Abstract # 1018 . For additional information, please contact Dr. Melinda Telli at mtelli@stanford.edu

Combined Homologous Recombination Deficiency (HRD) Scores and Response to Neoadjuvant Platinum-Based Chemotherapy in Triple Negative and/or *BRCA1/2* Mutation-Associated Breast Cancer

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BACKGROUND

- Genomic instability and a high frequency of *BRCA1* and *BRCA2* germline mutations are commonly associated with serous ovarian cancer and triple negative breast cancer (TNBC). Breast cancer that arises in *BRCA1/2* mutation carriers is characterized by homologous recombination deficiency (HRD).
- Recently, three independent DNA-based measures of genomic instability have been developed based on loss of heterozygosity (LOH) [1], telomeric allelic imbalance (TAI) [2], and large-scale state transitions (LST) [3].
- These measures have been shown to be associated with an increased likelihood of response to platinum containing regimens in TNBC or ovarian cancer.
- The HRD-LOH score is significantly associated with favorable response to neoadjuvant platinum-based therapy in PrECOG 0105 [4].
- We set out here to assess the combined HRD score, an unweighted sum of LOH, TAI, and LST scores in PrECOG 0105. In combination, previous studies have shown that these measures are a more robust predictor of HR deficiency than the individual components [5].

METHODS

HRD Score

- The HRD assay is a next generation sequencing assay performed using DNA extracted from formalin fixed paraffin-embedded or frozen tumor tissue [5].
- The ***HRD score*** is the unweighted sum of LOH (number of LOH regions >15 Mb but less than the length of a whole chromosome) + TAI (regions of allelic imbalance that extend to the subtelomere but do not cross the centromere) + LST (breakpoints between regions of imbalance >10Mb after filtering out regions <3 Mb).
- Variant and large rearrangement detection was performed on sequence from *BRCA1* and *BRCA2* [5].
- ***Homologous Recombination (HR) deficiency status***, either HR deficient or HR non-deficient, combines the HRD score with *BRCA1/2* mutation status. HR deficiency corresponds to a HRD score equal to or above a predefined threshold and/or a mutation in *BRCA1/2*.

Training Set to Establish HRD Threshold

- A training set was assembled using four publicly available or previously published cohorts (497 breast and 561 ovarian cases) [5-8] that included 78 breast and 190 ovarian tumors lacking a functional copy of either *BRCA1* or *BRCA2* (ie. *BRCA1/2* deficient) based on mutation and methylation data.
- These tumors had either (a) one deleterious mutation in *BRCA1* or *BRCA2* or promoter methylation of *BRCA1* with LOH at the affected gene or (b) two deleterious mutations in the same gene.
- This cohort was used to define a threshold for the HRD score intended to reflect HR deficiency versus HR intact status. The threshold selected was the 5th percentile of HRD scores in *BRCA1/2* deficient tumors.

Patient Samples and Clinical Data

- The PrECOG 0105 trial enrolled 93 patients with either triple negative or a *BRCA1/2* germline mutation-associated breast cancer. These patients were treated neoadjuvantly with either 4 or 6 cycles of a combination of carboplatin, gemcitabine, and iniparib [4].
- Pathologic response was assessed using the residual cancer burden (RCB) index [9] and two dichotomous measures of tumor response were used. Favorable pathologic response was defined as RCB 0/1. ***Pathologic complete response (pCR)*** was defined as RCB score of 0 [9].

RESULTS

- The 5th percentile of HRD scores in the combined breast and ovarian training set was 42 and high HRD was defined as scores ≥42 (Figure 1).
- In the PrECOG 0105 cohort, 68 samples had passing HRD scores (sufficient noise to signal ratio) and *BRCA1/2* mutation data.
- RCB 0/1 and pCR for these 68 patients is shown by *BRCA1/2* mutation status in Table 1.

Figure 1. *HRD score distribution in the training set.*

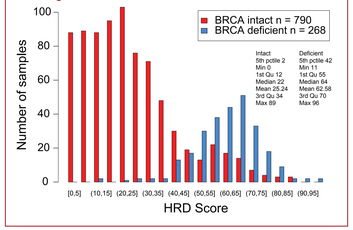
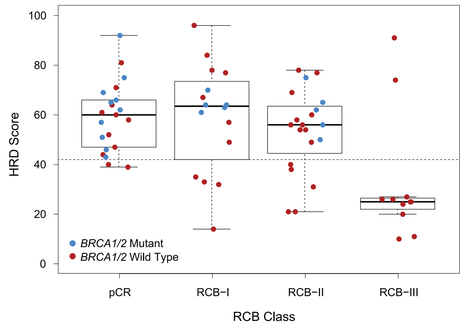


Table 1. BRCA1/2 mutation status and association with response (N=68)

Responder	Mutant Number (% response)	Non-Mutant Number (% response)	Odds Ratio (95% CI) Reference = Non-Mutant	Logistic p-value
RCB 0/1 = no	5	26		
RCB 0/1 = yes	15 (75.0%)	22 (45.8%)	3.55 (1.11, 1.3)	0.025
pCR = no	10	37		
pCR = yes	10 (50.0%)	11 (22.9%)	3.36 (1.11, 10.2)	0.031

- HRD score was analyzed as both a continuous and dichotomous (high vs. low) variable (Table 2, Figure 2).
- The continuous HRD score was significantly associated with RCB 0/1 (p = 0.0080), but not pCR (p = 0.10).
- The dichotomous HRD score was significantly associated with both RCB 0/1 (p = 0.0086) and pCR (p = 0.010).

