ECOG-ACRIN cancer research group
Reshaping the future of patient care

E3108

A Phase II Prospective Trial Correlating Progression Free Survival with CYP2D6 Activity in Patients with Metastatic Breast Cancer Treated with Single Agent Tamoxifen

STUDY CHAIR: Vered Stearns, M.D.
STUDY CO-CHAIR: Bryan Schneider, M.D.
STUDY STATISTICIAN: Anne O'Neill, M.S.
COMMITTEE CHAIR: George W. Sledge, Jr., M.D.
DEVELOPMENTAL THERAPEUTICS AND LABORATORY CO-CHAIR: David A. Flockhart, M.D., Ph.D.
CALGB CO-CHAIR: Minetta Liu, M.D.
SWOG CO-CHAIR: Caroline Lohrisch, M.D., FRCPC
NCCTG CO-CHAIR: Matthew P. Goetz, M.D.

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STUDY PARTICIPANTS

NRG / NRG Oncology Foundation, Inc
Cancer Trials Support Unit (CTSU)*
SWOG / SWOG
ALLIANCE / Alliance for Clinical Trials in Oncology
NCIC-CTG / NCIC Clinical Trials Group
*This study is supported by the NCI Cancer Trials Support Unit (CTSU). Institutions not aligned with ECOG-ACRIN will participate through the CTSU mechanism.

ACTIVATION DATE

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Addendum #2 – 5/11
Addendum #3 – 8/12
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STUDY CHAIR

Vered Stearns, MD
Bunting-Blaustein Cancer Research Building
1650 Orleans Street, Room 145
Baltimore, MD 21231-1000
Phone: 443-287-6489
Fax: 410-614-4073
Email: vstearn1@jhmi.edu

STUDY CO-CHAIR

Bryan P. Schneider, MD
Indiana Cancer Pavilion
535 Barnhill Drive, RT473
Indianapolis, IN 46202
Phone: 317-274-6473
Fax: 317-274-8022
Email: bpschnei@iupui.edu

STUDY CHAIR LIAISON (SCL)

Stacie Jeter
Bunting-Blaustein Cancer Research Building
1650 Orleans Street, Room 186
Baltimore, MD 21231-1000
Phone: 410-614-6138
Fax: 410-614-9421
Email: sjeter1@jhmi.edu
Page 410-283-6006 for « patient in office » questions only.

SWOG CO-CHAIR

Caroline Lohrisch, MD, FRCPC
Medical Oncology
Vancouver Cancer Centre, BCCA
600 W. 10th Aveenue
Vancouver, BC V5Z 4E6
Phone: 604-877-6000, Ext. 2740
Fax: 604-877-0585
Email: clohrisch@bccancer.bc.ca

CALGB CO-CHAIR

Minetta Liu, M.D.
Lombardi Comprehensive Cancer Center
Georgetown University Hospital
3800 Reservoir Rd. NW
Washington, DC 20007-2113
Phone: 202-444-6377
Fax: 202-444-9429
Email: liumc@georgetown.edu

NCCTG CO-CHAIR

Matthew P. Goetz, M.D.
Mayo Clinic
200 First Street S.W.
Rochester, MN 55905
Phone: 507-284-4857
Fax: 507-284-1803
Email: goetz.matthew@mayo.edu

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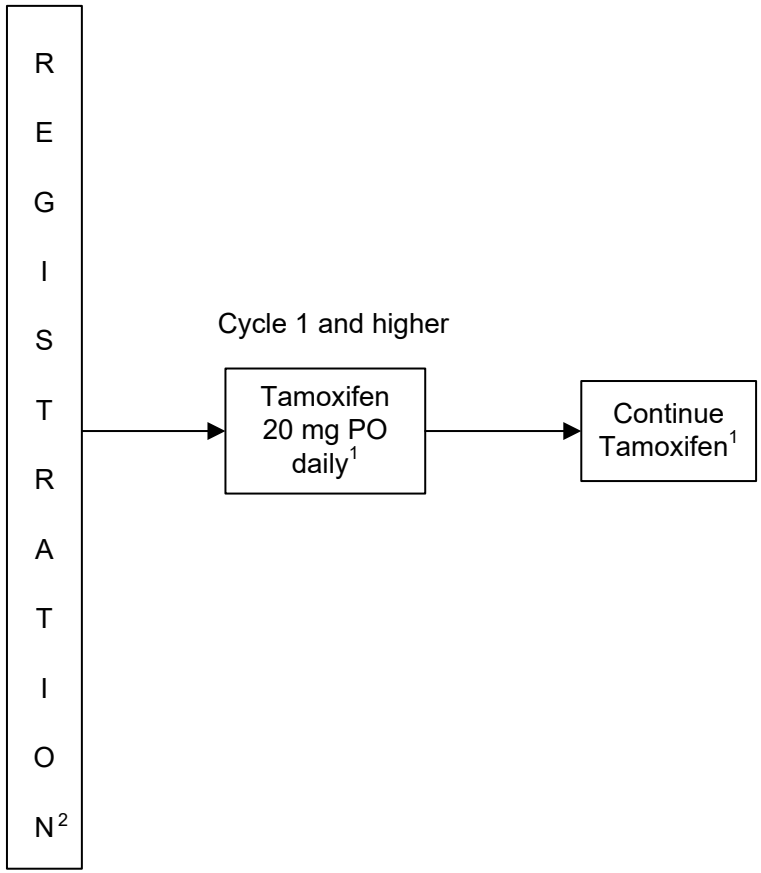
CANCER TRIALS SUPPORT UNIT (CTSU) ADDRESS AND CONTACT INFORMATION

To submit site registration documents:	**For patient enrollments:**	**Submit study data directly to the Lead Cooperative Group unless otherwise specified in the protocol:**
CTSU Regulatory Office 1818 Market Street, Suite 1100 Philadelphia, PA 19103 Phone – 1-866-651-CTSU Fax – 215-569-0206 Email: CTSURegulatory@ctsu.coccg.org (for submitting regulatory documents only)	Please refer to the patient enrollment section of the protocol for instructions on using the Oncology Patient Enrollment Network (OPEN) which can be accessed at https://www.ctsu.org/OPEN_SYSTEM/ or https://OPEN.ctsu.org. Contact the CTSU Help Desk with any OPEN-related questions at ctsucontact@westat.com.	ECOG-ACRIN Operations Office - Boston, FSTRF, 900 Commonwealth Avenue Boston, MA 02215 (ATTN: DATA). Phone # 617-632-3610 Fax # 617-632-2990 Data should be sent via postal mail (preferred), however fax is accepted. Do not submit study data or forms to CTSU Data Operations. Do not copy the CTSU on data submissions.
The most current version of the study protocol and all supporting documents must be downloaded from the protocol-specific Web page of the CTSU Member Web site located at https://www.ctsu.org. Access to the CTSU members' websiteis managed through the Cancer Therapy and Evaluation Program - Identity and Access Management (CTEP-IAM) registration system and requires user log on with CTEP-IAM username and password.		
For clinical questions (i.e. patient eligibility or treatment-related)contact the Study PI of the Coordinating Group.		
For non-clinical questions (i.e. unrelated to patient eligibility, treatment, or clinical data submission) contact the CTSU Help Desk by phone or e-mail: CTSU General Information Line – 1-888-823-5923, or ctsucontact@westat.com. All calls and correspondence will be triaged to the appropriate CTSU representative.		
For detailed information on the regulatory and monitoring procedures for CTSU sites please review the CTSU Regulatory and Monitoring Procedures policy located on the CTSU members' website https://www.ctsu.org > education and resources tab > CTSU Operations Information >CTSU Regulatory and Monitoring Policy		
The CTSU Web site is located at https://www.ctsu.org		

Schema



1 cycle = 28 days
Accrual = 240

1. Open label tamoxifen 20 mg PO daily until progression, unacceptable toxicities or any other condition outlined in Section 5.5.

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2. Collection of Baseline blood for the mandatory research studies should be done prior to protocol treatment (preferred), but may be done at the end of Cycle 3 visit. Additional blood is to be submitted at the end of Cycle 3 and at the end of treatment. See Section 7.2 and 11.

1. Introduction

Tamoxifen remains the most common endocrine intervention prescribed to women with all stages of hormone receptor positive breast cancer or to decrease the incidence of the disease. Recent data suggest that genetic variants in the cytochrome P450 2D6 (CYP2D6) gene or inhibition of the enzyme result in altered metabolic profile and reduced efficacy. The overall goal of this clinical trial is to determine whether variants in *CYP2D6* influence progression free survival and other outcomes in women with metastatic breast cancer, and to explore the role of other genetic variants.

Hypotheses:

Breast cancer patients with a CYP2D6 score of 0 (poor metabolizers) will have a reduced progression-free survival compared to those with a score of 1 or 2 (intermediate or extensive metabolizers, respectively, Hazard ratio 1.89 for poor metabolizer relative to extensive or intermediate metabolizer based on Mayo Clinic investigators).

Fewer breast cancer patients with a CYP2D6 score of 0 will be progression-free at 6 months compared to those with a score of 1 or with a score of 2. Furthermore, participants with higher endoxifen concentration will have improved time to progression compared to those with lower concentration.

We have observed significant correlation between ESR variants and tamoxifen-induced hot flashes. A correlation between ESR and tamoxifen efficacy has never been tested. We hypothesize that candidate variants in ESR1 and ESR2 may influence time to progression. In addition, other genes that are important in tamoxifen's metabolism have not been well-studied. Candidates include: ESR1 PvuII, ESR1 XbaI, and ESR2-02, UGT, and SULT1A1.

1.1 Hormone Treatment Recommendations in Breast Cancer

Despite the increase in breast cancer prevalence in recent years, disease specific mortality has declined. The improvement in survival has been attributed both to early diagnosis and to optimal local and systemic therapies, especially adjuvant endocrine treatments. While for people with hormone receptor positive breast cancer, the most common drug prescribed worldwide is tamoxifen. In the adjuvant setting, tamoxifen is prescribed for a total of five years based on cumulative data suggesting that five years of tamoxifen was better than two years but ten years were not better than five. More recently aromatase inhibitors have been introduced to the treatment of postmenopausal women and are now commonly administered for five years instead of tamoxifen or in a sequential manner following two to three years of tamoxifen for a total of five years or in the extended adjuvant setting for five years following five years of tamoxifen. National guidelines recommend that most postmenopausal women should be offered aromatase inhibitors in one of these settings. However, tamoxifen remains the drug of choice for premenopausal women and for men. Clinical trials comparing tamoxifen alone to the addition of ovarian suppression to tamoxifen or ovarian suppression and aromatase inhibitors in premenopausal women are still ongoing and results regarding the efficacy of each of those treatments and long term safety are not currently available. Therefore, ovarian suppression or aromatase inhibitors should generally not be used in premenopausal women outside of clinical trials unless tamoxifen is contraindicated.

Recommendations for adjuvant systemic therapy are based on estimates of risk of subsequent recurrence for an individual person as well as the risk for treatment related toxicity. Overall it is thought that the benefits of tamoxifen outweigh the potential risks for a population. However, it is well recognized that not all breast cancer patients will enjoy the same benefits from identical treatments. Several tumor characteristics may predict who may benefit from tamoxifen, for example high expression of estrogen receptor and progesterone receptor (ER/PR) is associated with a higher likelihood of benefit from tamoxifen compared to the presence of only one of these receptors, and no benefit is expected in the absence of hormone receptors. Only 50% of women with ER/PR expressing tumors will benefit from hormonal interventions. Other specific or aggregate tumor characteristics may predict response and are under extensive investigation.

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1.2 Pharmacogenetics of Tamoxifen Response

Host characteristics may also play an important role in predicting response to specific agents or treatments but have not been extensively studied. The recent sequencing of the human genome and new high throughput technologies have led to a greater appreciation of the role that pharmacogenetics and host factors may play as predictors of drug response. If so, assessment of host factors prior to initiation of specific agents may become standard practice. Recent pharamcogenetic data have demonstrated that tamoxifen metabolism, and perhaps efficacy, can be affected by polymorphisms in *CYP2D6* or due to interactions with drugs that inhibit the encoded enzyme. Prospective studies that included both genotype and metabolite data are not available. The overall goal of the proposal is to determine whether CYP2D6 status, other candidate genes, and tamoxifen metabolism influence outcomes of patients with metastatic breast cancer.

