Abstract P3-06-29: MammaPrint High1/High2 risk class as a biomarker of response to neratinib plus standard neoadjuvant therapy for breast cancer in the I-SPY 2 TRIAL

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Background: Further stratification of the 70-gene MammaPrintTM signature into 'high' and 'ultra-high' risk groups may help predict chemo-sensitivity. In I-SPY 2, patients were classified as MammaPrint High1 (MP1) or MammaPrint (ultra) High2 (MP2), with MP2 defined as MP_score <-0.154. MP1/MP2 classification was added to HR and HER2 to define the cancer subtypes used in the I-SPY 2 adaptive randomization engine. Neratinib (N), one of the experimental agents evaluated in I-SPY 2, graduated in the HR-HER2+ signature. All patients received at least standard chemotherapy (paclitaxel followed by doxorubicin/cyclophosphamide; T->AC). HER2- patients were randomized to receive N+T- >AC vs. T->AC. For HER2+ patients, neratinib was administered in place of trastuzumab (N+T->AC vs. H+T->AC). Here, we assess the performance of MP1/MP2 class as a specific biomarker of neratinib response.

Methods: 115 patients in the neratinib arm and 76 concurrently randomized controls had Agilent 44K microarrays and pCR data available for analysis. We assess association between MP1/MP2 and response in the neratinib and control arms alone using Fisher's exact test, and relative performance between arms (biomarker x treatment interaction, likelihood ratio $p < 0.05$) using a logistic model. This analysis is also performed adjusting for HR status as a covariate, and in receptor subsets. Our study is exploratory with no claims for generalizability of the data. Statistical calculations are descriptive (e.g. p-values are measures of distance with no inferential content). Our analyses do not adjust for multiplicities of other biomarkers in the trial but outside this study.

Results: There are 133 MP1 patients (neratinib: 74, Control: 59) and 58 MP2 patients (neratinib: 41, Control: 17), 84% (49) of which are Her2-. The distribution of pCR rates among MP1/MP2 dichotomized groups are summarized in Table 1.

	Neratinib (n=115)		Control (n=76)	
	MP1 (n=74)	MP2 (n=41)	MP1 (n=59)	MP2 (n=17)
HER2- (n=105)	0 / 17	15 / 33	7 / 39	5 / 16
HER2+ (n=86)	22 / 57	4 / 8	5 / 20	0 / 1

MP2, one of the 10 eligible signatures, did not meet the graduation threshold; and MP1/MP2 did not show a significant biomarker x treatment interaction (OR in neratinib relative to control arm = 1.25). The MP1/MP2 x treatment interaction remains non-significant after adjustment for HR and HER2 status (p=0.54). In HER2- patients receiving neratinib, 45% (15/33) of MP2 patients achieved a pCR, compared to 0% (0/17) of MP1 patients. In the HER2- controls, there is a 31% pCR rate in MP2 (5/16) vs. 18% in MP1 (7/39) patients (OR=2.14). This difference in performance between treatment arms appears

significant (p=0.041). 90% of HER2+ patients are MP1, thus MP1/MP2 status x treatment interaction within the HER2+ subtype cannot be evaluated.

Conclusion: Within the I-SPY 2 population as a whole, MP1/MP2 stratification does not appear to be a specific biomarker of response to neratinib relative to the control arm. The number of HER2- patients is small and precludes any definitive conclusion, but these data motivate further investigation of the biological mechanisms distinguishing MP1 from MP2 to better understand chemotherapy and/or neratanib responsiveness.