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Adjuvant ovarian function suppression and aromatase inhibitors in premenopausal patients with hormone receptor and HER2 positive breast cancer, by timing of chemotherapy and trastuzumab and response to neoadjuvant therapy

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ABSTRACT

Background: The benefit of adjuvant ovarian function suppression (OFS) and aromatase inhibitors (AI) in premenopausal patients with hormone receptor positive, HER2 positive (HR+/HER2+) breast cancer (BC) is unclear. We aimed to investigate this question in a retrospective cohort, stratified by timing (adjuvant or neoadjuvant) of chemotherapy and trastuzumab and by response to neoadjuvant therapy.

Methods: Patients aged <45Y at diagnosis, with stage I-III HR + HER2+ BC, treated with (neo)adjuvant chemotherapy and trastuzumab (± pertuzumab) and endocrine therapy were included. LHRH-agonists and oophorectomy were considered OFS. We compared distant disease-free survival (DDFS) with tamoxifen, OFS + tamoxifen and OFS + AI in three cohorts: neoadjuvant–pathologic complete response (pCR), neoadjuvant-residual disease (RD) and adjuvant. Endocrine therapy (ET) was modeled as a time dependent covariate in cox logistic regression analyses.

Results: The study included 1124 patients with median follow-up of 72.6 months (range:0–205 months). DDFS rates at 5 years were 83.9 %, 86.8 % and 92.1 % with tamoxifen, OFS + tamoxifen and OFS + AI respectively in the RD group, 94.3 %, 97.6 % and 96.5 % in the pCR group, and 94.3 %, 93.4 % and 98.6 % in the adjuvant group. OFS + AI was associated with better DDFS compared to tamoxifen in the RD group (n = 366) (multivariable weighted HR 0.28. 95 % CI 0.11-.069, p = 0.006), but associations of ET with DDFS in the pCR (n = 307, p = 0.59) and adjuvant (n = 451, p = 0.18) cohorts were not detected. Stage III was associated with worse DDFS in all groups.

Conclusion: OFS + AI were associated with better DDFS in patients with RD after neoadjuvant therapy. Our findings can assist shared decision-making on adjuvant endocrine therapy of these patients.

1. Background

It is currently unclear if all premenopausal patients with hormone receptor positive (HR+) and Human Epidermal growth factor Receptor 2 positive (HER2+) breast cancer (BC) benefit from adjuvant ovarian function suppression (OFS). Patients with HR + HER2+ BC comprised about 15 % of the SOFT trial population, that reported better disease free survival (DFS) with OFS for these patients [1]. A sub-analysis conducted in 147 premenopausal patients from the ShortHER trial similarly reported that OFS use was associated with improved DFS [2]. In the ALTTO study, treatment related amenorrhea was associated with better DFS in premenopausal patients with HR+/HER2+ tumors [3]. However, a real world analysis from Ontario reported no benefit of adjuvant OFS in premenopausal patients with HER2+ BC [4]. The use of aromatase inhibitors (AI) in premenopausal patients with HR + HER2+ localized BC is also controversial. Only 10–15 % of patients included in studies that compared OFS + AI with OFS + tamoxifen had HER2+ BC, and a clear benefit from AI was not detected in this population [1,5].

Standard of care therapy for HER2+ BC has changed in recent years. Neoadjuvant systemic therapy, usually with dual anti-HER2 blockade, is currently recommended for patients with clinical T2-4 and/or clinically node positive tumors [6,7] and can also be administered to patients with cT1cN0 tumors [8,9]. Pathological complete response (pCR) after neoadjuvant therapy is associated with a significant reduction in the risk of disease recurrence [10,11], and pathological response determines recommendations for adjuvant anti-HER2 therapy [12], but not adjuvant endocrine therapy [13,14].

OFS and AI are associated with an increased burden of adverse effects, including joint stiffness, hot flashes, sexual dysfunction, mood disorders and anxiety [15,16], that negatively impact quality of life and can lead to treatment discontinuation [17–19]. Data from non-cancer populations suggests that oophorectomy before age 45 without estrogen replacement is associated with increased mortality [20,21] and higher risks of ischemic heart disease [22] and cognitive decline [23], emphasizing the need to personalize decisions on adjuvant endocrine therapy in patients with early BC, including those with HER2+ BC.

The aim of this study was to assess the benefit of adjuvant OFS in patients with early-stage HR + HER2+ BC, stratified by timing (adjuvant vs neoadjuvant) of chemotherapy and trastuzumab (with or without pertuzumab) and pathological response to neoadjuvant therapy.

2. Methods

This consortium retrospectively analyzed data in 26 sites in Europe and Israel. Data was collected in an anonymized manner by the investigators at each site and analyzed centrally.

Women aged 45 years or younger at diagnosis, with ER and/or PR positive, HER2 positive, stage I-III BC, diagnosed between 2013 and 2020 and treated with adjuvant or neoadjuvant chemotherapy and trastuzumab (with or without pertuzumab) were included. HER2 positivity was defined by local pathology as immunohistochemistry (IHC) staining of +3 or of +2 with in situ hybridization (ISH) detected gene amplification. Patients were excluded if they did not have surgery or adjuvant therapy, if they did not have endocrine therapy or were treated for less than 1 year, unless treatment was stopped due to recurrence.

