The following protocol information is provided solely to describe how the authors conducted the research underlying the published report associated with the following article:

SWOG S0500: Circulating Tumor Cells and Response to Chemotherapy in Metastatic Breast Cancer

Smerage, et al

DOI: 10.1200/JCO.2014.56.2561

SWOG

A RANDOMIZED PHASE III TRIAL TO TEST THE STRATEGY OF CHANGING THERAPY VERSUS MAINTAINING THERAPY FOR METASTATIC BREAST CANCER PATIENTS WHO HAVE ELEVATED CIRCULATING TUMOR CELL LEVELS AT FIRST FOLLOW-UP ASSESSMENT

PARTICIPANTS: ALL SWOG MEMBER, CCOP, AND AFFILIATE MEDICAL ONCOLOGISTS; CTSU. **Patients enrollments from institutions that are not aligned with SWOG will be conducted via the NCI Cancer Trials Support Unit (CTSU) and all data should be sent to the SWOG Data Operations Office as specified in the CTSU logistical appendix (see Appendix 19.4).**

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

Institutions not aligned with SWOG will participate through the CTSU mechanism as outlined below and detailed in the CTSU logistical appendix.

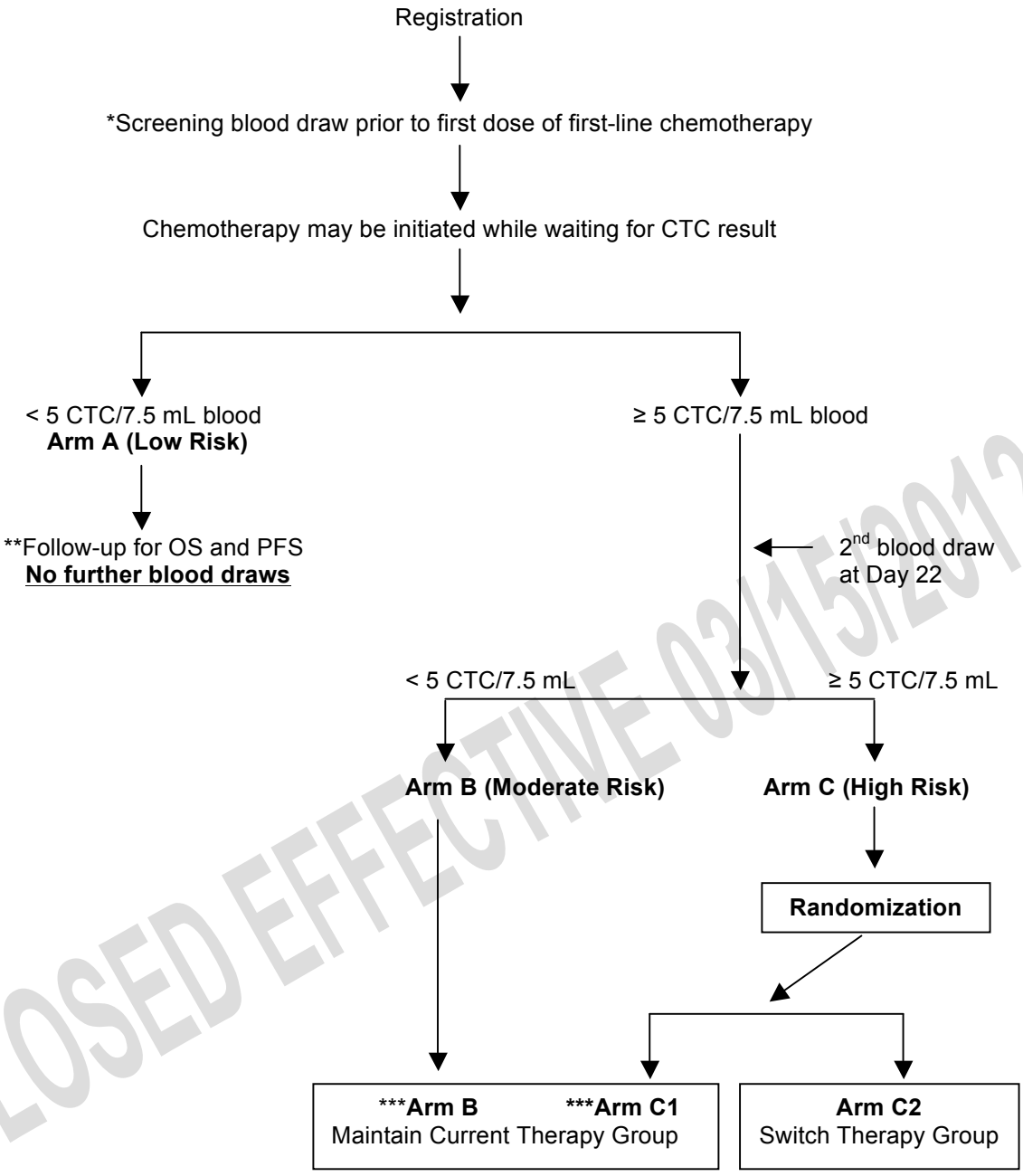
- The **study protocol and all related forms and documents** must be downloaded from the protocol-specific Web page of the CTSU Member Web site located at https://www.ctsu.org
- Send completed **site registration documents** to the CTSU Regulatory Office. Refer to the CTSU logistical appendix for specific instructions and documents to be submitted.
- **Patient enrollments** will be conducted by the CTSU. Refer to the CTSU logistical appendix for specific instructions and forms to be submitted.
- Data management will be performed by the Southwest Oncology Group. **Case report forms** (with the exception of patient enrollment forms)**, clinical reports, and transmittals** must be sent to the Southwest Oncology Group Data Operations Center unless otherwise directed by the protocol. Do not send study data or case report forms to the CTSU Data Operations.
- **Data query and delinquency reports** will be sent directly to the enrolling site by the Southwest Oncology Group. Please send query responses and delinquent data to the Southwest Oncology Group Data Operations Center and do not copy the CTSU Data Operations.
- Each site should have a designated CTSU Administrator and Data Administrator and must keep their CTEP AMS account contact information current. This will ensure timely communication between the clinical site and the SWOG data center.

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: 1-888/823-5923 Fax: 215/569-0206	CTSU Patient Registration Voice Mail: 1-888/462-3009 Fax: 1-888/691-8039 Hours: 9:00 am – 5:30 pm EST, Monday – Friday (excluding holidays) [Registrations received after 5:00 p.m. EST will be handled the next business day. For CTSU patient enrollments that must be completed within approximately one hour, or other extenuating circumstances, call 301/704-2376 between 9:00 a.m. and 5:30 p.m.]	Southwest Oncology Group Data Operations Center Fax: 1-800/892-4007 [Please do not use a cover sheet for faxed data.] Do not submit study data or forms to CTSU Data Operations. Do not copy the CTSU on data submissions.
For treatment- or toxicity-related questions contact the Study PI of the Coordinating Group.		
For eligibility questions contact the Southwest Oncology Group Data Operations Center by phone or email: Phone: 206/652-2267; Email: breastquestion@crab.org		
For questions unrelated to patient eligibility, treatment, or 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.		
The CTSU Registered Member Web site is located at https://www.ctsu.org		

CTSU logistical information is located in Appendix 19.3

SCHEMA



* Patients must be registered prior to initiation of testing (no more than one working day prior to initial CTC submission).

** Patients in the Low Risk Group (Arm A) may enroll in other clinical trials while being following for OS and PFS on **S0500**.

*** Patients in Arms B and C1 and their physicians will be blinded to which arm they are in by study design. Protocol requirements are the same for these two arms.

1.0 OBJECTIVES

1.1 To determine whether metastatic breast cancer patients who have elevated circulating tumor cells (CTCs) (≥ 5/7.5mL of whole blood) after three weeks of first-line chemotherapy derive increased overall survival (OS) from changing to an alternative chemotherapy at the next cycle, rather than waiting for clinical evidence of progressive disease.

1.2 To determine whether metastatic breast cancer patients who have elevated CTCs (≥ 5/7.5mL of whole blood) after three weeks of first-line chemotherapy derive increased progression-free survival (PFS) from changing to an alternative chemotherapy at the next cycle, rather than waiting for clinical evidence of progressive disease.

1.3 To confirm previous findings that patients with < 5 CTC/7.5 mL of blood on initial screening have longer median OS and PFS than patients with ≥ 5 CTC.

1.4 To determine whether sequentially collected CTC values continue to provide prognostic value at each individual time-point over the course of the study.

1.5 To compare toxicity between patients with and without elevated CTCs after 3-weeks of first-line chemotherapy and between the two randomized arms.

1.6 Correlative objectives:

a. To compare the prognostic and predictive value of CTC number to breast cancer tumor markers, including CA 15-3 and CEA.

b. To create a serum specimen bank for future biologic investigation.

2.0 BACKGROUND

Treatment of Metastatic Breast Cancer

Current therapeutic options available for metastatic breast cancer (MBC) include hormonal and chemotherapeutic agents, and targeted therapies such as trastuzumab. Although the number of drug regimens available to the oncologist is substantial, treatment of patients with metastatic breast cancer remains primarily palliative. *(1)* To achieve effective palliation, the clinician, after a comprehensive clinical evaluation, ideally selects the most effective treatment(s) with the fewest side effects. These modalities are then employed sequentially, commencing with the least toxic. Treatment is then monitored via clinical assessment of efficacy and toxicity and, upon documented disease progression, changed to a more aggressive therapy.

For patients with more indolent disease, the choice of therapy is dictated by the predictive marker profile of the primary tumor. Expression of the estrogen (ER) and progesterone (PR) hormone receptors support selection of endocrine therapy, while amplification/over-expression of HER2 indicates use of trastuzumab. However, not all patients with the appropriate disease phenotype will benefit from the indicated therapy. This is evidenced by the fact that approximately half (50-60%) of ER positive patients actually benefit from first line hormonal therapy while less than half (30-50%) of HER2 positive patients appear to respond to trastuzumab - alone or in concert with chemotherapeutic agents. *(1)* Likewise, in those patients for whom "chemotherapy" is felt to be the appropriate therapeutic choice (receptor negative, hormone refractory or those with rapidly progressive visceral disease) approximately 60 - 70% will benefit from the first regimen chosen. In summary, despite practicing evidenced-based medicine, the chosen therapy, on average, does not achieve the desired effect in 50% of patients. In essence, half of MBC patients will be subjected to all the adverse effects of therapy – physical, emotional and financial – with little or no hope of positive gain.

Ultimately new drugs and innovative treatment strategies are needed if there is to be significant improvement in the clinical outcome for these patients. One such novel approach to achieving better outcomes with existing drugs could be to change to an alternative therapeutic regimen after determining "early on" (within 3 - 4 weeks of initiating treatment) that the prescribed therapy is ineffective – i.e., the patient is on futile therapy. Currently this is not feasible, as treatment monitoring is based upon changes in serum markers and/or the size of measurable lesions as determined by imaging studies (CT, MRI, PET or SPET, and bone scintigraphy). All suffer from either a lack of precision, sensitivity and/or specificity – and they may or may not be readily accessible to the patient. Reliance on serum tumor markers is limiting due to an early "spike" phenomenon, which may provide confounding information early in the treatment phase. Regarding the use of imaging, the lesion may need to be observed for a substantial period of time before response can be reliably determined. Furthermore, in the case of breast cancer, many women (up to 40%) have non-measurable disease such as bone-only disease, pleural effusions, or ascites. To further complicate matters, many of the new targeted therapies are believed to be cytostatic, which means that they may not produce rapid decreases in tumor size even if they are working. Thus, it is evident that effective clinical evaluation requires innovative methods to detect response to therapy. One such method may be the CellSearch® in vitro diagnostic assay, which was developed to enumerate circulating tumor cells (CTC) in women with metastatic breast cancer (MBC).

Circulating Tumor Cells

Since the French physician Recamier coined the term metastasis in 1829, after postulating a link between metastatic and primary tumors, the existence, origin and clinical significance of "circulating" tumor cells has been in question. *(2)* However, evidence provided by Ashworth's demonstration of cancer cells in the circulation in 1869, Paget's "seed and soil" hypothesis in 1889, and more recently, Engell's documentation of the role of CTC in metastasis in 1955, have inspired the development of technologies with sufficient sensitivity and specificity to reliably examine the role of these rare cells in cancer biology. *(3 - 8)* It has been shown that CTCs in peripheral whole blood, in comparison to the leukocyte populations, occur at frequencies of as few as 1 cell in 10^{6-8} leukocytes/mL of whole blood, approximately 1 CTC per 1 – 5 mL of whole blood. Occasionally they do occur at much higher frequencies – a phenomenon which, based on previous studies, appears to be associated with an increase in disease activity. *(8)* It is this variability in the absolute number of CTC in the peripheral circulation that forms the biological basis for the CellSearch® assay.

