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

E2108

A Randomized Phase III Trial of the Value of Early Local Therapy for the Intact Primary Tumor in Patients with Metastatic Breast Cancer

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Addendum #1 – Incorporated Prior to Activation
Addendum #2 – 7/12
Addendum #3 – 2/13
Addendum #4 – 7/13
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Table of Contents

Rev. 2/13

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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. 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.		
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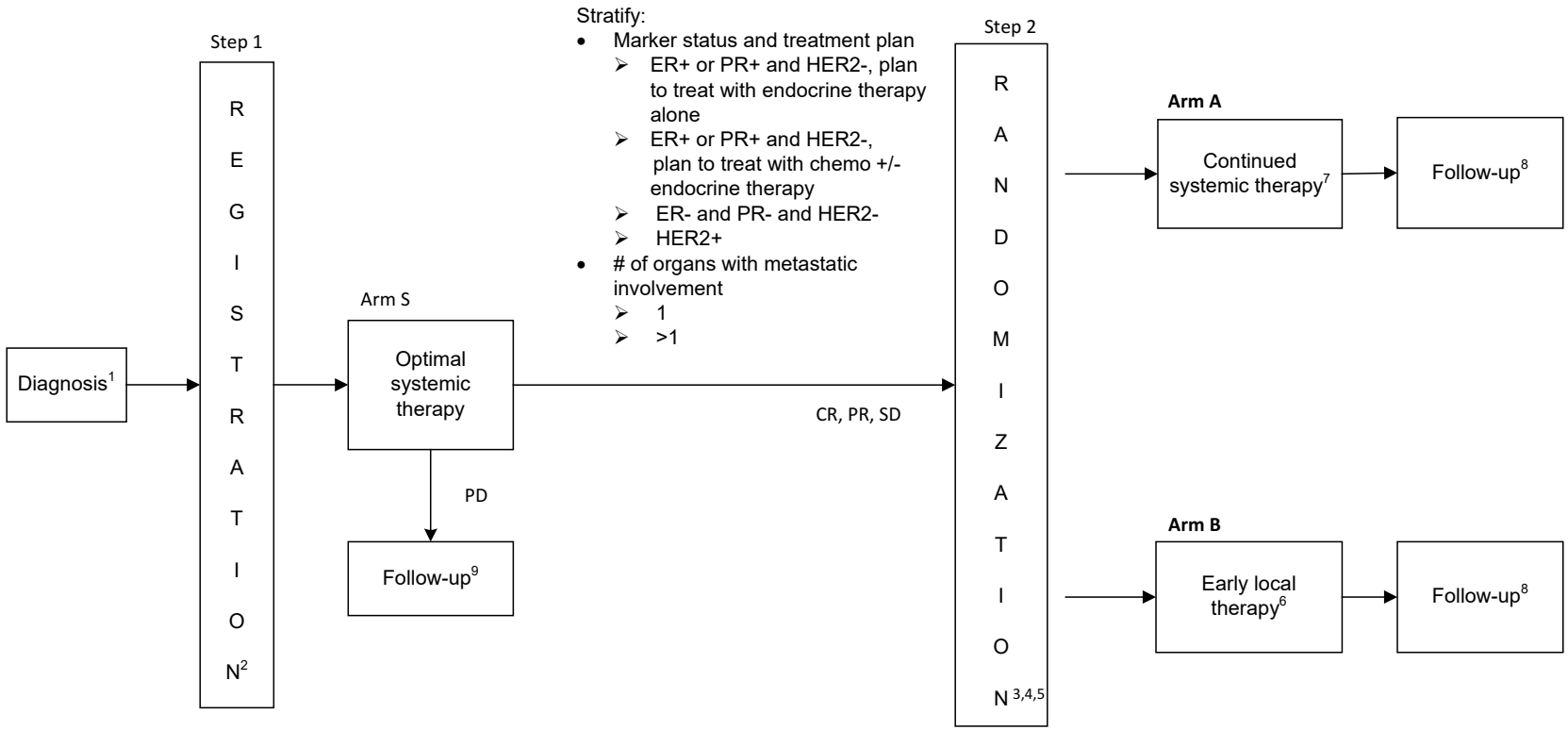
Schema



Rev. 7/13 Accrual = 368

1. Women with intact primary tumors AND metastatic disease at any site are eligible.

Rev. 7/12 2. Patients may register (Step 1) at anytime following the diagnosis of Stage IV breast cancer, either before or after the start of systemic therapy, up to the 30th week of treatment.

Rev. 7/12 3. Patients must be randomized (Step 2) within 32 weeks after the start of systemic therapy.

4. Patients may not be randomized (Step 2) less than 16 weeks after the start of systemic therapy.

5. At the time of randomization, patients must have documentation of CR, PR or SD as response to optimal systemic therapy.

Rev. 7/13 Rev. 4/14 6. Early local therapy (Arm B) is defined as surgery and radiotherapy for the primary tumor, following induction systemic therapy. Surgery is to occur no later than 10 weeks after randomization.

7. Continued systemic therapy is defined as therapy delivered only as needed for control of distant disease.

8. All randomized patients will be followed for treatment and disease status for 5 years post randomization.

9. Patients who are not randomized will be followed for survival for 5 years post registration.

1. Introduction

The importance of effective local therapy as a means of optimizing survival in women with Stages 0-III breast cancer is well established. However, approximately 5% of women with primary breast cancer in the United States present with Stage IV disease. The traditional approach to this problem has been to treat with systemic therapy, and to provide therapy for the primary tumor only when palliation is required. There is presently no consensus regarding optimal local therapy for these women, and treatment may vary from mastectomy (often justified as “toilette” mastectomy, in order to prevent uncontrolled local disease during the remainder of the patient’s life), to obtaining a tissue diagnosis with needle biopsy. If the primary tumor is excised for diagnosis, follow-up radiation is almost never used in the setting of distant metastases. According to the present paradigm, once metastases have occurred, local therapy provides no survival advantage, and should not be pursued. The alternative paradigm is that the primary tumor is a source of re-seeding of distant sites and therefore elimination of this source of metastasizing cells may be of benefit. Data from a SWOG trial of renal cell carcinoma are pertinent to this argument. The worth of nephrectomy was examined in patients with Stage IV disease, who were randomized to interleukin therapy, with or without nephrectomy. Results from this trial show an improvement in survival for the nephrectomy group, with overall median survival increasing from 8 months without nephrectomy, to 11 months for patients in the nephrectomy arm (1). These findings raise the possibility that aggressive local therapy may contribute to prolongation of survival in other tumors.

Data from other tumor types may also point to a possible survival advantage for patients with distant metastases undergoing resection of the primary tumor. A retrospective analysis of patients with asymptomatic primary colon cancer and distant metastases experienced longer survival following primary tumor resection (2). Resected patients had prolonged median (16 versus 9 months, $p < 0.001$) and 2-year (25% versus 6%, $p < 0.001$) survival compared with patients never resected. Similar results have been reported for gastric cancer (58, 59, 60, 61). These findings are undoubtedly influenced by a bias favoring patients who were selected for resection, but in the absence of randomized trials, the possibility that resection has a salutary effect on survival in patients with metastatic carcinomas of the colon or stomach remains open.

The past seven years have witnessed a re-examination of the use of local therapy in women with Stage IV disease, because of an accumulation of retrospective data suggesting that local therapy may also be important in this group of women, and may improve survival. At least nine retrospective studies (4-12) have examined the impact of surgical resection of the primary tumor in the setting of metastatic disease, and eight show a reduction in the hazard of death that ranges from 40% to 50%. Despite statistical adjustment for biases driving the use of surgery, the improvement in survival seen in the surgical group cannot be definitively attributed to the resection of the primary tumor since in most studies the women in the surgical groups were younger, had smaller tumors, fewer metastatic sites, and were more likely to have bone/soft tissue metastases rather than visceral disease. Additionally, it is not possible from these retrospective studies to assess the value of local therapy components other than resection of the primary tumor (i.e. axillary dissection and local radiotherapy). It is therefore necessary to conduct a randomized trial to formally test the hypothesis generated by these retrospective reviews. The inclusion of appropriate correlative science endpoints will provide unique opportunities to understand the biology of

metastatic disease, and will guide further advances in the management of women with metastatic breast cancer. The alternative to a randomized trial is a prospective registry study, but such a design will serve only to reinforce existing biases (the retrospective data discussed below testify to the fact that current clinical decision-making seems to reliably identify women who will do better). A prospective registry trial will not allow the crucial distinction of whether women chosen for surgery have tumors that are biologically indolent, or whether the course of their tumors is being altered by the use of local therapy.

The design of such a randomized trial should incorporate the standard elements of current therapy for metastatic breast cancer (i.e. the primacy of systemic therapy), allow flexibility in the choice of systemic therapy regimens that accommodate the biologic variation of breast cancer, and test the value of early, complete local therapy (resection with free surgical margins plus radiotherapy) against the current standard (i.e. local therapy at the discretion of the treating physician, only for palliation of progressive and symptomatic local disease)

1.1 Review of Retrospective Data

As reported in eight separate retrospective studies in the past four years, substantial numbers of women with de novo Stage IV breast cancer undergo surgical extirpation of the primary tumor. These studies are based on data from the National Cancer Database (NCDB) (4, 13), two European Tumor Registries (5, 12), four large comprehensive cancer centers (6, 8, 9, 10) , and the SEER database (7) and show that surgical resection of the primary tumor has been performed in 30-55% of women with de-novo Stage IV breast cancer. Data on the use of follow-up radiation therapy in this setting is very sparse, but a French study where primary radiotherapy was used for the in-breast disease shows very similar benefit (67). These studies are remarkably consistent in the finding that women who undergo surgical therapy for the primary tumor in the setting of metastatic disease fare better than those whose primary tumor is left intact. However, the entire published literature on this topic consists of retrospective reviews, all subject to the same selection bias: i.e., healthier women with lower disease burden were offered surgery.

Evidence supporting the hypothesis that local therapy is useful in women with metastatic breast cancer include the time-course of local failure and metastatic disease (14), and the survival benefit of locoregional radiotherapy when compared to patients treated with adjuvant systemic therapy alone (15-17). These data suggest that uncontrolled local disease may act as a source of continued seeding of distant metastases. Thus local tumor burden may affect outcome for patients with local regional disease and metastases, regardless of whether those metastases are covert (Stage II-III) or overt (Stage IV).

1.2 Observed Selection Biases

Across the majority of studies, women treated with surgical resection of the primary tumor tend to be younger, with better access to care (in the US, this equates with European ancestry and being married), smaller tumors, single organ-system metastatic involvement, and bony or soft tissue metastases (rather than visceral metastases). In the analyses where margin data were available for a majority of patients, the presence of tumor-free margins was significantly associated with improved survival and benefit of surgical resection (4, 5).

1.3 Parameters Not Addressed in Most Studies

These include the timing of metastatic diagnosis relative to the surgical procedure; the use of axillary dissection; and the use of loco-regional radiotherapy. The timing of the surgical procedure is important since women who underwent surgery with the diagnosis of Stage I-III breast cancer, were radiologically staged in the post-operative period, and found to have metastases may have a better prognosis than those who were diagnosed with metastases prior to surgery. This issue is not well-addressed in most of the published series, raises skepticism about existing retrospective data, and adds justification to the need for a randomized trial. In one small study where this distinction was clearly made, women who underwent surgery following the diagnosis of metastases derived no benefit from surgical resection of the primary (18). In another retrospective analysis, three intervals were defined, following diagnosis: less than 3 months, 3-9 months, and > 9 months. Women undergoing surgery in the first three months following diagnosis had shorter survival than those undergoing tumor resection more than three months after diagnosis (19). These authors did not specifically examine the timing of systemic therapy, but it is reasonable to assume that women undergoing immediate surgery were not known to have metastases, and did not receive systemic therapy prior to surgical intervention. These results highlight the fact that retrospective analyses will not provide an unbiased evaluation of the role of local therapy in the setting of metastatic disease, since most of the published studies describe their inclusion criterion as “stage IV at diagnosis” with no further discussion of the timing of surgery.

If surgical resection of the primary tumor is useful for women with metastases, this benefit seems to require minimization of the local tumor burden (as evidenced by data that suggest greater benefit with resection with tumor-free margins); it appears logical therefore that the excision of involved axillary nodes would also be beneficial. Such a trend towards a benefit of axillary dissection is observed in two studies but most analyses lack the data to examine this effect. In the NCDB study (4), although extent of nodal disease was not significantly related to survival, women undergoing total mastectomy were much more likely to have nodal dissection, and this may have contributed to the survival advantage observed in the TM group. In the Geneva study (5), axillary dissection was performed in 24% of patients, and there was a trend towards a larger benefit for women who had both negative surgical margins and axillary dissection (HR 0.2, 95% CI 0.02-1.9).

