MammaPrint Index as a predictive biomarker for neoadjuvant chemotherapy response and outcome in patients with HR+HER2- breast cancer in NBRST

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Background

- Indications for neoadjuvant chemotherapy (NCT) in hormone receptor positive (HR+), HER2- breast cancer remain controversial (1).
- Pathological complete response (pCR) rates range from 0-18%, and breast conservation is possible in up to 60% of cases.
- Genomic signatures may predict pCR and benefit of NCT better than conventional subtypes.
- The 70-gene MammaPrint (MP) test classifies patients with early breast cancer as having a Low or High Risk of distant metastasis (2-3).
- In the ISPY2 trial, further stratification of MP High Risk into High 1 or High 2 improved prediction of chemosensitivity, with significantly higher pCR rates in High 2 vs. High 1 tumors, particularly in response to immune therapy (4-6).

Objective: We evaluated the utility of High 1/High 2 risk as a biomarker for chemosensitivity and 5 year distant-metastasis free survival (DMFS) in NCT treated patients from the Neoadjuvant Breast Registry Symphony Trial (NBRST).

Methods

Study design: NBRST (NCT01479101) is an observational prospective study that evaluated the utility of MammaPrint and molecular subtyping signature, BluePrint, for neoadjuvant treatment decisions (6). Median follow-up was 5.3 years.

Patients and Genomic Testing: From 2011 to 2014, 1069 patients from 67 U.S. institutions with early breast cancer and who received neoadjuvant therapy were enrolled. A subset of patients with HR+HER2-, MammaPrint High Risk tumors who received NCT were included in this post-hoc analysis (n = 327)**.** Patient tumors were further stratified into the following MammaPrint groups:

High 1: index 0.000 to greater than -0.570
High 2: index -0.570 to -1.000

Statistical Analysis: 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. Differences in DMFS was evaluated by Kaplan Meier analysis and log-rank test.

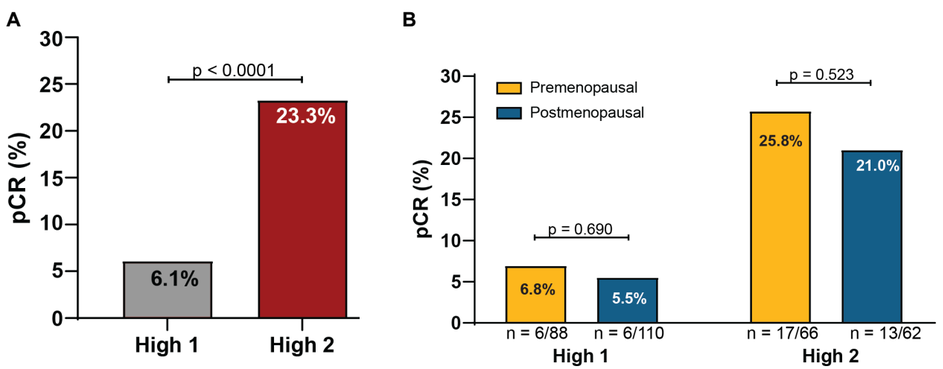
Results

Table 1. Clinical and genomic characteristics.

	MP High 1 (n = 198)	MP High 2 (n = 129)	*P**
Age	53 (22-79)	53 (23-79)	0.88
Grade[a], n (%)			
G1	15 (7.9)	2 (1.6)	
G2	95 (50.0)	18 (14.6)	
G3	80 (42.1)	103 (83.7)	**< 0.001**
T Stage[b], n (%)			
T1	22 (11.2)	12 (9.4)	
T2	108 (54.8)	75 (59.1)	
T3	54 (27.4)	30 (23.6)	
T4	13 (6.6)	10 (7.9)	0.79
N Stage[c], n (%)			
N0	56 (29.6)	43 (35.2)	
N1	115 (60.8)	61 (50.0)	
N2	16 (8.5)	14 (11.5)	
N3	2 (1.1)	4 (3.3)	0.18
BluePrint, n (%)			
Luminal-Type	193 (97.5)	47 (36.4)	
HER2-Type	1 (0.5)	1 (0.8)	
Basal-Type	4 (2.0)	81 (62.8)	**< 0.001**

[a]14 grade unknown; [b]3 T stage unknown; [c]16N stage unknown; *unknowns not included

