Role of Germline BRCA Status and Tumor Homologous Recombination (HR) Deficiency in Response to Neoadjuvant Weekly Paclitaxel Followed by Anthracycline-Based Chemotherapy

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Background

- Double-strand DNA breaks are repaired by homologous recombination (HR), mediated by the products of *BRCA1* and *BRCA2* and by nonhomologous end-joining.
- Both HR Deficiency and BRCA mutation status have been shown to predict response to platinum based therapy (both in neoadjuvant and metastatic setting).
- BRCA mutation status has been shown to predict resistance to q 3 week docetaxel in metastatic triple negative breast cancer (TNBC).
- However, in the neoadjuvant/adjuvant setting, little is known about the association of either biomarker with response to the individual elements of anthracycline/cyclophosphamide (AC) or to taxanes (T) because taxanes are commonly administered either concomitantly or sequential to AC.
- The goal of this study was to evaluate the association of HRD and germline BRCA mutation status with response to neoadjuvant chemotherapy regimen of weekly taxanes followed by AC or FEC chemotherapy in women with high risk breast cancer.

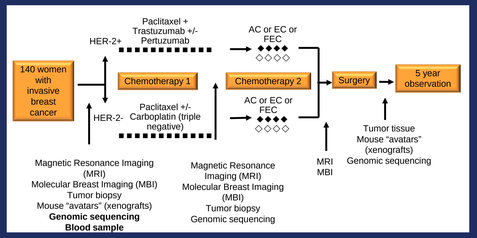
Methods

- With IRB approval and informed consent we conducted a prospective study of 140 women with Stage I-III breast cancer with high risk tumor biology being treated with neoadjuvant chemotherapy - Breast cancer genome guided therapy study (BEAUTY).
- Baseline peripheral blood sample was obtained and sequenced for germline BRCA status and baseline percutaneous tumor biopsy was obtained for assessment for HR deficiency.
- Neoadjuvant chemotherapy consisted of weekly paclitaxel (+/- trastuzumab for HER-2+ disease) followed by AC or (F)EC. Perjeta was permitted for HER-2+ disease after Oct 2013 and Carboplatin was permitted for TNBC after Mar 2014. Patients treated with carboplatin were excluded from this analysis.
- HR deficiency was determined by Myriad genetics blinded to patient characteristics or clinical outcome.
- Clinical molecular approximated subtype were classified based on ER, PR, HER-2 from percutaneous tumor biopsy at presentation and defined as follows:
  - Luminal = ER+, HER-2 negative
  - Triple negative = ER<10%, PR<10%, HER-2 neg
  - HER-2 = IHC 3+ or HER-2 amplified by ISH (regardless of ER)

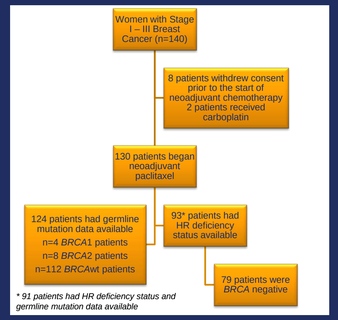
Methods

- Patients underwent MRI imaging at baseline and after completion of 12 weeks of paclitaxel. MRI scans were independently assessed by two study radiologists and discrepancies were settled by joint review of the scans. MRI response after 12 weeks of paclitaxel therapy was classified using WHO criteria based on changes in tumor size on MRI.
- Surgical resection with lumpectomy or mastectomy and nodal staging was performed after completion of T and AC chemotherapy.
- Both response to paclitaxel (as measured by MRI) and pCR (after T and AC) are examined in terms of germline BRCA mutation status (gBRCAmut vs. gBRCAwt) and HR deficiency.

Breast Cancer Genome Guided Therapy (BEAUTY) study



Consort Diagram



Definitions

- *gmBRCA* = deleterious mutation of *BRCA*1 or *BRCA*2 in the germline
- *tmBRCA* = deleterious mutation of *BRCA*1 or *BRCA*2 in the tumor
- *HRD score* = LOH score + TAI score + LST score
- HRD score ranges from 0-100. High HRD score was predefined as ≥42
- *HR deficient* = either a high HRD score or tumor *BRCA* mutation
- pCR defined as ypT0/is ypN0
- MRI response to taxane defined as ≥30% decrease in largest dimension of tumor on MRI after 12 weeks of paclitaxel
- MRI complete response to taxane defined as no residual disease on MRI after 12 weeks of paclitaxel

