Protocol Title: S1501: Prospective Evaluation of Carvedilol in Prevention of Cardiac Toxicity in Patients with Metastatic HER-2+ Breast Cancer, Phase III

Target Population: Metastatic HER2 Positive Breast Cancer

Summary: This phase III trial studies how well carvedilol works in preventing cardiac toxicity in patients with human epidermal growth factor receptor (HER)-2-positive breast cancer that has spread to other places in the body.

STEP 1 REGISTRATION ELIGIBILITY CRITERIA:

- Patients must have metastatic breast cancer and be initiating within 7 Days of Step 1 or continuing Trastuzumab-based HER-2 targeted therapy without concurrent Anthracyclines in first or second line setting.
  - Patients may have brain metastasis.
  - There is no limit for number of doses of HER-2 targeted therapy prior to registration.
  - NOTE: Patients on Lapatinib without Trastuzumab are not eligible.
  - NOTE: Planned treatment with concurrent HER-2 targeted therapy & Anthracyclines is not permitted.
- Patients must be at increased risk for cardiotoxicity defined by at least one of the following:
  - Previous anthracycline exposure, OR
  - 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)
    - Diabetes mellitus
    - Atrial fibrillation/flutter

  - Patients must not have taken within 21 Days prior to Step 1, be currently taking at the time of Step 1, or planning to take once registered to Step 1 a Beta Blocker, ARB, or ACE Inhibitor in order to be randomized (Arms 1 & 2).
    - Patients currently taking a Beta Blocker, ARB, or ACE Inhibitor at the time of Step 1 are eligible to register for the non-randomized observational cohort (Arm 3).
  - Patients must not be currently taking or planning to take during study treatment the following medications: B2 Agonists, Bosutinib, Ceritinib, Floctafenine, Methacholine, Pazopanib, Rivastigmine, Vincristine, or Silodosin.
  - Patients must have a Zubrod Performance status of 0-2.
  - Patients must have LVEF ≥ 50% by 2D Echocardiogram within 28 Days prior to registration.
    - ECHO must be obtained from a S1501 validated ECHO lab and submitted for central review by the S1501 ECHO core lab.
    - ECHO should not be submitted for central read until patient has been otherwise deemed eligible
  - Adequate bone marrow, kidney and liver function.
  - Patients must have ECHO with corrected QT (QTc) with correction within 28 Days prior to registration.
  - Patients must have a systolic blood pressure ≥80 mm Hg within 14 Days prior to registration.

STEP 2 REGISTRATION (Randomization) ELIGIBILITY CRITERIA:

- Patients must not be registered to Step 2 until receiving confirmation from the ECHO Core Lab that the patient’s LVEF by ECHO was ≥ 50% by central review.
  - Patients must be registered within 5 calendar days of receiving the e-mail notification

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For additional information: https://clinicaltrials.gov/ct2/show/NCT03418961

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