Cancer Research Consortium of West Michigan
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FAST FACTS

S1501, Prospective Observational Cohort Study of Patients with Metastatic HER-2+ Breast Cancer at Risk of Cardiac Toxicity.

STEP 1 REGISTRATION

Disease Related Criteria

1. Patients must:
   a) Have metastatic breast cancer,
   AND
   b) Be initiating within 11 calendar days of Step 1 Registration OR be continuing trastuzumab–based
   AND
   c) Be receiving the trastuzumab-based HER-2 targeted therapy for metastatic disease in first, second, third-, or fourth-line setting.
   d) Patients may have brain metastasis.
   e) There is no limit for number of doses of HER-2 targeted therapy prior to registration.
   Examples of eligible HER-2 targeted therapy:
   - Trastuzumab or a trastuzumab biosimilar
   - Trastuzumab + chemotherapy or hormonal therapy
   - Trastuzumab + other HER-2 targeted agent with or without chemotherapy (such as pertuzumab, lapatinib, and tucatinib)
   - Ado-trastuzumab (Kadcyla®)
   - Fam-trastuzumab deruxtecan (Enhertu)

NOTE: Patients on lapatinib without trastuzumab are not eligible. Planned treatment with concurrent HER-2 targeted therapy and anthracyclines is not permitted.

Prior/Concurrent Therapy Criteria

1. Patients must be at increased risk for cardiotoxicity defined by at least one of the following:
   a) Previous anthracycline exposure
   OR
   b) 1 or more of the following risk factors for heart disease:
   - LVEF 50-54% by local ECHO read*
   - Age ≥ 65
   - BMI ≥ 30 kg/m2
   - Current or prior anti-hypertensive therapy
   - Diagnosis of coronary artery disease (CAD)
   - Diagnosis of diabetes mellitus
   - Diagnosis of atrial fibrillation/flutter

   c) *ECHO can be performed at any time prior to registration with the most recent being sent.

2. Patients must not have taken within 21 days prior to Step 1 Registration, be currently taking at the time of Step 1 Registration or planning to take once registered to Step 1 a beta blocker, ARB, or ACE inhibitor, in order to be randomized (Arms 1 and 2).

Patients enrolling in the observational cohort (Arm 3) **must be** currently taking a beta blocker, ARB, or ACE inhibitor at the time of Step 1 Registration.

NOTE: Arm 3 was permanently closed to accrual between Revision #5 and Revision #7 (see Status Notice). Arms 1 and 2 have been permanently closed to accrual and Arm 3 has been reopened effective with the distribution of Revision #7. Participants enrolled prior to the closure of Arms 1 and 2 remain eligible and should continue study participation.

Clinical/Laboratory Criteria

1. Patients must have a Zubrod Performance Status of 0-2. (see Section 10.7).
2. Patients must be ≥ 18 years of age.
3. Patients must have a complete physical examination and medical history within 28 days prior to registration.
4. Patients must have LVEF ≥ 50% by echocardiogram (**2D or 3D**) within 28 days prior to registration. The echocardiogram must be obtained from the site's approved S1501 Validated ECHO Lab and submitted for central review by the S1501 ECHO Core Lab (see Section 15.2).

   If a 3D echocardiogram is performed at baseline, sites must ensure that standard 2D images, including 4-chamber and 2-chamber views, are also obtained and submitted at subsequent timepoints.

   Note: For sites performing a 3D scan at baseline, please see the Coverage Analysis Worksheet on CTSU for additional coverage considerations.

   All follow-up echocardiograms (every 12 weeks per Section 7.2) must be performed using **2D** imaging to allow for standardized assessments. Follow-up scans must be completed at a site that can provide 2D images per protocol requirements. The echocardiograms cannot be submitted for central read until after Step 1 registration is complete.
5. Patients must have adequate hepatic function as evidenced by all of the following within 28 days prior to registration: serum bilirubin < 3.0 x institutional upper limit of normal (IULN), SGOT/AST and SGPT/ALT < 5.0 x IULN.
6. Patients must not be dialysis dependent.
7. No other prior malignancy is allowed except for the following: adequately treated basal cell or squamous cell skin cancer, *in situ* cervical cancer, prostate cancer on active surveillance, 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 five years.
8. Patients must not be pregnant or nursing due to potential fetal or nursing infant harm. Women/men of reproductive potential must have agreed to use an effective contraceptive method. A woman is considered to be of "reproductive potential" if she has had menses at any time in the preceding 12 consecutive months. In addition to routine contraceptive methods, "effective contraception" also includes heterosexual celibacy and surgery intended to prevent pregnancy (or with a side-effect of pregnancy prevention) defined as a hysterectomy, bilateral oophorectomy or bilateral tubal ligation. However, if at any point a previously celibate patient chooses to become heterosexually active during the time period for use of contraceptive measures outlined in the protocol, he/she is responsible for beginning contraceptive measures.