Pathological complete response to neoadjuvant therapy was defined by lack of residual tumor in the breast and lymph nodes (ypT0N0) or in situ residual disease in the breast only (ypTisN0). Type and timing of neoadjuvant and adjuvant therapies were collected, including endocrine therapy switches and oophorectomy procedures. OFS was defined as either treatment with an LHRH agonist for at least 1 year or until recurrence or having undergone oophorectomy. Clinical and pathological T and N stage were recorded locally for all patients, and stage grouping was defined according to AJCC 8th edition. Disease stage was defined by clinical staging for the neoadjuvant groups and by pathological staging for the adjuvant group. Age was defined as a categorical variable. To choose the age cutoff, we performed Cox regression analyses at 1-year increments in the whole cohort to test the association of age with DDFS, and this association neared statistical significance at age 37. Additional covariates included grade and PR expression (positive or negative).

2.1. Statistical analysis

The primary endpoint was DDFS, defined as the time from start of endocrine therapy to distant recurrence or death, according to endocrine therapy in 3 patient cohorts: 1. Treated with neoadjuvant therapy and had a pCR (pCR cohort) 2. Treated with neoadjuvant therapy and had residual disease (RD cohort) 3. Treated with adjuvant chemotherapy and anti HER2 therapy (adjuvant cohort). In each cohort, we tested the association of treatment with OFS + tamoxifen/OFS + AI, each compared to tamoxifen alone, with DDFS.

Patients with missing values in key covariates were excluded (Fig. 1). For the remaining variables, missing values in categorical variables

(affecting less than 5 % of cases) were imputed using the mode. Continuous variables were imputed using a stochastic imputation method to preserve the original data distribution. Categorical variables were one-hot encoded, and numerical variables were formatted appropriately to ensure compatibility with statistical modeling techniques.

DDFS distributions were estimated using Kaplan-Meier curves. For this estimation we censored patients that switched therapy from tamoxifen to an OFS combination at switch. Group comparisons were conducted using the Cox proportional hazards model. We modeled ET as a time-varying covariate to account for treatment switches during follow-up. Patients were classified into three ET regimens: tamoxifen alone (reference), ovarian function suppression plus tamoxifen (OFS + tamoxifen), or ovarian function suppression plus aromatase inhibitor (OFS + AIs). When patients switched therapy from tamoxifen to an OFS combination (5.1 % of patients), we created separate time periods before and after the switch, with ET status updated accordingly. Since outcomes that occur after adjuvant treatment cessation should be calculated as outcomes of the respective adjuvant treatment, treatment time was artificially defined from exposure until censoring for the time dependent analyses. We performed univariable Cox regression for each covariate. Variables with $p < 0.2$ in univariable analysis were included in multivariable models. Age and time-varying ET regimens were included in all multivariable models based on clinical relevance. We assessed the proportional hazards assumption by adding covariate-by-time interaction terms. Non-significant interactions ($p > 0.05$) indicated the assumption was satisfied. For variables violating this assumption, hazard ratios represent average effects over the follow-up period. As a sensitivity analysis, we performed a 12-month landmark analysis. This included only patients who remained event-free at 12 months post-ET initiation. ET status was fixed as of the 12-month landmark, and follow-up time was reset to zero at this point. Both univariable and multivariable Cox models were fitted to analyze outcomes from the landmark forward.

All analyses were performed using Python with the lifelines package (version 3.12). Statistical significance was set at $p < 0.05$ (two-sided). Hazard ratios are reported with 95 % confidence intervals.

Post hoc power calculations were performed to assess the study's ability to detect differences in DDFS between ET regimens. Power for multivariable Cox regression analyses was estimated using methods described by Hsieh and Lavori [24], accounting for the number of events observed in each cohort, the number of covariates included in each model (4–5 covariates), correlation between the treatment variable and other covariates (conservatively estimated $R^2 = 0.15$), and a two-sided $\alpha = 0.05$. We evaluated power to detect a hazard ratio of 0.60, corresponding to a 40 % relative reduction in DDFS hazard.

2.2. Ethics

The study was approved by the institutional review boards in all participating sites. Informed consent was waived in accordance with local regulations due to the retrospective study design. Data collection was performed anonymously, according to local standards, and securely transferred to RAMBAM Health Care Campus for analysis.

3. Results

Of 1442 patients in the initial dataset, 1124 were included in the analysis (Fig. 1). Median age was 39 years (range 21–45 years), and median follow up was 72.6 months (range 0–205 months). The characteristics of patients in each group according to their adjuvant endocrine therapy are detailed in Table 1. Patients that switched ET (5.1 % of the cohort) were included under their primary ET in this table. Of patients treated with OFS combinations, 84.7 %, 84.6 % and 90 % were treated for longer than 2 years in the RD, pCR and adjuvant groups, respectively.

