Comparison in the Change of Proliferation Index Between Fulvestrant and Tamoxifen in Cyclin D1 +, Estrogen Receptor + Breast Cancer
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Mount Sinai Hospital

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VERSION 13 (09/013/2017)

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Amy Tiersten. MD, PI

Essential Elements

#13, 09/13/2017

STUDY SCHEMA

❖ RANDOMIZATION:

Subjects in this study will be randomized to one 14 day cycle of study drug to be given as follows:

- **ARM A:**
  - Tamoxifen 20 mg PO
    Cycle 1 Day 1-14
- **ARM B:**
  - Fulvestrant 750 mg IM in 3 divided doses
    Cycle 1 Day 1 only

STUDY SUMMARY

Fulvestrant is the only drug promoting the degradation of the estrogen receptor (ER). Despite the fact that fulvestrant has demonstrated superiority over aromatase-inhibitors (AI) and tamoxifen, it is approved only for use in postmenopausal breast cancer patients. In premenopausal patients, tamoxifen or AI with ovarian suppression remains the standard of care only because data supporting the use of fulvestrant in these women is lacking. Significant clinical and laboratory-based data links the cyclinD1-interactome to a proliferative effect of tamoxifen in cyclinD1 positive tumors. CyclinD1 is overexpressed in 35% of breast cancers, and serves as a major hub regulating a large transcriptional network. In addition to its role in cell cycle, the cyclinD1-interactome regulates the ER, metastasis, DNA repair pathways, and stem cell differentiation. While tamoxifen promotes the oncogenic effect of the cyclinD1-interactome, in marked contrast, by degrading the ER, fulvestrant disrupts the cyclinD1-interactome and promotes cell death. We therefore hypothesize that the cyclinD1-interactome can be used to orient the use of fulvestrant in both premenopausal and postmenopausal women. To test this hypothesis, we propose a pre-surgical randomized clinical trial of tamoxifen vs fulvestrant in the window between breast cancer diagnosis on core biopsy and definitive surgery. Women with ER/cyclinD1 positive tumors will be eligible. Response to tamoxifen or fulvestrant will be evaluated using standard proliferation index as well as gene expression signatures obtained in pre-clinical models of tamoxifen resistance and sensitivity to fulvestrant. In addition, we propose to use cutting edge new technology allowing ex-vivo expansion of primary culture from only a few cancer cells obtained by fine needle biopsy. We propose to compare the response of these primary cells to patient response. If successful, this work can support the expansion of use of fulvestrant to not only postmenopausal women but premenopausal women as well. In addition, it may serve as a proof of principle to maximize the use of biopsy material to predict treatment response.

BACKGROUND AND RATIONALE

The central goal of this protocol is to exploit the cyclinD1-interactome as a biomarker to orient the use of fulvestrant in pre-menopausal and post menopausal women. Fulvestrant is a newer estrogen receptor downregulator, which binds the estrogen receptor (ER) and is the only endocrine therapy drug able to promote the degradation of the ER. Unlike tamoxifen, fulvestrant has only antagonistic effects on the ER and does not increase the risk of endometrial carcinoma or thromboembolic disease. It is currently approved for postmenopausal women but is not currently used in premenopausal women. A small phase II randomized trial in postmenopausal women demonstrated a significant reduction in risk of disease progression with fulvestrant over the aromatase inhibitor anastrozole (2). Based on its mechanism of action it should work equally well in pre and postmenopausal women. However, our current standard of care remains the use of tamoxifen as first-line therapy for premenopausal women. Importantly, the

cyclinD1-interactome has been linked to not only resistance to tamoxifen but acceleration of tumor growth in pre-menopausal women. Following recurrence on tamoxifen, young women are treated with aromatase inhibitors plus ovarian suppression. Results of the SOFT and TEXT trials reported earlier this year indicate that premenopausal women on ovarian suppression randomized to the aromatase inhibitor exemestane had a significant reduction in risk of recurrence over women treated with tamoxifen (1). One randomized trial by Young and colleagues has compared the effects of a single dose of 750 mg fulvestrant to tamoxifen 20 mg daily between biopsy and surgery in premenopausal women with ER positive breast cancer. In this trial, statistically significant declines in expression of ER and Ki67 compared to baseline were observed with both drugs, while a statistically significant decline in PR was only observed with fulvestrant. This was contrary to a prior study using 250 mg of fulvestrant, which did not achieve a significant reduction in Ki-67, ER or PR levels.
Mechanistically, cyclin D1 was initially identified as a critical regulator of cell cycle transition from G1 to S phase by activating the cyclin dependent kinases (cdk) 4 and 6. Since then the oncogenic effect of cyclinD1 has been expanded to cdk-independent role in transcription. Notably, cyclinD1 interacts directly with the ER and serves as a major modulator of the transcriptional network of the ER (4-7). Genome-wide analysis of cyclinD1-dependent estrogen signaling revealed that 88% of estrogen-regulated genes are modulated by binding of cyclinD1 to the ER. ChIP sequencing of cyclinD1 demonstrated its role in chromosomal instability, DNA repair and stem cell proliferation (18). Further, cyclinD1 knockout mice show tissue-specific defect in mammary gland development in mice that is reminiscent to the effect of the deletion of the ER in the mammary gland. In addition, high throughput proteomic analysis revealed that cyclinD1 interacts with over 132 proteins (6). Therefore, biochemical, high throughput genomic, proteomic and mouse genetic analysis all converge to a critical role of cyclinD1 in the regulation of breast cancer which is mainly dependent on its interaction with the ER.

In support of the drastic impact of the cyclinD1-interactome on the ER are numerous clinical studies linking cyclinD1-overexpression to resistance to tamoxifen (19-21). A study by Jirstrom et al (11) focused on cyclinD1 in premenopausal women where the vast majority of patients received tamoxifen but no chemotherapy. After 15 years of follow-up, cyclinD1 overexpression was associated with a 70% reduction in survival. Likewise, cyclinD1 positive patients experienced a more than 6 fold increased risk of recurrence and 5 fold increased risk of death. These dramatic differences were seen in both lymph node positive as well as lymph node negative patients. The profound effects of cyclinD1 overexpression suggest that these tumors are not only resistant to tamoxifen but may undergo growth stimulation by tamoxifen. Adding to this observation is the finding that cyclinD1 is associated with the luminal-B sub-type of breast cancers, which are known to be more resistant to hormonal therapy.

The Germain laboratory aimed at recapitulating the cyclinD1-dependent proliferative effect of tamoxifen. Their study led to the finding that tamoxifen modulates the balance of the interaction between cyclinD1 and two transcription factors, the ER and STAT3. CyclinD1 activates the ER (4,8) but represses STAT3 (9,10).

