HOMOLOGOUS RECOMBINATION DEFICIENCY (HRD) AS A PREDICTIVE BIOMARKER OF RESPONSE TO PREOPERATIVE SYSTEMIC THERAPY (PST) IN TBCRC008 COMPRISING A PLATINUM IN HER2-NEGATIVE PRIMARY OPERABLE BREAST CANCER

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BACKGROUND

- Platinum-based chemotherapy regimens are associated with high rates of tumor response in some patients with breast cancer.[1,2]
- Platinum-sensitivity may relate to underlying defects in DNA double-strand break repair in select populations such as BRCA-associated breast cancer and subtypes of triple-negative breast cancer (TNBC).
- Biomarkers to predict response to platinum-based therapy in early breast cancer are needed.
- Homologous recombination deficiency (HRD) is a promising predictor of response to DNA damaging agents, such as platinums.[3-5]
- HRD has been investigated to date in BRCA-associated breast cancer and TNBC, but not in hormone receptor-positive breast cancer.
- TBCRC008 was a multicenter placebo-controlled trial that compared pathologic complete response (pCR, no invasive cancer in breast/axilla) following 12 weeks of preoperative carboplatin and albumin-bound paclitaxel (CP) with or without vorinostat in 62 patients with HER2-negative breast cancer (hormone receptor-positive or TNBC).[6]
- Eighteen patients received additional pre-operative treatment with doxorubicin and cyclophosphamide (AC) due to incomplete response or physician preference.
- Patients were stratified by estrogen receptor (ER) status.
- The pCR rate was similar in both arms (vorinostat 25.8%, placebo 29%).
- We performed an exploratory biomarker study correlating baseline tumor biopsy HRD status with pCR in the overall study population and in hormone receptor-positive and TNBC subgroups.

HYPOTHESIS

- We hypothesized that HRD (high HRD score ≥ 42 and/or tumor BRCA mutation) would predict pCR in patients with HER2-negative early breast cancer treated with preoperative therapy comprising a platinum, regardless of ER status.

OBJECTIVES

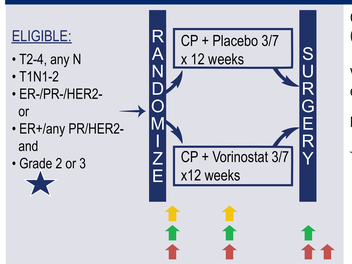
Primary

- Association of baseline HRD with pCR in patients with HER2-negative breast cancer treated with preoperative CP with or without vorinostat (overall population)
- Association of baseline HRD with pCR in patients with hormone-receptor positive, HER2-negative breast cancer treated with preoperative CP with or without vorinostat

Secondary

- Association of baseline HRD with pCR in patients with TNBC treated with preoperative CP with or without vorinostat
- Association of baseline high HRD score (≥42) with pCR in patients without a tumor BRCA (tBRCA) mutation treated with preoperative CP with or without vorinostat among those (overall population, hormone-receptor positive, and TNBC)
- Effect of vorinostat and other clinical variables on the association of HR deficiency and pCR
- Describe HRD scores in patients with hormone-receptor positive breast cancer compared to TNBC (overall population, those with and without tBRCA, and those with and without pCR)

STUDY SCHEMA



CP, Carboplatin (AUC2) and nab-Paclitaxel (100 mg/m^2), weekly x 12 weeks

Vorinostat /Placebo 400 mg PO, 3 days every 7 days x 12 weeks

N = 62 (31 participants per arm)

★ Baseline HRD score/ tumor BRCA determination

⬆ PET
⬆ Tumor biopsy
⬆ Blood sampling

METHODS

Definitions

- **HRD score:** sum of LOH score (number of LOH regions longer than 15 Mb but shorter than the length of a whole chromosome), TAI score (number of telomeric regions imbalance which extend to the subtelomere but do not cross the centromere) and LST score (number of chromosomal breaks between adjacent regions longer than 10 Mb after filtering out regions shorter than 3 Mb)
- **HRD score ranges from 0-100**
- **High HRD score:** ≥42
- **BRCA mutation:** deleterious or suspected deleterious mutation of *BRCA1* or *BRCA2* in the tumor
- **BRCA deficiency:** *BRCA1* or *BRCA2* mutation, with LOH in the affected gene
- **HR Deficient:** either high HRD score or tBRCA mutation
- **pCR:** no viable invasive cancer in breast and axilla

HRD Testing

- Available baseline archival formalin-fixed paraffin embedded core biopsy tumor samples were obtained from TBCRC008.
- 3-5 x 10μm slides for DNA extraction were analyzed by Myriad Genetics without knowledge of clinical variables.
- HRD-LOH, HRD-LST, HRD-TAI, and their sum (HRD score) was determined. Mutation screening and LOH were determined on the *BRCA1* and *BRCA2* genes.
- Blinded clinical data was provided and examined for missing data.
- Analysis population included all patients with available HRD and pCR data.

Statistics

- We compared the proportion of patients with pCR by HRD status using Fisher's exact test.
- A subset analysis compared pCR proportions by high (≥42) vs low (<42) HRD score in those without tBRCA mutation.
- A logistic regression model included HRD status, ER status, treatment arm, tumor grade and use of AC prior to definitive surgery.
- Sensitivity analysis was performed for patients who did not receive additional treatment with AC.
- P values less than or equal to 0.05 were considered statistically significant.
- Analyses were performed using SAS for Windows version 9.2 or later and/or R version 3.0.2 or later.