In patients with RD following neoadjuvant chemotherapy and anti-HER2 therapy (RD group), OFS was administered more frequently to younger patients. In addition, patients that received pertuzumab and/or

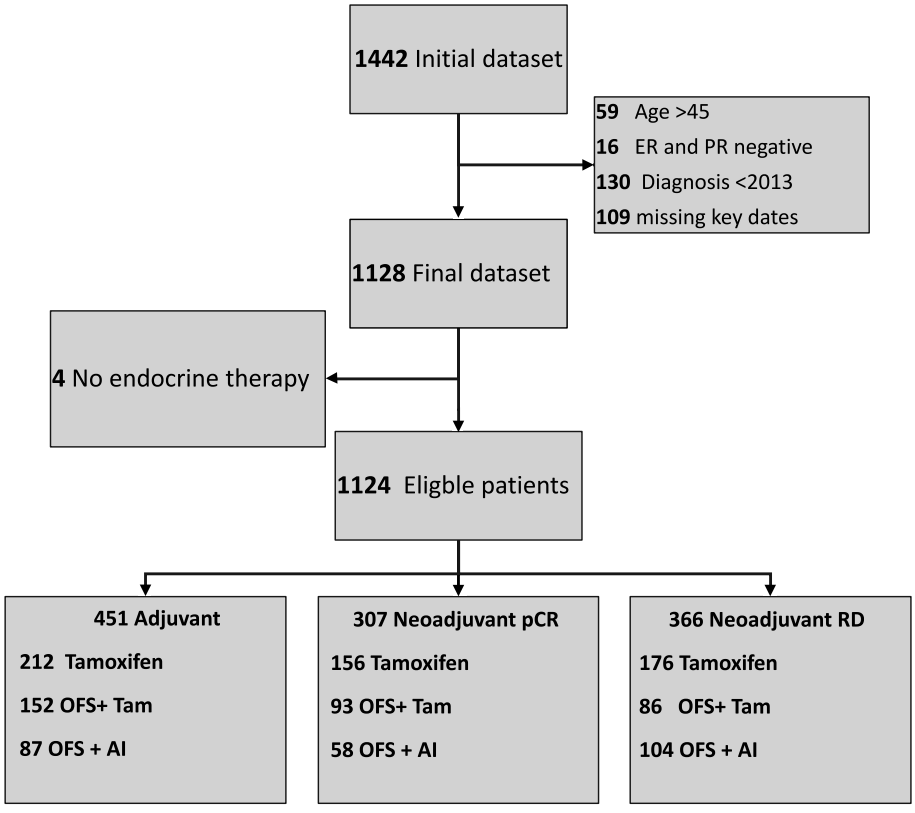

Fig. 1. Flowchart of patients included in the study.

Table 1
Distribution of covariates by type of endocrine treatment in the Neoadjuvant Pathological complete response, neoadjuvant residual disease and adjuvant groups.

