Original Study

Effectiveness of Adjuvant Ovarian Function Suppression in Premenopausal Women With Early Breast Cancer: A Multicenter Cohort Study

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Abstract

The use and effectiveness of adjuvant ovarian function suppression (OFS) for stage I to III hormone receptor-positive breast cancer is poorly characterized. In a multicenter retrospective cohort study of premenopausal women, we found that the use of OFS increased after 2014 from 16% to 25% of patients, in 30% of whom it was used in combination with aromatase inhibitors. Use of OFS improved overall survival.

Background: Ovarian function suppression (OFS) with tamoxifen or aromatase inhibitors (AIs) improves disease-free survival in premenopausal women with breast cancer, mostly in those at higher risk of recurrence. However, its real-world use and impact remain poorly understood. **Patients and Methods:** This is a multicenter retrospective cohort study of premenopausal women with stage I to III hormone receptor-positive breast cancer diagnosed from 2006 to 2015 that aimed to look at the uptake and effectiveness of the addition of OFS to backbone endocrine therapy (tamoxifen or AI). To deal with confounding, we used both multivariate modeling and propensity score matching. **Results:** Of 1717 eligible patients, 17.1% were treated with OFS. There was a substantial increase of use of OFS over time, especially from 2014 onward (16% vs. 25% after 2014), particularly for the combination with AI (0.4% vs. 8% after 2014). In a multivariate model, only younger age and year of diagnosis $\geq$ 2014 were associated with OFS utilization (both $P < .001$). With a median follow-up of 38 months (P25-P75, 19.6-66.4 months), patients receiving OFS had a better overall survival than those not receiving OFS (adjusted hazard ratio, 0.44; 95% confidence interval, 0.19-0.96; absolute benefit at 5 years, 2.1% [95.3% vs. 93.2% in those not receiving OFS]). A similar benefit was identified using propensity score matching. **Conclusions:** In the real-world setting, there was an increase in the use of OFS after 2014. After 2014, one-quarter of premenopausal women received adjuvant OFS, of which more than 30% received it in combination with an AI. In this study, the use of adjuvant OFS was associated with an overall survival benefit.

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Introduction

Breast cancer (BC) is the most frequently diagnosed and the most common cause of women's cancer-related deaths in the European Union, with an estimated incidence and death rate of approximately 108.8 and 22.4 cases per 100,000 women/year, respectively.[1] The generalization of screening and the introduction of incrementally more efficacious adjuvant treatments contributed substantially to improve the outcomes of patients diagnosed with BC in the early stages. For the two-thirds of patients with BC expressing the estrogen and/or progesterone receptors, collectively referred as

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hormone receptor-positive (HRe^+), the clinical utility of the use of hormone-related therapies is well-established.[2]

In the subset of premenopausal women, tamoxifen has been the mainstay of adjuvant endocrine therapy (ET) for more than 30 years.[3,4] However, recent studies showed that intensifying treatment with the combined use of ovarian function suppression (OFS) with either tamoxifen or aromatase inhibitors (AIs) further improves cancer outcomes.[5-7] Particularly, results of the SOFT (Suppression of Ovarian Function Trial) suggested that, after a median follow-up of 8 years and compared with tamoxifen alone, the addition of OFS to tamoxifen (OFS-T) improved overall survival (OS; a similar strong trend was also recorded for the association between OFS and an AI [OFS-AI]), especially in those patients judged to have a risk of recurrence justifying the use of adjuvant chemotherapy and among the very young patients (less than 35 years old).[6] In the group of women who were treated with chemotherapy, the 8-year OS estimates were 89.4% versus 87.2% versus 85.1% for the OFS-T, OFS-AI, and the tamoxifen-only arms, respectively (hazard ratio, 0.59; 95% confidence interval [CI], 0.42-0.84 for OFS-T vs. tamoxifen and hazard ratio, 0.79; 95% CI, 0.57-1.09 for OFS-AI vs. tamoxifen). In addition, for the group of women younger than 35, the 8-year disease-free survival (DFS) estimates (OS data not reported) were 80.0% versus 74.6% versus 64.9% for the OFS-AI, OFS-T, and tamoxifen-only arms, respectively. Furthermore, a consistent DFS advantage was also found for the combinations of OFS-AI and OFS-T when compared with tamoxifen in the overall cohort.

