Prediction of Chemotherapy Benefit by MammaPrint® in HR+HER2- Early-Stage Breast Cancer Revealed by the FLEX Registry of Real World Data

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Background

- Gene expression assays play a key role in personalizing adjuvant chemotherapy (CT) treatment decisions for patients with hormone receptor (HR)-positive, HER2-negative (HR+HER2-) early-stage breast cancer (EBC).
- The 70-gene signature, MammaPrint®, determines distant recurrence risk in EBC and has demonstrated its ability to guide CT de-escalation in patients with genomically Low Risk tumors based on the MINDACT trial.[1,2]
- In the FLEX Registry (NCT03053193) of Real World Data (RWD), we evaluated MammaPrint as a continuous variable to predict adjuvant CT benefit in patients diagnosed from 2017-2020 with HR+HER2- EBC.

Methods

Patient Population

Clinical Subtype	Treatment	Outcome	Propensity score matched	n	
HR+ HER2-	ET only	5-year distant recurrence or BC specific death (DRFI[3])	Meno status, tumor stage, nodal status	501	1002
	ET+CT			501	

Genomic testing: MammaPrint Index (MPI) is defined as UltraLow (+1.000 to +0.356), Low (+0.355 to +0.001), High 1 (0.000 to -0.569), and High 2 (-0.570 to -1.000) Risk of distant recurrence.

Statistics: Kaplan Meier analysis estimated 5-year Distant Recurrence-Free Interval (DRFI)[3] as a continuous function of the MPI for each treatment group, with predicted 95% confidence intervals (CIs). Cox proportional hazards model was used to test for interaction between CT treatment and clinical variables. P-values of <0.05 were considered significant.

Results

Table 1. Propensity Score Matched Clinical Characteristics

Characteristic	ET only (n=501)	ET+CT (n=501)	All (n=1002)	P-Value
Age (Years)				
Mean (SD)	59 (± 12)	58 (± 11)	59 (± 12)	0.12
Menopausal Status				
Pre-/Peri-	141 (29.2%)	119 (24.8%)	260 (27.0%)	0.319
Post-	342 (70.8%)	360 (75.2%)	702 (73.0%)	
Race				
White	428 (90.3%)	366 (77.4%)	794 (83.8%)	<0.001
Black	24 (5.1%)	61 (12.9%)	85 (9.0%)	
Latin American	14 (3.0%)	29 (6.1%)	43 (4.5%)	
AAPI	8 (1.7%)	16 (3.4%)	24 (2.5%)	
AIAN	0	1 (0.2%)	1 (0.1%)	
Tumor Stage				
T1	197 (42.4%)	183 (39.0%)	380 (40.7%)	0.853
T2	208 (44.7%)	230 (49.0%)	438 (46.9%)	
T3	54 (11.6%)	47 (10.0%)	101 (10.8%)	
T4	6 (1.3%)	9 (1.9%)	15 (1.6%)	
Lymph Node Status				
LN-	361 (78.0%)	341 (73.2%)	702 (75.6%)	0.225
LN+	102 (22.0%)	125 (26.8%)	227 (24.4%)	
Grade				
G1	185 (38.9%)	66 (14.1%)	251 (26.6%)	<0.001
G2	259 (54.4%)	254 (54.4%)	513 (54.4%)	
G3	32 (6.7%)	147 (31.5%)	179 (19.0%)	

Data presented in both tables as n (%) unless indicated otherwise. Unknown values excluded. Differences in clinical characteristics were assessed using Student's t-test, Chi-squared or Fisher's Exact Test. SD = standard deviation; AAPI = Asian or American Pacific Islander; AIAN = American Indian or Alaskan Native.

Figure 1. Risk of 5-year DRFI for patients receiving ET vs ET+CT across the MammaPrint Index

MammaPrint Risk Group	ET Risk % Average (% Range)	ET+CT Risk % Average (% Range)	Difference in Risk % Average (% Range)
UltraLow	1.0 (0.6 to 2.2)	0.4 (0.1 to 1.0)	0.6 (0.5 to 1.2)
Low	3.2 (2.2 to 4.5)	1.5 (1.0 to 2.1)	1.7 (1.2 to 3.3)
High 1	10.0 (5.6 to 14.6)	4.4 (2.6 to 6.4)	5.6 (3.0 to 8.2)
High 2	19.1 (14.8 to 24.8)	8.2 (6.5 to 10.6)	10.9 (8.3 to 14.2)

