Prediction of chemotherapy benefit by MammaPrint® in patients with HR+HER2- early-stage breast cancer from real-world evidence studies

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Background

A need exists to identify biomarkers that predict chemotherapy (CT) benefit among patients with HR+HER2- early-stage breast cancer. The 70-gene signature, MammaPrint (MP), determines distant recurrence (DR) risk in early-stage breast cancer. MP has demonstrated utility in predicting adjuvant and neoadjuvant chemotherapy response[1-5]. Here, we examined MP utility in predicting pathological Complete Response (pCR) to neoadjuvant CT and 5-year follow-up comparisons among patients who received adjuvant CT or endocrine therapy (ET) alone.

Methods

Patients	Trial	Treatment	Outcome	N	
with HR+HER2- early-stage breast cancer	NBRST	Neoadjuvant CT	pCR	462	
	FLEX (NCT03053193)	CT (+/- ET)	5-year distant recurrence risk	181	475
		ET only		294	

Genomic testing

MammaPrint index is defined as UltraLow (UL: +1.000 to +0.356), Low Risk (LR: +0.355 to +0.001), High 1 (H1: 0.000 to -0.569), and High 2 (H2: -0.570 to -1.000).

Statistics

Logistic regression was used to estimate likelihood of pCR and 5-yr DR risk (including breast cancer specific death) for CT vs ET, as a continuous function of the MP index.

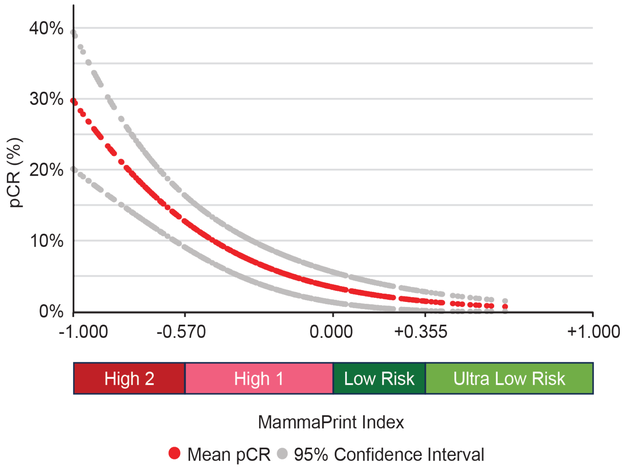
Results

Table 1. Clinical Characteristics of NBRST Patients

	High 1 (N=198)	High 2 (N=129)	Low Risk (N=99)	Overall (N=426)	P-value
Age (Years)					
Mean (SD)	53 (± 12)	50 (± 13)	54 (± 11)	52 (± 12)	0.126
Menopausal Status					
Post-	110 (55.6%)	62 (48.4%)	54 (55.7%)	226 (53.4%)	0.585
Pre-/Peri-	88 (44.4%)	66 (51.6%)	43 (44.3%)	197 (46.6%)	
Race					
Asian	5 (2.5%)	4 (3.1%)	1 (1.0%)	10 (2.3%)	0.646
Black	27 (13.6%)	23 (17.8%)	7 (7.1%)	57 (13.4%)	
Hispanic	19 (9.6%)	9 (7.0%)	6 (6.1%)	34 (8.0%)	
Other	4 (2.0%)	2 (1.6%)	1 (1.0%)	7 (1.6%)	
White	143 (72.2%)	91 (70.5%)	84 (84.8%)	318 (74.6%)	
Tumor Stage					
T1	22 (11.2%)	12 (9.4%)	12 (12.1%)	46 (10.9%)	0.964
T2	108 (54.8%)	75 (59.1%)	51 (51.5%)	234 (55.3%)	
T3	54 (27.4%)	30 (23.6%)	31 (31.3%)	115 (27.2%)	
T4	13 (6.6%)	10 (7.9%)	5 (5.1%)	28 (6.6%)	
Lymph Node Stage					
N0	56 (29.6%)	43 (35.2%)	39 (41.1%)	138 (34.0%)	0.476
N1	115 (60.8%)	61 (50.0%)	46 (48.4%)	222 (54.7%)	
N2	16 (8.5%)	14 (11.5%)	7 (7.4%)	37 (9.1%)	
N3	2 (1.1%)	4 (3.3%)	3 (3.2%)	9 (2.2%)	
Grade					
G1	15 (7.9%)	2 (1.6%)	22 (23.7%)	39 (9.6%)	<0.001
G2	95 (50.0%)	18 (14.6%)	57 (61.3%)	170 (41.9%)	
G3	80 (42.1%)	103 (83.7%)	14 (15.1%)	197 (48.5%)	

Data presented in both tables as N (%) unless indicated otherwise; Unknown values excluded;
N = sample size; SD = standard deviation