Regional radiotherapy data are also lacking in the published studies, although local radiation was used in women undergoing breast conserving surgery in Geneva, and the lack of radiotherapy increased the hazard of death independently. The inability to distinguish local radiation from radiation to metastatic sites is a limitation of the data in the NCDB, and in the SEER program, where radiotherapy to local or distant sites has not been distinguishable. In general, the use of locoregional radiotherapy is extremely variable in the reported literature, although a recent study suggests added benefit with the use of surgery plus radiotherapy [79]. Since radiotherapy is clearly crucial in the local control of non-metastatic breast cancer, and adds survival benefit in most categories of risk [78], radiotherapy constitutes a logical component of a test of loco-regional therapy in the metastatic setting. In fact if radiotherapy is not included in such a trial, and a benefit of surgical resection is

Rev. 7/13
Rev. 4/14

observed, the next logical question will relate to the possible enhancement of benefit with the use of radiotherapy. Similarly, if no benefit is observed, the obvious question will be whether the omission of radiotherapy was responsible for the negative finding. Thus it seems important to test the concept of complete local therapy rather than of surgery alone. These factors also argue against the option of making radiotherapy discretionary in such a trial; given the survival benefit attributable to the use of RT in the non-metastatic setting, and the suggestion that local control is associated with improved survival in the metastatic setting (20).

1.4 Data on Chest Wall Outcomes

The frequent use of surgical resection in women presenting with Stage IV disease is somewhat surprising. The main justification for surgical extirpation of the primary tumor in this setting so far has been the so-called “toilette” resection, but many of the patients undergoing partial and total mastectomy had T1 or T2 tumors. This trend highlights the fact that that uncontrolled local disease, with its attendant impact on quality of life, is a feared complication among both physicians and patients. It is reasonable to assume that no (or incomplete) resection is a risk factor for the occurrence of uncontrolled chest wall disease, but direct data regarding this are limited (68). A recent retrospective analysis included 111 women presenting with Stage IV breast cancer; chest wall outcomes were examined relative to the use of early (within 6 months of diagnosis) surgical resection of the primary tumor(20). The early use of surgery reduced the odds of symptomatic chest wall disease by 86% (adjusted OR 0.14, 95% CI 0.039,0.491), and a controlled chest wall reduced the hazard of death by 60% (HR 0.4, 95% CI 0.260, 0.662). In women with the analogous situation of synchronous local and distance recurrence following breast conserving therapy for an initial breast carcinoma, women undergoing resection of the in-breast recurrence, whether by mastectomy or repeat breast conservation, experienced better local control and overall survival (21).

1.5 Health-Related Quality of Life (HRQL) Assessment

Despite the wide recognition of the quality of life impact of uncontrolled chest wall disease in women with breast cancer, surprisingly little is known regarding the frequency of disease-related symptoms from uncontrolled chest wall disease among women with metastatic breast cancer. None of the studies that have examined the impact of surgical therapy on survival have looked at HRQL outcomes. HRQL is an important question in this population because treatment decision-making regarding elective local therapy should be driven by considering the side effects of local therapy versus the anticipated symptom burden associated with uncontrolled disease. Based on clinical observations, it is reasonable to assume that women receiving elective local therapy will experience treatment-related symptoms associated with surgery and radiation that may adversely impact HRQL. Women in the palliative local therapy may experience decrements to their HRQL due to disease-related symptoms, namely pain due to tumor replacement of the breast, ulceration, and skin nodules. Therefore, both treatment groups may experience decrements to their HRQL but from different sources (ie. treatment- vs. disease-related) and at different points in time (ie. at the time of elective local treatment vs. later on with disease progression). We have designed an HRQL assessment among trial participants

to quantify disease- and treatment-related symptoms among trial participants in each treatment arm. We anticipate that the overall impact to HRQL will be greater for the palliative treatment group.

We have identified the Functional Assessment of Cancer Therapy - Breast Trial Outcome Index as our primary HRQL endpoint. The FACT Trial Outcome Index provides a composite score which captures physical well-being, functional well-being and disease-specific concerns (ie. breast cancer) and is commonly used as an HRQL endpoint for cancer clinical trials. The 24-item FACT-Breast Trial Outcome Index (FACT-B TOI) consists of the physical and functional well-being scales (14 items) from the FACT – General 8 and the Breast Cancer Subscale (10 items) of the FACT. The FACT-General consists of 27 items that assess physical, functional, emotional and social well-being 8. The Breast Cancer Subscale of the FACT will also be administered to quantify disease- and
Rev. 4/14 treatment-related symptoms. The FACT Breast cancer subscale includes 10 items that measure HRQL concerns specific to breast cancer, including lymphedema and body image concerns. The FACT-B TOI and the FACT-B total score have been used to assess HRQL in numerous ECOG Breast Committee protocols (eg. E1193, E2100, E1105). Results from E1193 were used to develop minimally important difference scores (MIDs) for the FACT-B TOI (11). Secondary HRQL analyses will examine treatment arm differences on the FACT-Breast subscale score and the FACT-General score.

Exploratory analyses will examine specific symptoms, namely lymphedema, pain and discomfort in the breast and chest wall, and anxiety secondary to tumor growth. These target symptoms were selected based on clinical experience of the study chair in consultation with expert clinicians. In addition, five items from
Rev. 4/14 the FACT Breast cancer subscale and four items from the FACT-G have been selected a priori for individual item analysis to assess differences in pain, body image, and worry between treatment arms. Given the lack of an available scale to assess these concerns in a tailored and concise manner, we have written
Rev. 4/14 additional items for the FACT Breast cancer subscale to capture these concerns. We added four items to assess lymphedema. We added one item to assess worry about tumor growth. We added two items to assess discomfort in the breast and chest wall. We added two items to assess the effects of tumor nodules and ulcers on functional well-being. Because these items are exploratory, we will examine the psychometric properties of each item as well as composite scores (eg. summation of lymphedema items) prior to calculating treatment arm comparisons. In addition we will use data collected from this trial to validate these items. Since no validated instruments are available for issues related to chest wall symptoms, analyses to examine specific symptoms, namely lymphedema, pain and discomfort in the breast and chest wall, and anxiety secondary to tumor growth will need to be exploratory.

1.6 Scientific questions regarding the relationship between the primary tumor and metastatic sites

Data from studies going back several decades raises concerns that resection of the primary tumor in the setting of metastatic disease will enhance the growth of distant lesions (24, 25), and the pioneering work of Folkman and colleagues has identified protein factors synthesized by primary tumors which restrict tumor growth at metastatic sites, so that distant lesions grow once the primary is

resected (26). However, this phenomenon remains to be demonstrated in humans, whereas recent data suggest that the primary tumor may have a unique role in the propagation of metastases, by acting as a reservoir for tumor stem cells. An increasing body of evidence suggests that there is molecular communication between the primary tumor and the pre -metastatic niche (27). Secretion of growth factors (such as TGB-β□, proliferation factors, and stimulatory signals originating from the primary tumor may play a role in priming the niche for implantation and growth of the metastatic lesion. Provocative recent data suggest a specific role for mesenchymal stem cells which are released from the bone marrow and populate primary tumor sites more efficiently than metastatic sites (28). These mesenchymal stem cells then endow primary tumor cells with enhanced metastatic capacity, providing a possible explanation for a beneficial role for resection of the primary tumor even in the setting of established distant disease.

Another potential mechanism for interaction between the primary tumor and metastatic lesions is through tumor induced immunosuppression, defects in cytokine production, recognition of foreign antigens, and T and B cell function. In a study comparing the peripheral blood samples of breast cancer patients and healthy controls. CD4+ and CD8+ T cell subsets capable of producing type 1 and 2 cytokines were reduced in breast cancer patients(29). There was a correlation between the number of micrometastases (defined as circulating epithelial cells in the bone marrow) and the degree of immunosuppression. Using a mouse model, Danna et al were able to demonstrate that removal of an intact primary mammary tumor in the setting of metastatic disease could restore the immunocompetence of the host (30). Mice with bulky tumors had T and B cell deficiencies compared to healthy mice. After resection, antigen-specific antibody responses and T-cell responses to foreign antigen recovered compared to non-surgery mice.

Thus there are several potential biological explanations for the benefit of primary tumor resection which can be formally tested in the setting of a randomized clinical trial of local therapy in metastatic disease patients.

1.7 Study Design Considerations

E2108 is designed to examine the value of early local therapy for the primary tumor in Arm B versus standard of care in Arm A. Laboratory measurements that involve comparison of pre- and post- local therapy values can therefore only be performed in Arm B. However, the Circulating Tumor Cell (CTC) burden prior to primary site local therapy may be substantially reduced by the preceding induction systemic therapy. Statistical testing of CTC values pre and post local therapy in Arm B may therefore not be feasible. A more robust comparison would be one performed at six months following randomization, where local therapy would be completed in Arm B and the CTC burden would represent the cumulative effects of local and systemic therapy (Arm B) versus systemic therapy alone (Arm A).

2. Objectives

2.1 Primary Objectives

Rev. 7/13

To evaluate whether early local therapy of intact primary disease in patients with Stage IV breast cancer whose disease does not progress during initial optimal systemic therapy, will result in prolonged survival, compared to patients who receive local therapy for palliation only.

2.2 Secondary Objectives

2.2.1 To compare the time to uncontrolled chest wall disease between patients who receive early local therapy versus patients who receive palliative local therapy

Rev. 4/14

2.2.2 To determine whether there is a difference in HRQL between patients who receive early local therapy and those who receive palliative local therapy.

2.2.3 To determine whether the absolute value of the CTC burden at six months following randomization will be lower in Arm B than Arm A and whether this value is inversely related to survival.

2.2.4 To collect tumor and blood specimens for future exploration of the biological interactions between the primary tumor and metastatic lesions and the effect of primary tumor resection.

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 randomization by the treating physician.

Rev. 7/12
Rev. 7/13

NOTE: Patients may register (Step 1) at any time from the time of diagnosis of stage IV breast cancer (if eligibility criteria met) to the time when a maximum of 30 weeks of induction systemic therapy has been completed. (Induction systemic therapy includes chemotherapy, endocrine therapy, bone-specific agents, and biologic therapy.)

Rev. 7/12

NOTE: Patients must be randomized (Step 2) within 32 weeks after the start of systemic therapy.

NOTE: Patients may not be randomized (Step 2) less than 16 weeks after the start of systemic therapy.

3.1 Registration (STEP 1)

Rev. 7/12

_____ 3.1.1 Patients (male or female) must be older than 18 years and must have an intact *primary* (not recurrent) invasive carcinoma of the breast. Biopsy confirmation of the primary tumor should be by needle biopsy (preferred); incisional surgical biopsy is allowed as long as there is residual palpable or imageable tumor in the breast.

_____ 3.1.2 Patients with synchronous contralateral invasive breast cancer are excluded.

Rev. 7/12
Rev. 4/14

_____ 3.1.3 Patients should have at least one organ system involved with distant metastatic disease. If only a single metastatic lesion is present, biopsy is mandatory. See Section 6

Rev. 7/12, 2/13, 7/13
Rev. 4/14

_____ 3.1.4 Baseline studies must be performed 8 weeks prior to the start of systemic therapy, and must document the extent of disease in the breast; the specifics of this are at physician discretion, but must address clinical signs and symptoms (see Section 7.1). If pre-therapy scans were not performed, scans performed within the first 4 weeks

of systemic therapy, but prior to registration, will be accepted. Radiology reports documenting status of disease must be available.

Rev. 4/14 _____ 3.1.5 If palliative radiation to non-breast sites is required prior to initiation of systemic therapy, scans may be completed within 8 weeks prior to or 4 weeks following the start of radiation therapy.

Rev. 7/12 _____ 3.1.6 If patient has only one metastatic lesion/focus, this must be proven by biopsy and the pathology report confirming the diagnosis of primary breast cancer, as well as the metastatic site, must be available.

Single metastatic lesion? _____ (Yes/No) Biopsy? _____ (Yes/No)

Rev. 7/12 _____ 3.1.7 Patients may have had prior non-invasive (DCIS) cancer if there has been no recurrence; prior ipsilateral invasive cancer also allowed if more than 5 years previous.

_____ 3.1.8 Patients with a history of other primary cancers are eligible if the pathology report confirming the diagnosis of primary breast cancer is available and the other primary cancer was curatively treated with a 5-year disease-free interval.

Rev. 4/15 3.1.8.1 Patients with non-melanoma skin cancer are eligible; however, patients with squamos cell carcinoma of other sites (except in-situ cervix) are not eligible.

_____ 3.1.9 Women of childbearing potential and sexually active males must be strongly advised to use an accepted and effective method of contraception.

_____ 3.1.10 Patients with CNS metastases are eligible (as long as projected survival is > 6 months).

Rev. 7/12, 7/13 _____ 3.1.11 Patients who require radiotherapy to distant metastases during induction systemic therapy are eligible.

3.2 <u>Randomization (STEP 2)</u>

Rev. 7/12. 4/15 _____ 3.2.1 Date of randomization must be within 32 weeks of initiation of optimal systemic therapy.

Rev. 7/12 _____ 3.2.2 Patients must have completed at least 16 weeks of optimal systemic therapy (appropriate to the tumor biological profile and the patient's age and menopausal status).

NOTE: The patient will be considered eligible if the last day of the treatment cycle meets the 16 weeks criteria. For example, the last chemotherapy dose might be administered in week 15, while the cycle might end in week 16 or 17. In this case, the patient will be considered eligible for the study.

Rev. 7/12, 7/13 3.2.2.1 If systemic therapy is discontinued for toxicity, there is no distant progression and at least 12 weeks of therapy have been delivered, then the patient remains eligible. If systemic therapy is changed for reasons other than progression of disease (e.g. from chemotherapy to endocrine therapy), the patient remains eligible.

