Adjuvant ovarian function suppression (OFS) in HR+/HER2+ premenopausal breast cancer (BC) patients with pathologic complete response (pCR) or residual disease (RD) after neoadjuvant chemotherapy (NAC): a real-world study

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Background

- The HERA trial demonstrated survival benefits with the addition of OFS to adjuvant endocrine therapy (ET) in premenopausal patients (pts) with HR+/HER2+ early BC.
- However, the benefit of OFS over tamoxifen (TAM) alone remains unclear in the post-NAC setting, particularly among pts who achieve pCR or have RD.
- We aimed to evaluate real-world survival outcomes by comparing OFS-based ET versus TAM alone among pts who achieved pCR or had RD in this distinct BC subtype.

Methods

- This was a retrospective study of premenopausal pts ≤50y with HR+/HER2+ stage I-III BC who achieved pCR (ypTis/T0 ypN0) or had RD after NAC at MSK (2008–2025).
- Pts were categorized by adjuvant ET: OFS+ TAM or aromatase inhibitor (AI) vs. TAM alone. Pts receiving >1 ET type were classified by the therapy used for >75% of their total ET duration.
- Primary endpoints were DFS and OS, estimated using the Kaplan-Meier method and compared across ET groups using the log-rank test. Pt characteristics were compared using chi-squared, Wilcoxon rank-sum, and Fisher's exact tests.
- MV Cox proportional hazards models were conducted to further evaluate the adjusted associations between ET group and pt characteristics with DFS and OS.
- Baseline characteristics significantly associated with DFS in UV analyses were included in MV Cox models.
- ET exposure was modeled as a time-dependent covariate to account for differences in exposure time among pts receiving >1 ET type.

Results

Table 1. Patient characteristics by ET group.

Characteristic	Overall (N = 309)†	OFS + TAM/AI (N = 146)†	TAM alone (N = 163)†	p-value‡
Age at diagnosis, years, median (IQR)	40 (35, 44)	41 (35, 44)	40 (35, 44)	>0.9
Age at diagnosis, years, n (%)				0.8
<35	70 (23%)	32 (22%)	38 (23%)	
≥35	239 (77%)	114 (78%)	125 (77%)	
BMI, kg/m², median (IQR)	25 (22-30)	26 (22-30)	25 (21-30)	0.2
BMI, kg/m², n (%)				0.2
<25	147 (48%)	64 (44%)	83 (52%)	
25-30	86 (28%)	48 (33%)	38 (24%)	
>30	71 (23%)	33 (23%)	38 (24%)	
Unknown	5	1	4	
Race, n (%)				0.5
White	194 (66%)	93 (67%)	101 (66%)	
Black or African American	28 (9.6%)	16 (12%)	12 (7.8%)	
Asian	45 (15%)	18 (13%)	27 (18%)	
Other	25 (8.6%)	11 (8.0%)	14 (9.1%)	
Unknown	17	8	9	
Ethnicity, n (%)				>0.9
Hispanic or latino	40 (14%)	19 (14%)	21 (14%)	
Non-Hispanic or Non-latino	246 (86%)	115 (86%)	131 (86%)	
Unknown	23	12	11	
ER Primary, n (%)				0.02
Positive	282 (91%)	139 (95%)	143 (88%)	
Positive-low (ER <10%) or Negative	27 (8.7%)	7 (4.8%)	20 (12%)	
PR Primary, n (%)				0.12
Positive	258 (83%)	127 (87%)	131 (80%)	
Negative	51 (17%)	19 (13%)	32 (20%)	
Grade, n (%)				0.8
I-II (well/moderately differentiated)	80 (27%)	40 (28%)	40 (26%)	
III (poorly differentiated)	219 (73%)	105 (72%)	114 (74%)	
Unknown	10	1	9	
Histology, n (%)				0.2
Ductal	295 (95%)	143 (98%)	152 (93%)	
Lobular	6 (1.9%)	1 (0.7%)	5 (3.1%)	
Mixed	8 (2.6%)	2 (1.4%)	6 (3.7%)	
Clinical stage, n (%)				0.7
Stage I	11 (3.6%)	4 (2.8%)	7 (4.4%)	
Stage II	234 (77%)	111 (77%)	123 (77%)	
Stage III	60 (20%)	30 (21%)	30 (19%)	
Unknown	4	1	3	
Clinical T stage, n (%)				>0.9
Tis,T1,T2	241 (79%)	114 (79%)	127 (78%)	
T3,T4	66 (21%)	31 (21%)	35 (22%)	
Unknown	2	1	1	
Clinical N stage, n (%)				0.032
N0	131 (43%)	53 (37%)	78 (49%)	
N1, N2, N3	174 (57%)	92 (63%)	82 (51%)	
Unknown	4	1	3	

† Median (Q1, Q3); n (%); ‡ Wilcoxon rank sum test; Pearson's Chi-squared test; Fisher's exact test

BMI: Body Mass Index

Table 2. Tumor characteristics after neoadjuvant chemotherapy (NAC) by ET group.

