYP3A4 (weak/moderate) and a substrate of CYP3A4 (major). Due to potentialexemestane drug interactions, a complete patient medication list, including exemestane, should be screened prior to initiation of exemestane.

d. DOSING & ADMINISTRATION
Exemestane is administered in 25 mg tablets orally once daily after a meal.

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

f. HOW SUPPLIED
1. Exemestane is available in 25 mg tablets.
2. Exemestane is commercially available and will not be supplied.

6.1.2 Letrozole

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

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

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

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

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

c. ADVERSE EFFECTS
1. Adverse Events with Possible Relationship to Letrozole

Likely (>20%)
- Hotflashes

.
Less likely (< 20%)

- Edema
- Hypertention
- Cataracts
- Abdominal pain
- Constipation
- Diarrhea
- Dyspepsia
- Nausea
- Vomiting
- Nightsweats
- Pain
- Hypercalcemia
- Weight gain or loss
- Hypercholesteremia
- Arthralgia
- Arthritis
- Back pain
- Bone pain
- Limb pain
- Myalgia
- Osteoporosis
- Weakness
- Dizziness
- Fatigue
- Headache
- Somnolence
- Anxiety
- Depression
- Urinary tract infection
- Vaginal bleeding
- Vaginal irritation
- Cough
- Alopecia
- Pruritis
- Rash

Rare but serious (<3%)

- Chest pain
- Cerebrovascular event
- Thromboembolic event
- Infection
- Viral infection
- Influenza

- Fracture
- Dyspnea
- Pleural effusion

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

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

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

4. Hepatic Impairment: Letrozole in metabolized in the liver and dose adjustment is recommended in hepatic impairment.

d. DOSING & ADMINISTRATION

Letrozole is administered in 2.5 mg tablets orally once daily with or without food.

e. STORAGE & STABILITY

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

f. HOW SUPPLIED

Letrozole is commertially available in 2.5 mg tablets, and will not be supplied.

7.0 DOSE MODIFICATION

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

Missed doses are to be omitted rather than made up. If multiple toxicities are experienced, dose modifications will be based on the toxicity requiring the largest dose reduction. Reductions are based on the dose given in the preceding reporting period and

are based on toxicities observed since the prior toxicity evaluation. Once dose is reduced, patients will continue at new dose. No dose reescalations are allowed. There are no dose modifications for endocrine therapy.

7.1 Dose modifications and delays for aromatase inhibitors

There is no dose modification for anastrazole, letrozole or exemestane. Aromatase inhibitor therapy may be held for grade 3 or greater arthralgia or myalgia, and switching to another aromatase inhibitir will be allowed if symptoms resolve to grade 2 or less. If the aromatase inhibitor is held for greater than 4 consecutive weeks due to toxicity, then study treatment will be discontinued.

7.2 Dose modifications and delays for everolimus

For patients who do not tolerate the protocol-specified dosing schedule, dose adjustments are permitted in order to allow the patient to continue the study treatment. Details of study treatment schedule adjustments and dose levels are provided in Table 2.

Special Populations
Geriatrics (≥ 65 years) :
No dosage adjustment is required.
Renal impairment :
No dosage adjustment is required.
Ethnicity :
Pharmacokinetic characteristics are similar for Caucasian and Japanese subjects.
Pharmacokinetic studies in Black transplant patients have shown an average 20% higher clearance.

Table 2 Study treatment schedule adjustments and dose levels

Dose level	Dose and schedule
0 (starting dose)	10 mg/day
-1	5 mg/day
-2	2.5 mg/day

- If a patient is already at dose level -2 and again meets criteria for dose reduction, everolimus will be discontinued and the patient will continue on study treatment with the aromatase inhibitor therapy only.

Table 3 and Table 4 list the dosing guidelines for Everolimus-related non-hematologic and hematologic toxicities.

Table 3 Dosing guidelines for Everolimus-related non-hematologic toxicities

Toxicity	Action
Non-Infectious Pneumonitis	Please refer to Table 0.
Reactivation of HBV or HCV flare	Patients with a known diagnosis of hepatitis B or C infection will be excluded from study participation. Patient who meet criteria for hepatitis B or C screening and are found to have positive serology indicating an ongoing infection, will be excluded from study participation. For all other patient who start study treatment and are subsequently found to have a hepatitis B reactivation or hepatitis C flare, please refer to tables 6 and 7. Table
AST or ALT elevation Grade 1 (> ULN - 3.0 x ULN) Grade 2 (> 3.0 - 5.0 x ULN)	Maintain current dose level
AST or ALT elevation Grade 3 (> 5.0 - 20.0 ULN)*	Interrupt Everolimus administration until resolution to ≤ grade 1 (or ≤ grade 2 if baseline values were within the range of grade 2). If resolution occurs ≤ 7 days, Everolimus should be re-started at the dose level prior to interruption. If resolution takes > 7 days, or if event recurs within 28 days, hold Everolimus until recovery to ≤ grade 1 or baseline grade / value and reintroduce Everolimus at one dose level lower, if available.
AST or ALT elevation Grade 4 (> 20 x ULN)*	Interrupt Everolimus administration until resolution to ≤ grade 1 (or ≤ grade 2 if baseline values were within the range of grade 2). If resolution occurs ≤ 7 days, Everolimus should be re-started at one dose level lower. If resolution takes > 7 days, discontinue Everolimus.
Recurrence of grade 4 after dose reduction or toxicity requiring Everolimus interruption for > 28 days	Discontinue Everolimus.
Intolerable grade 2 mucositis, or grade 3 AE, except hyperglycemia or hypertriglyceridemia or hypercholesterolemia (see Section 7.3.6)	Interrupt Everolimus administration until resolution to ≤ grade 1 or baseline grade / value. If resolution occurs within ≤ 7 days, Everolimus should be re-started at the dose level prior to interruption. If resolution takes > 7 days, or if event recurs within 28 days, hold Everolimus until recovery to ≤ grade 1 or baseline grade / value and reintroduce Everolimus at one dose level lower, if available. Patients will be withdrawn from the study if they fail to recover to ≤ grade 1 or baseline grade / value within 28 days.
Any other grade 4	Hold Everolimus until recovery to grade ≤ 1 or baseline value Reintroduce Everolimus at one dose level lower, if available.
Grade 3 or 4 clinical liver failure (asterixis or encephalopathy/coma)	Discontinue Everolimus
Recurrence of intolerable grade 2 mucositis or grade 3 event after dose reduction	Reduce dose to the next lower dose level, if available. The lowest possible dose level of Everolimus is 2.5 mg daily. Below this level, Everolimus must be discontinued.
Recurrence of grade 4 after dose reduction	Discontinue Everolimus

Toxicity	Action
Any non-hematologic toxicity requiring Everolimus interruption for > 28 days	Discontinue Everolimus
* Should HCV flare be confirmed, the guidelines for flare must take precedence (Table)	

Table 4 Dosing guidelines for Everolimus-related hematologic toxicities

Toxicity	Action
Grade 2 thrombocytopenia (platelets <75, ≥ 50x109/L)	No action
Grade 3 thrombocytopenia (platelets <50, ≥ 25 x109/L)	Interrupt Everolimus until resolution to grade ≤1 If resolution occurs ≤ 7 days, reintroduce Everolimus at the dose level prior to interruption. If resolution occurs > 7 days, or event occurs within 28 days, reintroduce Everolimus at one dose level lower, if available.
Grade 4 thrombocytopenia (platelets < 25 x109/L)	Interrupt Everolimus until recovery to grade ≤ 1. Then reintroduce Everolimus at one dose level lower, if available.
Grade 3 neutropenia or anemia (neutrophil <1, ≥0.5 x109/L)	Interrupt Everolimus until resolution to grade ≤1 or baseline value If AE resolution occurs ≤ 7 days, reintroduce Everolimus at the same dose level. If AE resolution occurs > 7 days, or event occurs within 28 days, reintroduce Everolimus at one dose level lower, if available.
Grade 4 neutropenia or anemia	Interrupt Everolimus until recovery to grade ≤ 1 or baseline value. Reintroduce Everolimus at one dose level lower, if available.*
Febrile neutropenia	Interrupt Everolimus until resolution to grade ≤ 1 (or baseline value) and no fever. Reintroduce Everolimus at one dose level lower, if available.*
Recurrence of grade 3 toxicity after dose reduction	Reduce dose to the next lower dose level, if available. The lowest possible dose level of Everolimus is 5 mg every other day (2.5 mg daily). Below this level, Everolimus must be discontinued.
***Recurrence of grade 4 toxicity (including febrile neutropenia) after dose reduction**	**Discontinue Everolimus**
***Any hematologic toxicity requiring Everolimus interruption for > 28 days**	**Discontinue Everolimus**

7.3 Management of specific toxicities related to everolimus

Overall, safety data available from completed, controlled and uncontrolled studies indicate that everolimus is generally well tolerated at weekly or daily dose schedules. The safety profile is characterized by manageable adverse events (AEs). These AEs are generally reversible and non-cumulative.

Adverse events most frequently observed with everolimus are stomatitis, rash, fatigue, diarrhea, infections, nausea, decreased appetite, anemia, dysgeusia, pneumonitis, edema peripheral hyperglycemia, asthenia, pruritis, weight decrease, hypercholesterolemia, ,

epistaxis, cough and headache. Overall, the most frequently observed laboratory abnormalities include decreased hematology parameters including hemoglobin, lymphocytes, platelets, and neutrophils (or collectively as pancytopenia); increased clinical chemistry parameters including cholesterol, triglycerides, glucose, aspartate transaminases,creatinine, alanine transaminases, and bilirubin; and decreased clinical chemistry parameters including phosphate and potassium.. The majority of these AEs have been of mild to moderate severity (NCI CTC grade 1-2).

7.3.1 Management of infections

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

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

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

7.3.2 Management of skin toxicity

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

7.3.3 Management of Hypersensitivity reactions

Hypersensitivity reactions manifested by symptoms including, but not limited to, anaphylaxis, dyspnea, flushing, chest pain or angioedema (e.g. swelling of the airways or tongue, with or without respiratory impairment) have been observed with everolimus. Managment of hypersensitivity reactions will be up to the treating co-investigator’s discretion.

7.3.4 Renal Failure Events

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

Elevations of serum creatinine, usually mild, and proteinuria have been reported in patients taking everolimus. Monitoring of renal function, including measurement of blood urea nitrogen (BUN), urinary protein, or serum creatinine, is recommended prior to the start of everolimus therapy and periodically thereafter.

7.3.5 Management of stomatitis / oral mucositis / mouth ulcers

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

* using agents containing hydrogen peroxide, iodine, and thyme derivatives in management of stomatitis as they may worsen mouth ulcers.

