Analysis of DNA repair deficiency biomarkers as predictors of response to the PD1 inhibitor pembrolizumab: Results from the neoadjuvant I-SPY 2 TRIAL for Stage II-III high-risk breast cancer

[1]Christina Yau*, [1]Denise Wolf*, [1]Lamorna Brown-Swigart,[1]Gillian Hirst, [2]Ashish Sanil, [1]Ruby Singrao, I-SPY 2 TRIAL investigators, [3]Smita Asare, [4]Angie DeMichele, [2]Don Berry, [1]Laura Esserman, [1]Laura van 't Veer, [5]Rita Nanda, [6]Minetta Liu, [7]Doug Yee

[1]University of California, San Francisco; [2]Berry Consultants, LLC; [3]QuantumLeap Healthcare Collective; [4]University of Pennsylvania; [5]University of Chicago; [6]Mayo Clinic; [7]University of Minnesota.

Background

Pembrolizumab (P), an anti-PD-1 immune checkpoint inhibitor, has been approved for treatment of microsatellite instability-high and mismatch repair deficient cancers. In I-SPY 2, patients were randomized to receive standard chemotherapy alone or in combination with an experimental agent. P was one of the experimental agents evaluated in HER2- patients and graduated in the TN, HR+HER2-, and HER2- signatures. We hypothesize that a combination of two signatures predicting response to veliparib/carboplatin therapy in I-SPY 2 [MammaPrint High2 (MP2)/PARPi7-high] and reflecting DNA damage repair (DDR) deficiency, may also predict response to P. In addition, we also tested 9 gene expression signatures reflecting different aspects of DNA damage and repair: FA, MMR, BER, HR, TLS, NER, NHEJ, DR, and DNA damage sensing (DDS) pathways.

I-SPY 2 TRIAL

I-SPY 2: Phase 2 trial using response-adaptive randomization within biomarker subtypes to evaluate novel agents when added to standard neoadjuvant therapy for women with high-risk stage II/III breast cancer

Inclusion criteria: Tumor Size ≥ 2.5cm; MammaPrint high risk or HR-HER2- or HER2+

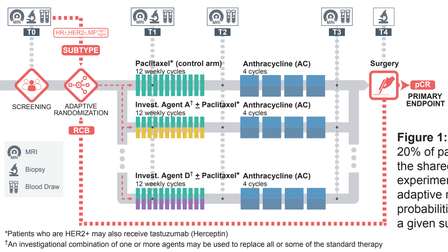
Primary Endpoint: Pathologic complete response (pCR)

Goal: To identify (graduate) regimens that have ≥ 85% predictive probability of success in a neoadjuvant 300-patient phase 3 trial of patients in 10 possible signatures defined by HR, HER2, and MammaPrint.

Pembrolizumab is one of ten experimental regimens evaluated to date

Table 1: Bayesian predictive probabilities of success of Pembrolizumab in Phase 3 testing within eligible signatures

Signature	Estimated pCR Rate (95% Probability Interval)		Probability Pembro Superior to Control	Predictive Probability of Success in Phase 3
	Pembro	Control		
HER2-	**0.44** (0.33 – 0.55)	**0.17** (0.11 – 0.23)	>0.999	**0.985**
HR-HER2-	**0.60** (0.44 – 0.75)	**0.22** (0.13 – 0.30)	>0.999	**0.996**
HR+HER2-	**0.30** (0.17 – 0.43)	**0.13** (0.07 – 0.19)	0.996	**0.834**



*Patients who are HER2+ may also receive tastuzumab (Herceptin)
†An investigational combination of one or more agents may be used to replace all or some of the standard therapy

Figure 1: I-SPY2 study schema. 20% of patients are randomized to the shared control arm. Among experimental arms (up to four), adaptive randomization is based on probabilities of achieving pCR within a given subtype for each agent.

Method

Data from 248 patients (P: 69; controls: 179) were available. Pre-treatment biopsies were assayed using Agilent gene expression arrays. All I-SPY 2 qualifying biomarker (QB) analyses follow a pre-specified analysis plan. We used logistic modeling to assess biomarker performance. A biomarker is considered a specific predictor of P response if it associates with response in the P arm but not the control arm, and if the biomarker x treatment interaction is significant (likelihood ratio test, p<0.05). This analysis is also performed adjusting for HR status as covariates, and within receptor subsets. For successful biomarkers, we use Bayesian modeling to estimate the pCR rates of 'predicted sensitive' patients in each arm. Our statistics are descriptive rather than inferential and do not adjust for multiplicities of other biomarkers outside this study.