Figure 1. pCR rates in patients with MammaPrint High 1 or High 2 tumors



- Of 327 patients with HR+HER2- tumors, 198 (61%) were High 1 and 129 (39%) were High 2 (Table 1).
- Most clinical characteristics were comparable between both groups. Although most were grade 3, High 2 tumors were observed among all grades (Table 1).
- Patients with High 2 tumors had significantly higher pCR rates vs. those with High 1 tumors (Figure 1A).
- Among both MP High Risk groups, pCR rates were comparable between premenopausal and postmenopausal patients (Figure 1B).
- Nearly all High 1 tumors were Luminal-Type, whereas more High 2 tumors were Basal-Type (Table 1). Of the MP High 2 risk group, events occurred earlier in patients with Basal-Type tumors compared to those with Luminal-Type tumors (Figure 2).
- Patients with High 2 risk had a significantly worse prognosis by over 12% than those with High 1 tumors. Most events (75.0%) occurred early (< 3 years) in High 2 tumors than High 1 tumors (48.8%) (Figure 3A).
- Patients that achieved pCR had improved outcomes, with similar 5-year DMFS probabilities between patients with High 1 or High 2 tumors (Figure 3B).
- Of patients with residual disease, those with High 2 tumors had significantly worse outcomes than High 1 tumors (Figure 3B).

Figure 2. 5-year DMFS of patients with MP High 2 tumors stratified by BluePrint

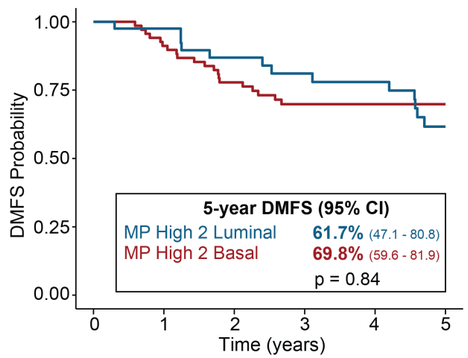
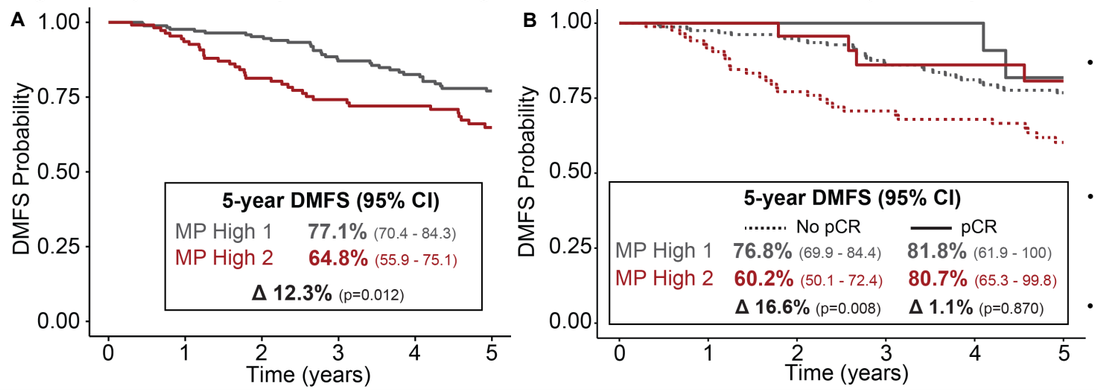


Figure 3. 5-year DMFS of patients with MP High 1 or High 2 tumors and stratified by NCT response



Conclusion

- These data establish neoadjuvant treatment utility for MammaPrint, which predicts pCR in patients with HR+HER2- treated with curative intent.
- Although both MP High Risk groups exhibit chemosensitivity, High 2 tumors have higher chemosensitivity than High 1 tumors.
- There was no intrinsic difference in chemosensitivity in breast cancers by menopausal status, suggesting that differences in treatment benefit between pre- and post-menopausal patients observed in other studies may not be due to tumor cytotoxicity from chemotherapy.
- These data highlight the critical importance of identifying patients with MammaPrint High 2 tumors early, in order to treat them neoadjuvantly and identify those that have residual disease to optimize treatment planning.
- Future studies should investigate whether addition of novel targeted therapies (i.e. CDK4/6 inhibitors or immune therapy) to standard NCT would enhance the pCR rates in these patient populations and improve outcome.

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