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

Stomatitis/oral mucositis/mouth ulcers due to Everolimus should be treated using local supportive care. Please note that investigators in earlier trials have described the oral toxicities associated with Everolimus as mouth ulcers, rather than mucositis or stomatitis. If your examination reveals mouth ulcers rather than a more general inflammation of the mouth, please classify the adverse event as such. The suggested paradigm for treatment of stomatitis/oral mucositis/mouth ulcers is as follows:

1. For mild toxicity (grade 1), no dose adjustment required. Manage with non-alcoholic mouth wash or salt water (0.9%) mouth wash several times a day until resolution.
2. For more severe toxicity (grade 2 in which case patients have pain but are able to maintain adequate oral alimentation, or grade 3 in which case patients cannot maintain adequate oral alimentation), the suggested treatments are topical analgesic mouth treatments (i.e., local anesthetics such as, benzocaine, butyl aminobenzoate, tetracaine hydrochloride, menthol, or phenol) with or without topical corticosteroids, such as triamcinolone oral paste 0.1% (Kenalog in Orabase®).
3. Agents containing alcohol, hydrogen peroxide, iodine, and thyme derivatives may tend to worsen mouth ulcers. These agents should be avoided.
4. Antifungal agents should be avoided unless a fungal infection is diagnosed. In particular, systemic imidazole antifungal agents (ketoconazole, fluconazole, itraconazole, etc.) should be avoided in all patients due to their strong inhibition of Everolimus metabolism, therefore leading to higher Everolimus exposures. Therefore, topical antifungal agents are preferred if an infection is diagnosed. Similarly, antiviral agents such as acyclovir should be avoided unless a viral infection is diagnosed.

7.3.6 Management of 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 should not be replaced. Patients should resume the next regularly scheduled dose.

7.3.7 Management of diarrhea

Diarrhea has been reported with everolimus. In general, diarrhea has been transient, usually not of sufficient severity to hinder administration of study drug. Appearance of grade 1-2 diarrhea attributed to study drug toxicity may be treated with supportive care such as loperamide, initiated at the earliest onset (for example 4 mg orally followed by 2 mg orally every 2 hours until diarrhea-free for 12 hours).

7.3.8 Management of hyperlipidemia and hyperglycemia

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

Adverse Drug Reaction	Severity	Afinitor Dose Adjustment and Management Recommendations
Metabolic events (e.g. hyperglycemia, dyslipidemia)	Grade 1	No dose adjustment required. Initiate appropriate medical therapy and monitor.
	Grade 2	No dose adjustment required. Manage with appropriate medical therapy and monitor.
	Grade 3	Temporary dose interruption. Re-initiate Afinitor at lower dose. Manage with appropriate medical therapy and monitor.
	Grade 4	Discontinue Afinitor and treat with appropriate medical therapy.

Treatment of hyperlipidemia should take into account the pre-treatment status and dietary habits of the patient. Blood tests to monitor hyperlipidemia must be taken in the fasting state. Grade 2 or higher hypercholesterolemia (>300 mg/dL or 7.75 mmol/L) or grade 2 hypertriglyceridemia or higher (> 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, fluvastatin) or appropriate triglyceride-lowering medication, in addition to diet.
Note: Concomitant therapy with fibrates and an HMG-CoA reductase inhibitor is associated with an increased risk of a rare but serious skeletal muscle toxicity manifested by rhabdomyolysis, markedly elevated creatine phosphokinase (CPK) levels and myoglobinuria, acute renal failure and sometimes death. The risk versus benefit of using this therapy should be determined for individual patients based on their risk of cardiovascular complications of hyperlipidemia.

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

7.3.4 Management of non-infectious pneumonitis

Non-infectious pneumonitis is a class effect of rapamycin derivatives. Cases of non-infectious pneumonitis (including interstitial lung disease) have also been described in patients taking Everolimus. Some of these have been severe and on rare occasions, a fatal outcome was observed.

- A diagnosis of non-infectious pneumonitis should be considered in patients presenting with non-specific respiratory signs and symptoms such as hypoxia, pleural effusion, cough or dyspnea, and in whom infectious, neoplastic and other non-medicinal causes have been

excluded by means of appropriate investigations. Patients should be advised to report promptly any new or worsening respiratory symptoms.

If non-infectious pneumonitis develops, the guidelines in Table 0 should be followed. Consultation with a pulmonologist is recommended for any case of pneumonitis that develops during the study.

Table 0 Management of non-infectious pneumonitis

Grading of Pneumonitis:

Grade 1 (Asymptomatic, radiographic findings only)

Grade 2 (Symptomatic, not interering with Activities of Daily Living)

Grade 3 (Symptomatic, Interfering with Activities of Daily Living. O2 indicated)

Grade 4 (Life-threatening, ventlatory support indicated)

Worst grade pneumonitis	Suggested investigations	Management of pneumonitis	Everolimus dose adjustment
Grade 1	CT scans with lung windows.	No specific therapy is required	No dose adjustment required. Initiate appropriate monitoring.
Grade 2	CT scan with lung windows. Consider pulmonary function testing includes: spirometry, DLCO, and room air O_2 saturation at rest. Consider a bronchoscopy with biopsy and/or BAL. Monitoring at each visit until return to ≤ grade 1. Return to initial monitoring frequency if no recurrence.	Symptomatic only. Consider corticosteroids and/or other supportive therapy if symptoms are troublesome.	Rule out infection and consider interruption of Everolimus until symptoms improve to Grade ≤ 1. Re-initiate Everolimus at one dose level lower. Discontinue Everolimus if failure to recover within ≤ 28 days.
Grade 3	CT scan with lung windows and pulmonary function testing includes: spirometry, DLCO, and room air O2 saturation at rest. Monitoring at each visit until return to ≤ grade 1. Return to initial monitoring frequency if no recurrence. Bronchoscopy with biopsy and/or BAL is recommended.	Consider corticosteroids if infective origin is ruled out. Taper as medically indicated.	Rule out infection and interrupt Everolimus until symptoms improve to Grade ≤ 1. Consider re-initiating Everolimus at one dose level lower (approximately 50% lower than the dose previously administered depending on individual clinical circumstances) Discontinue Everolimus if failure to recover within ≤ 28 days., or toxicity recurs at grade 3.
Grade 4	CT scan with lung windows and required pulmonary function testing, if possible, includes: spirometry, DLCO, and room air O2 saturation at rest. Monitoring at each visit until return to ≤ grade 1. Return to initial monitoring frequency if no recurrence. Bronchoscopy with biopsy and/or BAL is recommended if possible.	Consider corticosteroids if infective origin is ruled out. Taper as medically indicated.	Rule out infection and discontinue Everolimus.

Management of hepatitis reactivation / flare

Reactivation of Hepatitis B (HBV) has been observed in patients with cancer receiving chemotherapy[69]. Sporadic cases of Hepatitis B reactivation have also been seen in this setting

with everolimus. Use of antivirals during anti-cancer therapy has been shown to reduce the risk of Hepatitis B virus reactivation and associated morbidity and mortality[70]. A detailed assessment of Hepatitis B/C medical history and risk factors must be done for all patients at screening. Patients with the following risk factors must 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
- History of jaundice

Patients with a known diagnosis of hepatitis B or C infection will be excluded from study participation. Patient who meet criteria for hepatitis B or C screening and are found to have positive serology indicating an ongoing infection, will be excluded from study participation. For all other patient who start study treatment and are subsequently found to have a hepatitis B reactivation or hepatitis C flare, please refer to tables 6 and 7.

Table 6 Guidelines for the management of hepatitis B reactivation

HBV reactivation (with or without clinical signs and symptoms)*

For patients with baseline results: Positive HBV-DNA **OR** positive HBsAg --- **reactivation is defined as:** [Increase of 1 log in HBV-DNA relative to baseline HBV-DNA value OR new appearance of measurable HBV-DNA]	**Treat**: Start a second antiviral medication AND Interrupt Everolimus administration until resolution: 1. ≤ baseline HBV-DNA levels **If resolution occurs within ≤ 28 days**, Everolimus should be re-started at one dose lower, if available. If the patient is already receiving the lowest dose of Everolimus according to the protocol, the patient should restart at the same dose after resolution. Both antiviral therapies should continue at least 4 weeks after last dose of Everolimus. **If resolution occurs > 28 days** Patients should discontinue Everolimus but continue both antiviral therapies at least 4 weeks after last dose of Everolimus.
For patients with baseline results: Negative HBV-DNA **and** HBsAg **AND** **[**Positive HBsAb (with no prior history of vaccination against HBV), **OR** positive HBcAb**]** --- **Reactivation is defined as:** New appearance of measurable HBV-DNA	**Treat :** Start first antiviral medication AND **Interrupt** Everolimus administration until resolution: 2. ≤ undetectable (negative) HBV-DNA levels **If resolution occurs within ≤ 28 days**, Everolimus should be re-started at one dose lower, if available . If the patient is already receiving the lowest dose of Everolimus according to the protocol, the patient should restart at the same dose after resolution. Antiviral therapy should continue at least 4 weeks after last dose of Everolimus. **If resolution occurs > 28 days** Patients should discontinue Everolimus but continue antiviral therapy at least 4 weeks after last dose of Everolimus.

* All reactivations of HBV are to be recorded as grade 3 (e.g. CTCAE Version 3.0 - Investigations/Other: Viral Reactivation), unless considered life threatening by the investigator, in which case they should be recorded as grade 4. Date of viral reactivation is the date on which the rise or reappearance of HBV-DNA was recorded.

Table 7 Guidelines for the management of hepatitis C flare

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

* All flares of HCV are to be recorded as grade 3 (e.g. CTCAE Version 3.0 - Investigations - Other: Viral Flare), unless considered life threatening by the investigator; in which case they should be recorded as grade 4. Date of viral flare is the date on which both the clinical criteria described above were met. (e.g., for a patient whose HCV-RNA increased by 2 logs on 01 JAN 2011 and whose ALT reached > 5 x ULN on 22 JAN 2011, the date of viral flare is 22 JAN 2011).

8 CONCOMITANT MEDICATIONS

Patients must be instructed not to take any medications (over-the-counter or other products) during the protocol treatment period without prior consultation with the investigator. The investigator should instruct the patient to notify the study site about any new medications she takes after the start of study drug. All medications (other than study drug) and significant non-drug therapies (including physical therapy and blood transfusions) taken within 28 days of starting study treatment through the 30-day safety follow up visit should be reported on the CRF.

8.1 Prohibited concomitant medications

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 pneumonitisas described in Section 7.3.7) 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.
- Immunosuppressants may affect the response to vaccination and vaccination during treatment with Everolimus may therefore be less effective. The use of live vaccines should be avoided during treatment with Everolimus. Examples of live vaccines are: intranasal influenza, measles, mumps, rubella, oral polio, BCG, yellow fever, varicella, and TY21a typhoid vaccines.

- Drugs or substances known to be inhibitors or inducers of the isoenzyme CYP3A4 (as indicated in Section 8.1.1) must be avoided in association with blinded drug as these can alter metabolism. Strong inhibitors or inducers of the isoenzyme CYP3A4 must not be administered as systemic therapy.