Neoadjuvant residual disease:						
Categories		**Overall**	**Aromatase inhibitors+OFS N (%)**	**Tamoxifen N (%)**	**Tamoxifen + OFS N (%)**	**P-Value**
N		366	104	176	86	
Stage	1	41 (11.2)	6 (5.8)	29 (16.5)	6 (7.0)	0.091
	2	238 (65.0)	72 (69.2)	110 (62.5)	58 (67.4)	
	3	85 (23.2)	26 (25.0)	37 (21.0)	22 (25.6)	
Age Group	>37	225 (61.5)	64 (61.5)	124 (70.5)	37 (43.0)	<0.001
	<37	141 (38.5)	40 (38.5)	52 (29.5)	49 (57.0)	
Age	Median [Q1,Q3]	38.0 [34.0,43.0]	38.0 [34.0,41.0]	41 [35.8,44.0]	35.5 [32.0,39.0]	<0.001
	Range [min,max]	[18, 45]	[25, 45]	[23, 45]	[18, 44]	
PR	Negative	65 (17.8)	17 (16.3)	36 (20.5)	12 (14.0)	0.393
	Positive	301 (82.2)	87 (83.7)	140 (79.5)	74 (86.0)	
Grade	1	10 (2.7)	3 (2.9)	4 (2.3)	3 (3.5)	0.357
	2	232 (63.4)	62 (59.6)	121 (68.8)	49 (57.0)	
	3	124 (33.9)	39 (37.5)	51 (29.0)	34 (39.5)	
TDM-1	No	285 (77.9)	66 (63.5)	152 (86.4)	67 (77.9)	<0.001
	Yes	76 (20.8)	38 (36.5)	24 (13.6)	14 (16.3)	
Trastuzumab		230 (62.8)	59 (56.7)	128 (72.7)	43 (50.0)	<0.001
Trastuzumab + Pertuzumab		136 (37.2)	45 (43.3)	48 (27.3)	43 (50.0)	
pT stage	T0	31 (8.5)	10 (9.6)	12 (6.8)	9 (10.5)	0.657
	T1	255 (69.7)	73 (70.2)	127 (72.2)	55 (64.0)	
	T2-T4	80 (21.9)	21 (20.2)	37 (21.0)	22 (25.6)	
pN stage	N0	208 (56.8)	61 (58.7)	105 (59.7)	42 (48.8)	0.263
	N1-N3	145 (39.6)	40 (38.5)	65 (36.9)	40 (46.5)	
Time from diagnosis to ET (months)	Median [Q1, Q3]	8.6 [7.3,10.0]	8.5 [7.4,9.4]	9.0 [7.5,10.4]	7.8 [7.0,9.5]	0.007
	Range [min,max]	[0.2, 24.0]	[0.2, 20.1]	[1.4, 24.0]	[1.2, 23.5]	
Neoadjuvant Pathological complete response:						
Categories		**Overall**	**Aromatase inhibitors +OFS** N (%)	**Tamoxifen** N (%)	**Tamoxifen + OFS** N (%)	**P-Value**
N		307	58	156	93	
Stage	1	39 (12.7)	8 (13.8)	24 (15.4)	7 (7.5)	0.181
	2	194 (63.2)	35 (60.3)	91 (58.3)	68 (73.1)	
	3	74 (24.1)	15 (25.9)	41 (26.3)	18 (19.4)	
Age Group	>37	184 (59.9)	30 (51.7)	105 (67.3)	49 (52.7)	0.027
	<37	123 (40.1)	28 (48.3)	51 (32.7)	44 (47.3)	
Age	Median [Q1,Q3]	39.0 [33.5,42.0]	37.0 [32.0,41.8]	39.5 [35.0,42.0]	38.0 [34.0,41.0]	0.043
	Range [min,max]	[20, 45]	[26, 45]	[23, 45]	[20, 45]	
PR	Negative	66 (21.5)	9 (15.5)	37 (23.7)	20 (21.5)	0.431
	Positive	241 (78.5)	49 (84.5)	119 (76.3)	73 (78.5)	
Grade	1	3 (1.0)	0 (0.0)	2 (1.3)	1 (1.1)	0.315
	2	157 (51.1)	32 (55.2)	71 (45.5)	54 (58.1)	
	3	147 (47.9)	26 (44.8)	83 (53.2)	38 (40.9)	
Trastuzumab		131 (42.7)	22 (37.9)	75 (48.1)	34 (36.6)	0.148
Trastuzumab + Pertuzumab		176 (57.3)	36 (62.1)	81 (51.9)	59 (63.4)	
Time from diagnosis to ET (months)	Median [Q1, Q3]	8.0 [6.6,9.7]	8.0 [6.7,9.2]	8.5 [6.6,9.7]	7.8 [6.5,9.9]	0.661
	Range [min,max]	[0.8,35.6]	[1.3,18.5]	[4.2,26.0]	[0.8,35.6]	
Adjuvant:						
Categories		**Overall**	**Aromatase inhibitors+OFS** N (%)	**Tamoxifen** N (%)	**Tamoxifen + OFS** N (%)	**P-Value**
N		451	87	212	152	
Stage	1	168 (37.3)	36 (41.4)	72 (34.0)	60 (39.5)	0.267
	2	212 (47.0)	33 (37.9)	108 (50.9)	71 (46.7)	
	3	71 (15.7)	18 (20.7)	32 (15.1)	21 (13.8)	
Age Group	>37	290 (64.3)	54 (62.1)	167 (78.8)	69 (45.4)	<0.001
	<37	161 (35.7)	33 (37.9)	45 (21.2)	83 (54.6)	
Age	Median [Q1,Q3]	39.0 [34.0,42.0]	38.0 [34.0,42.0]	41.0 [37.0,43.0]	36.0 [31.0,41.0]	<0.001
	Range [min,max]	[21, 45]	[24, 45]	[23, 45]	[21, 45]	
PR	Negative	62 (13.7)	12 (13.8)	29 (13.7)	21 (13.8)	0.999
	Positive	389 (86.3)	75 (86.2)	183 (86.3)	131 (86.2)	
Grade	1	18 (4.0)	6 (6.9)	7 (3.3)	5 (3.3)	0.659
	2	207 (45.9)	38 (43.7)	99 (46.7)	70 (46.1)	
	3	226 (50.1)	43 (49.4)	106 (50.0)	77 (50.7)	
Trastuzumab		429 (95.1)	79 (90.8)	203 (95.8)	147 (96.7)	0.105
Trastuzumab + Pertuzumab		22 (4.9)	8 (9.2)	9 (4.2)	5 (3.3)	
Time from diagnosis to ET (months)	Median [Q1, Q3]	7.8 [6.6,9.6]	7.4 [5.8,9.1]	7.9 [6.7,9.6]	8.0 [6.8,9.9]	0.025
	Range [min,max]	[1.1, 32.0]	[1.4, 24.9]	[1.7, 18.2]	[1.1, 32.0]	

T-DM1 were treated with OFS + AIs more often. Baseline characteristics of patients per ET group are outlined in Table 1. Kaplan-Meier curves for DDFS are depicted in Fig. 2a. Forty-three patients out of 366 had a DDFS event. Estimated DDFS rates at 5 years were 92.1 % (82.7–96.5) with OFS + AI, 86.8 % (76.5–92.8) with OFS + tamoxifen and 83.9 % (76.8–89.0) with tamoxifen alone (p = 0.034 for OFS + AIs vs tamoxifen). Adjuvant treatment with OFS + AI's was associated with better DDFS compared with tamoxifen in both univariable (Table 2) and multivariable (Table 3) analyses (multivariable HR 0.28, 95 % CI 0.11–0.69, p = 0.006). Clinical stage III and age<37 were linked with worse DDFS in multivariable analysis (Table 3). In A sensitivity landmark analysis at 12 months, treatment with OFS + AI's was also associated with better DDFS compared to tamoxifen (multivariable HR 0.33, 95 % CI 0.12–0.89, p = 0.028)

