Subject: Evaluation of a BRCAness signature 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

Abstract:

Background: We developed a 77-gene BRCAness gene expression signature that predicts 'BRCA1-like' (vs. 'Sporadic-like') breast cancers with a validated high sensitivity and specificity rate. The BRCAness signature was developed as part of the RATHER project (EU#258967). We hypothesized that BRCA1-like tumors would have a higher sensitivity to PARP inhibitors, including veliparib. In the I-SPY II TRIAL, HER2- patients were randomized to receive standard chemotherapy or the oral PARP inhibitor veliparib in combination with carboplatin and chemotherapy (V/C). V/C graduated in the triple-negative (TN) signature. Here we assess the BRCAness signature as a specific biomarker of V/C response.

Material and Methods: 113 HER2- patients (V/C: 71 and concurrent controls: 42) were considered in this analysis. The BRCAness classification is computed from Agilent full genome array data of the 77 signature genes using our validated Diagonal Linear Discriminant Analysis (DLDA) model. We assess association between BRCAness classification and response in the V/C and control arms alone (Fisher Exact test), and relative performance between arms (biomarker x treatment interaction, likelihood ratio test) using a logistic model. To assess the BRCAness signature in the context of the graduating signature, we added the BRCA-like patients to the graduating TN subset and evaluated the treatment effect in this new '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: Of the 113 patients assessed, 55 are classified as BRCA-like. 16% of BRCA-like patients are HR+HER2-. The distribution of pCR rates among BRCAness signature dichotomized groups stratified by HR status are in Table 1.

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<th>V/C (n=71)</th>
<th>Control (n=42)</th>
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<tbody>
<tr>
<td>TN (n=58)</td>
<td>4 / 6</td>
<td>2 / 6</td>
</tr>
<tr>
<td>HR+HER2- (n=55)</td>
<td>1 / 26</td>
<td>4 / 7</td>
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The BRCAness signature classification associates with patient response in the V/C arm (OR = 6.8, p=0.0005) but not in the control arm (OR = 0.77, p=1). There is a significant biomarker x treatment interaction (OR in V/C arm relative to control arm = 9.1, p=0.021), which remains significant upon adjusting for HR status (p=0.019).

When the BRCA1-like patients are added to the graduating TN subset, the OR associated with V/C is 4.7, which is comparable to that of the TN signature (OR: 4.1), while increasing the prevalence of biomarker-positive patients by ~8%. Evaluation of the BRCAness signature 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 BRCAness signature is associated with response to veliparib/carboplatin combination therapy relative to control. We will compare with results of other biomarker signatures developed to predict PARP inhibitor response. All I-SPY 2 qualifying biomarker signatures require validation in larger trials prior to consideration to assist in patient selection of future PARP inhibitor trials.

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