8.1.1 Cytochrome P450 and P-glycoprotein inhibitors/inducers/substrates

Everolimus is a substrate of CYP3A4, and a substrate and moderate inhibitor of the multidrug efflux pump, PgP (PgP, MDR1, and ABCB1). Therefore, extent of absorption and subsequent elimination of systemically absorbed everolimus may be influenced by products that are substrates, inhibitors, or inducers of CYP3A4 and/or PgP. Concurrent treatment with strong CYP3A4-inhibitors should be avoided. Refer to Table 8 and 9 for a comprehensive list of inducers and inhibitors of CYP3A4 and a list of relevant substrates, inducers and inhibitors of PgP. Inhibitors of PgP may decrease the efflux of everolimus from brain or tumor and therefore increase everolimus concentrations in these tissues. In vitro studies showed that everolimus is a competitive inhibitor of CYP3A4 and of CYP2D6, potentially increasing the concentrations of products eliminated by these enzymes. Thus, caution should be exercised when co-administering everolimus with CYP3A4 and CYP2D6 substrates with a narrow therapeutic index. Clinical studies have been conducted in healthy subjects to assess pharmacokinetic drug interactions between everolimus and potential CYP3A modifiers (ketoconazole, verapamil, erythromycin, rifampin, midazolam, and HMGCoA reductase inhibitors (statins).
Everolimus is metabolized by CYP3A4 in the liver and to some extent in the intestinal wall. Therefore, the following are recommended:

- Co-administration with strong inhibitors of CYP3A4 (e.g., ketoconazole, itraconazole, ritonavir) or P-glycoprotein (PgP) inhibitor should be avoided. They may increase the serum concentration of Everolimus.
- Co-administration with moderate CYP3A4 inhibitors (e.g., erythromycin, fluconazole) or PgP inhibitors should be used with caution. They may increase the serum concentration of Everolimus. If a patient requires co-administration of moderate CYP3A4 inhibitors or PgP inhibitors, reduce the dose of everolimusby approximately 50% . Additional dose reductions to every other day may be required to manage toxicities. If the inhibitor is discontinued, the Everolimus dose should be returned to the dose used prior to initiation of the moderate CYP3A4/PgP inhibitor after a washout period of 2 to 3 days. Everolimus dose reductions are required for patients being treated for subependymal giant cell astrocytoma or renal cell carcinoma.
- Grapefruit or Seville oranges, and starfruit affect P450 and PgP activity. Concomitant use should be avoided.
- If patients require co-administration of a strong CYP3A4 inducer, consider doubling the daily dose of everolimus(based on pharmacokinetic data), using increments of 5 mg or less. This dose of everolimus is predicted to adjust the AUC to the range observed without inducers. However, there are no clinical data with this dose adjustment in patients receiving strong CYP3A4 inducers. If the strong inducer is discontinued, consider a washout period of at least 3 to 5 days (reasonable time for significant enzyme de-induction), before the everolimus dose is returned to the dose used prior to initiation of the strong CYP3A4 inducer.

- This dose adjustment of Everolimus is intended to achieve similar AUC to the range observed without inducers. However, there are no clinical data with this dose adjustment in patients receiving strong CYP3A4 inducers. If the strong inducer is discontinued the Everolimus dose should be returned to the dose used prior to initiation of the strong CYP3A4/PgP inducer.

Please refer to Table 8 listing relevant inducers and inhibitors of CYP3A and Table 9.0 for a list of relevant substrates, inducers, and inhibitors of PgP.

Table 8.0 Clinically relevant drug interactions: inducers, and inhibitors of isoenzyme CYP3A

Inducers
Strong inducers:
Avasamibe, carbamazepine, enzalutamide, mitotane, phenobarbital, phenytoin, rifabutin, rifampin (rifampicin), St. John's wort (hypericum perforatum),
Moderate inducers:
bosentan, efavirenz, etravirine, genistein, lersivirine, lopinavir, modafinil, nafcillin, ritonavir, semagacestat [talviraline], thioridazine, tipranavir
Weak inducers:
amprenavir, aprepitant, armodafinil (R-modafinil), bexarotene, boceprevir, brivacetam, clobazam, danshen, dexamethasone, Echinacea, eslicarbazepine, garlic (allium sativum), ginseng, gingko (ginkgo biloba), glycyrrhizin, methylprednisolone, nevirapine, oxcarbazepine, pioglitazone, prednisone, [pleconaril], primidone, quercetin, raltegravir, ritonavir, rufinamide, sorafenib, stribild (combo of elvitegravir, cobicistat, emtricitabine, and tenofovir), sulfinpyrazone, telaprevir, terbinafine, ticagleror, ticlopidine,
topiramate, [troglitazone] , vemurafenib, vicriviroc/ritonavir vinblastine
Inhibitors
Strong inhibitors:
boceprevir, clarithromycin, cobicistat, conivaptan, danoprevir / ritonavir, eltegravir/ritonavir, grapefruit juice, indinavir, indinavir/ritonavir, itraconazole, ketoconazole, lopinavir/ritonavir,, mibefradil, nefazodone, nelfinavir, posaconazole ritonavir, saquinavir, saquinavir/ritonavir, telaprevir, telithromycin, tipranavir/ritonavir, troleandamycin, voriconazole
Moderate inhibitors:
amprenavir, aprepitant, atazanavir, atazanavir/ritonavir, casopitant, cimetidine, ciprofloxacin, crizotinib, cyclosporine, darunavir, darunavir/ritonavir, diltiazem, dronedarone, erythromycin, fluconazole, fosamprenavir, grapefruit juice (citrus parasidi fruit juice), imatinib, lomitapide, netupitant, nilotinib, schisandra sphenanthera, tofisopam, verapamil
Weak inhibitors:
almorexant, alprazolam, alprazolam, amiodarone, amlodipine, amlodipine, atorvastatin, azithromycin, berberine, bicalutamide, bicalutamide, blueberry juice, cilostazol, cilostazol, cimetidine, clotrimazole, clozoxazone, cranberry juice, cyclosporine, delavirdine, everolimus, fluoxetine, fluvoxamine, fosaprepritant, ginkgo, goldenseal, isoniazid, isoniazid, ivacaftor, lacipidine, linagliptin, nilotinib, oral contraceptives, pazopanib, peppermint oil, propiverine, ranitidine, ranitidine, ranolaxine, ranolazine, resveratrol, roxithromycin, Seville orange, simeprevir, sitaxentan, tabimorelin, tacrolimus, teriflunomide, ticagrelor, tipranavir/ritonavir, tolvaptan, zileuton

Table 9.0 Clinically relevant drug interactions: substrates, inducers, inhibitors of PgP and PgP/CYP3A dual inhibitors

Substrates
afatinib, alfuzosin, aliskiren, alogliptin, ambrisentan, apixaban, apremilast, aprepitant, atorvastatin acid, atorvastatin, azithromycin, boceprevir, bosentan, carvedilol, caspofungin, ceritinib, cerivastatin, citalopram, colchicine, CP-481,715, cyclosporine, dabigatran, digoxin, docetaxel, domperidone, doxepin, doxorubicin, eribulin, everolimus, fentanyl,fexofenadine, fidaxomicin, fluvastatin, fosamprenavir, gatifloxacin, idelalisib, iloperidone, indacaterol, indinavir, , irbesartan, lacosamide, lapatinib, levetiracetam, levofloxacin, linagliptin, linezolid, loperamide, losartan, maraviroc, mirabegron, moxifloxacin, naloxegol, nateglinide, nevirapine, nintedanib, lodaterol, paclitaxel, pantoprazole, paroxetine, pazopanib, phenytoin, posaconazole, pravastatin, proguanil, quinidine, quinine, ranolazine, riociguat, risperidone, ritonavir, rivaroxaban, saquinavir, silodosin, simeprevir, simvastatin, sirolimus, sitagliptin, sofosbuvir, sorafenib, tacrolimus,talinolol, telaprevir, tenofovir, ticagrelor, tipranavir, tolvaptan, topotecan, umeclidinium, valsartan, vardenafil, vincristine, voclosporin, voriconazoleeverolimus
Inducers
avasimibe, carbamazepine, efavirenz, genistein, phenytoin, quercetin, rifampin, St John's wort
PgP Inhibitors and PgP/CYP3A Dual Inhibitors
PgP Inhibitors alogliptin, canaglifozin, cremophor RH40, curcumin, ketoconazole, lapatinib, lopinavir/ritonavir, mirabegron, propafenone, simepravir, valspodar, vandetanib, voclosporin **PgP/CYP3A Dual Inhibitors** amiodarone, captopril, carvedilol, clarithromycin, conivaptan, diltiazem, dronedarone, elacridar, erythromycin, felodipine, fluvoxamine, ginkgo (ginkgo biloba), indinavir, indinavir/ritonavir, itraconazole, mibefradil, milk thistle (silybum marianum), nelfinavir, nifedipine, nitrendipine, paroxetine, quercetin, quinidine, ranolazine, rifampin, ritonavir, saquinavir/ritonavir, Schisandra chinensis, St John's wort (hypericum perforatum), talinolol, telaprevir telmisartan, ticagrelor, tipranavir /ritonavir, tolvaptan, verapamil
Reference: Internal Clinical Pharmacology Drug-drug interaction (DDI) memo, updated Oct. 2, 2011, 29-Oct-2012, which summarizes DDI data from three sources including the FDA's "Guidance for Industry, Drug Interaction Studies", the University of Washington's Drug Interaction Database, and Indiana University School of Medicine's Drug Interaction Table.

9 VISIT SCHEDULE AND ASSESSMENTS

9.1 Baseline assessment

The following baseline assessments have to be performed at any time prior to initiation of treatment and must include:

- Determination of Oncotype Dx recurrence score.
- Determination of tumor HER2, ER and PR status

The following baseline assessments have to be performed within 4 weeks prior to initiation of treatment and must include:

- Complete history and review of systems including assessment of Eastern Cooperative Oncology Group Performance Status (ECOG) performance status,

review of concomitant medication and documentation of the date of the last dose of endocrine or chemotherapy received before entering the study.

- Complete physical examination including measurements of height, weight, and vital signs including oxygen saturation by pulse oximetry.
- Record breast tumor and axillary node measurements by physical exam for palpable tumors.
- Bilateral mammogram with clip placement to mark tumor bed
- MRI of the involved breast (or a unilateral ultrasound of the involved breast if a patient is unable to have a breast MRI due to claustrophobia, metal in body, or lack of insurance coverage, etc).
- If suspicious lymph nodes are detected clinically or by imaging, a diagnostic image guided fine needle aspiration or biopsy of the suspicious node is required.
- Complete blood count (CBC) including platelets and differential
- Comprehensive metabolic profile (CMP) including albumin, calcium, phosphorus, BUN, creatinine, total bilirubin, alkaline phosphatase, LDH, AST, ALT, Na, K, Cl, CO2 and fasting glucose.
- Fasting lipid profile
- Hemoglobin A1C
- PTT, PT and INR
- 12-lead ECG
- Complete microscopic urine analysis.
- CT scan of the chest and abdomen for clinical stage III or symptomatic stages II
- Bone scan for clinical stage III or symptomatic stage II.
- Bone density assessment (within 12 months). If results of baseline bone density confirm evidence of osteoporosis, treatment for osteoporosis will be left to the discretion of the treating physician.

9.2 Evaluation During Study

The following assessments will be performed every 4 weeks (+/- 3 days) except as noted:

- Medical history including ECOG performance status, treatment related AE assessment, concomitant medication review and study drug compliance assessment including dose and any treatment interruption.
- Physical examination including measurements of weight and vital signs including oxygen saturation by pulse oximetry.