Since 2006, the Registo Oncológico Regional do Sul (Portuguese southern cancer registry; ROR-S) collects detailed tumor and treatment data on a large cohort of women with newly diagnosed BC. In this study of premenopausal women treated with adjuvant endocrine therapy, we aim to: (1) characterize real-world prescription of OFS, and particularly, to describe how recent data from clinical trials modified routine ET practice; and (2) examine the short-term OS impact of OFS.

Patients and Methods

Study Design and Data Source

This is an observational retrospective cohort study. Clinical data concerning 5 large centers located in Lisbon, Portugal was retrieved from ROR-S. ROR-S is a population-based cancer registry that serves as the unifying framework for variables definition, data registry, and quality assurance. Owing to the observational nature of the study, treatments and follow-up were performed at patient-physician description. The ROR-S institutional review board approved the study protocol, and ROR-S performed the oversight of study conduct. Description of data collection and procedures were previously reported.[8] We followed the Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) statement in reports of cohort studies.

Patient Selection

All consecutive premenopausal women diagnosed with HRe^+, non-metastatic BC between January 2006 and December 2015, and treated at participating institutions (Centro Hospitalar de Lisboa Norte, Instituto CUF de Oncologia, Hospital da Luz, Hospital de Beatriz Ângelo, and Instituto Português de Oncologia de Lisboa) were included. Patients with no information about surgery and with incomplete or missing information on adjuvant therapy were excluded. For this study, 2 cohorts of patients were defined: those patients treated with adjuvant OFS and those not treated with adjuvant OFS.

Menopausal Status and Hormone Receptor Status

ROR-S does not collect menopausal status. For this study, premenopausal status was defined as age at date of diagnosis younger than 50, a reference age adjusted to the Portuguese population.[9] HRe positivity was defined as either estrogen receptor-positive and/or progesterone receptor-positive with positivity defined as $\geq$ 1% of tumor cell nuclei immunoreactivity or tumor classified as "HRe^+" in the patient medical records.

Study Outcomes and Variables

Outcomes. The primary study outcome was OS, defined as time from tumor diagnosis to death from any cause. Vital status, as registered on ROR-S, is obtained from a centralized and electronic platform of national death certificates (Sistema de Informação dos Certificados de Óbito [SICO], managed by Direção Geral de Saúde). Follow-up was available up to December 2016. Given the nature of the data source, recurrences were not available.

As secondary outcomes, we examined use of OFS and duration of OFS treatment. Administration of OFS was defined as the prescription of any OFS agent started after surgery and for at least 2 consecutive prescriptions. Duration of therapy was defined as the time from first to last treatment prescription plus 1 month (to account for treatment action). Four patients had oophorectomy shortly after introduction of adjuvant OFS and are here considered as continuing OFS. No patient had upfront oophorectomy.

Other Covariates. Study covariates included age at diagnosis, tumor characteristics (American Joint Committee on Cancer [AJCC] TNM staging, histology, grade, and human epidermal growth factor receptor 2 [HER2] status); treatment characteristics (local and systemic), and year of diagnosis (Table 1).