_____ 3.2.3 Documentation regarding the details of administration of all systemic chemotherapy must be available.

Rev. 7/12, 2/13 4/14 _____ 3.2.4 Patients must not have experienced distant disease progression since the start of systemic therapy, as evidenced by clinical and radiographic documentation of disease status before treatment and within 6 weeks prior to randomization, including:

a. No new sites of disease
b. No enlargement of existing sites by 20% or more in longest diameter
c. No symptomatic deterioration

Rev. 4/14 d. Imaging at step 2 should preferably be the same as at Step 1 (baseline). It must address all previous sites of disease and all clinical signs and symptoms. If all Step 1 imaging tests cannot be repeated, the reason should be documented (e.g. declined by insurance). Step 2 imaging must evaluate all known sites of disease and address all signs/symptoms present at Step 2.

Rev. 7/12 _____ 3.2.5 Patients must be judged to be candidates for complete resection with free margins followed by radiation therapy (if radiation therapy is indicated).

Rev. 7/12 _____ 3.2.6 Local disease at the primary site must be asymptomatic.

Rev. 7/12 _____ 3.2.7 Patients must have adequate organ function to undergo local therapy 4 weeks +/ - 2 weeks prior to randomization per investigator discretion and institutional guidelines.

Rev. 7/12 3.2.7.1 [Removed in Addendum #2]

Rev. 7/12 3.2.7.2 [Removed in Addendum #2]

Rev. 7/12 3.2.7.3 [Removed in Addendum #2]

Rev. 7/12 3.2.7.4 [Removed in Addendum #2]

Rev. 7/12 3.2.7.5 [Removed in Addendum #2]

_____ 3.2.8 Women must not be pregnant or breast-feeding due to toxicity of systemic therapy and radiotherapy to fetus/infant.

All females of childbearing potential must have a blood test or urine study within 2 weeks prior to randomization to rule out pregnancy.

Female? _____ (Yes/No)
Date of blood test or urine study: _____

_____ _____

Physician Signature Date

OPTIONAL: This signature line is provided for use by institutions wishing to use the eligibility checklist as source documentation.

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 **E2108** 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 **E2108**
- Click on the Site Registration Documents link

Requirements for E2108 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**

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

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 has 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.

4.1 Registration (Step 1)

Rev. 7/12

Patients may register to Step 1 at any time prior to the start of systemic therapy or < 30 weeks after the start of systemic therapy, with randomization to step 2 no earlier than 16 weeks after start of systemic therapy (once response or stable disease is documented).

Rev. 7/12

[Note deleted in Addendum #2]

The following information will be requested:

4.1.1 Protocol Number

4.1.2 Investigator Identification

4.1.2.1 Institution and affiliate name

4.1.2.2 Investigator's name

4.1.3 Patient Identification

4.1.3.1 Patient's initials and chart number

4.1.3.2 Patient's Social Security number

4.1.3.3 Patient demographics

4.1.3.3.1 Sex

4.1.3.3.2 Birth date

4.1.3.3.3 Race

4.1.3.3.4 Ethnicity

4.1.3.3.5 Nine-digit ZIP code

4.1.3.3.6 Method of payment

4.1.4 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.

4.1.5 Additional Requirements

4.1.5.1 Patients must provide a signed and dated, written informed consent form.

NOTE: Copies of the consent are not collected by the ECOG-ACRIN Operations Office - Boston.

Rev. 7/12, 2/13

4.1.5.2 Pathology materials and blood samples submitted as indicated in Section 9 for banking per patient consent.

NOTE: ECOG-ACRIN requires that biological samples submitted from patients participating in E2108 be entered and tracked via the online ECOG-ACRIN Sample Tracking System (STS). Any case reimbursements associated with sample

submissions must not be captured if samples are not logged into STS. See Section 9.3

NOTE: Institutions outside of the United States and Canada must confer with the receiving laboratory and the ECOG-ACRIN Operations Office - Boston regarding logistics for submission of fresh samples.

4.2 Randomization (Step 2)

Rev. 7/12 Randomization to step 2 is to occur within 16 to 32 weeks after start of systemic therapy (once response or stable disease is documented).

Rev. 7/12 Step 2 treatment must not to start prior to randomization and must start after completion of at least 16 weeks of systemic therapy and no more than 32 weeks from start of systemic therapy.

The following information will be requested:

4.2.1 Protocol Number

4.2.2 Investigator Identification

4.2.2.1 Institution and affiliate name.

4.2.2.2 Investigator's name.

4.2.3 Patient Identification

4.2.3.1 Patient's initials and chart number.

4.2.3.2 Patient's Social Security number.

4.2.3.3 Patient demographics

4.2.3.3.1 Sex

4.2.3.3.2 Birth date (mm/yyyy)

4.2.3.3.3 Race

4.2.3.3.4 Ethnicity

4.2.3.3.5 Nine-digit ZIP code

4.2.3.3.6 Method of payment

4.2.3.4 Patient sequence number assigned at pre-registration.

4.2.4 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.

4.2.5 Stratification Factors

4.2.5.1 Marker status and treatment plan

- ER+ or PR+, HER2-, plan to treat with endocrine therapy alone

- ER+ or PR+, HER2-, plan to treat with chemotherapy (with or without endocrine therapy)
- ER- or PR-, HER2-
- HER2+

4.2.5.2 Number of involved organ systems (beyond the primary tumor, chest wall, and locoregional nodes, i.e., axilla, internal mammary, supraclavicular).

- Single organ system with distant disease
- More than one organ system with distant disease (regional nodes in the axillary, supraclavicular, and internal mammary locations are not considered distant sites).

4.2.6 Additional Requirements

4.2.6.1 Patients must provide a signed and dated, written informed consent form.

Rev. 7/12, 2/13

4.2.6.2 Pathological materials and blood samples should be submitted as indicated in Section 9 for banking per patient consent.

NOTE: The establishment of research rates within the institution's financial office must be in place prior to the performance of the additional biopsies. See Section 9.4 for guidelines.

NOTE: ECOG-ACRIN requires that biological samples submitted from patients participating in E2108 be entered and tracked via the online ECOG-ACRIN Sample Tracking System (STS). Any case reimbursements associated with sample submissions must not be captured if samples are not logged into STS. See Section 9.3.

NOTE: Institutions outside of the United States and Canada must confer with the receiving laboratory and the ECOG-ACRIN Operations Office - Boston regarding logistics for submission of fresh samples.

4.3 Instructions for Patients who Do Not Start Assigned Protocol Treatment

If a patient does not randomize to Step 2, please document the reason on the E2108 Step 1 Vital Status form and submit this form through 5 years per the E2108 forms submission schedule.

After randomization to step 2, if a patient does not receive the assigned protocol treatment, follow-up data will still be collected and must be submitted according to the instructions in the E2108 Forms Packet. Document the reason for not starting protocol treatment on the off-treatment form.

5. Treatment Plan

5.1 Treatment

Rev. 7/12, 2/13

Patients may be registered to Step 1 (Arm S) prior to initiation of systemic therapy OR up to 30 weeks after start of systemic therapy. Full local and distant disease evaluation (clinical and radiological) must have been performed a maximum of 8 weeks prior to start of systemic therapy. Scans performed within 4 weeks following the start of systemic therapy, but prior to registration, will be acceptable as baseline studies, but complete imaging prior to start of therapy is preferred. If radiation at a distant site was required prior to start of systemic therapy, scans can be 8 weeks prior to or 4 weeks following the start of radiation.

Rev. 7/13

Rev. 2/13

All baseline studies documenting extent of disease must be repeated prior to Step 2 randomization. Patients with progressive disease per the criteria in Section 3.2.4 will not randomize to Step 2 but will be followed for survival. Those with stable or responsive disease will be randomized to receive elective local therapy (Arm B) versus the palliative local therapy (Arm A) when/if needed. Systemic therapy will continue on both treatment arms as directed by the treating physician. Patients who had advanced local disease at registration can be randomized if the local disease is now considered operable by conventional criteria.

5.1.1 Systemic Therapy (Step 1: Arm S)

Rev. 2/13

Optimal systemic therapy will be determined by the treating physician based on tumor profile, patient age, and menopausal status. The use of NCCN or equivalent guidelines are encouraged. First-line systemic therapy may also be offered on a Phase II or III trial, and may be randomized at Step 2, as long as there is no evidence of progression (see Section 6.1). A change in systemic therapy is allowed for toxicity or at physician discretion (e.g. switch from chemotherapy to endocrine therapy), as long as the change is not for disease progression. However, randomization at end of 1st regimen is encouraged.

Rev. 7/13

5.1.2 Local Therapy Treatments (Step 2: Arms A and B)

Rev. 4/14

5.1.2.1 Arm A: Continued Systemic Therapy

Systemic therapy will continue as directed by the treating physician.

Local therapy should be offered to patients only if needed for palliation of symptoms such as tumor ulceration, pain, bulky adenopathy causing arm symptoms, and other similar situations where therapy is designed specifically to address symptoms at the local site. It may consist of radiotherapy alone, surgery alone, or the combination.

5.1.2.2 Arm B: Early Local Therapy

Rev. 7/12
Rev. 4/14

Surgery is to occur no later than 10 weeks after randomization.

Rev. 4/14

Surgical treatment will be chosen by patient and physician according to the criteria that are generally accepted for breast conserving therapy (BCT) or total mastectomy

(TM). If BCT is chosen, free surgical margins must be achieved with re-excision or mastectomy (no minimum margin width is required). Axillary management should parallel that used for non-metastatic breast cancer. Axillary dissection is required if clinical and radiologic evaluation at initial registration was suggestive of axillary disease and axillary radiation is not planned. For women not receiving axillary dissection, sentinel node biopsy should document

Rev. 7/12

an axillary nodal burden of 1-2 involved lymph nodes (i.e. ACOSOG Z-11 criteria may be applied if axillary radiation is not planned). For women undergoing TM, reconstructive surgery will be allowed at the discretion of the treating physician, recognizing that this may delay the continuation of systemic therapy and complicate radiation planning. Surgical quality assurance will be coordinated with the ECOG-ACRIN Surgery Committee.

Systemic therapy may resume after recovery from surgery as directed by the treating physician. Systemic therapy will continue directed by the treating physician.

Following surgery, radiotherapy is to be given as outlined in Section 5.3.

5.2 Health-Related Quality of Life Assessment

Rev. 4/14

Overall health-related quality of life (physical, functional, emotional and social well-being) will be assessed by administering the FACT-G. Breast cancer-specific concerns will be assessed by administering the Breast Cancer subscale of the FACT. Participants will complete the 27-item FACT-G, the 10-item FACT-Breast subscale and 9 additional items that have been written for this trial. We will use the FACT-B TOI to assess HRQL. The FACT-B TOI is calculated by summing the physical well-being (7 items), functional well-being (7 items) and breast cancer-specific (10 items) scales from the FACT. In addition, five items from the FACT Breast cancer subscale and four items from the FACT-G have been selected a priori for individual item analysis to assess differences in pain, body image, and worry between treatment arms. Given the lack of an available scale to assess these concerns in a tailored and concise manner, we have written additional items for the FACT Breast cancer subscale to capture these concerns (four items to assess lymphedema, one item to assess worry about tumor growth, two items to assess discomfort in the breast and chest wall, and two items to assess the effects of tumor nodules and ulcers on functional well-being). Because these items are exploratory, we will examine the psychometric properties of each item as well as composite scores (eg. summation of lymphedema items) prior to calculating treatment arm comparisons. In addition we will use data collected from this trial to validate these items.

The FACT-Breast and additional items (referred to as the FACT-Breast + Local Symptoms-9 or FACT-B + LS-9) to assess HRQL will be administered at five time points: step 1: registration (+/- 14 days); step 2: randomization ; six months post-randomization (+/- 14 days); 18 months post-randomization (+/- 14 days);

Rev. 4/14

and 30 months post-randomization (+/- 14 days). It is anticipated that participants in the early local therapy arm (Arm B) will have completed surgery and radiation therapy at approximately 6 months post-randomization and will

likely still experience acute treatment-related symptoms, while most participants in the palliative local therapy arm (Arm A) will not have received any treatment as of 6 months post-randomization.

Therefore, a comparison at 18 months post-randomization on the FACT-B TOI score will be used as the primary HRQL endpoint analysis. A second HRQL analysis will examine FACT-B scores at about 30 months post-randomization. We hypothesize that the HRQL for the breast/chest wall items will be better for the control arm at the 6 month timepoint, and will be better in the experimental arm at the 18 month time point. An additional timepoint for Arm A patients will be at the point of decision for local therapy. No formal comparative analysis is planned for this data, but it will serve to document the degree of symptoms that trigger the decision for palliative therapy in the control arm.

Timing of FACT-B + LS-9 Administration

Rev. 4/14 / Rev. 4/14 Questionnaires*	Step 1: Registration (+/- 14 days)	Step 2: Randomization	At 6 months post randomization (+/- 14 days)	At 18 months post randomization (+/- 14 days)	At 30 months post-randomization (+/- 14 days)	At decision for early local therapy (prior to surgery – Arm A patients only) (+/- 14 days)	Approximate time to complete
FACT-B + LS-9	X	X	X	X	X	X	15 minutes

* Please note that the QOL questionnaire is only available in English.

