Improved Neoadjuvant Chemosensitivity Prediction for HR+HER2- Breast Cancer Patients with MammaPrint High 2 risk in the FLEX Trial and Descriptive Analysis of Dutch Routine-Testing

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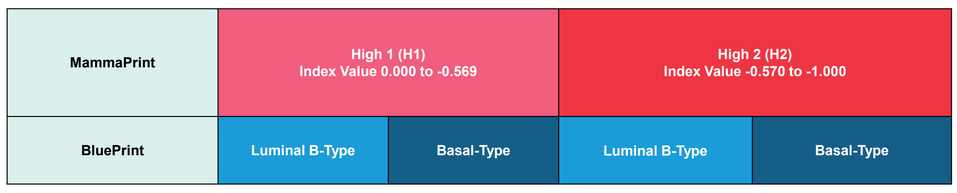
BACKGROUND

Hormone receptor-positive (HR+), HER2-negative early-stage breast cancer (EBC) displays notable heterogeneity and diverse responses to neoadjuvant chemotherapy (NCT). Utilizing genomic profiling has become crucial in guiding pre-operative treatment decisions by predicting the probability of achieving a pathological complete response (pCR) and demonstrating chemosensitivity. The MammaPrint (MP) test, analyzing 70 genes, effectively categorizes patients with EBC into Low or High-Risk groups for distant metastasis development [1-3]. Further refinement of the High-Risk group into High 1 (H1) and High 2 (H2) subcategories has demonstrated significantly improved pCR rates in MP H2 tumors compared to MP H1, particularly with NCT or targeted therapies such as immunotherapy. This study evaluates the efficacy of MP H1/H2 risk stratification as a biomarker for chemosensitivity in patients with HR+HER2- EBC participating in the real-world FLEX Trial [4,5]. Furthermore, data from the observational FLEX Trial and routine-testing in the Netherlands from 2019-2023 submitted to Agendia are compared.

METHODS

This analysis includes patients with HR+HER2-, MP High Risk tumors with available treatment response data from the FLEX Trial (NCT03053193) and data from routine diagnostics. This analysis specifically focuses on patients with HR+, HER2-negative, MP High Risk tumors for which treatment response data are available. Within the MP High Risk category, patients were further stratified into two groups: H1 (MP index 0.000 to -0.569) and H2 (MP index -0.570 to -1.000). Additionally, BluePrint classified tumors into Luminal-, HER2-, or Basal-Type categories. In the FLEX cohort, the endpoint of pathological complete response (pCR) was evaluated in a subset of patients who received neoadjuvant chemotherapy (NCT), totaling n=260.



RESULTS

MammaPrint H1 and H2 in FLEX

- MammaPrint classified 64% of tumors as H1 and 36% as H2.
- There was no significant difference in menopausal status, tumor stage, or lymph node status between the two groups.
- While a majority (80%) of H2 tumors were classified as Grade 3, only 60% of tumors classified as Grade 3 were identified as H2.
- The majority (97%) of H1 tumors were classified as Luminal B, in contrast to H2 tumors, where 46% were classified as Luminal B and 54% were classified as Basal according to BP classification.
- While H2 tumors were more prevalent in Low and Medium ER-staining groups, 23% of High ER-staining tumors were identified as H2.

Table 1. Clinical Characteristics in FLEX

Clinical Characteristics	High 1 n = 166	High 2 n = 94	P-value
BluePrint, n(%)			
Luminal B-Type	158 (96.9)	42 (46.2)	**<0.001**
Basal-Type	5 (3.1)	49 (53.8)	
Age, (Years)			
Median (SD)	55 ± 13	53 ± 13	0.593
Menopausal, n(%)			
Post-	96 (61.9)	54 (63.5)	0.964
Pre-/peri-	59 (38.1)	31 (36.5)	
Tumor grade (G), n(%)			
G1	11 (7.0)	1 (1.1)	**<0.001**
G2	98 (62.4)	17 (19.1)	
G3	48 (30.6)	71 (79.8)	
Tumor stage (T), n(%)			
T1	30 (24.6)	16 (25.0)	0.59
T2	63 (51.6)	39 (60.9)	
T3	23 (18.9)	5 (7.8)	
T4	6 (4.9)	4 (6.3)	
ER Staining, n(%)			
Low (<10%)	2 (1.3)	14 (17.5)	**<0.001**
Medium (10-50%)	8 (5.1)	22 (27.5)	
High (>50%)	146 (93.6)	44 (55.0)	
Lymph node status (N), n(%)			
LN-	48 (40.3)	32 (51.6)	0.57
LN+	71 (59.7)	30 (48.4)	

Difference in pCR rate between MP H1 and H2 tumors

- pCR rate was significantly higher in H2 tumors compared to H1 tumors.
- H1 tumors had a pCR rate of 6.6%, whereas H2 tumors had a pCR rate of 28.7%.

Difference in pCR rates by BP subtypes

- Basal-Type H2 tumors, with a sample size of 49, showed the highest pCR rate of 38.8%.
- Within the group of BP Luminal B tumors, those categorized as MP H2 had a notably higher pCR rate compared to those categorized as MP H1.
- Luminal B H1 tumors had a pCR rate of 6.3%, while Luminal B H2 tumors showed a pCR rate of 16.7%.

