A Non-randomized, Observational Trial of Short-term Pre-operative Endocrine Therapy in ER Positive Breast Cancer to Investigate Changes in Genomic Expression Using the Oncotype DX® Recurrence Score®

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A Non-randomized, Observational Trial of Short-term Pre-operative Endocrine Therapy in ER Positive Breast Cancer to Investigate Changes in Genomic Expression Using the Oncotype DX® Recurrence Score®

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Background

- Pre-operative systemic treatment is commonly employed for women with locally advanced breast cancer. Women with early-stage, hormone receptor-positive breast cancer whose resections may be delayed for 30 to 60 days while they undergo pre-operative evaluation, may benefit from receiving pre-operative endocrine therapy while awaiting surgery.
- Short-term neoadjuvant endocrine therapy has been reported to be well tolerated and results in a modest clinical response. [1,2]
- One rationale for not initiating such treatment is that the cancer may be rendered less chemosensitive should final pathology dictate that adjuvant chemotherapy would be beneficial.
- The 21-gene Recurrence Score (RS) assay has been shown to be a predictor of both chemo- and endocrine-therapy responsiveness and may be useful as an indicator of sensitivity during and after neoadjuvant therapy.[3-6]

Objective

- Compare core biopsy and excisional surgical specimens with respect to RS and single gene RT-PCR scores for ER, PR and HER2, in a cohort of women receiving short-term, pre-operative endocrine therapy

Materials and Methods

- Treatment: 4-8 weeks of daily letrozole (2.5 mg) for post-menopausal women or tamoxifen (20 mg) for pre-menopausal women
- Clinical response was assessed by ultrasound (US) and clinical examination.
  - Complete response (CR): no tumor on palpation and/or imaging
  - Partial response (PR): ≥30% reduction
  - Progressive disease (PD): >20% increase
  - Stable disease (SD): other than above
- The Oncotype DX breast cancer assay was performed on core biopsy and excisional specimens by standardized methods in the Genomic Health Clinical Laboratory.
  - All samples were reviewed by board certified pathologists. When necessary, samples were manually micro-dissected to enrich for tumor.
  - The 21-gene RS assay, including ER, PR, and HER2 gene expression, was assessed by RT-PCR.
- Single gene cut-point values (reference normalized expression, log2 scale):
  - ER: Negative <6.5, Positive ≥6.5
  - PR: Negative <5.5, Positive ≥5.5
  - HER2: Negative <10.7, Equivocal 10.7 - <11.5, Positive ≥11.5
- This is an exploratory, hypothesis-generating study. Scatter plots of core biopsy vs excisional specimen results were produced. Pearson correlation coefficients and 95% confidence intervals (CI) were calculated to assess correlation from core biopsies to excisional specimens. Paired t-tests were performed on a post-hoc basis to examine if there were any directionally consistent changes.

Table 1: Study Eligibility Criteria

Criterion Description	Eligible Values
Age	35 – 85 Years
ECOG Performance Status (PS)	0 , 1, or 2
Tumor Size	Greater than 0.5 cm in diameter, sonographically visible
HER2 Status*	Negative

*† Assessed by IHC * HER2 status 0 or 1+ by IHC or negative by FISH*

Table 2: Baseline Characteristics for 19 T1, N0, M0 Patients

Variable	n (%)	Variable	n (%)
Single Gene Status		Menopausal Status	
ER Positive†	19 (100%)	Pre	3 (16%)
PR Positive†	19 (100%)	Post	16 (84%)
HER2*		Age (years)	
0,1+	17 (89%)	<50	4 (21%)
2+/FISH-	2 (11%)	50-59	3 (16%)
Tumor Grade		60-69	7 (37%)
Well Differentiated	9 (47%)	70-79	5 (26%)
Moderately Differentiated	8 (42%)	Endocrine Therapy	
Poorly Differentiated	2 (11%)	Tamoxifen	3 (16%)
		Letrozole	16 (84%)