Characteristic	Overall (N = 309)	OFS + TAM/AI (N = 146)	TAM alone (N = 163)	p-value†
Pathologic response, n (%)				0.3
pCR	157 (51%)	67 (46%)	90 (55%)	
Stage I	89 (29%)	47 (32%)	42 (26%)	
Stage II	46 (15%)	22 (15%)	24 (15%)	
Stage III	17 (5.5%)	10 (6.8%)	7 (4.3%)	
Post-NAC overall grade, n (%)				0.12
I (well differentiated)	16 (5.7%)	7 (5.2%)	9 (6.2%)	
II (moderately differentiated)	88 (32%)	52 (39%)	36 (25%)	
III (poorly differentiated)	11 (3.9%)	4 (3.0%)	7 (4.8%)	
Unevaluable (Minimal or no RD with N+)	7 (2.5%)	4 (3.0%)	3 (2.1%)	
Unknown	30	12	18	
Post-NAC ER, n (%)				0.2
Positive	120 (42%)	64 (47%)	56 (37%)	
Negative	4 (1.4%)	1 (0.7%)	3 (2.0%)	
Unevaluable (Minimal or no RD with N+)	8 (2.8%)	5 (3.6%)	3 (2.0%)	
Unknown	20	9	11	
Post-NAC PR, n (%)				0.2
Positive	77 (27%)	43 (31%)	34 (23%)	
Negative	46 (16%)	22 (16%)	24 (16%)	
Unevaluable (Minimal or no RD with N+)	8 (2.8%)	5 (3.6%)	3 (2.0%)	
Unknown	21	9	12	
Post-NAC HER2 Overall, n (%)				0.12
Positive	84 (30%)	42 (31%)	42 (28%)	
Negative	35 (12%)	22 (16%)	13 (8.8%)	
Unevaluable (Minimal or no RD with N+)	8 (2.8%)	5 (3.7%)	3 (2.0%)	
Unknown	25	10	15	

† Pearson's Chi-squared test; Fisher's exact test

Table 3. Treatment characteristics by ET group.

Characteristic	Overall (N = 309)	OFS + TAM/AI (N = 146)	TAM alone (N = 163)	p-value†
NAC chemotherapy, n (%)				0.002
ACTHP	214 (69%)	101 (69%)	113 (69%)	
TCHP	59 (19%)	34 (23%)	25 (15%)	
THP	15 (4.9%)	9 (6.2%)	6 (3.7%)	
ACTH	8 (2.6%)	1 (0.7%)	7 (4.3%)	
Other+HP	13 (4.2%)	1 (0.7%)	12 (7.4%)	
Adjuvant HER2 blockade, n (%)				<0.001
T-DM1	77 (25%)	52 (36%)	25 (15%)	
Pertuzumab and Trastuzumab	205 (66%)	86 (59%)	119 (73%)	
Trastuzumab monotherapy	23 (7.4%)	8 (5.5%)	15 (9.2%)	
None	4 (1.3%)	0 (0%)	4 (2.5%)	
Primary breast surgery, n (%)				0.5
Breast-Conserving Surgery (BCS)	121 (39%)	54 (37%)	67 (41%)	
Total Mastectomy (TM)	188 (61%)	92 (63%)	96 (59%)	
Axila surgery, n (%)				0.6
SLNB	234 (76%)	112 (77%)	122 (75%)	
ALND	74 (24%)	33 (23%)	41 (25%)	
Unknown	1	1	0	
Adjuvant radiotherapy, n (%)	229 (74%)	113 (77%)	116 (71%)	0.2
Switch adjuvant ET, n (%)	36 (12%)	25 (17%)	11 (6.7%)	0.005

† Pearson's Chi-squared test; Fisher's exact test

SNLB: Sentinel Lymph Node Biopsy; ALND: Axillary Lymph Node Dissection

Table 4a. DFS multivariable Cox model by ET group, adjusted for pathologic stage and adjuvant HER2 therapy in the overall cohort.

Characteristic	Event N	HR†	95% CI†	p-value
Adjuvant ET				
OFS+TAM/AI	12	—	—	
Tamoxifen alone	27	1.9	0.91, 3.98	0.088
Pathologic stage				
pCR	11	—	—	
Stage I	11	1.79	0.73, 4.44	0.2
Stage II	7	1.9	0.69, 5.22	0.2
Stage III	10	7.52	2.83, 20.0	<0.001
Adjuvant HER2 Therapy				
T-DM1	6	—	—	
Pertuzumab and Trastuzumab	18	0.98	0.34, 2.79	>0.9
Trastuzumab monotherapy	13	3.6	1.27, 10.3	0.016
None	2	4.62	0.84, 25.5	0.079

† HR = Hazard Ratio, CI = Confidence Interval

Table 4b. DFS multivariable Cox model by ET group, adjusted for pathologic stage among patients with pathologic complete response.

