MammaPrint® and BluePrint® predict pathological response to neoadjuvant chemotherapy in patients with HR+HER2- early stage breast cancer enrolled in FLEX

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Introduction

- Pathological Complete Response (pCR) rates with neoadjuvant chemotherapy (NCT) are low for patients with hormone receptor-positive (HR+), HER2-negative early stage breast cancer (EBC)
- NBRST[1,2] and I-SPY2[3] trials show MammaPrint risk of recurrence and BluePrint molecular subtyping signatures can predict pCR likelihood in HR+HER2- EBC
- The FLEX trial is a prospective, longitudinal, observational real world data trial enrolling EBC patients with MammaPrint and BluePrint on their primary cancer
- This analysis evaluates MammaPrint and BluePrint as biomarkers for predicting pathological response (PR = pCR + minimal residual cancer burden [RCB-1]) and pCR in patients with HR+HER2- EBC from FLEX

Methods

Study Cohort

- Patients included in this analysis were enrolled in the FLEX trial (NCT03053193)
- Eligible patients had HR+HER2- EBC, were treated with neoadjuvant chemotherapy (NCT), and had available pCR and/or RCB data (N = 457)

MammaPrint and BluePrint Genomic Testing Results:

MammaPrint	Low Risk (N=44)	High 1 Risk (H1)* (N=254)	High 2 Risk (H2) (N=159)	
BluePrint	Luminal A-Type	Luminal B-Type	Luminal B-Type	Basal-Type

* 6 of the MammaPrint High 1 risk cancers were BluePrint Basal

Statistics

- Study endpoints included Pathological Response (PR = pCR + minimal residual cancer burden [RCB-I]) and pCR
- Differences in clinical characteristics and response rates were evaluated by Chi-Squared test or two-sided proportional Z-test
- The association between MammaPrint, BluePrint, and PR was assessed using multivariate logistic regression and was adjusted for menopausal status, T stage, nodal status, grade, and chemotherapy regimen
- P-values of less than 0.05 were considered significant

Table 1. Clinical Characteristics of FLEX patients with HR+HER2- disease treated with NCT

Characteristic	Low	High 1		High 2		P-value
	Luminal A (N=42)	Luminal B (N=242)	Basal (N=6)	Luminal B (N=70)	Basal (N=83)	
Age (Years)						
Mean (SD)	53 (± 12)	54 (± 12)	64 (± 8.7)	54 (± 13)	53 (± 13)	0.186
Menopausal Status						
Pre-/Peri-	16 (39.0%)	89 (39.0%)	1 (25.0%)	23 (34.8%)	28 (35.4%)	0.975
Post-	25 (61.0%)	139 (61.0%)	3 (75.0%)	43 (65.2%)	51 (64.6%)	
Race						
AAPI	0 (0%)	4 (1.7%)	0 (0%)	2 (3.1%)	3 (4.1%)	0.635
American Indian or Alaska Native	0 (0%)	1 (0.4%)	0 (0%)	0 (0%)	0 (0%)	
Black	6 (15.8%)	33 (14.4%)	1 (16.7%)	10 (15.4%)	14 (18.9%)	
Latin American	1 (2.6%)	13 (5.7%)	0 (0%)	6 (9.2%)	1 (1.4%)	
Mixed	1 (2.6%)	2 (0.9%)	0 (0%)	0 (0%)	0 (0%)	
White	30 (78.9%)	176 (76.9%)	5 (83.3%)	47 (72.3%)	56 (75.7%)	
Tumor Stage						
T1	3 (9.4%)	48 (24.4%)	2 (40.0%)	7 (14.0%)	19 (28.8%)	<0.001
T2	10 (31.3%)	104 (52.8%)	1 (20.0%)	33 (66.0%)	38 (57.6%)	
T3	15 (46.9%)	34 (17.3%)	2 (40.0%)	5 (10.0%)	6 (9.1%)	
T4	4 (12.5%)	11 (5.6%)	0 (0%)	5 (10.0%)	3 (4.5%)	
Lymph Node Status						
LN-	12 (37.5%)	63 (33.0%)	4 (80.0%)	19 (37.3%)	39 (63.9%)	<0.001
LN+	20 (62.5%)	128 (67.0%)	1 (20.0%)	32 (62.7%)	22 (36.1%)	
Grade						
G1	2 (5.3%)	18 (8.0%)	0 (0%)	1 (1.5%)	0 (0%)	<0.001
G2	35 (92.1%)	126 (56.0%)	3 (50.0%)	21 (31.8%)	4 (5.1%)	
G3	1 (2.6%)	81 (36.0%)	3 (50.0%)	44 (66.7%)	74 (94.9%)	
Chemo Regimen						
ACT +/- Platinum	32 (84.2%)	160 (74.4%)	2 (100%)	50 (84.7%)	50 (90.9%)	0.043
TC	6 (15.8%)	55 (25.6%)	0 (0%)	9 (15.3%)	5 (9.1%)	

