Title: MammaPrint High1/High2 risk class as a biomarker of response to veliparib/carboplatin plus standard neoadjuvant therapy for breast cancer in the I-SPY 2 TRIAL

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Body: 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. HER2- patients were randomized to receive standard chemotherapy or the oral PARP inhibitor veliparib in combination with carboplatin (V/C) and chemotherapy. V/C graduated in the triple-negative (TN) signature, where MP2 was not an eligible signature for graduation. Here, we assess the performance of MP1/MP2 class as a specific biomarker of response to V/C.

Methods: 115 HER2- patients (V/C: 71 and concurrent controls: 44) were considered in this analysis. We assess association between MP1/MP2 and response in the V/C 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. To assess MP1/MP2 in the context of the graduating signature, we added the MP2 patients to the graduating TN subset and evaluated the treatment effect in this 'biomarker-positive' group. 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). This analysis does not adjust for multiplicities of other biomarkers in the trial but outside this study.

Results: In the V/C arm vs. concurrent controls, there were 66 MP1 (V/C: 32, Control: 34) and 49 MP2 patients (V/C: 39, Control: 10), 78% of which are TN. The distribution of pCR rates among MP1/MP2 dichotomized groups are summarized in Table 1.

	V/C (n=71)		**Control** (n=44)	
	MP1 (n=32)	MP2 (n=39)	MP1 (n=34)	MP2 (n=10)
TN (n=59)	3 / 8	19 / 30	3 / 13	2 / 8
HR+HER2- (n=56)	1 / 24	4 / 9	4 / 21	0 / 2

The OR between MP1/MP2 risk groups for predicting pCR is 9.71 in the V/C arm (p=6.63E-05), in comparison to an OR of 0.97 in the control arm (p=1). There is a significant biomarker x treatment interaction (p=0.023), which remains upon adjusting for HR status (p= 0.028). Based on the I-SPY 2 Bayesian model, a Phase III trial with 300 MP2 patients has a 95% predictive probability of success.

When the MP2 patients are added to the graduating TN subset, the OR associated with V/C is 4.36, which is comparable to that of the TN signature (OR: 4.29), while increasing the prevalence of biomarker-positive patients by ~10%.

Conclusion: In our exploratory analysis, MP2 suggests higher sensitivity to V/C combination therapy relative to controls. This observation has prompted an investigation into the biological mechanisms distinguishing the MP1/MP2 subtype that may account for this specificity.