5.2.1 QOL Instrument Administration Instructions

5.2.1.1 The questionnaires must be administered at the timepoints listed above. The patient should be instructed to respond to the questionnaires in terms of his/her experience during the time frame specified on each questionnaire.

5.2.1.2 The CRN/CRA should read the instructions printed on the questionnaire to the patient and ensure the patient understands the instructions. It is important to assure the patient that all material on the questionnaire is confidential and will not be shared with the health care team and that it will not become part of the medical record. It is permissible to assist the patient with the completion of the questionnaires as long as the staff person does not influence the patient's responses.

5.2.1.3 Whenever possible, the HRQL assessment should be administered at the clinic visit before the patient is seen by the physician, before evaluations are performed and before test results are shared with the patient. In the event that the questionnaires are not administered at the clinic visit, the HRQL data can be collected by telephone or mail as backup methods provided that HRQL data is captured prior to initiation of treatment.

5.2.1.4 Assistance in reading the questionnaire is permitted if the patient is unable to complete the questionnaire on his/her own (e.g. difficulty in reading, elderly). It is important not to influence the response of the patient. Note why the patient required assistance and the type of assistance given.

5.2.1.5 Patients should be instructed to answer all the questions regardless of whether the symptoms or conditions asked about are related to the cancer or cancer treatment. Discourage family members from being present during questionnaire completion or from influencing the patient's responses.The questionnaires must be reviewed by the protocol nurse or research coordinator as soon as the patient completes them to ensure all items were marked appropriately. If the patient has marked more than one answer per question, ask the patient which answer best reflects how they are feeling. If the patient has skipped a question or questions, the patient should be asked if he/she would like to answer it. If the patient refuses, it should be indicated on the questionnaire that he/she declined to answer the item.

5.2.1.6 If the patient refuses or cannot complete the questionnaire at any time point, he or she should be asked to do so at the next scheduled HRQL assessment.

5.2.1.7 The patient may decline to complete the HRQL assessment for any reason. The reason must be documented on the Assessment Compliance Form.

5.2.1.8 If a patient misses an appointment on the scheduled date, the questionnaires may be completed by telephone on the appointed date or they may be completed at the time the appointment is rescheduled. If the missed scheduled date is on a treatment date, the quality of life assessment will be done when the patient comes for the rescheduled treatment.

5.2.1.9 If a patient cannot complete the quality of life questionnaires because he/she is too sick, this should be documented on the Assessment Compliance Form.

Rev. 7/12

5.3 Radiation Therapy

Radiation therapy (if indicated) must begin within 12 weeks of final therapeutic surgical procedure (including re-excision for free margins and completion of axillary dissection). After breast conservation surgery, all patients will receive definitive breast irradiation. Definitive breast irradiation will include the whole breast. A boost to the primary tumor bed is optional, provided that the margins of excision are pathologically confirmed as negative. Nodal radiation can be added for node positive patients at the discretion of the treating radiation oncologist.

After mastectomy, post mastectomy radiation treatment (PMRT) will be given at the discretion of the treating surgeon and radiation oncologist. All patients with 4

or more pathologically positive axillary lymph nodes will be treated with PMRT. For patients with 1-3 pathologically positive axillary lymph nodes, consultation with a radiation oncologist is recommended to determine whether PMRT is indicated. For other borderline indications for PMRT, consultation with a radiation oncologist is recommended. Target volumes for PMRT will include at a minimum the chest wall plus a supraclavicular field. Other nodal volumes can be included within the target volume at the discretion of the treating radiation oncologist. A boost within the chest wall field is optional. Bolus for the chest wall field can be either 1 cm every other day or ½ cm every day. The chest wall can be irradiated using either electrons or tangential photon beams.

CT based simulation is strongly recommended, but is not required. IMRT is allowed provided NCI guidelines are followed and all required Benchmarks have been completed (see below). For left sided radiation treatment, the volume of heart included within the radiation fields should be carefully assessed.

5.3.1 Required Benchmarks

Centers participating in this protocol using 3D conformal techniques are required to complete the 3D Benchmark; those treating with IMRT must complete the IMRT Questionnaire and either the QARC Benchmark or irradiate the RPC's IMRT head and neck phantom. All Benchmark material can be obtained from the Quality Assurance Review Center (www.QARC.org) and must be submitted before patients on this protocol can be evaluated. Contact the RPC (http://rpc.mdanderson.org/rpc) for information regarding their IMRT phantoms. **Patients will be considered unevaluable if approved benchmarks are not on file at QARC.**

5.3.2 Equipment

Modality: All patients must be treated with a linear accelerator with nominal photon energy between 4 to 18MV (typically 6 MV). Electron therapy is permitted for supplemental boost to the intact breast (after breast conserving surgery) or to the chest wall. Co-60 may be used for post-mastectomy RT.

Calibration: The calibration of therapy machines used in this protocol shall be verified by the Radiological Physics Center (RPC).

5.3.3 Target Dose

5.3.3.1 Dose Definition

The absorbed dose is specified as Gy to muscle.

5.3.3.2 Total Dose

Rev. 2/13

<u>For breast conserving therapy:</u> radiation fractionation options for the whole breast treatment are: (a) conventional fractionation of 1.8 or 2.0 Gy per day to 45 - 50.4 Gy; or (b) accelerated whole breast radiation to a dose of 42.56 Gy in 16 fractions of 2.66 Gy each (Whelan 2002). If a boost to the primary tumor site is given using conventional fractionation, then the recommended total dose to the primary tumor site is 60-66 Gy. If a boost to the primary tumor site is not given, then the whole breast dose is

required to be either: (a) 2.0 Gy daily fractions to 50 Gy total dose in 25 fractions; or (b) 42.56 Gy in 16 fractions of 2.66 Gy each. For accelerated whole breast fractionation, a boost to the primary tumor site is optional. Nodal radiation can be added for node positive patients at the discretion of the treating radiation oncologist.

For post mastectomy radiation therapy: Fractionation may be either (a) 1.8 Gy per fraction, 50.4 Gy to the chest wall, and 45 Gy to the supraclavicular field or (b) 2.0 Gy per fraction, 50 Gy to the chest wall, and 46 Gy to the supraclavicular field. IMN's and full axilla may be treated at the discretion of the radiation oncologist. A chest wall boost of up to 10 Gy may be given at the discretion of the radiation oncologist.

Rev. 2/13

5.3.4 Time and Dose Considerations

5.3.4.1 Fractionation

Patients will receive one treatment per day, five days per week (Monday through Friday). All fields will be treated each day. At least two fractions must be given during the first week of treatment.

5.3.4.2 Interruptions

No special considerations need to be made for treatment delays of 1 week or less. If treatment is delayed more than 1 week but less than 2 weeks, notify the study chair. If treatment delays of more than two weeks occur, the patient will be considered off-study. The reason(s) for any break must be clearly recorded in the treatment record.

If there are any changes in the patient's status (i.e., early discontinuation of protocol treatment, delay in starting radiotherapy, or break in radiotherapy) these should be communicated in writing to QARC by fax (401) 753-7601 or email to ECOG@qarc.org with a copy to the Radiation Oncology Co-Chair.

5.3.5 Treatment Technique

Guidelines for breast conservation treatment (i.e., breast conserving surgery followed by definitive breast irradiation) have been published by a number of expert groups or panels (70,72,76,77). Similarly, guidelines for post mastectomy radiation treatment (PMRT) have been published by a number of expert groups or panels (70,71,73,74,77).

It is anticipated that most patients will be planned using CT based planning tools. Guidelines are also presented for fluoroscopy based planning techniques.

5.3.5.1 Fluoroscopy-based WBI Treatment Plan

5.3.5.1.1 Fluoroscopy-based Plan

Dose distribution is evaluated on an external patient contour at central axis after tangents are established clinically with fluoroscopy. **The lumpectomy cavity must have been marked with surgical clips. Ideally, surgical clips should mark the cephalad, caudad, medial, lateral, anterior and posterior extent of the lumpectomy cavity.**

5.3.5.1.2 Target breast Volume

At the time of simulation the clinical breast volume to be targeted in the tangent fields with appropriate margin is determined by the radiation oncologist.

5.3.5.1.3 Tangent Fields

The borders for the tangent fields are set so that it includes the targeted clinical breast volume determined above plus a 1–2 cm margin. It is recommended that techniques be applied that assure posterior or deep borders are co-planar in order to minimize exit into the lungs.

5.3.5.1.4 Constraints for Critical Non-Target Organs

The perpendicular distance from the chest wall to the posterior field edge can include **at maximum** 3 cm of lung tissue at any point along the length of the tangent on a film. For left-sided cancers, field arrangements should be used that minimize inclusion of the heart-shadow seen on fluoro/film within the field, and include no more than 1.5 cm of heart within the field.

5.3.5.1.5 External Contour Dose Prescription and Evaluation of Isodose Distribution

An external patient contour through the central axis is used for dose prescription. The whole breast dose will be prescribed to two thirds the perpendicular distance from the anterior/apical contour surface to the posterior border of the tangent field at mid-separation. Wedges and compensators may be used to keep the maximum dose within 15% of the prescription.

5.3.5.1.6 Verification of the Lumpectomy Cavity Coverage Within the Prescription Isodose for the Whole Breast

The tangent fields must include the surgical clips that demarcate the lumpectomy cavity with a 2 cm margin. The radiation oncology facility must submit a scanned copy or digital picture of one of the tangent films demonstrating the coverage of the surgical clips around the lumpectomy cavity.

5.3.5.2 CT-based WBI Treatment Plan

5.3.5.2.1 CT Planning

This includes dose distribution evaluated on a single central axis CT slice or multiple CT levels after tangents are established clinically (by fluoroscopy or CT) **or** target breast volume defined on CT and tangents and dose distribution based on dose-volume specification to breast and constraints for critical nontarget organs.

5.3.5.2.2 Target Breast Volumes

At the time of the simulation/CT, the clinical breast volume to be targeted in the tangent fields, with appropriate margin, is determined by the radiation oncologist.

5.3.5.2.3 Tangential Fields

The borders for the tangent fields are set so that they include the targeted clinical breast volume determined above plus a 1–2 cm margin. Examples of typical clinical boundaries for tangent fields are:

Medial: usually midsternum

Lateral: usually midaxillary line

Caudad: 1-2 cm below the inframammary line

Cephalad: commonly at the base of the clavicle heads or the sternal manubrium joint. These boundaries may need to be modified depending on the location of the lumpectomy cavity when it is visualized on CT. For CT-based planning, radiopaque markers are placed on these borders. It is recommended that techniques be applied that assure posterior or deep borders are

co-planar in order to minimize exit into the lungs.

5.3.5.2.4 Nodal Volume Coverage

If irradiated, the internal mammary lymph nodes should be contoured from the inferior chest wall field edge and include the medial supraclavicular region. These lymph nodes follow the contour of the internal mammary artery. They do not have to be intentionally treated. Axillary and supraclavicular lymph nodes at levels 1, 2, and 3 can be contoured as a single object, or contoured separately. The lower border of the supraclavicular field will typically be matched to the superior edge of the tangent fields, and the upper border will extend on or about to the level of C4 to cover the supraclavicular lymph nodes. The medial field edge will extend to the area of the lateral vertebral body and extend laterally beyond the humeral head. The humeral head and skin folds can be blocked at the discretion of the treating radiation oncologist. Angled fields are permitted to limit swallowing discomfort. It is recognized that the most posterior aspect of the axilla at the level of the latisimus will not be fully covered with an anterior field, and a supplemental posterior boost field is discretionary.

5.3.5.2.5 Constraints for critical non-target organs

The perpendicular distance from the chest wall to the posterior field edge can include **at maximum** 3 cm of lung tissue at any point along the length of the tangent on a film, or a digitally reconstructed radiograph (DRR) of the field. For left-sided cancers, field arrangements that minimize inclusion of the heart in the field should be used, and include no more than 1.5 cm of heart within the field.

5.3.5.2.6 Dose prescription and evaluation of isodose distribution

The dose will be prescribed at two thirds the perpendicular distance from the skin overlying the breast to the posterior border of the tangent field at mid-separation on the central axis slice. Wedges and

compensators, may be used to keep the maximum dose within 15% of the prescription. The use of bolus is strongly discouraged.

5.3.5.2.7 Tissue Heterogeneity

Calculations shall take into account the effect of tissue heterogeneities.

5.3.5.2.8 Verification of the lumpectomy cavity coverage within the prescription isodose for the whole breast

- **Verification process when the lumpectomy cavity can be identified on CT:** Review of the dose distribution on CT slices that include the lumpectomy cavity is requested to verify that the cavity, as demarcated by surgical clips or post operative seroma, is being covered by the prescription isodose. Acceptable WBI must demonstrate that the cavity is included in ≥ 90% isodose line. If not, changes in the field width, gantry, collimator, or selection of wedges or other adjustment must be done to achieve this. The radiation oncology facility is to submit one axial CT slice demonstrating that the identified lumpectomy cavity is covered by > 90% isodose line and a DRR of the tangent field.
- **Verification process when the lumpectomy cavity cannot be identified on CT:** For some patients receiving WBI after chemotherapy, the lumpectomy cavity may have resolved and is no longer visible on the CT for radiation planning. In these instances, the postoperative CT submitted for registration to this study can be used. The radiation oncologist can identify on the postoperative registration CT a representative axial slice with the lumpectomy cavity present. A comparable anatomic axial slice from the radiation planning CT with the isodoses present should be found and verify that the ≥ 90% isodose line is covering the region where the lumpectomy cavity was previously visible. Both the CT slice from

the registration scan demonstrating the cavity location and the radiation planning scan documenting the isodose coverage are to be submitted. A DRR of the WBI tangent fields should also be submitted.

