

Cardiac SAFETY of HER2 targeted therapy in patients with HER2 positive breast cancer and reduced left ventricular function: SAFE-HEaRt

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Background: HER2 targeted therapies have survival benefit in adjuvant and metastatic HER2+ breast cancer but are associated with cardiac dysfunction. FDA recommendations limit the use of HER2 targeted agents to patients with normal left ventricular (LV) systolic function as there is no prospective evidence of their cardiac safety in patients with cardiomyopathy. Recently reported and ongoing primary prevention trials in patients undergoing HER2 therapies have excluded patients with abnormal LV function thus leaving the gap in knowledge about the cardiac safety and management of these patients.

Design: The objective of this study is to evaluate the cardiac safety of HER2 targeted therapy in patients with HER2+ breast cancer and mildly reduced LVEF with optimized cardiac therapy. Thirty patients with HER2+ breast cancer (stage I-IV), reduced LVEF (<50% and \geq 40%) and planned to receive HER2 therapy (trastuzumab, pertuzumab or T-DM1) for \geq 3 months will be enrolled. All patients undergo baseline assessments to exclude treatable causes of cardiomyopathy and initiate treatment with beta-blockers and ACE-inhibitors in maximum tolerated doses prior to the initiation or continuation of HER2 therapy. Patients are followed by serial echocardiograms and cardiac visits during and 6 months post completion of planned oncological therapy. The primary endpoint is the proportion of patients who complete planned HER2 treatment without the development of a cardiac event (presence of symptoms and signs attributable to HF and/or sudden cardiac death) or asymptomatic worsening of cardiac function defined as asymptomatic decline in LVEF > 10% points from baseline and/or to LVEF < 35%. Myocardial strain and blood biomarkers including brain natriuretic peptide, troponin I, and high-sensitivity cardiac troponin T, are examined. Early stopping rules are incorporated for safety based on cardiac death and symptomatic HF.

Conclusions: The SAFE-HEaRt study will provide the first safety data on the use of HER2 targeted therapies in patients with mildly reduced LV function with concomitant cardiac treatment and form the basis for consideration of clinical practice changes.