COBRA (Consortium On Breast Cancer Pharmacogenomics) investigators reported that women who have been on chronic adjuvant tamoxifen therapy and have been prescribed the strong CYP2D6 inhibitor such as paroxetine had a marked reduction in concentration of the active tamoxifen metabolite endoxifen. This metabolite is present in very low concentrations in the blood, however, it has 100 fold greater affinity to the estrogen receptor compared to the parent drug tamoxifen and may be therefore a very important metabolite of tamoxifen determining drug efficacy. Endoxifen's potency is similar to another metabolite 4-hydroxy tamoxifen, however it is present in 5-7 fold greater concentration compared to the latter metabolite (1-3). Based on the pharmacogenetic and metabolic studies of tamoxifen, the North Central Cancer Treatment Group (NCCTG)/Mayo Clinic and COBRA investigators determined *CYP2D6* genotype through extracting DNA from formalin-fixed paraffin-embedded archival tumor specimens of 190 post-menopausal women who received 5 years of tamoxifen 20 mg daily through a prospective, phase III trial. Women with two CYP2D6*4 variant alleles (poor metabolizers) had a worse outcome compared to those with one variant (intermediate metabolizers) and those with two wild-type alleles (extensive metabolizers) (4, 5). In addition, women who have taken a CYP2D6 inhibitor had also experienced a worse disease free survival. Overall survival was not affected. A recent update with an extended follow-up and a more comprehensive genotype analysis of these original patients showed a hazard

ratio of 4.0 in relapse-free time among poor metabolizers relative to extensive metabolizers.

Since this initial report, several other datasets have been evaluated and results have been published, however most include archival tissue or mixed populations of women who may have received chemotherapy, different duration of tamoxifen therapy, and different menopausal status (6-9). The data are summarized briefly below and in table 1 (10).

Several groups reported a correlation between *CYP2D6* variants and reduced tamoxifen efficacy (Table 1). German investigators evaluated the predictive value of genetic variants of *CYP2D6*, *CYP2C19*, and three other cytochrome P450 enzymes for tamoxifen treatment outcome. Tamoxifen-treated patients carrying the *CYP2D6* alleles that are associated with impaired formation of antiestrogenic metabolites including *4, *5, *10, *41, had significantly more recurrences of breast cancer, shorter relapse-free periods and worse event-free survival rates compared with carriers of functional alleles. Interestingly, patients with the *CYP2C19* high enzyme activity promoter variant *17 had a more favorable clinical outcome than carriers of *1, *2, and *3 alleles (11). In a Korean cohort, the authors reported that *CYP2D6* status influenced tamoxifen metabolism in the adjuvant setting, and response to the treatment in the metastatic setting in women with or without variants in the gene (12). Results from 67 Japanese patients revealed similar results (13). Finally, in the Italian chemoprevention study, women who received tamoxifen who were CYP2D6*4/*4 carriers had a higher likelihood of developing breast cancer (14). At the same time, three large studies have not demonstrated an association (7, 8, 15).

Of note, CYP2D6 does not appear to be a prognostic marker in breast cancer. In one cohort, samples were obtained from women who did not receive systemic therapy. A significant correlation was not observed between genotypes and tumor size, nodal status, histologic grade, or ER status. In the women who did not receive tamoxifen, there was no association between metabolizer status and outcome (P = 0.37) (11).

Table 1. Summary of studies to date correlating CYP2D6 variants with clinical outcome, [modified from (10)]

Author Year	Setting and Study Summary	Patients: Number and Characteristics	CYPD2D6 variants	Other Genotypes	Comments[&]	Outcomes
Goetz 2005 (4)	Adjuvant. Retrospective review of participants in a prospective study.	256 Post-menopausal. ER-positive.	*4, *6	CYP3A5*3		CYP2D6*4/*4 vs other: RFS HR 1.85, P=0.176. DFS HR 1.86, P=0.089. No association found with CYP3A5*3
Goetz 2007 (5)	Adjuvant. Retrospective Same cohort as Goetz 2005.	190 Post-menopausal. ER-positive.	*4, *6		13 patients on inhibitors	PM vs other: TTR HR 1.91, P=0.034. RFS HR 1.74, P= 0.017.
Wegman 2005 (15)	Adjuvant. Retrospective review of participants in a prospective study.	226 Post-menopausal. Some received CT. Not exclusively HR+.	*4	SULT1A1*1,*2	Tamoxifen 40mg/d x 2 yrs	CYP2D6*4 carrier Lower risk of recurrence RR 0.28, P=0.0089. SULT1A1*1,*2 No association found SULT1A1*1/*1 Lower risk of recurrence RR 0.48, P=0.0074. CYP2D6*4 and/or SULT1A1*1/*1 Lower risk of distant recurrence RR 0.38, P= 0.0041.
Wegman 2007 (8)	Adjuvant. Retrospective	677 Post-menopausal HR+	*4	CYP3A5*3, SULT1A1*1,*2 and UGT2B15*1,*2	Tamoxifen 40mg/d x 2 or 5 yrs (until 1994) or 20mg/d (after 1994)	CYP2D6*4/*4 vs CYP2D6*1 or *1/*1: improved DFS P= 0.04 and 0.05 CYP3A5*3,SULT1A1*1*2 and UGT2B15*1,*2 No association found CYP3A5*3/*3, Tam 5 ys, improved RFS HR 0.20, P=0.002.

Nowell 2005 (7)	Adjuvant. Retrospective	337 Pre- and Post-menopausal 162 on tam 175 no tam	*4	SULT1A1*1,*2 and UGT2B15*1,*2	Tamoxifen treatment details not provided	CYP2D6*4 vs other in Tam-treated Hazard Ratios: OS 0.77, 95% CI 0.32-1.81 SULT1A1*2: Trend towards increased recurrence of disease with increasing alleles Patients on tam with both UGT2B15*2 and SULT1A1*2 had decreased OS Hazard ratio 4.4, 95% CI 1.17-16.55
Schroth 2007 (11)	Adjuvant. Retrospective	486 Pre- and post-menopausal. -206 HR+ received Tam -280 received CT or no therapy 53.8% of whom were HR+.	*4,*5,*10,*4	CYP2C19*2,*3,*17 CYP2B6 CYP2C9*2,*3 CYP3A5*3	Tamoxifen treatment details not provided	Tam-treated PM vs other RFS HR 2.24, P=0.02. EFSR HR 1.89, P=0.02. CYP2C19*17 vs other CPY2C19 alleles: HR for RFT 0.45; 95% CI, 0.21-0.92 P = .03
Lim 2007 (12)	Adjuvant. Prospective. Also includes a prospective metastatic cohort.	211 Pre- and post-menopausal. HR+. -190 adjuvant -21 metastatic	*5,*10	Pregnane X receptor (PXR)	Tamoxifen treatment details not provided 20mg/d for at least 8 weeks before pharmaco-kinetic studies	CYP2D6*10/*10 lower concentration of Tam metabolites P<0.0001. More often found among non-responders than responders 100% vs 50%, P=0.0186. Median TTP 5 vs 21.8 ms, P=0.0032 No correlation found between PXR variants and metabolite concentrations

Xu 2008 (16)	Adjuvant. Retrospective Also include a prospective cohort.	152 Pre- and post-menopausal women receiving Tam. -141 no Tam. 37 women on Tam 10 mg/d for >4 weeks	*10,		Tamoxifen 20mg/d for retrospective analysis 10mg/d for >4 weeks for prospective PK studies. No patients were co-prescribed inhibitors	Tam-treated: CYP2D*10/10 vs CYP2D6*10/*1 or 1/*1: DFS HR 4.7, P=0.04. CYP2D6*10/10 Lower concentration of Tam metabolites, P=0.04.
Kiyotani 2008 (13)	Adjuvant. Retrospective	67 Pre-and post-menopausal. HR+ Tam monotherapy.	*4,*5,*6,*10,*21,*41			CYP2D6*10/*10 vs *1/*1 : Recurrence OR 16.63, P=0.0057. RFS CYP2D6*10/*10 vs *1/*1 or *1/*10 : P=0.0031 or P=0.0010.
Newman 2008 (17)	Adjuvant. Retrospective	115 Familial breast cancer -47 BRCA1+ -68 BRCA2+	*3, *4, *5, *41		Tamoxifen 20mg/d x median of 4 yrs. Inhibitors co-prescribed in 4 patients only	Cox HR for overall low CYP2D6 activity group adjusted for nodal status : BCR 2.1, P=0.14 RFS 1.9, P=0.19 OS 2.5, P=0.17 BRCA2 and low CYP2D6 activity vs BRCA2 and normal CYP2D6 activity: OS 6.9yrs vs 28.1yrs P=0.008
Bonanni 2006 (14)	Chemo-prevention. Retrospective	47 Enrolled in a prospective study	32 alleles, classifying to PM, IM, EM UM.		Tam 20 mg/d x 5 yrs vs placebo x 5 yrs	Increased risk of PM vs others to develop breast cancer, P=0.035.

Comments[&]: 1) Tamoxifen was administered at 20 mg/day for 5 years unless otherwise specified; 2) concomitant medication information was not available unless otherwise specified

HR+ = hormone receptor positive, HR = hazard ratio, OR = odds ratio, ER = estrogen receptor, RFT = relapse free time, CT = chemotherapy, RFS = relapse free survival, OS = overall survival, DFS = disease free survival, Tam = tamoxifen, mg/d = milligrams per day, yrs = years. BCR = breast cancer recurrence, PM = poor metabolizer, IM = intermediate metabolizer, EM = extensive metabolizer, UM = ultrametabolize

The table highlights some of the shortcomings with studies performed to date and the difficulties interpreting results. The majority of studies were retrospective and only a few included women previously enrolled in a single prospective trial. More then one dose or schedule of tamoxifen may have been studied, and not all women had tumors that were hormone receptor positive. Indeed, a recent preliminary report from the International Tamoxifen Consortium at the San Antonio Breast Cancer Symposium (December 2009) failed to show a correlation between CYP2D6 status and long-term outcomes.

Ideally, a prospective study of adjuvant tamoxifen should be conducted to compare long term outcomes of people with or without variants. However, due to the widespread use of aromatase inhibitors in postmenopausal women, the most common population affected by the disease, such a trial will be very difficult to conduct. While there are many ongoing attempts to evaluate datasets from large studies that have already been completed, these sets do not include tamoxifen metabolite information and most include only paraffin blocks, thus not allowing for complex pharmacogenetic profiling. An alternative is to evaluate progression-free survival and other outcomes in the metastatic setting. Therefore we propose a phase II study in patients who are candidates for tamoxifen treatment in the metastatic setting with either no prior therapy or with prior aromatase inhibitor therapy and will compare outcomes in those with and without variants in the CYP2D6 gene.

In addition, only a few studies attempted to evaluate the influence of variants in other candidate genes on drug efficacy and prospective analysis is lacking. We will study other candidate genes and will also explore whole genome analysis.

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1.3 Genetic Predictors of Other Tamoxifen-Associated Outcomes

Genetic variants in genes responsible for tamoxifen's pharmacokinetics (eg CYP2D6) and pharmacodynamics (eg ESR) may also influence drug-related secondary benefits and adverse events.

For example, in the COBRA prospective tamoxifen pharmacogenomics study, an association was initially observed between *ESR1* XbaI genotype and baseline low-density lipoprotein (LDL) and total cholesterol. The XbaI genotype was also associated with tamoxifen-induced change in total cholesterol (post-menopause) and triglycerides and HDL (pre-menopause). The tamoxifen-induced change in triglycerides was also associated with the *ESR2* genotype (rs#4986938) (18). The analysis in the initial cohort was carried out by PCR followed by restriction-enzyme digestion. After reanalysis using more robust TaqMan assays, the findings related to ~10% of the genotypes for the *ESR1* XbaI SNP were revised. For the other genotypes (i.e., *ESR1* PvuII, *ESR2*, and *CYP2D6*), the results were nearly identical to those in the previous study. Upon reanalysis, previously reported associations between the *ESR1* Xba1 genotypes and baseline triglyceride and LDL cholesterol levels were no longer observed emphasizing the need for additional study (19).

Other studies reported correlation with ESR and events such as hot flashes and deep venous thromboses (DVT). In the prospective COBRA tamoxifen study, baseline hot flash score was significantly associated with both the *ESR1* XbaI (rs#9340799) and PvuII (rs#2234693) genotypes (20). The combined haplotype analysis indicated that for an increase in one copy of the CG haplotype, the

subjects had a 2.5-fold higher baseline hot flash score. In addition, an *ESR2* SNP (rs#4986938) was associated with a decreased risk of developing tamoxifen-induced hot flashes (OR 0.12; 95% CI, 0.04-0.41; P = .0001). When the PvuII and the *ESR2* genotypes were combined, they were also significantly associated with the tamoxifen-induced hot flash score. In a retrospective study conducted in collaboration between COBRA and with investigators at the Marshfield Clinic, the *ESR1* XbaI SNP (rs#9340799) was significantly associated with tamoxifen-induced DVTs(21). The hazard ratio for patients with at least one G allele was 3.47.

2. Objectives

2.1 Primary Objective

To correlate CYP2D6 score (0 vs. 1+2) and progression-free survival.

2.2 Secondary Objectives

2.2.1 To correlate CYP2D6 score (0 vs. 1 vs. 2) and progression-free survival.

2.2.2 To correlate CYP2D6 score (0 vs. 1 + 2) and proportion of patients who are progression-free at 6 months.

2.2.3 To correlate endoxifen concentration with response.

2.2.4 To correlate CYP2D6 score with response.

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2.2.5 To correlate the presence of candidate estrogen receptor (ESR) 1 and 2 variant alleles, UGT7, SULT1A1, other candidate genes and biomarkers to progression-free survival and other tamoxifen related outcomes.

