HR+ HER2- Early Breast Cancer (EBC) Patients ≥70 with High Risk 70-gene Signature Benefit from (Neo)adjuvant Chemotherapy (CT): Real World FLEX Study

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Background

- Women ≥ 70 years of age are less likely to receive chemotherapy (CT) due to quality-of-life concerns and comorbidities.[1,2]
- These patients (pts) are underrepresented in studies assessing the utility of genomic profiling to guide CT decisions.[1,2]
- **Objective:** To evaluate the utility of the 70-gene recurrence risk assay MammaPrint (MP), we examined the relationship of age (≥70 vs <70), comorbidities, and treatment outcomes stratified by MP result in pts with HR+HER2- early-stage breast cancer (EBC).

Methods

STUDY COHORT

- The FLEX Study (NCT03053193) includes stage I-III pts with EBC who had MP performed and consented to full transcriptome and clinical data collection. A total of 6,237 HR+HER2- EBC pts were included. 1,145 were ≥70 (18%) and 4792 <70 (82%)

STATISTICS

- Clinical characteristic differences between age groups were assessed by Chi-squared, Fisher's exact, or Wilcoxon-Mann-Whitney tests. 4-year (yr) Distant Recurrence Free Survival (DRFS) was assessed using Kaplan-Meier survival analysis with log-rank tests.
- Comorbidity scoring assigned conditions into 7 categories (adapted from the Charlson Comorbidity Index[3]). Pts were assigned 1 point for each category with a reported condition; multiple conditions in a single category counted as 1 point (Table 1).
- A multivariate Cox regression model evaluated predictors of DRFS in pts ≥70, adjusting for treatment-genomic risk interactions.

Table 1. Comorbidity Scoring

Category	Conditions	Weight
Neurodegenerative	Alzheimer disease or dementia, Parkinson's disease	1
Cardiovascular	Atrial Fibrillation, Coronary Artery Disease, Cardiomyopathy, Heart Failure, Hypertension	1
Thromboembolic	Deep vein thrombosis (DVT), Pulmonary embolism (PE), Stroke	1
Respiratory	COPD / emphysema	1
Metabolic/Endocrine	Diabetes Type 1, Diabetes Type 2	1
Renal	Chronic Kidney Disease	1
Psychiatric	Schizophrenia and Other Psychotic Disorders	1

Table 2. Clinical Characteristics

	<70 (N=4792)	≥ 70 (N=1445)	All (N=6237)	P-value
MP Group				
UltraLow	702 (14.6%)	219 (15.2%)	921 (14.8%)	0.0115
Low	1892 (39.5%)	599 (41.5%)	2491 (39.9%)	
High1	1759 (36.7%)	541 (37.4%)	2300 (36.9%)	
High2	439 (9.2%)	86 (6.0%)	525 (8.4%)	
BP Subtype				
Luminal A	2471 (51.6%)	790 (54.7%)	3261 (52.3%)	0.0275
Luminal B	1872 (39.1%)	564 (39.0%)	2436 (39.1%)	
Basal	202 (4.2%)	40 (2.8%)	242 (3.9%)	
HER2	2 (0.0%)	2 (0.1%)	4 (0.1%)	
Not requested	245 (5.1%)	49 (3.4%)	294 (4.7%)	
Menopausal Status				
Pre-/Peri-	1237 (25.8%)	3 (0.2%)	1240 (19.9%)	<0.001
Post-	3236 (67.5%)	1406 (97.3%)	4642 (74.4%)	
Unknown	319 (6.7%)	36 (2.5%)	355 (5.7%)	
Race/Ethnicity				
AAPI	118 (2.5%)	14 (1.0%)	132 (2.1%)	<0.001
AIAN	6 (0.1%)	2 (0.1%)	8 (0.1%)	
Black	430 (9.0%)	99 (6.9%)	529 (8.5%)	
Latin American/Hispanic	298 (6.2%)	53 (3.7%)	351 (5.6%)	
Multiple	16 (0.3%)	6 (0.4%)	22 (0.4%)	
White	3615 (75.4%)	1203 (83.3%)	4818 (77.2%)	
Unknown	309 (6.4%)	68 (4.7%)	377 (6.0%)	
Tumor Size				
T1	3128 (65.3%)	999 (69.1%)	4127 (66.2%)	0.153
T2	1369 (28.6%)	380 (26.3%)	1749 (28.0%)	
T3	202 (4.2%)	44 (3.0%)	246 (3.9%)	
Unknown	93 (1.9%)	22 (1.5%)	115 (1.8%)	
Lymph Node Status				
LN-	3557 (74.2%)	1086 (75.2%)	4643 (74.4%)	<0.001
LN+	1122 (23.4%)	275 (19.0%)	1397 (22.4%)	
Unknown	113 (2.4%)	84 (5.8%)	197 (3.2%)	
Grade				
G1	1511 (31.5%)	457 (31.6%)	1968 (31.6%)	0.0575
G2	2498 (52.1%)	804 (55.6%)	3302 (52.9%)	
G3	746 (15.6%)	175 (12.1%)	921 (14.8%)	
Unknown	37 (0.8%)	9 (0.6%)	46 (0.7%)	
Systemic Type				
ET only	2755 (57.5%)	1069 (74.0%)	3824 (61.3%)	<0.001
ET+CT	2037 (42.5%)	376 (26.0%)	2413 (38.7%)	