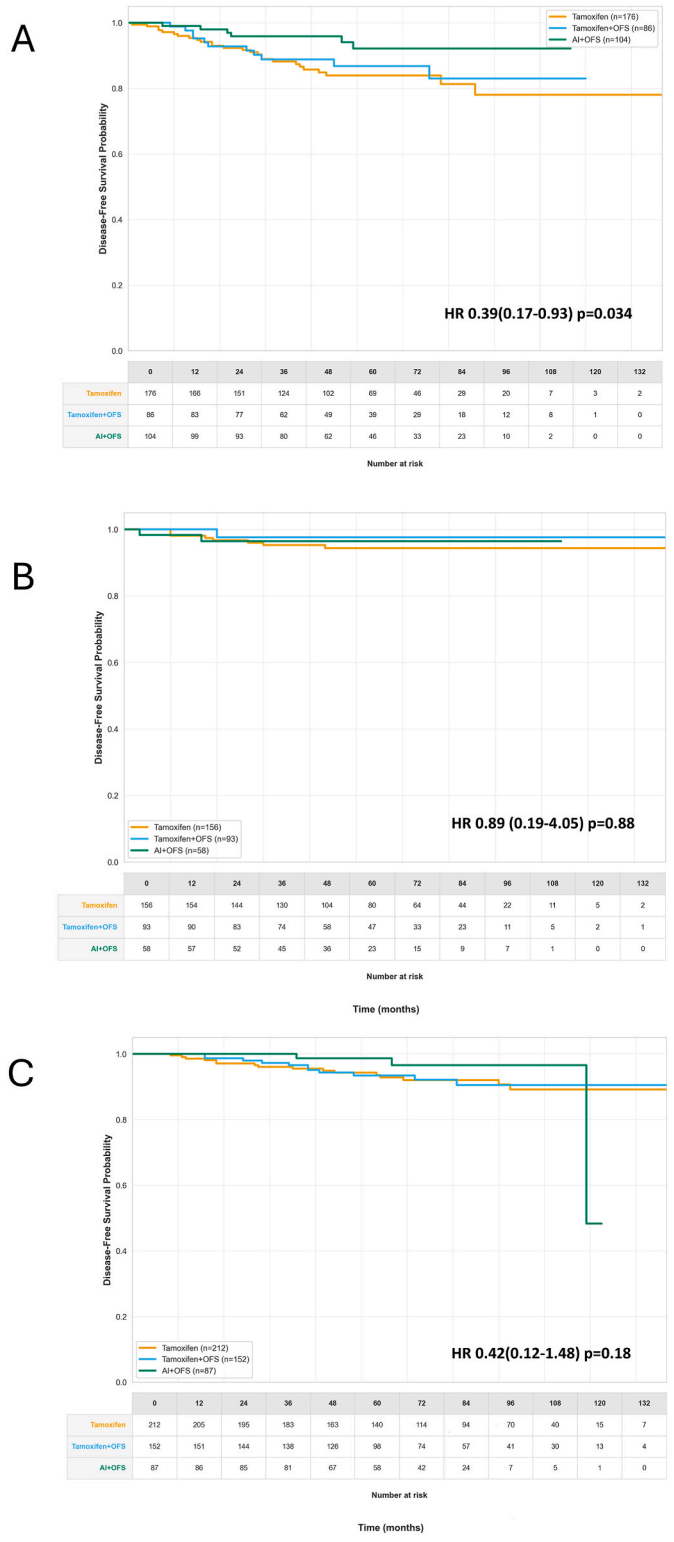

Fig. 2. Kaplan-Meyer curves for distant disease-free survival by endocrine therapy. A: Residual disease group. B: Pathological complete response group. C: Adjuvant group. HR presented for the comparison of ovarian function suppression and aromatase inhibitors with tamoxifen alone. Patients that switched from tamoxifen to OFS + tamoxifen or OFS + AIs were censored at switch.

In patients with a pCR following neoadjuvant chemotherapy and anti-HER2 therapy (pCR group), OFS was administered more frequently to younger patients (Table 1). Kaplan-Meier curves for DDFS are depicted in Fig. 2b. Twelve patients out of 307 had a DDFS event. Estimated DDFS rates at 5 years was 94.3 % (88.9–97.1) with tamoxifen, 97.6 % (90.7–99.4) with OFS + tamoxifen and 96.5 % (86.6–99.1) with OFS + AI. Type of endocrine therapy was not associated with DDFS in univariate (Table 2) and multivariable (Table 3) analyses (multivariable HR for OFS + AIs vs tamoxifen 0.65, 95 % CI 0.14–3.09, p = 0.59). Clinical stage III was the only covariate associated with DDFS in univariable analysis (Table 2), with a trend for an association in multivariable analysis (multivariable HR for clinical stage III vs stage I + II 3.06, 95 % CI 0.98–9.5, p = 0.053) (Table 3). A sensitivity landmark analysis at 12 months similarly did not detect an association between endocrine therapy and DDFS (multivariable HR for OFS + AIs vs tamoxifen 0.47, 95 % CI 0.05–4.08), p = 0.492).

In the group of patients treated with adjuvant chemotherapy and

Table 2
Univariable analysis of the association of covariates with DDFS.