3. Selection of Patients

Each of the criteria in the checklist that follows must be met in order for a patient to be considered eligible for this study. Use the checklist to confirm a patient's eligibility. For each patient, this checklist must be photocopied, completed and maintained in the patient's chart.

In calculating days of tests and measurements, the day a test or measurement is done is considered Day 0. Therefore, if a test is done on a Monday, the Monday four weeks later would be considered Day 28.

ECOG-ACRIN Patient No. _____

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

Physician Signature and Date _____

NOTE: All questions regarding eligibility should be directed to the study chair or study chair liaison.

NOTE: Institutions may use the eligibility checklist as source documentation if it has been reviewed, signed, and dated prior to registration/randomization by the treating physician.

3.1 Eligibility Criteria

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_____ 3.1.1 Must have estrogen and/or progesterone receptor positive histologically confirmed adenocarcinoma of the breast. Receptor status may be based on any time during treatment prior to study registration, and from any site (i.e. primary recurrent, or metastatic).

_____ 3.1.2 Patients must have measurable or non-measurable Stage III/locally advanced or metastatic carcinoma of the breast where surgery is not possible, as defined in Section 6.1.1. Lesions must be evaluated within 4 weeks prior to registration.

_____ 3.1.3 Age ≥ 18 years.

_____ 3.1.4 Women must not be pregnant or breast-feeding due to harmful effects of tamoxifen.

Breast feeding? _____ (Yes or No)

NOTE: All females of childbearing potential must have a blood test within 2 weeks prior to registration to rule out pregnancy. A female of childbearing potential is any woman, regardless of sexual orientation or whether they have undergone tubal ligation, who meets the following criteria:

1) Has not undergone a hysterectomy or bilateral oopherectomy;

Or

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2) Has not been naturally postmenopausal for at least 24 consecutive months (i.e., has had menses at any time in the preceding 24 consecutive months).

Female of child bearing potential? _____ (Yes or No)

Date of pregnancy test: _____

_____3.1.5 Women of childbearing potential and sexually active males must be strongly advised to use an accepted and effective method of non-hormonal contraception. Acceptable contraception includes barrier methods (e.g., condoms or diaphragm) or intrauterine devices or IUDs (these may include low-dose hormones at the discretion of the Study Chair).

_____3.1.6 ECOG performance status of 0-2.

Rev. 5/11, 8/12 _____3.1.7 Systemic Therapy

_____3.1.7.1 Patients who have received agents that modulate or downregulate the estrogen receptor for breast cancer prevention (e.g. tamoxifen, raloxifene, fulvestrant) or bone health (raloxifene) are eligible if they were on treatment for at least 6 months, did not have a diagnosis of breast cancer on the medication, and have discontinued the agents 6 months prior to study registration.

Rev. 5/11, 8/12 _____3.1.7.2 Adjuvant Setting

_____ 3.1.7.2.1 Chemotherapy or trastuzumab or bevacizumab in the adjuvant setting is allowed but must have been completed at least 4 weeks prior to study registration. Other prior non-hormonal investigational agents in the adjuvant setting must have completed at least 4 weeks prior to study registration and should be discussed with the study PI.

_____ 3.1.7.2.2 Prior aromatase inhibitors (e.g. anastrozole, letrozole, exemestane, aminoglutethamide) are allowed in the adjuvant setting.

The following treatments (3.1.7.2.3 and 3.1.7.2.4) are allowed provided that the patient must have discontinued the agents 6 months prior to study registration:

_____ 3.1.7.2.3 Prior tamoxifen as adjuvant treatment is allowed as long as the patient did not have disease relapse or progression while on adjuvant tamoxifen or within 4 weeks of last dose.

_____ 3.1.7.2.4 Patients who have received other agents that modulate or downregulate the estrogen receptor (e.g. raloxifene, fulvestrant) in the adjuvant setting are eligible if they were on treatment for at least 6 months prior to disease progression in the locally advanced or metastatic setting.

Rev. 8/12 _____ 3.1.7.3 Locally Advanced or Metastatic Setting

_____ 3.1.7.3.1 Patients must not have had more than 2 lines of non-hormonal treatment in the locally advanced or metastatic setting, including trastuzumab (Herceptin), bevacizumab, or other agents; treatment in the locally advanced or metatastic setting must have been completed at least 2 weeks prior to study registration.

_____ 3.1.7.3.2 Prior aromatase inhibitors (e.g. anastrozole, letrozole, exemestane, aminoglutethamide) are allowed in the locally advanced or metastatic setting.

_____ 3.1.7.3.3 Prior tamoxifen is not allowed in the locally advanced or metastatic setting.

_____ 3.1.7.3.4 Patients who have received other agents that modulate or downregulate the estrogen receptor (e.g. raloxifene, fulvestrant) in the locally advanced or metastatic setting are eligible if they were on treatment for at least 6 months and must have discontinued these agents 6 months prior to study registration

_____ 3.1.8 Non-protocol concurrent hormonal therapy is not allowed.

_____ 3.1.9 Concurrent chemotherapy is not allowed.

Rev. 5/11 _____ 3.1.10 Patients, must have adequate hematologic and renal function at the discretion of the treating physician and hepatic function as defined by the following within 4 weeks prior to registration:

_____ 3.1.10.1 Total bilirubin ≤ 1.5 x upper limit of normal

Total bilirubin: _____ ULN:_____

Date of Test: _____

Rev. 8/12 _____ 3.1.10.2 SGPT (ALT) ≤ 2.5 x upper limit of normal OR ≤ 5 x upper limit of normal if liver metastases.

ALT: _____ ULN:_____

Date of Test: _____

Rev. 8/12 _____ 3.1.10.3 SGOT (AST) ≤ 2.5 x upper limit of normal OR ≤ 5 x upper limit of normal if liver metastases.

AST: _____ ULN:_____

Date of Test: _____

Rev. 5/11 _____ 3.1.11 Patients with a history of central nervous system metastasis are allowed provided they have been treated (surgery, radiation, or radiosurgery) at least 4 weeks prior to initiating study drug and do not require medication(s) to control symptoms. Patients with known leptomeningeal disease are not eligible.

Rev. 5/11 _____ 3.1.12 Patients may receive concurrent radiation therapy to painful sites of bony disease or areas of impending fracture as long as the radiation therapy is initiated prior to study entry and sites of measurable and non-measurable disease outside the radiation therapy port are available to follow. Patients who have received prior radiation therapy must have recovered from toxicity of the prior radiation therapy.

_____ 3.1.13 Patients must not take the following medications that are strong to moderate inhibitors of *CYP2D6* and may alter tamoxifen metabolism: paroxetine (Paxil), fluoxetine (Prozac), buproprion (Wellbutrin) and quindine (Cardioquin) within 2 weeks of registration.

_____ 3.1.14 Patients must not suffer from medical or psychiatric conditions that would interfere with protocol compliance, the ability to provide informed consent, or assessment of response or anticipated toxicities.

_____ 3.1.15 Patients must be disease-free of prior invasive malignancies for ≥ 5 years with the exception of curatively-treated basal cell or squamous cell carcinoma of the skin or carcinoma *in situ* of the cervix.

Rev. 5/11, 8/12 _____ 3.1.16 Patients may not initiate bisphosphonate or denosumab therapy while receiving treatment on this study. Patients who have begun receiving bisphosphonate or denosumab therapy prior to registration may continue at the same intervals used prior to study registration.

_____ 3.1.17 Patients must be disease-free of prior invasive malignancies for ≥ 5 years with the exception of curatively-treated basal cell or squamous cell carcinoma of the skin or carcinoma *in situ* of the cervix.

Rev. 5/11 _____ 3.1.18 Patients may not initiate bisphosphonate therapy while receiving treatment on this study. Patients who have begun receiving bisphosphonate therapy prior to registration may continue at the same intervals used prior to study registration.

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4. Registration Procedures

CTEP Investigator Registration Procedures

Food and Drug Administration (FDA) regulations and National Cancer Institute (NCI) policy require all investigators participating in any NCI-sponsored clinical trial to register and to renew their registration annually.

Registration requires the submission of:

- a completed ***Statement of Investigator Form*** (FDA Form 1572) with an original signature
- a current Curriculum Vitae (CV)
- a completed and signed ***Supplemental Investigator Data Form*** (IDF)
- a completed ***Financial Disclosure Form*** (FDF) with an original signature

Fillable PDF forms and additional information can be found on the CTEP website at <http://ctep.cancer.gov/investigatorResources/investigator_registration.htm>. For questions, please contact the ***CTEP Investigator Registration Help Desk*** by email at <pmbregpend@ctep.nci.nih.gov>.

CTEP Associate Registration Procedures / CTEP-IAM Account

The Cancer Therapy Evaluation Program (CTEP) Identity and Access Management (IAM) application is a web-based application intended for use by both Investigators (i.e., all physicians involved in the conduct of NCI-sponsored clinical trials) and Associates (i.e., all staff involved in the conduct of NCI-sponsored clinical trials).

Associates will use the CTEP-IAM application to register (both initial registration and annual re-registration) with CTEP and to obtain a user account.

Investigators will use the CTEP-IAM application to obtain a user account only. (See CTEP Investigator Registration Procedures above for information on registering with CTEP as an Investigator, which must be completed before a CTEP-IAM account can be requested.)

An active CTEP-IAM user account will be needed to access all CTEP and CTSU (Cancer Trials Support Unit) websites and applications, including the CTSU members' website.

Additional information can be found on the CTEP website at <http://ctep.cancer.gov/branches/pmb/associate_registration.htm>. For questions, please contact the ***CTEP Associate Registration Help Desk*** by email at <ctepreghelp@ctep.nci.nih.gov>.

CTSU Registration Procedures

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

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

Downloading Site Registration Documents:

Site registration forms may be downloaded from the **E3108** protocol page located on the CTSU members' website.

- Go to https://www.ctsu.org and log in to the members' area using your CTEP-IAM username and password
- Click on the Protocols tab in the upper left of your screen
- Click on the **ECOG-ACRIN** link to expand, then select trial protocol **E3108**
- Click on the Site Registration Documents link

Requirements for E3108 site registration:

- **CTSU IRB Certification** (for sites not participating via the NCI CIRB)
- **CTSU IRB/Regulatory Approval Transmittal Sheet** (for sites not participating via the NCI CIRB)

Submitting Regulatory Documents

Submit completed forms along with a copy of your IRB Approval *and Model Informed Consent* to the CTSU Regulatory Office, where they will be entered and tracked in the CTSU RSS.

CTSU Regulatory Office

1818 Market Street, Suite 1100
Philadelphia, PA 19103

Phone: 1-866-651-2878
FAX: (215) 569-0206

E-mail: CTSURegulatory@ctsu.coccg.org (for regulatory document submission only)

Required Protocol Specific Regulatory Documents

1. **CTSU Regulatory Transmittal Form.**
2. **Copy of IRB Informed Consent Document.**

   NOTE: Any deletion or substantive modification of information concerning risks or alternative procedures contained in the sample informed consent document must be justified in writing by the investigator and approved by the IRB.

3. **A. CTSU IRB Certification Form.**
   Or
   B. Signed HHS OMB No. 0990-0263 (replaces Form 310).
   Or
   C. IRB Approval Letter

   NOTE: The above submissions must include the following details:
   - **Indicate all sites approved for the protocol under an assurance number.**
   - **OHRP assurance number of reviewing IRB**
   - **Full protocol title and number**

- **Version Date**
- **Type of review (full board vs. expedited)**
- **Date of review.**
- **Signature of IRB official**

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Checking Your Site's Registration Status:

Check the status of your site's registration packets by querying the RSS site registration status page of the members' section of the CTSU website. (Note: Sites will not receive formal notification of regulatory approval from the CTSU Regulatory Office.)

- Go to https://www.ctsu.org and log in to the members' area using your CTEP-IAM username and password
- Click on the Regulatory tab at the top of your screen
- Click on the Site Registration tab
- Enter your 5-character CTEP Institution Code and click on Go

Patient Enrollment

Patients must not start protocol treatment prior to registration.

Treatment should start within three working days after registration.

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Patient registration can occur only after pre-treatment evaluation is complete, eligibility criteria have been met, and the study site is listed as 'approved' in the CTSU RSS. Patients must have signed and dated all applicable consents and authorization forms.

Patient enrollment will be facilitated using the Oncology Patient Enrollment Network (OPEN). OPEN is a web-based registration system available on a 24/7 basis. To access OPEN, the site user must have an active CTEP-IAM account (check at <https://eapps-ctep.nci.nih.gov/iam/index.jsp>) and a 'Registrar' role on either the LPO or participating organization roster.

All site staff will use OPEN to enroll patients to this study. It is integrated with the CTSU Enterprise System for regulatory and roster data . OPEN can be accessed at https://open.ctsu.org or from the OPEN tab on the CTSU members' side of the website at https://www.ctsu.org.