Figure 1. Probability of achieving pCR with Neoadjuvant Chemotherapy across MammaPrint Index

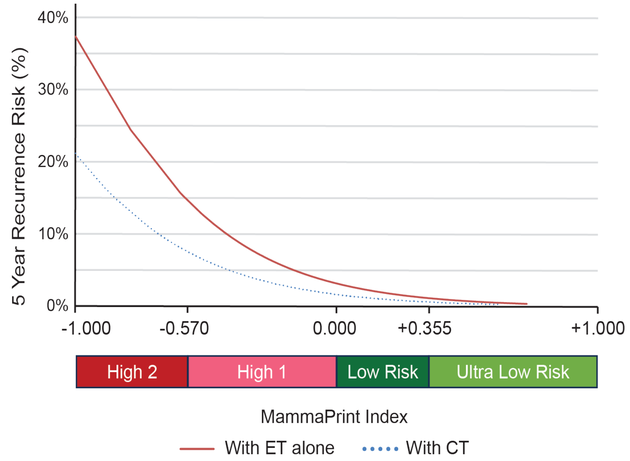


- Neoadjuvantly treated patients were significantly more likely to achieve pCR as MP risk increased, with up to 30% pCR observed in H2 tumors ($p < 0.001$) (**Figure 1**).
- The MP index demonstrated effective performance for predicting 5-yr DR risk in the ET group, with an Area under the ROC Curve (AUC) of 0.73 (p=0.005), and the CT group, with an AUC of 0.77 (p=0.008) (**Figure 2**).
- ET only treated pts had greater 5-yr DR risk with increasing MP risk compared to patients treated with CT.
- Comparing ET vs CT groups, <1.5% and <1.0% difference in 5-yr DR risk was observed for MP indices in the LR and UL range, respectively.
- In contrast, CT benefit increased with increasing MP risk, with 2-7% absolute risk difference observed in H1, and 8-16% difference among H2 tumors.

Table 2. Clinical Characteristics of FLEX Patients

	CT +/- ET (N=181)	ET only (N=294)	Overall (N=475)	P-value
Age (Years)				
Mean (SD)	59 (± 11)	62 (± 11)	61 (± 11)	0.0597
Menopausal Status				
Post-	134 (75.7%)	239 (84.5%)	373 (81.1%)	0.0735
Pre-/Peri-	43 (24.3%)	44 (15.5%)	87 (18.9%)	
Race				
Asian or Pacific Islander	4 (2.3%)	5 (1.8%)	9 (2.0%)	0.252
American Indian or Alaska Native	0 (0%)	1 (0.4%)	1 (0.2%)	
Black	12 (6.8%)	12 (4.3%)	24 (5.3%)	
Latin American/Hispanic	0 (0%)	10 (3.6%)	10 (2.2%)	
White	160 (90.9%)	253 (90.0%)	413 (90.4%)	
Tumor Stage				
T1	86 (64.7%)	124 (68.9%)	210 (67.1%)	0.366
T2	39 (29.3%)	53 (29.4%)	92 (29.4%)	
T3	8 (6.0%)	3 (1.7%)	11 (3.5%)	
Lymph Node Status				
Negative	104 (83.2%)	153 (87.9%)	257 (86.0%)	0.526
Positive	21 (16.8%)	21 (12.1%)	42 (14.0%)	
Lymph Node Stage				
N0	104 (83.2%)	153 (87.9%)	257 (86.0%)	0.769
N1	20 (16.0%)	19 (10.9%)	39 (13.0%)	
N2	1 (0.8%)	2 (1.1%)	3 (1.0%)	
Grade				
G1	46 (26.4%)	91 (32.3%)	137 (30.0%)	0.777
G2	98 (56.3%)	147 (52.1%)	245 (53.7%)	
G3	30 (17.2%)	44 (15.6%)	74 (16.2%)	

Figure 2. Probability of Distant Recurrence with Adjuvant CT or ET alone across MammaPrint Index



Conclusions

- These data show that MammaPrint indices within LR and UL ranges exhibit low chemosensitivity and do not derive significant CT benefit, consistent with results in MINDACT[1].
- The increasing chemotherapy benefit observed with increasing MP risk is consistent with the reduction in recurrence risk reported by Knauer et al.[2] for adjuvant therapy, as well as neoadjuvant results from I-SPY 2, NBRST, and FLEX data[3-5].
- These data indicate the utility of MammaPrint to predict neoadjuvant and adjuvant CT benefit in patients with HR+HER2- breast cancer.

References: 1. Cardoso et al., N Engl J Med, 2016; 2. Knauer et al. Breast Cancer Res Treat., 2010; 3. Pusztai et al., Cancer Cell, 2021; 4. Whitworth et al., JCO Precis Oncol, 2022; 5. O'Shaughnessy et al., SABCS, 2023