Neoadjuvant HER2-Targeted Therapy Response by BluePrint® Gene Expression-Based Molecular Subtyping in patients with HER2+ Early-Stage Breast Cancer from FLEX

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Introduction

- 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.
- The heterogeneity within cHER2+ tumors can be distinguished based on molecular subtyping, which provides insights into the molecular biology of the tumor.
- Genomic assays MammaPrint® (MP) and BluePrint® (BP) predict therapy response and inform treatment decisions.

Objective: We evaluated the role of BP in identifying cHER2+ tumors more likely to respond to NHT based on MP and BP classification.

Methods

- Patients with IHC/FISH-defined cHER2+ disease (n=940) from FLEX (NCT03053193) were included in this analysis (HR+HER2+ n=720; HR-HER2+ n= 220).
- 353 patients received NHT and among these patients, 183 (51.8%) had Pertuzumab + Trastuzumab treatment.
- Patients were stratified into MP UltraLow, Low, High 1, or High 2 Risk groups, while BP categorized them as Luminal, HER2, or Basal.
- Differences in clinical characteristics across BP subtypes and pathological complete response (pCR) rates for Pertuzumab + Trastuzumab treated BP Luminal and HER2 tumors were assessed using Chi-Square or Fisher's exact tests and proportional Z-test, respectively.

Figure 1. Sankey diagram depicting further classification by MP and BP of cHER2+ tumors