Prior to accessing OPEN site staff should verify the following:

- All eligibility criteria have been met within the protocol stated timeframes.
- All patients have signed an appropriate consent form and HIPAA authorization form (if applicable).

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

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

The following information will be requested:

4.1 Protocol Number

4.2 Investigator Identification

- 4.2.1 Institution and affiliate name (Institution CTEP ID)
- 4.2.2 Investigator's name (NCI number)
- 4.2.3 Cooperative Group Credit
- 4.2.4 Credit Investigator
- 4.2.5 Protocol specific contact information

4.3 Patient Identification

- 4.3.1 Patient's initials (first and last) and chart number
- 4.3.2 Patient's Social Security number and/or Hospital ID
- 4.3.3 Patient demographics
  - 4.3.3.1 Sex
  - 4.3.3.2 Birth date (mm/yyyy)
  - 4.3.3.3 Race
  - 4.3.3.4 Ethnicity
  - 4.3.3.5 Nine-digit ZIP code
  - 4.3.3.6 Method of payment
  - 4.3.3.7 Country of residence

4.4 Eligibility Verification

Patients must meet all of the eligibility requirements listed in Section 3. An eligibility checklist has been appended to the protocol. A confirmation of registration will be forwarded by the ECOG-ACRIN Operations Office - Boston.

4.5 Additional Requirements

- 4.5.1 Patients must provide a signed and dated, written informed consent form.
- 4.5.2 Pathological materials should be submitted as indicated in Section 10 for banking per patient consent.

  NOTE: Please submit block from primary tumor and, when available, from metastatic site.
- 4.5.3 Whole blood must be submitted for genotype verification as indicated in Section 11. Plasma must be submitted for the laboratory studies outlined in Section 11.

  NOTE: ECOG-ACRIN requires that biological samples submitted from patients participating in E3108 be entered and tracked via the online ECOG-ACRIN Sample Tracking System (STS). See Section 10.4.

4.6 Instructions for Patients who Do Not Start Assigned Protocol Treatment

If a patient does not receive any assigned protocol treatment, baseline and follow-up data will still be collected and must be submitted according to the instructions in the E3108 Forms Packet. Document the reason for not starting protocol treatment on the off-treatment form. Also report the date and type of the first non-protocol treatment that the patient receives on the Non-Protocol Therapy Form.

5. Treatment Plan

5.1 Administration Schedule

1 cycle = 28 days

Open label tamoxifen 20 mg PO (single dose) daily until progression, unacceptable toxicities, or any other condition outlined in Section 5.5.

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5.2 Adverse Event Reporting Requirements

5.2.1 Purpose

Adverse event data collection and reporting, which are required as part of every clinical trial, are done to ensure the safety of patients enrolled in the studies as well as those who will enroll in future studies using similar agents. Adverse events are reported in a routine manner at scheduled times during a trial (please refer to the E3108 Forms Packet for the list of forms with directions for routine adverse event reporting). Additionally, certain adverse events must be reported in an expedited manner for more timely monitoring of patient safety and care. The following sections provide information about expedited reporting.

5.2.2 Determination of reporting requirements

Reporting requirements may include the following considerations: 1) whether the patient has received an investigational or commercial agent; 2) the characteristics of the adverse event including the grade (severity), the relationship to the study therapy (attribution), and the prior experience (expectedness) of the adverse event; 3) the phase (1, 2, or 3) of the trial; and 4) whether or not hospitalization or prolongation of hospitalization was associated with the event.

Commercial agents are those agents not provided under an IND but obtained instead from a commercial source. The NCI, rather than a commercial distributor, may on some occasions distribute commercial agents for a trial.

Steps to determine if an adverse event is to be reported in an expedited manner:

Step 1: *Identify the type of event:* The descriptions and grading scales found in the revised NCI Common Terminology Criteria for Adverse Events (CTCAE) will be utilized for AE reporting. All appropriate treatment areas should have access to a copy of the CTCAE version 4.0. A copy of the CTCAE version 4.0 can be downloaded from the CTEP website (http://ctep.cancer.gov).

Step 2: Grade the event using the NCI CTCAE version 4.0.

Step 3: Determine whether the adverse event is related to the protocol therapy (investigational or commercial). Attribution categories are as follows: Unrelated, Unlikely, Possible, Probable, and Definite.

Step 4: Determine the prior experience of the adverse event. Expected events are those that have been previously identified as resulting from administration of the agent. An adverse event is considered unexpected, for expedited reporting purposes only, when either the type of event or the severity of the event is **NOT** listed in:

- **Arm A** – the drug package insert or protocol

Step 5: Review Section 5.2.6 for E3108 and/or ECOG-ACRIN specific requirements for expedited reporting of specific adverse events that require special monitoring.

NOTE: For general questions regarding expedited reporting requirements, please contact the AEMD Help Desk at aemd@tech-res.com or 301-897-7497.

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5.2.3 Reporting Procedure

This study requires that expedited adverse event reporting use CTEP's Adverse Event Reporting System (CTEP-AERS). CTEP's guidelines for CTEP-AERS can be found at http://ctep.cancer.gov. A CTEP-AERS report must be submitted electronically to ECOG-ACRIN and the appropriate regulatory agencies via the CTEP-AERS Web-based application located at http://ctep.cancer.gov.

In the rare event when Internet connectivity is disrupted a 24-hour notification is to be made by telephone to

- the AE Team at ECOG-ACRIN (617-632-3610)
- the FDA (800-332-1088)

An electronic report MUST be submitted immediately upon re-establishment of internet connection.

Supporting and follow up data: Any supporting or follow up documentation must be faxed to ECOG-ACRIN (617-632-2990), Attention: AE within 48-72 hours. In addition, supporting or follow up documentation must be faxed to the FDA (800-332-0178) in the same timeframe.

NCI Technical Help Desk: For any technical questions or system problems regarding the use of the CTEP-AERS application, please contact the NCI Technical Help Desk at ncictephelp@ctep.nci.nih.gov or by phone at 1-888-283-7457.

5.2.4 When to report an event in an expedited manner

When an adverse event requires expedited reporting, submit a full CTEP-AERS report within the timeframes outlined in Section 5.2.6.

NOTE: Adverse events that meet the reporting requirements in Section 5.2.6 and occur within 30 days of the last dose of protocol treatment must be reported on an expedited adverse event report form (using CTEP-AERS). For any adverse events that occur more than 30 days after the last dose of treatment, only those that have an attribution of possibly, probably, or definitely AND meet the reporting

requirements in Section 5.2.6 must be reported on an expedited adverse event report form (using CTEP-AERS).

5.2.5 Other recipients of adverse event reports

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

5.2.6 Expedited reporting for commercial agents

Commercial reporting requirements are provided below. The commercial agent used in arm A of this study is Tamoxifen.

Expedited reporting requirements for adverse events experienced by patients on arm(s) with commercial agents only –Arm A

Attribution	Grade 4		Grade 5[a]		ECOG-ACRIN and Protocol-Specific Requirements
	Unexpected	Expected	Unexpected	Expected	See footnote (b) for special requirements.
Unrelated or Unlikely			7 calendar days	7 calendar days	
Possible, Probable, Definite	7 calendar days		7 calendar days	7 calendar days	

7 Calendar Days: Indicates a full CTEP-AERS report is to be submitted within 7 calendar days of learning of the event.

a This includes all deaths within 30 days of the last dose of treatment regardless of attribution.
NOTE: Any death that occurs > 30 days after the last dose of treatment and is attributed possibly, probably, or definitely to the treatment must be reported within 7 calendar days of learning of the event.

b Protocol-specific expedited reporting requirements: The adverse events listed below also require expedited reporting for this trial:

Serious Events: Any event following treatment that results in *persistent or significant disabilities/incapacities, congenital anomalies, or birth defects* must be reported via CTEP-AERS within 7 calendar days of learning of the event. For instructions on how to specifically report these events via CTEP-AERS, please contact the AEMD Help Desk at aemd@tech-res.com or 301-897-7497. This will need to be discussed on a case by case basis.

Thromboembolic events: Any grade 3 or higher thromboembolic event must be reported via CTEP-AERS within 7 calendar days of learning of the event, regardless of attribution or expectedness.

Secondary endometrial cancer: Any confirmed diagnosis of secondary endometrial cancer must be reported via CTEP-AERS within 7 calendar days of learning of the event, regardless of relationship to protocol treatment. In addition, a completed Second Primary Form must be submitted to the ECOG-ACRIN Operations Office - Boston within 30 days of diagnosis.

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5.2.7 Reporting of Other Second Primary Cancers

All cases of second primary cancers that occur following treatment on NCI-sponsored trials must be reported to ECOG-ACRIN:

- **A second malignancy is a cancer that is UNRELATED to any prior anti-cancer treatment (including the treatment on this protocol). Second malignancies require ONLY routine reporting as follows:**

1. Submit a completed Second Primary Form within 30 days to ECOG-ACRIN at

   ECOG-ACRIN Operations Office - Boston
   FSTRF
   900 Commonwealth Avenue
   Boston, MA 02215

2. Submit a copy of the pathology report to ECOG-ACRIN confirming the diagnosis

- **A <u>secondary</u> malignancy is a cancer CAUSED BY any prior anti-cancer treatment (including the treatment on this protocol). Secondary malignancies require both routine and expedited reporting as follows:**

  1. Submit a completed Second Primary Form within 30 days to ECOG-ACRIN at

     ECOG-ACRIN Operations Office - Boston
     FSTRF
     900 Commonwealth Avenue
     Boston, MA 02215

  2. Report the diagnosis via CTEP-AERS at http://ctep.cancer.gov

     Report under treatment related secondary malignancy

  3. Submit a copy of the pathology report to ECOG-ACRIN and NCI/CTEP confirming the diagnosis.

NOTE: The Second Primary Form and the CTEP-AERS report should <u>not</u> be used to report recurrence or development of metastatic disease.

NOTE: If a patient has been enrolled in more than one NCI-sponsored study, the Second Primary Form must be submitted for the most recent trial. ECOG-ACRIN must be provided with a copy of the form and the associated pathology report and cytogenetics report (if available) even if ECOG-ACRIN was not the patient's most recent trial.

NOTE: Once data regarding survival and remission status are no longer required by the protocol, no follow-up data should be submitted via CTEP-AERS or by the Second Primary Form.

5.3 <u>Dose Modifications</u>

NOTE: If tamoxifen administration is held for any reason, patient can remain on study for up to 7 days. If tamoxifen administration is held for > 7 days, patient will be considered off-treatment.

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NOTE: Tamoxifen dose reductions are not allowed.

All toxicities should be graded according to the NCI Common Terminology Criteria for Adverse Events (CTCAE) version 4.0.

All appropriate treatment areas should have access to a copy of the CTCAE version 4.0. The CTCAE version 4.0 can be found on the CTEP website (http://ctep.cancer.gov).

5.4 Supportive Care

All supportive measures consistent with optimal patient care will be given throughout the study.

Patients receiving bisphosphonate therapy prior to beginning this trial may continue at the same intervals used prior to entering the study. Bisphosphonate therapy may not be initiated while being treated on this trial.

Patients must not take the following medications that are strong to moderate inhibitors of CYP2D6 and may alter tamoxifen metabolism: paroxetine (Paxil), fluoxetine (Prozac), buproprion (Wellbutrin), and quindine (Cardioquin) 2 weeks prior to registration or at any time while on-study.

5.5 Duration of Therapy

Patients will receive protocol therapy unless:

5.5.1 Progressive disease by RECIST criteria. See Section 6.1.

5.5.2 Severe toxicity at discretion of the treating physician (including thromboembolic disease, endometrial cancer).

5.5.3 Extraordinary Medical Circumstances: If at any time the constraints of this protocol are detrimental to the patient's health, protocol treatment should be discontinued. In this event submit forms according to the instructions in the E3108 Forms Packet.

5.5.4 Patient withdraws consent.

5.5.5 If tamoxifen is held for > 7 days.

5.6 Duration of Follow-up

For this protocol, all patients, including those who discontinue protocol therapy early, will be followed for response until progression, even if non-protocol therapy is initiated, and for survival for 5 years from the date of registration. For patients who remain on-treatment, treatment data will be collected for 5 years from the date of registration

6. Measurement of Effect

6.1 Antitumor Effect – Solid Tumors

For the purposes of this study, patients' disease should be evaluated according to the schedule in Section 7. If a patient's disease responds, a confirmatory scan must be performed at least 4 weeks following initial documentation of objective response.

Response and progression will be evaluated in this study using the international criteria proposed by the revised Response Evaluation Criteria in Solid Tumors (RECIST) guideline (version 1.1) [*Eur J Ca* 45:228-247, 2009]. Changes in the largest diameter (unidimensional measurement) of the tumor lesions and the shortest diameter in the case of malignant lymph nodes are used in RECIST.