Characteristic	Event N	HR†	95% CI†	p-value
Adjuvant ET				
OFS+TAM/AI	2	—	—	
Tamoxifen alone	8	3.46	0.72, 16.6	0.12
Clinical stage				
Stage I-II	5	—	—	
Stage III	5	4.67	1.33, 16.5	0.016

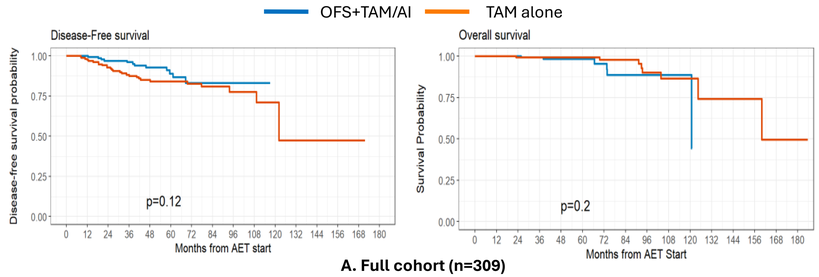
† HR = Hazard Ratio, CI = Confidence Interval

Table 4c. DFS multivariable Cox model by ET group, adjusted for pathologic stage and adjuvant HER2 therapy among patients with residual disease.

Characteristic	Event N	HR†	95% CI†	p-value
Adjuvant ET				
OFS+TAM/AI	10	—	—	
Tamoxifen alone	18	1.55	0.65, 3.67	0.3
Pathologic stage				
Stage I-II	18	—	—	
Stage III	10	4.09	1.71, 9.79	0.002
Adjuvant HER2 Therapy				
T-DM1	6	—	—	
Pertuzumab and Trastuzumab	9	0.93	0.30, 2.83	0.9
Trastuzumab monotherapy	11	3.47	1.16, 10.4	0.026
None	2	7.59	1.38, 41.8	0.02

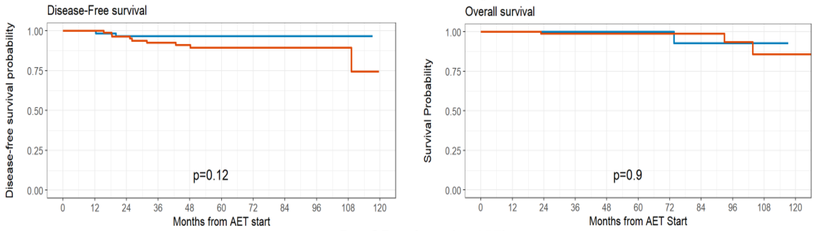
† HR = Hazard Ratio, CI = Confidence Interval

Figure 1. Five-year disease-free survival and overall survival in the full cohort (A), pCR cohort (B), and RD cohort (C).



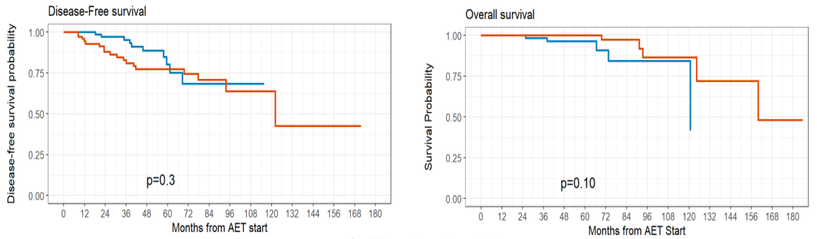
A. Full cohort (n=309)

- Five-year DFS was 89% (95% CI, 82-96) with OFS+TAM/AI vs. 84% (95% CI, 78-91) with TAM (*p=0.12*).
  - No difference in OS (*p=0.2*).



B. pCR cohort (n=157)

- Five-year DFS was 97% (95% CI, 92-100) with OFS+TAM/AI vs. 89% (95% CI, 83-97) with TAM (*p=0.12*).
  - No difference in OS (*p=0.9*).



C. RD cohort (n=152)

- Five-year DFS was 80% (95% CI, 68-95) with OFS+TAM/AI vs. 77% (95% CI, 67-89) with TAM (*p=0.3*).
  - No difference in OS (*p=0.10*).

Conclusions

In this real-world cohort of premenopausal pts with HR+/HER2+ BC after NAC, a trend toward improved DFS was observed in pts treated with OFS+TAM/AI compared to TAM alone, independent of pathologic stage and adjuvant HER2-targeted therapy, with borderline statistical significance. These findings support the need for larger retrospective cohorts to better clarify the role of OFS for HR+/HER2+ BC in the post-NAC setting.

Disclosures

- The first and presenting author declares no conflicts of interest.
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