Chemotherapy Response by Germline *BRCA* Status

- The MRI response rate (≥ 30% decrease in tumor size) to paclitaxel therapy was:
  - 50% (95% CI: 21.1-78.9%) in the 12 g*BRCA*mut patients
  - 50% (95% CI: 40.4-59.6%) in the 112 g*BRCA*wt patients
- There were 24 complete MRI responses to paclitaxel therapy -- 2 in g*BRCA*mut and 22 in g*BRCA*wt patients
- pCR rate was 50% in the 12 g*BRCA*mutpts (95% CI: 21.1-78.9%) and 31.3% in the 112 g*BRCA*wt patients (95% CI: 22.8-40.7%)

Table 1: Germline BRCA and response to paclitaxel (by MRI) and to both T and AC (pCR)

	MRI Partial or Complete Response	MRI Complete Response	pCR
BRCA 1 (n=4)	**1/4 (25%)**	**0/4 (0%)**	**2/4 (50%)**
Triple negative	1/2 (50%)	0/2 (0%)	1/2 (50%)
HER-2	0/0	0/0	0/0
Luminal	0/2 (0%)	0/2 (0%)	1/2 (50%)
BRCA 2 (n=8)	**5/8 (62.5%)**	**2/8 (25%)**	**4/8 (50%)**
Triple negative	2/4 (50%)	1/4 (25%)	4/4 (100%)
HER-2	0/0	0/0	0/0
Luminal	3/4 (75%)	1/4 (25%)	0/4 (0%)
BRCA wt (n=112)	**56/112 (50.0%)**	**22/112 (19.6%)**	**35/112 (31.3%)**
Triple negative	19/35 (54.3%)	10/35 (28.6%)	17/35 (48.6%)
HER-2	26/36 (72.2%)	11/36 (30.6%)	16/36 (44.4%)
Luminal	11/41 (26.8%)	1/41 (2.4%)	2/41 (4.9%)

HRD status

- HRD status was available on 93 patients (see Table 2).
- 31 were HR deficient and 62 HR non-deficient, 14 were tmBRCA and 10 gmBRCA.

Table 2: Characteristics by HRD status of the Evaluable Analysis Set of 93 patients

Characteristics	Evaluable Analysis Set (N=93)	HR Deficient (N=31)	HR Non-Deficient (N=62)
Median age (range)	50 (21-73)	49 (21-73)	50 (23-73)
Clinical T stage			
T1/T2	46 (49.5%)	19 (61.3%)	27 (43.5%)
T3/T4	47 (50.5%)	12 (38.7%)	35 (56.5%)
Clinical N stage			
N0/N1	87 (93.5%)	30 (96.8%)	57 (91.9%)
N2/N3	6 (6.5%)	1 (3.2%)	5 (8.1%)
Nottingham grade			
1/2	37 (39.8%)	6 (19.4%)	31 (50.0%)
3	56 (60.2%)	25 (80.6%)	31 (50.0%)
Tumor histology			
Infiltrating ductal	84 (90.3%)	29 (93.5%)	55 (88.7%)
Other (ILC, IMC, Other)	9 (9.7%)	2 (6.5%)	7 (11.3%)
Tumor ER status			
Negative	44 (47.3%)	22 (71.0%)	22 (35.5%)
Positive	49 (52.7%)	9 (29.0%)	40 (64.5%)
Clinical molecular subtype			
Triple negative	29 (31.2%)	20 (64.5%)	9 (14.5%)
HER-2	29 (31.2%)	3 (9.7%)	26 (41.9%)
Luminal	35 (37.6%)	8 (25.8%)	27 (43.5%)
PAM50 status			
Basal	33 (35.5%)	18 (58.1%)	15 (24.2%)
HER-2	22 (23.7%)	4 (12.9%)	18 (29.0%)
Luminal A	12 912.9%)	0 (0.0%)	12 (19.4%)
Luminal B	18 (19.4%)	4 (12.9%)	14 (22.6%)
Normal	4 (4.3%)	2 (6.5%)	2 (3.2%)
Not available	4 (4.3%)	3 (9.7%)	1 (1.6%)

Binary HRD Score

- We additionally analyzed the binary HRD score in tumors that did not contain a tmBRCA.
- 79 tumors did not contain a tmBRCA
  - 21 were triple negative, 29 luminal, and 29 HER-2 positive
  - 17 had high HRD score and 62 had low HRD score

Table 3 and Figure 1: HR deficiency status and MRI response to paclitaxel (+/- anti-HER-2 based therapy) and pCR in evaluable analysis set (n=93)