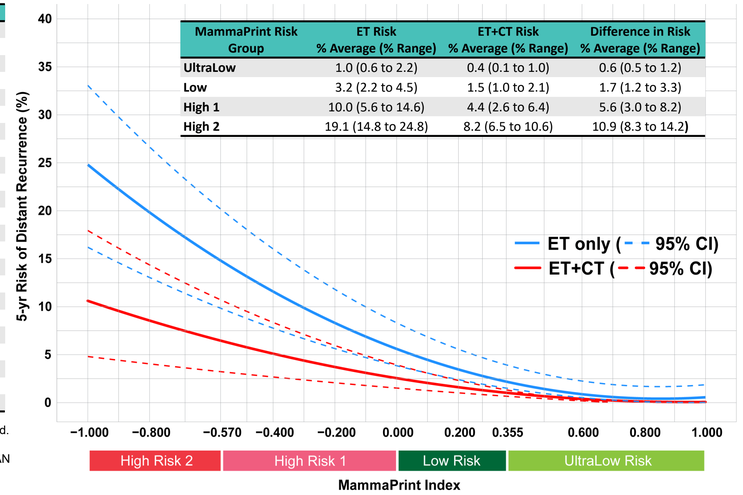


Table 2. Cox proportional hazards model assessing interaction between CT treatment and clinical variables

Variable	Adjusted HR	Interaction P-value
MammaPrint Index	0.15 (0.02-0.97)	**0.047**
Age	0.95 (0.89-1.02)	0.158
Menopausal Status		
Post-	-	**0.025**
Pre-/Peri-	0.08 (0.01-0.74)	
Tumor Stage		
T1	-	0.52
T2	1.08 (0.30-3.97)	
T3	1.67 (0.35-8.03)	
Lymph Node Status		
LN-	-	0.114
LN+	2.62 (0.79-8.63)	
Grade		
G1	-	0.695
G2	1.05 (0.31-3.58)	
G3	0.99 (0.10-9.76)	

Hazards Ratio (HR) presented as HR (95% CI). CI = confidence interval.

Figure 2. Association of MammaPrint Index and 5-year chemotherapy benefit

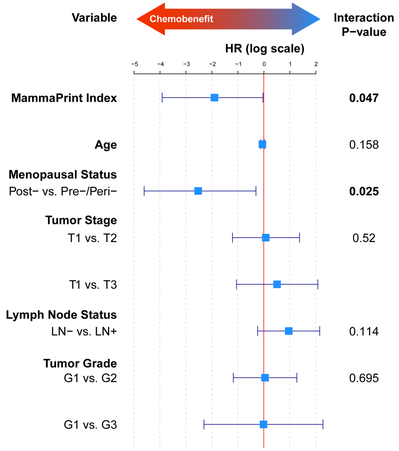
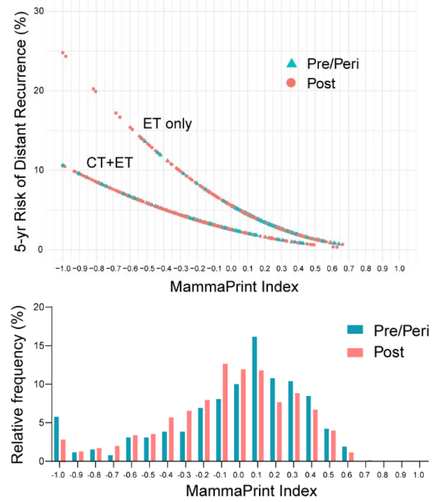


Figure 3. Patient distribution by menopausal Status



- Clinical features were comparable between treatment groups, except Grade 3 was significantly more likely among ET+CT treated patients (**Table 1**).
- The MPI was strongly predictive of measuring 5-year DRFI in ET only (R^2=0.99, p<0.001) and ET+CT patients (R^2 = 0.90, p<0.001).
- Significant DRFI risk differences were observed between ET and ET+CT as MPI risk increased. Minimal CT benefit was observed for Low and UltraLow Risk, while High 2 tumors observed a CT benefit of up to 14.2% compared to ET alone (**Figure 1**).
- In a subgroup of Clinical Low Risk, MammaPrint High Risk (n=209), ET+CT group had lower risk of a DRFI event (1.8%) than the ET only group (4.5%).
- A Multivariate Model demonstrated that CT benefit was dependent on increasing MPI risk (HR = 0.15; 95% CI 0.02-0.97, p = 0.047) (**Table 2, Figure 2**).
- CT benefit was also significantly associated with premenopausal status, however, sensitivity analysis revealed higher proportions of premenopausal patients compared to postmenopausal patients within the MammaPrint Low Risk range (**Figure 3**).

Conclusions

- In this Real World Evidence prospective, propensity score matched study of 1002 patients, patients with increasing MPI risk (High Risk) had significantly lower risk of DRFI events when treated with ET+CT compared to ET alone.
- Consistent with findings from MINDACT, patients with MammaPrint indices within Low and UltraLow Risk ranges did not derive significant CT benefit.
- Chemotherapy benefit is not predicted by higher tumor grade after adjusting for MPI and clinical factors.
- Observed CT benefit in premenopausal patients with MammaPrint Low Risk may be due to ovarian function suppression.[4]
- These RWD confirm MammaPrint's comprehensive utility, as prognostic of recurrence risk and predictive of CT benefit for patients with HR+HER2- early-stage breast cancer.

References: 1. Piccart et al. Lancet Oncol. 2021. 2. Lopes Cardoso et al. JCO. 2022. 3. Tolaney et al. JCO. 2021. 4. Whitworth et al. Ann Surg Oncol. 2022.