- Record breast tumor and axillary node measurements by physical exam for palpable tumors.
- CBC, including differential and platelets
- CMP including albumin, calcium, phosphorus, BUN, creatinine, total bilirubin, alkaline phosphatase, LDH, AST, ALT, Na, K, Cl, CO2 and fasting glucose.
- PTT,PT and INR
- Radiological Assesment: The involved breast, and axilla (in patients with enlarged axillary nodes at baseline), will be reimaged by MRI between weeks 12 and 13 and again after completing neoadjuvant therapy. If a patient is unable to have a breast MRI (due to claustrophobia, metal in body, or lack of insurance coverage, etc) a breast ultrasound will be used to replace MRI at baseline, at 12-13 weeks and after completing neoadjuvant therapy. Other imaging, such as ultrasonography or MRI, is at the discretion of the treating physicians.
- Breast imaging may be repeated any time during therapy if clinical suspicion of progression of disease.
- Dispense study medication in appropriate supply
- Accountability and compliance check of returned pill diary and study medication
- Fasting lipid profile every 2 cycles (every 8 weeks)

9.3 Treatment discontinuation for disease progression

If any of the following events occur during study treatment, the patient will be considered to have failed upfront endocrine therapy and everolimus. She will be removed from the study and offered other treatment, which could include immediate surgery - if the patient's tumor is resectable - or neoadjuvant chemotherapy; response to any subsequent preoperative therapy and findings at surgery will be recorded in these patients.

- If a patient's tumor increases in size over baseline $\geq$20% by clinical examination at any point during study treatment
- If a patient's tumor increases in size over baseline $\geq$20% radiographically on the 12-13 week breast MRI (or ultrasound when indicated)

9.4 Surgical evaluation:

Surgery will be scheduled 3-8 weeks after completion of last chemotherapy.

A. Patients with evidence of tumor response (including stable disease) : Patients completing 26 weeks of neoadjuvant AI plus everolimus who are deemed resectable will undergo surgery. The decision regarding lumpectomy or mastectomy will be at the discretion of the treating surgeon. All patients will have axillary lymph node sampling with a technique that is deemed appropriate by the treating surgeon:

    - For clinically node negative disease at baseline, defined as negative clinical exam and ultrasonogram or negative lymph node biopsy in case of a suspicious

lymph node by imaging, sentinel node sampling is preferred over full axillary lymph node dissection. Subsequent full axillary lymph node dissection is at the discretion of the treating physicians.

- For patients with clinically positive nodes at baseline – defined as palpable nodes or overtly abnormal nodes on imaging or and/or histologically confirmed node positive disease at baseline, who are clinically node-negative after completion of neoadjuvant therapy, sentinel node sampling is permitted, with subsequent full axillary lymph node dissection at the discretion of the treating physicians.
- For patients with bulky or matted lymph nodes at baseline or persistently clinically positive axillary nodes at the time of surgery, full axillary lymph node dissection is preferred.

B. Patients with evidence of disease progression during therapy: Patients who progress clinically or by imaging assessment during therapy will be removed from protocol treatment and further treatment including immediate referral to surgery or additional chemotherapy will be at the discretion of the treating physician. Response to any subsequent preoperative therapy and findings at surgery will be recorded.

A copy of the pathology report is required. The patient's response to treatment will be recorded (clinical and at surgery ypT and ypN stage) and a PEPI (Preoperative Endocrine Prognostic Index) score calculated, which requires breast and nodal staging as well as repeat measurements of tumor ER expression and Ki67 (APPENDIX B)

9.5 Post-operative treatment:

Post-operative treatment is at the discretion of the treating physicians. Participation in subsequent adjuvant clinical trials is allowed.

9.6 Biomarker Assessment:

Baseline formalin fixed paraffin embedded **(**FFPE) tissue block will be obtained from the diagnostic breast biopsy to collect 4 unstained slides and an additional single tissue core (ranging from 0.6mm to 4.0mm in diameter, obtained with a microarray instrument). In addition, a tissue block from the residual tumor tissue will be obtained from the surgical specimen to collect 10 unstained slides and an additional single tissue core (ranging from 0.6mm to 4.0mm in diameter, obtained with a microarray instrument).

Specimens collected at Yale University Cancer Center will be shipped to the following address:

ATTN: Lawrence Rispoli
300 George Street, Suite 120
New Haven, CT 06511

Speciments collected at Thomas Jefferson University Sidney Kimmel Cancer Center will be shipped to the following address:

ATTN: Angela Pallotto
Main Building
132 South 10th Street, Room 1170
Philadelphia, PA 19107

All samples collected as part of this study will be sent to the address above at Thomas Jefferson University for storage at the end of the study.The samples from the baseline biopsies and the surgical specimens will be used (when feasible) for measurement of Ki67 and research analyses. Ki67 analysis will be performed at any Clinical Laboratory Improvement Amendments (CLIA) certified laboratory including the Yale Specialized Translational Services (STS) laboratory. ER expression will be repeated on the surgical specimen for PEPI score calculation. The planned molecular analysis of these tissues may include gene expression profiling, and PI3K pathway biomarkers by Automated Quantitative Analysis to develop an assay that may predict response or resistance to an everolimus and aromatase inhibitor combination. Candidate markers include pS6, mTOR, p4E-BP1, pAKT and APC.

9.7 End of Study Evaluation

Once post-operative therapy is completed, the final study follow up visit will be within 4-6 weeks after completion of surgery and will include:

- Complete review of systems and medical history including ECOG performance status assessment, endocrine therapy related AE assessment and record concomitant medications
- Physical examination including measurement of weight and vital signs including oxygen saturation by pulse oximetry.
- CBC, including differential and platelets, serum albumin, calcium, phosphorus, BUN, creatinine, total bilirubin, alkaline phosphatase, LDH, AST, ALT, Na, K, Cl, CO2 assessment and fasting glucose.
- Complete microscopic urine analysis
- PTT, PT and INR

10 STUDY CALENDAR

	Baseline	**W1**	**W5**	**W9**	**W13**	**W17**	**W21**	**W25**	**W26**	**Surgery**	**End of Study Evaluation**
	within 4 weeks prior*	Assessments every 4 wks (+/- 3 Days)								3-8 wks post chemo	4-6 wks after surgery
Informed Consent	X										
HER2, ER, PR Assessment[1]	X										
Oncotype Dx Recurrence Score[2]	X										
Physical											
Complete Medical History[3]	X	X	X	X	X	X	X	X			X
Complete Physical Exam[4]	X	X	X	X	X	X	X	X			X
Clinical Tumor Assessment[5]	X	X	X	X	X	X	X	X			
ECOG PS	X	X	X	X	X	X	X	X			X
Concomitant Medications	X	X	X	X	X	X	X	X			X
Toxicity Assessment		X	X	X	X	X	X	X			
Study Drug Compliance[6]		X	X	X	X	X	X	X			
Laboratory											
CBC Complete w/Diff	X	X	X	X	X	X	X	X			X
CMP	X	X	X	X	X	X	X	X			
PTT, PT & INR	X	X	X	X	X	X	X	X			X
Micro Urinalysis	X										X
Fasting Lipid Profile	X		X		X		X				
Hemoglobin A1c	X										
Hepatitis B & C screening[7]	X										

	Baseline	W1	W5	W9	W13	W17	W21	W25	W26	Surgery	End of Study Evaluation
Pathology											
FFPE Tissue[8]	X									X	
Imaging											
Bilateral Mammogram[9]	X										
MRI of Involved Breast[10,11]	X				X[9]				X[9]		
12-lead ECG	X										
CT scan chest/abd[12]	X										
Bone scan[12]	X										
Bone Density Assessment[13]	X										
Treatment											
Aromatase Inhibiters[14]		X	X	X	X	X	X	X	X		
Everolimus		X	X	X	X	X	X	X	X		
Surgery[15,16]										X	
Post-operative treatment[17]											X

Study subjects who come off treatment for progression or toxicity, should be followed through surgery and end of study visit. For study subjects who come off treatment for toxicity, continue to follow for up to 4 weeks or until resolution of toxicity.

1. ER/PR/HER2 receptor from diagnositic biopsy results will be collected. Receptor status can be performed at any time prior to starting study treatment.
2. Oncotype Dx recurrence score from diagnostic biopsy will be collected. Oncotype Dx analysis can be performed at any time prior to starting study treatment.
3. Complete history and review of systems and documentation of the date of the last dose of endocrine or chemotherapy received before entering the study (baseline).
4. Complete physical examination including measurements of height (only at baseline), weight, and vital signs including oxygen saturation by pulse oximetry.

5. Record breast tumor and axillary node measurements by physical exam for palpable tumors. If suspicious lymph nodes are detected clinically or by imaging, a diagnostic image guided fine needle aspiration or biopsy of the suspicious node is required.
6. Study drug compliance assessment including dose and any treatment interruption.
7. For high risks subjects only. See exclusion criteria # 10.
8. Baseline fresh frozen formalin fixed paraffin embedded (FFPE) tissue block will be obtained from the diagnostic breast biopsy to collect 4 unstained slides and an additional single tissue core (ranging from 0.6mm to 4.0mm in diameter, obtained with a microarray instrument). In addition, a tissue block from the residual tumor tissue will be obtained from the surgical specimen to collect 10 unstained slides and an additional single tissue core (ranging from 0.6mm to 4.0mm in diameter, obtained with a microarray instrument).
9. Mammogram should be done within 4 weeks prior to start of treatment. Mammogram is to be done with clip placement to mark tumor bed. Breast imaging may be repeated any time during therapy if clinical suspicion of progression of disease.
10. Or a unilateral ultrasound of the involved breast if a patient is unable to have a breast MRI due to claustrophobia, metal in body, or lack of insurance coverage, etc. Breast imaging may be repeated any time during therapy if clinical suspicion of progression of disease.
11. The involved breast, and axilla (in patients with enlarged axillary nodes at baseline), will be reimaged by MRI between weeks 12 and 13 and again after completing neoadjuvant therapy. If a patient is unable to have a breast MRI, a breast ultrasound will be used to replace MRI at baseline, at 12-13 weeks and after completing neoadjuvant therapy. Other imaging, such as ultrasonography or MRI, is at the discretion of the treating physicians.
12. For clinical stage III or symptomatic stages II
13. Bone density assessment (within 12 months). If results of baseline bone density confirm evidence of osteoporosis, treatment for osteoporosis will be left to the discretion of the treating physician.
14. Standard dose of one of the following aromatase inhibitors (physician's choice): Anastrozole 1 mg, Letrozole 2.5 mg, Exemestane 25 mg.
15. Surgery will be scheduled 3-8 weeks after completion of last dose of aromatase inhibitor and everolimus. Patients with evidence of tumor response (including stable disease): Patients completing 26 weeks of neoadjuvant AI plus everolimus who are deemed resectable will undergo surgery. The decision regarding lumpectomy or mastectomy will be at the discretion of the treating surgeon. All patients will have axillary lymph node sampling with a technique that is deemed appropriate by the treating surgeon (refer to protocol).
16. B) Patients with evidence of disease progression during therapy: Patients who progress clinically or by imaging assessment during therapy will be removed from protocol treatment and further treatment including immediate referral to surgery or additional

chemotherapy will be at the discretion of the treating physician. Response to any subsequent preoperative therapy and findings at surgery will be recorded (refer to protocol).