RESULTS

- HRD status and pCR data were available for 48/62 patients (30 hormone receptor-positive, 18 TNBC) (Table 1).
- Of these, 46% of tumors were HR deficient (n=22/48, 33% hormone receptor-positive [10/30], 67% TNBC [12/18]).
- We observed a significantly higher pCR rate in patients with HR deficiency vs not (50% vs 7.7%, p=0.002) in the overall population (Table 3A).
- A similar trend was observed in patients with hormone receptor-positive breast cancer (30% vs 5%, p=0.095) and TNBC (66.7% vs 16.7%, p=0.13) (Table 3A).

Table 1. Analysis Population

	All Patients	Hormone Receptor-Positive	TNBC
Clinical data	62	38	24
Biopsy available	56	34	22
HR deficiency status could be determined	49	30	19
pCR data available	48	30	18
Main analysis population	48 (77%)	30 (79%)	18 (75%)
Subgroup analysis population (tBRCA non mutated)	40	25	15

Table 3. Analysis of pCR Endpoint

Total n, pCR%	HR Non-Deficient	HR Deficient	P value*	Odds Ratio (95% CI)
A. Main Analysis				
All patients	2/26 (7.7%)	11/22 (50.0%)	0.002	12.0 (2.3, 63.6)
Hormone receptor-positive	1/20 (5.0%)	3/10 (30.0%)	0.095	8.1 (0.7, 91.9)
TNBC	1/6 (16.7%)	8/12 (66.7%)	0.13	10.0 (0.9, 117.0)
B. Subgroup Analysis (tBRCA non-mutants)				
All patients	2/26 (7.7%)	9/14 (64.3%)	<0.001	21.6 (3.5, 132.0)
Hormone receptor-positive	1/20 (5.0%)	1/5 (20.0%)	0.37	4.75 (0.2, 93.0)
TNBC	1/6 (16.7%)	8/9 (88.9%)	0.011	40.0 (2.0, 794.3)

*P value from Fisher's exact test

- In a subgroup analysis (n=40) of patients without tBRCA (25 hormone receptor-positive, 15 TNBC), a significantly higher pCR rate was observed in those with high vs low HRD score (64.3% vs 7.7%, p <0.001) (Table 3B).

Table 2. HR Deficiency Status by Demographic and Clinical Variables

Characteristic	Value	HR Non-Deficient (n=26)	HR Deficient (n=22)
Age	<50	15 (58%)	13 (59%)
	≥50	11 (42%)	9 (41%)
Race	White	18 (69%)	14 (64%)
	Black	6 (23%)	4 (18%)
	Other	2 (8%)	4 (18%)
Menopausal Status	Pre	13 (50%)	13 (59%)
	Post	13 (50%)	9 (41%)
Prior gBRCA Testing	No deleterious mutation	8 (31%)	3 (14%)
	Deleterious Mutation	0 (0%)	7 (32%)
	Unknown	18 (69%)	12 (54%)
Tumor BRCA	No Deleterious Mutation	26 (100%)	14 (64%)
	Deleterious Mutation	0 (0%)	8 (36%)
ER Status	ER/PR-positive	20 (77%)	10 (45.5%)
	TNBC	6 (23%)	12 (54.5%)
T stage	T1c/ T2	14 (54%)	16 (73%)
	T3/4	12 (46%)	6 (27%)
Grade	2	9(35%)	1 (5%)
	3	12 (46%)	19 (86%)
	Unknown	5 (19%)	2 (9%)
Ki67 % (central)	<20	5 (19%)	0 (0%)
	>20	21 (81%)	21 (95%)
	Unknown	0 (0%)	1 (5%)
Treatment Arm	Placebo	13 (50%)	12 (54.5%)
	Vorinostat	13 (50%)	10 (45.5%)
Weeks of carboplatin	<10	3 (11%)	2 (9%)
	10-11	2 (8%)	0 (0%)
	12	21 (81%)	20 (91%)
Additional AC	No	19 (73%)	19 (86%)
	Yes	7 (27%)	3 (14%)
pCR	No	24 (92%)	11 (50%)
	Yes	2 (8%)	11 (50%)

- After adjusting for ER status, randomized treatment, use of AC treatment, and tumor grade, patients whose tumors exhibited HR deficiency had a greater than 6 fold increase in pCR compared to those without HR deficiency (adjusted odds ratio = 6.76, 95% CI = 0.85-53.99, p=0.072) (Table 4).

Table 4. Logistic Regression Model

Variables		Odds Ratio	P Value
HR deficient	Yes **vs** No	6.76	0.072
ER status	Hormone receptor-positive **vs** TNBC	0.23	0.10
Treatment	Vorinostat **vs** Placebo	0.47	0.39
Additional AC	Yes **vs** No	0.84	0.88

CONCLUSIONS AND FUTURE DIRECTIONS

- This is the first study to evaluate the predictive role of HRD status in patients with ER-positive, HER2-negative early breast cancer treated with platinum-based therapy.
- Our results also support prior observations that HRD status is a promising potential predictive biomarker of response to platinum agents in TNBC.
- Further evaluation of this question is warranted in both TNBC and ER-positive breast cancer, and will help determine if the predictive effect is restricted to platinum based chemotherapy.

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