DNA repair deficiency biomarkers identify ER+ breast cancer patients who may benefit from veliparib/carboplatin: Results from the I-SPY 2 trial.

Laura van 't Veer, Laura Esserman, Ashish Sanil, Annuska Glas, Tessa Severson, Sabine C. Linn, Lamorna Brown Swigart, Gillian Hirst, I-SPY 2 Trial Investigators, Olufunmilayo I. Olopade, Hope S. Rugo, Don Berry, Denise M Wolf, Christina Yau; UC San Francisco, San Francisco, CA; Berry Consultants, LLC, Austin, TX; Agendia, Amsterdam, Netherlands; Netherlands Cancer Institute (NKI), Amsterdam, Netherlands; Antoni Van Leeuwenhoek Hospital, Amsterdam, Netherlands; QuantumLeap Healthcare Collaborative, San Francisco, CA; The University of Chicago Medical Center, Chicago, IL; UC San Francisco Helen Diller Family Comprehensive Cancer Center, San Francisco, CA

Abstract Text:

Background: In the I-SPY 2 TRIAL, HER2- patients were adaptively randomized to receive standard chemotherapy or the PARP inhibitor veliparib with carboplatin (V/C) and chemotherapy. V/C graduated in the triple-negative (TN) subtype, and we've previously shown that DNA repair deficiency signatures [BRCAness and PARPi-7] may predict V/C response. Here we combine these signatures into a composite measure of DNA repair deficiency. **Methods**: 115 HER2- patients (V/C: 71 and concurrent controls: 44) are considered in this analysis. BRCA1/2 germline mutation is assessed by Myriad Genetics. The PARPi-7 and BRCAness signature scores are computed from Agilent 44K array data. A patient is predicted DNA repair deficient if carrying a BRCA1/2 mutation or BRCA-like or PARPi7-high. We modify the I-SPY 2 Bayesian model to include DNA repair deficiency status to estimate the predictive probability of V/C demonstrating superiority to control in a 1:1 randomized phase 3 trial of 300 'biomarker-positive' patients. Our study is exploratory with no claims for generalizability and does not adjust for multiplicities of other biomarkers outside this study. **Results:** 15 patients are BRCA1/2 mutation carriers, of which 13 are PARPi7-high or BRCA-like. Comparing PARPi7 and BRCAness (62 PARPi7-low, 53 PARPi7-high; 59 non-BRCA1-like, 56 BRCA1-like) we find only moderate concordance (64%; kappa = 0.29). Altogether, 77 patients are predicted to be DNA repair deficient by one of these measures. 38% (21/56) of HR+/HER2- patients are predicted DNA repair deficient, along with nearly all (56/59) TN. In the V/C arm, 5/13 HR+/HER2- DNA repair deficient patients and 22/38 TN patients had a pCR (vs 0/8 and 5/21 controls respectively). When DNA repair deficient HR+/HER2- patients are added to the TN subset, the probability of phase 3 success is 94%, which is comparable to the graduating TN signature [97% in this model] while increasing patient prevalence. **Conclusions:** Our exploratory analysis suggests that 38% of HR+/HER2- patients in I-SPY 2 are DNA repair deficient and may benefit from V/C. If validated, DNA repair deficiency biomarkers may be used to select HR+/HER2- patients for future PARP inhibitor trials.