The Assay - Veridex, LLC Technology

The Veridex, LLC CellSearch® System employs immunomagnetic separation technology in which the blood specimen is incubated with magnetic beads coated with antibodies directed against the epithelial cell adhesion molecule (EpCAM). *(9)* A magnet is then used to isolate the immunomagnetically labeled epithelial cells. For patients with metastatic breast cancer, 7.5 mL of blood is the volume usually analyzed. After immunomagnetic isolation the cells are stained with fluorescently labeled anti-cytokeratin antibodies and the fluorescent nuclear stain DAPI. A fluorescently labeled pan-leukocyte MAb is included as a counter-stain to discriminate contaminating white blood cells. Sample processing is fully automated. After isolation and staining, the CTCs are placed in a proprietary chamber for viewing on a semi-automated fluorescence microscope. Image analysis software pre-selects specific objects based on fluorescence staining patterns and intensities. The objects are presented as thumbnail images in a web browser display (Figure 1). The images generated are then reviewed by a trained technician and/or pathologist. The outcome/report is a quantitative analysis of the CTC contained in the blood specimen.

The CellSearch® System has been shown to be highly accurate and reproducible. *(10)* Blood samples spiked with standardized numbers of cultured human breast cancer cells demonstrate a linear recovery over a range of 5 to 1,142 cells (correlation coefficient R^2=0.99), with an average recovery of > 85% at each level. There is also strong agreement between duplicate samples (correlation coefficient R^2=0.975) and between independent operators reviewing the same digital images (correlation coefficient R^2=0.994).

The CellSearch® assay has been cleared by the FDA for use in the enumeration of CTCs and for the prediction of PFS and OS in patients being treated for metastatic breast cancer.

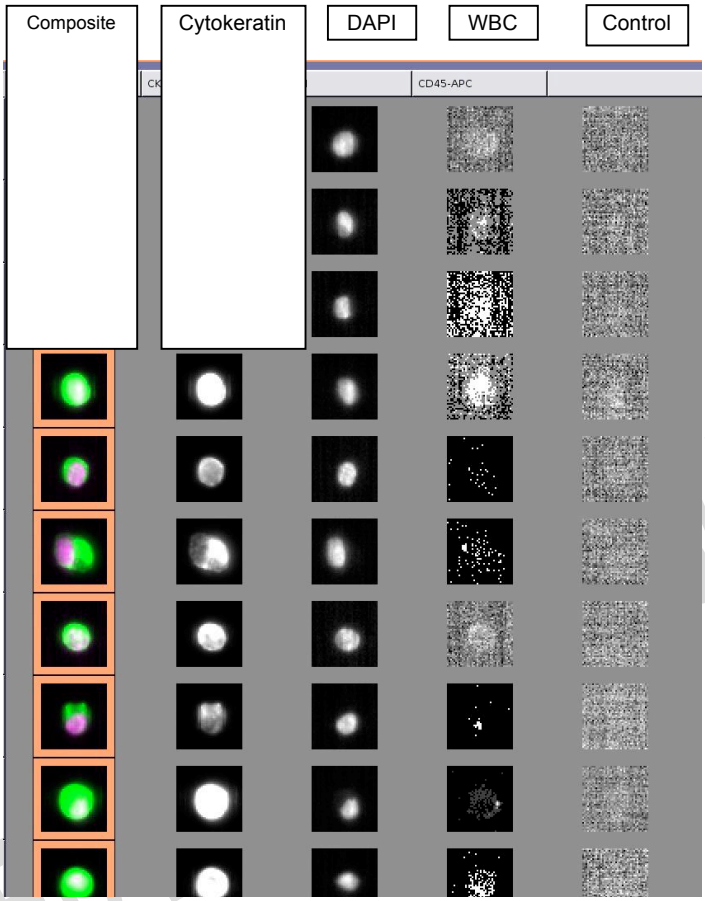


Figure 1. Digital images are obtained by the semi-automated fluorescent microscope. Software pre-selects objects for review. Trained operator confirms that selected objects are tumor cells and places a check mark in the adjacent box. The computer tallies the number of confirmed CTCs and prepares report.

Pivotal Trial Results (IMMC-01)

IMMC-01 was a prospective, multi-institutional clinical trial that enrolled 177 women with measurable metastatic breast cancer who were about to start a new therapy because of recent progression. (*11, 12*) In this study, CTCs were found to be highly prognostic when measured at both baseline and at first follow-up (~3-5 weeks after the initiation of therapy). One hundred sixty-three of the 177 patients had a 1st follow-up blood draw. The first 102 patients enrolled (95 of which had a first follow-up blood draw) were used in a training set to establish a cutoff of ≥ 5 CTC/7.5mL blood, which best distinguished short progression-free survival (PFS) and/or overall

survival (OS). This cutoff was then validated using the remaining 75 patients (68 of which had a first follow-up blood draw). Overall, 87/177 (49%) had ≥ 5 CTC at baseline, and 49/163 (30%) had persistent or newly elevated levels at first follow-up. Five or more CTCs at baseline were associated with significantly shorter median PFS (2.7 vs. 7.0 months, p=0.0001) and OS (10.2 vs. 21.9 months, p<0.0001). At first follow-up after initiation of therapy, this difference between the unfavorable (i.e. ≥ 5 CTC) and favorable (i.e. < 5 CTC) groups increased (PFS: 2.1 vs. 7.0 months, p<0.0001 and OS: 8.2 vs. 21.9 months; p<0.0001) (Figure 2, panels A and B). The number of CTCs was the strongest and most significant predictor of poor outcome in multivariate analyses. Nearly identical outcomes were seen when analysis was restricted to just patients initiating first line chemotherapy (83 of 177 patients). *(13)*

CTC Analysis in Bone-Only Metastatic Breast Cancer

A second trial evaluating CTCs in patients with bone-only metastatic breast cancer has recently completed accrual. *(14)* In this study, CTC levels were drawn at baseline and first follow-up with endpoints of PFS and OS. For patients with CTC ≥ 5 the median PFS was 3.5 months vs. 14.4

months for patients with CTC < 5. Median OS has not yet been reached for these populations, but logrank analysis has reached statistical significance (p=0.02), and the Cox hazards ratio for OS is 5.46. It is noted that the ability of CTCs to predict longer PFS is even greater in the bone only setting when compared to CTCs in patients with measurable disease.

The studies described above report the prognostic value of CTCs in patients categorized as receiving either chemotherapy or hormonal therapy. The data do not specify the prognostic value of CTC in conjunction with any specific agents. Thus all chemotherapy agents or combinations of agents are allowed in the **S0500** study. The biologic agents, trastuzumab and bevacizumab, are also believed to cause decreases in CTC numbers, but the data remain limited, and the value of the 3 week timepoint is unknown for these agents. As a result, the study requires that all patients started on trastuzumab or bevacizumab should continue these biologic agents through the switch for all patients randomized to switch to new cytotoxic agents.

Because this assay has been validated only in women, men are excluded from this study.

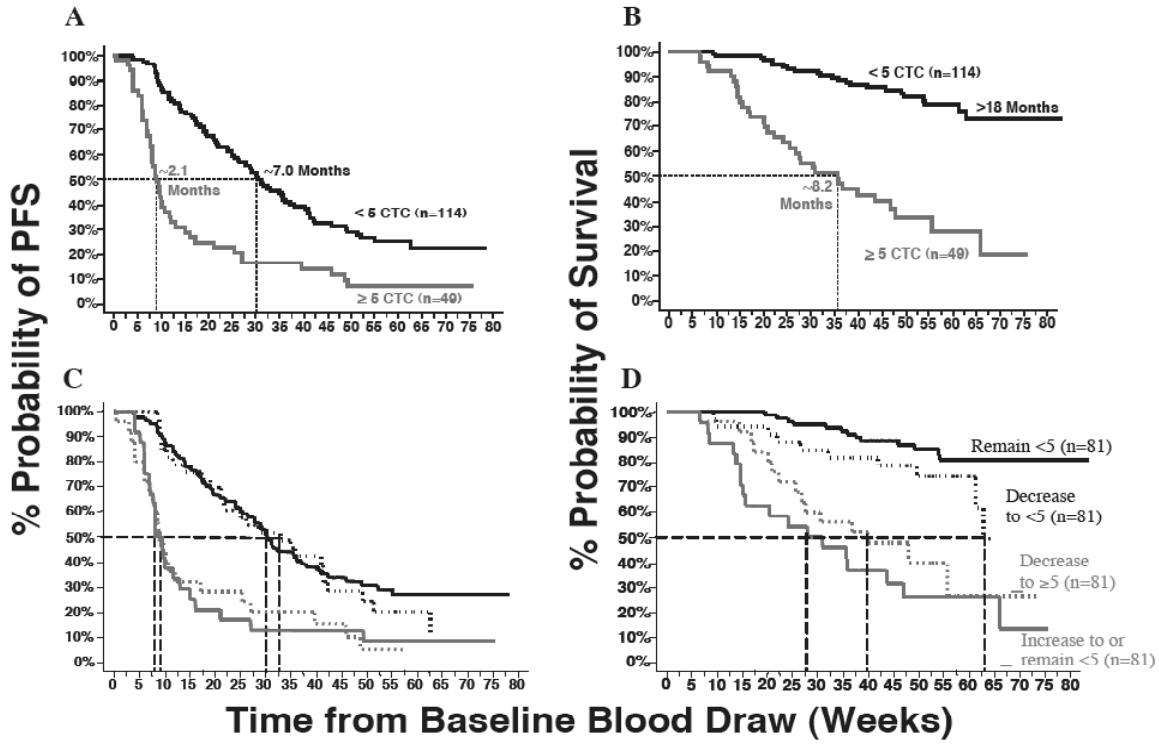


Figure 2

Panels A and B display Kaplan-Meier curves for PFS and OS for patients with ≥ 5 (grayline) or < 5 (black line) CTC in 7.5mL of blood at first follow-up evaluation after initiation of a new line of therapy. PFS and OS was calculated from the time of the baseline blood draw. The median of PFS (n=163) was 2.1 and 7 months respectively (p<0.0001). The median OS (n=163) was 8.2 vs. > 18 months respectively (p<0.0001).

Panels C and D display the probabilities of PFS and OS of patients with: 1) < 5 CTC at both the baseline and first follow-up blood draws (solid black line, n=81); 2) ≥ 5 CTC at baseline that decreased below 5 CTC at first follow-up (dotted black line n=33); 3) a decrease in CTC from baseline but still ≥ 5 CTC at the first follow-up (dotted gray line n=25); and 4) an increase in CTC from baseline level with ≥ 5 CTC at the first follow-up (solid gray line, n=24).

Study Rationale

The data above suggest that ≥ 5 CTC/7.5 mL of whole blood is a poor prognostic indicator. These patients may be on futile therapy, an observation with potential utility. Retrospective analysis of the IMMC-01 data also demonstrated that in certain instances, changing these patients to a new therapy was to their benefit (Figure 2, panels C and D). These results have led to the hypothesis that an immediate change of therapy for the group identified by the assay as being on futile therapy (after one cycle of new chemotherapy) may improve PFS, OS and/or Quality of Life (QOL). It should also be noted that, even if certain of these patients with ≥ 5 CTC/7.5 mL should prove to be 'refractory' to any further treatment and would therefore, not experience a direct positive gain in PFS and/or OS, discontinuing a futile therapy would still benefit the patient by not exposing them to additional unnecessary toxicities. The primary objective of this clinical protocol is, therefore, to test whether patients with elevated CTC (≥ 5) at first follow-up assessment of their current therapy might be better served by changing to an alternative therapy immediately, rather than completing the standard number of cycles of the current therapy.

The randomized portion of this study focuses on the population of patients with elevated CTCs after the first round of chemotherapy (first follow-up). Patients will first be screened based upon the presence of elevated CTCs prior to initiation of chemotherapy (baseline). In the IMMC-01 study, only 3% of patients converted from low CTCs at baseline to elevated CTCs at first follow-up so screening out these patients initially will have little impact. The patient population will be women with metastatic carcinoma of the breast who are beginning their first line of chemotherapy. Patients with CTC < 5/7.5 mL blood prior to initiation of treatment will be followed for OS and PFS only. This group is designated as Arm A. Patients with CTC ≥ 5/7.5 mL blood prior to initiation of treatment, but have CTC < 5 at their first follow-up time point will continue on their original therapy (Arm B). Patients with CTC ≥ 5/7.5 mL blood, both prior to initiation of treatment and at the first follow-up time point, will be randomized to either continue on their original therapy (Arm C1) or to change therapy (Arm C2). All patients will have disease imaging with CT or MRI and bone scans or PET scans pre-treatment. Subsequent imaging for monitoring will be done every 12 weeks. A final imaging study will be obtained when the patients come off protocol treatment at the time of progression.