Neoadjuvant Residual disease:		
covariate	HR (95 % CI)	P-value
Stage 2 vs 1	0.51 (0.28–0.93)	0.027
Stage 3 vs 1	2.98 (1.64–5.43)	<0.001
Age <37	1.75 (0.96–3.18)	0.067
PR_Positive	0.71 (0.35–1.45)	0.35
Grade_2	0.90 (0.49–1.65)	0.73
Grade_3	1.15 (0.62–2.13)	0.67
Pertuzumab + Trastuzumab vs Trastuzumab	0.81 (0.42–1.55)	0.52
TDM-1	0.53 (0.19–1.48)	0.22
pN1-3 vs pN0	1.56 (0.86–2.85)	0.14
pT2-4 vs pT1	1.49 (0.78–2.87)	0.23
Time from diagnosis to ET start	1.05 (0.96–1.15)	0.27
OFS + AI vs Tamoxifen	0.39 (0.17–0.93)	0.034
OFS + Tamoxifen vs Tamoxifen	1.09 (0.55–2.17)	0.80
Neoadjuvant pathological complete response:		
covariate	**HR (95 % CI)**	**P-value**
Stage 2 vs 1	0.56 (0.18–1.74)	0.32
Stage 3 vs 1	3.25 (1.05–10.09)	0.041
Age <37	1.54 (0.50–4.79)	0.45
PR Positive	0.84 (0.23–3.12)	0.80
Grade 2 vs 1	0.31 (0.084–1.15)	0.08
Grade 3 vs 1	3.33 (0.90–12.29)	0.071
Pertuzumab + Trastuzumab vs Trastuzumab	1.10 (0.35–3.48)	0.87
Time from diagnosis to ET start	1.00 (0.86–1.17)	0.98
OFS + AI vs Tamoxifen	0.89 (0.19–4.05)	0.88
OFS + Tamoxifen vs Tamoxifen	0.47 (0.10–2.15)	0.33
Adjuvant:		
covariate	**HR (95 % CI)**	**P-value**
Stage 2 vs 1	1.04 (0.51–2.12)	0.93
Stage 3 vs 1	3.95 (1.91–8.14)	<0.001
Age <37	1.37 (0.67–2.83)	0.39
PR Positive	1.42 (0.43–4.68)	0.57
Grade 2 vs 1	1.22 (0.60–2.49)	0.59
Grade 3 vs 1	0.74 (0.36–1.53)	0.42
Pertuzumab + Trastuzumab vs Trastuzumab	1.56 (0.37–6.55)	0.55
Time from diagnosis to ET start	1.00 (0.89–1.13)	0.98
OFS + AI vs Tamoxifen	0.51 (0.15–1.69)	0.27
OFS + Tamoxifen vs Tamoxifen	1.10 (0.52–2.31)	0.81

Table 3
Multivariable analysis of the association of covariates with DDFS.

Neoadjuvant residual disease:		
covariate	HR (95 % CI)	P-value
Stage 2 vs 1	2.19 (0.51–9.51)	0.29
Stage 3 vs 1	5.93 (1.35–26.05)	0.018
Age <37	2.00 (1.07–3.73)	0.029
pN1-3 vs pN0	1.43 (0.77–2.65)	0.26
OFS + AI vs Tamoxifen	0.28 (0.12–0.70)	0.006
OFS + Tamoxifen vs Tamoxifen	0.56 (0.27–1.18)	0.13
Neoadjuvant pathological complete response:		
covariate	**HR (95 % CI)**	**P-value**
Stage 3 vs 1 + 2	3.06 (0.98–9.52)	0.053
Age <37	1.63 (0.52–5.12)	0.40
OFS + AI vs Tamoxifen	0.65 (0.14–3.09)	0.59
OFS + Tamoxifen vs Tamoxifen	0.45 (0.093–2.12)	0.31
Adjuvant:		
covariate	**HR (95 % CI)**	**P-value**
Stage_3 vs 1 + 2	4.20 (2.03–8.72)	<0.001
Age <37	1.59 (0.72–3.51)	0.25
OFS + AI vs Tamoxifen	0.42 (0.12–1.48)	0.18
OFS + Tamoxifen vs Tamoxifen	0.89 (0.39–2.07)	0.79

anti-HER2 therapy (adjuvant group), OFS was administered more frequently to younger patients (Table 1). Kaplan-Meier curves for DDFS are depicted in Fig. 2c. Thirty patients out of 451 had a DDFS event. DDFS rates at 5 years were 94.3 % (89.9–96.8) with tamoxifen, 93.4 % (87.7–96.5) with OFS + tamoxifen and 98.6 % (90.7–99.8) with OFS + AI. While there was a numerical difference in DDFS favoring OFS + AI, this difference was not statistically significant in univariable or multivariate analyses (Tables 2 and 3) (multivariable HR for OFS + AIs vs tamoxifen 0.42, 95 % CI 0.12–1.48, p = 0.18). Stage III was the only covariate associated with DDFS (multivariable HR for stage III vs stage I 4.2, 95 % CI 2.03–8.7, p = 0.00011). A sensitivity landmark analysis at 12 months similarly did not detect an association between endocrine therapy and DDFS (multivariable HR for OFS + AIs vs tamoxifen 0.45, 95 % CI 0.13–1.58, p = 0.21).