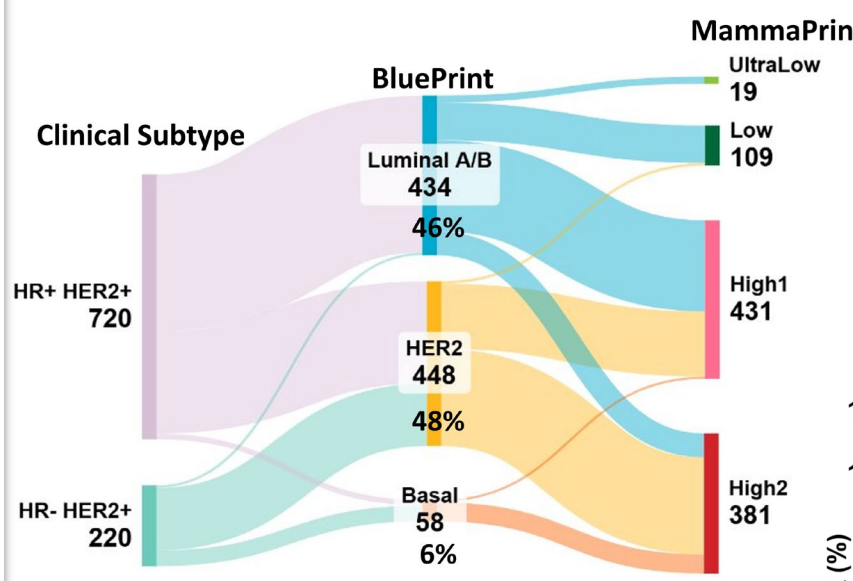

Figure 2. Rates of pCR in cHER2+ tumors to NHT by BP

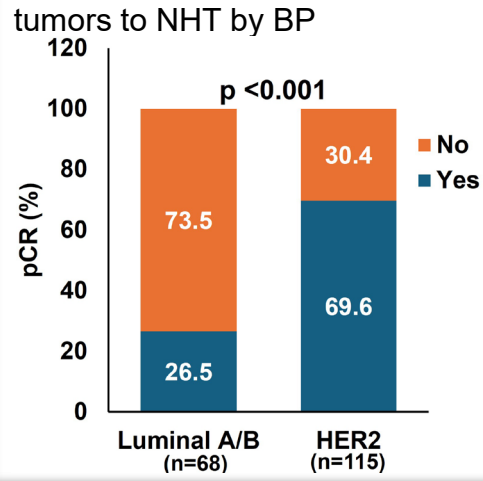

Figure 3. Rates of pCR in HR+HER2+ tumors to NHT by BP

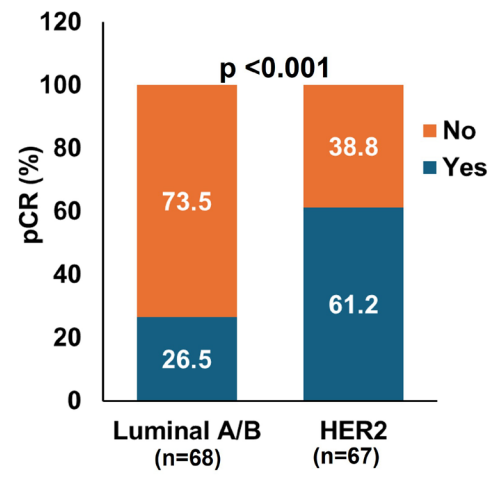

Table 1. Clinical Characteristics of FLEX patients with cHER2+ tumors

Characteristic	Luminal A (N=121) (%)	Luminal B (N=313) (%)	HER2 (N=448) (%)	Basal (N=58) (%)	P value
Age (Years)					
Mean (SD)	60.4 (± 12)	59.1 (± 13)	55.5 (± 13)	58.5 (± 13)	<0.001
Menopausal Status					
Pre-/Peri-	23 (21.1)	64 (21.8)	135 (32.1)	13 (23.2)	0.008
Post-	86 (78.9)	229 (78.2)	286 (67.9)	43 (76.8)	
Race					
White	106 (90.6)	236 (77.9)	337 (79.5)	46 (82.1)	0.253
Black	7 (6.0)	42 (13.9)	53 (12.5)	4 (7.1)	
AAPI	2 (1.7)	9 (3.0)	19 (4.5)	3 (5.4)	
Latin American	2 (1.7)	14 (4.6)	12 (2.8)	3 (5.4)	
Mixed	0 (0)	2 (0.7)	3 (0.7)	0 (0)	
Clinical Subtype					<0.001
HR+HER2+	120 (99.2)	307 (98.1)	278 (62.1)	15 (25.9)	
HR-HER2+	1 (0.8)	6 (1.9)	170 (37.9)	43 (74.1)	
Histological Subtype					<0.001
IDC	87 (73.1)	275 (90.5)	420 (95.0)	53 (100.0)	
ILC	29 (24.4)	17 (5.6)	1 (3.4)	0 (0)	
Mixed	3 (2.5)	12 (3.9)	7 (1.6)	0 (0)	
Grade					<0.001
G1	26 (21.5)	24 (8.1)	17 (4.0)	1 (1.9)	
G2	83 (68.6)	152 (51.2)	154 (35.8)	7 (13.0)	
G3	12 (9.9)	121 (40.7)	259 (60.2)	46 (85.2)	
T Stage					<0.001
T1	53 (71.6)	99 (45.0)	138 (41.9)	14 (36.8)	
T2	19 (25.7)	106 (48.2)	140 (42.6)	15 (39.5)	
T3	2 (2.7)	8 (3.6)	35 (10.6)	6 (15.8)	
T4	0 (0)	7 (3.2)	16 (4.9)	3 (7.9)	
N Stage					0.001
N0	59 (84.3)	151 (74.8)	196 (62.2)	27 (75.0)	
N1	9 (12.9)	40 (19.8)	103 (32.7)	6 (16.7)	
N2	1 (1.4)	8 (4.0)	14 (4.4)	1 (2.8)	
N3	1 (1.4)	3 (1.5)	2 (0.6)	2 (5.6)	
MammaPrint					<0.001
UltraLow	19 (15.7)	0 (0)	0 (0)	0 (0)	
Low	102 (84.3)	0 (0)	7 (1.6)	0 (0)	
High 1	0 (0)	248 (79.2)	177 (39.5)	6 (10.3)	
High 2	0 (0)	65 (20.8)	264 (58.9)	52 (89.7)	

Results

- MP classification of cHER2+ tumors (HR+HER2+ and HR-HER2+): 2% UltraLow, 11.6% Low, 45.8% High 1 and 40.5% High 2 (**Figure 1**).
- BP further classified 46% as Luminal A/B, 48% as HER2, and 6% as Basal (**Figure 1**).
- HR-HER2+ patients with BP HER2 tumors were younger, premenopausal, and had larger tumors compared to patients with Luminal-subtype (T3: 10.6% vs. 3.4%) (**Table 1**).
- Nodal involvement was more common in BP HER2 (37.8%) and Basal tumors (**Table 1**).
- Regardless of ER status, BP HER2 tumors (69.6%) achieved significantly higher pCR rate than BP Luminal (26.5%) in the cHER2+ tumors subset (**Figure 2**).
- pCR rates were significantly higher in BP HER2 tumors (61.2%) in HR+HER2+ subset compared to BP Luminal (26.5%) (**Figure 3**).

Conclusions & Future Directions

- MP and BP further classified cHER2+ tumors into distinct subtypes and BP identified the HER2 subtype as the most responsive to NHT.
- Consistent with ISPY2, BP HER2 tumors showed significantly higher pCR rates than BP Luminal, suggesting that additional therapeutic strategies are needed to increase the pCR rates in Luminal cancers.
- Prognostic value of pCR vs no pCR may be different by subtype, and follow-up for outcomes such as DMFS and DMFI is a future goal within the FLEX trial.

References

1. Jeong YH, et al., J Cancer, 2021; 2. Dowling, et al., Front Oncol, 2023; 3. Beitsch, et al., Ann Surg Onc, 2017; 4. Thomas A, et al., JCO 2022

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