Blinding

In an effort to minimize physician and patient bias in the assessment of PFS, the randomized arms will be partially blinded. All patients will be told their baseline CTC levels. Thus they will know that they are in a high-risk prognostic group based upon their baseline values, but none of the patients will be told the result of their first follow-up CTC test. Patients in the arm randomized to switch therapy (Arm C2) will know that they have elevated CTCs by the change in their therapy. Those in the arm randomized to continue the same therapy (Arm C1) will not know if they are in Arm B or Arm C1 because they will be blinded to this result. The investigators are concerned that knowledge of the CTC results in Arm C1 would lead to the unintentional over interpretation of symptoms as clinical signs of progression, which would lead to early reassessment by imaging. If Arms B and C1 are not blinded, this bias could lead to a false positive result for the trial overall. This blinding strategy was selected from many other options because it minimized bias and was considered ethical under the concept of equipoise.

It is noted that standard of care for the treatment of metastatic breast cancer is to continue therapy until either undue toxicity or until objective evidence of disease progression. The current clinical data for CTCs (described above) indicate that CTCs are a strong prognostic factor, but these data do not indicate whether changing therapy results in improved outcome. The CTC assay is commercially available for determining prognosis, but it is not standard-of-care or evidence-based-care to change therapy based upon the results at first follow-up.

Statement of equipoise

The point of equipoise can be stated in two different ways. First, it is not known whether switching to a new therapy prior to documented clinical and/or radiographic evidence of progression is beneficial for patients who will progress rapidly. Second, not all patients with elevated CTCs progressed rapidly. Approximately 15% of the patients with elevated CTCs have a PFS greater than 7 months (Figure 2, panel A), and we currently do not know how to further identify this subset of patients.

For all of these reasons, it is ethical to include the blinded Arms B and C1 (no change in therapy), which is currently standard of care. It is ethical not to tell this group their CTC status because it does not guarantee a poor outcome and because we do not know if the intervention of switching therapy is beneficial.

Inclusion of Women and Minorities (Screened)

Ethnic Category	Females	Males	Total
Hispanic or Latino	33	0	33
Not Hispanic or Latino	618	0	618
Ethnic Category: Total of all subjects screened	651	0	651
Racial Category			
American Indian or Alaskan Native	1	0	1
Asian	8	0	8
Black or African American	59	0	59
Native Hawaiian or other Pacific Islander	20	0	20
White	563	0	563
Racial Category: Total of all subjects screened	651	0	651

Inclusion of Women and Minorities (Randomized)

Ethnic Category	Females	Males	Total
Hispanic or Latino	6	0	6
Not Hispanic or Latino	114	0	114
Ethnic Category: Total of all subjects	120	0	120
Racial Category			
American Indian or Alaskan Native	0	0	0
Asian	1	0	1
Black or African American	11	0	11
Native Hawaiian or other Pacific Islander	4	0	4
White	104	0	104
Racial Category: Total of all subjects randomized	120	0	120

The study will be open to women only, as the CellSearch® assay has not been validated for men. Differences among treatment arms are not expected to be a function of race or ethnicity. Thus, the study is not designed to detect differences within race or ethnicity subsets. This will be explored as part of the final analysis.

3.0 DRUG INFORMATION

Drug information is not applicable to this study.

4.0 STAGING CRITERIA

All staging will be based on the American Joint Committee on Cancer Staging System, 6th Edition (2002)

DEFINITION OF TNM

Distant Metastasis (M)

M1 Distant Metastasis

STAGE GROUPING

Stage IV	Any T	Any N	M1

5.0 ELIGIBILITY CRITERIA

Each of the criteria in the following section must be met in order for a patient to be considered eligible for registration. Use the spaces provided to confirm a patient's eligibility. For each criterion requiring test results and dates, please complete the Prestudy Form and submit to the Data Operations Center in Seattle (see Section 14.0). Any potential eligibility issues should be addressed to the Data Operations Office in Seattle at 206/652-2267 prior to registration.

SWOG Patient No. _____

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

_____ 5.1 Patients must be women with histologically confirmed breast cancer and clinical evidence of Stage IV disease (see Section 4.0).

_____ 5.2 Patients must have either 1) measurable disease with or without non-measurable disease, or 2) non-measurable disease only, but the non-measurable disease must include bone metastases. (Note: Patients who only have non-measurable disease without bone involvement are not eligible). All patients must have a CT scan or MRI of the chest and abdomen AND a whole body bone scan or PET scan within 28 days of registration. All other x-rays, scans, or physical examinations used for tumor measurement must have been completed within 28 days prior to registration. X-rays, scans, or other tests for assessment of non-measurable disease must have been performed within 42 days prior to registration. All disease must be assessed and documented on the Baseline Tumor Assessment Form (Form #848).

_____ 5.3 Patients must have HER-2 status determined by IHC and/or FISH assay. HER-2 positivity is defined as any IHC 3+ or FISH+. If the IHC result is indeterminate (2+), FISH must be performed to classify the patient as positive or negative.

_____ 5.4 Patients must be planning to receive chemotherapy. Patients must not have received any prior chemotherapy for metastatic disease. Prior use of hormonal therapy, bisphosphonate therapy, trastuzumab and/or bevacizumab in the metastatic setting is acceptable. Patients may have received any number or type of exogenous hormonal therapies, either for metastatic disease and/or as adjuvant therapy.

_____ 5.5 Patients with prior adjuvant chemotherapy must have completed adjuvant chemotherapy at least 12 months prior to registration.

_____ 5.6 Patients must have recovered from any prior surgery. Two weeks are recommended from the time of any minor surgery and four weeks for any major surgery.

_____ 5.7 Patients must agree to the CTC blood draws as outlined in Section 15.2, and submit the initial blood draw **within one day of registration**. Patients must agree to the serum draws to test for the tumor markers, CA 15-3 and CEA, as outlined in Section 15.1. Patients who are willing to have their serum specimens retained for banking must provide additional patient consent as outlined in Section 15.1.

_____ 5.8 The name and contact information of a contact person at the treating institution is required for communication of the CTC results. The name, phone number, and email address of the contact person must be supplied at the time of patient registration.

Name of contact person to receive results of CTC testing _____

Contact person's telephone number _____

Contact person's fax number _____

Contact person's email address _____

SWOG Patient No. _____

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

_____ 5.9 Patients must have a performance status of 0 – 2 according to Zubrod criteria (see Section 10.4).

_____ 5.10 Patients with brain metastases must have stable disease for more than 90 days after completing radiotherapy to the brain.

_____ 5.11 Patients must not have leptomeningeal disease.

_____ 5.12 Pregnant or nursing women may not participate in this study due to the potential for congenital abnormalities and the harm to nursing infants when treated with standard of care regimens and because pregnant women are also limited in the types of treatment that they can be given.

_____ 5.13 No prior malignancy is allowed except for adequately treated basal cell or squamous cell skin cancer, any adequately treated Stage I or II cancer from which the patient is currently in complete remission, or any other cancer from which the patient has been disease-free for 5 years.

5.14 If Day 28 or 42 falls on a weekend or holiday, the limit may be extended to the next working day.

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 4 weeks later would be considered Day 28. This allows for efficient patient scheduling without exceeding the guidelines.

_____ 5.15 All patients must be informed of the investigational nature of this study and give written informed consent in accordance with institutional and federal guidelines.

_____ 5.16 At the time of patient registration, the treating institution's name and ID number must be provided to the Statistical Center in order to ensure that the current (within 365 days) date of institutional review board approval for this study has been entered into the data base.

6.0 STRATIFICATION FACTORS

6.1 Patients will be randomly assigned to Arm C1 or Arm C2 according to a dynamic allocation scheme. Treatment arms will be balanced with respect to the following stratification factors:

a. Measurable disease with or without non-measurable disease vs. non-measurable disease only including bone metastasis.

b. HER-2 positive vs. HER-2 negative: Either IHC or FISH may be used to classify the patient. If IHC is negative (0 or 1+) or positive (3+), FISH need not be performed. If IHC is indeterminate (2+), FISH must be performed to determine final classification. Therefore, to be HER-2 positive, either FISH must be positive or IHC positive (3+). If FISH is performed, this test result will always be used as the final determinant.

6.2 Randomization

Randomization will be based upon the number of CTCs at Week 4 (Day 22). The blood will be obtained before the second cycle of chemotherapy. This sample will be sent the same day as the day on which it is drawn to the central laboratory (Veridex, LLC) for analysis. The result will be returned to the SWOG Statistical Center who will classify the patients into Arm B (CTC < 5) or Arm C (CTC ≥ 5).

a. Arm B patients will remain on their current therapy.

b. Arm C will be randomly assigned to remain on their current therapy (maintain current therapy - Arm C1) or to change to an alternative therapy (switch therapy - Arm C2). Randomized therapy will begin with Week 5 for both groups.

Note: If a patient was on a chemotherapy regimen with a 3-week (21 day) cycle, then the start of Cycle 2 will be delayed by one week to await the result of the CTC test. In this case, randomized therapy will be given on Day 29 rather than the usual Day 22.

6.3 Blinding

Patients in Arms B and C1 and their physicians will be blinded to which arm they are in by study design. Patients and physicians will be informed when a patient is to "maintain current therapy" or to "switch therapy". The results from the Day 22 CTC assay will not be reported to either the patients or physician.

NOTE: All patients and physicians will receive the results of the baseline CTC assay performed on or before Day 1 of the study. Thus, all patients and physicians will know the baseline risk.

7.0 TREATMENT PLAN

For questions regarding this study please contact Dr. Smerage at 734/615-1623 or Dr. Hayes at 734/615-6725.

7.1 Good Medical Practice

The following pre-study tests/assessments are recommended within 28 days prior to registration in accordance with good medical practice. Results of these tests do not determine eligibility and minor deviations from normal limits would be acceptable if they do not affect patient safety in the clinical judgment of the treating physician. If there are

significant deviations in these tests/assessments that could impact patient safety, it is highly recommended that the registering investigator discuss the patient with the Study Coordinator prior to registering.

a. CBC (ANC ≥ 1,500/mcL, platelets ≥ 100,000/mcL)

b. Hemoglobin ≥ 8 g/dL

c. Serum creatinine ≤ 2.0 mg/dL

d. Adequate liver function with bilirubin ≤ 2.0 mg/dL, SGPT or SGOT ≤ 3 x institutional upper limit of normal (IULN) or < 5 x IULN in the presence of liver metastasis, alkaline phosphatase ≤ 3 x IULN or < 5 x IULN in the presence of liver or bone metastasis.

e. HCG test that is negative (Women of reproductive potential should be advised on the use of effective contraceptive use during chemotherapy.)

NOTE: This study does not specify the chemotherapy drugs to be used in treatment so additional pre-study tests may be appropriate. Additional tests should be ordered at the discretion of the treating physician.

7.2 Patient selection and timing of initial CTC blood draw

Patients will be identified as women with metastatic breast cancer who are about to begin first-line chemotherapy. They may have newly metastatic disease with no prior therapies for metastatic cancer, or they may be patients who have progressive metastatic disease while on hormonal therapy and who are about to switch to chemotherapy.

After obtaining informed consent, blood samples will be drawn to determine the baseline CTC count. Patients with elevated CTCs (> 5 CTC/7.5 mL blood) are at high risk of early progression. They will initiate standard of care chemotherapy per protocol, and they will have a second CTC count drawn on Day 22 to determine whether they are in Arms B, C1, or C2.

Patients who have < 5 CTC/7.5 mL of blood at baseline (Arm A) will not have further CTC testing performed and choice of treatment will be at the discretion of the clinician. These patients are eligible for participation in other first-line chemotherapy treatment trials. Progression and survival will be assessed in 100 patients not enrolled in other trials. The SWOG statistical center will inform the institution of the initial CTC value and the expected testing and follow-up for each patient.