17. Post-operative treatment is at the discretion of the treating physicians. Participation in subsequent adjuvant clinical trials is allowed.

11 Evaluation of Safety

Information about all adverse events, whether volunteered by the subject, discovered by investigator questioning, or detected through physical examination, laboratory test or other means, will be collected and recorded and followed as appropriate.

11.1 Specification of Safety Parameters

11.1.1 Unanticipated Problems

Unanticipated problems (UAPs) include, in general, any incident, experience, or outcome that meets the following criteria:

- unexpected in terms of nature, severity, or frequency given (a) the research procedures that are described in the protocol-related documents, such as the IRB-approved research protocol and informed consent document; and (b) the characteristics of the participant population being studied;

UAPs are considered to pose risk to participants or others when they suggest that the research places participants or others at a greater risk of harm (including physical, psychological, economic, or social harm) than was previously known or recognized.

11.1.2 Adverse Event

An adverse event is any untoward or unfavorable medical occurrence in a human participant, including any abnormal sign (for example, abnormal physical exam or laboratory finding), symptom, or disease, temporally associated with the participant's participation in the research, whether or not considered related to the participant's participation in the research.

11.1.3 Laboratory test abnormalities

Laboratory abnormalities that constitute an Adverse event in their own right (are considered clinically significant, induce clinical signs or symptoms, require concomitant therapy or require changes in study treatment), should be recorded on the Adverse Events CRF. Whenever possible, a diagnosis, rather than a symptom should be provided (e.g. anemia instead of low hemoglobin). Laboratory abnormalities that meet the criteria for Adverse Events should be followed until they have returned to normal or an adequate explanation of the abnormality is found. When an abnormal laboratory or test result corresponds to a sign/symptom of an already reported adverse event, it is not necessary to separately record the lab/test result as an additional event.

Laboratory abnormalities, that do not meet the definition of an adverse event, should not be reported as adverse events. A Grade 3 or 4 event (severe) as per CTCAE does not automatically indicate a SAE unless it meets the definition of serious as defined below and/or

as per investigator's discretion. A dose hold or medication for the lab abnormality may be required by the protocol and is still, by definition, an adverse event.

11.1.4 Serious Adverse Events

A serious adverse event (SAE) is one that meets one or more of the following criteria:

- Results in death
- Is life-threatening (places the participant at immediate risk of death from the event as it occurred)
- Is disabling or incapacitating
- Results in inpatient hospitalization or prolongation of existing hospitalization
- Results in a persistent or significant disability or incapacity
- Results in a congenital anomaly or birth defect
- An important medical event that may not result in death, be life threatening, or require hospitalization may be considered an SAE when, based upon appropriate medical judgment, the event may jeopardize the participant or may require intervention to prevent one of the outcomes listed in this definition.

11.2 Safety Assessment and Follow-Up

The PI will follow adverse events with start dates occurring any time after informed consent is obtained until 7 (for non-serious AEs) or 30 days (for SAEs) after the last day of study participation. At each study visit, the investigator (or designee) will inquire about the occurrence of AE/SAEs since the last visit. Events will be followed for outcome information until resolution or stabilization.

11.3 Recording Adverse Events

The following subsections detail what information must be documented for each adverse event occurring during the time period specified in Section 11.4.

At each contact with the subject, the investigator must seek information on adverse events by specific questioning and, as appropriate, by examination. Information on all adverse events should be recorded immediately in the source document, and also in the appropriate adverse event module of the case report form (CRF). All clearly related signs, symptoms, and abnormal diagnostic procedures results should be recorded in the source document, though should be grouped under one diagnosis.

All adverse events occurring during the study period must be recorded.

The clinical course of each event should be followed until resolution, stabilization, or until it has been determined that the study treatment or participation is not the cause. Serious adverse events that are still ongoing at the end of the study period must be followed up to determine the final outcome. Any serious adverse event that occurs after the study period and is considered to be possibly related to the study treatment or study participation should be recorded and reported immediately.

11.3.1 Relationship to Study Intevention

The relationship to study intervention or study participation must be assessed and documented for all adverse events. Evaluation of relatedness must consider etiologies such as natural history of the underlying disease, concurrent illness, concomitant therapy, study-related procedures, accidents, and other external factors.

The following guidelines are used to assess relationship of an event to study intervention:

1. Related (Possible, Probable, Definite)
    a. The event is known to occur with the study intervention.
    b. There is a temporal relationship between the intervention and event onset.
    c. The event abates when the intervention is discontinued.
    d. The event reappears upon a re-challenge with the intervention.
2. Not Related (Unlikely, Not Related)
    a. There is no temporal relationship between the intervention and event onset.
    b. An alternate etiology has been established.

11.3.2 Expectedness

The PI is responsible for determining whether an AE is expected or unexpected. An AE will be considered unexpected if the nature, severity, or frequency of the event is not consistent with the risk information previously described for the intervention. Risk information to assess expectedness can be obtained from preclinical studies, the investigator's brochure, published medical literature, the protocol, or the informed consent document.

11.3.3 Severity of Event

Adverse events will be graded for severity according to the Common Terminology Criteria for Adverse Events (CTCAE) version 4.0.

11.3.4 Intervention

Any intervention implemented to treat the adverse event must be documented for all adverse events.

11.4 Safety Reporting

The study period during which adverse events must be reported is normally defined as the period from the initiation of any study procedures to the end of the study treatment follow-up. For this study, the study treatment follow-up is defined as 30 days following the last administration of study treatment.

For patients whose Oncotype Dx recurrence score is unknown and who sign the molecular pre-screening ICF, AEs which occur after signature of this consent will only be captured if they meet the definition of serious as outlined in Section 11.1.2 and are reported to be causally related with study procedures (e.g. an invasive procedure such as biopsy). Once the main study ICF is signed, all AEs per the descriptions below will be captured in the Adverse Event CRF.

Patients whose Oncotype Dx recurrence score is known will sign the main study ICF.

For patients with unknown Oncotype Dx Recurrence Scores and who sign the molecular pre-screening ICF, SAE collection will start upon signing the molecular pre-screening ICF. SAEs will only be reported if the event is suspected to be causally related to a study procedure as assessed by the investigator (e.g. an invasive procedure such as biopsy). SAEs will be followed until resolution or until clinically relevant improvement or stabilization. If the main ICF is not signed (molecular screen failure), SAE collection ends 30 days after the last study related procedure.

For patients with known Oncotype Dx Recurrence Scores who sign the main study ICF, SAE collection starts at time of main study informed consent whether the patient is a screen failure or not.

11.4.1 Reporting to IRB

11.4.1.1 Unanticipated Problems

All incidents or events that meet criteria for unanticipated problems (UAPs) as defined in Section 11.1.1 require the creation and completion of an unanticipated problem report form (OHR-20).

UAPs that pose risk to participants or others, and that are not AEs, will be submitted to the TJU IRB on an OHR-20 form via the eazUP system within 10 working days of the investigator becoming aware of the event.

UAPs that do not pose risk to participants or others will be submitted to the TJU IRB at the next continuing review.

Participating sites will submit UAPs to their local IRB per local institutional requirements. Participating sites will provide TJU with a copy of all UAP reports.

11.4.1.2 Adverse Events

Grade 1 AEs will be reported to the IRB at continuing review.

Grade 2 AEs will be reported to the IRB at the time of continuing review.

11.4.1.3 Serious Adverse Events

SAEs will be reported to the IRB on OHR-10 forms via the electronic reporting system (eSAEy) according to the required time frames described below.

Grade 3-4 AEs that are unexpected and deemed to be at least possibly related to the study will be reported to the IRB within 2 working days of knowledge of the event.

Grade 3-4 AEs that are deemed unrelated to the study will be reported to the IRB within 5 working days.

Grade 5 AEs will be reported to the IRB within one working day of knowledge of the event.

All SAEs will be submitted to the IRB at continuing review, including those that were reported previously.

11.4.2 Reporting to SKCC DSMC

On a quarterly basis, all AEs and SAEs, safety and toxicity data, and any corrective actions will be submitted to the DSMC per the DSMP. The quarterly report to DSMC will also include any unanticipated problems that in the opinion of the PI should be reported to the DSMC.

For expedited reporting requirements, see Appendix C: DSMC AE/SAE Reporting Requirements.

11.4.3 Reporting to Drug Supplier

The principal investigator has the obligation to report all serious adverse events to the IRB and the Novartis Pharmaceuticals Drug Safety and Epidemiology Department (DS&E).

To ensure patient safety, every SAE, regardless of suspected causality, occurring after the patient has provided informed consent and until at least 30 days after the patient has stopped study treatment/participation , must be reported to Novartis within 24 hours of learning of its occurrence. Information about all SAEs is collected and recorded on a Serious Adverse Event Report Form. The investigator must assess and record the relationship of each SAE to each specific study treatment (if there is more than one study treatment), complete the SAE Report Form in English, and **send the completed, signed form along with the Novartis provided fax cover sheet to the Novartis Oncology Drug Safety and Epidemiology (DS&E) department by fax (fax: 877-778-9739) within 24 hours.**

Any additional information for the SAE including complications, progression of the initial SAE, and recurrent episodes must be reported as follow-up to the original episode within 24 hours of the investigator receiving the follow-up information. An SAE occurring at

a different time interval or otherwise considered completely unrelated to a previously reported one should be reported separately as a new event.

Any SAEs experienced after this 30 days period should only be reported to Novartis if the investigator suspects a causal relationship to the study drug. Follow-up information is submitted in the same way as the original SAE Report. Each re-occurrence, complication, or progression of the original event should be reported as a follow-up to that event regardless of when it occurs. The follow-up information should describe whether the event has resolved or continues, if and how it was treated, whether the blind was broken or not, and whether the patient continued or withdrew from study participation.

If the SAE is not previously documented in the Everolimus Investigator Brochure or Package Insert (new occurrence) and is thought to be related to the Novartis study drug, a DS&E associate may urgently require further information from the investigator for Health Authority reporting. Novartis may need to issue an Investigator Notification (IN), to inform all investigators involved in any study with the same drug that this SAE has been reported. Suspected Unexpected Serious Adverse Reactions (SUSARs) will be collected and reported to the competent authorities and relevant ethics committees in accordance with Directive 2001/20/EC or as per national regulatory requirements in participating countries.

11.1 Reporting for Subsites

All SAEs occurring at a participating site must be reported to the Thomas Jefferson University clinical study coordinator and Novartis (per section 11.4.3) within 24 hours of notification. The initial notification can take place via email, followed by the submission of a formal report.

SAEs should be reported to Thomas Jefferson University s The Off-site OHR-10 form (or On-site OHR-10 for Network site or sites using the TJU IRB) located in Appendix D, and should comprise a full written summary, detailing relevant aspects of the adverse events in question, including grading and attribution to study drug. Where applicable, information from relevant hospital case records and autopsy reports should be included.

SAE reports should be signed by the sub-site PI, and then faxed to the Thomas Jefferson University coordinator within 24 hours at: 215-923-9974 attention: Noelle Sowers.