Figure 1. pCR rate by MammaPrint in FLEX

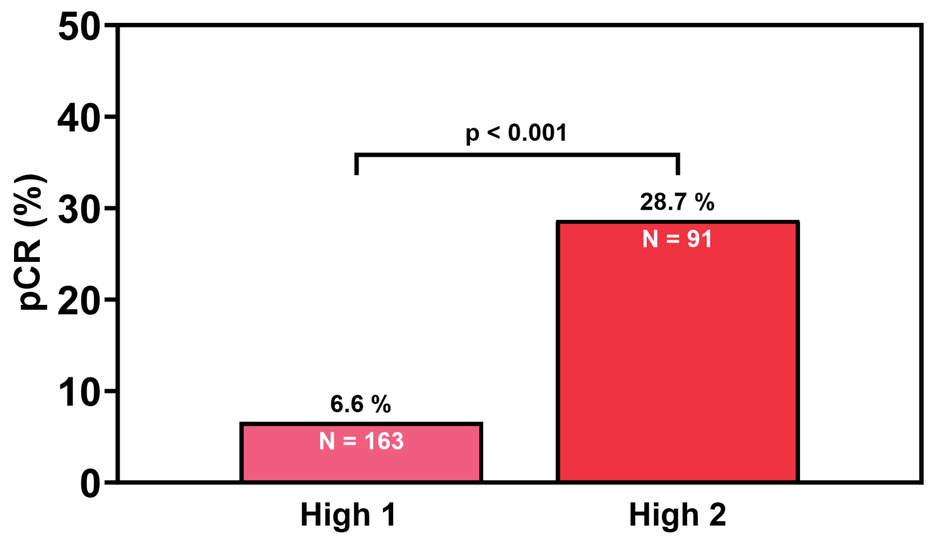
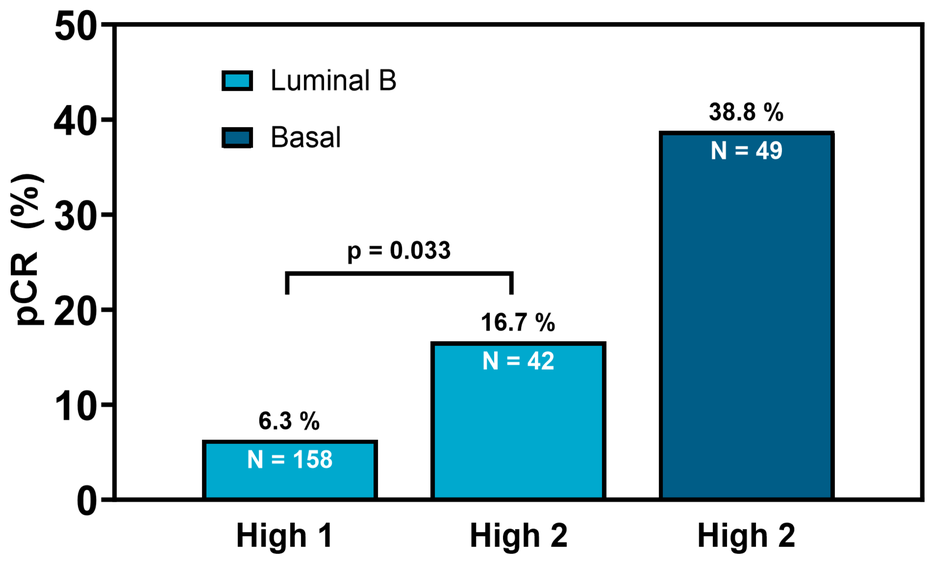


Figure 2. pCR rate by BluePrint in FLEX



MammaPrint H1 and H2 in Dutch routine-diagnostics

- Diagnostic samples from the Netherlands showed a distribution of 86% H1 versus 14% H2. Patients tested in routine-diagnostics in the Netherlands were mostly treated in the adjuvant setting.
- Similar to FLEX, nearly all (99%) H1 tumors were Luminal-Type, while for H2 tumors, 82% were Luminal-Type and 18% were Basal-Type in Dutch routine testing.

CONCLUSION

- The real-world data from the FLEX registry of MammaPrint and BluePrint has shown their utility in predicting the probability of a pCR after NCT in HR+, HER2- EBC.
- In the FLEX data set, clinical factors and tumor grading alone were not able to differentiate patients between MammaPrint High 1 and High 2 tumors.
- Both MammaPrint High 1 and High 2, show a response to chemotherapy. However, High 2 tumors have a significantly higher chemosensitivity than High 1 tumors.
- The lower proportion of MammaPrint High 2 in Dutch routine testing is likely a result of a lower baseline clinical risk that is generally observed in a patient group primarily treated in the adjuvant setting, versus a cohort that is entirely treated in the neoadjuvant setting, as was also observed in the High 1 versus High 2 analysis of FLEX in a subgroup treated only in the adjuvant setting[6].
- These findings are relevant for cases identified with a MammaPrint High 2 tumor and a first indication in what the MammaPrint High 1 versus High 2 risk categories could contribute to MammaPrint-guided treatment decision making in the Netherlands.

References: 1. Cardoso et al. N. Engl. J. Med., 2016; 2. Piccart et al. Lancet Oncol, 2021; 3. Whitworth et al. Annals of Surg Onc, 2022; 4. Van't Veer et al. EORTC-NCI-AACR, 2018; 5. Huppert et al. J. Clin. Oncol, 2022; 6. O'Shaughnessy et al. ASCO Abstract #551 2024.