The timing of the initial blood draw will impact the possibility of participation in other first-line chemotherapy trials. For patients considering participation in other first-line chemotherapy trials, registration and baseline CTC blood draw may be performed up to 14 days prior to starting chemotherapy. This will allow time for the CTC result to be communicated to the clinic. As stated above, all patients with < 5 CTC/7.5 mL whole blood at baseline will be eligible for participation in other first-line trials. For patients who are not contemplating participation in other first-line chemotherapy trials, chemotherapy may be initiated prior to receiving the CTC result. **The baseline CTC blood draw must occur prior to the first dose of chemotherapy**.

NOTE: If initial baseline blood draw is not analyzable, a baseline redraw is allowed up to one week after patient has started chemotherapy. Record in the "comments" section of the CTC Blood Draw and Results CRF (Form #40051) that this is a redraw of baseline as well as the number of days after the start of chemotherapy. Any follow-up blood draws should be scheduled according to the date of initial, non-analyzable baseline draw.

7.3 Communication of CTC Results

a. Veridex, LLC will send the **S0500** CTC Blood Draw and Results CRF (Form #40051) to the SWOG Statistical Center by facsimile, as well as an email confirmation from Veridex stating that the results were faxed. The email address at the Southwest Oncology Group Statistical Center for reporting CTC results is S0500@crab.org. Emails sent to this address will be forwarded automatically to the personnel maintaining daily coverage of **S0500** reporting. The Statistical Center will confirm receipt of the result to Veridex, LLC by email. The CTC results will be received at the Statistical Center from Veridex, LLC within six days of the blood collection date for reporting back to the investigational site.

b. If the report is for the initial screening CTC (baseline), the SWOG Statistical Center will contact the investigational site by email and facsimile. The Statistical Center will inform the investigational site that their patient had a negative result (CTC < 5) or positive result (CTC ≥ 5) and remind the institution of subsequent procedures. The investigational site will confirm receipt of the report to SWOG by email.

c. If the report is for the second CTC test (at Week 4), the Statistical Center will place the patient into Arm B, C1, or C2 depending upon the CTC results. Patients will be placed into Arm B if their CTC count was ≥ 5 at baseline and < 5 at 4 weeks. Patients will be electronically randomized into Arm C1 or C2 if both their first and second CTC tests demonstrate a CTC count ≥ 5. The Statistical Center will then contact the investigational site by email and facsimile. The Statistical Center will inform the investigational site that their patient should either 1) stay on current treatment, or 2) change treatment. The investigational site will confirm receipt of the report to the SWOG Statistical Center by email.

d. Following the second CTC test, all CTC values will be entered into the database at the Statistical Center. The investigational site will not be notified of the results.

7.4 Selection of Treatment

a. This protocol is testing a treatment strategy rather than any particular treatment regimen. First line chemotherapy will be left to the discretion of the treating physician. This may be single-agent chemotherapy or multi-agent chemotherapy, and it may be given on any schedule including but not limited to daily, weekly, two of every 3 weeks, or once every 3 - 4 weeks dosing.

b. Second line chemotherapy in Arm C2 (Arm randomized to change therapy) will also be left to the discretion of the treating physician. This may be single-agent chemotherapy or multi-agent chemotherapy. However, second-line chemotherapy should be a different class(es) of therapy than first line. For example, if first line therapy contains a taxane (such as paclitaxel), second line therapy should not include a taxane (either paclitaxel, docetaxel, or Abraxane).

c. Concomitant hormonal therapy and bisphosphonate therapy are allowed during first-line chemotherapy and may be continued through the switch in those patients randomized to switch their chemotherapy.

Note on Biologic agents: Both trastuzumab and bevacizumab are allowed treatments on this trial.

- Continuous trastuzumab is consider by the investigators to be standard of care for all patients with tumors that have HER2 over-expression (IHC3+) or amplification (FISH+), unless there is a medical contraindication to its use. Thus trastuzumab should be continued in all patients randomized to switch therapy.

- Bevacizumab is not considered by the investigators to be standard of care. However, it is anticipated that this drug will be used off label in some cases due to the reported interim results of the ECOG E2100 study. All patients who begin bevacizumab as part of their initial therapy must continue bevacizumab if they are randomized to switch. Patients who do not receive bevacizumab during initial therapy may have bevacizumab added if they are randomized to switch therapy.

7.5 Follow-up blood draws

a. Refer to the study calendar for scheduling of follow-up blood draws. All patients with CTC > 5 will have a second blood draw on Day 1 of Week 4. Some patients may require an additional visit to the clinic for this blood draw, on a day when they do not see the physician. The timing of this blood draw is important because it will be used to randomize the patients.

b. A third blood draw will be performed in either Week 8 or Week 9 (Day 50 or 57, respectively), and it can be done on the day of a scheduled visit to see the physician. No extra visit should be required.

c. Additional blood draws are scheduled to correspond with the imaging reassessments at Weeks 13, 25, and 37. These should not require extra visits to the clinic.

d. All patients with CTCs ≥ 5 will have a final blood draw at the time of progression.

7.6 Allowed alterations to treatment

Patients will be considered to be on study until they are determined to have progression of disease as described in Section 10.0. The following changes in treatment may be made without affecting study status.

a. Discontinuation of therapy due to toxicity

Any therapy may be stopped due to undue toxicity as determined by the treating physician. If there is no evidence of progression, an alternative chemotherapy may be initiated at the discretion of the treating physician.

b. Discontinuation of therapy due to "maximal benefit"

Any therapy may be stopped without evidence of progression, if after a minimum of 24 weeks (following second scheduled imaging) the treating physician determines that the patient has achieved maximum benefit from the current therapy, and if the treating physician feels that the patient would be best served with a chemotherapy "holiday." Patients who stop therapy due to "maximal benefit" cannot resume chemotherapy until after clinical evidence of progression. Patient may continue trastuzumab even if cytotoxic therapies are stopped. Note: a rise in serum tumor markers alone is not criteria for evidence of progression (see Section 10.0).

c. Hormonal "maintenance" therapy

Patients who stop therapy due to "maximal benefit" may be placed on hormonal agents for the purpose of "maintenance" therapy until time of progression.

7.7 Criteria for removal from protocol strategy

a. Progression of disease or symptomatic deterioration as defined in Section 10.0 after a minimum of 6 weeks of therapy.

b. Failure to submit specimen for CTC screening at Week 4.

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

7.8 Long-term follow-up

All patients will be followed for 5 years or until death, whichever occurs first.

8.0 TOXICITIES TO BE MONITORED AND DOSAGE MODIFICATIONS

8.1 Two different versions of the NCI Common Terminology Criteria for Averse Events (CTCAE) will be used on this study.

a. Serious Adverse Event (SAE) reporting

The CTCAE (NCI Common Terminology Criteria for Adverse Events) Version 4.0 will be utilized **for SAE reporting only**. The CTCAE Version 4.0 is identified and located at the CTEP website at http://ctep.cancer.gov/protocolDevelopment/electronic_applications/ctc.htm.

b. Routine toxicity reporting

This study will utilize the CTCAE Version 3.0 for routine toxicity reporting. A copy of the CTCAE Version 3.0 can be downloaded from the CTEP homepage (http://ctep.cancer.gov). All appropriate treatment areas should have access to a copy of the CTCAE Version 3.0.

8.2 The study does not direct choice of therapy or dose, and as a result there are no study-specific drug toxicities.

8.3 Choice of chemotherapeutic agents and criteria for dose modifications will be at the discretion of the treating physician. Dose modifications are not specified by the protocol. For protocol strategy related questions, please contact Dr. Smerage at 734/936-0453 or Dr. Hayes at 734/615-6725.

8.4 Unexpected or fatal toxicities (including suspected reactions) must be reported to the Operations Office, the Study Coordinator, the IRB, and the NCI. The procedure for reporting adverse reactions is outlined in Section 16.0.

9.0 STUDY CALENDAR

10.0 CRITERIA FOR EVALUATION AND ENDPOINT DEFINITIONS

10.1 Measurability of lesions

a. **Measurable disease**: Lesions that can be accurately measured in at least one dimension by 1) medical photograph (skin or oral lesion), palpation, plain x-ray, CT, MRI or other conventional technique with longest diameter 2 cm or greater in the axial plane (bone lesions not included), or 2) spiral CT with longest diameter 1 cm or greater. Ultrasound is suitable only for superficial disease (superficial palpable nodes, subcutaneous lesions, thyroid nodules).

Conventional CT and MRI should be performed with cuts of 10 mm or less in slice thickness contiguously. Spiral CT should be performed using a 5 mm contiguous reconstruction algorithm.

b. **Non-measurable disease**: All other lesions including lesions too small to be considered measurable, pleural or pericardial effusions, ascites, bone disease, inflammatory breast disease, leptomeningeal disease, lymphangitis, pulmonitis, abdominal masses not confirmed and followed by imaging techniques, cystic lesions or disease documented by indirect evidence only (e.g., by lab values), previously radiated lesions that have not progressed.

10.2 Objective status at each evaluation:

Objective Status is to be recorded at each evaluation. All measurable lesions up to a maximum of 5 lesions per organ and 10 lesions in total, representative of all involved organs, should be identified as target lesions at baseline. All measurable lesions not identified as target lesions are non-target lesions and are included as non-measurable disease. Measurements must be provided for target measurable lesions, while presence or absence must be noted for non-target measurable and non-measurable disease.

a. **Progression**: One or more of the following must occur:

1. 20% increase in the sum of longest diameters of target measurable lesions over smallest sum observed (over baseline if no decrease during therapy) using the same techniques as baseline.

2. **Bone-only disease progression** is defined as development of one or more new lytic bone lesions on plain film x-ray from baseline, development of one or more new lesions on bone scan or PET scan that are confirmed to be lytic by plain film x-ray, or bone lesions that require therapy such as surgery, radiation therapy, radiofrequency ablation or other local therapy. Note: Lesions that increase in size or intensity on bone scan or PET scan and new lesions on bone scan or PET scan that do not correlate with lytic lesions on plain film x-ray will not constitute progression.

3. Unequivocal progression of non-measurable disease in the opinion of the treating physician (an explanation must be provided).

4. Appearance of any new lesion/site.

5. Death due to disease without prior documentation of progression and without symptomatic deterioration (see definition below).

b. **Symptomatic deterioration**: Global deterioration of health status requiring discontinuation of treatment without objective evidence of progression. Efforts should be made to obtain objective evidence of progression after discontinuation.

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

d. **Objective status notes:**

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

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

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

4. For bone disease documented on bone scan only, increased uptake does not constitute unequivocal progression.

5. Appearance or worsening of pleural effusions does not constitute unequivocal progression unless cytologically proven of neoplastic origin.

6. Serum tumor markers will not be considered evidence for progression of disease.

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

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

10.5 **Progression Free Survival (PFS)**: From date of registration to date of first documentation of progressive disease (as defined in Section 10.2d), death due to any cause or symptomatic deterioration (as defined in Section 10.2e), whichever occurs first. Patients last known to be alive and progression-free are censored at date of last contact.

10.6 **Time to Death**: From date of registration to date of death due to any cause. Patients last known to be alive are censored at date of last contact.

11. 0 STATISTICAL CONSIDERATIONS

11.1 Based on the trial IMMC-01, we assume that 50% of the patients will have a baseline CTC ≥ 5 and that 30% will continue to be ≥ 5 at the first follow-up. We expect to register 500 patients to **S0500** with 250 expected to screen negative (CTC < 5) at baseline (Arm A). Of the 250 who screen positive at baseline, 100 are expected to have the CTC < 5 at the first follow-up (Arm B). Of the remaining 150 patients who have two tests with CTC ≥ 5, up to 20% will already have progressed by the first follow-up time. Therefore, we expect 120 patients to be eligible for randomization to the two arms (C1 and C2) with equal probability of assignment to the two arms.

11.2 The overall target sample size for enrollment is 500, but the target sample size for the randomized trial is 120. We will continue accrual until the randomized trial has 120 eligible patients enrolled. We anticipate enrolling 30 patients per year to Arms C1 and C2 for 4 years to achieve the randomized trial target sample size. We estimate this will require registering 125 patients per year. Follow-up for progression will continue for a maximum of 3 years after the last patient is enrolled to the randomized trial.

11.3 Revised screening accrual goal (June 2011). Sections 11.1 and 11.2 remain as written in the original protocol. However, it has become clear that we will need to screen more than 500 patients to reach the randomized accrual goal of 120. We currently estimate that 651 patients will need to have a baseline evaluation of CTC in order to meet the randomized accrual goal of 120. The higher number screened is based on some incomplete CTC evaluations at baseline as well as a slightly lower rate showing positivity at both Day 0 and Day 21. The estimated number of screened patients is 651, but could be slightly low or higher. The actual goal for the trial remains 120 *randomized* patients.

