

David B. Page¹, Ahmed Elkhany², Laila Samiian³, Jailan Elayoubi⁴, Rakhshanda Layeequr Rahman⁵, Eduardo Dias⁶, Alfredo A. Santillan⁷, Eric Allen Brown⁸, Linsey P. Gold⁹, Laurie Beth Matt-Amaral¹⁰, Nayana Dekhne³, Beth-Ann Lesnikoski¹¹, Regina Hampton¹², Henry Jacob Conter¹³, Sahra Uygun¹⁴, Nicole Stivers¹⁴, Andrea Menicucci¹⁴, William Audeh¹⁴, Joyce O'Shaughnessy¹⁵

¹ Providence Cancer Institute, Portland, OR; ² Baylor College of Medicine, Houston, TX; ³ Baptist MD Anderson Cancer Center, Jacksonville, FL; ⁴ Department of Hematology and Oncology, Karmanos Cancer Institute, Wayne State University, Detroit, MI; ⁵ Texas Tech University Health Sciences Center School of Medicine, Lubbock, TX; ⁶ Nashville Breast Center, Nashville, TN; ⁷ Texas Oncology, San Antonio, TX; ⁸ Comprehensive Breast Care, Troy, MI; ⁹ Cleveland Clinic Akron General, Akron, OH; ¹⁰ William Beaumont Hospital, Royal Oak, MI; ¹¹ DC Breast Care, Lanham, MD; ¹² F. William Osler Health System, Toronto, ON; ¹³ Agendia USA, Sherman Oaks, CA; ¹⁴ Agendia, Inc., Irvine, CA; ¹⁵ Baylor University Medical Center, Texas Oncology, Sarah Cannon Research Institute, Dallas, TX.

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Background

- Neoadjuvant outcomes are variable in human epidermal growth factor receptor 2-positive (HER2+) early breast cancer (EBC), highlighting the unmet need for predictive biomarkers
- The Blueprint (BP) assay classifies tumors by molecular intrinsic subtype, whereas the ImPrint hormone receptor-positive (HR+) and ImPrint triple-negative genomic signatures predicted immune sensitivity in the ISPY2 trial (Huppert et al. Ann Oncol. 2024)
- Because HER2+ EBCs are genomically heterogeneous, and because anti-HER2 has an immunologic mechanism of action, we hypothesized that BP and ImPrint could predict outcomes (pathologic complete response, pCR) following neoadjuvant chemotherapy + anti-HER2 (trastuzumab + pertuzumab, HP)

Methods

Study Cohort

The analysis included patients with clinically HER2-positive (cHER2+) EBC enrolled in the prospective, observational FLEX study who received neoadjuvant chemotherapy with trastuzumab plus pertuzumab and had available pCR data (n=252).

Molecular and Immune Profiling

Tumors were classified by Blueprint (BP) molecular subtype (HER2-type, Luminal A/B, Basal). ImPrint status was analyzed by hormone receptor (HR) status (HR+/ImPrintHR+ and HR-/ImPrintTN).

Statistics

pCR rates were compared by BP, ImPrintHR+/ImPrintTN, and their combination using Fisher's exact test. Multivariable logistic regression evaluated associations of BP and ImPrint with pCR, adjusting for tumor size and nodal status.