Data presented as n (%) unless indicated otherwise; N=13 patients received a Platinum containing agent; Unknown values excluded; N, sample size; SD, standard deviation; ACT, anthracyclines, cyclophosphamide, and taxanes; TC, taxanes and cyclophosphamide

Figure 2. Rates of pCR among MammaPrint and BluePrint subtypes when stratified by clinical lymph node (LN) status

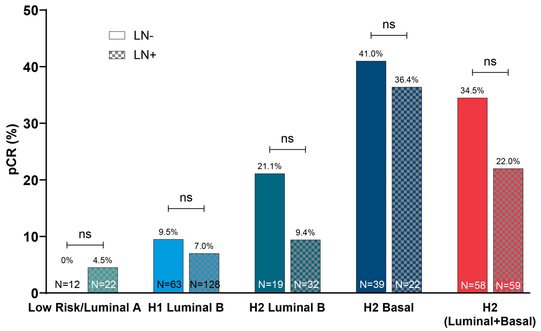
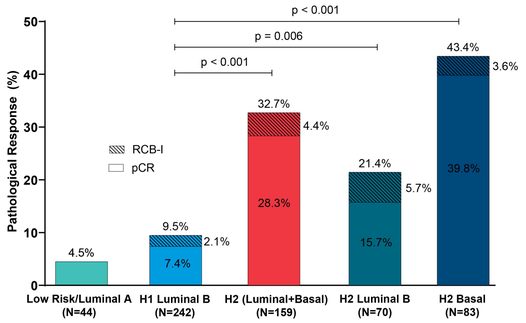


Figure 1. Pathological response (PR) to neoadjuvant chemotherapy by MammaPrint and BluePrint



Pathological response (PR) = pCR + RCB-I

Table 2. Multivariate analysis for association of clinical and genomic factors with PR

Characteristic	Odds Ratio	95% CI	P-value
MammaPrint			
High 1	1.00	-	-
High 2	3.33	[1.51, 7.61]	**0.003**
Menopausal Status			
Post-	1.00	-	-
Pre-/Peri-	0.69	[0.32, 1.44]	0.324
Tumor Stage			
T1	1.00	-	-
T2	1.23	[0.53, 3.01]	0.644
T3/T4	0.91	[0.28, 2.78]	0.865
Lymph Node Status			
LN-	1.00	-	-
LN+	0.65	[0.31, 1.35]	0.246
Grade			
Non G3	1.00	-	-
G3	2.02	[0.85, 4.90]	0.112
Chemotherapy Regimen			
TC	1.00	-	-
ACT +/- Platinum	1.39	[0.53, 3.99]	0.521

Data presented as Odds Ratio (95% CI, p-value). Low Risk excluded due to small sample size.

Results

- MammaPrint classification: LR 10%, H1 56%, and H2 34%
- Nearly 60% of patients were LN+. Higher stage and grade cancers were significantly more likely to be MammaPrint High Risk (**Table 1**)
  - Most H1 tumors were Luminal B (98%) (2% were Basal), while 45% of H2 tumors were Luminal B and 54% were Basal (1% were HER2-Type)
  - Patients with H2 tumors were generally treated with anthracyclines +/- platinum containing agents
- Pathological Response (PR=pCR+RCB-I) rates were significantly higher in High 2 Basal (43.4%, p<0.001) and High 2 Luminal B (21.4%, p=0.006) compared to H1 Luminal B (9.5%) (**Figure 1**)
  - PR rates were mostly driven by pCR rates, with fewer than 10% of patients having RCB-I in each subtype
- There were no significant differences in the pCR rates between node negative and positive disease (**Figure 2**)
- MammaPrint High 2 was significantly associated with higher PR (OR=3.33, 95% CI 1.51–7.61, p=0.003) and pCR (OR=3.48, 95% CI 1.47–8.63, p=0.005) **(Table 2)**
  - Menopausal status, T stage, nodal status, grade, and chemotherapy regimen did not significantly predict for PR or pCR

Conclusions

- MammaPrint and BluePrint predict for sensitivity to NCT in HR+HER2-EBC
- Patients with MammaPrint H2 tumors, including Luminal B and Basal subtypes, are more likely to have PR or pCR with NCT, compared to Low Risk and H1 patients
- These data suggest that MammaPrint H2 identifies HR+HER2- cancers with higher sensitivity to NCT, which may enable downstaging and may improve overall outcomes
- Treatment with an anthracycline did not independently predict for PR/pCR across subtypes. Prior studies have shown that anthracycline therapy increased pCR rates in MammaPrint H2 but not H1 disease.[4] This will be further analyzed in FLEX as more NCT patients are enrolled

References: 1. Whitworth et al., Ann Surg Oncol. 2022.; **2.** Beitsch et al., ASCO. 2023.; **3.** Pusztai et al., Cancer Cell. 2021.; 4. Audeh et al., MBCC. 2024.