11.4 Based on the previous analysis of OS in patients with CTC ≥ 5, we expect median overall survival to be about 8 months. We are interested in detecting an overall survival hazard ratio of 1.70 or greater for patients on Arm C1 relative to Arm C2. In short, the effect on OS would need to be dramatic to recommend changing therapy after a single course of therapy. We use a 2-sided α=0.05 test since it is possible that changing therapies could be detrimental instead of advantageous. Then power is 81.4% to detect a difference in OS between the two randomized groups. For the secondary outcome PFS, we will have 82.8% power to detect a HR of 1.70 if median PFS is 3 months. The primary analyses will be stratified log-rank tests with stratification on HER2 status and disease type. Cox regression analysis will be used to estimate the hazard ratio and confidence intervals and to test for interactions with the stratifying variables.

11.5 We project 116 of the 120 randomized patients will have died by the end of the study. Three interim analyses will be performed after 25% (29 deaths), 50% (58 deaths), and 75% (87 deaths) of the expected deaths have been recorded. Under the accrual given in 11.2, the interim analyses would occur approximately at 22, 34, and 45 months after the start of the trial. We use Lan-DeMets two-sided symmetric spending rule so that the cumulative α=0.05 (2-sided) at the conclusion of the trial. The 2-sided interim analyses will be performed at α=0.00002, α=0.00304, and α=0.01832 with the final analysis performed at α=0.044. If the interim analysis shows a statistically significant difference, early termination of the trial will be discussed with the Data Safety and Monitoring Committee.

11.6 Randomization will be stratified based upon the presence of bone-only disease vs. measurable disease, and upon the presence or absence of HER-2 over-expression/amplification. It is noted that multi-agent chemotherapy generally results in greater response rate and as a result, longer PFS. However, it is controversial whether multi-agent chemotherapy results in increased overall survival when compared to single-agent sequential therapy in unselected patient populations. *(15, 16)*

11.7 For objective 1.3, testing the prognostic value of the baseline CTC on overall survival we will have 90% power to detect a hazard ratio of 1.47 comparing Arm A (n=100 with OS) to all other patients (n=250). We cannot estimate power for objective 1.4 due to the lack of important information. A Cox regression analysis will be performed treating CTC as a time-dependent covariate to analyze OS and PFS in for patients in Arms B and C.

11.8 We will compare toxicity for patients in Arm B to Arms C1 and C2 combined. For common toxicities we could detect a 19% difference in toxicity rates with 80% power. We will also compare Arm C1 to C2 with regard to toxicity. We could detect a 28% difference in toxicity between C1 and C2 with 80% power.

11.9 Correlation with traditional tumor markers: For each marker logistic regression will be performed evaluating progression at three months. The c-statistic is a measure of goodness of fit and is actually computed as area under a ROC curve. We will assess the c-statistics for each marker individually: CTC, CEA, and CA 15-3. Additionally, the markers will be tested together in a multivariate model to determine if there is an independent contribution of CTCs above that of CA 15-3 and/or CEA. All individuals with marker values will be included in this study.

11.10 Establishment of serum bank: The samples will be stored for future analyses. The results of the primary objectives will be utilized to create hypotheses to be tested using these frozen serum samples.

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

12.0 DISCIPLINE REVIEW

There will be no discipline review for this study.

13.0 REGISTRATION GUIDELINES

13.1 Patients must be registered prior to initiation of testing (no more than one working day prior to the initial CTC submission).

13.2 For either phone or web registration, the individual registering the patient must have completed the appropriate Southwest Oncology Group Registration Form. The completed form must be referred to during the registration but should not be submitted as part of the patient data.

The individual registering the patient must also be prepared to provide the treating institution's name and ID number in order to ensure that the current (within 365 days) date of institutional review board approval for this study has been entered into the data base. Patients will not be registered if the IRB approval date has not been provided or is > 365 days prior to the date of registration.

13.3 Registration procedures

a. You may register patients from Member, CCOP and approved Affiliate institutions to a therapeutics study using the SWOG Registration program. To access the Registration program go to the SWOG Web site (http://swog.org) and click on the *Logon* link to go to the SWOG Members Area logon page (https://swog.org/visitors/logon.asp). This Web program is available at any time except for periods listed **under *Down Times*.** Log on as an Individual User using your SWOG Roster ID Number and individual web user password. Help for the logon process may be found at https://swog.org/visitors/logonhelp.asp. After you

have logged on, click on the *Clinical Trials* link and then the *Patient Reg* link to go to the Entry Page for the Patient Registration program. If you are a Registrar at an institution with Internet access you are encouraged to register this way. For new users, the link to a "Starter Kit" of help files may be found by clicking on **Starter Kit link at the logon page.**

To register a patient the following must be done (in order):

1. You are entered into the Southwest Oncology Group Roster and issued a SWOG Roster ID Number,

2. You are associated as an investigator or CRA/RN to the institution where a registration is occurring, and

3. You are granted permission to use the Patient Registration program at that institution.

For assistance with points 1 and 2 call the SWOG Operations Office at 210/614-8808. For point 3 you must contact your Web User Administrator. Each SWOG institution has one or more Web User Administrators who may set up Web Users at their institution and assign permissions and passwords to these users. For other password problems or problems with the Patient Registration program, please e-mail webreghelp@crab.org. Include your name, Roster ID Number, and telephone number, when the problem occurred, and exactly what you were doing.

b. If the Web Reg program is not used, the registration must be done by phone.

Member, Affiliate and CCOP Institutions

Registration by phone of patients from member, affiliate and CCOP institutions must be done through the Southwest Oncology Group Data Operations Center in Seattle by telephoning 206/652-2267, 6:30 a.m. to 4:00 p.m. Pacific Time, Monday through Friday, excluding holidays.

13.4 For either method of registration, exceptions to Southwest Oncology Group registration policies will not be permitted.

a. Patients must meet all eligibility requirements.

b. Institutions must be identified as approved for registration.

c. Registrations may not be cancelled.

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

14.0 DATA SUBMISSION SCHEDULE

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

14.2 Master forms are included in Section 18.0 and (with the exception of the sample consent form and the Registration Form) must be submitted to the Data Operations Center in Seattle. Data from approved SWOG institutions must be submitted on-line via the Web; see Section 14.3a for details. Exceptions to online data submission are patient-completed (e.g. Quality of Life) forms and source documents (e.g. pathology/operative/lab reports).

14.3 Data Submission Procedures.

a. Southwest Oncology Group institutions must submit data electronically via the Web by using the SWOG CRA Workbench. To access the CRA Workbench, go to the SWOG Web site (http://swog.org) and logon to the Members Area. After you have logged on, click on the *CRA Workbench* link to access the home page for CRA Workbench website. Next, click on the *Data Submission* link and follow the instructions. For new users, the link to a "Starter Kit" of help files may be found by clicking on the **Starter Kit** link at the Members' logon page.

To submit data via the web the following must be done (in order):

1. You are entered into the Southwest Oncology Group Roster and issued a SWOG Roster ID Number,
2. You are associated as an investigator or CRA/RN at the institution where the patient is being treated or followed, and
3. Your Web User Administrator has added you as a web user and has given you the appropriate system permissions to submit data for that institution.

For assistance with points 1 and 2 call the Operations Office at 210/614-8808. For point 3, contact your local Web User Administrator (refer to the "Who is my Web User Administrator?" function on the swog.org Members logon page). For other difficulties with the CRA Workbench, please email *technicalquestion@crab.org*.

b. If you need to submit data that are not available for online data submission, the only alternative is via facsimile. Should the need for this occur, institutions may submit data via facsimile to 800/892-4007 or 206/342-1680 locally. Please do not use cover sheet for faxed data.

14.4 WITHIN 7 DAYS OF REGISTRATION:

Submit a copy of the following:

a. **S0500** Prestudy Form (Form #29563)

b. Baseline Tumor Assessment Form (Form # 848)

c. Pathology report

14.5 AFTER REGISTRATION AND PRIOR TO FIRST DOSE OF CHEMOTHERAPY:

a. Submit the **S0500** CTC Blood Draw and Results CRF (Form #40051) and the CTC blood specimens to Veridex, LLC, as specified in Section 15.2. **NOTE: The 10 mL red-top tube (see Section 15.1b must be obtained prior to filling the CellSave® tube using the same needle stick. This decreases the chance of contamination of the CTC sample with skin epithelial cells, which may occur when the needle enters the skin.**

b. Submit serum specimen for CA 15-3 and CEA testing as specified in Section 15.1b.

c. Submit the **S0500** CTC Submission Form (Form #39382) to the Data Operations Center.

14.6 (FOR PATIENTS WITH ≥ 5 CTCs/7.5 mL BLOOD AT INITIAL SCREENING)
AT DAY 22, DAY 50 OR 57, DAY 85, DAY 169, DAY 253, AND AT THE TIME OF DISEASE PROGRESSION OR DISCONTINUATION OF TREATMENT:

a. Submit the **S0500** CTC Blood Draw and Results CRF (Form #40051) and the CTC blood specimens to Veridex, LLC, as specified in Section 15.2. Submit serum specimens for CA 15-3 and CEA testing as specified in Section 15.1b. With additional patient consent, these specimens will be retained for banking.

b. Submit the **S0500** CTC Submission Form (Form #39382) to the Data Operations Center.

14.7 AFTER FIRST CYCLE:

a. Submit the **S0500** Treatment Summary Form (Form #50428).

14.8 (FOR PATIENTS WITH ≥ 5 CTC/7.5 mL BLOOD AT INITIAL SCREENING)
AFTER THE FIRST CYCLE OF SECOND-LINE CHEMOTHERAPY (FOR PATIENTS ASSIGNED TO SWITCH THERAPY), AFTER EACH CHANGE IN THERAPY DUE TO TOXICITY OR PROGRESSION, DISCONTINUATION OF THERAPY DUE TO MAXIMAL BENEFIT, INITIATION OF MAINTENANCE HORMONAL THERAPY, OR CHANGE IN THERAPY DUE TO OTHER REASONS:

Submit a copy of the **S0500** Treatment Summary Form (Form #50428).

14.9 (FOR PATIENTS WTH ≥ 5 CTC/7.5 mL BLOOD AT INITIAL SCREENING) AFTER 3 WEEKS, 6 WEEKS, AND EVERY 6 WEEKS THEREAFTER UNTIL PROGRESSION:

Submit the **S0500** Adverse Event Summary Form (Form #18074).

14.10 EVERY 3 MONTHS UNTIL PROGRESSION AND THEN EVERY 6 MONTHS FOR 5 YEARS OR UNTIL DEATH:

Submit a copy of the Follow-Up Form (Form #64587).

14.11 (FOR PATIENTS WITH ≥ 5 CTC/7.5 mL BLOOD AT INITIAL SCREENING) EVERY 12 WEEKS UNTIL PROGRESSION:

Submit the Follow-Up Tumor Assessment Form (Form #38305). Patients with bone-only disease at registration should submit the **S0500** Follow-Up Bone-Only Disease Assessment Form (Form #62610) instead of the Follow-Up Tumor Assessment Form (Form #38305).

14.12 WITHIN 14 DAYS OF PROGRESSION/RELAPSE:

For Arm A (low risk) patients submit the Follow Up Form (Form #64587).

For all other patients, submit the Follow Up Form (Form #64587) and the Follow-Up Tumor Assessment Form (Form #38305) and the **S0500** CTC Submission Form (Form #39382) to the Data Operations Center. Patients with bone-only disease at registration should submit the **S0500** Follow-Up Bone-Only Disease Assessment Form (Form #62610) instead of the Follow-Up Tumor Assessment Form (Form #38305).

14.13 WITHIN 4 WEEKS OF KNOWLEDGE OF DEATH:

For Arm A (low risk) patients, or if death occurs after patient is off treatment, submit a final copy of the Follow Up Form (Form #64587) and the Notice of Death (Form #49467).

For all other patients, if death occurs while on treatment submit a copy of the **S0500** Treatment Summary Form (Form #50428), the **S0500** Adverse Event Summary Form (Form #18074), and the Notice of Death (Form #49467).

15.0 SPECIAL INSTRUCTIONS

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

a. **Institutions are required to submit serum to test for levels of the tumor markers CA 15-3 and CEA. Institutions are encouraged to seek additional patient consent to allow leftover serum to be kept for banking.**

b. Collection:

1. Blood for tumor markers (CA 15-3 and CEA) and serum banking: Obtain 10 mL serum samples (red-top tube, Vacutainer®) within one working day after registration (see Section 13.1) (prior to initiation of treatment). All patients with ≥ 5 CTC/7.5 mL blood at the initial screening will also have serum for banking obtained on Day 22, Day 50 or 57, Day 85, Day 169, and Day 253. A final sample will be collected at the time of disease progression or discontinuation of protocol strategy, whichever occurs first. All blood samples should be obtained prior to infusion of chemotherapy or before taking first dose of any oral therapy.