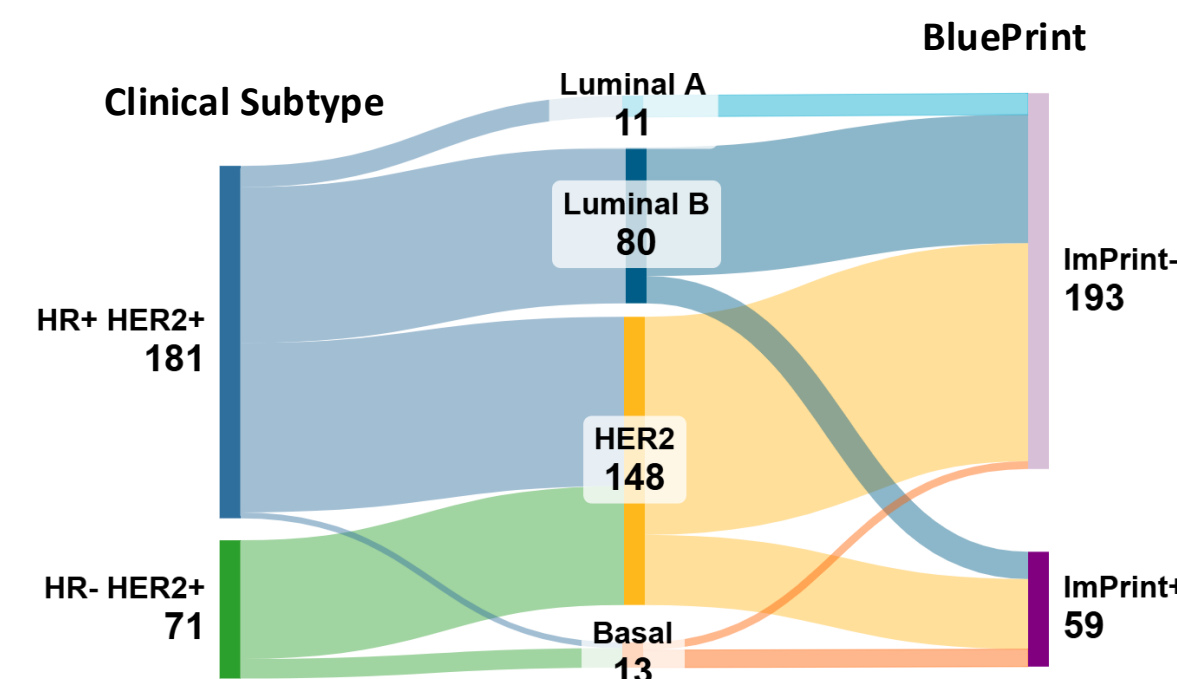
Results

Table 1. Clinical characteristics of eligible FLEX patients

	HR+HER2+ (N=181)	HR-HER2+ (N=71)	Total (N=252)	P value
Age				0.112
Median	52	56	53.5	
Mean	52	55	53	
SD	12	12	12	
Menopausal				0.102
Pre-/Peri-	74 (40.9%)	21 (29.6%)	95 (37.7%)	
Post-	101 (55.8%)	47 (66.2%)	148 (58.7%)	
NA	6 (3.3%)	3 (4.2%)	9 (3.6%)	
Race/ethnicity				0.778
AAPAI	6 (3.3%)	3 (4.2%)	9 (3.6%)	
Black	21 (11.6%)	9 (12.7%)	30 (11.9%)	
Latin American	27 (14.9%)	14 (19.7%)	41 (16.3%)	
White	114 (63.0%)	41 (57.7%)	155 (61.5%)	
NA	13 (7.2%)	4 (5.6%)	17 (6.7%)	
Grade				< 0.001
G1	6 (3.3%)	1 (1.4%)	7 (2.8%)	
G2	82 (45.3%)	14 (19.7%)	96 (38.1%)	
G3	86 (47.5%)	54 (76.1%)	140 (55.6%)	
NA	7 (4%)	2 (2.8%)	9 (3.6%)	
T Size				0.332
T1	35 (19.3%)	9 (12.7%)	44 (17.5%)	
T2	88 (48.6%)	33 (46.5%)	121 (48.0%)	
T3	17 (9.4%)	7 (9.9%)	24 (9.5%)	
T4	7 (3.9%)	6 (8.5%)	13 (5.2%)	
NA	34 (18.8%)	16 (22.5%)	50 (19.8%)	
LN Status				0.058
LN-	127 (70.2%)	57 (80.3%)	184 (73.0%)	
LN+	49 (27.1%)	11 (15.5%)	60 (23.8%)	
NA	5 (2.8%)	3 (4.2%)	8 (3.2%)	
MammaPrint				< 0.001
Ultralow	0 (0.0%)	0 (0.0%)	0 (0.0%)	
Low	12 (6.6%)	0 (0.0%)	12 (4.8%)	
High Risk 1	100 (55.2%)	10 (14.1%)	110 (43.7%)	
High Risk 2	69 (38.1%)	61 (85.9%)	130 (51.6%)	
Blueprint				< 0.001
Luminal A	11 (6.1%)	0 (0.0%)	11 (4.4%)	
Luminal B	80 (44.2%)	0 (0.0%)	80 (31.7%)	
HER2	87 (48.1%)	61 (85.9%)	148 (58.7%)	
Basal	3 (1.7%)	10 (14.1%)	13 (5.2%)	
ImPrint (HR for HR+, TN for HR-)				< 0.001
Negative	151 (83.4%)	42 (59.2%)	193 (76.6%)	
Positive	30 (16.6%)	29 (40.8%)	59 (23.4%)	
pCR				< 0.001
Yes	66 (36.5%)	56 (78.9%)	122 (48.4%)	
No	115 (63.5%)	15 (21.1%)	130 (51.6%)	