The STAT3 transcription factor upon phosphorylation promotes transcription of a number of genes leading to cell survival and proliferation. Consequently STAT3 is recognized as a potent oncogene and on inhibition will induce tumor regression in animal models (12). CyclinD1 is a known transcriptional target leading to down-regulation of STAT3, however, in the presence of tamoxifen, STAT3 is activated by cyclinD1 (13). Two additional important regulators of STAT3 are the progesterone receptor (PR) and the ErbB2 receptor. Of note, patients with ER+ and ErbB2+ disease often demonstrate resistance to anti-estrogen therapy. Co-expression of these proteins with PR in luminal B type breast cancers suggests a central oncogenic node driving the growth of these tumors. PR and ErbB2 have been shown to collaborate for the transcriptional activation of STAT3 (14). Consequently this collective evidence indicates a self-regulatory component to the cyclinD1-interactome mediating STAT3 activity. Such negative feedback loops are common in signaling cascades as mechanism to control length and strength of a proliferative signal. The Germain group found that treatment with tamoxifen leads to the titration of

cyclinD1 to the ER and promotes its activity, while STAT3 is no longer inhibited by cyclin D1, these findings suggest that treatment with tamoxifen abolishes the negative feedback loop between cyclinD1 and STAT3. Therefore treatment with tamoxifen allows hyperactivation of the ER, elevating PR and collaborating with ErbB2 to promote STAT3. In turn, STAT3 would promote more transcription of cyclinD1, and rather than inhibiting STAT3, in presence of tamoxifen cyclinD1 would further amplify signaling. Since fulvestrant leads to degradation of the ER, treatment with fulvestrant abolishes flow of signal across the cyclinD1-STAT3 network.

In drastic contrast, the Germain group found that cyclinD1 overexpressing cells are more sensitive to fulvestrant due to the unique ability of fulvestrant to degrade the ER, therefore disrupt the interaction of cyclinD1 with the ER and favor the repression of STAT3. This result led to the hypothesis that cyclinD1 may correlate with response to fulvestrant in patients. To test this possibility, we initiated a retrospective study where clinical follow-up of patients treated with fulvestrant was correlated with the expression level of cyclinD1 by IHC. ***We found that while the median time to progression (TTP) was of 133 days in the cyclin D1 negative group, the median TTP was 1149 days in the cyclinD1 positive patients (Figure 1).*** Since the results were highly statistical significant (p=0.027), these results constitute a strong scientific rationale supporting the hypothesis that the cyclinD1-interactome may be used to orient the use of fulvestrant, rather than tamoxifen in premenopausal and postmenopausal women. The significance of this work is that it could help identify patients for whom tamoxifen may be not only ineffective but detrimental. Pre-treatment analytics could allow therapy to be directed to fulvestrant for this subgroup, thereby maximizing the chance of long term success after endocrine therapy. It is our obligation to acquire clinical data to build on existing knowledge and offer better treatment for this patient population.

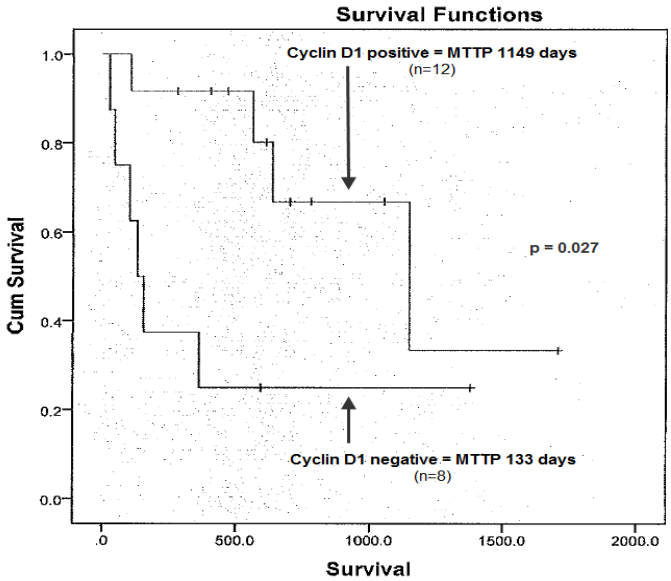

Figure1 Cyclin D1 predicts better response to fulvestrant

STUDY OBJECTIVES

Primary Objectives

Research Question: Does treatment with fulvestrant result in a significant change in proliferation index compared to tamoxifen in premenopausal and postmenopausal patients with cyclin D1 +, estrogen receptor + breast cancer?

The objective will be to answer this question via a small scale preoperative window trial randomizing these women to 2 weeks of therapy with either tamoxifen or fulvestrant.

Secondary Objectives

- Determine whether tamoxifen or fulvestrant have differential treatment effects for premenopausal and postmenopausal patients.
- Determine the change in estrogen receptor and progesterone receptor levels between core biopsy and definitive surgery in patients treated with fulvestrant or tamoxifen.
- Determine whether tamoxifen-resistance and fulvestrant-sensitivity gene expression signatures are observed in patients with cyclinD1 overexpressing breast cancers.
    - A gene signature that distinguishes cells that are responsive to tamoxifen and those that are resistant to tamoxifen has been established using cell lines in vitro. Similarly, a gene signature of the same cells in response to fulvestrant was also determined. Using these signatures obtained in vitro, we will compare whether the same gene signature characterizes tumors that are resistant or sensitive to tamoxifen and fulvestrant respectively in patients samples using selected gene by nanostring analysis by RNA extraction from paraffin embedded sections.
- Determine whether patient's response to tamoxifen or fulvestrant correlates with the response of their primary cells in vitro.
    - The organoid core facility has recently developed a method by which cells from primary tumors from patients can be grown in vitro. When samples are available for culture in vitro, we will test whether the cells derived from individual patients respond the same as the tumor in vivo in the same patient. For this experiment, cells in culture will be treated with the same drug (tamoxifen or fulvestrant) as the patient has received. We will conduct standard proliferation assays (MTT) assay over a range of doses of the drug as we are aware that intratumoral doses achieved clinically and doses in vitro can be quite different. If successful this analysis would validate the use of such organoid culture to predict patient response in the future. Therefore, we view this analysis as an opportunity to determine proof of principal of such technique and may have wide impact for several studies in the future.

