MammaPrint® and BluePrint® predict anthracycline chemosensitivity in patients with HR+HER2- early-stage breast cancer enrolled in FLEX

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Introduction

- HR+HER2-negative early-stage breast cancers often yield <10% pathologic Complete Response (pCR) rates to neoadjuvant chemotherapy (NCT).
- MammaPrint (MP), classifies patients as having an Ultra Low, Low, High 1, or High 2 Risk of distant recurrence and is a continuous predictor of pCR[1-3].
- NBRST, I-SPY 2, and FLEX study data demonstrate that MP and BluePrint (BP) molecular subtyping signatures may identify cohorts of patients with high pCR in response to NCT[4-8].
- For patients eligible for NCT, there remains an unmet need to help inform whether anthracycline-based therapies, associated with debilitating acute toxicities and long-term cardiovascular risk[9], should be considered over taxane + cyclophosphamide (TC) regimens.

Objective

Examine MammaPrint and BluePrint utility to predict pCR rates between standard of care neoadjuvant regimens:

TC (taxane and cyclophosphamide) **vs** AC-T/TAC (TC with anthracycline)

Methods

Study Cohort

- Patients enrolled in the ongoing prospective, observational FLEX Trial (NCT03053193) with HR+HER2-, MP High Risk tumors, treated with NCT, with pCR data were included.
- Patients were tested with MammaPrint, with or without BluePrint, and consented to clinically annotated full genome data collection.

Genomic Testing

MammaPrint	High 1 (H1)* Index Value 0.000 to -0.569	High 2 (H2) Index Value -0.570 to -1.000	
BluePrint [3]	Luminal B-Type	Luminal B-Type	Basal-Type

* High 1 Basal-Type excluded from analysis due to low sample size (N = 2)

Statistics

- Differences in clinical characteristics were assessed by Chi-Squared or Fisher's exact test.
- Differences in pCR were assessed by two-sided proportional z-test.
- P-values of 0.05 or less were considered significant.

Table 1. Clinical Characteristics

	High 1*	High 2		
	Luminal B (N=139)	Basal (N=34)	Luminal B (N=39)	P-value
Age (Years)				
Mean (SD)	55 (± 13)	52 (± 13)	53 (± 13)	1
Menopausal Status				
Post-	82 (63.1%)	21 (67.7%)	22 (61.1%)	0.46
Pre-/Peri-	48 (36.9%)	10 (32.3%)	14 (38.9%)	
Race				
Asian or Pacific Islander	3 (2.3%)	0 (0%)	2 (5.4%)	0.71
American Indian or Alaska Native	1 (0.8%)	0 (0%)	0 (0%)	
Black	21 (15.9%)	3 (9.4%)	6 (16.2%)	
Latin American/Hispanic	9 (6.8%)	0 (0%)	4 (10.8%)	
Mixed race	1 (0.8%)	0 (0%)	0 (0%)	
White	97 (73.5%)	29 (90.6%)	25 (67.6%)	
Tumor Stage				
T1	27 (26.0%)	7 (26.9%)	6 (25.0%)	0.44
T2	52 (50.0%)	17 (65.4%)	13 (54.2%)	
T3	20 (19.2%)	2 (7.7%)	2 (8.3%)	
T4	5 (4.8%)	0 (0%)	3 (12.5%)	
Lymph Node Status				
Negative	40 (39.6%)	16 (64.0%)	8 (34.8%)	0.04
Positive	61 (60.4%)	9 (36.0%)	15 (65.2%)	
Lymph Node Stage				
N0	40 (39.6%)	16 (64.0%)	8 (34.8%)	0.21
N1	52 (51.5%)	8 (32.0%)	14 (60.9%)	
N2	5 (5.0%)	0 (0%)	0 (0%)	
N3	4 (4.0%)	1 (4.0%)	1 (4.3%)	
Grade				
G1	9 (6.8%)	0 (0%)	1 (2.7%)	<0.001
G2	83 (62.9%)	2 (6.5%)	13 (35.1%)	
G3	40 (30.3%)	29 (93.5%)	23 (62.2%)	
Neoadjuvant Chemo				
AC-T/TAC	100 (71.9%)	31 (91.2%)	32 (82.1%)	0.06
TC	39 (28.1%)	3 (8.8%)	7 (17.9%)	