The following general principles must be followed:

1. To assess objective response, it is necessary to estimate the overall tumor burden at baseline to which subsequent measurements will be compared. All baseline evaluations should be performed as closely as possible to the beginning of treatment and **never more than four weeks** before registration.
2. Measurable disease is defined by the presence of at least one measurable lesion.
3. All measurements should be recorded in metric notation by use of a ruler or calipers.
4. The same method of assessment and the same technique must be used to characterize each identified lesion at baseline and during follow-up.

6.1.1 Definitions

Evaluable for Objective Response

Only those patients who have measurable disease present at baseline, have received at least one cycle of therapy, and have had their disease re-evaluated will be considered evaluable for response. These patients will have their response classified according to the definitions stated below. (Note: Patients who exhibit objective disease progression prior to the end of cycle 1 will also be considered evaluable.)

Evaluable Non-Target Disease Response

Patients who have lesions present at baseline that are evaluable but do not meet the definitions of measurable disease, have received at least one cycle of therapy, and have had their disease re-evaluated will be considered evaluable for non-target lesion assessment. The response assessment is based on the presence, absence, or unequivocal progression of the lesions.

6.1.2 Disease Parameters

Measurable Disease

Measurable lesions are defined as those that can be accurately measured in at least one dimension (longest diameter to be recorded)

as ≥ 20 mm by chest x-ray, as ≥ 10 mm with CT scan, or ≥ 10 mm with calipers by clinical exam. All tumor measurements must be recorded in millimeters.

NOTE: Tumor lesions that are situated in a previously irradiated area are not considered measurable.

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 (CT scan slice thickness recommended to be no greater than 5 mm). At baseline and in follow-up, only the **short** axis will be measured and followed.

Non-measurable Disease

All other lesions (or sites of disease), including small lesions (longest diameter < 10 mm or pathological lymph nodes with ≥ 10 to < 15 mm short axis), are considered non-measurable disease. Bone lesions, leptomeningeal disease, ascites, pleural/pericardial effusions, lymphangitis cutis/pulmonitis, inflammatory breast disease, and abdominal masses (not followed by CT or MRI), are considered as non-measurable. Non-measurable also includes lesions that are < 20 mm by chest x-ray.

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

'Cystic lesions' thought to represent cystic metastases can be considered as measurable lesions, if they meet the definition of measurability described above. However, if non-cystic lesions are present in the same patient, these are preferred for selection as target lesions.

Target Lesions

All 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), be representative of all involved organs, but in addition should be those that lend themselves to reproducible repeated measurements. It may be the case that, on occasion, the largest lesion does not lend itself to reproducible measurement in which circumstance the next largest lesion which can be measured reproducibly should be selected.

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 only the short axis is added into the sum. The baseline sum of the diameters will be used as reference to further characterize any

objective tumor regression in the measurable dimension of the disease.

Non-target Lesions

All other lesions (or sites of disease) including any measurable lesions over and above the 5 target lesions should be identified as **non-target lesions** and should also be recorded at baseline. Measurements of these lesions are not required, but the presence or absence of unequivocal progression of each should be noted throughout follow-up.

6.1.3 Methods 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 and never more than 4 weeks before registration.

The same method of assessment and the same technique must 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 unless the lesion(s) being followed cannot be imaged but are assessable by clinical exam.

Clinical Lesions

Clinical lesions will only be considered measurable when they are superficial (e.g., skin nodules and palpable lymph nodes) and ≥10 mm in diameter as assessed using calipers (e.g., skin nodules). 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

This guideline has defined measurability of lesions on CT scan based on the assumption that CT slice thickness is 5 mm or less. If CT scans have slice thickness greater than 5 mm, the minimum size for a measurable lesion should be twice the slice thickness. MRI is also acceptable in certain situations (e.g. for body scans).

Use of MRI remains a complex issue. MRI has excellent contrast, spatial, and temporal resolution; however, there are many image acquisition variables involved in MRI which greatly impact image quality, lesion conspicuity, and measurement. Furthermore, the availability of MRI is variable globally. As with CT, if an MRI is performed, the technical specifications of the scanning sequences used should be optimized for the evaluation of the type and site of disease. Furthermore, as with CT, the modality used at follow-up must be the same as was used at baseline and the lesions should be measured/assessed on the same pulse sequence. It is beyond the

scope of the RECIST guidelines to prescribe specific MRI pulse sequence parameters for all scanners, body parts, and diseases. Ideally, the same type of scanner should be used and the image acquisition protocol should be followed as closely as possible to prior scans. Body scans should be performed with breath-hold scanning techniques, if possible.

PET-CT

At present, the low dose or attenuation correction CT portion of a combined PET-CT is not always of optimal diagnostic CT quality for use with RECIST measurements. However, if the site can document that the CT performed as part of a PET-CT is of identical diagnostic quality to a diagnostic CT (with IV and oral contrast), then the CT portion of the PET-CT can be used for RECIST measurements and can be used interchangeably with conventional CT in accurately measuring cancer lesions over time. Note, however, that the PET portion of the CT introduces additional data which may bias an investigator if it is not routinely or serially performed.

Ultrasound

Ultrasound is not useful in assessment of lesion size and should not be used as a method of measurement. Ultrasound examinations cannot be reproduced in their entirety for independent review at a later date and, because they are operator dependent, it cannot be guaranteed that the same technique and measurements will be taken from one assessment to the next. If new lesions are identified by ultrasound in the course of the study, confirmation by CT or MRI is advised. If there is concern about radiation exposure at CT, MRI may be used instead of CT in selected instances.

Endoscopy, Laparoscopy

The utilization of these techniques for objective tumor evaluation is not advised. However, such techniques may be useful to confirm complete pathological response when biopsies are obtained or to determine relapse in trials where recurrence following complete response (CR) or surgical resection is an endpoint.

Tumor Markers

Tumor markers alone cannot be used to assess response. If markers are initially above the upper normal limit, they must normalize for a patient to be considered in complete clinical response. Specific guidelines for both CA-125 response (in recurrent ovarian cancer) and PSA response (in recurrent prostate cancer) have been published [*JNCI* 96:487-488, 2004; *J Clin Oncol* 17, 3461-3467, 1999; *J Clin Oncol* 26:1148-1159, 2008]. In addition, the Gynecologic Cancer Intergroup has developed CA-125 progression criteria which are to be integrated with objective tumor assessment for use in first-line trials in ovarian cancer [*JNCI* 92:1534-1535, 2000].

Cytology, Histology

These techniques can be used to differentiate between partial responses (PR) and complete responses (CR) in rare cases (e.g., residual lesions in tumor types, such as germ cell tumors, where known residual benign tumors can remain).

The cytological confirmation of the neoplastic origin of any effusion that appears or worsens during treatment when the measurable tumor has met criteria for response or stable disease is mandatory to differentiate between response or stable disease (an effusion may be a side effect of the treatment) and progressive disease.

6.1.4 Response Criteria

6.1.4.1 Evaluation of Target Lesions

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Complete Response (CR)

Disappearance of all target lesions. Any pathological lymph nodes (whether target or non-target) must have reduction in short axis to < 10 mm. To be assigned a status of complete response, changes in tumor measurements must be confirmed by a repeat assessment performed no less than four weeks after the criteria for response is met.

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Partial Response (PR)

At least a 30% decrease in the sum of the diameters of target lesions, taking as reference the baseline sum diameters. To be assigned a status of partial response, changes in tumor measurements must be confirmed by a repeat assessment performed no less than four weeks after the criteria for response is met.

Progressive Disease (PD)

At least a 20% increase in the sum of the diameters of target lesions, taking as reference the smallest sum on study (this includes the baseline sum if that is the smallest on study). In addition to the relative increase of 20%, the sum must also demonstrate an absolute increase of at least 5 mm. (Note: the appearance of one or more new lesions is also considered progression, See Section 6.1.4.3).

Stable Disease (SD)

Neither sufficient shrinkage to qualify for PR nor sufficient increase to qualify for PD, taking as reference the smallest sum diameters while on study. (Note: a change of 20% or more that does not increase the sum of the diameters by 5 mm or more is coded as stable disease)

To be assigned a status of stable disease, measurements must have met the stable disease criteria at least once after study entry at a minimum interval of 12 weeks.

6.1.4.2 Evaluation of Non-Target Lesions

Complete Response (CR)

Disappearance of all non-target lesions and normalization of tumor marker level. All lymph nodes must be non-pathological in size (< 10 mm short axis)

NOTE: If tumor markers are initially above the upper normal limit, they must normalize for a patient to be considered in complete clinical response.

Non-CR/Non-PD

Persistence of one or more non-target lesion(s) and/or maintenance 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 (see Section 6.1.4.3). *Unequivocal progression* should not normally trump target lesion status. It must be representative of overall disease status change, not a single lesion increase.

When the patient also has measurable disease, there must be an overall level of substantial worsening in non-target disease such that, even in the presence of SD or PR in target disease, the overall tumor burden has increased sufficiently to merit discontinuation of therapy. A modest "increase" in the size of one or more on-target lesions is usually not sufficient to qualify for unequivocal progression status. The designation of overall progression solely on the basis of change in non-target disease in the face of SD or PR of target disease will therefore be extremely rare.

When the patient only has non-measurable disease, the increase in overall disease burden should be comparable in magnitude to the increase that would be required to declare PD for measurable disease: i.e., an increase in tumor burden from "trace" to "large", an increase in nodal disease from "localized" to "widespread", or an increase sufficient to require a change in therapy.

Although a clear progression of "non-target" lesions only is exceptional, the opinion of the treating physician should prevail in such circumstances, and the progression status should be confirmed at a later time by the review panel (or Principal Investigator).

6.1.4.3 Evaluation of New Lesions

The appearance of new lesions constitutes Progressive Disease (PD).

6.1.4.4 Evaluation of Best Overall Response

The best overall response is the best response recorded from the start of the treatment until disease progression/recurrence or non-protocol therapy (taking as reference for progressive disease the smallest measurements recorded since the treatment started). The patient's best response assignment will depend on the achievement of both measurement and confirmation criteria.

For Patients with Measurable Disease (i.e., Target Disease)

Target Lesions	Non-Target Lesions	New Lesions*	Best Overall Response	Remarks
CR	CR	No	CR	
CR	Non-CR/Non-PD***	No	PR	
CR	Not evaluated	No	PR	
PR	Non-PD***/not evaluated	No	PR	
SD	Non-PD***/not evaluated	No	SD	Documented at least once ≥ 12 wks. from study entry
PD	Any	Yes or No	PD	No prior SD, PR or CR
Any	PD**	Yes or No	PD***	
Any	Any	Yes	PD	

* See RECIST 1.1 manuscript for further details on what is evidence of a new lesion.

** In exceptional circumstances, unequivocal progression in non-target lesions may be accepted as disease progression.

*** PD in non-target lesions should not normally trump target lesion status. It must be representative of overall disease status change, not a single lesion increase. Please refer to the Evaluation of Non-Target Lesions-Progressive Disease section for further explanation.

NOTE: Patients with a global deterioration of health status requiring discontinuation of treatment without objective evidence of disease progression at that time should be reported as "*symptomatic deterioration."* Every effort should be made to document the objective progression even after discontinuation of treatment.

For Patients with Only Non-Measurable Disease (i.e., Non-Target Disease)

Non-Target Lesions	New Lesions	Overall Response
CR	No	CR
Non-CR/non-PD	No	Non-CR/non-PD*
Not all evaluated	No	not evaluated
Unequivocal PD	Yes or No	PD
Any	Yes	PD
* 'Non-CR/non-PD' is preferred over 'stable disease' for non-target disease since SD is increasingly used as an endpoint for assessment of efficacy in some trials so to assign this category when no lesions can be measured is not advised		

6.1.5 Duration of Response

Duration of Overall Response

The duration of overall response is measured from the time measurement criteria are met for CR or PR (whichever is first recorded) until the first date that recurrent or progressive disease is objectively documented (taking as reference for progressive disease the smallest measurements recorded since the treatment started).

The duration of overall CR is measured from the time measurement criteria are first met for CR until the first date that progressive disease is objectively documented.

Duration of Stable Disease

Stable disease is measured from the start of the treatment until the criteria for progression are met, taking as reference the smallest measurements recorded since the treatment started, including the baseline measurements.

To be assigned a status of stable disease, measurements must have met the stable disease criteria at least once after study entry at a minimum interval of 12 weeks.

7. Study Parameters

7.1 Therapeutic Parameters

1. Prestudy scans and x-rays used to assess all measurable or non-measurable sites of disease must be done within **4 weeks** prior to registration.
2. Prestudy CBC (with differential and platelet count) should be done ≤ **4 weeks** prior to registration.
3. All required prestudy chemistries, as outlined in Section 3, should be done ≤ **4 weeks** prior to registration.

