Homologous Recombination Deficiency (HRD) as a predictive biomarker of response to neoadjuvant platinum-based therapy in patients with triple-negative breast cancer (TNBC): A pooled analysis

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Background and Rationale

- Genomic instability and a high frequency of *BRCA1* and *BRCA2* germline mutations are commonly associated with triple-negative breast cancer (TNBC).
- TNBC patients with homologous recombination (HR) deficient tumors have significantly higher pathologic complete response (pCR, ypT0/is ypN0) rates when treated with platinum-based chemotherapy regimens than TNBC patients whose tumors are HR non-deficient.
- We performed a pooled analysis of 6 phase II studies that included patients with TNBC treated with neoadjuvant platinum-based chemotherapy to better estimate the pCR rates amongst HR deficient and HR non-deficient tumors.

Study Design

A total of 267 patients with TNBC and known HR deficiency status from the following neoadjuvant clinical trials were available for analysis:

Trial	N	Weeks of Therapy	Neoadjuvant Regimen
Gepar Sixto[1]	101	18	Paclitaxel, non-pegylated liposomal doxorubicin, carboplatin and bevacizumab
PrECOG 0105[2]	72	12-18	Carboplatin, gemcitabine, and iniparib
NCT00580333[3]	32	12	Cisplatin with bevacizumab
NCT01372579[4]	26	12	Carboplatin and eribulin
NCT00148694[5]	18	12	Cisplatin
TBCRC 008[6]	18	12	Carboplatin, nab-paclitaxel, with or without vorinostat

HRD status was assessed on pre-treatment breast biopsy samples. Pathological complete response defined as no invasive disease in the breast/axilla with residual in situ disease allowed = ypT0/is ypN0.

Primary Analysis:

- Correlation of pCR and HR deficiency status

Secondary Analyses:

- Correlation of pCR and binary HRD score (<42 versus ≥ 42)
- Correlation of pCR and HR deficiency in the *BRCA1/2* negative subgroup

Cases with missing HR deficiency status were excluded. Logistic regression models were used to adjust for study effects. Analyses were adjusted for patient age at diagnosis, clinical stage, duration of planned neoadjuvant therapy and trial.

Determination of HRD Status

- The HRD assay is a next generation sequencing assay performed using DNA extracted from formalin fixed paraffin-embedded or frozen tumor tissue.
- 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).[7]
- Variant and large rearrangement detection was performed on sequence from *BRCA1* and *BRCA2*.
- 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 42 and/or a mutation in *BRCA1/2*.[7]

Results

Patient Characteristics

Variable	Level	All Patients n (%)	HR Deficient n (%)	HR Non-Deficient n (%)	*BRCA* Neg & HRD High n (%)
		267 (100%)	**178 (66.6%)**	**89 (33.3%)**	**106 (39.7%)**
Clinical Stage	I	29 (11.0%)	22 (12.6%)	7 (7.9%)	9 (8.7%)
	II	201 (76.1%)	134 (76.6%)	67 (75.3%)	86 (83.5%)
	III	34 (12.9%)	19 (10.9%)	15 (16.9%)	8 (7.8%)
Intended Therapy Duration	12 weeks	105 (39.3%)	60 (33.7%)	45 (50.6%)	42 (39.6%)
	18 weeks	162 (60.7%)	118 (66.3%)	44 (49.4%)	64 (60.4%)
pCR	No	157 (58.8%)	84 (47.2%)	73 (82.0%)	53 (50.0%)
	Yes	110 (41.2%)	94 (52.8%)	16 (18.0%)	53 (50.0%)
***BRCA* Mutation**	No	192 (73.2%)	106 (60.2%)	86 (100%)	106 (100%)
	Yes	70 (26.7%)	70 (39.8%)	0 (0%)	0 (0%)
Variable	**Level**	**All Patients**	**HR Deficient**	**HR Non-Deficient**	***BRCA* Neg & HRD High**
		Mean (range)	**Mean (range)**	**Mean (range)**	**Mean (range)**
Age	Years	48.8 (23-78)	46.5 (23-73)	53.4 (24-78)	48.3 (28-73)