5.3.5.3 Fluoroscopy-based PMRT treatment plan

For patients planned using fluoroscopy-based simulation techniques, the chest wall will be treated from the inferior aspect of the clavicular head to the level of the diaphragm or to the level of 2cm below the contralateral inframmary fold. A wire will be placed on the chest wall scar to validate scar location on simulation images. Medial and lateral field edges will extend from the midline to the mid-axillary line. Field edges marked on a CT scan will be submitted for review.

For patients treated to the supraclavicular field, the inferior border will be matched to the superior border of the chest wall field using a non-divergent technique. The medial edge will be at the lateral edge of the vertebral body. An angled technique is permitted to limit swallowing discomfort. The upper border will extend on or about to the level of C4 to cover the supraclavicular lymph nodes.. The lateral border will be lateral to the humeral head with blocking of the humeral head and skin folds based on operative findings and judgment of the treating radiation oncologist. This field can be treated to a depth of 3-5 cm depending on the anatomic location of the nodal structures, and a posterior axillary boost is optional.

5.3.5.4 CT-based PMRT treatment plan

The chest wall will be contoured from the level of the diaphragm or from the level 2cm below the contralateral inframmary fold to the inferior aspect of the clavicular head with field edges extending from the midline to the mid-axillary line. Bolus will be required, either 1cm every other day or ½cm daily.

If irradiated, the internal mammary lymph nodes should be contoured from the inferior chest wall field edge and include the medial supraclavicular region. These lymph nodes follow the contour of the internal mammary artery. They do not have to be intentionally treated. Axillary and supraclavicular lymph nodes at levels 1,2, and 3 can be contoured as a single object, or contoured separately. The lower border of the supraclavicular field will typically be matched to the superior edge of the tangent fields, and the upper border will extend on or about to the level of C4 to cover the supraclavicular lymph nodes. The medial field edge will extend to the area of the lateral vertebral body and extend laterally beyond the humeral head. The

humeral head and skin folds can be blocked at the discretion of the treating radiation oncologist. Angled fields are permitted to limit swallowing discomfort. It is recognized that the most posterior aspect of the axilla at the level of the latisimus will not be fully covered with an anterior field, and a supplemental posterior boost field is discretionary.

5.3.5.5 IMRT

5.3.5.5.1 Treatment Volumes

The definition of target volumes will be in accordance with ICRU Reports #50 and #62.

For patients treated with breast conservation, the target volume will include the entire breast and surgical cavity. The breast will be drawn as a CTV with a 5 mm PTV. Modifications of the PTV into pulmonary and cardiac tissue are permitted based on dose histogram guidelines listed below. PTV will be modified to maintain 3-5mm distance below the skin surface. The surgical cavity will be drawn as a CTV with a 5 mm PTV. The breast should be contoured from the inframammary fold to the inferior clavicular head. The surgical cavity should be contoured to include the entire excision cavity including a 1-2 cm extension beyond the image guided abnormality in all planes.

Extension of radiation therapy into nodal regions is permitted on study at the discretion of the treating radiation oncologist. If the breast is treated with IMRT, non-IMRT treatment of nodal regions is permitted on study. See Section 5.2.5.2. (Nodal Volume Coverage for CT-based WBI treatment plan) for guidelines on nodal volume coverage.

Post mastectomy patients can be treated with IMRT at the discretion of the treating radiation oncologist. The chest wall will be contoured from the level of the diaphragm to the inferior clavicular head. Bolus will be used and incorporated into the treatment plan to insure appropriate coverage of skin tissue. Nodal volume coverage, as desired, will be identical to patients treated for intact breast. Supplemental therapy to the chest

wall can be delivered at the discretion of the treating radiation oncologist. If IMRT is used, this can be done as a continuation of the IMRT plan. Alternative plans, including electron therapy, are permitted.

5.3.5.5.2 Dose Prescription

Dose shall be prescribed to an isodose surface that encompasses the PTV and that satisfies the dose uniformity requirements below.

5.3.5.5.3 Tissue Heterogeneity

Calculations shall take into account the effect of tissue heterogeneities.

5.3.5.5.4 Dose Uniformity

For IMRT the entire PTV shall be encompassed within the 95% isodose surface and no more than 10% of the PTV should receive more than 110% of the prescription dose, as evaluated by dose volume histogram.

5.3.5.5.5 Organs at Risk (OAR)

Dose constraints and guidelines should be as follows:

No more than 40% of the lung in the involved side should receive greater than 2000 cGy.

No more than 25% of the total lung volume should receive more than 2000 cGy.

The heart should be contoured as a single object from the apex to the aortic root (heart base). No more than 30% of the volume should receive more than 3000 cGy.

No more than 10% of the chest wall for both intact breast and mastectomy patients should receive more than 7000 cGy.

5.3.6 Dose Calculation and Reporting

5.3.6.1 Isodose Distributions

Isodose distributions must be submitted for the treatment plan. Outlines of the planning target volume and critical organs must be shown. Isodose values must be clearly labeled. Isodose distributions shall include axial, sagittal and coronal planes through the center of the PTV.

5.3.6.2 Dose Volume Histograms

For CT based planning dose volume histograms must include the CTV, PTV, and OARs as noted above. If IMRT is used, a DVH in absolute dose must also be submitted for "unspecified tissue," i.e., tissue contained within the skin, but excluding the CTV, PTV and OARs.

5.3.6.3 IMRT Plan Verification

If IMRT is used, the monitor units generated by the IMRT planning system must be independently checked prior to the patient's first treatment. Measurements in a QA phantom can suffice for a check as long as the plan's fluence distributions can be recomputed for a phantom geometry.

5.3.6.4 Digital Submission

Submission of treatment plans in digital format (either Dicom RT or RTOG format) is encouraged. Instructions for data submission are on the QARC website at www.QARC.org.

Hardcopy isodose distributions for the total dose plan in the axial, sagittal and coronal planes, which includes the isocenter of the planning target volume, must be submitted along with total dose DVHs for digital data validation. These may be sent to QARC as screen captures (FTP, emailed or mailed on a CD).

5.3.7 QA Documentation

5.3.7.1 On-Treatment Review

Submit the following for on-treatment review within the first three days of treatment:

- The CT scan used for treatment planning, including delineation of the target volumes and critical structures.
- Digitally reconstructed radiographs (DRR) for each treatment field or simulator films. It is strongly encouraged that the CTV and PTV be displayed on the DRR's.
- First day portal films (or hard copy of real time portal images) if achievable.
- Pictures of the patient in the treatment position.
- Prescription sheet for the entire treatment course (excluding boost treatment).
- RT-1/IMRT Dosimetry Summary Form (located at www.QARC.org).

- A room's eye view (REV), i.e., a composite illustration of all the fields and their angles, if available from your planning system.
- Treatment planning system summary report that includes the monitor unit calculations, beam parameters, calculation algorithm, and volume of interest dose statistics.
- Color isodose distributions for the total dose plan in the axial, sagittal and coronal planes, which includes the isocenter of the planning target volume. The target volumes and the prescription point must be clearly shown.
- Color Dose volume histograms for the entire treatment course or total prescribed dose for the CTV and PTV and any critical structures (see section 5.2.6). If IMRT treatment planning is used, a DVH must also be submitted for a category of tissue called "unspecified tissue," which is defined as tissue contained within the skin, but which is not otherwise identified by containment within any other structure.
- Documentation of an independent check of the calculated dose if IMRT is used.
- A copy of the ECOG-ACRIN E2108 On Study Form
- Copy of the ECOG-ACRIN E2108 Checklist for Submission of Radiation Oncology Quality Assurance Materials (located at www.QARC.org).

5.3.7.2 Post-Treatment Review

Within one week of the completion of radiotherapy, the following data shall be submitted.

- A copy of the patient's radiotherapy record including prescription, and the daily and cumulative doses to all required areas and specified dose points.
- Copies of additional simulation and verification (portal) films for any field modifications made subsequent to the initial reporting of data for on-treatment review.
- Copies of revised RT-1/IMRT form, when modifications have been made subsequent to the initial reporting.
- Copies of calculations and isodoses performed subsequent to the submission of the on-treatment data.

- Copy of the ECOG-ACRIN E2108 Checklist for Submission of Radiation Oncology Quality Assurance Materials (located at www.QARC.org).

NOTE: Black and white copies of color documentation are not acceptable.

5.3.8 Address

These data should be forwarded to:

Quality Assurance Review Center
640 George Washington Highway Suite 201
Lincoln, RI 02865-4207
Phone: (401) 753-7600
Fax: (401) 753-7601

Instructions on digital data submission are available on line from the QARC website at http://www.qarc.org/ (see Digital Data section).

E-mailed data can be sent to: ECOG@QARC.org

5.3.8.1 Questions

Questions regarding the dose calculations or documentation should be directed to:

Physics/Dosimetry
Quality Assurance Review Center
640 George Washington Highway Suite 201
Lincoln, RI 02865-4207
Phone: (401) 753-7600
Fax: (401) 753-7601

Questions regarding the radiotherapy section of this protocol should be directed to the Radiation Oncology Co-Chair.

5.3.9 Definitions of Deviations in Protocol Performance

5.3.9.1 Prescription Dose

Minor Deviation: The dose to the prescription isodose surface differs from that in the protocol by between 6% and 10%.

Major Deviation: The dose to the prescription isodose surface differs from that in the protocol by more than 10%.

5.3.9.2 Dose Uniformity

Fluoroscopy based (2D) Treatment Planning: The dose variation on an axial contour through the center of the target volume is greater than -5% or +15% of the protocol dose.

3D/IMRT Treatment Planning: Any part of the CTV receives less than 95% of the protocol dose, or more than

10% of the PTV receives more than 110% of the protocol dose.

5.3.9.3 Volume

Minor Deviation: Margins less than specified or fields excessively large as deemed by the study.

Major Deviation: Transection of tumor or potentially tumor bearing area (CTV).

Rev. 7/12

5.4 Adverse Event Reporting Requirements

Step 1: *Identify the type of event:* The descriptions and grading scales found in the revised NCI Common Terminology Criteria for Adverse Events (CTCAE) version 4.0 will be utilized. 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 web site (http://ctep.cancer.gov).

Step 2: *Grade the event using the NCI CTCAE* v 4.0.

Rev. 7/12

5.4.1 Reporting Methods

Rev. 4/14

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 NCI (301-230-0159)

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 NCI (301- 230-0159) 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.

5.4.2 Other Recipients of Adverse Event Reports

ECOG-ACRIN will forward CTEP-AERS reports to the appropriate regulatory agencies and pharmaceutical company, if applicable.

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.

5.4.3 Expedited Reporting for Protocol E2108 – Arms A and B

Attribution			Grade 5[a]		
			Unexpected	Expected	
Possible, Probable, Definite			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 on either arm 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.

Rev. 7/12

5.4.4 Reporting secondary primary cancers

All cases of second primary cancers, including acute myeloid leukemia (AML) and myelodysplastic syndrome (MDS), that occur following treatment on NCI-sponsored trials must be reported to ECOG-ACRIN:

- **A <u>second</u> 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
  3. If the patient has been diagnosed with AML/MDS, submit a copy of the cytogenetics report (if available) to ECOG-ACRIN
- **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 a.) leukemia secondary to oncology chemotherapy, b.) myelodysplastic syndrome, or c.) treatment related secondary malignancy

3. Submit a copy of the pathology report to ECOG-ACRIN and NCI/CTEP confirming the diagnosis.
4. If the patient has been diagnosed with AML/MDS, submit a copy of the cytogenetics report (if available) to ECOG-ACRIN and NCI/CTEP.

NOTE: The Second Primary Form and the CTEP-AERS report should not 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.

5.5 Supportive Care

5.5.1 All supportive measures consistent with optimal patient care will be given throughout the study. Growth factor support while on cytotoxic chemotherapy is allowed at the discretion of the treating physician.

5.6 Duration of Study Participation

All patients will be followed until progression and for survival. Those randomized to Early Local Therapy will receive protocol-specified surgery and radiation immediately after randomization. Study participation will continue for 5 years unless:

5.6.1 Patient withdraws consent.

5.6.2 Death.

6. Measurement of Effect

6.1 Response to Optimal Systemic Therapy on Step 1

Rev. 2/13

6.1.1 To be randomized, patients must not have experienced disease progression since the start of systemic therapy, as evidenced by clinical and radiographic documentation of disease status at baseline (see 3.1.4 for definition of baseline evaluation) compared to

Rev. 4/14

equivalent tests performed within 6 weeks prior to randomization, including:

6.1.1.1 No new sites of disease

6.1.1.2 No enlargement of existing sites by 20% or more (sum of the longest diameter of measurable lesions)

6.1.1.3 No symptomatic deterioration, defined as a global deterioration of health status requiring discontinuation of treatment without objective evidence of disease progression. Women whose loco-regional disease remains symptomatic at the end of induction therapy (i.e. ulcerations, skin nodules or pain from replacement of the breast with tumor or chest wall invasion) so that they require immediate local therapy for palliation are classified as having symptomatic deterioration and will not be randomized. They will be followed for survival.

