DNA repair deficiency biomarkers identify HR+/HER2- breast cancer patients who may benefit from veliparib/carboplatin: results from the I-SPY 2 TRIAL

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ASCO 2015 #521

Background

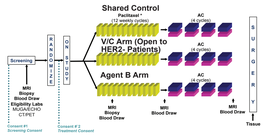
In I-SPY 2, HER2- patients were adaptively randomized to receive standard chemotherapy or the PARP inhibitor veliparib with carboplatin (V/C) and chemotherapy.

V/C graduated in the triple-negative (TN) subtype, and we have previously shown that DNA repair deficiency signatures [PARPi-7 and BRCAness] may predict V/C response.

Here we combine these signatures into a composite measure of DNA repair deficiency and investigate whether this measure can identify a subset of HR+/HER2- patients likely to respond to V/C.

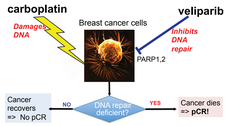
I-SPY 2 TRIAL

- Adaptive clinical trial for women with newly diagnosed, locally advanced breast cancer to enrich for pre-specified breast cancer subtypes defined by HR, HER2 and MammaPrint showing highest efficacy
- Inclusion: 'MammaPrint high risk' or 'MammaPrint low risk and HR- OR HER2+'
- Goal: To identify (graduate) regimens that have ≥ 85% predictive probability of success in a neoadjuvant 300-patient phase 3 trial of patients in 1 of 10 possible signatures defined by HR, HER2, and MammaPrint High1/2 risk status.
- I-SPY 2 Biomarker component: ***Designed to facilitate evaluation of novel biomarkers of response in conjunction with the pre-defined signatures***



V/C is one of 7 experimental arms in I-SPY 2

V/C was open to HER2- patients and graduated in the triple negative (TN) Signature!

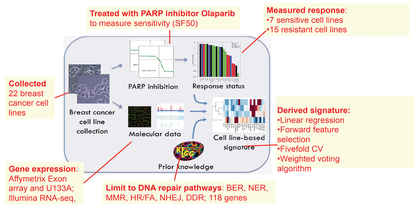


SIGNATURE	Estimated pCR Rate (90% probability interval) Veliparib/ Carbo	Concurrent Control	Probability Veliparib + Carbo is Superior to Control	Predictive Probability of Success in Phase 3
All HER2-	33% (22-43%)	22% (10-33%)	92%	55%
HR+/HER2-	14% (4-27%)	19% (8-36%)	28%	9%
HR-/HER2-	52% (35-68%)	26% (11-48%)	99%	90%

PARPi-7 and BRCAness signatures

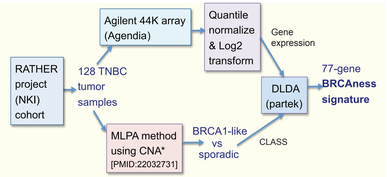
7 DNA-repair deficiency genes in the *PARPi-7 signature*

- **BRCA1, CHEK2, MAPKAPK2, MRE11A, NBN, TDG, and XPA**



77-gene *BRCAness expression signature*

-Originally derived from copy number aberration (CNA) differences between BRCA-mutated and sporadic TNBC

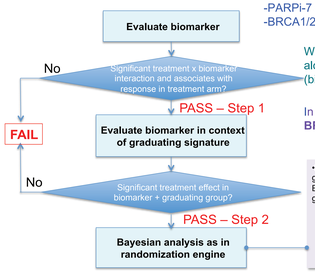


*Daemen A, Wolf D.M., Korkola J.E., Griffith O.L., Frankum J.R., Brough R, Jakkula L.R., Wang N.J., Natrajan R, Reis-Filho J.S., Lord C.J., Ashworth A, Spellman P.T., Gray J.W., van 't Veer L.J. Cross-platform pathway-based analysis identifies markers of response to the PARP inhibitor Olaparib. Breast Cancer Res Treat, 2012, August 9

*Lips EH, Laddach N, Savola SP, Vollebergh MA, Oonk AM, Imholz AL, Wessels LF, Wesseling J, Nederlof PM, Rodenhuis S. Quantitative copy number analysis by Multiplex Ligation-dependent Probe Amplification (MLPA) of BRCA1-associated breast cancer regions identifies BRCAness. Breast Cancer Res. 2011 Oct 27;13(5):R107

Materials and Methods

115 HER2- patients (V/C: 71 and concurrent controls: 44) were considered in this analysis.



-PARPi-7 and BRCAness signatures are computed from Agilent 44K array data.
-BRCA1/2 germline mutation is assessed by Myriad Genetics.

We assess association between a biomarker and response in the V/C and control arms alone (Fisher $p < 0.05$), and relative performance between arms (biomarker x treatment interaction, likelihood ratio $p < 0.05$) using a logistic model.