Statistical Analysis

Descriptive statistics of patient, disease, and treatment characteristics were performed. Differences of these features by use of OFS were tested using the χ^2 test or Wilcoxon rank-sum test, as appropriate, and univariate and multivariate logistic regression models. Variables included in the multivariate logistic model included year of diagnosis, age at diagnosis, histologic type, grade, HER2 status, type of surgery, radiotherapy, and (neo)adjuvant chemotherapy. Time-to-event outcomes were estimated and plotted using the Kaplan-Meier method. Survival rates were compared using Cox proportional hazards models. To deal with confounding, both multivariate Cox proportional hazards models and propensity score (PS) matching with a 1:1 matching were performed. Variables included both in the multivariate model and PS matching included: age at diagnosis, stage, histologic grade, HER2 status, use of (neo) adjuvant chemotherapy, type of surgery, and year of diagnosis. The patient characteristics of the matched samples are shown in

Table 1 Patient Demographics, Tumor Characteristics, and Type of Concomitant Treatment by Type of Adjuvant Endocrine Therapy

Variable List	No OFS (Tamoxifen Only), n (%)	OFS, n (%)	OFS, n (%)		*P* Value (No OFS vs. OFS)
			OFS + Tamoxifen	OFS + AI	
Number of patients	1423 (82.9)	294 (17.1)	261 (15.2)	33 (1.9)	–
Demographic and clinicopathologic characteristics					
Age, y					
≤35	93 (6.5)	102 (34.7)	92 (32.3)	10 (30.3)	<.001
>35 to ≤40	233 (16.4)	109 (37.1)	100 (38.3)	9 (27.3)	
>40 to ≤50	1097 (77.1)	83 (28.2)	69 (26.4)	14 (42.4)	
Year of diagnosis					
2006-2009	468 (32.9)	77 (26.2)	74 (28.4)	3 (9.1)	.003
2010-2012	487 (34.2)	90 (30.6)	88 (33.7)	2 (6.1)	
2013-2015	468 (32.9)	127 (43.2)	99 (37.9)	28 (84.8)	
pT (tumor size, pathologic)					
pT0/1	913 (65.9)	190 (66.9)	169 (67.3)	21 (63.6)	.320
pT2	422 (30.5)	79 (27.8)	70 (27.9)	9 (27.3)	
pT3/4	50 (3.6)	15 (5.3)	12 (4.8)	3 (9.1)	
Missing	38 (2.7)	10 (3.4)	10 (3.8)	0	
pN (nodes, pathologic)					
Negative	845 (60.2)	176 (60.5)	160 (62.0)	16 (48.5)	.847
pN1	380 (27.0)	74 (25.4)	64 (24.8)	10 (30.3)	
pN2	133 (9.5)	29 (10.0)	25 (9.7)	4 (12.1)	
pN3	46 (3.3)	12 (4.1)	9 (3.5)	3 (9.1)	
Missing	19 (1.3)	3 (1.0)	3 (1.2)	0	
Simplified TNM staging					
Stage I	603 (43.6)	129 (45.1)	117 (46.3)	12 (36.4)	.703
Stage II	583 (42.1)	113 (39.5)	100 (39.5)	13 (39.4)	
Stage III	198 (14.3)	44 (15.4)	36 (14.2)	8 (24.2)	
Missing	39 (2.7)	8 (2.7)	8 (3.1)	0	
Histology					
Invasive carcinoma of NST	1217 (85.5)	268 (91.2)	238 (91.2)	30 (90.9)	.024
Invasive lobular carcinoma	126 (8.9)	13 (4.4)	11 (4.2)	2 (6.1)	
Other	80 (5.6)	13 (4.4)	12 (4.6)	1 (3.1)	
Histologic grade					
Grade 1	268 (20.1)	44 (15.6)	37 (14.9)	7 (21.2)	.002
Grade 2	849 (63.6)	168 (59.6)	152 (61.0)	16 (48.5)	
Grade 3	219 (16.4)	70 (24.8)	60 (24.1)	10 (30.3)	
Missing	87 (6.1)	12 (4.1)	12 (4.6)	0	
Hormone receptor status					
ER and PR positive	1159 (89.0)	240 (86.6)	210 (85.7)	30 (93.7)	.259
ER or PR positive	143 (11.0)	37 (13.4)	35 (14.3)	2 (6.3)	
HER2 receptor					
Negative	1120 (85.6)	227 (81.1)	202 (81.5)	25 (78.1)	.058
Positive	189 (14.4)	53 (18.9)	46 (18.6)	7 (21.9)	
Missing	114 (8.0)	14 (4.8)	13 (5.0)	1 (3.0)	