Data are presented as n (%) unless otherwise specified. Statistical significance was defined as p<0.05. Abbreviations: NA, unknown; AAPAI, Asian American and Pacific Islander; LN, lymph node

Figure 1. Distribution of Blueprint molecular subtypes among patients with cHER2-positive early breast cancer



- Among 252 patients with pCR data, 72% had HR+/HER2+ and 28% had HR-/HER2+ disease
- In HR+/HER2+, 52% were Blueprint non-HER2 (Luminal A 6%, Luminal B 44%, Basal 2%); in HR-/HER2+, 14% were non-HER2 (all Basal)
- pCR rates differed by Blueprint subtype and ImPrint status, with highest rates in Blueprint HER2-type and ImPrint-positive tumors across HR+/HER2+ and HR-/HER2+ disease
- Luminal B and ImPrint-negative tumors showed lower pCR rates
- Blueprint subtype and ImPrint positivity independently predicted pCR in HR+/HER2+ tumors



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Figure 2. Pathologic complete response (pCR) rates by Blueprint subtype, ImPrint status, and combined biomarker stratification

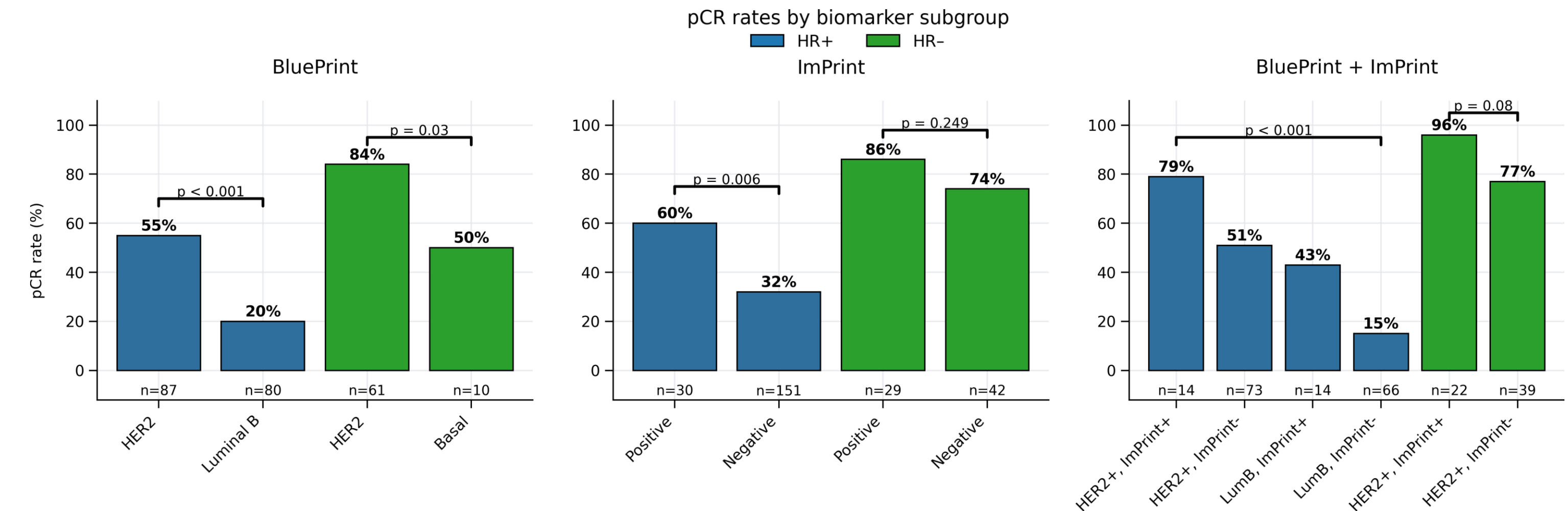
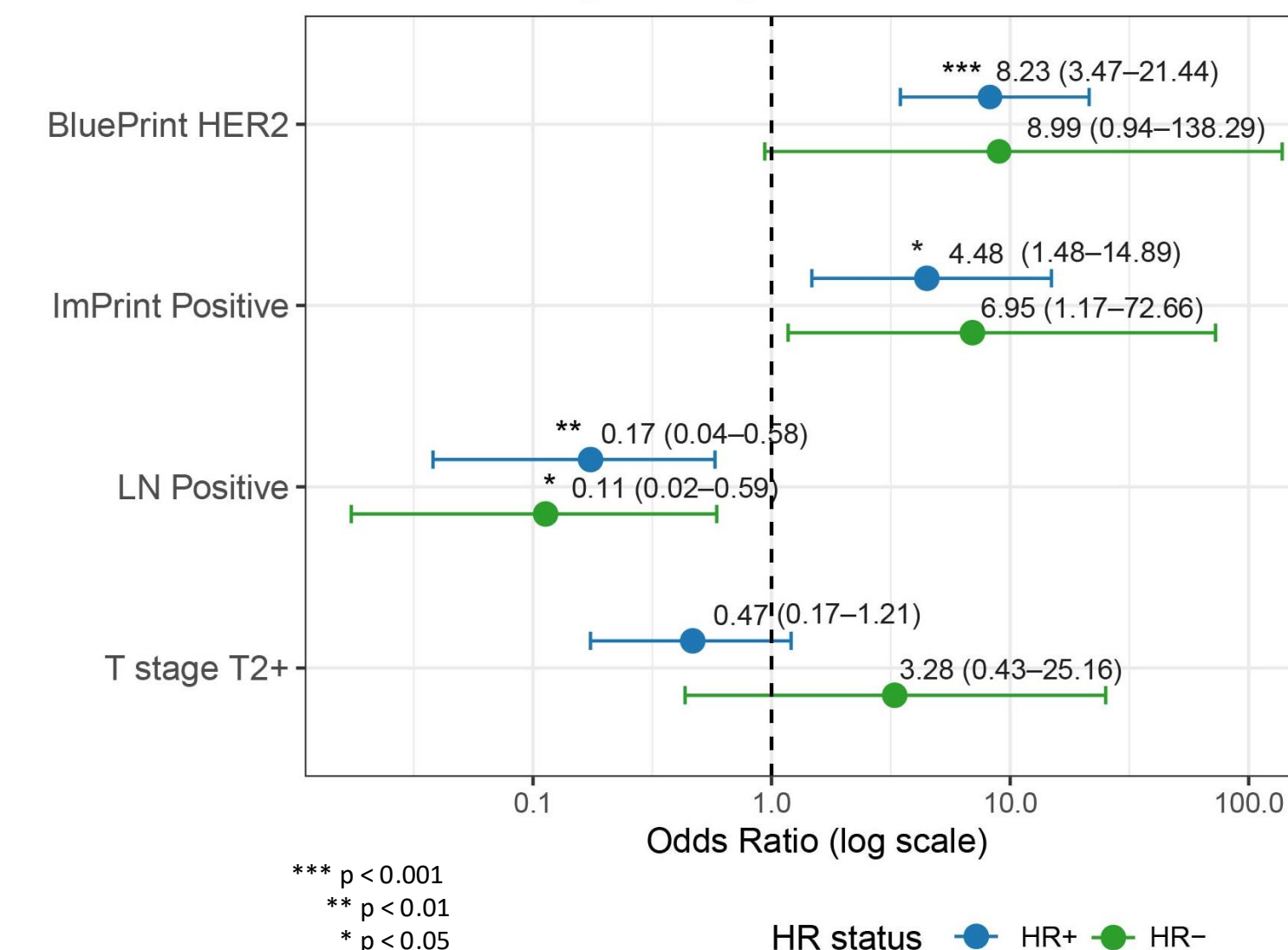


Figure 3. Association of Blueprint subtype and ImPrint status with pathologic complete response in multivariable logistic regression models



Conclusions

- These findings support the clinical utility of integrating tumor biology and immune profiling to refine patient stratification in HER2-positive early breast cancer
- An integrated genomic approach that combines BP and ImPrint maximizes prediction of pCR outcome in this dataset, particularly for the HR+/HER2+ subgroup
- These data could be useful for guiding clinical decision-making, including selection of chemotherapy backbone and adjuvant therapy
- Importantly, this approach may help identify patients who are overtreated or undertreated with current strategies, including those with exceptional treatment sensitivity who may be candidates for chemotherapy de-escalation.