We performed a post hoc power calculation to detect a risk reduction of 40 % for a DDFS event, which would translate to a 2–3 % absolute difference in the pCR and adjuvant groups, and the results are presented in the supplementary table. Of note, due to low event rates, the cohorts were underpowered to detect these differences.

4. Discussion

In this study, use of adjuvant OFS and AI was associated with better DDFS compared to tamoxifen alone in premenopausal patients with HR + HER2+ that had residual disease after neoadjuvant chemotherapy and trastuzumab. We did not detect significant associations between endocrine therapy and DDFS in patients with a pCR following neoadjuvant therapy and in those treated with adjuvant chemotherapy and trastuzumab. This is the first study that assessed the benefit of OFS in premenopausal patients with HR + HER2+ BC, stratified by timing of chemotherapy and trastuzumab (neoadjuvant vs adjuvant) and by response to neoadjuvant therapy. Our findings can assist clinicians and patients contemplating adjuvant endocrine therapy in this clinical setting. Analyzing these 3 patient groups separately allowed us to adjust for covariates specific to each group, for example use of trastuzumab-emtansine and pathological stage in patients with RD, improving accuracy and applicability of our results.

HR + HER2+ tumors are biologically heterogeneous. The intrinsic subtype of at least 50 % is luminal A, luminal B or normal like, with HER2 enriched subtype comprising 20–50 % [25–30]. The HER2 enriched subtype is associated with an increased likelihood of pCR to neoadjuvant therapy with HER2-targeting agents compared to luminal subtypes [25,26,28,29]. Expression of the luminal differentiation signature, which is evaluated in the HER2DX assay, is also associated with a lower pCR likelihood [31]. Thus, residual disease after neoadjuvant treatment of HR + HER2+ BC is associated with luminal features and, consequently, higher endocrine sensitivity.

Patients with RD after neoadjuvant therapy are at higher risk of relapse, and are treated with trastuzumab-emtansine [12]. Adjuvant Neratinib can also be administered [32], and the role of adjuvant trastuzumab-deruxtecan is currently being tested in this setting [33]. In our cohort of premenopausal patients with RD, treatment with OFS + AI was associated with a markedly improved DDFS compared to tamoxifen. OFS + tamoxifen was not significantly better than tamoxifen in this cohort, suggesting that OFS and AIs is the preferred adjuvant endocrine therapy in this patient population. However, a beneficial effect of OFS + tamoxifen might be evident in larger studies. We also detected an association between younger age and worse DDFS in patients with RD, strengthening the importance of ovarian function in this setting.

Our results also indicate that menopausal status and type of endocrine therapy administered should be recorded and accounted for in studies that investigate the impact of novel therapies and biomarkers on the outcomes of patients with HR + HER2+ BC and RD after neoadjuvant treatments. A recent study that tested the association of tumor biomarkers with prognosis of patients with HER2+ BC and RD after neoadjuvant therapy showed that expression of luminal gene signatures is associated with improved prognosis [34], highlighting the relevance of the estrogen receptor pathway activation and endocrine therapy received for understanding prognosis and treatment of these patients. Of note, clinical stage III was the strongest prognostic factor in this patient group (HR 5.93, 95 % CI 1.35–26.04 in multivariable analysis).

We did not detect a significant association between endocrine therapy and DDFS in patients with a pCR following neoadjuvant therapy. This may be related to a more HER2 dependent biology [26–30,35] and the favorable prognosis of these patients. Of note, there was a 3 % numerical difference in DDFS at 5 years favoring OFS + tamoxifen vs tamoxifen, but this cohort was underpowered to detect such a difference with statistical significance. We were also unable to assess the effect of OFS by stage due to the low event rate, however in accordance with previous studies [36], patients with clinical stage III had reduced DDFS rates in this study, even if they had a pCR. Thus, it seems that patients with clinical stage I-II HR + HER2+ BC and a pCR can be treated with tamoxifen alone, since any risk reduction with OFS in this population would be clinically insignificant, while patients with clinical stage III and a pCR may derive benefit from OFS with Tamoxifen or AIs. Larger studies of this unique patient population could clarify the benefit of OFS and AIs.

Patients treated with adjuvant chemotherapy and trastuzumab had good outcomes regardless of adjuvant endocrine therapy, probably reflecting the lower disease burden in these patients. This is in line with previous reports in this patient population [37]. Similarly, this cohort was underpowered to detect small absolute differences in DDFS. Pathological stage III was associated with worse DDFS, and OFS, with tamoxifen or AI, seems appropriate for those patients.

Our study has several limitations, such as its retrospective design and lack of data on ovarian function after chemotherapy. To account for possible imbalances in the proportion of patients with chemotherapy induced ovarian dysfunction between treatment groups, we adjusted for age in all multivariable analyses. In addition, we did not have data on endocrine therapy adherence. In the RD group, we collected data on tumor and lymph node stage, but not on residual cancer burden (RCB), a well-known prognostic factor after neoadjuvant therapy. However, current guidelines do not recommend the routine assessment of RCB in clinical practice [13,14]. The pCR and adjuvant groups had low event rates and were thus underpowered to detect small absolute benefits in DDFS. Nevertheless, this is the largest published cohort of premenopausal patients with HR + HER2+ BC [1,2,4] and the only one stratified by neoadjuvant therapy response.