NOTE: The 10 mL red-top tube must be obtained prior to filling the CellSave® tube using the same needle stick. This decreases the chance of contamination of the CTC sample with skin epithelial cells, which may occur when the needle enters the skin.

c. Procedures:

1. Prepare participant's paper work to include SWOG STUDY NUMBER, Participant ID number, visit number, collection date and time, and initials of the phlebotomist.

2. Prepare collection material and make sure the ID of the participant to be drawn matches the demographics on the requisition of the draw.

3. Seat the participant for at least five minutes prior to blood collection.

4. Collect samples preferably under fasting conditions.

5. Using a red-top Vacutainer® blood collection tube (plastic vacutainer tubes preferred) and a double-ended Vacutainer® needle, draw blood. Place the tube in a rack at room temperature for at least one hour and not more than two hours.

6. Label specimen with visit number, collection date and time, initials of the phlebotomist, participant study ID number, and treatment cycle number.

7. Ship samples with an ice pack and the shipment packing list produced by SpecTrack within 24 hours of collection by overnight delivery, Monday through Thursday.

Reference

1. CAP, So you are going to collect a blood specimen. An Introduction to Phlebotomy, 6th Ed., 1994

2. Ernst, DJ, Calan, R.NCCLS simplifies order of draw: a brief history, MLO, 2004

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Table 1

Type of Specimen	Vacutainer® Collection Tube	Anticoagulant	Mix	USE
Serum	Red Top	None	Do not mix	Biomarkers

NOTES TO AVOID HEMOLYSIS

Do not use small-bore needles
Invert filled tubes gently
Do not keep tourniquet on too long
Allow the cleaned venipuncture site to dry completely before skin puncture
Do not expose to extreme heat or cold

d. Specimen Submission instructions can be accessed on the SWOG Specimen Submission webpage (http://swog.org/Members/ClinicalTrials/Specimens/STspecimens.asp), or via the link on the **S0500** protocol abstract page on the SWOG website (www.swog.org).

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

15.2 Submission of blood for analysis of circulating tumor cells (CTC)

a. **Institutions are required to submit blood samples for CTC analysis. (For a description on the method of analysis, see Section 19.3.)**

b. Directions for obtaining, handling, and shipping samples for CTC testing:

1. Supply Ordering: Prior to patient registration, all requests for blood collection tubes must be placed through the Veridex Customer Service department. The supplies can be obtained by completing the CTC Supply Form and submitting the form by e-mail to BSCSR2@ocdus.jnj.com.

(Note: A Microsoft Word version of the CTC Supply Order Form can be downloaded from the **S0500** abstract page of the SWOG website (www.swog.org). The supply form will allow the user to enter information directly onto the form and should be included as an attachment with the e-mail message.)

Phone: 1-877-VERIDEX (1-877-837-4339), option 2
Fax: 585-453-3344
E-Mail: BSCSR2@ocdus.jnj.com

The product code numbers for the supplies are as follows:

Product Code Number	Product Description	Quantity
952820	CellSave Preservative Tube	Pack 20
13731	Insulated Shipper	EA
5544A	Pre-Printed FedEx Airbill	EA

The hours of operation for Customer Service are Monday–Friday, 8:00 AM – 5:00 PM EST. **Although Veridex will attempt to ship supplies out as quickly as possible, please try to place orders approximately one week before supplies are needed.** To facilitate the ordering process, you will need to provide your customer number (if you do not have your customer number it will be provided for you after your first order), study number (e.g. SWOG **S0500**), your contact information, and the items (product code, name, and quantity) you require when placing an order.

2. Timing of Collection: Blood for testing for all study patients is to be obtained within one working day after registration (see Section 13.1) (prior to initiation of treatment). All patients with ≥ 5 CTC/7.5 mL blood at the initial screening will also have blood for testing obtained on Day 22, Day 50 or 57, Day 85, Day 169, and Day 253. A final sample will be collected at the time of disease progression or discontinuation of protocol strategy, whichever occurs first. All blood samples should be obtained prior to infusion of chemotherapy or before taking first dose of any oral therapy.

3. Materials required for blood collections are two (2) 10 mL purple/yellow top CellSave® blood collection tubes, Vacutainer® brand adapter, and needles. The blood may be drawn by a physician, registered nurse, or a licensed phlebotomist at the clinical site. **NOTE: The 10 mL red-top tube (see Section 15.3 Serum Submission Instructions) must be obtained prior to filling the CellSave® tube using the same needle stick. This decreases the chance of contamination of the CTC sample with skin epithelial cells, which may occur when the needle enters the skin.**

4. Complete the top portion of the **S0500** CTC Blood Draw and Results CRF (Form #40051) (see Section 18.2g), noting the lot number and expiration date of each of the CellSave® tubes. Mark the CellSave® tubes number 1 and number 2 (corresponding to the lot number and expiration date on the **S0500** CTC Blood Draw and Results CRF [Form #40051]). For each patient, perform a venous puncture using a Vacutainer® brand adapter and needle and fill each of the blood collection tubes (minimum blood volume of 9 mL for each tube). Alternatively, blood samples may be obtained from a port or other central venous catheter using appropriate access needles and techniques. Invert each tube a minimum of eight (8) times to ensure proper mixing of the additives contained in each tube. Write the SWOG patient number and the date of collection on the tubes. Complete the remainder of the **S0500** CTC Blood Draw and Results CRF (Form #40051).

5. The filled CellSave® tubes must be maintained at ambient (15–30°C) temperature, avoiding extremes of heat and cold, at all times. The **S0500** CTC Blood Draw and Results CRF (Form #40051) will be used to record the following information: Site identification; SWOG patient number (same number as written on the filled blood tubes); site comments; date and time of blood draw; lot number and expiration date of CellSave® tubes; phlebotomy problems; and any additional comments.

6. Wrap the CellSave® tubes in the shipping blanket. This gives added thermal protection during shipment. Place the samples inside the plastic bag, then into the jar. Cap the jar and place it in the styrofoam shipping box. Place the completed lab requisition form in the box. Place ROOM TEMPERATURE gel packs in the box to stabilize the temperature at 15-30ºC. Place the styrofoam lid. Seal the insulated box (see Appendix 19.3 for additional information).

7. Remove the sticky backing from the airbill and place it on the insulated shipper. For packages sent out on a Friday, hand write a manual Fed-Ex airbill and check the box for "Saturday Delivery" in Section 6, place a "Saturday Delivery" sticker on the outside of the shipper, and sign under Section 8 (Release Signature).

8. Place the completed **S0500** CTC Blood Draw and Results CRF(s) (Form #40051) into the shipper box.

9. Seal the insulated shipper box and contact your local Fed-Ex representative for pick-up (800-463-3339). Be sure to notify Veridex via e-mail at DL-VRXUS-ClinicalServicesUS@its.jnj.com or by voice mail at 215-346-8499, with the SWOG patient ID number and the tracking number on the Fed-Ex airbill(s).

10. Ship all blood tubes by overnight delivery to Veridex, LLC on the same date as the blood draw using Federal Express Priority Overnight Service to:

Lab #122:	Veridex, LLC Attn: Pharma Services Lab 3401 Masons Mill Road, Suite 100 Huntingdon Valley, PA 19006
Contact:	Madeline Repollet, M.S., CT (ASCP) Manager, Pharma Testing Services
Phone:	215/346-8432
E-mail:	mrepolle@its.jnj.com

16.0 ETHICAL AND REGULATORY CONSIDERATIONS

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

Informed Consent

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

Institutional Review

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

Monitoring

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

GUIDELINES FOR REPORTING OF SERIOUS ADVERSE EVENTS ON PROTOCOLS USING NON-PROTOCOL-PRESCRIBED COMMERCIAL DRUGS

The following SAEs experienced by patients accrued to this protocol **should be reported by telephone to the Operations Office (210/614-8808), within 24 hours of occurrence**, to your Institutional Review Board (IRB) and by written notification to the Food and Drug Administration (FDA), within 15 calendar days:

(a) Any adverse event which is **both** serious (life threatening, Grade 4 or fatal, Grade 5) **and** unexpected.[1,2,3]

(b) Any increased incidence of an expected SAE which has been reported in the literature.

(c) Any death on study if attributed at least possibly related to the protocol treatment.

The SAE report should be documented using FDA Form 3500. Complete the report on-line at https://www.accessdata.fda.gov/scripts/medwatch/, or Mail FDA Form 3500 to the address below:

MEDWATCH
Food and Drug Administration
5600 Fishers Lane
Rockville, MD 20852-9787

Send a copy of the FDA Form 3500, documentation of notification of your IRB, and substantiating clinical source data to the Operations Office within 15 calendar days:

Southwest Oncology Group
ATTN: SAE Program
4201 Medical Drive Suite 250
San Antonio, Tx 78229-5631

[1] See NCI Common Terminology Criteria for Adverse Events v. 4.0 (CTCAE).

[2] Lists of expected adverse events can be found in the Introduction section, Section 8, and Informed Consent Form of the protocol.

[3] Adverse events judged unlikely or definitely not treatment related should not be reported. However, a report shall be submitted if there is a reasonable suspicion that the event is possibly, probably, or definitely treatment related.

17.0 BIBLIOGRAPHY

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18.0 MASTER FORMS SET

18.1 The Model Informed Consent Form is included in this section, preceded by "Notes for Local Institution Consent Form Authors" and "Notes for Local Investigators." The study - as well as the local consent form meeting the guidelines noted in these documents - must be reviewed and approved by the Institutional Review Board prior to registration and treatment of patients on this study.

18.2 This section includes copies of all data forms which must be completed for this study.

a. **S0500** Registration Form (Form #36395) and Southwest Oncology Group Registration Form Code Sheet (10/24/06)

b. **S0500** Prestudy Form (Form #29563) (2/15/07)

c. Baseline Tumor Assessment Form (Form #848) (09/01/03)

d. **S0500** Treatment Summary Form (Form # 50428) (6/15/07)

e. **S0500** Adverse Event Summary Form (Form #18074) (2/15/07)

f. **S0500** Follow-Up Bone-Only Disease Assessment Form (Form #62610) (10/1/06)

g. **S0500** CTC Blood Draw and Results CRF (Form #40051) (6/24/09)

h. **S0500** CTC Submission Form (Form #39382)

i. Follow-Up Form (Form # 64587) (09/15/03)

j. Follow-Up Tumor Assessment Form (Form #38305) (09/01/03)

k. Notice of Death (Form # 49467) (09/01/03)

Informed Consent Template For **S0500**

*NOTES FOR LOCAL INSTITUTION INFORMED CONSENT AUTHORS:

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

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

Readability Statistics:	
Flesch Reading Ease	60.8 (targeted above 55)
Flesch-Kincaid Grade Level	8.7 (targeted below 8.5)

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

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

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

*NOTES FOR LOCAL INVESTIGATORS:

- The goal of the informed consent process is to provide people with sufficient information for making informed choices. The informed consent form provides a summary of the clinical study and the individual's rights as a research participant. It serves as a starting point for the necessary exchange of information between the investigator and potential research participant. This model for the informed consent form is only one part of the larger process of informed consent. For more information about informed consent, review the "Recommendations for the Development of Informed Consent Documents for Cancer Clinical Trials" prepared by the Comprehensive Working Group on Informed Consent in Cancer Clinical Trials for the National Cancer Institute. The Web site address for this document is http://cancer.gov/clinicaltrials/understanding/simplification-of-informed-consent-docs/
- A blank line, _____, indicates that the local investigator should provide the appropriate information before the document is reviewed with the prospective research participant.
- Suggestion for Local Investigators: An NCI pamphlet explaining clinical trials is available for your patients. The pamphlet is entitled: "If You Have Cancer…What You Should Know about Clinical Trials". This pamphlet may be ordered on the NCI Web site at http://cissecure.nci.nih.gov/ncipubs/details.asp?pid=1035 or call 1-800-4- CANCER (1-800-422-6237) to request a free copy.
- Optional feature for Local Investigators: Reference and attach drug sheets, pharmaceutical information for the public, or other material on risks. Check with your local IRB regarding review of additional materials.