*† Assessed by IHC *Assessed by IHC/FISH*

Figure 1: Clinical Response by US/Exam

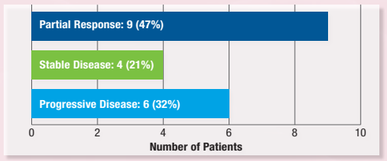
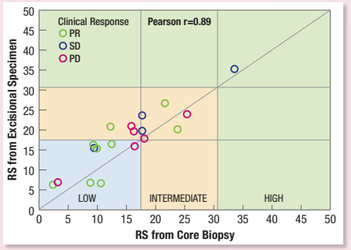
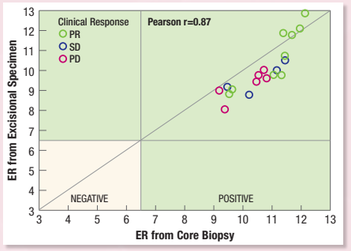


Figure 2: Correlation of Pre-Neoadjuvant RS with Post-Neoadjuvant RS



Mean change in RS = 2.8 unit (normalized expression, log2 scale) increase (95% CI 1.1-4.6), p=0.003 from paired t-test

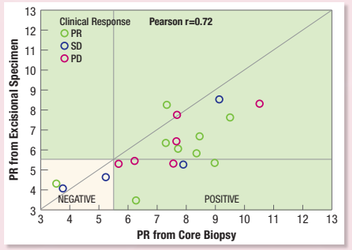
Figure 3: Correlation of Pre-Neoadjuvant ER with Post-Neoadjuvant ER



Mean change in ER = 0.64 unit (normalized expression, log2 scale) decrease (95%CI 0.32-0.96), p<0.001 from paired t-test

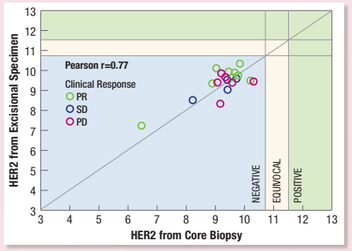
Trend toward higher ER in PR vs SD/PD (mean difference= 0.8 units, p=0.064).

Figure 4: Correlation of Pre-Neoadjuvant PR with Post-Neoadjuvant PR



Mean change in PR = 1.25 unit (normalized expression, log2 scale) decrease (95% CI 0.64-1.86), p<0.001 from paired t-test

Figure 5: Correlation of Pre-Neoadjuvant HER2 with Post-Neoadjuvant HER2



No change in HER2 ([mean change = 0.09 unit (normalized expression, log2 scale)), 95% CI -0.16 to 0.35, p=0.45 from paired t-test

Results

- 21 patients consented to this study and initiated short-term neoadjuvant therapy:
  - 19 completed therapy, underwent surgery, and had evaluable core biopsy and excisional specimens
  - 2 patients were excluded from this analysis:
    - 1 patient had no residual cancer in the excisional specimen
    - 1 patient did not have evaluable core and excisional specimens

Strengths and Limitations

Strengths

- Prospective study of changes in biomarkers in early-stage, ER+ breast cancer treated with endocrine therapy

Limitations

- Small sample size (n=19)
- Only 3 pre-menopausal patients; too few to examine potential differences by menopausal status.
- Potential selection bias
- Only 1/19 patients in high RS group.
- Hypothesis tests not pre-specified

Summary and Discussion

- Expression levels of ER, PR, and HER2 from core biopsies and excisional specimens were correlated (Pearson correlation coefficients, r = 0.87, 0.72, and 0.77, respectively), as was RS (r = 0.89), following short term neoadjuvant endocrine therapy.
- In this study, on average, therapy reduced the expression of ER and PR, while HER2 expression was unchanged. The changes in ER and PR expression contributed to a modest increase (mean = 2.8 units, p = 0.003) in the Oncotype DX RS.
- The prognostic and predictive capability of the Oncotype DX RS in ER-positive, early-stage breast cancer has been demonstrated in multiple clinical studies; none of these patients had received neoadjuvant therapy.
  - There are no data on the prognostic or predictive ability of the RS from tumor samples obtained after neoadjuvant therapy.
  - The clinical significance of the changes in ER, PR and RS observed in this study is therefore unclear.

Conclusions

In this small, hypothesis-generating study:

- Expression of ER and PR both decreased by small but statistically significant amounts, which contributed to a small but statistically significant increase in RS (2.8 units).
- The clinical significance of these observed changes are unclear.
- Decreases in ER have been observed following short term aromatase inhibitor treatment in some studies,[7-8] but not others.[9]

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