Statistical Analysis Plan

Robertson et al (2007) gave a mean change from baseline in Ki67 of a 2.8% decline and a standard deviation of 22.5% of cells staining for Ki67 for patients receiving fulvestrant 250 mg. In the placebo group they reported a mean reduction and standard deviation of 7.1% +/- 18.0%. There was no significant difference (p=0.97) between groups. In the present study, we hypothesize that for women with cyclin D1 overexpression, high dose fulvestrant will have a higher mean reduction in Ki67 than tamoxifen. 58 patients (29 patients in each study treatment arm) will be required to detect a difference between treatments of 15% in cells staining for Ki67 (mean reduction from baseline of 5% for Ki67 level in the tamoxifen group vs. 20% in the fulvestrant group) with power 0.80 for a two-sided test at the 0.05 level. We estimate that 10% of those enrolled to the tamoxifen arm may dropout from the study; however, since fulvestrant is given as a one-time dose, we do not expect attrition from this arm of the study. To account for drop-outs 32 patients will be randomized to each arm.

Treatment assignment

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A total of 64 patients will be randomized in a 1:1 allocation (32 patients to the tamoxifen arm and 32 to the fulvestrant arm) stratified by menopausal status (pre vs. post).. Randomization will be initiated at Mount Sinai by the research pharmacy, using separate randomization lists for pre and post menopausal patients..

Endpoints

Primary endpoint:

- The change in proliferation index between core biopsy and definitive surgery as measured by the percentage of cells staining for Ki67 in each treatment arm, stratified by menopausal status.

Secondary endpoints:

- Determine whether there is a differential treatment effect between tamoxifen and fulvestrant for pre and post menopausal patients.
- The change in estrogen receptor and progesterone receptor levels between core biopsy and definitive surgery in patients treated with fulvestrant or tamoxifen.
- Determine whether tamoxifen-resistance and fulvestrant-sensitivity gene expression signatures are observed in patients with cyclinD1 overexpressing breast cancers.
- Determine whether patient's response to tamoxifen or fulvestrant correlates with the response of their primary cells in vitro.

Data Analysis:

An intent to treat analysis will be applied to this study. All primary and secondary analysis will be performed, stratified by menopausal status(pre vs. post). Primary continuous response rate of percentage of cells staining for Ki67 between treatment groups will be analyzed using stratified analysis of covariance (ANCOVA). Treatment groups will be compared by stratified analysis of covariance with respect to the outcome variable of post treatment percentage of cells staining for Ki67 with covariate baseline percentage of cells staining for Ki67, allowing for estimation of the mean change from baseline. Assumptions underlying ANCOVA will be evaluated. Transformation of the data will be undertaken if appropriate. A treatment diary will be used for patients enrolled to the tamoxifen arm to record all treatment doses and to help account for any missing data.

A secondary analysis will be a per protocol analysis. Potential interaction will be tested for treatment by stratum (menopausal status) to determine if there exists a differential treatment effect for pre and post menopausal subjects. The mean change in levels (expressed as a percentage of cells staining positive within the breast tumor) of ER (and PR) between pre-treatment and post-treatment will be compared between treatment arms by ANCOVA stratified by menopausal status as in the statistical analysis of the primary objective.

Gene signatures that distinguish cells that are responsive and those that are resistant to tamoxifen have been established using cell lines in vitro. Gene signatures for responsiveness/resistance to fulvestrant have also been established. Presence of these gene signatures will be determined for all patients in this study. Patients having signatures for responsiveness or resistance to tamoxifen (fulvestrant) will be compared with respect to change in Ki67 after treatment with tamoxifen (fulvestrant) by stratified ANCOVA.

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To determine whether patient's response to tamoxifen or fulvestrant correlated with response in their primary cells in vitro, cells from primary tumors from patients will be grown in vitro. Proliferation assays over a range of doses in vitro, of the same drug that the patient received will be conducted. Correlations between in vitro assay results and patient assay results will be examined by Pearson correlation or Spearman correlation for data not normally distributed for pre- and post-menopausal patients. Dose response will also be analyzed by regression analysis.

Stopping Rule:

Keeping in mind the potential proliferative effect of tamoxifen, this trial will include an early stopping rule, where if the mean change from baseline in the Ki67 proliferation index among the first fourteen patients in the tamoxifen arm is an increase of at least 25%, that arm of the trial will be terminated. Although fulvestrant is unlikely to cause acceleration of proliferation, the same stopping rule will be applied to the fulvestrant arm as well. A mean increase of 25% in 14 patients would give an 80% confidence interval that the true mean Ki67 increase in a treatment arm is in the range of 16% to 34%.

An additional stopping rule will be implemented based on the number of patients experiencing a high level of proliferation (50% or higher). If 2 of the first 10 patients in a treatment arm experience an increase from baseline in the Ki67 proliferation index of 50% or more, then that treatment arm will be terminated.

PATIENT ELIGIBILITY

Inclusion and Exclusion Criteria

Inclusion criteria:

- Written informed consent prior to beginning specific protocol procedures, including expected cooperation of the patients for the study treatment regimen and follow-up, must be obtained and documented according to the local regulatory requirements
- Adult women greater than 18 years of age
- Eastern Cooperative Oncology Group (ECOG) performance status (PS) 0-2
- New diagnosis of invasive cyclin D1 +, ER+, PR +/-, Her2- breast cancer
    - Cyclin D1 positive as defined as a total immunohistochemical score of 5 or greater
    - Hormone receptor positive as defined as ≥ 10% positive stained cells
    - HER2-normal (IHC score 0-1 or FISH negative [in-situ hybridization (ISH) ratio <= 2.0 status])
- Tumor size at least 5 mm with planned primary surgery at Mount Sinai
- A negative urine dipstick pregnancy test

Exclusion criteria:

- Estrogen receptor negative invasive breast carcinoma as defined as less than 10% stained cells
- Prior antiestrogen therapy except in the context of fertility treatment
- Tumor size less than 5 mm
- Prior diagnosis of thrombosis or known hypercoagulable state
- Known history of bleeding diathesis

- Known liver disease
- Prior treatment with neoadjuvant therapy
- Inflammatory breast cancer defined as clinically significant erythema of the breast and/or documented dermal lymphatic invasion (not direct skin invasion by tumor or peau d'orange without erythema).
- Current severe or uncontrolled systemic disease
- Pregnancy or lactation period. Patients of childbearing potential must implement adequate non-hormonal contraceptive measures (barrier methods, intrauterine contraceptive devices) during study treatment.
- Prior malignancy (including invasive or ductal in-situ breast cancer) within 5 years prior to randomization, except curatively treated basal cell carcinoma of the skin and carcinoma in situ of the cervix.

STUDY TREATMENT PLAN [see email attachment]

Time and Events

	Screening	Treatment prior to surgery	*Surgery
Days		1-14	*15-18
Physical Examination	**X**		
Vital Signs	**X**		
Weight	**X**		
Performance Status	**X**		
Urine Pregnancy Test	**X**		

*** subject active participation in this study ends after 14 days. The subject will move on to surgery, off study.**

Dosage and Administration
Newly diagnosed premenopausal and postmenopausal breast cancer patients with ER+ tumors in whom primary surgery is planned will be recruited during their initial consultation with surgeons at the Dubin Breast Center or Mount Sinai St. Luke's. After giving informed consent, patients will be randomized to receive fourteen (14) days of a study treatment regimen with tamoxifen 20 mg orally daily (Arm A) versus a single dose of fulvestrant on day 1 only, 750 mg (three 5 mL injections slowly over 1-2 minutes per injection in the buttocks) (Arm B) between the initial core biopsy and definitive excisional surgery.