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

S0500, "A Randomized Phase III Trial to Test the Strategy of Changing Therapy Versus Maintaining Therapy for Metastatic Breast Cancer Patients Who Have Elevated Circulating Tumor Cell Levels at First Follow-up Assessment"

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

You are being asked to take part in this study because you are a woman with breast cancer that has spread to other parts of your body. *(11/21/06)*

Why is this study being done?

The purpose of this experimental study is to find out if the CellSearch® blood test, which identifies tumor cells in the blood, can predict survival outcome in patients with metastatic breast cancer. *(6/1/09)* These tumor cells are called circulating tumor cells (CTCs). The CellSearch® blood test may allow doctors to tell if your current chemotherapy is not working before you show signs that your cancer is getting worse. *(6/1/09)* This is based upon a prior study that showed that most women with high numbers of CTCs had worsening of their breast cancer within 1-3 months. *(11/21/06)* In this prior study, increase in the size of a tumor or spread of cancer in the body was determined by standard clinical tests such as physical examinations, x-rays and scans, and not by the CellSearch® blood test. *(6/1/09)* This study will test whether switching to another form of treatment based upon the results of the CellSearch® blood test helps people live longer. *(6/1/09)* In addition, this study will be used to further confirm results of the prior study, which showed that patients with < 5 CTCs before they begin treatment are more likely to live longer than those with ≥ 5 CTCs. *(11/21/06) (5/15/07)*

How many people will take part in the study?

About 651 women will take part in this study. *(11/21/06) (11/11/11)*

What will happen if I take part in this research study?

Before you begin the study …

You will need to have the following exams, tests or procedures to find out if you can be in the study. These exams, tests or procedures are part of regular cancer care and may be done even if you do not join the study. If you have had some of them recently, they may not need to be repeated. This will be up to your study doctor.

- Medical History and Physical Exam
- Weight and Performance Status
- Disease Assessment including CT scans, MRI scans, bone scan, PET scans and/or x-rays. *(5/15/07)*
- Routine laboratory blood tests (to measure your kidney and liver function)
- Pregnancy test (if determined to be appropriate by your treating physician)

During the study …

If the exams, tests and procedures show that you can be in the study, and you choose to take part, then you will need the following tests and procedures. They are part of regular cancer care.

- Medical history and physical exam
- Weight and performance status
- Disease assessment including CT scans, MRI scans, bone scans, PET scans and/or x-rays. *(5/15/07)*
- Routine laboratory blood tests (to measure your kidney and liver function).

The timing of the exams and tests above will be determined by the treatment that is given to you by your study doctor. The dates of these clinical visits will be discussed with you by your study doctor.

You will need these tests and procedures that are either being tested in this study or being done to see how the study is affecting your body.

- Measurement of circulating tumor cells (CTCs) in the blood (**all patients):** about 2-3 teaspoons of blood will be collected for this test. Blood will be collected before treatment begins. All patients will be told the results of this first CTC test.

  Patients with < 5 CTCs will continue to receive their regular treatment without change, and no further blood draws will be performed. These patients will be followed to find out how long they respond to treatment and how long they live. <u>This group of women with < 5 CTC is called **Arm A.**</u>

- Repeat measurements of circulating tumor cells (CTCs) in the blood (**only for patients with CTC ≥ 5 at the time of initial screening):** about 2-3 teaspoons of blood will be collected for these tests. Blood will be collected at Day 22, Day 50 or 57, Day 85, Day 169, Day 253, and at the time your cancer becomes worse or when the doctor decides to discontinue this protocol strategy. *(11/21/06, 5/15/07)*

  Except for the initial blood test, neither the patient nor the doctor will be given the results of any of the CTC blood tests. *(11/21/06)*

- The CTC blood drawing procedure requires that a separate tube of blood be drawn first to prevent contamination with skin cells. This separate tube of blood (about 10 mL or 2 - 3 teaspoons) will be submitted to a special laboratory and used to measure the breast cancer tumor markers CA 15-3 and CEA. *(11/21/06)* The results of these tests will be compared to the results of the CTC testing. *(added 11/21/06)* In addition, we will ask your permission to save any leftover serum from this blood sample for future research. This will be discussed in more detail below.

Your study doctor will choose a treatment program that is believed to be best for you. For women with ≥ 5 CTCs at baseline the CellSearch® test will be performed 3 weeks after your first dose of chemotherapy and will be used to determine if you are at higher risk of having your cancer worsen on this current therapy. *(6/1/09)* You and your study doctor will not be told the results of the CellSearch® blood test. *(6/1/09)*

- **Approximately half of the women on this study will have low numbers of CTCs (< 5 CTCs) after completing one cycle of chemotherapy.** These women are not believed to be at higher risk. *(11/21/06)* These women will continue on the same chemotherapy. *(11/21/06)* They will continue to be followed on study until the doctor finds evidence that the breast cancer has become worse. These women are in the "maintain current therapy" group or Arm B.

- **Approximately half of the women on this study will have elevated numbers of CTCs (≥ 5 CTCs) after completing one cycle of chemotherapy. These women will be randomized to either maintain current therapy or switch therapy.** Randomization means that you are put into a group by chance. A computer program will place you in one of the study groups. Neither you nor your doctor can choose the group you will be in. You will have an equal chance of being placed in any group.

  Women randomized to the "maintain current therapy" group or Arm C1 will remain on the same therapy. The doctor will monitor the cancer using standard methods including physical exam, CT scans, bone scans, and x-rays. These patients will continue to be followed on the study until the doctor finds evidence that the breast cancer has become worse.

  Women randomized to the "switch therapy" group or Arm C2 will change chemotherapy to a different drug or combination of drugs. The selection of the new chemotherapy will be made by the patients own doctor based upon what they believe is best. The study does not specify what therapy the doctor should choose. The doctor will monitor the cancer using standard methods including physical exam, CT scans, bone scans, and x-rays. These patients will continue to be followed on the study until the doctor finds evidence that the breast cancer has become worse.

  If your doctor is told that you are to "maintain current therapy", neither you nor your doctor will know whether you are in the Arm B group or in the Arm C1 group. *(added 11/21/06)*

Only chemotherapy will be changed based on the CTC results. If your study doctor is also prescribing a hormonal therapy or a biological therapy at the same time as chemotherapy, then these hormonal or biological therapies will continue at the discretion of you and your doctor regardless of the CTC level. *(11/21/06)*

How long will I be in the study?

You will be followed with collection of blood specimens and information about your treatment and progress until your doctor finds evidence your cancer has worsened. *(11/21/06)* This will be different for each patient and may vary from weeks to months to years. After your cancer worsens we will no longer collect the blood specimens. Further follow-up and treatment decisions will be made between you and your doctor. We would like to keep track of your medical condition for a minimum of 5 years after you start the study. *(11/21/06)* Every 6 months your doctor will send us an update on your condition. *(sentences deleted 11/21/06)*

Can I stop being in the study?

Yes. You can decide to stop at any time. Tell the study doctor if you are thinking about stopping or decide to stop. He or she will tell you how to stop safely.

It is important to tell the study doctor if you are thinking about stopping so that you can discuss what follow-up care and testing could be most helpful for you.

The study doctor may stop you from taking part in this study at any time if he/she believes it is in your best interest; if you do not follow the study rules; or if the study is stopped.

What side effects or risks can I expect from being in the study?

It is possible that you will not have any benefit in the control of your cancer from participation in this trial. This study is being performed to determine whether changing therapy based on CTC levels improves outcome.

There is also a chance that participation in this trial will be detrimental to the treatment of your cancer. Not all patients with elevated CTCs after one cycle of chemotherapy have rapid worsening of their cancer. As a result some of the women who are randomized to switch to alternative therapy (about 15-20% of the women randomized to switch therapy) will be switched off chemotherapy that was working. After you complete this study, your doctor will have the option of using the original chemotherapy drug(s) again.

The chemotherapy you receive will be determined by your doctor, not by the study. To find out more about the risks of your own chemotherapy ask your doctor.

One risk is the release of information from your health records. The Southwest Oncology Group will protect your records so that your name, address, and telephone number will be kept private. The chance that this information will be given to someone else is very small. This is discussed in greater detail below in the section called "Will my medical information be kept private?"

For more information about any other risks, ask your study doctor.

Are there benefits to taking part in the study?

Taking part in this study may or may not make your health better. While doctors hope that the CellSearch® blood test will improve the effectiveness of cancer treatment compared to the usual methods of monitoring of breast cancer, there is no proof of this yet. *(6/1/09)* **We do know that the information from this study will help doctors learn more about the CellSearch® blood test in monitoring cancer. This information could help future cancer patients.** *(6/1/09)*

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

Your other choices may include:

- Getting treatment or care for your cancer without being in a study
- Taking part in another study
- Getting no treatment

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

Will my medical information be kept private?

We will do our best to make sure that the personal information in your medical record will be kept private. However, we cannot guarantee total privacy. Your personal information may be given out if required by law. If information from this study is published or presented at scientific meetings, your name and other personal information will not be used.

Organizations that may look at and/or copy your medical records for research, quality assurance, and data analysis include:

- Local Institutional Review Board (IRB)
- The National Cancer Institute (NCI)

- The Food and Drug Administration (FDA), involved in reviewing and inspecting the data and results of this clinical study, and in keeping research safe for participants in this study. *(11/21/06)*
- The Southwest Oncology Group
- The Cancer Trials Support Unit (CTSU), a research group sponsored by the National Cancer Institute (NCI) to provide greater access to cancer trials.
- Veridex, LLC: manufacturer of the CellSearch® blood test and sponsor of this investigation. *(11/21/06) (6/1/09)*
- Veridex Pharma Laboratory Services: The laboratory that will be performing CTC enumeration. *(added 11/21/06) (6/1/09)*
- Data Safety and Monitoring Board (DSMB), an independent group of experts will be reviewing the data from this research throughout the study.

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

What are the costs of taking part in this study?

The cost of the CellSearch® CTC, CA 15-3, and CEA blood tests will be paid for by the study. Neither you nor your insurance company will be billed for these blood tests. *(6/1/09)*

The treatments received during this clinical trial are not experimental. They will be determined by your doctor and are considered standard of care. The costs of these treatments are not paid for by the study, and you and/or your health plan/ insurance company will need to pay for all of the costs of treating your cancer in this study. Taking part in this study may or may not cost your insurance company more than the cost of getting regular cancer treatment.

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

For more information on clinical trials and insurance coverage, you can visit the National Cancer Institute's Web site at http://cancer.gov/clinicaltrials/understanding/insurance-coverage . You can print a copy of the "Clinical Trials and Insurance Coverage" information from this Web site.

Another way to get the information is to call 1-800-4-CANCER (1-800-422-6237) and ask them to send you a free copy.

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

It is important that you tell your study doctor, _____ *[investigator's name(s)]*, if you feel that you have been injured because of taking part in this study. You can tell the doctor in person or call him/her at _____ *[telephone number]*.

You will get medical treatment if you are injured as a result of taking part in this study. You and/or your health plan will be charged for this treatment. The study will not pay for medical treatment.

What are my rights if I take part in this study?

Taking part in this study is your choice. You may choose either to take part or not to take part in the study. If you decide to take part in this study, you may leave the study at any time. No matter what decision you make, there will be no penalty to you and you will not lose any of your regular benefits. Leaving the study will not affect your medical care. You can still get your medical care from our institution.

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

In the case of injury resulting from this study, you do not lose any of your legal rights to seek payment by signing this form.

Who can answer my questions about the study?

You can talk to your study doctor about any questions or concerns you have about this study. Contact your study doctor _____ *[name(s)]* at _____ *[telephone number]*.

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

***You may also call the Operations Office of the NCI Central Institutional Review Board (CIRB) at 888-657-3711 (from the continental US only).** *[*Only applies to sites using the CIRB.]*

Please note: This section of the informed consent form is about additional research studies that are being done with people who are taking part in the main study. You may take part in these additional studies if you want to. You can still be a part of the main study even if you say 'no' to taking part in any of these additional studies.

You can say "yes" or "no" to each of the following studies. Please mark your choice for each study.

Future Contact

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

Yes No

Additionally, we would also like to bank any leftover serum specimens for future, unspecified scientific testing. An additional consent form and information is attached for this purpose.

Consent Form for Use of Specimens for Research

About Using Specimens for Research

We would like to keep leftover serum specimens for future research. If you agree, these specimens will be kept and may be used in research to learn more about cancer and other diseases. Please read the information sheet called "How are Specimens Used for Research" to learn more about specimen research.

The research that may be done with your specimens are not designed specifically to help you. It might help people who have cancer and other diseases in the future.

Reports about research done with your specimens will not be given to you or your doctor. These reports will not be put in your health record. The research will not have an effect on your care.

