# MammaPrint® Index predicts neoadjuvant chemosensitivity in patients with HR+HER2- early-stage breast cancer in the real-world evidence FLEX study

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San Antonio Breast Cancer Symposium ® December 5-9, 2023

**Presentation ID: PO5-15-04**

## Background

- Neoadjuvant chemotherapy (**NCT**) yields low pathologic Complete Response (**pCR**, ypT0/is ypN0) rates in unselected hormone receptor positive (HR+), HER2- early-stage breast cancer (**ESBC**).
- Genomic signatures may predict chemosensitivity and treatment benefit better than receptor status based clinical subtyping.
- The 70-gene expression signature, MammaPrint (**MP**), classifies patients with ESBC as having a High or Low Risk of distant recurrence and has been shown to be a continuous predictor of pCR.[1-3]
- In the NBRST and I-SPY2 trials, further stratification of MammaPrint High Risk into High Risk 1 (**H1**) or High Risk 2 (**H2**) showed significantly higher pCR rates to NCT or targeted agents in MP H2 cancers compared to MP H1 tumors.[4-6] MP H2 cancers also have high *CCNE2* expression and low sensitivity to endocrine therapy (SET) gene signature, both associated with CDK4/6 inhibitor resistance.[7,8]

## Objective

We evaluated MammaPrint H1 and H2 status as a biomarker for neoadjuvant chemosensitivity in patients with HR+, HER2- ESBC enrolled in the real-world evidence FLEX study.

## Methods

**Study cohort**

- FLEX (NCT03053193) is an ongoing prospective, observational trial that has currently enrolled 12,328 patients with ESBC who were tested with MammaPrint as standard of care, with or without molecular subtyping signature, BluePrint (**BP**), and consented to clinically annotated full genome data collection (data locked Feb. 2023).
- Patients with HR+, HER2-, MP High Risk tumors who received NCT and had pCR data available were included in this analysis (n = 214).

**Genomic testing**

- Patients were stratified into MP H1 (index 0.000 to -0.569) and H2 (index -0.570 to -1.000) groups. BP classified MP High Risk tumors into Luminal B-, HER2-, or Basal-Type.[3]

**Statistics**

- Differences in clinical characteristics and pCR rates between H1 and H2 tumors was assessed by Chi-Squared test and two-sided proportional z-test, respectively.
- The association between MP H1 and H2, BP subtype, and pCR was assessed using logistic regression and was adjusted for age, menopausal status, grade, T stage, N stage, and NCT regimen.

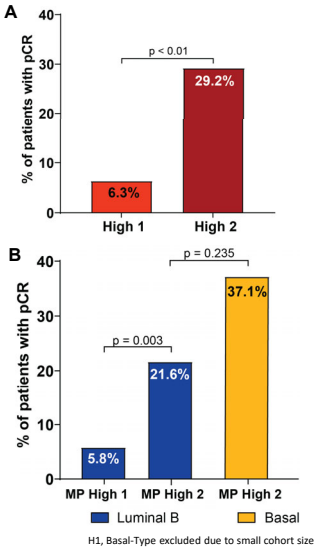
## Results

**Table 1. Clinical characteristics**

| Clinical Characteristics* | High 1 n = 142 | High 2 n = 72 | P |
|---|---|---|---|
| **Age, median (range)** | 56 (27-87) | 52 (27-77) | 0.04 |
| **Menopausal** | | | |
| Post- | 85 (65.4) | 41 (61.2) | 0.67 |
| Pre-/peri- | 45 (34.6) | 26 (38.8) | |
| **Race** | | | |
| White | 98 (76.6) | 52 (76.5) | 1.00 |
| Black | 17 (13.3) | 9 (13.2) | |
| Latin American | 8 (6.3) | 4 (5.9) | |
| AAPI | 5 (3.9) | 3 (4.4) | |
| **Tumor grade (G)** | | | |
| G1 | 7 (5.3) | 1 (1.4) | **<0.001** |
| G2 | 86 (65.2) | 12 (17.4) | |
| G3 | 39 (29.5) | 56 (81.2) | |
| **Tumor stage (T)** | | | |
| T1 | 29 (29.0) | 13 (27.1) | 0.59 |
| T2 | 49 (49.0) | 26 (54.2) | |
| T3 /T4 | 22 (22.0) | 9 (18.8) | |
| **Lymph node status (N)** | | | |
| LN- | 35 (35.4) | 24 (51.1) | 0.26 |
| LN+ | 64 (64.6) | 23 (48.9) | |
| **NCT regimen** | | | |
| TC | 35 (24.6) | 9 (12.7) | **<0.001** |
| AC-T | 96 (67.6) | 58 (81.7) | |
| Other | 11 (7.7) | 4 (5.6) | |
| **BluePrint** | | | |
| Luminal B-Type | 139 (97.9) | 37 (51.4) | **<0.001** |
| Basal-Type | 3 (2.1) | 35 (48.6) | |