NOTE: 1 cycle = 28 days

	Pre-Study		End of Cycles 1 and 2[9]	End of Cycle 3[9]	Every 3 cycles (after cycle 3) [9]	At discontinuation of treatment[10]	Post treatment up to 5 years from study entry
	≤ 4 weeks prior to registration	≤ 2 weeks prior to registration					
Height	X						
History, Physical Exam, ECOG PS, Vital signs, Weight	X		X	X	X	X	X[3]
Concomitant Medications	X		X	X	X		X[8]
CBC[1]	X			X	X	X	
Bilirubin, SGOT (AST), SGPT (ALT)	X			X	X	X	
Lipid profile[11]	X			X			
HCG [2]		X					
Rev. 8/12 Bone scan	X[6]			X[6]	X[6]		X[6,8]
Tumor assessment by PE	X			X	X	X	X[8]
Tumor assessment by CT or MRI[7]	X			X	X	X	X[8]
Research blood submissions[5]	X[4]			X		X	

1. CBCs (with differential and platelet count) which includes WBC, ANC, Platelets, Hgb, and Hct.
Rev. 5/11 2. All females of child-bearing potential must have a blood or urine test within 2 weeks prior to registration to rule out pregnancy.
3. Every 3 months if patient is < 2 years from study entry, every 6 months if patient is 2-5 years from study entry. No specific requirements if patient is more than 5 years from study entry.

Rev. 8/12 4. It is strongly encouraged that the whole blood collected for the genotype verification is collected prior to protocol treatment, but may be collected at the end of cycle three (3) if unable to collect at baseline.

Rev. 8/12 5. Refer to Sections 7.2 and 11 for submission instructions.

Rev. 5/11, 8/12 6. Baseline bone scan required in all patients; repeat in follow-up as clinically indicated.

NOTE: If bone scan done within 6 months prior to registration showed no evidence suggesting bone metastases and no clinical indication of skeletal pain or other evidence suggesting bone metastases, a repeat baseline bone scan is not required.

Rev. 5/11, 8/12 7. CT or MRI of chest/abdomen/pelvis are required at baseline. Those tests required to follow known site(s) of disease should be repeated at the end of Cycle 3 and then every 3 cycles during treatment and according to the follow up schedule if off treatment, until first progression of disease.

NOTE: If CT or MRI of chest and/or abdomen/pelvis done within 6 months prior to registration showed no evidence of disease in the area(s) and no clinical indication suggesting new metastases, full re-staging including all areas is not required; however, ensure that disease is evaluable per RECIST requirements (Section 6).

Rev. 5/11 8. Concomitant medication and tumor assessments are to be done up to (and including) the assessment which shows first progression of disease. If patient discontinues treatment due to reasons other than disease progression, concomitant medication and tumor assessments should be performed until disease progression on the following schedule: Every 3 months if patient is < 2 years from study entry, every 6 months if patient is 2-5 years from study entry. No specific requirements if patient is more than 5 years from study entry.

Rev. 5/11 9. All tests should be performed at the end of the cycle. A +/- 7 day window will be allowed in case of scheduling problems.

Rev. 5/11 10. Repeat any test not done within the prior 28 days.

Rev. 5/11 11. Lipid profile should be fasting.

7.2 Biological Sample Submissions

1. Pathological materials should be submitted for banking as outlined in Section 10 per patient consent.

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2. Whole blood and plasma must be submitted as outlined in Section 11 for CYP2D6 status and tamoxifen and metabolite levels.

NOTE: It is required that biological sample submissions be logged into the ECOG-ACRIN Sample Tracking System (STS) (see Section 10.4) for purposes of monitoring compliance.

NOTE: An informed consent must be signed prior to the use of any samples for any laboratory study or banking.

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	Pre-Study[1]	End of Cycle Three (3)	Off-Treatment	Submit to:
Block from Primary Tumor	X			ECOG-ACRIN Central Biorepository and Pathology Facility
Block from Metastatic Site (when available)	X			
Rev. 8/12 Plasma (one (1) 6mL sodium heparin green top tube)*		X	X	
Rev. 8/12 Whole Blood (one (1) 8-10mL EDTA purple top tube - K3)*	X[2]			Indiana University School of Medicine

*Mandatory

1. Baseline, prior to treatment.
2. Whole blood is strongly encouraged to be collected at baseline, prior to treatment, but may be collected at the end of cycle three (3) if unable to collect at baseline.

8. Drug Formulation and Procurement

8.1 Tamoxifen

8.1.1 Other Names

Nolvadex, tamoxifen citrate, NSC# 180973

8.1.2 Classification

Hormone antagonist (antiestrogen).

8.1.3 Mode of Action

Tamoxifen and its metabolites possess antiestrogenic activity due to their ability to compete with estradiol for binding to receptors in the cells of tumors that contain high amounts of estrogen receptors (such as breast cancer). The estrogen receptor complex is translocated from the cytoplasm of cancer cells to the nucleus where it reduces DNA synthesis and cellular responses to estrogen. Tamoxifen also displays mild estrogenic activity and induces secretion of transforming growth factor beta (TGF-beta), which has inhibitory effects on many types of epithelial cells.

8.1.4 Storage and Stability

Tamoxifen is stored at room temperature protected from light.

8.1.5 Dose Specifics

20 mg PO daily (as a single dose)

8.1.6 Preparation

Not applicable, tablet is ready for administration.

8.1.7 Route of Administration

Oral.

8.1.8 Incompatibilities

Tamoxifen is a potent inhibitor of hepatic cytochrome P450 mixed function oxidases (MFO). The effect of tamoxifen on the metabolism and excretion of other drugs requiring MFO for activation is unknown. Phenobarbital decreased tamoxifen serum level significantly in one patient. Concomitant bromocriptine therapy has been shown to elevate serum tamoxifen levels Tamoxifen may potentate the anticoagulant effects of warfarin.

8.1.9 Availability / How Supplied

Tamoxifen is commercially available in 10 mg and 20 mg tablets.

8.1.10 Side Effects

1. Hematologic: Thrombocytopenia, usually mild and transient, leukopenia, anemia.
2. Dermatologic: Rash, erythema.

3. Gastrointestinal: Nausea, vomiting, anorexia (may lead to weight loss), diarrhea or constipation, distaste for food.
4. Genitourinary: Vaginal bleeding or discharge, menstrual changes (amenorrhea, menstrual irregularities), pruritus vulvae.
5. Hepatic: Increased liver enzymes, cholestasis, increased bilirubin, and fatty changes in the liver.
6. Neurologic: Depression, dizziness, lightheadedness, headache, confusion, lassitude, and syncope.
7. Cardiovascular: Hot flashes, thrombophlebitis, thromboembolism, pulmonary embolism, fluid retention and edema. Thrombotic events, DVT, clotting factor abnormalities.
8. Ocular: Retinopathy, corneal opacity, slight increased risk of cataracts; corneal scarring and retinal changes have been reported.
9. Metabolic: Hypercalcemia.
10. Other: Tumor "flare" may occur in the first month of therapy, manifested as an increase in tumor-related symptoms, such as bone pain, increase in tumor size, erythema. Weight gain, fluid retention, and edema.
11. Effects in pregnancy: classified as Category D; women should not become pregnant while taking tamoxifen.
12. Secondary cancers: Tamoxifen increases the risk for uterine cancer and the possibility of death from this disease. Patients receiving tamoxifen should have routine gynecologic exams and report any menstrual irregularities, abnormal vaginal bleeding, changes in vaginal discharge and/or pelvic pain or pressure. Tamoxifen may possibly increase the risk for gastrointestinal cancers.

8.1.11 Nursing/Patient Implications

1. Monitor carefully for tumor flare reactions.
2. Teach patients and families to recognize signs and symptoms of hypercalcemia.
3. Advise patient of potential vaginal bleeding and menstrual changes, hot flashes.
4. Teach patients and families to recognize the signs and symptoms of thromboembolic events, namely deep vein thrombosis (DVT) and pulmonary embolism (PE).

NOTE: A patient medication diary is available in Appendix IV to monitor tamoxifen administration.

8.1.12 References

Legha SS. Tamoxifen in the treatment of breast cancer. Ann Intern Med 1988; 109:219-228.

Love RR. Tamoxifen therapy in primary breast cancer: Biology, efficacy and side effects. J Clin Oncol 1989; 7:803-815.

Kaiser-Kupfer MI, Lippman ME. Tamoxifen retinopathy. Cancer Treat Rep 1978; 62:315-320.

Lipton A, Harvey HA, Hamilton RW. Venous thrombosis as a side effect of tamoxifen treatment. Cancer Treat Rep 1984; 68:887-889.

Please see tamoxifen package insert for more information.

9. Statistical Considerations

The primary purpose of this study is to evaluate whether patients with blood samples with CYP2D6 score of 0 (poor metabolizer) have a reduced progression-free survival (PFS) relative to patients with samples with a CYP2D6 score of 1 or 2 (intermediate and extensive metabolizers, respectively). A total of 240 patients will be enrolled in this study. Assuming a monthly accrual of 10 patients, 24 months of accrual is needed. The below calculations assume that 85% (204/240) of the patients enrolled have samples where a CYP2D6 score of 0, 1, or 2 can be assigned.

CYP2D6 SCORING

We will use a scoring system that has been recently modified from Gaedigk et al (18) to include known CYP2D6 variants and inhibitors:

CYP2D6 Allele	**Points Assigned/Allele**
*1, *1xN, *2, *2xN, *35	1
*9, *10, *17, *41	0.5
*3, *4, *5, *6, *11	0
Medication	**Points Adjustment**
Paroxetine, Fluoxetine , Bupropion	-2
Sertraline, Duloxetine, Citalopram, Escitalopram, Celecoxib, Diphenhydramine, Chlorpheniramine	-1
Venlafaxine	-0

An overall comparison of patients with scores CYP2D6=0 vs. CYP2D6= 1 or 2 with respect to progression-free survival will be made. It is estimated that approximately 10% will have a score=0, 40% with a score=1 and 50% with a score=2. A hazard ratio (HR) greater than 1.95 or 2 is of interest to influence change in practice. The table below shows the HRs that can be detected with 80% power when all patients have been followed at least 3 months and disease in 180/204 (88%) has progressed. A log-rank test with a 2-sided 5% type I error rate will be used for the comparison.

Hazard Ratios that can be detected with 80% power

Prevalence of patients with CYP2D6 Score=0				
8%		10%		12%
2.09		1.95		1.86

For example, if 10% of the patients have samples with a CYP2D6 score=0, there is 80% power to detect a hazard ratio of 1.95 (comparing score=0 to score=1 or 2).

Due to the disproportionate expected percentage of poor vs. intermediate and extensive metabolizers, Cox proportional hazards models will be used to estimate the effect of CYP2D6 score with respect to PFS while adjusting for possible confounding factors such as prior AI use and other biomarkers that are being assessed in this study, to assess the

effect of prior AI use and other biomarkers alone with respect to PFS, and to test for interactions between the various baseline factors with respect to PFS.

Due to the low estimated percentage of patients with a CYP2D6 score =0, a stopping rule is incorporated into this design. If the rate of accrual of poor metabolizers is less than 8% or less than 1 patient with a CYP2D6 score=0 per month in the first 18 months that the study is open, the study will be suspended for further evaluation of feasibility.

The distribution of progression-free survival for the patients with a CYP2D6 score=0, 1, and 2 will be estimated using the Kaplan Meier method. Best overall response rate will be summarized as a proportion overall and within patients with a CYP2D6 score=0 vs. 1+2 and within score=0, 1, and 2. Proportion progression-fee at 6 months will be summarized overall and within patients with CYP2D6 score=0 vs. 1+2, and within score= 0, 1, and 2. Endoxifen levels will be summarized descriptively overall and within responders and non-responders. Comparisons between responders and non-responders with respect to endoxifen levels will be explored using a Wilcoxon rank sum test.

Safety Monitoring

Interim analyses of toxicity are performed twice yearly for all ECOG-ACRIN studies. Reports of these analyses are sent to the ECOG-ACRIN Principal Investigator or Senior Investigator at the participating institutions. Expedited reporting of certain adverse events is required, as described in Section 5.2.

9.1 Gender and Ethnicity

Based on previous data from E1103, the anticipated accrual in subgroups defined by gender and race is:

Ethnic Category	**Gender**		
	Females	**Males**	**Total**
Hispanic or Latino	13		13
Not Hispanic or Latino	227		227
Ethnic Category: Total of all subjects	240		240
Racial Category			
American Indian or Alaskan Native	0		0
Asian	4		4
Black or African American	44		44
Native Hawaiian or other Pacific Islander			
White	192		192
Racial Category: Total of all subjects	240		240

The accrual targets in individual cells are not large enough for definitive subgroup analyses. Therefore, overall accrual to the study will not be extended to meet individual subgroup accrual targets.

10. Pathology Review

NOTE: ECOG-ACRIN requires that all biological samples submitted be entered and tracked via the online ECOG-ACRIN Sample Tracking System (STS). An STS shipping manifest form must be generated and shipped with the sample submissions. See Section 10.4.

10.1 Pathological materials from the primary tumor and metastatic site, when available, should be submitted for banking for future studies.