MP2 and PARPi7

Association with Response

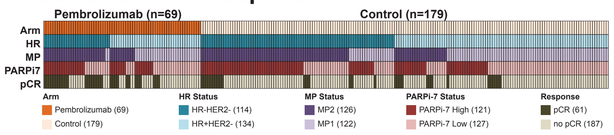
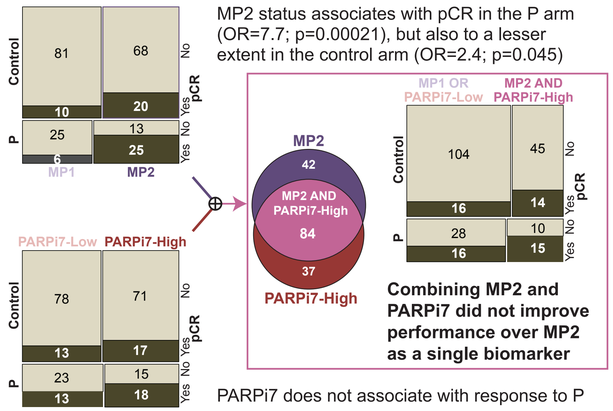


Figure 2: Ordered heatmap showing prevalence of MP2 and PARPi-7 High patients stratified by arm and HR status



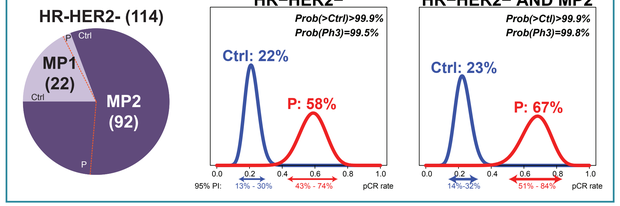
MP2 status associates with pCR in the P arm (OR=7.7; p=0.00021), but also to a lesser extent in the control arm (OR=2.4; p=0.045)

Combining MP2 and PARPi7 did not improve performance over MP2 as a single biomarker

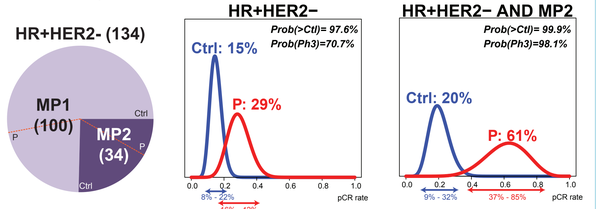
PARPi7 does not associate with response to P

MP2 in context of graduating signatures

81% of HR-HER2- patients are MP2; and TN/MP2 patients have an estimated pCR rate of 67% in the P arm.

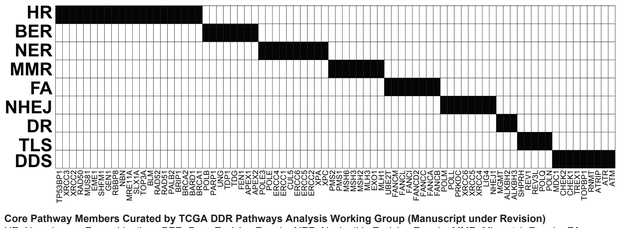


Although only ~30% of HR+HER2- patients were MP2, their estimated pCR rate in the P arm is 61%, compared to 29% in unselected HR+/HER2- patients.



DNA Repair Pathway Signatures

DDR Pathways Members

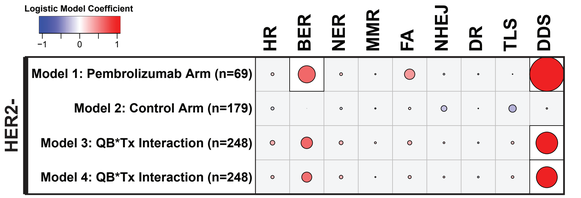


Core Pathway Members Curated by TCGA DDR Pathways Analysis Working Group (Manuscript under Revision)
HR: Homologous Recombination ; BER: Base Excision Repair ; NER: Nucleotide Excision Repair ; MMR: Mismatch Repair ; FA: Fanconi-Anemia ; NHEJ: Non-homologous End Joining ; DR: Direct Repair ; TLS: Translesion Synthesis; DDS: DNA Damage Sensing

DNA Repair Pathway Signatures

Association with Response

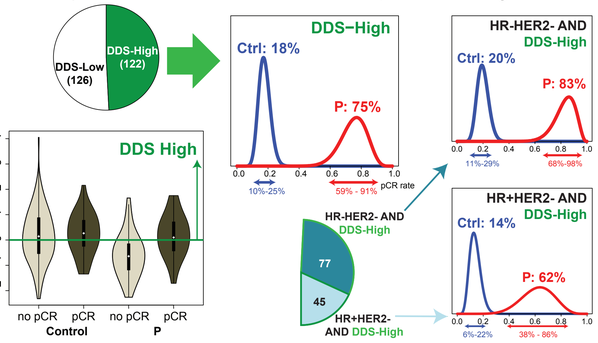
Of the 9 DDR pathway signatures tested, both BER and DDS associate with pCR in P, but only DDS associates with pCR in the P arm, and not the control arm, with a significant interaction with treatment that retains significance in a model adjusting for HR status.



Logistic Regression Models: Model 1: pCR ~ QB (in Tx Arm) ; Model 2: pCR ~ QB (in Control Arm) ; Model 3: pCR ~ QB + Tx + QB*Tx ; Model 4: pCR ~ QB + Tx + QB*Tx + HR

DDS in context of graduating signatures

When dichotomized to optimize the biomarker x treatment interaction, the estimated pCR rate is 75% in P vs 18% in control, in the DDS-High subset.



Conclusion

In this small study, MP2 status and a DNA damage sensing pathway but not the PARPi7 or other repair pathways show promise as predictive biomarkers for immune checkpoint inhibition therapy in breast cancer.