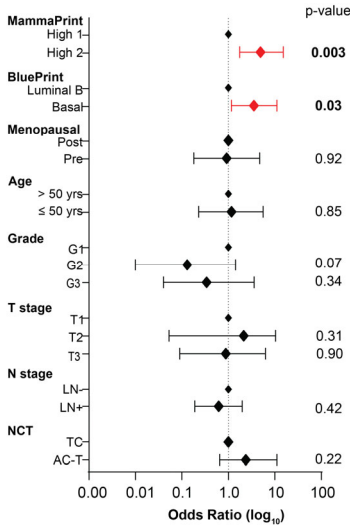
*Unknown excluded; data presented as n(%) unless otherwise indicated

**Figure 1. pCR rate by MammaPrint and BluePrint**




H1, Basal-Type excluded due to small cohort size

**Figure 2. Association of clinical and genomic factors with pCR**




- MammaPrint classified 66% of HR+, HER2- breast cancers as H1 and 34% as H2.
- Menopausal status, race, tumor stage, and lymph node status were comparable between both groups (Table 1).
- Although most (81%) H2 tumors were Grade 3, only 59% of all Grade 3 tumors were H2.
- Nearly all (98%) H1 tumors were Luminal B whereas for H2 tumors, 51% were Luminal B and 49% were Basal by BP classification.
- pCR rate was significantly higher in H2 tumors compared to H1 tumors (Figure 1A).
- Basal-Type, H2 tumors (n = 35) exhibited the highest pCR rate of 37.1% (Figure 1B).
- Among BP Luminal B tumors, those with MP H2 tumors had a significantly higher pCR rate vs. MP H1 tumors (Figure 1B).
- Multivariate analysis revealed MP H2 and BP Basal-Type were significantly associated with likelihood of pCR, whereas clinical variables including age, grade, and NCT regimen (TC [docetaxel + cyclophosphamide]; AC-T [doxorubicin, cyclophosphamide, followed by paclitaxel]) were not associated with increased likelihood of pCR (Figure 2).

## Conclusions

- These real-world data demonstrate MammaPrint and BluePrint clinical utility to predict the likelihood of achieving pCR after NCT in HR+HER2- ESBC.
- Clinical factors and grade are not sufficiently precise to predict pCR in patients with HR+, HER2- ESBC.
- Although both MP High Risk groups exhibit chemosensitivity, High 2 tumors have higher chemosensitivity than High 1 tumors. Future studies will evaluate the correlation between NCT regimens (TC vs AC-T), pCR, and whole transcriptome changes to understand the underlying biology of treatment response.
- Patients with High 2 tumors treated with PD-L1 or PARP inhibitors added to chemotherapy in the I-SPY2 trial had significantly higher pCR rates than High 2 tumors treated with NCT alone. Therefore, for patients with MP High 2 tumors, NCT is appropriate, and these patients may further benefit from the addition of targeted agents to standard NCT.
- Response to neoadjuvant immunotherapy is currently being evaluated in patients with HR+ HER2-, Stage II-III, MP High 2 breast cancer in the SWOG 2206 trial (NCT06058377) that is open to accrual.

**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. Pusztai et al. Cancer Cell, 2021; 7. Mittempergher et al. SABCS, 2019; 8. Licata et al. Br. J. Cancer 2023