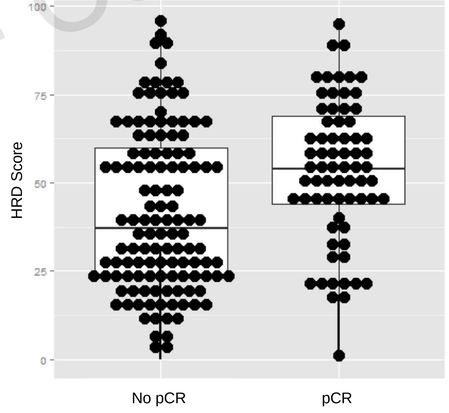

Figure 1. HRD score by pCR status in *BRCA1/2* mutation negative subset

- Patients lacking *BRCA1* or *BRCA2* mutations with higher HRD scores were more likely to achieve a pCR

p = 0.0005

HR deficiency and response

Variable	Category	Unadjusted OR	Adjusted OR	95% CI	P value
HR deficiency status	Non-deficient (ref)	1.0	1.0		<0.0001
	Deficient	5.11	4.64	2.32-9.27	
Age	Increment of 10 years		0.81	0.62-1.06	0.109
Intended Therapy Duration	12 weeks (ref)		1.0		0.291
	18 weeks		2.38	0.42-13.47	
Clinical Stage	I (ref)		1.0		0.118
	II		0.41	0.16-1.09	
	III		0.31	0.09-1.08	
Trial	Gepar Sixto (ref)		1.0		0.002
	Others		0.37-2.38		

- **In this primary analysis, HR deficiency status was associated with an improved odds of pCR.**
- **Adjusted OR = 4.64; p<0.0001**

HR deficiency in *BRCA* negative and response

Variable	Category	Unadjusted OR	Adjusted OR	95% CI	P value
HR Deficiency Status	Non-deficient (ref)	1.0	1.0		<0.0001
	Deficient	4.37	4.55	2.12-9.74	
Age	Increment of 10 years		0.75	0.54-1.05	0.084
Intended Therapy Duration	12 weeks (ref)		1.0		0.316
	18 weeks		2.96	0.24-10.07	
Clinical Stage	I (ref)		1.0		0.600
	II		0.55	0.11-1.33	
	III		0.70	0.13-3.47	
Trial	Gepar Sixto (ref)		1.0		0.004
	Others		0.30 – 4.78		

Binary HRD score and response

Variable	Category	Unadjusted OR	Adjusted OR	95% CI	P value
Binary HRD Score	Low (ref)	1.0	1.0		<0.0001
	High	5.11	4.44	2.25-8.75	
Age	Increment of 10 years		0.80	0.61-1.05	0.109
Intended Therapy Duration	12 weeks (ref)		1.0		0.291
	18 weeks		2.42	0.43-13.73	
Clinical Stage	I (ref)		1.0		0.118
	II		0.39	0.15-1.02	
	III		0.36	0.10-1.28	
Trial	Gepar Sixto (ref)		1.0		0.002
	Others		0.34-2.46		

Conclusions

- In this pooled analysis of 6 phase II trials of platinum-based neoadjuvant chemotherapy, **HR deficiency status was significantly associated with an improved odds of pCR** among those with and without a *BRCA1/2* mutation.
  - Adjusted OR for pCR in HR deficient = 4.64; p<0.0001
  - Adjusted OR for pCR in HR deficient & no *BRCA1/2* mutation = 4.55; p<0.0001
  - Overall, 67% of cases were HR deficient
  - Associations between response and stage, age and planned duration of therapy were not significant
  - Trial was correlated with response
- The neoadjuvant chemotherapy regimens included were heterogeneous (non-anthracycline/non-taxane, taxane-based or anthracycline and taxane-based) and the number of cytotoxic chemotherapies varied (1-3) as did the use of other other investigational therapies (bevacizumab, iniparib, vorinostat).

References

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