Table 1 Continued

Variable List	No OFS (Tamoxifen Only), n (%)	OFS, n (%)	OFS, n (%)		*P* Value (No OFS vs. OFS)
			OFS + Tamoxifen	OFS + AI	
Treatment characteristics					
Surgery					
Breast-conserving surgery	701 (51.6)	121 (43.4)	105 (42.5)	16 (50.0)	.012
Mastectomy	658 (48.4)	158 (56.6)	142 (57.5)	16 (50.0)	
Missing	64 (4.5)	15 (5.1)	14 (5.4)	1 (3.0)	
Radiotherapy					
Yes	1065 (74.8)	204 (69.4)	80 (30.7)	10 (30.3)	.053
No	358 (25.2)	90 (30.6)	181 (69.3)	23 (69.7)	
(Neo)adjuvant chemotherapy					
No	388 (27.3)	62 (21.1)	58 (22.2)	4 (12.1)	.028
Yes	1035 (72.7)	232 (78.9)	203 (77.8)	29 (87.9)	
Yes, neoadjuvant	276 (19.4)	83 (28.2)	68 (26.1)	15 (45.5)	

Abbreviations: AI = aromatase inhibitor; ER = estrogen receptor; HER2 = human epidermal growth factor receptor 2; NST = no special type; OFS = ovarian function suppression; PR = progesterone receptor.

Supplemental Table 1 (in the online version). Two sensitivity analysis were performed: (1) to deal with eventual immortal-time bias, we performed a sensitivity analysis including only patients alive 1 year after surgery; and (2) to test the robustness of findings in patients with longer follow-up, we completed a sensitivity analysis including only patients with a minimum follow-up of 3 and 5 years. All time-to-event analyses met proportional hazards assumption as assessed by the Schoenfeld residuals. We performed a complete full data analysis. The dataset had 100% completion data for survival outcomes, and for other variables, missing values did not exceed 8%. Missing information was considered missing at random. All tests were 2-sided, and *P*-values of $\leq$ .05 were considered statistically significant. The analyses were performed using Stata 13.1 (StataCorp LP). For PS matching, Stata ado-file psmatch2 was used.[10]