This study has additional strengths. It represents real-world patient

population treated by modern standards in large and small centers in Europe and Israel. We collected data from patient's files throughout follow-up and accounted for therapy switches and oophorectomies, to capture OFS initiated at any time during endocrine therapy and analyzed this data in time-dependent analyses. Of OFS treated patients, 87 % had OFS for 2 years or longer, suggesting that OFS duration in this study was sufficient [4,38].

5. Conclusion

In this study, adjuvant OFS + AI was associated with better DDFS in patients with RD following neoadjuvant therapy. Patients with a pCR and those treated in the adjuvant setting had low rates of distant recurrences regardless of ET administered. Our results support a personalized approach to endocrine therapy in premenopausal patients with HR + HER2+ localized BC, taking into account disease stage and neoadjuvant therapy response.

CRediT authorship contribution statement

Ayelet Shai: Writing – review & editing, Writing – original draft, Visualization, Validation, Supervision, Project administration, Methodology, Investigation, Formal analysis, Data curation, Conceptualization. **Hans Wildiers:** Writing – original draft, Supervision, Project administration, Methodology, Investigation, Data curation, Conceptualization. **Claudio Venieri:** Writing – review & editing, Writing – original draft, Supervision, Resources, Project administration, Investigation, Data curation. **Katarzyna Pogoda:** Writing – review & editing, Investigation, Data curation. **Barbro Linderholm:** Writing – review & editing, Writing – original draft, Project administration, Investigation, Data curation, Conceptualization. **Matteo Lambertini:** Writing – review & editing, Writing – original draft, Methodology, Investigation, Data curation. **Leonor Matos:** Writing – review & editing, Investigation, Data curation. **Eleonora De Maio D'Esposito:** Writing – review & editing, Investigation, Data curation. **Nawale Hajjaji:** Writing – review & editing, Investigation, Data curation. **Erika Matos:** Writing – review & editing, Investigation, Data curation. **Lucía González Cortijo:** Writing – review & editing, Investigation, Data curation. **Giuseppe Fotia:** Writing – review & editing, Investigation, Data curation. **Ana Fortuna:** Writing – review & editing, Investigation, Data curation. **Tal Sella:** Writing – review & editing, Writing – original draft, Investigation, Data curation. **Helena Gouveia:** Writing – review & editing, Writing – original draft, Investigation, Data curation. **Laurent Rosset:** Writing – review & editing, Investigation, Data curation. **Anastasia Constantinidou:** Writing – review & editing, Investigation, Data curation. **Eurydice Angeli:** Writing – review & editing, Investigation, Data curation. **Irfan Cicin:** Writing – review & editing, Investigation, Data curation. **Vivianne Tjan-Heijnen:** Writing – review & editing, Writing – original draft, Investigation, Data curation. **Natacha Ruyssers:** Writing – review & editing, Investigation, Data curation. **Sofie Demasure:** Writing – review & editing, Investigation, Data curation. **Areen Abu Remilah:** Writing – review & editing, Investigation, Data curation. **Greet Huygh:** Writing – review & editing, Investigation, Data curation. **Shani Paluch-Shimon:** Writing – review & editing, Writing – original draft, Investigation, Data curation. **Edoardo Chiappe:** Writing – review & editing, Investigation, Data curation. **Natali Shirron:** Writing – review & editing, Visualization, Validation, Methodology, Investigation, Formal analysis. **Patrick Neven:** Writing – review & editing, Investigation. **Mehmet Artac:** Writing – review & editing, Investigation, Data curation. **Bilgesah Kilictas:** Writing – review & editing, Investigation, Data curation. **Jalal Baranseh:** Writing – review & editing, Investigation, Data curation. **Elena Vicente-Rubio:** Writing – review & editing, Investigation, Data curation. **Mustafa Atci:** Writing – review & editing, Investigation, Data curation. **Ottavia Amato:** Writing – review & editing, Project administration, Methodology. **Frederieke van Duijnhoven:** Writing – review & editing, Writing – original draft, Supervision, Project administration, Methodology, Investigation, Formal analysis, Data curation, Conceptualization.

Data sharing

Data included in this study cannot be shared according to data transfer agreements with participating centers, according to local regulations.

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Supplementary table.

Post hoc power to detect a 40 % reduction (HR 0.6) in DDFS:

Cohort	Comparison	N_Events	N_Covariates	Power
Adjuvant	Tamoxifen vs Tamoxifen + OFS	30	5	25.10 %
Adjuvant	Tamoxifen vs AI + OFS	30	5	25.10 %
Adjuvant	Tamoxifen + OFS vs AI + OFS	30	5	25.10 %
pCR	Tamoxifen vs Tamoxifen + OFS	12	4	12.60 %
pCR	Tamoxifen vs AI + OFS	12	4	12.60 %
pCR	Tamoxifen + OFS vs AI + OFS	12	4	12.60 %
Residual disease	Tamoxifen vs Tamoxifen + OFS	43	5	33.90 %
Residual disease	Tamoxifen vs AI + OFS	43	5	33.90 %
Residual disease	Tamoxifen + OFS vs AI + OFS	43	5	33.90 %

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