Homologous Recombination Deficiency (HRD) Score Predicts Response to Cisplatin Neoadjuvant Chemotherapy in Patients with Triple Negative Breast Cancer

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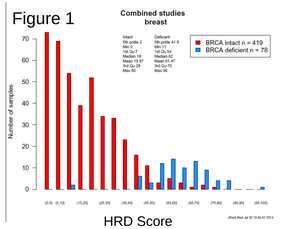
BACKGROUND

• Triple negative breast cancers (TNBC) share many characteristics with BRCA1-associated cancers including a high burden of genomic aberrations. *BRCA1* or *BRCA2* (*BRCA1/2*) mutated cancers have defects in DNA repair including homologous recombination deficiency (HRD) and have increased sensitivity to platinum salts[1].
• Two neoadjuvant clinical trials demonstrated that a subset of sporadic, non-*BRCA1/2* mutated TNBC are also sensitive to platinum[2,3]. Further, several recent multicenter trials have shown improvement in pathologic response with the addition of platinum to standard of care regimens for TNBC but with increased toxicities[4,5].
• Three summary metrics of DNA aberrations were recently described. NTAI (number of telomeric allelic imbalances) was shown to be associated with response to cisplatin in TNBC[6]. LOH (oss of heterozygosity) and LST (long segment transitions) were independently identified as associated with *BRCA1/2* mutation or methylation[7,8].
•HRD score = LOH + TAI + LST
• The HRD score was evaluated in an independent cohort of 1058 breast and ovarian cancers of which 268 were BRCA1/2 mutated or BRCA1 methylated. A threshold of 42 was defined based on the 5th percentile of HRD scores in the tumors with *BRCA1/2* mutation or methylation. The distribution of the HRD score in the breast cancers is shown in Figure 1.
• HR deficiency is defined as HRD score ≥42 *or BRCA1/2* mutant.

Figure 1



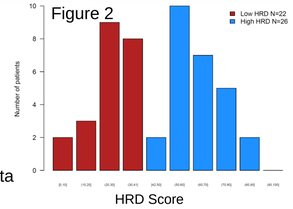
METHODS

• Archival formalin-fixed paraffin embedded core biopsy tumor samples were obtained from 70 patients with TNBC from 2 neoadjuvant cisplatin clinical trials conducted at DFHCC[2,3] .
• Five to ten 5-micron tissue sections were sent to Myriad Genetic Laboratories. Eight samples had insufficient tumor tissue and were not processed. DNA was extracted from 62 samples and was analyzed using the HRD and BRCA1/2 sequencing assay. The distribution of HRD scores observed in this cohort is shown in Figure 2.
• Pathologic response was categorized by the residual cancer burden (RCB) class[9] with pathologic partial response (pPR) defined as RCB 0 or I and pathologic complete response (pCR) as RCB 0.
• Logistic regression was used to assess HR deficiency as a predictor of response to therapy. All analysis was conducted according to a pre-specified statistical analysis plan. Standard maximum likelihood was used to test models of pPR, while Firth's penalized likelihood was used to test pCR.All clinical and molecular data was blinded until after finalization of the HRD and HR deficiency determination.

RESULTS

- 62/70 with adequate FFPE tumor tissue
- 51/62 (82%) passed HRD testing
- 53/62 (85%) passed BRCA1/2 testing
- HRD score = LOH + TAI + LST
- HR Deficient = HRD ≥ 42 or BRCA1/2 mutated
  - 31/62 (50%) HR deficient
  - 22/62 (35%) HR proficient
  - 9/62 (15%) HR undetermined
- 50/62 (80%) with both HR deficiency status and response data

Figure 2

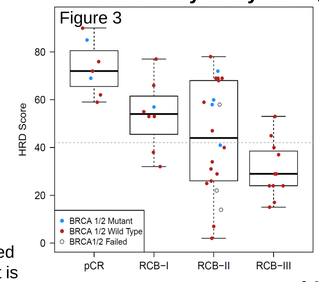


Primary analysis: HR deficiency status and response (n=50).