6.2 Changes in Disease Status on Step 2

6.2.1 Local/Regional Assessment

The breast as well as cervical, supraclavicular, infraclavicular and axillary lymph nodes and chest wall disease must be assessed.

Breast evaluation will consist of:

a) physical examination with complete documentation of the following: tumor in two longest dimensions; skin invasion (yes/no) skin ulceration (yes/no); tumor mobility (free/attached to fascia/chest wall fixation).

Rev. 7/12, 2/13

b) Breast imaging studies with mammogram OR ultrasound OR breast MRI measurement are requested at baseline (see 3.1.4 and 7.1 for definition of baseline evaluation). However, if in the judgment of the physician, physical exam provides sufficient documentation of tumor size and T stage, and breast imaging has not been performed in the baseline period, the patient is still eligible. Preferably, the same imaging studies should be repeated in the pre-randomization interval (within 6 weeks prior to randomization). If the same study cannot be repeated (e.g. insurance denial of MRI), an equivalent study (e.g. mammogram or ultrasound) may be performed.

Rev. 7/13

Rev. 7/12

Rev. 4/14

c) [Deleted in Addendum #2]

d) nodal evaluation and documentation of nodal involvement by physical examination is required

e) documentation of chest wall disease: if skin nodules are present, the sum of the longest diameter of the largest five nodules should be recorded. If ulceration is present, this should be recorded (yes/no) and the area of ulceration measured in cm.

6.3 Endpoints

6.3.1 Local Regional Recurrence (among patients randomized to Arm B)

The new development or clinically significant increase in size of any supraclavicular, infraclavicular, internal mammary or axillary adenopathy or chest wall disease or invasive in-breast recurrence

6.3.2 Local/Regional Progression (among patients randomized to Arm A)

The development of symptoms leading to a decision for local therapy.

6.3.3 Uncontrolled Chest Wall Disease

Clinical or radiological evidence of local tumor on the chest wall or the presence of skin involvement, ulceration, or symptoms.

6.3.4 Distant Progression

The development of new sites of non-local/regional metastatic disease or clinically significant increase in the size of existing lesions.

6.3.5 Survival

Date of randomization to date of death.

6.3.6 Quality of Life

Rev. 4/14

Quality of life endpoints will be measured using patient-reported outcomes questionnaires. Domains to be assessed and instruments to be administered include FACT-G physical and functional well-being (FACT-B TOI), and domains specific to breast cancer (FACT Breast cancer subscale).

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 **≤ 8 weeks** prior to the initiation of systemic therapy. If pre-therapy scans were not performed, scans performed within the first 4 weeks of systemic therapy will be accepted. The same window applies to history and physical, Local/Regional assessment, ECOG PS, weight and height.
2. Step 2 CBC (with differential and platelet count) must be done during the **6 weeks** preceding randomization.
3. All required Step 2 chemistries must be done **6 weeks** preceding randomization.
4. Step 2 scans and x-rays used to assess all measurable or non-measurable sites of disease must be done within the **6 weeks** preceding randomization. The same window applies to history and physical, Local/Regional assessment, ECOG PS, weight.

	Step 1: Registration	Step 2: At randomization	6 months post randomization	12 months post randomization	18 months post randomization	30 months post randomization	At decision for local therapy (Arm A)[3]	Long-Term followup[5]
History & Physical	X[1]	X[4]	X[12]	X[12]	X[12]	X[12]	X[4]	Q 3 months years 0-2; Q 6 months years 2-5
Local/Regional[12] Assessment	X[1,8]	X[4]	X[12]	X[12]	X[12]	X[12]	X[4]	
ECOG PS[12]	X[1]	X[4]	X[12]		X		X[4]	
Weight	X[1]	X[4]	X[12]		X		X[4]	
Height[12]	X[1]							
CT chest/abdomen[1,10]	X	X	X		X	X	X[4]	
Bone scan[1,10]	X	X	X		X		X[4]	
Mammogram[9,]	X	X			X		X[4]	
Breast Ultrasound[9]	X	X			X		X	
Pregnancy Test[2]	X	X						
QOL assessment[11]	X[4]	X[7]	X		X	X	X	
CTC Enumeration[6]		X[7]	X					
Biological Sample Submissions	See Section 7.2							

1. CT scans with bone windows or PET CT are allowed instead of CT chest/abdomen and bone scan. If performed at baseline, should be repeated within 6 weeks prior to randomization and during follow-up, if possible. If not possible (e.g. denied by insurance), other appropriate tests can be substituted that will evaluate all prior sites of disease and will address any new signs/symptoms.
2. Urine or serum pregnancy test must be done in women of child-bearing potential < 2 weeks prior to randomization.

Rev. 7/12
3. In Arm A patients, if a decision is made to deliver palliative local therapy, a complete local-regional assessment must document reason for palliative treatment and must include same imaging tests that were performed at start of systemic therapy, if possible If not possible, (e.g. denied by insurance), other appropriate tests can be substituted that will evaluate all prior sites of disease and will address any new signs/symptoms.

Rev. 4/14
Rev. 7/12
4. [Deleted in Addendum #2]

Rev. 7/12
5. Patients who are not randomized will be followed for survival for 5 years post registration.

6. Collect only if performed as part of standard clinical assessments and covered by third party reimbursement.

7. Collect prior to randomization.

8. Pathology reports confirming diagnosis of breast cancer and, if only one metastatic lesion is present, the metastatic site must be submitted to the ECOG-ACRIN Operations Office - Boston within one month of registration to step 1.

Rev. 7/12, 7/13
9. Breast imaging studies with mammogram OR ultrasound OR breast MRI measurement are requested at baseline (see 3.1.4 and 7.1 for definition of baseline evaluation). However, if in the judgment of the physician, physical exam provides sufficient documentation of tumor size and T stage, and breast imaging has not been performed in the baseline period, the patient is still eligible. If possible, the same imaging studies should be repeated in the pre-randomization interval (within 6 weeks prior to randomization). If not possible (e.g. denied by insurance), other tests can be substituted that will evaluate the breast and will address any new signs/symptoms. Mammogram and ultrasound may be unilateral (affected side) or bilateral, at physician discretion. Breast imaging is not required if the breast is replaced by tumor or ulcerated in a way that makes breast imaging not feasible. If so, physical exam documentation must reflect this. A physical exam can only be used for pre-randomization evaluation of the breast if imaging is not feasible and tumor is palpable: in this case, physical exam findings describing the tumor must be documented. During follow-up breast imaging studies with mammogram OR ultrasound OR MRI need to be performed.

Rev. 4/14
Rev. 4/14
10. If the patient is being registered >4 weeks after initiation of systemic therapy, and the test was not performed within the baseline window (8 weeks before to 4 weeks after start of systemic therapy), physician may declare (if appropriate) that test was not indicated, and the patient may still be registered.

Rev. 4/14
11. Window is +/- 14 days for each QOL administration time point **(except step 2 randomization).**

Rev. 4/14
12. Window is ± 14 days.

7.2 Biological Sample Submissions

Rev. 7/12 Pathology and blood samples should be submitted to the ECOG-ACRIN Central Biorepository and pathology Facility (CBPF) for banking per patient consent as outlined in Section 9.

Rev. 7/12 **NOTE:** It is required that biological sample submissions be logged into the ECOG-ACRIN Sample Tracking System (STS) (see Section 9.3)

Rev. 2/13 **NOTE:** [Deleted in Addendum #3]

NOTE: Institutions outside of the United States and Canada must confer with the receiving laboratory and the ECOG-ACRIN Operations Office - Boston regarding logistics for submission of fresh samples.

Rev. 7/12

Biological Samples	Step 1: Registration	Step 2: Randomization[3]	Six (6) Months Post Randomization	Twelve (12) Months Post Randomization
Submit from patients who answer "YES" to "*I agree my tissue will be submitted for research*."				
Rev. 7/12 Block from Primary Tumor	X[1]	Arm B (Surgical Specimen) Arm A (Palliative Care Surgical Specimen)		
Block from Metastatic Site	X[2]			
Submit from patients who answer "YES" to "*I agree biopsies may be done to obtain research specimens*" at sites that have met the guidelines outlined in Section 9.4[5]				
Rev. 7/12 Block from Primary Tumor		Arm A[3]		
Rev. 7/12 Block from Metastatic Site		X[7]		
Rev. 7/12 **Submit from** patients who answer "YES" to "*I agree to provide additional blood for research*." Collection and shipping kits are available[4]				
Peripheral Blood: DNA PAXgene or ACD tube, (1) 8.5mL	Sample may be drawn any time while participating in the protocol, although baseline (prior to treatment) preferred			
Serum: SST Red/Grey Marble top tube, (1) 10mL		X	X	X
Plasma and residual cells: EDTA Purple top tube (1) 10mL		X	X	X

1. Time of diagnosis/staging, prior to beginning induction systemic therapy.
2. Rev. 2/13 If available/feasible from both Arm A and Arm B participants. Submit per patient consent. If not considered clinically necessary will qualify for research biopsy rates as outlined below.
3. Rev. 7/12 Collect at the time of local therapy/at randomization for Arm B patients. For Arm A patients collect within three (3) months of randomization. If palliative surgery is performed for Arm A patients, the primary tumor block should be submitted.

4. To order kits, complete the E2108 Collection and Shipping Kit Order Form (Appendix VI) and Fax to Zemotak – International at (800) 815-4675.

5. Biopsy research rates and reimbursement guidelines are outlined in Section 9.4. Prior to recruiting patients to the additional biopsy portion, the following conditions must be met:

Rev. 2/13

   a. The research rates of $950 per breast biopsy and $2,350 for metastatic biopsy are deemed acceptable by the IRB or central research office.

Rev. 2/13

   b. The research rate is reported to the institution's financial office and an account established in the cooperative group's principal investigator's name.

Rev. 7/12

6. [Footnote deleted in Addendum #2]

Rev. 7/12, 2/13

7. Collect within three (3) months of randomization for Arms A and B, if clinically indicated or if patient consents to research biopsy.

8. Statistical Considerations

8.1 Primary Endpoint

Overall survival, defined as time from randomization to death from any cause. All patients will be followed for survival through 5 years. Cases with incomplete follow-up or without record of vital status will be censored at the date of last contact.

8.2 Secondary Endpoints

8.2.1 Uncontrolled Chest Wall Disease

The chest wall/breast will be called "controlled" if there is no clinical or radiological evidence of the local tumor; or if there is evidence of the primary tumor but no skin nodules, ulceration, or chest wall fixation. Time to uncontrolled chest wall disease is defined as time from randomization to the development of uncontrolled chest wall disease. Patients with controlled chest wall will be censored at the last date of evaluation.

8.2.2 Health-related Quality of Life

Rev. 4/14

The FACT-Breast Trial Outcome Index will be used as the primary HRQL endpoint. FACT-B TOI scores at baseline, randomization, 6, 18 and 30 months after randomization will be calculated and compared for participants randomized to early local therapy versus palliative local therapy. The change of FACT-B TOI scores over time will be compared between treatment arms as well. For the palliative local therapy arm, the change of QOL from randomization to the time of decision for local therapy will also be measured.

8.3 Patient Registration

Rev. 7/12

Registration must occur prior to or within 30 weeks of initiation of systemic therapy and prior to any local therapy. Patients who have not progressed during induction systemic therapy will be randomized between the two arms: Arm A (control: delayed palliative local therapy for symptomatic local progression) and Arm B (experimental: immediate local therapy). Randomization will be conducted using permuted blocks within strata with dynamic balancing within main institutions and their affiliate networks. Institutions obtain treatment assignments through the ECOG-ACRIN web registration program. Patients who progress during induction systemic therapy will undergo therapy at their physician's direction and will be monitored for local and distant events.

Rev. 7/13

8.4 Sample Size

The primary comparison will be an intention-to-treat analysis including all randomized patients. It is expected that the three-year survival in the control arm will be 30%. The primary analysis of survival will be performed using a one-sided logrank test stratified on the stratification factors including marker status and treatment plan, number of involved organ systems, using an overall type I error of 5%. Allowing for the interim analysis plan discussed below, a total accrual of 186 responders and a total information of 110 deaths is planned, to give 85% power

to detect a 19.3% difference in the three-year survival rates (i.e., 49.3 % in the experimental arm). To allow for 15% probability of crossover between two arms (sum of the probabilities of patients on the experimental arm crossing over to the control arm and vice versa), both numbers are inflated by a factor of 1.38 (based on the Lachin-Foulkes correction)(53) to a total accrual of 258 responders and a total information of 152 deaths. Assuming an exponential distribution, this difference corresponds to an improvement in median survival from 21.4 to 33.5 months. Assuming 70% of the recruited patients are eligible and responding, a total of 368 patients will be needed to accrue 258 responders. Assuming an accrual rate of 6 patients per month, 62 months of accrual will be needed. The sample size was computed using seqopr6 (part of the study design library at the ECOG-ACRIN Statistical Office).