In an exploratory analysis, **a patient is classified as DNA repair deficient if carrying a BRCA1/2 mutation or BRCA-like or PARPi7-high.**

•For the Biomarker+ OR graduating group and the Biomarker AND within graduating group
•Estimate pCR probability in treatment and control arms
•Estimate predictive probability of success in 300 patient Phase III trial

To assess composite DNA repair deficiency in the context of the graduating signature, we added the 'repair deficient' HR+/Her2-patients to the graduating TN subset and evaluated the treatment effect in this 'biomarker-positive' group.

These analyses are exploratory and do not adjust for multiplicities of other biomarkers in the trial.

DNA repair deficient by one or more measures

Association with response (p<0.05)

Biomarker	V/C Arm	Control	Interaction (biomarker x treatment)	Interaction Adjusting for Subtype
BRCA1/2 Mutation	YES	--	--	--
PARPi-7	YES	NO	YES	YES
BRCAness	YES	NO	YES	YES

Since both BRCAness and PARPi-7 reflect defective DNA repair mechanisms and succeed as specific predictors of V/C combination therapy in I-SPY 2 *we wondered:*

Are these signatures identifying the same patients?

Biomarker Concordance

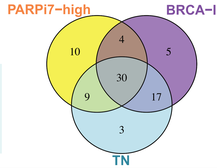
BRCA1/2 Mutation
- Variance of unknown signifcance
- No mutation/Favor polymorphism
- Deleterious or Suspected Deleterious mutation
- NA

PARPi-7
- Low
- High

BRCA-like
- No
- Yes

Comparing PARPi7 and BRCAness (62 PARPi7-low, 53 PARPi7-high; 59 non-BRCA-like, 56 BRCA-like) we find *only moderate concordance* (64%; kappa=0.29).

15 patients are BRCA1/2 mutation carriers, of which 13 are PARPi7-high or BRCA-like.



Altogether, 77 patients are predicted to be **DNA repair deficient** by one of these measures (BRCA mutation+ or **PARPi7-high** or **BRCA-like**).

38% (21/56) of HR+/HER2- patients are predicted DNA repair deficient, along with nearly all (56/59) TN.

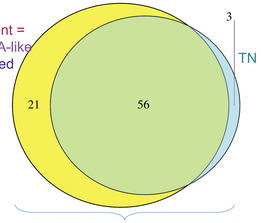
'DNA Repair Deficiency' within HR+/Her2- and in the Context of the Graduating TN Subset

Distribution of pCR rates among dichotomized groups stratified by HR status

	V/C (n=71)		Control (n=44)	
	DNA repair deficient* Low (n=21)	DNA repair deficient High (n=50)	DNA repair deficient Low (n=17)	DNA repair deficient High (n=27)
TN (n=59)	1 / 1	21 / 37 (57%)	0 / 2	5 / 19 (26%)
HR+HER2- (n=56)	**0 / 20 (0%)**	**5 / 13 (38%)**	4 / 15 (27%)	**0 / 8 (0%)**

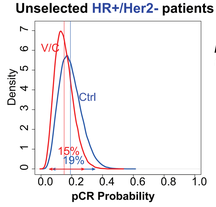
In the V/C arm, 5/13 HR+/HER2- DNA repair deficient patients and 22/38 TN patients had a pCR (vs 0/8 and 5/21 controls respectively).

* DNA repair deficient = PARPi7-high or BRCA-like or BRCA1/2 mutated



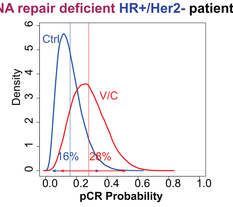
Bayesian Estimates of pCR Rates Within Patient Groups

Unselected HR+/Her2- patients



***Refine** HR+/Her2-subset to enrich for DNA repair deficiency*

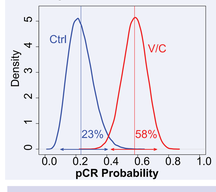
DNA repair deficient HR+/Her2- patients



TN OR (PARPi7-high or BRCA-like or BRCA1/2 mutated)

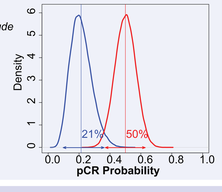
	Prob V/C superior to control	Predictive Prob Phase 3 Success (300 pt)
HR+/Her2-	0.3	0.11
HR+/Her2-/DNA repair deficient	0.8	0.59
TN	1.0	0.97
TN OR DNA repair deficient	1.0	0.95

TN patients in this model



***Expand** population of 'likely respoders' to include DNA repair deficient HR+/Her2- patients*

TN plus DNA repair deficient HR+/Her2- patients



When the **HR+/Her2-** patients who are **PARPi7-high**, **BRCA-like** or **BRCA1/2 mutation** carriers are added to the graduating **TN** subset, the probability of V/C phase 3 success is 95%, which is comparable to the TN signature (97%), while increasing the prevalence of biomarker-positive patients by 18%

[adds *38% of HR+/Her2-* in the V/C and concurrent control arms of I-SPY2].

Conclusion

Here, HR+/Her2- tumors are identified as DNA repair deficient if carrying a BRCA1/2 mutation or BRCA-like or PARPi7-high.

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 merit further investigation for selecting HR+/HER2- patients for future early phase PARP inhibitor trials.