(address section deleted 11/11/11)

Things to Think About

The choice to let us keep specimens for future research is up to you. No matter what you decide to do, it will not affect your care.

If you decide now that your specimens can be kept for research, you can change your mind at any time. Just contact us and let us know that you do not want us to use your specimens, then any specimens that remain will no longer be used for research.

In the future, people who do research may need to know more about your health. While the Southwest Oncology Group may give them reports about your health, it will not give them your name, address, phone number, or any other information that will let the researchers know who you are.

Sometimes specimens are used for genetic research (about diseases that are passed on in families). Even if your specimens are used for this kind of research, the results will not be put in your health records.

Your specimens will be used only for research and will not be sold. The research done with your tissue may help to develop new products in the future.

Benefits

The benefits of research using specimens include learning more about what causes cancer and other diseases, how to prevent them, and how to treat them.

Risks

The greatest risk to you is the release of information from your health records. We will do our best to make sure that your personal information will be kept private. The chance that this information will be given to someone else is very small.

Making Your Choice

Please read each sentence below and think about your choice. After reading each sentence, circle "Yes" or "No." If you have any questions, please talk to your doctor or nurse, or call our research review board at IRB's phone number.

No matter what you decide to do, it will not affect your care.

1. My specimens may be kept for use in research to learn about, prevent, treat or cure cancer.

Yes No

2. My specimens may be kept for use in research about other health problems (for example: diabetes, Alzheimer's disease, or heart disease).

Yes No

3. Someone may contact me in the future to ask me to allow other uses of my specimens.

Yes No

If you decide to withdraw your specimens from a Southwest Oncology Group Specimen Repository in the future, a written withdrawal of consent should be submitted through your treating physician to the Southwest Oncology Group Operations Office. If you decide to withdraw your permission from the banking part of the study, then any remaining blood specimens will be destroyed.

Where can I get more information?

You may call the National Cancer Institute's Cancer Information Service at:

1-800-4-CANCER (1-800-422-6237) or **TTY: 1-800-332-8615**

You may also visit the NCI Web site at http://cancer.gov/

- **For NCI's clinical trials information, go to: http://cancer.gov/clinicaltrials/**
- **For NCI's general information about cancer, go to http://cancer.gov/cancerinfo/**

You will get a copy of this form. If you want more information about this study, ask your study doctor.

Signature

I have been given a copy of all _____ [insert total of number of pages] **pages of this form. I have read it or it has been read to me. I understand the information and have had my questions answered. I agree to take part in this study.**

Participant _____

Date _____

Specimen Consent Supplemental Sheets

How are Specimens Used for Research?

Where do specimens come from?

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

Why do people do research with specimens?

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

What type of research will be done with my specimen?

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

How do researchers get the specimen?

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

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

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

Why do you need information from my health records?

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

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

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

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

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

How am I protected?

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

What if I have more questions?

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

19.0 APPENDIX

19.1 CellSearch® Assay – Methods

19.2 Cancer Trials Support Unit (CTSU) Participation Procedures

19.3 Packing and Shipping Instructions

19.1 CellSearch® Assay – Methods

Processing of Blood Samples

The blood samples will be processed using the CellSearch® System. A blood sample (CellSave® tube) will be processed using the AutoPrep® automated sample preparation system and CTCs will be enumerated using the CellTracks® Analyzer II system.

a. CellSearch® Systems

1. Operator Training: System Operators will receive training at Veridex. Follow-up examinations will be given to document operator proficiency. Training manuals and documentation of training will be maintained at Veridex.

2. Image interpretation and enumeration of CTCs: Determination of CTC counts will be made by trained operators. Circulating tumor cells are identified based on analysis of results from the CellTracks® Analyzer II. Tumor cells will be identified by the instrument software, and objects will be confirmed visually by the operator.

3. Quality Control of the AutoPrep® and CTC analysis systems is maintained via Operator Training procedures, daily, weekly and monthly maintenance of systems, use of a two-level control cell sample for AutoPrep® according to standard protocols as described in the Operator Manuals.

b. Assay Procedures

1. Upon specimen arrival at the laboratory, the laboratory personnel will ensure that one of the two tubes of blood collected will be tested and the other stored in case it is required due to any circumstances leading to the inability to test the first tube. This will mitigate the potential of being unable to perform a CTC count at each blood draw.

2. The sample will be processed within 96 hours of the time of the draw using the CellSearch® System.

3. All patient specimens are to be assayed using the CellSearch® Assay as per the manufacturer's instructions. CTCs will be isolated using the CellTracks® AutoPrep® sample processor. A volume of 7.5 mL from the sample will be diluted with buffer and centrifuged for processing on the AutoPrep system. Plasma is withdrawn and additional buffer added. Epithelial cell-specific immunomagnetic particles (EpCAM-ferrofluid) is added and incubated for 30 minutes at room temperature. Unbound sample is then aspirated while the sample is in a magnetic field. Buffer is added and the sample is mixed and separated in a magnetic field. Supernatant is removed and a permeabilizing agent added, followed by a nucleic acid dye, anti-cytokeratin (a marker of epithelial cells), and anti-CD45. The specimen is mixed and incubated for 15 minutes. The sample is washed with buffer, magnetically separated, and labeled cells are fixed. Multiple lots of CellSearch® Reagents and Control materials will be used in the performance of this clinical trial; these materials must

be used prior to their expiration date. Operators must run control cells daily to ensure proper operation of the AutoPrep®, according to the manufacturer's instructions. Enumeration of CTCs will be done on the CellTracks® Analyzer II. The AutoPrep® instrument transfers the sample to a cartridge that can be placed in the CellTracks® Analyzer II for examination. Selected cells will be reviewed for identification.

c. Study Devices and Uses

All of the CellSearch® instruments used in this study will be operated by trained experienced operators in the CLIA certified laboratory at Veridex, LLC.

19.2 Cancer Trials Support Unit (CTSU) Participation Procedures

REGISTRATION/RANDOMIZATION

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

Each CTSU 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 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 website at https://www.ctsu.org.

All forms and documents associated with this study can be downloaded from the **S0500** web page on the CTSU registered member Web site (https://www.ctsu.org). Patients can be registered only after pre-treatment evaluation is complete, all eligibility criteria have been met, and the study site is listed as 'approved' in the CTSU RSS.

Requirements for S0500 site registration:

- CTSU IRB Certification
- IRB/Regulatory Approval Transmittal Sheet
- Sites should follow the supply ordering instructions (Section 15.2b) to receive blood collection tubes and shipping supplies for blood analysis and FedEx Air bills. Orders should be placed at least one week before supplies are needed.

Prestudy requirements for patient enrollment on S0500:

- Patient must meet all inclusion criteria, and no exclusion criteria should apply.
- Patient has signed and dated all applicable consents and authorization forms.
- All baseline laboratory tests and prestudy evaluations performed.

CTSU Procedures for Patient Enrollment

1. Contact the CTSU Patient Registration Office by calling 1-888-462-3009. Leave a voicemail to alert the CTSU Patient Registrar that an enrollment is forthcoming. For immediate registration needs, i.e. within one hour, call the registrar cell phone at 301/704-2376.

2. Complete the following forms:

   - CTSU Patient Enrollment Transmittal Form
   - Eligibility Criteria Checklist (Section 5.0 of the protocol)
   - S0500 Registration Form (Complete all sections of the form except for SWOG-specific data fields).

3. Fax these forms to the CTSU Patient Registrar at 1-888-691-8039 between the hours of 9:00 a.m. and 5:30 p.m., Mon-Fri, Eastern Time (excluding holidays). The CTSU registrar will check the investigator and site information provided to ensure that all regulatory requirements have been met. The registrar will also check that forms are complete and follow-up with the site to resolve any discrepancies.

4. Once investigator eligibility is confirmed and enrollment documents deemed complete, the CTSU registrar will contact SWOG to obtain assignment of a treatment arm and assignment of a unique patient ID (to be used on all future forms and correspondence). The CTSU registrar will relay this information to the enrolling site and follow up with a confirmation via e-mail or fax.

   Patients must be registered prior to initiation of treating no more than one working day prior to the initial CTC submission.

DATA SUBMISSION AND RECONCILIATION

1. All case report forms (CRFs) and other documents associated with this study must be downloaded from the **S0500** Web page located on the CTSU registered member Web site (https://www.ctsu.org). Sites must use the current form versions and adhere to the **S0500** schedule for data submission per protocol Section 14.0.

2. Submit all completed CRFs (with the exception of patient enrollment forms), clinical reports, and transmittals directly to the SWOG Data Operations Center. The preferred method of sending data is via fax at 800/892-4007. Do NOT include a cover sheet for faxed data.

3. The SWOG Data Operations Center will send query notices and delinquency reports directly to the site for reconciliation. Please fax query responses and delinquent data to the SWOG Data Operations Center and do NOT copy the CTSU Data Operations. When faxing data include the query sheet that was originally sent from SWOG.

4. Each site should have a designated CTSU Administrator and Data Administrator and **must keep their CTEP AMS account contact information current**. This will ensure timely communication between the clinical site and the SWOG Data Operations Center.

SPECIAL MATERIALS OR SUBSTUDIES

All specimens submitted for this study must be entered and tracked using the SWOG On-line Specimen Tracking System, as specified in protocol Section 15.0.

You can also access the Tracking System from the CTSU Member Web Site. Go to the **S0500** protocol page and click on the provided link located under the Case Report Forms section.

Specimen collection for correlative studies (See Section 15.0)

- Sites are required to submit blood samples for analysis of circulating tumor cells (CTC) as outlined in protocol Section 15.2. Blood collection tubes should be onsite at time of patient registration. See Section 15.2b for the initial supply ordering instructions.
- Sites are required to submit serum specimens to test for levels of the tumor markers CA 15-3 and CEA as outlined in protocol Section 15.1b. Sites are encouraged to seek additional consent to allow leftover serum to be kept for banking.

SERIOUS ADVERSE EVENT (AE) REPORTING (See Section 16.0)

1. CTSU sites must comply with the expectations of their local Institutional Review Board (IRB) regarding documentation and submission of adverse events. Local IRBs must be informed of all reportable serious adverse reactions.

2. CTSU sites will assess and report adverse events according to the guidelines and timelines specified in Section 16.0.

3. Do NOT send adverse event reports to the CTSU.

REGULATORY AND MONITORING

Study Audit

To assure compliance with Federal regulatory requirements [CFR 21 parts 50, 54, 56, 312, 314 and HHS 45 CFR 46] and National Cancer Institute (NCI)/ Cancer Therapy Evaluation Program (CTEP) Clinical Trials Monitoring Branch (CTMB) guidelines for the conduct of clinical trials and study data validity, all protocols approved by NCI/CTEP that have patient enrollment through the CTSU are subject to audit.

Responsibility for assignment of the audit will be determined by the site's primary affiliation with a Cooperative Group or CTSU. For Group-aligned sites, the audit of a patient registered through CTSU will become the responsibility of the Group receiving credit for the enrollment. For CTSU Independent Clinical Research Sites (CICRS), the CTSU will coordinate the entire audit process.

For patients enrolled through the CTSU, you may request the accrual be credited to any Group for which you have an affiliation provided that Group has an active clinical trials program for the primary disease tpe being addressed by the protocol (e.g. NSABP members may only request credit for protocols pertaining to breast or colorectal cancers). Registrations to protocols for other disease sites may still take place through CTSU without credit for your NSABP activities. Per capita reimbursement will be issued directly from CTSU.

Details on audit evaluation components, site selection, patient case selection, materials to be reviewed, site preparation, on-site procedures for review and assessment, and results reporting and follow-up are available for download from the CTSU Operations Manual located on the CTSU Member Web site.

Health Insurance Portability and Accountability Act of 1996 (HIPAA)

The HIPAA Privacy Rule establishes the conditions under which protected health information may be used or disclosed by covered entities for research purposes. Research is defined in the Privacy Rule referenced in HHS 45 CFR 164.501. Templated language addressing NCI-U.S. HIPAA guidelines are provided in the HIPAA Authorization Form located on the CTSU website.

The HIPAA Privacy Rule does not affect participants from outside the United States. Authorization to release Protected Health Information is NOT required from patients enrolled in clinical trials at non-US sites.

Clinical Data Update System (CDUS) Monitoring

This study will be monitored by the Clinical Data Update System (CDUS) Version 3.0. Cumulative CDUS data will be submitted quarterly to CTEP by electronic means. The sponsoring Group fulfills this reporting obligation by electronically transmitting to CTEP the CDUS data collected from the study specific case report forms.

19.3 Packing and Shipping Instructions

Separate page