Rev. 7/13, 4/14

8.5 Interim Monitoring and Analysis Plan

Interim analyses of survival will be performed for all semi-annual DSMC meetings beginning when approximately 23% of the planned full information (36 deaths) has been observed; continuing until either the criterion for early stopping is met or full information is reached. To preserve the overall type I error rate, critical values at the interim analyses will be determined using a truncated version of the Lan-DeMets error spending function corresponding to the O'Brien-Fleming boundary (54). Boundary values at a minimal significance less than .0005 will be truncated at .0005, with the boundary also adjusted to preserve the overall type I error rate of 5%. Under the accrual and death rate assumptions above, interim analyses would be expected to occur at 28, 34, 40, 46, 52, 58 and 64 months after activation, at information times of 23%, 33%, 43%, 54%, 65%, 77%, 89% with a final analysis at approximately 70 months after activation at 100% of the information time. Due to delays in initiation of accrual and delays in data submission and processing, it is likely that the actual analysis times will be 6-12 months later.

The study will also be monitored for early stopping in favor of the null hypothesis using Jennison-Turnbull repeated confidence interval (RCI) (52) methodology. At each interim analysis the RCI on the hazard ratio will be computed using the critical values from the error spending function. If this RCI does not include the target alternative hazard ratio of 1.57 (control/experimental), then the study would be stopped early for lack of benefit. The hazard ratio of 1.57 is attenuated for the effect of noncompliance based on Lachin-Foulkes' modified hazards (53) while the actual hazard ratio will be adjusted at the time of analysis based on actual compliance rates. If criteria for early stopping are not met, then the final analysis will be performed when approximately 152 deaths have been observed.

Secondary objectives include comparison of proportions of patients with uncontrolled chest wall, time to uncontrolled chest wall disease and

Rev. 4/14

HRQLbetween arms. The proportion of patients with uncontrolled chest wall at 18 and 30 months post randomization will also be compared using the two-point procedure described in Freidlin, Korn, and *et. al.* (51). The fraction of uncontrolled chestwall at 6 months post randomization will also be compared

Rev. 4/14

using Fisher's exact test. HRQL scores will be compared using the methods described below.

Rev. 4/14

8.6 HRQL Power Estimate and Analysis Plan

Rev. 4/14

Health Related Quality of Life (HRQL) will be assessed using the FACT-B TOI, FACT-G, FACT Breast cancer subscale score and the additional items added to the Breast Cancer Subscale. The average total score for each scale will be recorded for both arms at baseline, randomization, six months post-randomization, 18 months post-randomization, and 30 months post-randomization and their change over time will be compared using mixed effects models. More specifically, we will fit a model with treatment assignment, assessment time, treatment assignment by assessment time interaction and other possible predictors. If the interaction of treatment assignment and assessment time is significant, then the change of HRQL over time would be different for the two arms. This model also accommodates inter-patient variability

Rev. 7/13

by modeling patient-specific regression lines. If there is high proportion of informative missingness in the HRQL data, we will analyze the data using the joint modeling of longitudinal data (here, HRQL) and survival time as described in Schluchter, 1992 and Schluchter, Greene and Beck, (55, 56). We will also test whether the HRQL increase or decrease from randomization to the time of decision for local therapy for the palliative local therapy arm, using a paired t test.

Rev. 4/14

The primary endpoint for HRQL is FACT-B TOI. Looking at FACT-B TOI data, using a 2-sided t test at level 0.20, there is 79% power to detect a difference of 4.5 points between the two arms with SD 14 (from E2100), assuming 69% of responders who received assigned treatment (89 per arm) have HRQL data at 18 months post-randomization. The Wilcoxon Rank Sum test will be used to compare the two arms if the scores are not normally distributed.

Rev. 4/14

8.7 Correlative Science (CTC) Power estimate

Two sample t-test/Wilcoxon test will be conducted to test whether the CTC burden at 6 months after randomization will be lower in Arm B than in Arm A. Cox proportional hazards (PH) model will be used to examine whether patients with lower CTC burden at 6 months after randomization have prolonged survival. The treatment assignment, CTC burden or possibly their interaction will be included in the Cox PH model.

Assuming 60% of the patients would provide their CTC at 6 months after

Rev. 7/13

randomization, we would have 155 evaluable patients, with 77 patients per arm. Assuming the standardized difference is 0.339 (difference in mean/standard deviation; e.g. the difference in CTC at 6 months after randomization for the two

Rev. 7/13

arms is 1 and the SD is 3), then the given sample size will provide 77% power using a two sample t test with two-sided significance level of 0.20.

A paired t-test/ Wilcoxon test would be used to test whether there is a reduction in CTC burden from randomization to 6 month assessmentsin Arm B. A Cox PH model will be conducted to evaluate whether a larger reduction in CTC predicts longer survival.

A two sample t-test/Wilcoxon test would be used to test whether the reduction in CTC in Arm B is larger than Arm A. A Cox PH model will be used to evaluate whether a larger reduction predicts longer survival.

8.8 Gender and Ethnicity

Based on previous data from E2100 and E1100, the anticipated accrual in subgroups defined by gender and ethnicity/race is:

Rev. 7/13

Ethnic Category	**Gender**		
	Females	**Males**	**Total**
Hispanic or Latino	27	0	27
Not Hispanic or Latino	339	2	341
Ethnic Category: Total of all subjects	366	2	368
Racial Category			
American Indian or Alaskan Native	0	0	0
Asian	8	0	8
Black or African American	34	0	34
Native Hawaiian or other Pacific Islander	0	0	0
White	324	2	326
Racial Category: Total of all subjects	366	2	368

The accrual targets in individual cells are not large enough for definitive treatment comparisons to be made within these subgroups. Therefore, overall accrual to the study will not be extended to meet individual subgroup targets.

8.9 Compliance Monitoring

Rev. 7/13

The DSMC will monitor the compliance throughout the trial. If there is large deviation from the assumed compliance rate, i.e., the sum of the cross-over rates in either direction cross 15%, the design modification or early termination of the trial will be discussed at the DSMC meeting. We would also consider a formal stopping rule if the cross-over rate is higher than expected after recruiting 200 patients, by evaluating the impact of the unexpected accumulative cross-over rate on the power. If the accumulative cross-over rate is higher than assumed, for example, 20%, then the power would be reduced to 82%. A 30% rate yields a power as 71%, which might be considered as acceptable. In a more extreme case, if the rate reaches 50%, then the power would be only 46%, which is too low to detect any benefit for the elective local therapy. On the other hand, if the accumulative cross-over rate is lower than assumed (15%), then we would gain more power with the current design. For example, if the rate is 10%, the power would increase to 89%.

Rev. 7/13

8.10 Study Monitoring

Rev. 7/13

This study will be monitored by the ECOG-ACRIN Data Safety Monitoring Committee (DSMC). The DSMC meets twice each year. For each meeting, all monitored studies are reviewed for safety and progress toward completion. When appropriate, the DSMC will also review interim analyses of outcome data. Copies of the toxicity reports prepared for the DSMC meetings are included in the study reports prepared for the ECOG-ACRIN group meeting (except that for double blind studies, the DSMC may review unblinded toxicity data, while only pooled or

blinded data will be made public). These group meeting reports are made available to the local investigators, who may provide them to their IRBs. Only the study statistician and the DSMC members will have access to interim analyses of outcome data. Prior to completion of this study, any use of outcome data will require approval of the DSMC. Any DSMC recommendations for changes to this study will be circulated to the local investigators in the form of addenda to this protocol document. A complete copy of the ECOG-ACRIN DSMC Policy can be obtained from the ECOG-ACRIN Operations Office - Boston.

9. Correlative Studies

Tumor tissue (primary and metastatic) and blood specimens are to be submitted per patient consent for future exploration of the biological interactions between the primary tumor and metastatic lesions and the effect of primary tumor resection on survival.

9.1 Sample Submission Requirements

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 9.3.

Rev. 2/13 A table summarizing the biological sample submissions is located in Section 7.2

9.1.1 Tumor Tissue

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).

Rev. 7/12 Pathology samples are submitted per patient consent as indicated below.

Forms to be submitted with each submission

- Pathology Material Submission Form (#638 v04.2), Parts A & B completed. Please identify the clinical status of the submitted material (i.e., pretreatment as opposed to remission and relapse).
- A copy of the surgical pathology report.
- Immunologic studies, if available.

Rev. 7/12
- Sample Tracking System Shipping Manifest Form.

Rev. 7/12 Pathology Sample Submissions

- From patients who consent "YES" to "*I agree my tissue will be submitted for research".*
    - Diagnostic primary tumor tissue block collected prior to start of systemic therapy.
    - Metastatic tumor biopsy tissue block collected prior to start of systemic therapy, if available.

    NOTE: If unable to submit blocks, submit fifteen (15) 5-micron sections on uncharged slides and, if materials are available, two (2) 4-mm core punches. Contact the ECOG-ACRIN CBPF for alternatives at 1-844-744-2420 or eacbpf@mdanderson.org.

    - Surgical primary tumor tissue block
        - Arm B: at time of local therapy/at randomization
        - Arm A: at time of palliative surgery

NOTE: If unable to submit blocks, submit two (2) 4-mm core punches. Contact the CBPF for alternatives at 1-844-744-2420 or eacbpf@mdanderson.org.

- From patients who consent "YES" to "*I agree biopsies may be done to obtain research specimens*" at sites that have met the guidelines outlined in Section 9.4. Biopsies which are not performed for clinical purposes, but only to collect research specimens will be reimbursed as outlined in Section 9.4 AND are not to be billed to insurance.
    - ARM A: Primary tumor tissue block collected within three (3) months of randomization.
    - BOTH ARMS: Metastatic tumor biopsy tissue block. Collect within three (3) months of randomization.

NOTE: **Only blocks will be accepted**, though sites are allowed to keep an H&E slide.

Rev. 7/12, 2/13

9.1.2 Blood Sample Submissions

Blood samples are to be submitted from patients who answer "YES" to "*I agree to provide additional blood for research."*

Blood tubes are to be drawn in the following order: No anticoagulant (SST or red top), ACD (yellow top), EDTA (purple top), PAXgene DNA tube.

Blood tubes should be labeled with the ECOG-ACRIN protocol number "E2108", patient initials, ECOG-ACRIN patient sequence number, institution name, date and time drawn and time point.

Frozen samples are to be shipped on dry ice. If not shipped the day of collection, store frozen below –20°C (-70°C preferred) until shipped. Specimens stored at temperatures higher than -70°C are to be shipped within one (1) week of collection.

9.1.2.1 Collection Time Points

1. ACD or PAXgene DNA tube: Baseline prior to start of treatment preferred, but may be collected any time while on study.
2. Serum and Plasma + Residual Cells
    - Randomization, prior to start of local therapy.

Rev. 7/12

- Six (6) months post randomization.

Rev. 7/12

- Twelve (12) months post randomization.

Rev. 7/12

9.1.2.2 Collection and Shipping Kits

Kits will include vacutainers and cryovials for the aliquots of the serum and plasma.

Baseline kits must be requested within 48 hours (two business days) following registration. All other kits must be

requested at least 48 hours prior to scheduled use. You will need to request kits at each time point.

Complete the E2108 Collection and Shipping Kit Order Form, Appendix VI and Fax to Zemotak – International at (800) 815-4675.

Rev. 7/12

Kits will be shipped overnight on the next working day and will include collection and shipping materials, and instructions for processing.

Questions regarding kits should be directed to Zemotak - International at zemchi@aol.com.

9.1.2.3 Preparation Guidelines

Rev. 2/13

Serum - SST (red/grey marble top tube)

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

a. Draw peripheral blood into vacutainer.

b. Allow blood to coagulate 20 minutes, then centrifuge at 25°C, 1500xg (2700-3000 rpm) for 15 minutes.

c. Pipette the serum into four (4) cryotubes provided in the kit.

d. Store frozen, below –20°C (-70 °C preferred), until shipped.

(**NOTE:** Red top, no anti-coagulant tube may substitute.)

Plasma - EDTA (purple top tube) + Residual Cells (WBC&RBC)

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

a. Draw peripheral blood (10mL) into vacutainer and gently invert 8-10 times.

Rev. 2/13

b. Within 20 minutes of collection, centrifuge at 1500xg (2700-3000 rpm) at 4°C for 15 minutes.

Rev. 7/12

c. Pipette the plasma into four (4) cryotubes provided in the kit and store frozen, below –20°C (-70°C preferred), until shipped.

d. Remaining Cells: Replace the stopper on the EDTA tube containing the cells and ship ambient the day of collection.

Peripheral Blood – ACD (yellow top tube)

a. Blood should be collected directly into vacutainer tube using the butterfly needle set.

b. After blood collection, gently invert the tube 8 to 10 times.

c. May be shipped day of collection at Ambient Temperature (or with Cool Pack during hot season).

OR below -70°C and ship with serum and plasma samples. If specimen is collected at same time as the serum and plasma, sample may be stored at –20°C until shipped.

(***NOTE:*** DNA PAXgene or EDTA tube may substitute).

9.2 Shipping Procedures

Rev. 7/12

These guidelines are for the U.S., Hawaii, Puerto Rico and Proximal Canadian sites only. International sites must contact the CBPF to set up special arrangements.

