Clinical trial in progress: A phase 2 study of neoadjuvant chemotherapy plus trastuzumab and pertuzumab in HER2-negative breast cancer patients with abnormal HER2-driven signaling transduction

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Background:

HER2 breast cancer is currently diagnosed by measuring the HER2 receptor or gene amplification status in the patient's tumor cells using IHC or FISH testing. This approach does not identify whether the disease mechanism, abnormal HER2 signaling, is present. Recent studies have found that 20% of HER2-negative breast cancer patients have the same abnormal HER2 signaling activity found in HER2-positive breast cancer cell lines. In studies using HER2-positive and HER2-negative xenograft mouse tumor models, abnormal HER2 signaling correlated to HER2 drug response better than HER2 receptor status. Based on these studies, a Phase 2 study was initiated to evaluate the benefit HER2-negative breast cancer patients with abnormal HER2-driven signaling may receive from treatment with HER2-targeted therapies.

Methods:

This is a prospective, single arm, open label, multicenter interventional study designed to evaluate the efficacy of neoadjuvant doxorubicin plus cyclophosphamide followed by weekly paclitaxel plus trastuzumab and pertuzumab in early stage HER2-negative breast cancer patients who have abnormal HER2 signaling activity determined by a live cell HER2 signaling function test. Patients will be required to have a prescreening research core needle biopsy to procure a fresh tumor specimen that will be analyzed to assess whether their HER2 signaling activity is abnormal or normal. Patients must have abnormal HER2 signaling activity to be enrolled. The primary objective of the study is to evaluate whether patients with HER2-negative breast cancers who have abnormal HER2-driven signaling pathways and receive HER2-targeted therapy with neoadjuvant chemotherapy will have a higher rate of pCR in the breast and lymph nodes than has been found historically in patients with HER2-negative breast cancer who have received neoadjuvant chemotherapy. It is expected that approximately 270 patients will need to be prescreened in order to enroll 54 patients (26 ER+/HER2- and 28 ER-/HER2-) who have abnormal HER2 signaling activity. The sample size calculations for the ER+ and ER- sub-groups assumed the historical pCR rate is 11% and 34%, respectively. In each of these two sub-groups, a Sargent two-stage three-outcome optimal design has been used where the type I error is set at 0.05, the type II error is set at 0.1 and the probabilities of a true outcome (positive or negative) are both set at 0.8.