The clinical investigator and the submitting pathologist have the responsibility for submitting pathology materials for banking. When a patient is registered to receive protocol therapy, the submitting pathologist and clinical research associate should refer to Appendix II (Pathology Submission Guidelines) which provides the following:

10.1.1 Instruction Sheet from ECOG-ACRIN Central Biorepository and Pathology Facility providing details for the Submission of Pathology Materials.

10.1.2 Memorandum to the submitting pathologist from Stanley Hamilton, M.D., chair, ECOG-ACRIN Laboratory Science and Pathology Committee, providing details for the Submission of Pathology Materials.

10.1.3 A list of required materials.

10.2 Materials Required For This Protocol

10.2.1 Forms

- A copy of the surgical pathology report
- Immunologic studies, if available

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- Sample Tracking System Shipping Manifest Form (see Section 10.4)
  - If STS is unavailable, complete ECOG-ACRIN Generic Specimen Submission Form (#2981). Please identify the clinical status of the submitted material (i.e., pretreatment as opposed to remission and relapse). Please log information into STS once accessible.

In addition to the surgical pathology report, if immunologic studies have been performed at the home institution, it is necessary that these be forwarded as well.

10.2.2 Pathology Sample Submissions

- Original diagnostic paraffin embedded primary tumor block and block from metastatic site (when available).

NOTE: If unable to submit blocks submit fifteen (15) 5-micron sections on uncharged slides or contact the CBPF for alternatives at 1-844-744-2420 or eacbpf@mdanderson.org.

NOTE: Submit only from patients who have consented to banking.

10.3 Shipping Procedures

Log the samples into the ECOG-ACRIN Sample Tracking System (STS) the day of shipment. If the STS is unavailable, an Generic Specimen Submission Form (#2981) must be submitted with the samples. Once STS is available, retroactively log the shipment into STS, using the actual collection and shipping dates.

10.3.1 Submission Schedule

The pathology samples should be submitted within one month of patient registration.

10.3.2 Shipping Address

ECOG-ACRIN Central Biorepository and Pathology Facility
MD Anderson Cancer Center
Department of Pathology, Unit 085
Tissue Qualification Laboratory for ECOG-ACRIN, Room G1.3586
1515 Holcombe Boulevard
Houston, TX 77030
Toll Free Phone: 1-844-744-2420 (713-745-4440 Local or International Sites)
Fax: (713) 563-6506
Email: eacbpf@mdanderson.org

An STS shipping manifest form must be generated and shipped with all sample submissions.

NOTE: A copy of the completed submission form will be sent to the Operations Office by the CBPF.

10.4 ECOG-ACRIN Sample Tracking System

It is **required** that all samples submitted on this trial be entered and tracked using the ECOG-ACRIN Sample Tracking System (STS). The software will allow the use of either 1) an ECOG-ACRIN user-name and password previously assigned (for those already using STS), or 2) a CTSU username and password.

When you are ready to log the collection and/or shipment of the samples required for this study, please access the Sample Tracking System software by clicking https://webapps.ecog.org/Tst

Important: Please note that the STS software creates pop-up windows, so you will need to enable pop-ups within your web browser while using the software. A user manual and interactive demo are available by clicking this link: http://www.ecog.org/general/stsinfo.html Please take a moment to familiarize yourself with the software prior to using the system.

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A shipping manifest form must be generated and shipped with all sample submissions.

Please direct your questions or comments pertaining to the STS to ecog.tst@jimmy.harvard.edu.

10.4.1 Study Specific Notes

An Generic Specimen Submission Form (#2981) will be required only if STS is unavailable at time of sample submission. Indicate the appropriate Lab ID # on the submission form:

- 0001 = ECOG-ACRIN CBPF
- 0149 = Indiana University School of Medicine
- Retroactively enter all collection and shipping information when STS is available.

10.5 Banking

Blocks/slides submitted will be retained at the ECOG-ACRIN Central Biorepository for use in future ECOG-ACRIN approved studies. Blocks will be available for purposes of individual patient management on specific written request. If future use is denied or withdrawn by the patient, the samples will be removed from consideration for use in any future study.

11. Correlative Studies

NOTE: ECOG-ACRIN requires that all biological samples submitted be entered and tracked via the online ECOG-ACRIN Sample Tracking System. An STS shipping manifest form must be generated and shipped with the sample submissions. See Section 10.4.

11.1 The main goal of the study is to correlate the presence of genetic polymorphism, tamoxifen metabolites, and benefit from the drug.

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11.1.1 Sample Submission Schedule – Genotype Verification (Mandatory)

Whole blood must be collected at baseline, prior to treatment (strongly encouraged), but may be collected at the end of cycle three (3) if unable to collect at baseline.

All questions regarding sample collection, preparation and shipping should be sent to: Anne Nguyen, Tel: 317-630-8795, Pager: 317-312-1314, Fax: 317-630-8185, Email: annnguye@iupui.edu

11.1.2 Sample Preparation Guidelines

Label blood samples with ECOG-ACRIN Protocol Number (E3108), ECOG-ACRIN Five Digit Sequence Number, Collection Date and Collection Time.

Whole Blood, EDTA purple top tube (Pharmacogenomics)

- Draw 8-10mL of blood into one (1) EDTA (purple top) vacutainer tube.
- Pipette whole blood into two (2) cryotubes of 4-5mL each.
- Freeze and store samples at -70°C or lower until time of shipment.

11.1.3 Shipping Procedures

Log the samples into the ECOG-ACRIN STS the day of shipment. If the STS is unavailable, an ECOG-ACRIN Generic Specimen Submission Form (#2981) must be submitted with the samples. Once STS is available, retroactively log the shipment into STS, using the actual collection and shipping dates.

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Frozen blood samples should be shipped the day after collection. Ship blood samples overnight on dry ice. Blood samples collected on Thursday or Friday should be shipped the following Monday.

Ship to:

Anne Nguyen
Indiana University School of Medicine
Division of Clinical Pharmacology
1001 West 10th Street
WD Myers Bldg., W7123
Indianapolis, IN 46202
Tel: 317-630-8795
Pager: 317-312-1314
Fax: 317-630-8185

Email: annnguye@iupui.edu

An STS shipping manifest form must be generated and shipped with all sample submissions.

Samples should not be shipped on Friday or the day before an observed holiday.

11.2 Sample Submission Schedule – Tamoxifen Metabolites (Mandatory)

Plasma must be collected at the following time points:

- End of Cycle 3
- Off Treatment

Questions pertaining to sample collection and shipment can be directed to Adekunle Raji at the CBPF at 1-844-744-2420 or araji@mdanderson.org. (International sites should contact Raji for special processing and shipping instructions.)

11.2.1 Sample Preparation Guidelines

Blood tubes should be labeled with the ECOG-ACRIN protocol number “E3108", patient initials, ECOG-ACRIN patient sequence number, institution name, date and time drawn and time point.

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Plasma, Sodium Heparin green top tube

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- Draw 6mL of blood into one (1) sodium heparin (green top) vacutainer tube. Cover blood immediately after collection.

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- Centrifuge tube at 4°C for 15 minutes at 3500 RPM.

  NOTE: Tamoxifen metabolites are extremely sensitive. Work in low-light areas during processing (tin foil may be removed briefly while in centrifuge).

- Pipette plasma into three (3) cryotubes of 1mL each; place any remaining plasma into a fourth cryotube.

  NOTE: Wrap each cryotube entirely with foil; a sample label must be placed on the cryotube itself and an additional label placed on the foil.

- Freeze and store samples at -70°C or lower until time of shipment.

11.2.2 Shipping Procedures

Log the samples into the ECOG-ACRIN Sample Tracking System (STS) the day of shipment. If the STS is unavailable, a Generic Specimen Submission Form (#2981) must be submitted with the samples. Once STS is available, retroactively log the shipment into STS, using the actual collection and shipping dates.

Samples should be shipped Sunday through Thursday, to arrive Monday through Friday. The laboratory is closed weekends and holidays.

Frozen blood samples must be shipped overnight on dry ice. It is recommended that multiple patient samples be batched and shipped together on a quarterly basis.

Shipping Address:

ECOG-ACRIN Central Biorepository and Pathology Facility
MD Anderson Cancer Center
Department of Pathology, Unit 085
Tissue Qualification Laboratory for ECOG-ACRIN, Room G1.3586
1515 Holcombe Boulevard
Houston, TX 77030
Toll Free Phone: 1-844-744-2420 (713-745-4440 Local or International Sites)
Fax: (713) 563-6506
Email: eacbpf@mdanderson.org

An STS shipping manifest form must be generated and shipped with all sample submissions.

11.3 Methods

Genotyping of tamoxifen disposition genes: DNA will be extracted from whole blood as we have previously described (3). Tamoxifen disposition appears to be associated with genetic variants in at least 4 genes. We will genotype 14 genetic variants in these genes, including variants in the *CYP2D6* and UGT2B7 genes, using predesigned Taqman assays.

A 10 ml sample of blood will be collected in a heparinized (green-top) tube and transported over ice, wrapped in aluminum foil. Plasma from this sample will be used to analyze levels of tamoxifen, 4-hydroxy tamoxifen and 4-hydroxy-N-desmethyl-tamoxifen using an HPLC assay with UV detection as described below.

Tamoxifen and its metabolite concentrations in plasma were determined by using high-performance liquid chromatography with online photocyclization as previously described by Fried and Wainer (19), with minor modifications (20). In brief, this method allows for the rapid extraction and specific detection of tamoxifen and its metabolites on the basis of a technique originally described by Kikuta and Schmid (21) that used a mobile phase of 65% acetonitrile, 35% potassium phosphate (pH 3.0) and eluted the metabolites on a 4.6 x 250 mm 0.5-µm cyanonitrile column (21). This method has been modified to use a novel column-switching technique (19) that allows for high recovery and precise separation of the drug and metabolites. Consistent separation of tamoxifen, N-desmethyl-tamoxifen, 4-hydroxy-tamoxifen, endoxifen, and N-didesmethyl-tamoxifen was achieved using this method. We found that the limits of quantification were 0.5 ng/mL and 0.25 ng/mL for endoxifen and 4-hydroxy-tamoxifen, respectively. The inter- and intra-day coefficients of variation were less than 10% at the midpoint of the standard curves for each metabolite tested.

11.4 Banking

The residuals and/or derivatives of blood samples collected for this study will be retained at the ECOG-ACRIN Central Repository for possible use in ECOG-ACRIN approved future studies. If future use is denied or withdrawn by the patient, the samples will be removed from consideration for use in any future study.

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11.5 Sample Inventory Submission Guidelines

Inventories of all samples collected, aliquoted, and used on the above mentioned laboratory studies will be submitted electronically by secure web application to the ECOG-ACRIN Operations Office - Boston on a monthly basis or upon request by any laboratory holding and/or using specimens associated with this study.

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11.6 Lab Data Transfer Guidelines

The data collected or generated on the above mentioned laboratory studies will be submitted electronically via secure data portal to the ECOG-ACRIN Operations Office - Boston on a quarterly basis. The quarterly cut-off dates are March 31, June 30, September 30, and December 31.

12. Records to Be Kept

Please refer to the E3108 Forms Packet for the forms submission schedule and copies of all forms. The E3108 Forms Packet may be downloaded by accessing the ECOG World Wide Web Home Page (http://www.ecog.org). Forms must be submitted to the ECOG-ACRIN Operations Office - Boston, FSTRF, 900 Commonwealth Avenue, Boston, MA 02215 (ATTN: DATA).

This study will be monitored by the CTEP Data Update System (CDUS) version 3.0. Cumulative CDUS data will be submitted quarterly from the ECOG-ACRIN Operations Office - Boston to CTEP by electronic means.

Please contact the ECOG-ACRIN Operations Office - Boston prior to destroying any source documents.

13. Patient Consent and Peer Judgment

Current FDA, NCI, state, federal and institutional regulations concerning informed consent will be followed.

