Molecular Insights into HR+/HER2+ Early-Stage Breast Cancer: Neoadjuvant Therapy Responses by MammaPrint® and BluePrint® genomic subtypes

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FLEX

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Background

- Clinical HER2+ (cHER2+) early-stage breast cancer (EBC) accounts for 15-20% of invasive EBC cases[1].
- Neoadjuvant HER2-targeted therapy (NHT) combined with chemotherapy is the standard treatment for HER2+ EBC, regardless of ER status[2].
- NBRST[3] and I-SPY2[4] trials showed varying NHT responses in cHER2+ tumors based on genomic molecular subtypes, emphasizing the need to understand tumor biology.
- Genomic assays MammaPrint® (MP) and BluePrint® (BP) predict therapy response and inform treatment decisions.

Objective: We explored the biological pathways underlying differential NHT response in triple positive (HR+HER2+) tumors using whole transcriptome analysis (WTA) in FLEX.

Methods

Study Cohort

- Patients with IHC/FISH-defined HR+/HER2+ EBC (N = 720) enrolled in the ongoing prospective, observational FLEX Trial (NCT03053193), were included in this study. Data regarding pCR vs no pCR following neoadjuvant trastuzumab/pertuzumab/chemotherapy were available on 135 pts to date.

MammaPrint	High 2 Risk (H2) -1.000 to -0.570		High 1 Risk (H1) -0.569 to 0.000	Low Risk +0.001 to +0.355	UltraLow Risk +0.356 to +1.000
BluePrint	Luminal B	Basal	Luminal B	Luminal A	Luminal A

- Differences in clinical characteristics across BP subtypes and pathological complete response (pCR) rates for Pertuzumab + Trastuzumab treated BP Luminal A/B and HER2 cancers were assessed using Chi-Square or Fisher's exact tests and proportional Z-test, respectively.
- Differential gene expression (DGE) analysis of whole transcriptome (WT) profiles was performed on tumors from pts with and without pCR, using limma package in R, followed by pathway enrichment analysis in Metascape.

References

1. Jeong YH, et al., J Cancer, 2021
2. Dowling, et al., Front Oncol, 2023
3. Whitworth, et al. JCO 2022
4. Thomas A, et al., JCO 2022

Table 1. Clinical Characteristics of IHC/FISH-defined HR+/HER2+ EBC patients

Characteristic	Luminal A (n=120) (%)	Luminal B (n=307) (%)	HER2 (n=278) (%)	Basal (n= 15) (%)	P value
Age (Years)					
Mean (SD)	60.5 (± 12)	58.9 (± 13)	55.0 (± 13)	59.3 (± 13)	<0.001
Menopausal Status					0.002
Pre-/Peri-	23 (21.3%)	64 (22.3%)	92 (35.2%)	3.0 (20.0%)	
Post-	85 (78.7%)	223 (77.7%)	169 (64.8%)	12 (80.0%)	
Race					0.226
White	105(90.5%)	231 (77.8%)	210 (79.8%)	14 (93.3%)	
Black	7 (6.0%)	41 (13.8%)	37 (14.1%)	0 (0.0%)	
Latin American	2 (1.7%)	14 (4.7%)	6 (2.3%)	0 (0.0%)	
AAPI	2 (1.7%)	9 (3.0%)	9 (3.4%)	1 (6.7%)	
Mixed	0 (0.0%)	2 (0.7%)	1 (0.4%)	0 (0.0%)	
Histology					<0.001
IDC	86 (72.9%)	269 (90.3%)	256 (93.1%)	15 (100.0%)	
ILC	29 (24.6%)	17 (5.7%)	14 (5.1%)	0 (0.0%)	
Mixed	3 (2.5%)	12 (4.0%)	5 (1.8%)	0 (0.0%)	
Grade					<0.001
G1	26 (21.7%)	23 (7.9%)	13 (4.9%)	0 (0.0%)	
G2	82 (68.3%)	150 (51.4%)	107 (40.4%)	2 (13.3%)	
G3	12 (10.0%)	119 (40.8%)	145 (54.7%)	13 (86.7%)	
T Stage					<0.001
T1	53 (71.6%)	97 (44.5%)	90 (43.9%)	3 (50.0%)	
T2	19 (25.7%)	106 (48.6%)	86 (42.0%)	2 (33.3%)	
T3	2 (2.7%)	8 (3.7%)	22 (10.7%)	1 (16.7%)	
T4	0 (0.0%)	7 (3.2%)	7 (3.4%)	0 (0.0%)	
N Stage					0.3200
N0	59 (84.3%)	150 (75.0%)	137 (70.6%)	4 (80.0%)	
N1	9 (12.9%)	40 (20.0%)	52 (26.8%)	1 (20.0%)	
N2	1 (1.4%)	7 (3.5%)	5 (2.6%)	0 (0.0%)	
N3	1 (1.4%)	3 (1.5%)	0 (0.0%)	0 (0.0%)	

Unknown values excluded. SD = standard deviation; AAPI = Asian or American Pacific Islander.