Log the samples into the ECOG-ACRIN Sample Tracking System (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.

Rev. 2/13

Access to the shipping account for specimen shipments to the ECOG-ACRIN CBPF at MD Anderson Cancer Center can only be obtained by logging onto fedex.com with an account issued by the ECOG-ACRIN CBPF. For security reasons, the account number will no longer be provided in protocols, over the phone, or via email. If your site needs to have an account created, please contact the ECOG-ACRIN CBPF by email at eacbpf@mdanderson.org.

9.2.1 Submission Schedule

The pathology samples should be submitted within one month of collection.

Blood samples are to be shipped Sunday through Thursday, to arrive Monday through Friday. The laboratory is closed weekends and holidays. The DNA blood sample may be shipped at ambient (or cool pack if warm) on day of collection or shipped with the serum, plasma and cells on dry ice via overnight courier.

Rev. 7/12

Frozen specimens stored at temperatures higher than -70°C are to be shipped within one (1) week of collection.

Rev. 2/13

9.2.2 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 Blvd
Houston, TX 77030
Phone: Toll Free 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 Coordinating Center by the Pathology Coordinating Office.

NOTE: If STS is unavailable, please notify the ECOG-ACRIN CBPF of the shipment by faxing the Notice of Shipment Form (Appendix VII) to 713-563-6506 on the day of shipment.

9.3 ECOG-ACRIN Sample Tracking System

It is **required** (barring special circumstances) 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: Additionally, 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.

Rev. 7/12

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.

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 on the submission form:

- ECOG-ACRIN Central Biorepository and Pathology Facility

Notify the ECOG-ACRIN CBPF of the shipment by faxing a copy of the Generic Specimen Submission Form to 713-563-6506 on the day of shipment. Retroactively enter all collection and shipping information when STS is available.

9.4 Institutional Reimbursements

9.4.1 Accrual to Laboratory Studies

To receive site reimbursement for biospecimen submissions, completion dates must be entered in the OPEN Funding screen post registration. Please refer to the protocol specific funding page on the CTSU members' website for additional information. Timely entry of completion dates is recommended as this will trigger site reimbursement.

9.4.2 Biopsy Reimbursements

Rev. 7/12, 2/13

Additional research biopsies will be obtained from the primary tumor (Arm A only) and metastatic site (both Arms) at randomization, as well as in cases where the metastatic biopsy at study entry is not considered clinically necessary. The biopsies are reimbursable up to a maximum of $950 per breast biopsy and $2,350 per metastatic biopsy.

Rev. 2/13

All sites are eligible for the reimbursement for the research biopsies regardless of cooperative group. However, it is up to the site to set up the mechanism for the 'billing' of these biopsies. ECOG-ACRIN recommends billing the cooperative group Principal Investigator (PI) of the site. Contact your coordinating group's operations office and ask to whom this account should be named

Rev. 7/12

Please note that blocks **MUST** be submitted in order to receive the reimbursement. Since these biopsies are being performed strictly for the research for this trial, blocks are required to be submitted in order to receive the reimbursement.

Prior to recruiting patients to the biopsy portion, the following conditions must be met:

Rev. 2/13

a. The research rates of $950 per breast biopsy and $2,350 per metastatic biopsy are deemed acceptable by the IRB or central research office.

Rev. 2/13

b The research rate is reported to the institution's financial office and an account established in the institution's cooperative group principal investigator's name.

Rev. 2/13

c. The patient provides written consent to undergo the additional biopsies.

NOTE: If the above rates are not accepted by your central research office do not present this additional research biopsy option to your patients

Rev. 2/13

Receipt of the biopsies will be verified prior to the release of any funds. Expenses for biopsies will be paid only to participating institutions, not to any other persons or entities, at the stated research rate of $950 per breast biopsy and $2,350 per metastatic biopsy.

NOTE: Neither patients nor their insurance companies are to be billed for the collection or submission of these research biopsy samples.

Distribution of the reimbursements requires:

- Submission of the requested biopsy samples using the ECOG-ACRIN Sample Tracking System (STS)
- Receipt and verification of the requested biopsy samples by the ECOG-ACRIN Central Biorepository and Pathology Facility via the ECOG-ACRIN STS. (Refer to Section 9.3 for STS requirements)

Rev. 2/13

- Receipt of E2108 Biopsy Reimbursement Form (Appendix VII) to the ECOG-ACRIN Operations Office - Boston.

Rev. 2/13

Reimbursements will be paid from the ECOG-ACRIN Operations Office - Boston to the ECOG-ACRIN Principal Investigator (PI) of the submitting ECOG-ACRIN institution.

Rev. 2/13

For sites whose accruals are credited to any other cooperative group (including the CTSU), the reimbursements will be routed through the respective group's operations office. ECOG-ACRIN does not dictate

how these funds flow from another cooperative group's operations office to the site. Please verify this internal billing mechanism with the appropriate operations office to determine the routing procedure.

Rev. 2/13

If your site is associated with more than one cooperative group, you will need to determine how your accruals to this trial are credited (e.g., if your site belongs to SWOG and CTSU and your accruals are credited as CTSU, then the CTSU PI is the individual for whom the account and funds are managed)

Rev. 2/13

Payments are made annually.

9.5 Banking

Specimens will be retained at the ECOG-ACRIN Central Repository 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.

Rev. 7/12

9.6 Sample Inventory Submission Guidelines

Inventories of all samples collected, aliquoted, and used will be submitted electronically via 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.

10. Records to Be Kept

Please refer to the E2108 Forms Packet for the forms submission schedule and copies of all forms. The E2108 Forms Packet may be downloaded by accessing the ECOG-ACRIN 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.

10.1 ECOG-ACRIN Radiation Oncology Quality Assurance Materials

Please see Section 5.3.7 for a list of radiotherapy quality assurance materials that should be submitted to QARC. All materials should be sent directly to the QARC offices as indicated in Section 5.3.8.

A checklist detailing the complete list of required data is available on the QARC website at www.QARC.org. Click on the ECOG-ACRIN link to access the checklist.

11. Patient Consent and Peer Judgment

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

12. References

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Rev. 4/14

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A Randomized Phase III Trial of the Value of Early Local Therapy for the Intact Primary Tumor in Patients with Metastatic Breast Cancer

Appendix I

Informed Consent Template for Cancer Treatment Trials (English Language) - [Deleted in Addendum #3]

INFORMED CONSENT INTENTIONALLY REMOVED FROM PROTOCOL DOCUMENT

A Randomized Phase III Trial of the Value of Early Local Therapy for the Intact Primary Tumor in Patients with Metastatic Breast Cancer

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 E2108
4. ECOG-ACRIN Generic Specimen Submission Forms (#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)

Instructions:

1. Place the Patient ID label provided by the ECOG-ACRIN Operations Office - Boston in Part A of the Pathology Material Submission Form.

   If a label is not available, **TYPE or PRINT** the following information in **Part A** of the form:

   Patient's name (last, first)

   Protocol number

   Protocol case number (the patient's ECOG-ACRIN sequence number; for intergroup studies, include both the ECOG-ACRIN and other group's sequence numbers)

   Patient's hospital number

   Institution

   Affiliate (if appropriate)
2. Complete blank areas of the pathologist's instructional memo and forward it, along with the List of Required Material and the Pathology Material Submission Form, to the appropriate pathologist.
3. The pathologist should return the required pathology samples and surgical pathology reports, along with the completed Pathology Material Submission Form (#638 v04.2) (Part B completed). If any other reports are required, they should be obtained from the appropriate department at this time.
4. Keep a copy of the Pathology Material Submission Form (#638 v04.2) for your records. (The original should be sent to the CBPF.)
5. Double-check that ALL required forms, reports and pathology samples are included in the package to the Central Biorepository and Pathology Facility. (See appropriate List of Required Material.)

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

Mail pathology materials to:

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 Blvd
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 Central Biorepository and Pathology Facility by telephone 1-844-744-2420 or by fax 713-563-6506.

LIST OF REQUIRED MATERIAL

E2108: A Randomized Phase III Trial of the Value of Early Local Therapy for the Intact Primary Tumor in Patients with Metastatic Breast Cancer

Pre-study (collected prior to the start of systemic therapy)

1. Institutional pathology report ***(must be included with EVERY pathology submission)***.
2. Pathology materials:
   - Original diagnostic paraffin embedded primary tumor block
   - block from metastatic site (when available)

Rev. 7/12 **NOTE:** If unable to submit blocks, submit fifteen (15) 5-micron sections on uncharged slides and, if materials are available, two (2) 4-mm core punches.

Randomization or at time of local treatment

1. Institutional pathology report **(must be included with EVERY pathology submission)**.

Rev. 7/12 2. Pathology materials:
   - ARM B: Surgical primary tumor tissue block
   - ARM A: Surgical primary tumor block from palliative care surgery

NOTE: If unable to submit blocks, submit two (2) 4-mm core punches. Contact the ECOG-ACRIN PCO CBPF for alternatives at 1-844-744-2420 (312) 503-3384 or eacbpf@mdanderson.org

   - ARM A: Primary tumor tissue block collected by biopsy (within three (3) months of randomization)
   - BOTH ARMS: Metastatic tumor biopsy tissue block (collect within three (3) months of randomization)

NOTE: **Only blocks will be accepted**, though sites are allowed to keep an H&E slide.

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

Coordinating Center
Frontier Science
900 Commonwealth Avenue • Boston, MA 02215
(617) 632-3610 • Fax: (617) 632-2990
Randomization: (617) 632-2022

Group Chair: Robert L. Comis, M.D.
Group Statistician: Robert Gray, Ph.D.

Jean MacDonald, Director of Research Operations
Mary Steele, Director of Group Administration

TO: _____

(Submitting Pathologist)

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

DATE: _____

SUBJECT: Submission of Pathology Materials for E2108: A Randomized Phase III Trial of the Value of Early Local Therapy for the Intact Primary Tumor in Patients with Metastatic Breast Cancer

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

Please complete PART B of the Submission Form. Keep a copy for your records and return the completed Submission Form, 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.

Blocks and/or slides submitted for this study will be retained at the ECOG-ACRIN Central Repository for future studies.

If you have any questions regarding this request, please contact the Central Biorepository and Pathology Facility at 1-844-744-2420 or 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

A Randomized Phase III Trial of the Value of Early Local Therapy for the Intact Primary Tumor in Patients with Metastatic Breast Cancer

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-ACRIN 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 participation of people like you in clinical trials, we will improve treatment and quality of life for those with your type of 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]

A Randomized Phase III Trial of the Value of Early Local Therapy for the Intact Primary Tumor in Patients with Metastatic Breast Cancer

Appendix IV

ECOG Performance Status

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

A Randomized Phase III Trial of the Value of Early Local Therapy for the Intact Primary Tumor in Patients with Metastatic Breast Cancer

Appendix V

E2108 Collection and Shipping Kit Order Form

NOTE: Starter kits are not available. It is preferred that kit requests be made AFTER patient registration.

NOTE: Please complete this form correctly, including the valid ECOG-ACRIN case number and complete shipping address. If information is missing the kit processing will be delayed.

Date: _____

ECOG-ACRIN Patient Case Number: _____

NOTE: Please note in the comments section if the kit had to be ordered prior to patient registration and the justification for this.

Ship Kit to:

Institution Contact: _____

Phone Number for Contact: _____

Fax Number for Contact: _____

E-mail for Contact: _____

Institution Address: _____

_____

_____

Fax completed form to Zemotak - International at (800) 815-4675.

NOTE: Questions regarding kits should be directed to Zemotak - International at zemchi@aol.com and ecog-acrin.tst@jimmy.harvard.edu.

Comments:

_____

_____

_____

A Randomized Phase III Trial of the Value of Early Local Therapy for the Intact Primary Tumor in Patients with Metastatic Breast Cancer

Appendix VI

E2108 Shipment Notification Form

Date: _____

It is required that samples submitted from patients participating in E2108 be entered and tracked via the online ECOG-ACRIN Sample Tracking System (see Section 9.3).

A Randomized Phase III Trial of the Value of Early Local Therapy for the Intact Primary Tumor in Patients with Metastatic Breast Cancer

Appendix VII
E2108 Biopsy Reimbursement Form

This form is to be used to request reimbursement for the performance and submission of the additional biopsies as outlined in E2108 Section 9.

NOTE: *Patients (nor their insurance) companies are not to be billed for the collection and submission of the research biopsies.*

Today's Date: _____

ECOG-ACRIN Patient Sequence Number	Date Biopsy Performed	Time Point	Tissue Type (Primary Site or Metastatic Site)	Type of Biopsy (Image-Guided [Deep Seated] or Superficial)	Date Sample Shipped
_____	_____	_____	_____	_____	_____
_____	_____	_____	_____	_____	_____

Institution Contact Name: _____ **Contact Phone Number:** _____

Tax ID#: _____

(My signature below confirms that these patients are registered to the protocol referenced above and that the patient numbers and dates above are true representations of the costs for which reimbursements are being requested.)

Signature: _____

Name (printed): _____

Please Mail or Fax to:

ECOG-ACRIN Operations Office - Boston
Attn: ECOG Translational Science Team (TST)
900 Commonwealth Avenue
Boston, MA 02215
FAX: (617) 582-8578

Rev. 7/13