Figure 1. DRFS for patients ≥70 with High Risk HR+HER2- early breast cancer: CT vs. No CT

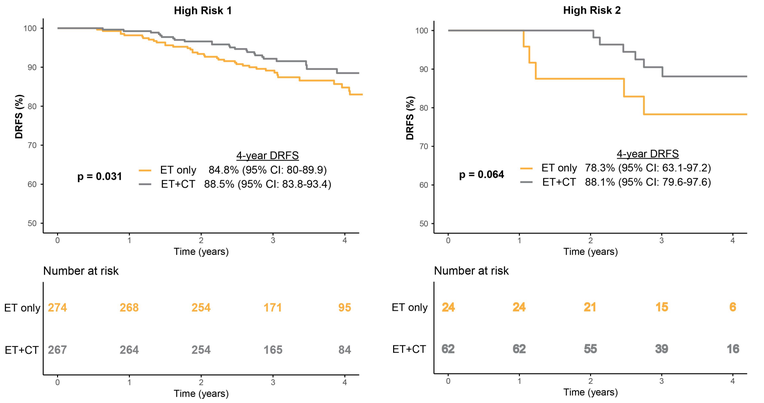


Table 3. Descriptive Stats

Comorbidity Weight	<70 (N=950)	≥70 (N=317)	Overall (N=1267)	P-value
0	399 (42.0%)	53 (16.7%)	452 (35.7%)	<0.001
1	406 (42.7%)	177 (55.8%)	583 (46.0%)	
2	124 (13.1%)	80 (25.2%)	204 (16.1%)	
3+	21 (2.2%)	7 (2.2%)	28 (2.2%)	
Mean (SD)	0.76 (± 0.78)	1.1 (± 0.70)	0.85 (± 0.77)	<0.001

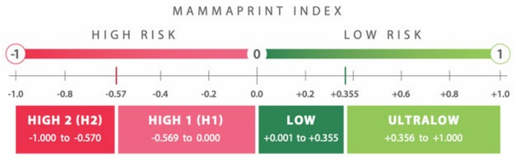
Data presents n (%) unless indicated otherwise. p<0.05 indicates significance. Abbreviations: AAPI, Asian American and Pacific Islander; AIAN, American Indian or Alaska Native; ET, endocrine therapy; HR, Hazard Ratio, CI, Cofinance Interval

Table 4. Multivariate Cox regression for predictors of DRFS with Interaction terms

Variable		HR (95% CI, p-value)
Comorbidity Weight	0	reference
	1	1.01 (0.54-1.91, p=0.969)
	2+	2.94 (1.58–5.46, p=0.001)
Tumor Size	T1	reference
	T2	1.44 (1.13–1.83, p=0.003)
	T3	3.09 (2.11-4.53, p<0.001)
Lymph Node Status	LN-	reference
	LN+	1.58 (1.24–2.01, p<0.001)
Grade	G1	reference
	G2	1.35 (1.02-1.79, p=0.039)
	G3	1.48 (1.00–2.18, p=0.049)
MammaPrint	H1 w/ CT	0.51 (0.29-0.88, p=0.015)
	H2 w/ CT	0.35 (0.16–0.77, p=0.009)

Results

- There were more MP Low and UltraLow tumors in the ≥70 vs. <70 group (Ultralow 15.2% vs 14.6%, Low 41.5% vs 39.5%, High 1 (H1) 37.4% vs 36.7%, and High 2 (H2) 6.0% vs 9.2%, p = 0.0115) (Table 2)
  - Pts aged ≥70 with MammaPrint High Risk cancers were less likely to receive CT than those <70 (H1: 49.4% vs 77.1%, H2: 72.1% vs 90.9%, p<0.001).
- Pts ≥70 (83.2%) were more likely to have 1 or more comorbidities to those <70 (58.0%, p<0.001; Table 3).
  - A larger proportion of ≥70 pts vs <70 had a comorbidity score of 2 (25.2% vs 13.1%). Scores of 3+ were rare at 2.2% in both groups.
- The 4-year DRFS for pts ≥70 with MP High Risk cancers showed a trend towards improved outcomes for those treated with CT vs. endocrine therapy alone, especially in H2 cancers (H1 88.5% vs 84.8%, p=0.031, H2 88.1% vs 78.3%, p=0.064) (Figure 1).
- In the interaction model, CT was associated with significantly improved DRFS in H1 (HR=0.51, p=0.015) and H2 (HR=0.35, p=0.009) pts ≥70 (Table 4).



Conclusions

- This Real-World Evidence study demonstrates that pts ≥70 with HR+ HER2− EBC are less likely to receive CT than younger pts, despite a substantial number being classified as MammaPrint High.
- Among pts ≥70 with MP High, CT use was associated with improved DRFS, after adjusting for comorbidities.
- While the unadjusted difference in 4-year DRFS for the H2 subgroup did not reach significance, multivariate analysis showed a significant association between CT and reduced recurrence risk. These findings suggest that MP may provide additional risk information supporting individualized treatment decisions in pts ≥70 with HR+HER2- even after adjusting for comorbidities.

References: 1. Hutchins et al., N Engl J Med, 1999; 2. Lacaze et al., Cancers, 2021; 3. Charlson et al., J Chronic Dis,1987

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