Data presented as n (%) unless indicated otherwise; Unknown values excluded; *High 1 Basal patients were excluded due to small sample size (N = 2)

Figure 1. MammaPrint High 1 and High 2 Risk Predicts Neoadjuvant Chemotherapy Response

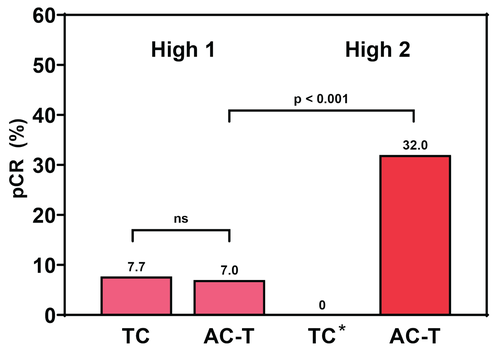
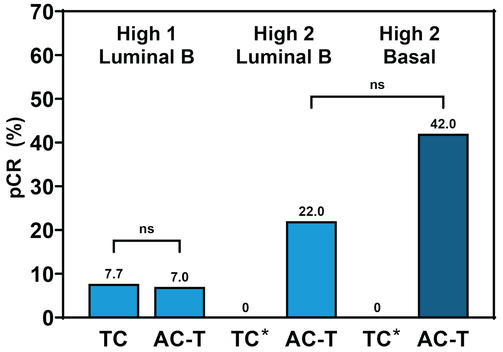


Figure 2. Neoadjuvant Chemotherapy Response based on BluePrint Subtypes in High Risk Tumors



pCR = pathological Complete Response; TC = taxane and cyclophosphamide; AC-T = TC and anthracycline, AC-T or TAC regimens; ns = not significant; * insufficient sample size/pCR events in TC treated groups for statistical comparison

Results

- MammaPrint classified 66% of HR+, HER2- breast cancers as H1 and 34% as H2 (**Table 1**).
  - Menopausal status, race, tumor stage, and lymph node status were comparable between patients with H1 and H2 tumors.
  - Although most (71%) H2 tumors were Grade 3, only 57% of all Grade 3 tumors were H2.
  - Most H1 tumors were Luminal B-Type, while similar proportions of H2 tumors were Basal-Type (47%) and Luminal B-Type (53%).
- Among H1 tumors, pCR rates to AC-T/TAC vs TC treatments were comparable (**Figure 1**).
  - In contrast, no H2 tumors (N = 10) achieved pCR to TC treatments, whereas AC-T/TAC treatment was significantly more effective for H2 compared to H1 (p < 0.001) tumors.
- Among BluePrint subtypes, H2 Basal-Type achieved the highest pCR rates with AC-T/TAC, although not significant when compared to H2 Luminal B-Type (**Figure 2**).

Conclusions

- MammaPrint and BluePrint genomic testing provides predictive utility for personalized neoadjuvant chemotherapy treatment planning.
- Patients with High 2 tumors were more likely to achieve a pCR to anthracycline-based neoadjuvant chemotherapy compared to High 1.
- Anthracycline does not appear to improve pCR rates for patients with High 1, Luminal B-Type tumors, when compared to taxane + cyclophosphamide neoadjuvant therapy, alone.
- In an effort to further examine the utility of MammaPrint for neoadjuvant treatment planning, the SWOG 2206 trial (NCT06058377) is currently enrolling and evaluating patients with MammaPrint High 2 tumors' response to neoadjuvant immunotherapy.

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