Title: Evaluation of an in vitro derived signature of olaparib response (PARPi-7) as a predictive biomarker of response to veliparib/carboplatin plus standard neoadjuvant therapy in high-risk breast cancer: results from the I-SPY 2 TRIAL

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Body: Background: We developed a 7-gene DNA-repair deficiency signature (PARPi-7) that predicts breast cancer cell line sensitivity to the PARP inhibitor olaparib [PMID: 22875744]. We hypothesized that this signature would also predict response to other PARP inhibitors including veliparib. In the I-SPY 2 TRIAL, 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. Here we assess the PARPi-7 as a specific biomarker of V/C response.

Methods: 115 HER2- patients (V/C: 71 and concurrent controls: 44) were considered in this analysis. The PARPi-7 signature score is computed from Agilent 44K array data as published using expression levels of BRCA1, CHEK2, MAPKAPK2, MRE11A, NBN, TDG, and XPA. We assess association between PARPi-7 and response in the V/C and control arms alone (Wald $p < 0.05$), and relative performance between arms (biomarker x treatment interaction, likelihood ratio $p < 0.05$) using a logistic model. In an exploratory analysis, we dichotomized patients by the PARPi-7 score using the published in vitro derived cutpoint (0.037). To assess PARPi-7 in the context of the graduating signature, we added the PARPi-7 High 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). Our analyses do not adjust for multiplicities of other biomarkers in the trial but outside this study. Results: The PARPi-7 signature associates with patient response in the V/C arm (OR = 3.9, p=0.00056) but not in the control arm (OR = 0.87, p=0.68). There is a significant biomarker x treatment interaction (OR in V/C arm relative to control arm = 4.48, p=0.0028), which remains significant upon adjusting for HR status (p=0.0018). In an exploratory analysis, PARPi-7 dichotomized using the published in vitro derived cutpoint yields 62 PARPi-7 Low and 53 PARPi-7 High patients. 26% of PARPi-7 High patients are not TN. The distribution of pCR rates among PARPi-7 dichotomized groups are in Table 1.

	V/C (n=71)		Control (n=44)	
	PARPi-7 Low (n=38)	PARPi-7 High (n=33)	PARPi-7 Low (n=24)	PARPi-7 High (n=20)
TN (n=59)	5 / 13	17 / 25	1 / 7	4 / 14
HR+HER2- (n=56)	2 / 25	3 / 8	4 / 17	0 / 6

When the PARPi-7 High patients are added to the graduating TN subset, the OR associated with V/C is 5.12, which is comparable to that of the TN signature (OR: 4.29), while increasing the prevalence of

biomarker-positive patients by ~12%. Evaluation of PARPi-7 in the context of the graduating signature under the I-SPY 2 Bayesian model is pending.

Conclusion: Our sample size is small. Our pre-specified analysis suggests the PARPi-7 signature shows promise for predicting response to veliparib/carboplatin combination therapy relative to control. If verified in a larger trial, this cell-line derived signature may contribute to the selection criteria of PARP inhibitor trials in the future.