	MRI Response to Paclitaxel		pCR	
	HR Non-Deficient	HR Deficient	HR Non-Deficient	HR Deficient
All Patients	27/60 (45.0%) (32.1%, 58.4%)	20/30 (66.7%) (47.2%, 82.7%)	13/62 (21.0%) (11.7%, 33.2%)	14/31 (45.2%) (27.3%, 64.0%)
	P-value = 0.073		P-value = 0.028	
Triple Negative	3/9 (33.3%) (7.5%, 70.1%)	14/20 (70.0%) (45.7%, 88.1%)	4/9 (44.4%) (13.7%, 78.8%)	11/20 (55.0%) (31.5%, 76.9%)
	P-value = 0.106		P-value = 0.700	
HER-2	18/26 (69.2%) (48.2%, 85.7%)	3/3 (100%) (29.2%, 100%)	9/26 (34.6%) (17.2%, 55.7%)	2/3 (66.7%) (9.4%, 99.2%)
	P-value = 0.540		P-value = 0.539	
Luminal	6/25 (24.0%) (9.4%, 45.1%)	3/7 (42.9%) (9.9%, 81.6%)	0/27 (0%) (0.0%, 12.8%)	1/8 (12.5%) (0.3%, 52.7%)
	P-value = 0.370		P-value = 0.229	

P-values are from Fisher's Exact Test for proportions

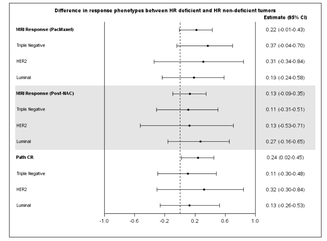
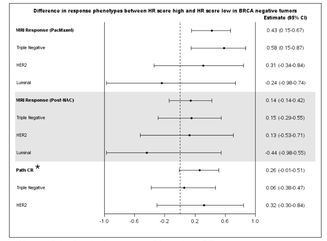


Table 4 and Figure 2: HRD score and MRI response to paclitaxel (+/- anti-HER-2 based therapy) and pCR in tumor *BRCA* non-mutants (n=79)

	MRI Response to Paclitaxel		pCR	
	HRD Score Low	HRD Score High	HRD Score Low	HRD Score High
All Patients	27/60 (45.0%) (32.1%, 58.4%)	14/16 (87.5%) (61.7%, 98.5%)	13/62 (21.0%) (11.7%, 33.2%)	8/17 (47.1%) (23.0%, 72.2%)
	P-value = 0.004		P-value = 0.059	
Triple Negative	3/9 (33.3%) (7.5%, 70.1%)	11/12 (91.7%) (61.5%, 99.8%)	4/9 (44.4%) (13.7%, 78.8%)	6/12 (50.0%) (21.1%, 78.9%)
	P-value = 0.016		P-value = 1.000	
HER-2	18/26 (69.2%) (48.2%, 85.7%)	3/3 (100%) (29.2%, 100%)	9/26 (34.6%) (17.2%, 55.7%)	2/3 (66.7%) (9.4%, 99.2%)
	P-value = 0.540		P-value = 0.539	
Luminal	6/25 (24.0%) (9.4%, 45.1%)	0/1 (0%) (0%, 97.5%)	0/27 (0%)	0.2 (0%)
	P-value = 1.000		P-value = N/A	

P-values are from Fisher's Exact Test for proportions



* None of the luminal tumors achieved a pCR

Conclusions

- **HR deficiency was frequently observed in women with TNBC (69%). In contrast, HR deficiency was less common in women with Luminal (23%) and HER-2 (10%) subtypes.**
- **HR deficiency was associated with pCR to sequential weekly paclitaxel and AC chemotherapy, however this effect was not observed when looking at pCR within the clinical molecular subtypes.**
- **In TNBC patients, we observed notably higher MRI response to weekly paclitaxel in those with high HRD score compared to those with low HRD score, but this effect did not remain significant for pCR after the addition of AC chemotherapy.**
- **In Luminal and HER-2 subtypes the number of patients with HR deficiency was low. Therefore, firm conclusions cannot be drawn regarding HR deficiency in these subtypes.**
- **In contrast to prior studies in the metastatic setting in which patients with *BRCA* mutations had lower response rates to q3 week docetaxel, we observed that MRI response to weekly paclitaxel was similar regardless of germline *BRCA* mutation status (50% in germline *BRCA* carriers and 50% in *BRCAwt*).**
- **Women with germline mutations did not have significantly different pCR rates to sequential weekly paclitaxel and AC chemotherapy (50%) versus *BRCAwt* patients (31%).**
- **Given prior studies demonstrating that HR deficiency and germline *BRCA* mutations are biomarkers associated with platinum response, future studies should assess whether these biomarkers can be used to select women for platinum-based therapy. Additional analysis of HRD status as a predictive marker for platinum response in TNBC patients will be assessed in CALGB 40603.**

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