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Duration of Therapy

Patients will be treated for 1 cycle. For this protocol, a cycle is defined as 14 days. Patients will be randomized to receive fourteen (14) days of treatment with tamoxifen daily (Arm A) versus a single dose of fulvestrant on day 1 only (Arm B)

Protocol defined study therapy ends after 14 days. The planned surgery to be performed between day 15 and day 18 will be performed at the surgeon's discretion and will not be part of the study observation.

Duration of Followup

For research purposes, subjects will be clinically followed with two phone calls, at day 7 and day 13, during the fourteen (14) day treatment window. Adverse events will be collected during the fourteen day study treatment period with tamoxifen or fulvestrant, leading up to definitive surgery. Adverse events that remain unresolved at the end of the 14 day treatment period will be addressed by the treating medical oncologist

Toxicities and Dosing Delays/Modifications

Both tamoxifen and fulvestrant are part of anti-estrogen standard of care in treatment of patients with both early stage and advanced forms of breast cancer. They have been extensively studied and their side effect / toxicity profiles are well characterized. Anti-estrogen therapy in pre- and postmenopausal women may induce headache, mood changes, hot flashes, and vaginal discharge. Longer treatment durations of tamoxifen have been associated with a rare risk of the development of uterine carcinoma and thromboembolic events such as deep vein thrombosis and pulmonary embolus. Patients randomized to fulvestrant will also be exposed to risks from intramuscular injection such as local injection site pain.

Removal of Patients from Therapy

Both agents in this study (tamoxifen and fulvestrant) have been used extensively in clinical practice with well-known side effects. Likewise both agents have been previously used in the pre-operative setting of a clinical trial (Young 2008). While several studies indicate that tamoxifen does not provide benefit to patients with cyclin D1 positive tumors, the study by Jirstrom et al, actually suggests that tamoxifen may accelerate the growth of tumors (Jirstrom 2005). Pre-clinical data in cell lines supports this conclusion as well. Thus, there is a concern that giving tamoxifen pre-operatively to patients with cyclin D1 positive tumors could accelerate tumor growth. This concern is however limited by two facts; first the length of the treatment in this study is very short and second, tamoxifen is currently used in the neo-adjuvant setting in Europe and less frequently, in the US. Keeping in mind the potential proliferative effect of tamoxifen, this trial will include an early stopping rule, where if the mean change from baseline in the Ki67 proliferation index among the first fourteen patients in the tamoxifen arm is an increase of at least 25%, recruitment of patients to the tamoxifen arm of the trial will be stopped. Although fulvestrant is unlikely to cause acceleration of proliferation, the same stopping rule will be applied to the fulvestrant arm as well. A mean increase of 25% in 14 patients would give an 80% confidence interval that the true mean Ki67 increase in a treatment arm is in the range of 16% to 34%.

An additional stopping rule will be implemented based on the number of patients experiencing a high level of proliferation (50% or higher). If 2 of the first 10 patients in a treatment arm experience an increase from baseline in the Ki67 proliferation index of 50% or more, then that treatment arm will be terminated.

Patient Withdrawal from Study Participation

Participation in the study is voluntary. Subjects may choose to withdraw at any point. They need only to inform a member of the study team. A letter of withdrawal would be the ideal procedure; however, verbal notification to any of the research study personnel would be sufficient. The request would be documented in the medical record. Already collected data will be used to aid study interpretation however, no new data would be collected.

STUDY PROCEDURES

The principal investigator and study coordinator will be responsible for data accuracy and completeness. Data will be collected electronically using Mount Sinai's secure Web-based Electronic Research Application Portal (ERAP).

The study will take place in the Dubin Breast Center at Mount Sinai Hospital, Mount Sinai West and Mount Sinai St. Luke's.

Newly diagnosed breast cancer patients with ER+ tumors in whom primary surgery is planned at Mount Sinai will be recruited during their initial consultation with surgeons at the Dubin Breast Center *or Mount Sinai St. Luke's.* Patients agreeable to participation in the study will have their tumor assessed for cyclin D1. Patients with cyclin D1 positive tumors will undergo the following screening procedures.

Baseline Screening Procedures:

Subjects will have the following standard blood tests, urine tests and physical exams performed as part of routine care for subjects with breast cancer:

- A medical history, which includes questions about the patient's medical and psychiatric history, current medications, and any allergies.
- Standard physical exam which includes an examination of the whole body that will include measurements of height, weight, body temperature, blood pressure and heart rate.
- Urine test, which will be utilized to perform a urine dipstick pregnancy test.
- Performance status, which evaluates how one is able to carry on one's usual activities

The results of these tests will be used to establish the subject's baseline physical condition prior to enrollment in the protocol.

Randomization to study Regimen

After giving informed consent, patients will be randomized to receive one 14-day cycle of either:

Arm A

- Fourteen (14) days of treatment with tamoxifen 20 mg orally each day

Or

Arm B

- Fulvestrant 750 mg (three (3) 5 mL injections slowly over 1-2 minutes per injection in the buttocks) on **day 1 only**

The initial core biopsy for routine diagnosis will be performed prior to the 14 day study regimen. Then the subjects will receive 14 days of Fulvestrant or Tamoxifen as described above. After the

14 day study regimen is complete, the subjects will move on to definitive excisional surgery, between day 15 to day 18, at Mount Sinai, which will be performed at their surgeon's discretion.

CORRELATIVE LABORATORY RESEARCH

Laboratory Determinations and Pathology Review

A study pathologist will determine Ki67 and cyclin D1 status on the initial core biopsy and the excisional surgical specimen. Scoring of the ER, PR and Her2, will be performed using the standard clinical method used for all breast cancer patients at Mount Sinai. For patients with 1+ or higher staining for Her2 on IHC, ISH will be sent. This analysis will be performed by the pathology department as part of the standard clinical management.

The intensity and distribution of cyclin D1 staining will be semiquantitatively scored using the Allred scoring method. The intensity of the immunohistochemical reaction by light microscopy will be recorded as 0 (negative) when no staining of the nuclei is seen even at high magnification, 1+ (weak) if staining is visible only at high magnification, 2+ (moderate) when staining is readily visible at low magnification and 3+ (strong) if staining is strikingly positive even at low power magnification. The extent of tumor cell nuclei showing positive staining will be scored as 0 (<10%), 1 (11-25%), 2 (26-50%), 3 (51-75%), 4 (76-90%), and 5 (>90%). Scores for intensity and extent will then be totaled to assign a tumor as having negative (0), weak (1 to 3), moderate (4 to 6), or strong (7 to 8) cyclin D1 expression as has been standardized by Reis-Filho and colleagues. A total score of greater than or equal to 5 will be used as the cut off for cyclin D1 positivity as per the retrospective study conducted by Cascetta and colleagues.