Responder	Deficient Number (% response)	Proficient Number (% response)	Odds ratio (95% CI)	Logistic p-value
pPR = no	14	19	*Reference: proficient*	
pPR = yes	15 (52%)	2 (9.5%)	10.18 (2.00, 51.89)	0.0011
pCR = no	21	21	*Reference: proficient*	
pCR = yes	8 (28%)	0 (0%)	17.00 (1.91, 2249)	0.0066

Secondary analyses: Quantitative HRD score and response (n=48)

Figure 3



Responder	N	Mean (s.d.)	Odds ratio* (95% CI)	Logistic p-value
pPR = no	33	39.8 (20.8)		
pPR = yes	15	62.9 (16.1)	10.5 (2.3, 48.6)	3.1×10^{-4}
pCR = no	41	42.6 (20.3)		
pCR = yes	7	73.3 (11.4)	117 (2.9, 4764)	7.0×10^{-5}

*Odds ratio per IQR

Multivariate model of pPR: (n=50)

Variable	Levels	Number of patients (%)	Odds ratio* (95% CI)	Logistic p-value
HR status	Proficient	21 (42%)	*Reference*	
	Deficient	29 (58%)	12.08 (1.96, 74.4)	0.0017
Treatment	Cisplatin	18 (36%)	*Reference*	
	Cisplatin+bevacizumab	32 (64%)	2.23 (0.52, 9.64)	0.27
Tumor size* (cm)	Mean = 3.7 IQR = (2.7, 4.0)		1.40 (0.84, 2.35)	0.19
Baseline nodal status	Negative	27 (54%)	*Reference*	
	Positive	23 (46%)	2.29 (0.56, 9.33)	0.24
Age at diagnosis* (years)	Mean = 49.8 IQR = (43.0, 56.8)		0.97 (0.90, 1.05)	0.49

*Odds ratio per IQR

BRCA1/2 mutation (N=45; 6 mBRCA1, 1 mBRCA2) :

- mean HRD score was significantly higher in BRCA1/2 mutated (germline or somatic) compared to non-mutated tumors (63.1 vs. 45.3; p-value = 0.015).
- BRCA1/2 mutated compared to non- mutated tumors was *not* significantly associated with pPR rate (42.9% vs 31.6%; p = 0.57) or pCR rate (28.6% vs 13.2%; p-value = 0.33)

BRCA1/2 wild-type subset: HRD score and response (n=38)

Responder	HRD ≥ 42 Number (% response)	HRD < 42 Number (% response)	Odds ratio (95% CI)	Logistic p-value
pPR = no	9	17	*Reference: Proficient*	
pPR = yes	10 (52.6%)	2 (10.5%)	9.44 (1.69, 52.7)	0.0039
pCR = no	14	19	*Reference: Proficient*	
pCR = yes	5 (26.3%)	0 (0%)	14.79 (1.49, 2001)	0.018

CONCLUSIONS

- The HRD assay can be successfully performed in FFPE breast core biopsy samples
- The HRD score can be used as a tool to identify patients with breast tumors with underlying HR deficiency, including in BRCA1/2 non-mutated tumors.
- HR deficiency defined by high HRD score (≥ 42) or BRCA1 or BRCA2 mutation can identify a subgroup of TNBC that are significantly more responsive to cisplatin.
- HRD score (with the predefined threshold) was significant at predicting cisplatin response whereas neither BRCA mutation nor clinical variables were significant predictors.
- Ongoing trials are prospectively evaluating the ability of HRD score to predict response to platinum versus taxane chemotherapy in TNBC (NCT01982448)

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* ALR, DPS, ZS, NJB and ZCW are inventors on a patent for a component of the HRD assay that is licensed to Myriad Genetic Laboratories Inc.

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