The TJU coordinator will notify the TJU PI and obtain the TJU PI signature, and report these events to the TJU Medical Monitor/IRB appropriately (within 5 working days if it deems an amendment, or in a spreadsheet at the time of annual review if no amendment is necessary).

Any non-reportable AE must be kept by the sub-site on an ongoing tracking log to be reviewed by TJU quarterly (see Appendix E).

Unanticipated problems (UAPs) occurring at participating sites that pose risk to subjects or others, and that are not AEs/SAEs, should be reported to TJU within 10 working days using

form OHR-20 and should be faxed to the Thomas Jefferson University coordinator within 5 days at: **215-923-9974 attention: Noelle Sowers**.

11.2 Coordinating Site

All reportable AEs/SAEs occurring at the coordinating site must be reported to TJU IRB/Medical Monitor using the On-site OHR-10 Form, and should comprise a full written summary detailing relevant aspects of the adverse events in question, including grading and attribution to study drug. Where applicable, information from relevant hospital case records and autopsy reports should be included.

Reportable AE/SAEs from TJU will then also be faxed to the Participating Site coordinator per same guidelines as outlined above.

All unexpected AE./SAEs that are probably or definitively related to the study procedures from either the participating site or the coordinating site must be reported to the TJU IRB within 48 hours of the TJU Principal Investigator being notified of the event.

Any on-study death (regardless of relationship) and any unforeseen death, that indicates that the participant or others may be at increased risk of harm, must be submitted to the TJU IRB/Medical Monitor within 24 hours of notification. Any unrelated SAE should be reported within 5 working days. The TJU study team will notify the TJU IRB appropriately.

Additional follow-up SAE reports should be submitted when available.

Unanticipated problems that pose risk to subjects or others, and that are not AEs/SAEs should be reported to TJU IRB within 10 working days using form OHR-20 and should be faxed to the Participating Site coordinator within 24 hours.

12 Study Oversight

In addition to the PI's responsibility for oversight, study oversight will be under the direction of the SKCC's Data and Safety Monitoring Committee (DSMC). The DSMC operates in compliance with a Data and Safety Monitoring Plan (DSMP) that is approved by the Clinical Trials Oversight Committee (CTOC).

13 Clinical Site Monitoring and Auditing

Clinical site monitoring and auditing is conducted to ensure that the rights of human participants are protected, that the study is implemented in accordance with the protocol and/or other operating procedures, and that the quality and integrity of study data and data collection methods are maintained. Monitoring and auditing for this study will be performed in accordance with the SKCC's Data and Safety Monitoring Plan (DSMP) developed by the SKCC Data and Safety Monitoring Committee (DSMC). The DSMP specifies the frequency of monitoring, monitoring procedures, the level of clinical site monitoring activities (e.g., the percentage of participantparticipant data to be reviewed), and the distribution of monitoring

reports. Some monitoring activities may be performed remotely, while others will take place at the study site(s). Appropriate staff will conduct monitoring activities and provide reports of the findings and associated action items in accordance with the details described in the DSMP.

The investigator will permit study-related monitoring, audits, and inspections by the IRB, the funding sponsor, government regulatory bodies, and University compliance and quality assurance groups of all study related docuemnts (e.g. source documents, regulatory documents, data collection instruments, study data etc). The investigator will ensure the capability for inspections of applicable study-related facilities (e.g. pharmacy, diagnostic laboratory, etc).

Participation as an investigator in this study implies acceptance of potential inspection by government regulatory authorities and applicable University compliabce and quality assurance offices.

Representatives from the Thomas Jefferson University study team will monitor on site at the participating site (or virtually if geographically impossible) within 4 weeks of the first subject enrolling, and every 4-6 weeks thereafter as outlined in the TJU Monitoring Policy. Additional study monitoring by an independent auditing agency will be conducted at 10% and 50% of site accrual per the TJU Data and Safety Monitoring Plan. This will either occur on-site, if feasible, or will require participating sites to send TJU all source documents, patient charts, etc to TJU for audit.

Teleconferences with the PIs, research nurses/coordinators, and regulatory staff will occur quarterly. This will be a forum to discuss study related issues including accrual. SAE/AEs experienced, stud response, deviations/violations and study management issues. Minutes of these discussions will be taken to document the date of these meetings, the participants and the issues that were discussed. Copies of these minutes will be maintained in the Regulatory Binders at all participating sites.

14 STATISTICAL CONSIDERATION

14.1 Primary Endpoint

The primary study endpoint is PEPI score 0 as defined in Appendix B. These results will be retrieved from the routine pathology report. The PEPI score will be reported using descriptive statistics and 95% confidence intervals.

14.2 Secondary Endpoint

1. Clinical and radiographic response rate will be assessed by two measures. Radiographic tumor size measurements by MRI (or ultrasound when MRI not feasible) and physical examination after completion of all chemotherapy compared to baseline. Response will be categorized following RECIST criteria (Appendix A). The results will be reported as descriptive statistics with 95% confidence intervals.

2. Toxicity will be recorded using the standard NCI Common Toxicity Criteria as per http://ctep.cancer.gov/forms/CTCAEv4.pdf.and . Results will be reported in a tabular format by worst grade and occurrence per patient over the entire study period
3. Measurements of Ki67 at baseline and after completion of neoadjuvant therapy.
4. Baseline and residual cancer tissue will be collected for future biomarker analysis. Considering the small sample size of the study the biomarker results will be exploratory and hypothesis generating. The planned molecular analysis of these tissues may include gene expression profiling, and PI3K pathway markers.

14.3 Sample Size calculation

This is a single arm phase II study to evaluate neoadjuvant endocrine therapy with everolimus in postmenopausal women with ER+/HER2 – breast cancers with low and intermediate risk ($\leq$ 25) Recurrence Scores. The primary endpoint will be response defined as a PEPI-0 rate. A treatment with minimal activity would be expected to have PEPI-0 rate of 25%. Alternatively, a treatment will be considered worthy of further study if its true PEPI-0 rate is 45% or better.

Simon's optimal two-stage design is employed for this single-arm phase II trial and a total of 27 eligible patients will be enrolled. First, 15 eligible patients will be enrolled in the study. if 5 or more of 15 eligible patients achieve a PEPI score of 0, we will enroll another 12 patients into the study. If 10 or more of the 27 eligible patients achieve a PEPI score of 0, we will conclude that the regimen warrants further study. This design has a power of 80% and a one-sided significance level of 0.1. The probability of stopping early if the treatment is ineffective (true PEPI-0 rate of $\leq$ 25%) is 69%. Assuming that 10-20% of enrolled patients will be inevaluable, we plan to enroll up to 33 in total.

Protocol amendments, or changes in study conduct

Any change or addition (excluding administrative) to this protocol requires a written protocol amendment that must be reviewed by Novartis and the investigator before implementation. Amendments significantly affecting the safety of subjects, the scope of the investigation or the scientific quality of the study require additional approval by the IRB at each study center. A copy of the written approval of the IRB must be provided to Novartis. Examples of amendments requiring such approval are:

1. increases in drug dose or duration of exposure of subjects,
2. significant changes in the study design (e.g. addition or deletion of a control group),
3. increases in the number of invasive procedures,
4. addition or deletions of a test procedure required for monitoring of safety.

These requirements for approval should in no way prevent any immediate action from being taken by the investigator or by Novartis in the interests of preserving the safety of all patients included in the trial. If an immediate change to the protocol is felt to be necessary by the investigator and is implemented for safety reasons Novartis must be notified and the IRB at the center must be informed immediately. Amendments affecting only administrative aspects of the study do not require formal protocol amendments or IRB approval but the IRB must be

kept informed of such administrative changes. Examples of administrative changes not requiring formal protocol amendments and IRB approval include:

1. changes in the staff used to monitor trials
2. minor changes in the packaging or labeling of study drug.

15 Source Documents and Access to Source Data/Documents

Study staff will maintain appropriate medical and research records for this study, in compliance with ICH E6, and regulatory and institutional requirements for the protection of confidentiality of participant information. Study staff will permit authorized representatives of SKCC and regulatory agencies to examine (and when required by applicable law, to copy) research records for the purposes of quality assurance reviews, audits, and evaluation of the study safety, progress and data validity.

16 Ethics/Protection of Human Participants

16.1 Ethical Standard

The investigator will ensure that this study is conducted at all participating sites in full conformity with the principles set forth in The Belmont Report: Ethical Principles and Guidelines for the Protection of Human Subjects of Research, as drafted by the US National Commission for the Protection of Human Subjects of Biomedical and Behavioral Research (April 18, 1979) and codified in 45 CFR Part 46 and/or the ICH E6.

16.2 Institutional Review Board

The protocol, informed consent form(s), recruitment materials, and all participant materials will be submitted to a properly constituted independent Institutional Review Board (IRB), in agreement with local legal prescriptions, for review and approval. Approval of both the protocol and the consent form must be obtained before any participant is enrolled. Any amendment to the protocol will require review and approval by the IRB before the changes are implemented in the study.

16.3 Informed Consent Process

Informed consent is a process that is initiated prior to the individual agreeing to participate in the study and continues throughout study participation. Extensive discussion of risks and possible benefits of study participation will be provided to participants and their families, if applicable. A consent form describing in detail the study procedures and risks will be given to the participant. Consent forms will be IRB-approved, and the participant is required to read and review the document or have the document read to him or her. The investigator or designee will explain the research study to the participant and answer any questions that may arise. The participant will sign the informed consent document prior to any study-related assessments or procedures. Participants will be given the opportunity to discuss the study with their surrogates or think about it prior to agreeing to participate. They may withdraw consent

at any time throughout the course of the study. A copy of the signed informed consent document will be given to participants for their records. The rights and welfare of the participants will be protected by emphasizing to them that the quality of their clinical care will not be adversely affected if they decline to participate in this study. The consent process will be documented in the clinical or research record.

16.4 Participant Confidentiality

Participant confidentiality is strictly held in trust by the investigators, study staff, and the drug supplier and their agents. This confidentiality is extended to cover testing of biological samples and genetic tests in addition to any study information relating to participants.

The study protocol, documentation, data, and all other information generated will be held in strict confidence. No information concerning the study or the data will be released to any unauthorized third party without prior written approval of the sponsor.

The study monitor or other authorized representatives of the sponsor may inspect all study documents and records required to be maintained by the investigator, including but not limited to, medical records (office, clinic, or hospital) for the study participants. The clinical study site will permit access to such records.

17 Data Handling and Record Keeping

The investigators are responsible for ensuring the accuracy, completeness, legibility, and timeliness of the data reported. All source documents should be completed in a neat, legible manner to ensure accurate interpretation of data. The investigators will maintain adequate case histories of study participants, including accurate case report forms (CRFs), and source documentation.

17.1 Data Management Responsibilities

Data collection and accurate documentation are the responsibility of the study staff under the supervision of the investigator. All source documents and laboratory reports must be reviewed by the study team and data entry staff, who will ensure that they are accurate and complete. Unanticipated problems and adverse events must be reviewed by the investigator or designee.

17.2 Study Records Retention

Study records will be maintained for at least three years from the date that the grant federal financial report (FFR) is submitted to the NIH.