14. References

1. Stearns V, Johnson MD, Rae JM, *et al.* Active tamoxifen metabolite plasma concentrations after coadministration of tamoxifen and the selective serotonin reuptake inhibitor paroxetine. Journal of the National Cancer Institute 2003;95(23):1758-64.
2. Jin Y, Desta Z, Stearns V, *et al.* CYP2D6 genotype, antidepressant use, and tamoxifen metabolism during adjuvant breast cancer treatment. Journal of the National Cancer Institute 2005;97(1):30-9.
3. Borges S, Desta Z, Li L, *et al.* Quantitative effect of CYP2D6 genotype and inhibitors on tamoxifen metabolism: implication for optimization of breast cancer treatment. Clin Pharmacol Ther 2006;80(1):61-74.
4. Goetz MP, Rae JM, Suman VJ, *et al.* Pharmacogenetics of tamoxifen biotransformation is associated with clinical outcomes of efficacy and hot flashes. J Clin Oncol 2005;23(36):9312-8.
5. Goetz MP, Knox SK, Suman VJ, *et al.* The impact of cytochrome P450 2D6 metabolism in women receiving adjuvant tamoxifen. Breast cancer research and treatment 2007;101(1):113-21.
6. Nowell S, Sweeney C, Winters M, *et al.* Association between sulfotransferase 1A1 genotype and survival of breast cancer patients receiving tamoxifen therapy. Journal of the National Cancer Institute 2002;94(21):1635-40.
7. Nowell SA, Ahn J, Rae JM, *et al.* Association of genetic variation in tamoxifen-metabolizing enzymes with overall survival and recurrence of disease in breast cancer patients. Breast cancer research and treatment 2005;91(3):249-58.
8. Wegman P, Elingarami S, Carstensen J, Stal O, Nordenskjold B, Wingren S. Genetic variants of CYP3A5, CYP2D6, SULT1A1, UGT2B15 and tamoxifen response in postmenopausal patients with breast cancer. Breast Cancer Res 2007;9(1):R7.
9. Wegman PP, Wingren S. CYP2D6 variants and the prediction of tamoxifen response in randomized patients: author response. Breast Cancer Res 2005;7(6):E7.

10. Higgins M, Rae JM, Flockhart D, Hayes DF, Stearns V. Pharmacogenetics of Tamoxifen: Who should undergo CYP2D6 genetic testing? . J Natl Compr Canc Netw 2009;In Press.
11. Schroth W, Antoniadou L, Fritz P*, et al.* Breast cancer treatment outcome with adjuvant tamoxifen relative to patient CYP2D6 and CYP2C19 genotypes. J Clin Oncol 2007;25(33):5187-93.
12. Lim HS, Ju Lee H, Seok Lee K, Sook Lee E, Jang IJ, Ro J. Clinical implications of CYP2D6 genotypes predictive of tamoxifen pharmacokinetics in metastatic breast cancer. J Clin Oncol 2007;25(25):3837-45.
13. Kiyotani K, Mushiroda T, Sasa M*, et al.* Impact of CYP2D6*10 on recurrence-free survival in breast cancer patients receiving adjuvant tamoxifen therapy. Cancer science 2008;99(5):995-9.
14. Bonanni B, Macis D, Maisonneuve P*, et al.* Polymorphism in the CYP2D6 tamoxifen-metabolizing gene influences clinical effect but not hot flashes: data from the Italian Tamoxifen Trial. J Clin Oncol 2006;24(22):3708-9; author reply 9.
15. Wegman P, Vainikka L, Stal O*, et al.* Genotype of metabolic enzymes and the benefit of tamoxifen in postmenopausal breast cancer patients. Breast Cancer Res 2005;7(3):R284-90.
16. Xu Y, Sun Y, Yao L*, et al.* Association between CYP2D6 *10 genotype and survival of breast cancer patients receiving tamoxifen treatment. Ann Oncol 2008;19(8):1423-9.
17. Newman WG, Hadfield, K.D., Latif, A.,Roberts, S.A., Shenton, A., McHague, C., Lalloo, F., Howell, S., Evans, G. Impaired tamoxifen metabolism reduces survival in familial breast cancer patients. Clin Cancer Res 2008;14(18):5913-8.
18. Gaedigk A, Simon SD, Pearce RE, Bradford LD, Kennedy MJ, Leeder JS. The CYP2D6 activity score: translating genotype information into a qualitative measure of phenotype. Clin Pharmacol Ther 2008;83(2):234-42.
19. Fried KM, Wainer IW. Direct determination of tamoxifen and its four major metabolites in plasma using coupled column high-performance liquid chromatography. J Chromatogr B Biomed Appl 1994; 655: 261-8.
20. Lee KH, Ward BA, Desta Z, Flockhart DA, Jones DR. Quantification of tamoxifen and three metabolites in plasma by high-performance liquid chromatography with fluorescence detection: application to a clinical trial. J Chromatogr B Analyt Technol Biomed Life Sci 2003; 791: 245-53.
21. Kikuta C, Schmid R. Specific high-performance liquid chromatographic analysis of tamoxifen and its major metabolites by "on-line" extraction and post-column photochemical reaction. J Pharm Biomed Anal 1989; 7: 329-37.

A Phase II Prospective Trial Correlating Progression Free Survival with CYP2D6 Activity in Patients with Metastatic Breast Cancer Treated with Single Agent Tamoxifen

Appendix I

Informed Consent Template for Cancer Treatment Trials (English Language) - [Deleted in Addendum #4]

INFORMED CONSENT INTENTIONALLY REMOVED FROM PROTOCOL DOCUMENT

Appendix II

Pathology Submission Guidelines

The following items are included in Appendix II:

1. Guidelines for Submission of Pathology Materials (instructional sheet for Clinical Research Associates [CRAs])
2. Instructional memo to submitting pathologists
3. List of Required Materials for E3108
4. ECOG-ACRIN Generic Specimen Submission Form (#2981)

Guidelines for Submission of Pathology Materials

The following items should always be included when submitting pathology materials to the ECOG-ACRIN Central Biorepository and Pathology Facility:

- Institutional Surgical Pathology Report
- Pathology materials (see attached List of Required Material)
- Generic Specimen Submission Form (#2981)

Instructions:

1. Complete blank areas of the pathologist's instructional memo and forward it, along with the List of Required Material to the appropriate pathologist.
2. The pathologist should return the required pathology samples and surgical pathology reports, along with the completed Generic Specimen Submission Form (#2981) (Part B completed). If any other reports are required, they should be obtained from the appropriate department at this time.
3. Keep a copy of the Generic Specimen Submission Form (#2981)for your records. (The original should be sent to the CBPF.)
4. Double-check that ALL required forms, reports and pathology samples are included in the package to the ECOG-ACRIN Central Biorepository and Pathology. (See appropriate List of Required Material.)

Pathology specimens submitted WILL NOT be processed by the Pathology Coordinating Office until all necessary items are received.

5. Mail pathology materials to:

    ECOG-ACRIN Central Biorepository and Pathology FacilityMD Anderson Cancer Center
    Department of Pathology, Unit 085
    Tissue Qualification Laboratory for ECOG-ACRIN, Room G1.3586
    1515 Holcombe Boulevard
    Houston, TX 77030

If you have any questions concerning the above instructions or if you anticipate any problems in meeting the pathology material submission deadline of one month, contact the Pathology Coordinator at the ECOG-ACRIN CBPF by telephone 1-844-744-2420, by fax (713) 563-6506, or by email eacbpf@mdanderson.org.

List of Required Material

E3108: A Phase II Prospective Trial Correlating Progression Free Survival with CYP2D6 Activity in Patients with Metastatic Breast Cancer Treated with Single Agent Tamoxifen

Pre-Treatment

1. Generic Specimen Submission Form (#2981)
2. Institutional pathology report ***(must be included with EVERY pathology submission)***.
3. Pathology materials.
   - Original diagnostic paraffin embedded primary tumor block and block from metastatic site (when available)

NOTE: If unable to submit blocks, submit fifteen (15) 5-micron sections on uncharged slides or contact the CBPF for alternatives at 1-844-744-2420 or eacbpf@mdanderson.org.

NOTE: Submit only from patients who have consented to banking.

Robert L. Comis, MD, and Mitchell D. Schnall, MD, PhD
Group Co-Chairs

MEMORANDUM

TO: _____
(Submitting Pathologist)

FROM: Stanley Hamilton, M.D., Chair
ECOG-ACRIN Laboratory Science and Pathology Committee

DATE: _____

SUBJECT: Submission of Pathology Materials for E3108: A Phase II Prospective Trial Correlating Progression Free Survival with CYP2D6 Activity in Patients with Metastatic Breast Cancer Treated with Single Agent Tamoxifen

The patient named on the attached requesthas been entered onto an ECOG-ACRIN protocol by _____ (ECOG-ACRIN Investigator). This protocol requests the submission of pathology materials for banking.

Keep a copy of the submission for your records and return, the surgical pathology report(s), the slides and/or blocks and any other required material (see List of Required Material) to the Clinical Research Associate (CRA). The CRA will forward all required pathology material to the ECOG-ACRIN Central Biorepository and Pathology Facility (CBPF).

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Blocks and/or slides submitted for this study will be retained at the ECOG-ACRIN CBPF for future studies. Blocks will be returned for purposes of patient management care upon request.

If you have any questions regarding this request, please contact the ECOG-ACRIN CBPF at 1-844-744-2420, or by fax (713) 563-6506.

The ECOG-ACRIN CRA at your institution is:

Name: _____

Address: _____

Phone: _____

Thank you.

ECOG-ACRIN Generic Specimen Submission Form

Form No. 2981v3

Institution Instructions: This form is to be completed and submitted with **all specimens** ONLY if the Sample Tracking System (STS) is not available. **Use one form per patient, per time-point.** All specimens shipped to the laboratory must be listed on this form. Enter all dates as MM/DD/YY. Keep a copy for your files. Retroactively log all specimens into STS once the system is available. **Contact the receiving lab to inform them of shipments that will be sent with this form.**

Protocol Number _____ **Patient ID** _____ **Patient Initials** Last _____ First _____

Date Shipped _____ **Courier** _____ **Courier Tracking Number** _____

Shipped To (Laboratory Name) _____ **Date CRA will log into STS** _____

FORMS AND REPORTS: Include all forms and reports as directed per protocol, e.g., pathology, cytogenetics, flow cytometry, patient consult, etc.

Required fields for all samples				**Additional fields for tissue submissions**				**Completed by Receiving Lab**
Protocol Specified Timepoint:								
Sample Type (fluid or fresh tissue, include collection tube type)	**Quantity**	**Collection Date and Time 24 HR**		**Surgical or Sample ID**	**Anatomic Site**	**Disease Status** (e.g., primary, mets, normal)	**Stain or Fixative**	**Lab ID**

Fields to be completed if requested per protocol. Refer to the protocol-specific sample submissions for additional fields that may be required.					
Leukemia/Myeloma Studies:	**Diagnosis**	**Intended Treatment Trial**	**Peripheral WBC Count (x1000)**	**Peripheral Blasts %**	**Lymphocytes %**
Study Drug Information:	**Therapy Drug Name**	**Date Drug Administered**	**Start Time 24 HR**	**Stop Time 24HR**	
Caloric Intake:	**Date of Last Caloric Intake**		**Time of Last Caloric Intake 24HR**		

CRA Name _____ **CRA Phone** _____ **CRA Email** _____

Comments

9/12/14

Appendix III

Patient Thank You Letter

We ask that the physician use the template contained in this appendix to prepare a letter thanking the patient for enrolling in this trial. The template is intended as a guide and can be downloaded from the ECOG web site at http://www.ecog.org. As this is a personal letter, physicians may elect to further tailor the text to their situation.

This small gesture is a part of a broader program being undertaken by ECOG-ACRIN and the NCI to increase awareness of the importance of clinical trials and improve accrual and follow-through. We appreciate your help in this effort.

[PATIENT NAME] [DATE]

[PATIENT ADDRESS]

Dear [PATIENT SALUTATION],

Thank you for agreeing to take part in this important research study. Many questions remain unanswered in cancer. With the help of people like you who participate in clinical trials, we will achieve our goal of effectively treating and ultimately curing cancer.

We believe you will receive high quality, complete care. I and my research staff will maintain very close contact with you. This will allow me to provide you with the best care while learning as much as possible to help you and other patients.

On behalf of ***[INSTITUTION]*** and the ECOG-ACRIN Cancer Research Group, we thank you again and look forward to helping you.

Sincerely,

[PHYSICIAN NAME]

Appendix IV

Medication Diary for Tamoxifen

Please complete this diary on a daily basis. Write in the amount of the dose of tamoxifen that you took in the appropriate "Day" box.

On the days that you do not take any study drug, please write in "0". If you forget to take your daily dose, please write in "0", but remember to take your prescribed dose at the next regularly scheduled time.

If you experience any health/medical complaints or take any medication other than those in this study, please record this information.

You should take tamoxifen (one 20 mg pill) every day until your health care team tells you to stop.

Cycle # (Month):

Week of: _____

Study Drug	Day 1	Day 2	Day 3	Day 4	Day 5	Day 6	Day 7
Tamoxifen							

Week of: _____

Study Drug	Day 8	Day 9	Day 10	Day 11	Day 12	Day 13	Day 14
Tamoxifen							

Week of: _____

Study Drug	Day 15	Day 16	Day 17	Day 18	Day 19	Day 20	Day 21
Tamoxifen							

Week of: _____

Study Drug	Day 22	Day 23	Day 24	Day 25	Day 26	Day 27	Day 28
Tamoxifen							

HEALTH/MEDICAL COMPLAINTS

Please record all health/medical complaints you may have experienced below.

Please describe what you experienced	Date started	Date stopped

OTHER MEDICATION

Record only medication (prescription and/or over-the-counter, including herbal medications and vitamins) taken other than tamoxifen.

Name of Medication	Why did you take the medication?	Date medication started?	Date medication stopped

Patient Signature

_____