Following examination by the study pathologist of the Ki67 immunohistochemically stained sections and an additional section stained with H&E, areas of viable tumor tissue within the cores will be identified, the extent of antibody staining assessed using appropriate protocols for digital image capture and analysis. It is our expectation that the cores will show considerable intratumoral heterogeneity in the extent of staining and that individual strongly staining nuclei may be interspersed among weakly or negatively stained cells. In order to address the problem of intratumoral heterogeneity, we will obtain digital images of the entire tissue section and determine the number of positively stained nuclei per 100,000 μm^2 of viable tumor tissue.

In addition, manual scoring of cyclinD1, STAT3, STAT5 and Ki67 will also be performed. The manual scoring will be performed as described previously where a score for percentage of cells stained and a score for intensity of scoring is obtained and then added to obtain an Allred score.

For the ER, we predict that pre-treatment specimens from both arms will show evidence of ER staining in the nucleus. In post-treatment specimens, the fulvestrant alone arm will show reduced nuclear staining of ER and some cytoplasmic staining of ER. The staining of ER will be assessed with the 6F11 monoclonal antibody (Vision Biosystem) as this is the antibody used clinically at this time. Intensity will be scored (0, 1+, 2+, 3+) by the level of staining in the nucleus and cytoplasm. ER will also be expressed as a percentage (0-100%) of cells staining positive within the breast tumor.

For the PR, we predict that pre-treatment specimens from both arms will show evidence of PR staining in the nucleus. In post-treatment specimens, the fulvestrant alone arm will show reduced staining of PR given the downregulation of the ER by fulvestrant. Intensity will be scored (0, 1+, 2+, 3+). PR will also be expressed as a percentage (0-100%) of cells staining positive within the breast tumor.

Tunel assay will be used to determine the percentage of cells that underwent apoptosis. Paraffin embedded sections will be stained using the apoptosis detection kit TACS-KL Basic (TA100, R&D systems Inc, Minneapolis) according to the manufacturer's protocol. Sections will be counterstained with 0.2% hematoxylin to detect intact nuclei. Our data suggest that more apoptotic cells will be detected in

the cyclinD1 overexpressing tumors in response to fulvestrant compared to the tamoxifen. This analysis will therefore allow us to test this possibility in humans. Further, the analysis of the rate of apoptosis will provide an independent readout of the effect of treatments in addition to proliferation measured by Ki67.

For tumors greater than 1 cm, a small portion of the surgical specimen not needed for diagnostics will be divided: half will be frozen for subsequent RNA extraction and expression profiling, and half will be utilized for primary tissue culture.

For RNA extraction and gene expression profiling, a gene signature that distinguishes cells that are responsive to tamoxifen and those that are resistant to tamoxifen has been established using cell lines in vitro. Similarly, a gene signature of the same cells in response to fulvestrant was also determined. Using these signatures obtained in vitro, we will compare whether the same gene signature characterizes tumors that are resistant or sensitive to tamoxifen and fulvestrant respectively in patients samples using selected gene by nanostring analysis by RNA extraction from paraffin embedded sections.

In order to assess response of a patient's primary cells in vitro, the organoid core facility has recently developed a method by which cells from primary tumors from patients can be grown in vitro. When samples are available for culture in vitro, we will test whether the cells derived from individual patients respond the same as the tumor in vivo in the same patient. For this experiment, cells in culture will be treated with the same drug (tamoxifen or fulvestrant) as the patient has received. We will conduct standard proliferation assays (MTT) assay over a range of doses of the drug as we are aware that intratumoral doses achieved clinically and doses in vitro can be quite different. If successful this analysis would validate the use of such organoid culture to predict patient response in the future. Therefore, we view this analysis as an opportunity to determine proof of principal of such technique and may have wide impact for several studies in the future.

Removal of Subjects

As stated earlier, given that data from Jirstrom and colleagues suggests that tamoxifen may accelerate the growth of cyclin D1 positive tumors, an early stopping rule will be employed. Thus, if t the mean change from baseline in the Ki67 proliferation index among the first fourteen patients in the tamoxifen arm is an increase of at least 25%, recruitment of patients to the tamoxifen arm of the trial will be stopped. Although fulvestrant is unlikely to cause acceleration of proliferation, the same stopping rule will be applied to the fulvestrant arm as well. A mean increase of 25% in 14 patients would give an 80% confidence interval that the true mean Ki67 increase in a treatment arm is in the range of 16% to 34%.

An additional stopping rule will be implemented based on the number of patients experiencing a high level of proliferation (50% or higher). If 2 of the first 10 patients in a treatment arm experience an increase from baseline in the Ki67 proliferation index of 50% or more, then that treatment arm will be terminated.

MEASUREMENT OF EFFECT

Robertson et al (2007) gave a mean change from baseline in Ki67 of a 2.8% decline and a standard deviation of 22.5% of cells staining for Ki67 for patients receiving fulvestrant 250 mg. In the placebo group they reported a mean reduction and standard deviation of 7.1% +/- 18.0%. There was no significant difference (p=0.97) between groups. In the present study, we hypothesize that for women with cyclin D1 overexpression, high dose fulvestrant will have a higher mean reduction in Ki67 than tamoxifen. 58 patients (29 patients in each study treatment arm) will be required to detect a difference between treatments of 15% in cells staining for Ki67 (mean reduction from baseline of 5% for Ki67 level in the tamoxifen group vs. 20% in the fulvestrant group) with power 0.80 for a two-sided test at the 0.05 level. We estimate that 10% of those enrolled to the tamoxifen arm may dropout from the study; however, since fulvestrant is

given as a one-time dose, we do not expect attrition from this arm of the study. To account for drop-outs 32 patients will be randomized to each arm.

ADVERSE EVENTS

Monitoring

The principal investigator and study coordinator will be responsible for data accuracy and completeness. Subjects will be monitored for side effects of study medication, medication compliance, and birth control practices/pregnancy. Data will be collected electronically using Mount Sinai's secure Web-based Electronic Research Application Portal (ERAP).

Safety and data information will be reviewed by the PI and attending breast physicians at Dubin Breast Center and Mount Sinai St. Luke's. as per routine standard care procedures for post breast cancer surgical patients and ongoing laboratory testing procedures and data collection as described in the protocol.