Figure 4. Pathway enrichment from WT analysis of BP HER2 cancers from pts that had pCR vs no pCR in response to NHT

Genes annotated to the enriched pathways upregulated in BP HER2 cancers from pts who had pCR

GO:0030510	GO:0010811	GO:007160	GO:0031345	GO:0034330
LTF	LTF	CCL21	NR2F1	CHRDL1
TFAP2B	OLFM4	COL17A1	CCL21	CLDN11
CHRDL1	CCL21	MUC4	CHRDL1	COL17A1
SFRP1	MMRN1		SFRP1	NRXN1
NRXN1	SFRP1		NRXN1	
	CHN2			

Figure 1. Sankey diagram depicting further classification by MP and BP of HR+/HER2+ tumors

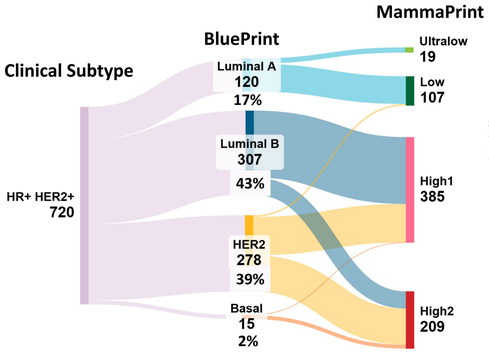


Figure 2. Rates of pCR in HR+HER2+ cancers with NHT by BP

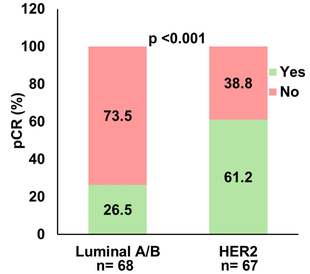
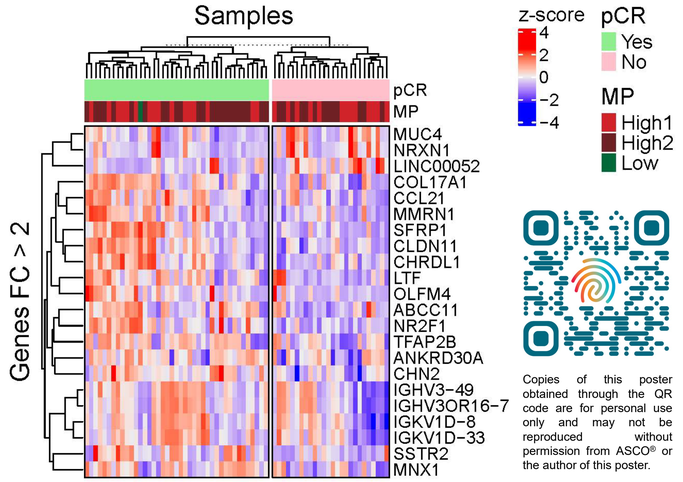


Figure 3. WT comparison of BP HER2 tumors from pts who had pCR vs no pCR in response to NHT



Results

- Among HR+/HER2+ cancers (n=720), MP classified 19 (2.6%) as UltraLow, 107 (14.9%) as Low, 385 (53.5%) as High1, and 209 (29.0%) as High2 **(Figure 1)**.
- BP classified 120 pts (17%) as Luminal A, 307 (43%) as Luminal B, 278 (39%) as HER2, and 15 (2%) as Basal **(Figure 1)**. Among ILC tumors, 48% were Luminal A, 28% Luminal B, and 23% HER2 by BP **(Table 1).**
- BP HER2 cancers were associated with younger age (54 vs 60, p<0.001), premenopausal status (p=0.002), higher grade (G3: 54.7%, p<0.001), and T3 tumors (10.7% vs 3-4%, p<0.001) compared to Luminal A/B subtypes **(Table 1)**.
- BP HER2 cancers showed significantly higher pCR rates with NHT compared to Luminal A/B tumors (n=41, 61.2% vs n=18, 26.5%, respectively, p<0.001) **(Figure 2)**.
- WT analysis in BP HER2 tumors from pts with pCR showed 23 genes with 2-fold change (not statistically significant after correction), 20 of which were upregulated and associated with regulation of BMP and increased cell-substrate/cell matrix adhesion, compared to cancers from pts with residual disease **(Figures 3 and 4)**.

Conclusions & Future Directions

- BP identified heterogeneity within HR+/HER2+ EBC, with ~60% further classified genomically as non-HER2-type.
- Consistent with I-SPY2, BP HER2 tumors showed higher pCR rates than Luminal A/B, underscoring the need for improved therapies for pts with Luminal A/B subtypes, and the potential value of BP in predicting HER2-targeted therapy response.
- WT analysis revealed DGE between pCR and non-pCR in BP HER2 cancers, but findings were not statistically significant.
- Future WT analysis in larger cohorts of HR+/HER2+ EBC patients enrolled in FLEX, further classified by BP may elucidate the biology of these cancers from pts with pCR vs non-pCR.