Figure 2. *Box plot of HRD score vs. RCB class. Box outlines the 25th and 75th percentiles; solid line is the median.*



Note: 28/48 (58%) *BRCA1/2* wild type patients had high HRD scores

Table 2. Association of HRD score, HR deficiency and response.

Quantitative HRD Score (N=68)				
Responder	N	Mean (SD)	Odds Ratio per IQR* (95% CI)	Logistic p-value
RCB 0/1 = no	31	46.1 (22.3)		
RCB 0/1 = yes	37	59.1 (17.4)	2.50 (1.22, 5.14)	0.0080
pCR = no	47	50.5 (22.7)		
pCR = yes	21	59.2 (13.9)	1.82 (0.87, 3.82)	0.10
HRD Score: High vs. Low (N=68)				
Responder	HRD High Number (% response)	HRD Low Number (% response)	Odds ratio (95% CI) Reference = low HRD score	Logistic p-value
RCB 0/1 = no	17	14		
RCB 0/1 = yes	31 (64.6%)	6 (30.0%)	4.25 (1.38, 13.1)	0.0086
pCR = no	29	18		
pCR = yes	19 (39.6%)	2 (10.0%)	5.90 (1.23, 28.4)	0.010
HR Deficiency Status (N=72)**				
Responder	Deficient Number (% response)	Non-Deficient Number (% response)	Odds ratio (95% CI) Reference = low HRD score	Logistic p-value
RCB 0/1 = no	17	15		
RCB 0/1 = yes	34 (66.7%)	6 (28.6%)	5.00 (1.65, 15.2)	0.0029
pCR = no	30	19		
pCR = yes	21 (41.2%)	2 (9.5%)	6.65 (1.40, 31.6)	0.0050

* IQR = 27.5
**4 additional patients were determined to be HR deficient based on HRD score (2) or *BRCA1/2* mutation status (2) only.

- HR deficiency was significantly associated with both RCB 0/1 and pCR (OR = 5.00 [1.65, 15.2], p = 0.0029; OR = 6.65 [1.40, 31.6], p = 0.0050), and identified responders lacking a deleterious *BRCA1/2* mutation (Table 2).
- *BRCA1/2* mutation status provides the highest positive predictive value (PPV) of both RCB 0/1 and pCR in this cohort, while its negative predictive value (NPV) is lower compared to HRD score or HR deficiency status (Figure 3). These differences were not statistically significant.
- When the analysis was confined to tumors with intact *BRCA1/2*, HR deficiency was no longer significantly associated with RCB 0/1 or pCR; however power to detect this association was limited.

Figure 3. *Relative response rates for (A) RCB 0/1 and (B) pCR stratified by HRD score, BRCA1/2 mutation status, or HR deficiency status. ND: Non-deficient; D: Deficient; WT: Wild Type.*

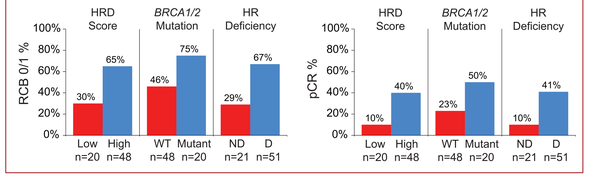


Table 3. Multivariate models of RCB 0/1 and pCR (N=71**)

		RCB 0/1			pCR		
	Number of patients (%)	% RCB 0/1	Odds ratio (95% CI)	p-value	% pCR	Odds ratio (95% CI)	p-value
HR deficiency status							
Non-Deficient	21 (30%)	29	*Reference*	0.0075	10		0.077
Deficient	50 (70%)	68	6.33 (1.46, 27.4)		42	4.39 (0.73, 26.4)	
Grade							
II	17 (24%)	53	*Reference*	0.55	12		0.058
III	54 (76%)	57	0.66 (0.17, 2.59)		39	4.53 (0.82, 25.1)	
Stage*							
I	9 (13%)	89	*Reference*	0.0036	44		0.28
II	52 (73%)	56	0.04 (0.00, 0.54)		33	0.25 (0.04, 1.51)	
III	10 (14%)	30	0.02 (0.00, 0.33)		20	0.20 (0.02, 2.19)	
Chemotherapy							
4 cycles	11 (15%)	55	*Reference*	0.90	18		0.15
6 cycles	60 (85%)	57	0.90 (0.18, 4.51)		35	3.46 (0.57, 21.1)	
Age at diagnosis (yrs)**							
			OR per IQR = 14 0.50 (0.22, 1.12)	0.081		OR per IQR = 14 0.47 (0.19, 1.14)	0.083

*Non-significant interaction between HR deficiency status and stage (full model p-value is 0.45 for RCB 0/1; 0.73 for pCR.)
**Missing one observation of age

- HR deficiency remained a significant predictor of RCB 0/1 when the score was adjusted by clinical variables including grade, stage, cycles of chemotherapy, and age at diagnosis (p = 0.0075) (Table 3).

CONCLUSIONS

- In this study, HRD status provides significant improvement over clinical variables, or *BRCA1/2* status, in identifying tumors with an increased likelihood of response to platinum-based neoadjuvant therapy among patients with TNBC.
- Clinical use of the HRD test has the potential to identify TNBC patients likely to respond to DNA damaging therapy beyond those currently identified by germline *BRCA1/2* mutation screening. Prospective evaluation is warranted.

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