Subjects will only receive only one cycle of study medication. Afterward they will receive treatment with surgery and postsurgical follow-up as their conditions warrant.

Subjects will be evaluated for side effects using the CTC criteria version 4.0
If a temporary or permanent suspension of our study occurs, we will notify the IRB at once.

The principal data and safety monitor will be the PI, Amy Tiersten, MD. The co-investigator who will also oversee data and safety monitoring will be Hank Schmidt, MD. Both of these physicians routinely care for cancer patients being treated with endocrine therapies and both have experience conducting clinical research.

Definitions

Definition of adverse event

An adverse event is the development of an undesirable medical condition or the deterioration of a pre-existing medical condition following or during exposure to a pharmaceutical product, whether or not considered causally related to the product. An undesirable medical condition can be symptoms (eg, nausea, chest pain), signs (eg, tachycardia, enlarged liver) or the abnormal results of an investigation (eg, laboratory findings, electrocardiogram). In clinical studies, an AE can include an undesirable medical condition occurring at any time, including run-in or washout periods, even if no study treatment has been administered. The term AE is used to include both serious and non-serious AEs.

Definitions of serious adverse event

A serious adverse event is an AE occurring during any study phase (ie, run-in, treatment, washout, follow-up), that fulfils one or more of the following criteria:

- Results in death
- Is immediately life-threatening
- Requires in-patient hospitalization or prolongation of existing hospitalization
- Results in persistent or significant disability/incapacity or substantial disruption of the ability to conduct normal life functions

- Is an important medical event that may jeopardize the subject or may require medical intervention to prevent one of the outcomes listed above.

The causality of SAEs (their relationship to all study regimens/procedures) will be assessed by the investigator(s) and communicated to AstraZeneca.

Recording of adverse events

Time period for collection of adverse events

Adverse events will be collected during the fourteen day treatment regimen with tamoxifen or fulvestrant leading up to definitive surgery.

Follow-up of unresolved adverse events

Adverse events that remain unresolved at the end of the two week study regimen period will be addressed by the treating medical oncologist.

The following variables will be collected for each AE:

- AE (verbatim)
- The date when the AE started and stopped
- Intensity or changes in intensity where appropriate
- Common Terminology Criteria for Adverse Events (CTCAE- version 4.0), to describe the severity of organ toxicity for patients receiving cancer therapy. Toxicity is graded as mild (Grade 1), moderate (Grade 2), severe (Grade 3), or life-threatening (Grade 4), with specific parameters according to the organ system involved. Death (Grade 5) is used for some of the criteria to denote a fatality.
- Whether the AE is serious or not
- Investigator causality rating against the Investigational Product (yes or no)
- Action taken with regard to investigational product
- AE caused subject's withdrawal from study *(*yes or no*)*
- Outcome

In addition, the following variables will be collected for SAEs:

- Date AE met criteria for serious AE
- Date Investigator became aware of serious AE
- AE is serious due to
- Date of hospitalization
- Date of discharge
- Probable cause of death
- Date of death
- Autopsy performed
- Causality assessment in relation to Study procedure(s)
- Causality assessment in relation to Other medication
- Causality assessment in relation to Additional Study Drug
- Description of AE.

It is important to distinguish between serious and severe AEs. Severity is a measure of intensity whereas seriousness is defined by the criteria in the section entitled, "Definitions of serious adverse event." An AE of severe intensity need not necessarily be considered serious. For example, nausea that persists for several hours may be considered severe nausea, but not a

SAE. On the other hand, a stroke that results in only a limited degree of disability may be considered a mild stroke but would be a SAE.

Adverse Events based on signs and symptoms

When collecting AEs, the recording of diagnoses is preferred (when possible) to recording a list of signs and symptoms. However, if a diagnosis is known and there are other signs or symptoms that are not generally part of the diagnosis, the diagnosis and each sign or symptom will be recorded separately.

Adverse Events based on examinations and tests

Deterioration as compared to baseline in protocol-mandated vital signs should therefore only be reported as AEs if they fulfill any of the SAE criteria or are the reason for discontinuation of treatment regimen.

If deterioration in a vital sign is associated with clinical signs and symptoms, the sign or symptom will be reported as an AE and the associated vital sign will be considered as additional information. In the absence of clinical signs or symptoms, clinically relevant deteriorations in non-mandated parameters should be reported as AE(s).

Any new or aggravated clinically relevant abnormal medical finding at a physical examination as compared with the baseline assessment will be reported as an AE.

Reporting of serious adverse events to sponsor

Investigators and other site personnel must inform the FDA, via a MedWatch/AdEERs form, of any serious or unexpected adverse events that occur in accordance with the reporting obligations of 21 CFR 312.32, and will concurrently forward all such reports to AZ. A copy of the MedWatch/AdEERs report must be faxed to AstraZeneca at the time the event is reported to the FDA. It is the responsibility of the investigator to compile all necessary information and ensure that the FDA receives a report according to the FDA reporting requirement timelines and to ensure that these reports are also submitted to AstraZeneca at the same time.

When reporting to AstraZeneca, a cover page should accompany the MedWatch/AdEERs form indicating the following:

- Investigator Sponsored Study (ISS)
- The investigator IND number assigned by the FDA
- The investigator's name and address
- The trial name/title and AstraZeneca ISS reference number

Investigative site must also indicate, either in the SAE report or the cover page, the causality of events in relation to all study medications and if the SAE is related to disease progression, as determined by the principal investigator.

Send SAE report and accompanying cover page by way of fax to AstraZeneca's designated fax line: 1-866-984-7229

Serious adverse events that do not require expedited reporting to the FDA need to be reported to AstraZeneca preferably using the MedDRA coding language for serious adverse events.

This is not a blinded trial.

All SAEs have to be reported to AstraZeneca, whether or not considered causally related to the investigational product. All SAEs will be documented. The investigator is responsible for informing the IRB and/or the Regulatory Authority of the SAE as per local requirements.

Stopping Rules
Both agents in this study (tamoxifen and fulvestrant) have been used extensively in clinical practice with well-known side effects. Likewise both agents have been previously used in the pre-operative setting of a clinical trial (Young 2008). While several studies indicate that tamoxifen does not provide benefit to patients with cyclin D1 positive tumors, the study by Jirstrom et al, actually suggests that tamoxifen may accelerate the growth of tumors (Jirstrom 2005). Pre-clinical data in cell lines supports this conclusion as well. Thus, there is a concern that giving tamoxifen pre-operatively to patients with cyclin D1 positive tumors could accelerate tumor growth. This concern is however limited by two facts, first the length of the treatment regimen in this study is very short and second, tamoxifen is currently used in the neo-adjuvant setting in Europe and less frequently in the US. Please see “Removal of Patients from Therapy” section for further details.