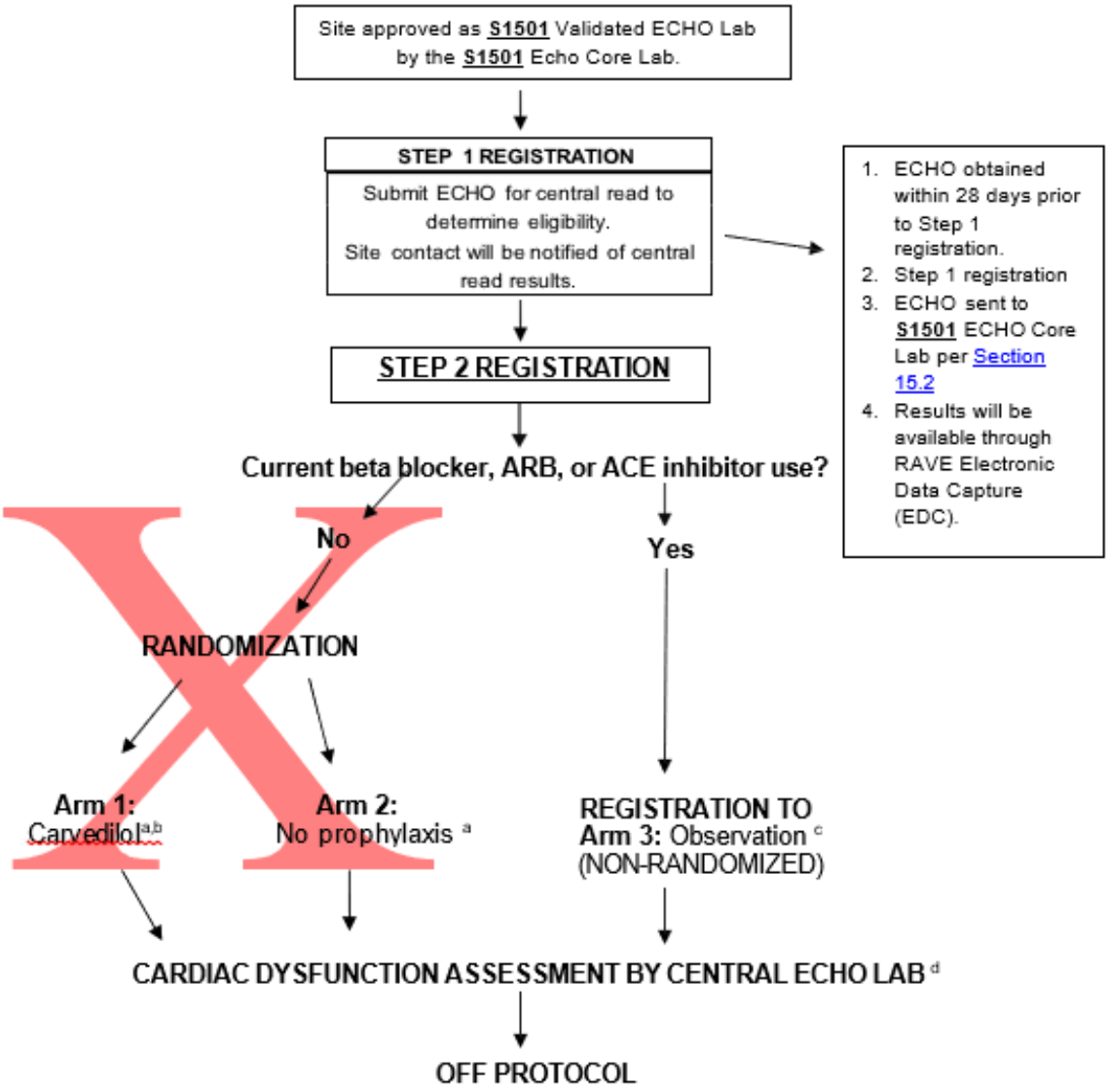
Specimen Submission Criteria

1. Patients must be willing to submit blood specimens as outlined in Section 15.1.
2. Sites must seek additional patient consent for the future use of specimens as described in Section 15.0.

STEP 2 REGISTRATION (Randomization)

1. **Patients must not be registered to Step 2 until confirming via RAVE EDC that the patient's LVEF by echocardiogram was ≥ 50% by central review. Patients must be registered within 21 calendar days of submission of the ECHO study.** Please refer to Section 13.1.b for information regarding preferred timing for Step 2 registration.
2. Site must verify that there is no known change in the Step 1 eligibility since initial registration.

SCHEMA



Footnotes:

NOTE: Arms 1 and 2 have been permanently closed to accrual and Arm 3 has been reopened effective with the distribution of Revision #7.

[a] HER-2 targeted therapy continuation/discontinuation at the discretion of treating physician.

[b] For patients on Arm 1, carvedilol is reimbursed by the study while the patient is on study for up to 108 weeks from randomization. Upon removal from study, non -reimbursed carvedilol continuation is at the discretion of the patient and treating physician.

[c] Arm 3 was permanently closed to accrual between Revision #5 and Revision #7 (see Status Notice). Arm 3 is reopened, effective with the distribution of Revision #7.

[d] Standard of care ECHOs are expected to be performed every 12 weeks, to monitor cardiotoxicity, for patients already receiving trastuzumab-based targeted therapy prior to registration and will continue to be followed with a standard of care ECHO. No additio nal ECHOs will be required for study participation, including for participants whose ECHO timing differs from the recommended 12-week timing.