Study documents should be retained for a minimum of 2 years after the last approval of a marketing application in an ICH region and until there are no pending or contemplated marketing applications in an ICH region or until at least 2 years have elapsed since the formal discontinuation of clinical development of the investigational product. These documents should be retained for a longer period, however, if required by local regulations. No records will be destroyed without the written consent of the sponsor, if applicable. It is the

responsibility of the sponsor to inform the investigator when these documents no longer need to be retained.

17.3 Protocol Deviations

A protocol deviation is any noncompliance with the clinical study protocol, Good Clinical Practice, or Manual of Procedures requirements. The noncompliance may be on the part of the participant, the investigator, or study staff. As a result of deviations, corrective actions are to be developed by the study staff and implemented promptly.

All deviations from the protocol must be addressed in study participant source documents and promptly reported to the IRB and other regulatory bodies according to their requirements.

18 Study Finances

18.1 Funding Source

Novartis Pharmaceuticals is providing the investigational product, everolimus (Afinitor), for this study.

18.2 Conflict of Interest

Any investigator who has a conflict of interest with this study (patent ownership, royalties, or financial gain greater than the minimum allowable by their institution, etc.) must have the conflict reviewed by a properly constituted Conflict of Interest Committee with a Committee-sanctioned conflict management plan that has been reviewed and approved by the study sponsor prior to participation in this study. All Jefferson University Investigators will follow the TJU Conflicts of Interest Policy for Employees (107.03).

18.3 Participant Stipends or Payments

Participants will not be paid as part of this study.

19 Publication and Data Sharing Policy

This study will comply with the NIH Public Access Policy, which ensures that the public has access to the published results of NIH funded research. It requires scientists to submit final peer-reviewed journal manuscripts that arise from NIH funds to the digital archive PubMed Central upon acceptance for publication.

The International Committee of Medical Journal Editors (ICMJE) member journals have adopted a clinical trials registration policy as a condition for publication. The ICMJE defines a clinical trial as any research project that prospectively assigns human participants to intervention or concurrent comparison or control groups to study the cause-and-effect relationship between a medical intervention and a health outcome. Medical interventions include drugs, surgical procedures, devices, behavioral treatments, process-of-care changes, and the like. Health outcomes include any biomedical or health-related measures obtained in patients or participants, including pharmacokinetic measures and adverse events. The ICMJE

policy requires that all clinical trials be registered in a public trials registry such as ClinicalTrials.gov, which is sponsored by the National Library of Medicine. Other biomedical journals are considering adopting similar policies. The ICMJE does not review specific studies to determine whether registration is necessary; instead, the committee recommends that researchers who have questions about the need to register err on the side of registration or consult the editorial office of the journal in which they wish to publish.

U.S. Public Law 110-85 (Food and Drug Administration Amendments Act of 2007 or FDAAA), Title VIII, Section 801 mandates that a "responsible party" (i.e., the sponsor or designated principal investigator) register and report results of certain "applicable clinical trials:"

Trials of Drugs and Biologics: Controlled, clinical investigations, other than Phase I investigations, of a product subject to FDA regulation;

Trials of Devices: Controlled trials with health outcomes of a product subject to FDA regulation (other than small feasibility studies) and pediatric postmarket surveillance studies.

NIH grantees must take specific steps to ensure compliance with NIH implementation of FDAAA.

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APPENDIX A
Response Evaluation Criteria in Solid Tumors (RECIST Criteria)

The baseline longest diameter of the primary breast cancer assessed by mammogram (or ultrasonogram or MRI at physicians discretion) will be used as the reference by which to characterize objective tumor response in the breast.

- Complete response (CR)

Disappearance of all evidence of tumor for at least two cycles of therapy.

- Partial response

At least a 30% decrease in the sum of the longest diameter of target lesions, taking a reference the baseline sum longest diameter.

- Stable disease (SD)

Neither sufficient shrinkage to qualify for partial response nor sufficient increase to qualify for progressive disease, taking as reference the smallest sum longest diameter since the treatment started.

- Progressive disease (PD)

At least a 20% increase in the sum of the longest diameter of target lesions, taking as reference the smallest sum longest diameter recorded since the beginning of treatment or the appearance of one or more new lesions Clinical progressive disease

Subjects, who in the opinion of the treating physician investigator have had a substantial decline in their performance status and have clinical evidence of progressive disease may be classified as having progressive disease.

1. Definitions

Every patient who completed at least one cycle (4 weeks) of therapy may be assessed for response. Response and progression will be evaluated in this trial using the RECIST Version 1.1. Lesions are either measurable or non-measurable using the criteria provided below.

Measurable Disease:	**Tumor lesions:** Must be accurately measured in at least one dimension (longest diameter in the plane of measurement is to be recorded) with a minimum size of: • 10 mm by CT scan (CT scan slice thickness no greater than 5 mm). • 10 mm caliper measurement by clinical exam (lesions that cannot be accurately measured with calipers should be recorded as non-measurable). • 20 mm by chest x-ray. **Skin lesions:** Documentation by color photography, including a ruler to estimate the size of the lesion, is recommended. **Malignant lymph nodes:** To be considered pathologically enlarged and measurable, a lymph node must be >15 mm in short axis when assessed by CT scan. At baseline and in follow-up, only the short axis will be measured and followed.
Non-Measurable Evaluable Disease:	All other lesions, including small lesions (longest diameter <10 mm or pathological lymph nodes with >10- to <15-mm short axis) as well as truly non-measurable lesions. Lesions considered truly non-measurable include: leptomeningeal disease, ascites, pleural or pericardial effusion, inflammatory breast disease, lymphangitic involvement of skin or lung, abdominal masses, abdominal organomegaly identified by physical exam that is not measurable by reproducible imaging requirements.

Target Lesions:	The most reproducible measurable lesions, up to a maximum of 2 lesions per organ and 5 lesions in total, representative of all involved organs should be identified as target lesions and recorded and measured at baseline. Target lesions should be selected on the basis of their size (lesions with the longest diameter), should be representative of all involved organs, and in addition should be those that lend themselves to reproducible repeated measurements. Pathological nodes which are defined as measurable and that may be identified as target lesions must meet the criterion or a short axis of >15 mm by CT scan. A sum of the diameters (longest for non-nodal lesions, short axis for nodal lesions) for all target lesions will be calculated and reported as the baseline sum diameters. If lymph nodes are to be included in the sum, then as noted above, only the short axis is added into the sum. The baseline sum diameters will be used as reference to further characterize any objective tumor response.
Non-Target Lesions:	**All other lesions should be identified as non-target lesions at baseline. Measurements of these lesions are not required, but the presence or absence of each should be noted throughout follow-up.**

i. **Guidelines for Evaluation of Measurable Disease**

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

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

Clinical Lesions:	Clinical lesions will only be considered measurable when they are superficial (e.g., skin nodules and palpable lymph nodes). In the case of skin lesions, documentation by color photography, including a ruler to estimate the size of the lesion, is recommended.
Chest X-ray:	Lesions on chest X-ray are acceptable as measurable lesions when they are clearly defined and surrounded by aerated lung. However, CT is preferable.

Conventional CT and MRI:	CT and MRI are the best currently available and reproducible methods to measure target lesions selected for response assessment. Conventional CT and MRI should be performed with cuts of 10 mm or less in slice thickness, contiguously. Spiral CT scan should be performed using a 5-mm contiguous reconstruction algorithm. This applies to tumors of the chest, abdomen, and pelvis. Head and neck tumors and those of extremities usually require specific protocols.
Ultrasound:	When the primary trial endpoint is objective response, ultrasound should not be used to measure tumor lesions. It is, however, a possible alternative to clinical measurements of superficial palpable lymph nodes, subcutaneous lesions, and thyroid nodules. Ultrasound may also be useful to confirm the complete disappearance of superficial lesions usually assessed by clinical examination.
Endoscopy and Laparoscopy:	Use of endoscopy and laparoscopy for objective tumor evaluation has not yet been fully and widely validated. Therefore, use of these techniques for objective tumor response should be restricted to validation purposes in specialized centers. Such techniques can be useful in confirming complete pathological response when biopsies are obtained.
Tumor Markers:	Tumor markers alone cannot be used to assess response. If markers are initially above the upper limit of normal, they must normalize for a patient to be considered in complete clinical response when all lesions have disappeared.
Cytology and Histology:	Cytology and histology can be used to differentiate between PR and CR in rare cases (e.g., after treatment to differentiate between residual benign lesions and residual malignant lesions in tumor types such as germ cell tumors).

ii. **Response Criteria**

Evaluation of Target Lesions

Complete Response (CR): Disappearance of all target lesions.

Partial Response (PR): At least a 30% decrease in the sum of the longest diameter (LD) of target lesions, taking as reference the baseline sum LD.

Stable Disease (SD): Neither sufficient shrinkage to qualify for PR nor sufficient increase to qualify for PD, taking as reference the smallest (nadir) sum LD since the treatment started.

Progressive Disease (PD): At least a 20% increase in the sum of the LD of target lesions, taking as reference the smallest (nadir) sum since the treatment started, or the appearance of one or more new lesions. Requires not only 20% increase, but absolute increase of a minimum of 5 mm over sum.

Evaluation of Non-Target Lesions

Complete Response (CR): Disappearance of all non-target lesions and normalization of tumor markers. All lymph nodes must be non-pathological in size (<10 mm short axis).

Stable Disease (SD): Persistence of one or more non-target lesions and/or persistence of tumor marker level above the normal limits.

Progressive Disease (PD): Appearance of one or more new lesions and/or unequivocal progression of existing non-target lesions. When the patient also has measurable disease, to achieve "unequivocal progression" on the basis of the non-target disease, there must be an overall level of substantial worsening in non-target disease such that, even in presence of SD or PR in the target disease, the overall tumor burden has increased sufficiently to merit discontinuation of therapy.

Evaluation of Best Overall Response

The best overall response is the best response recorded from the start of the treatment until disease progression/recurrence (taking as reference for progressive disease the smallest measurements recorded since the treatment started). In general, the patient's best response assignment will depend on the achievement of both measurement and confirmation criteria.
Confirmation of response (by repeat scans after 4 weeks or as specified in the protocol) is required for trials in which response rate is the primary endpoint, but is not required in randomized trials or trials with primary survival endpoints (i.e., where response is not a primary endpoint).

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

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

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

Non-Measurable Disease Only

When a patient only has non-measurable disease: this circumstance arises in some trials when it is not a criterion of study entry to have measurable disease. The same general concepts apply here as noted above, however, in this instance; there is no measureable disease assessment to factor into the interpretation of an increase in non-measurable disease burden. Because worsening in non-target disease cannot be easily quantified (by definition: if all lesions are truly non-measurable) a useful test that can be applied when assessing patients for unequivocal progression is to consider if the increase in overall disease burden based on the change in non-measurable disease is comparable in magnitude to the increase that would be required to declare PD for measurable disease: i.e. an increase in tumor burden representing an additional 73% increase in 'volume' (which is equivalent to a 20% increase diameter in measurable lesion). Examples include an increase in a pleural effusion from 'trace' to 'large', an increase in lymphangitic disease from localized to widespread, or may be described in protocols as 'sufficient to require a change in therapy'. If 'unequivocal progression' is seen, the patient should be considered to have had overall PD at that point. While it would be ideal to have objective criteria to apply non-measureable disease, the very nature of that disease makes it impossible to do so; therefore the increase must be substantial.