DRUG INFORMATION

Fulvestrant

For each drug provide the following:

- Other names **Faslodex**
- Classification - type of agent: **Anti-estrogen**
- Mode of action: blocks estrogen in the body, antineoplastic effect against breast cancer in post- menopausal women
- Storage and stability: **Faslodex, an injection for intramuscular administration, is supplied as 5-mL prefilled syringes containing 50 mg/mL fulvestrant.**
- Protocol dose: **750 mg IM in 3 divided doses day 1.**
- Preparation: **The single dose and multiple dose PK parameters for the 500 mg dosing regimen with an additional dose (AD) at Day 15 are reported in Table 3. The additional dose of Faslodex given two weeks after the initial dose allows for steady state concentrations to be reached within the first month of dosing.**
- Route of administration for this study: **IM injection into buttock muscle**.
- Incompatibilities: **No known drug interactions.**
- Availability**: Provided by AstraZeneca free of charge**.
- Side effects**: bone pain, muscle pain, joint pain nausea vomiting loss of appetite, constipation, weakness, feeling tired, cough, trouble breathing, abnormal liver function tests, hot flashes, injection site pain.**

- Nursing implications:

Return and Retention of Study Drug

N/A

Tamoxifen

- Other name: **Nolvadex**
- Classification - type of agent: **Non-steroidal antiestrogen**
- Mode of action: **antineoplactic agent effective against breast cancer**
- Storage and stability: **Store at room temperature**
- Protocol dose: **20 mg**.
- Preparation: **Tablets**
- Route of administration for this study: **PO**
- Incompatibilities: **erythromycin, cyclosporin, nifedipine and diltiazem competitively inhibited formation of N-desmethyl tamoxifen. Tamoxifen reduced the plasma concentration of letrozole by 37% when these drugs were coadministered. Rifampin, a cytochrome P-450 3A4 inducer reduced tamoxifen AUC. Tamoxifen should not be coadministered with anastrozole.**
- Availability: **Provided by the study sponsor free of charge.**
- Side effects: ***may include*** **cataracts, changes in menstrual period, constipation, diarrhea, edema (swelling), fatigue, fluid retention, flushing, headache, hot flashes, high blood pressure, muscle pain, nausea, shortness of breath, vaginal discharge, vomiting, weight loss**.

Return and Retention of Study Drug

N/A

CORRELATIVES/SPECIAL STUDIES

N/A, Laboratory research will be conducted on tumor specimens obtained as part of routine standard care.

Following examination by the study pathologist of the Ki67 immunohistochemically stained sections and an additional section stained with H&E, areas of viable tumor tissue within the cores will be identified, the extent of antibody staining assessed using appropriate protocols for digital image capture and analysis. It is our expectation that the cores will show considerable intratumoral heterogeneity in the extent of staining and that individual strongly staining nuclei may be interspersed among weakly or negatively

stained cells. In order to address the problem of intratumoral heterogeneity, we will obtain digital images of the entire tissue section and determine the number of positively stained nuclei per 100,000 μm^2 of viable tumor tissue

The intensity and distribution of cyclin D1 staining will be semiquantitatively scored using the Allred scoring method. The intensity of the immunohistochemical reaction by light microscopy will be recorded as 0 (negative) when no staining of the nuclei is seen even at high magnification, 1+ (weak)if staining is visible only at high magnification, 2+ (moderate when staining is readily visible at low magnification and 3+ (strong) if staining is strikingly positive even at low power magnification. The extent of tumor cell nuclei showing positive staining will be scored as 0 (<10%), 1 (11-25%), 2 (26-50%), 3 (51-75%), 4 (76-90%), and 5 (>90%). Scores for intensity and extent will then be totaled to assign a tumor as having negative (0), weak (1 to 3), moderate (4 to 6), or strong (7 to 8) cyclin D1 expression as has been standardized by Reis-Filho and colleagues. A total score of greater than or equal to 5 will be used as the cut off for cyclin D1 positivity as per the retrospective study conducted by Cascetta and colleagues.

In addition, manual scoring of cyclinD1, STAT3, STAT5 and Ki67 will also be performed. The manual scoring will be performed as described previously where a score for percentage of cells stained and a score for intensity of scoring is obtained and then added to obtain an Allred score.

For the ER, we predict that pre-treatment specimens from both arms will show evidence of ER staining in the nucleus. In post-treatment specimens, the fulvestrant alone arm will show reduced nuclear staining of ER and some cytoplasmic staining of ER. The staining of ER will be assessed with the 6F11 monocloncal antibody (Vision Biosystem) as this is the antibody used clinically at this time. Intensity will be scored (0, 1+, 2+, 3+) by the level of staining in the nucleus and cytoplasm. ER will also be expressed as a percentage (0-100%) of cells staining positive within the breast tumor.

For the PR, we predict that pre-treatment specimens from both arms will show evidence of PR staining in the nucleus. In post-treatment specimens, the fulvestrant alone arm will show reduced staining of PR given the downregulation of the ER by fulvestrant. Intensity will be scored (0, 1+, 2+, 3+). PR will also be expressed as a percentage (0-100%) of cells staining positive within the breast tumor.

Tunel assay will be used to determine the percentage of cells that underwent apoptosis, Paraffin embedded sections will be stained using the apoptosis detection kit TACS-KL Basic (TA100, R&D systems Inc, Minneapolis) according to the manufacturer's protocol. Sections will be counterstained with 0.2% hematoxylin to detect intact nuclei. Our data suggest that more apoptotic cells will be detected in the cyclinD1 overexpressing tumors in response to fulvestrant compared to the tamoxifen. This analysis will therefore allow us to test this possibility in humans. Further, the analysis of the rate of apoptosis will provide an independent readout of the effect of treatments in addition to proliferation measured by Ki67.

For tumors greater than 1 cm, a small portion of the surgical specimen not needed for diagnostics will be divided: half will be frozen for subsequent RNA extraction and expression profiling, and half will be utilized for primary tissue culture.

For RNA extraction and gene expression profiling, a gene signature that distinguishes cells that are responsive to tamoxifen and those that are resistant to tamoxifen has been established using cell lines in vitro. Similarly, a gene signature of the same cells in response to fulvestrant was also determined. Using these signatures obtained in vitro, we will compare whether the same gene signature characterizes tumors that are resistant or

sensitive to tamoxifen and fulvestrant respectively in patients samples using selected gene by nanostring analysis by RNA extraction from paraffin embedded sections.

