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Evaluation of HER family protein signaling network as a predictive biomarker for pCR for breast cancer patients treated with neratinib in the I-SPY 2 TRIAL

Background: We hypothesize that response to the pan-ERBB inhibitor, neratinib (N), may be predicted by pre-treatment HER2-EGFR signaling. In the I-SPY 2 TRIAL, N graduated in the HR-/HER2+ signature. All patients received at least standard chemotherapy. For HER2+ patients, N was administered in place of trastuzumab. We evaluated 18 HER family signaling proteins as biomarkers of N response using reverse phase protein microarray (RPMA) data from pre-treatment LCM purified tumor epithelium.

Methods: 168 patients (N: 106, concurrent controls: 62) had RPMA and pCR data. 18 biomarkers relating to HER family signaling were evaluated: AKT S473, AKT T308, EGFR, EGFR Y1068, EGFR Y1148, EGFR Y1173, EGFR Y992, ERBB2, ERBB2 Y1248, ERBB3 total, ERBB3 Y1289, ERK1/2 T202/Y204, Heregulin, mTOR, mTOR S2448, PI3K p85 Y458/p55 Y199, PTEN S380, and SHC Y317. We assessed association between biomarker and response in the N and control arms alone (likelihood ratio test), and relative performance between arms (biomarker x treatment interaction) using a logistic model. Analysis was also performed adjusting for HR/HER2 status. In an exploratory analysis, we selected the marker with the greatest interaction (phosphorylated EGFR (Y1173)) to dichotomize patients optimally based on the data and assessed it in the context of the graduating signature by adding the EGFR Y1173-High patients to the HR-/HER2+ subtype and evaluating the treatment effect in this ‘biomarker-positive’ group. Our study is exploratory with no claims for generalizability of the data and does not account for multiplicities. Statistical calculations are descriptive (e.g. p-values are measures of distance with no inferential content).

Results: 7 HER pathway markers (EGFR Y1068, EGFR Y1173, EGFR Y992, ERBB2 total, ERBB2 Y1248, ERBB3 Y1289, SHC Y317) are associated with response in the N but not the control arm. However, the difference in performance between arms did not reach significance by permutation testing. Adjusting for HR/HER2 status, EGFR Y1173 shows a significant biomarker x treatment interaction ($p = 0.049$). In an exploratory analysis, we dichotomized patients by their EGFR Y1173 levels and evaluated the distribution of pCR rates (Table 1).

	Neratinib (n=106)		Control (n=62)	
	EGFR Y1173 Low (n=31)	EGFR Y1173 High (n=75)	EGFR Y1173 Low (n=29)	EGFR Y1173 High (n=33)
HR-HER2+ (n=28)	0 / 4	12 / 18	1 / 1	1 / 5
Not HR-HER2+ (n=140)	3 / 27	24 / 57	5 / 28	5 / 28

OR between EGFR Y1173 groups in the N relative to control arm is 10.1. When EGFR Y1173 High patients are added to the graduating HR-/HER2+ subset, the OR associated with treatment