2. Response Duration

Response duration is measured from the time of first response (either CR or PR whichever is recorded first) until there is clinically or radiologically documented evidence of disease progression. Response duration, by definition, is only assessed in patients who experience objective tumor response (CR or PR). Duration of stable disease is measured from the start of the treatment until the criteria for disease progression is met. The reference measurement used should be the smallest measurements recorded since the treatment started.

3. Time to Progression

Time to progression is measured from the beginning of treatment (day 1 of cycle 1) until objective clinical and/or radiological evidence of tumor progression, as outlined above, is documented. Every patient who completes at least 1 course (4 weeks) of treatment will be evaluated for time to progression.

APPENDIX B

The preoperative endocrine prognostic index

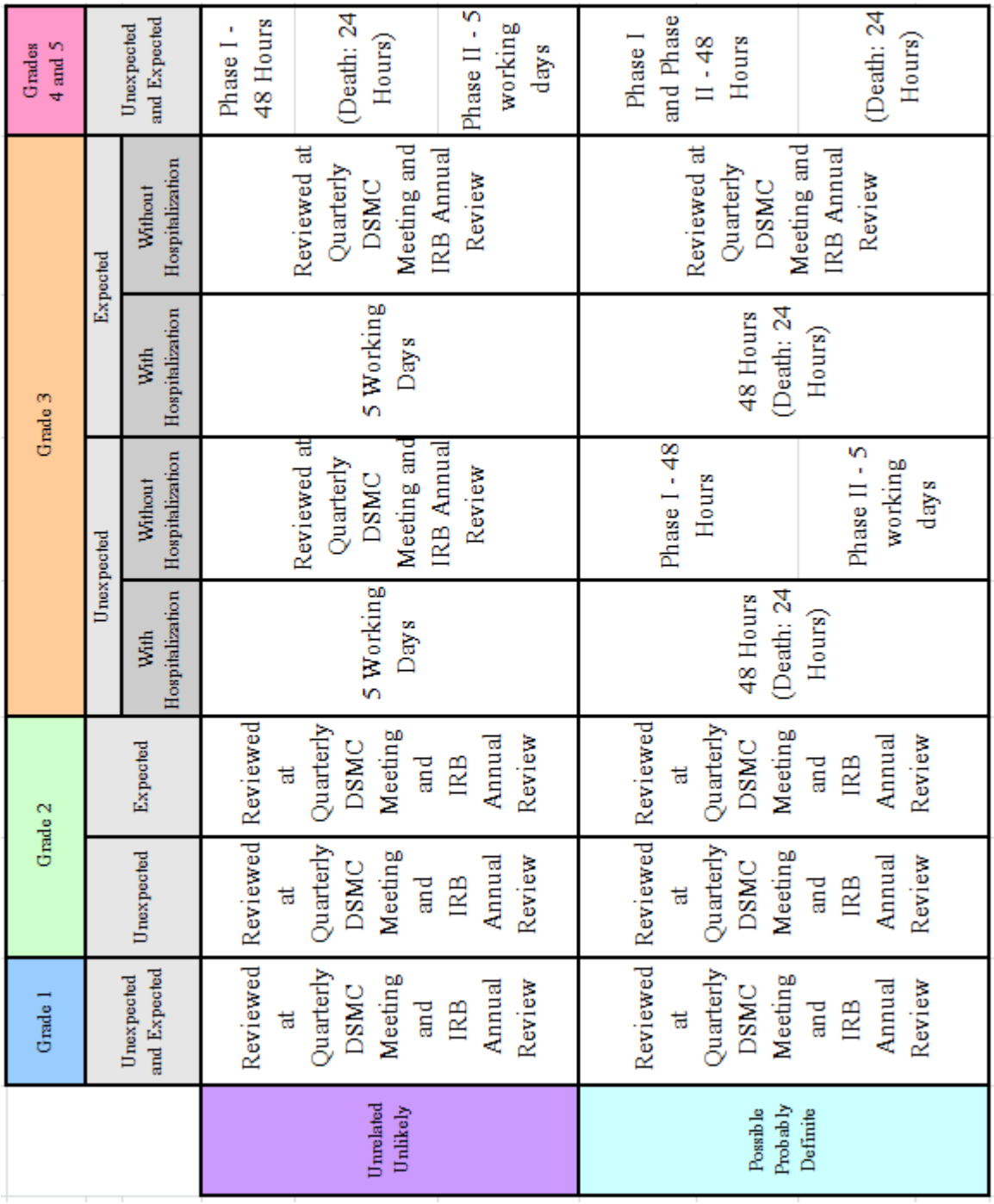
Pathology, biomarker status	RFS		BCSS	
	HR	Points	HR	Points
Pathological tumor size				
T1/2	—	0	—	0
T3/4	2.8	3	4.4	3
Node status				
Negative	—	0	—	0
Positive	3.2	3	3.9	3
Ki67 level				
0%–2.7% (0–1†)	—	0	—	0
>2.7%–7.3% (1–2†)	1.3	1	1.4	1
>7.3%–19.7% (2–3†)	1.7	1	2.0	2
>19.7%–53.1% (3–4†)	2.2	2	2.7	3
>53.1% (>4†)	2.9	3	3.8	3
ER status, Allred score				
0–2	2.8	3	7.0	3
3–8	—	0	—	0

*To obtain the preoperative endocrine prognostic index (PEPI) score, risk points for relapse-free survival (RFS) and breast cancer–specific survival (BCSS) were assigned depending on the hazard ratio (HR) given in Table 3. The points scale was adapted from the cardiovascular literature on predicting outcomes for myocardial infarction (11). The total PEPI score assigned to each patient is the sum of the risk points derived from the pT stage, pN stage, Ki67 level, and estrogen receptor (ER) status of the surgical specimen. An HR in the range of 1–2 receives one risk point; a HR in the 2–2.5 range, two risk points; a HR greater than 2.5, three risk points. The total risk point score for each patient is the sum of all the risk points accumulated from the four factors in the model. For example, a patient with a T1N0 tumor, a Ki67 staining percentage of 1 and an ER Allred score of 6 will have no risk points assigned. In contrast, a patient with a T3N1 tumor, a Ki67 staining percentage of 25, and an ER Allred score of 2 will have a total relapse score of 3 + 3 + 2 + 3 = 11.

†The natural logarithm interval corresponding to the percent Ki67 values on the original percentage scale

Appendix C

SKCC DSMP's AE/SAE Reporting Requirements



	Grade 1	Grade 2		Grade 3				Grades 4 and 5
				Unexpected		Expected		
	Unexpected and Expected	Unexpected	Expected	With Hospitalization	Without Hospitalization	With Hospitalization	Without Hospitalization	Unexpected and Expected
Unrelated Unlikely	Reviewed at Quarterly DSMC Meeting and IRB Annual Review	Reviewed at Quarterly DSMC Meeting and IRB Annual Review	Reviewed at Quarterly DSMC Meeting and IRB Annual Review	5 Working Days	Reviewed at Quarterly DSMC Meeting and IRB Annual Review	5 Working Days	Reviewed at Quarterly DSMC Meeting and IRB Annual Review	Phase I - 48 Hours (Death: 24 Hours) Phase II - 5 working days
Possible Probably Definite	Reviewed at Quarterly DSMC Meeting and IRB Annual Review	Reviewed at Quarterly DSMC Meeting and IRB Annual Review	Reviewed at Quarterly DSMC Meeting and IRB Annual Review	48 Hours (Death: 24 Hours)	Phase I - 48 Hours Phase II - 5 working days	48 Hours (Death: 24 Hours)	Reviewed at Quarterly DSMC Meeting and IRB Annual Review	Phase I and Phase II - 48 Hours (Death: 24 Hours)

.Appendix D

OHR-10 (7/06)
OFF-SITE ONLY

THOMAS JEFFERSON UNIVERSITY ADVERSE REACTION REPORT FORM

TO BE COMPLETED BY PRINCIPAL INVESTIGATOR WHEN AN ADVERSE REACTION (AE) OCCURS IN STUDIES CONDUCTED OFF-SITE.

This Form Must Be Typewritten

POLICY: Any serious and/or unexpected (not in consent form) off-site adverse event (AE) that is deemed by the principal investigator to be probably or definitely related to the study drug, and that necessitates a change to the protocol and/or consent form, must be reported within five days of receipt of report. AEs judged to be unrelated to the drug, the result of progressive disease, or other factors such as accidents or unrelated medical procedures, need not be reported. (Consult IRB Policy & Procedures Handbook or website for more information.)

Principal Investigator/Department:_____IRB Control #_____
Title of Project:_____
_____
Sponsor (if applicable):_____Study Drug(s)/Device:_____

Provide a brief and concise description of adverse reaction (no narrative, please):

Is this:	A new report?	Yes ☐	No ☐	Have you previously reported this adverse reaction to the IRB?:
	A follow-up report?	Yes ☐	No ☐	For this study? Yes ☐ No ☐
				For this patient? Yes ☐ No ☐
				Date Reported: _____

How many times has this reaction occurred in individual patients participating in this study?: _ *(usually in the company narrative)*

What is the total national/international enrollment for the study?____

In the Principal Investigator's opinion, was the event drug-related or caused by the procedures associated with this protocol?

(Circle One): UNRELATED PROBABLY RELATED DEFINITELY RELATED

If UNRELATED, **DO NOT SUBMIT TO IRB.** Keep report for your records.

Is the risk of this adverse reaction described in the consent form? Yes ☐ No ☐
If **Yes**, **DO NOT SUBMIT TO IRB.** Keep report for your records.
If **No**, should this risk be described in the consent form? Yes ☐ No ☐

If **Yes**, submit revision to consent form. *(Provide 35 collated, stapled copies of: OHR-12, revised consent form with changes highlighted, current stamped consent form, and adverse event report(s).)*	If **No**, provide justification for not including this reaction as a risk in the consent form:

Has this AE changed the risk to benefit ratio of the study in any way? Yes ☐ No ☐ Explain:

****

Individual Preparing this Report: _____Date: _____

CERTIFICATION: I certify that I have reviewed this report of an adverse reaction.

Principal Investigator:_____Date:_____

Instructions: Please submit 3 stapled, collated sets of:
OHR-10, Medwatch/ sponsor report, & current stamped consent form

IRB Reviewer:_____
Initials:_____
Date:_____

Appendix E

Adverse Events Log

Patient Name: _____ **Study Agents:** _____
Protocol: _____ **Cycle/ Week #:**_____

Adverse Event	Grade	☒ if started prior to tx	Start Date	End Date	Continuing ?	Relationship to Treatment	Relationship to Study Drug	SAE?	Action(s) Taken	Comments

Grade: Use CTCAE Version 3, or as specified by the protocol
Relationship: Definite, Probable, Possible, Unlikely, Unrelated

Reviewed and Approved
PI Signature: _____
Date: _____