In order to assess response of a patient's primary cells in vitro, the organoid core facility has recently developed a method by which cells from primary tumors from patients can be grown in vitro. When samples are available for culture in vitro, we will test whether the cells derived from individual patients respond the same as the tumor in vivo in the same patient. For this experiment, cells in culture will be treated with the same drug (tamoxifen or fulvestrant) as the patient has received. We will conduct standard proliferation assays (MTT) assay over a range of doses of the drug as we are aware that intratumoral doses achieved clinically and doses in vitro can be quite different. If successful this analysis would validate the use of such organoid culture to predict patient response in the future. Therefore, we view this analysis as an opportunity to determine proof of principal of such technique and may have wide impact for several studies in the future.

Study Design/Study Endpoints

Robertson et al (2007) gave a mean change from baseline in Ki67 of a 2.8% decline and a standard deviation of 22.5% of cells staining for Ki67 for patients receiving fulvestrant 250 mg. In the placebo group they reported a mean reduction and standard deviation of 7.1% +/- 18.0%. There was no significant difference (p=0.97) between groups. In the present study, we hypothesize that for women with cyclin D1 overexpression, high dose fulvestrant will have a higher mean reduction in Ki67 than tamoxifen. 58 patients (29 patients in each study arm) will be required to detect a difference between study treatments regimens of 15% in cells staining for Ki67 (mean reduction from baseline of 5% for Ki67 level in the tamoxifen group vs. 20% in the fulvestrant group) with power 0.80 for a two-sided test at the 0.05 level. To account for drop-outs 32 patients will be randomized to each arm.

Primary endpoint:

- The change in proliferation index between core biopsy and definitive surgery as measured by the percentage of cells staining for Ki67 in each treatment arm.

Secondary endpoints:

- The change in estrogen receptor and progesterone receptor levels between core biopsy and definitive surgery in patients treated with fulvestrant or tamoxifen.
- Determine whether tamoxifen-resistance and fulvestrant-sensitivity gene expression signatures are observed in patients with cyclinD1 overexpressing breast cancers.
- Determine whether patient's response to tamoxifen or fulvestrant correlates with the response of their primary cells in vitro.

Sample Size and Accrual

Dubin Breast Center and *Mount Sinai St. Luke's* encounters over 300 breast cancers per year and offers all resources required for multidisciplinary diagnosis and treatment of breast cancer in premenopausal and postmenopausal women targeted in this study. Patients seen in Surgical Oncology clinic at the Dubin Breast Center *or Mount Sinai St. Luke's* referred for treatment of breast carcinoma will be identified and recruited by surgeons at the time of their initial office visit. This protocol will randomize 64 ER+, cyclin D1 + women with breast cancer. It is expected that 100 patients will be eligible for this

study and that approximately 20 will enroll per year. Thus, this trial is expected to take 3 years to accrue fully.

1.0 STUDY MANAGEMENT

1.1 Conflict of Interest

Any research personnel who has a conflict of interest with this study (patent ownership, intellectual property, royalties, or financial gain greater than the minimum allowable by their institution, etc.) must declare their conflict of interest to the appropriate institutional review bodies. Local institutional conflict of interest policies will be followed for all research personnel associated with the research project.

11.2 Institutional Review Board (IRB) Approval and Consent

It is expected that the IRB will have the proper representation and function in accordance with federally mandated regulations. The IRB will approve the consent form and protocol.

In obtaining and documenting informed consent, the investigator will comply with the applicable regulatory requirement(s), and will adhere to Good Clinical Practice (GCP) and to ethical principles that have their origin in the Declaration of Helsinki.

Before recruitment and enrollment onto this study, the patient will be given a full explanation of the study and will be given the opportunity to review the consent form. Each consent form must include all the relevant elements currently required by the FDA Regulations and local or state regulations. Once this essential information has been provided to the patient and the investigator is assured that the patient understands the implications of participating in the study, the patient will be asked to give consent to participate in the study by signing an IRB-approved consent form.

Prior to a patient's participation in the trial, the written informed consent form will be signed and personally dated by the patient and by the person who conducted the informed consent discussion.

1.3 Required Documentation

This is not a multi-institutional site study coordinated by MSSM.

1.4 Registration Procedures

All patients must be enrolled onto trial through the Cancer Clinical Trials Office Central Registration process. Prior to registration, a member of the study staff must scan and email the following documents as individual PDF files to the Central Registration Mailbox (central.registration@mssm.edu) with a cc to the Central Registrars.

- Signed Informed Consent(s)
- Signed CCTO Registration Form
- Signed Eligibility Checklist
- Additional supporting documentation (i.e. lab/scan reports) may be included at the study teams' discretion.

The designated Central Registrar will review all received documents for consistency and completeness.

- If there is any concern or discrepancy noted, the study staff member who originated the central registration request will be contacted immediately for clarification.

If the patient is deemed eligible for study enrollment based on a thorough review by the Central Registrar, the patient will be entered into the CTMS system and a Registration Confirmation Letter is generated and sent to the following individuals:

- Study team
- Treating Physician
- Research Infusion Nurse designee
- Research Pharmacy

DATA MANAGEMENT AND MONITORING/AUDITING

MSSM Principal Monitor
Team Member:
Last Name: **Tiersten**
First Name: **Amy**
Academic Title: **Professor**
Department: **Hematology/Medical Oncology**
Mailing Address: **Dubin Breast Center**
Phone: **1176 Fifth Avenue**
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Tel: **212-241-3300**
Fax: **646-537-9639**
E-mail: **amy.tiersten@mssm.edu**

MSSM Additional Monitor
Team Member: **Co-Investigator**
Last Name: **Schmidt,**
First Name: **Paul**
Academic Title: **Assistant Professor**
Department: **Surgery**
Mailing Address: **Dubin Breast Center, 1176 Fifth Avenue, New York, NY 10029**
Phone: **212 241-5928**
Fax:
E-mail: **hank.schmidt@mountsinai.org**

Specific items that will be monitored: safety (e.g., adverse events, subject compliance with the protocol, drop outs, etc.).

The principal investigator and study coordinator will be responsible for data accuracy and completeness. Subjects will be monitored for side effects of study medication, medication compliance, and birth control practices/pregnancy. Data will be collected electronically using Mount Sinai's secure Web-based Electronic Research Application Portal (ERAP).

Safety and data information will be reviewed by the PI and attending breast physicians at Dubin Breast Center and or Mount Sinai St. Luke's as per routine standard care procedures for breast cancer surgical patients.

Subjects will only receive one cycle of the study regimen. Afterward they will receive treatment with surgery and postsurgical follow-up as their conditions warrant.

Subjects will be evaluated for side effects using the CTC criteria version 4.0
If a temporary or permanent suspension of our study occurs, we will notify the IRB at once.

Comparison in the Change of Proliferation Index between Fulvestrant and Tamoxifen in Cyclin D1 +, Estrogen Receptor + Breast Cancer
Amy Tiersten. MD, PI
Essential Elements
#13, 09/13/2017

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