Results

Study Sample and Baseline Characteristics

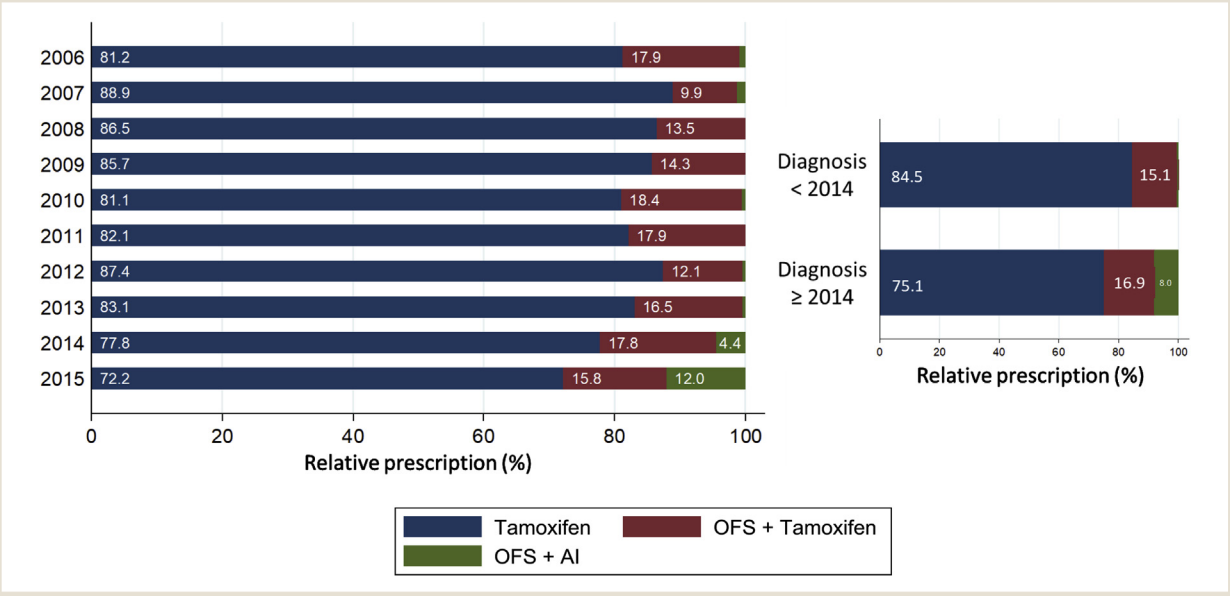
A total of 1717 consecutive eligible patients were included in the study analysis (see Supplemental Figure 1 in the online version), of which 294 (17.1%) received adjuvant OFS (goserelin in almost all cases) and 1423 (82.9%) did not. Baseline demographic and clinicopathologic characteristics, as well as treatments received, are summarized in Table 1. Patients treated with OFS were younger (34.7% vs. 6.5% $\leq$ 35 years) and had less differentiated tumors (grade 3 in 24.8% vs. 16.4%), but similar TNM stage. Treatments also differed, with patients treated with OFS more frequently receiving mastectomy (56.6% vs. 48.4%) and (neo)adjuvant chemotherapy (78.9% vs. 72.7%). OFS was more commonly administered in combination with tamoxifen than with an AI (detailed below), and patients receiving tamoxifen (compared with those treated with an AI) tended to have node-negative tumors (62.0% vs. 48.5%), less frequently had histologic grade 3 tumors (24.1% vs. 30.3%), and less frequently received adjuvant chemotherapy (administered in 77.8% vs. 87.9%).

Patterns of ET Use

In this cohort of premenopausal women, only a minority (294; 17.1%) of patients received OFS as part of the adjuvant ET strategy. The median time to introduction of OFS was 5.1 months (interquartile range [IQR], 1.4-8.6; max, 14.0). Of those receiving OFS, 261 (15.2%) received it in combination with tamoxifen, whereas 33 (1.9%) received it in combination with an AI. There was evidence of OFS use since the beginning of the cohort in 2006, but in 2014, there was a significant increase in the use of OFS: 15.5% received OFS before 2014, whereas approximately 25% received OFS in or after 2014 (Figures 1 and 2). A similar trend was noted for the combination with AI, with 0.4% receiving OFS in combination with an AI before 2014, and 8% from 2014 onwards; in contrast, the combination with tamoxifen was relatively stable (15.1% before 2014 and 16.9% from 2014 onwards). Prescription of OFS over time and according to age and disease stage is depicted in Figure 3. A consistent trend for OFS use in younger patients was clear, reaching 87.5% of patients in those $\leq$ 35 years old in 2015 in contrast with 13.2% in those $>$ 40 years old in the same year.

In the univariate analysis, features associated with the use of OFS included age at diagnosis, year of diagnosis, histologic type, grade, type of surgery, and treatment with radiotherapy and (neo)adjuvant chemotherapy. However, in the multivariate model, only age at diagnosis (reference $>$ 40 and $\leq$ 50 years; odds ratio [OR], 14.7; 95% CI, 9.7-22.1 for $\leq$ 35 and OR, 6.1; 95% CI, 4.3-8.7 for $>$ 35 and $\leq$ 40 years) and year of diagnosis after 2014 (OR, 1.9; 95% CI, 1.3-2.7) were associated with the use of OFS (Table 2). Despite the predominant use of combination with tamoxifen, 32% of patients received an AI in the interval from 2014 to 2015.

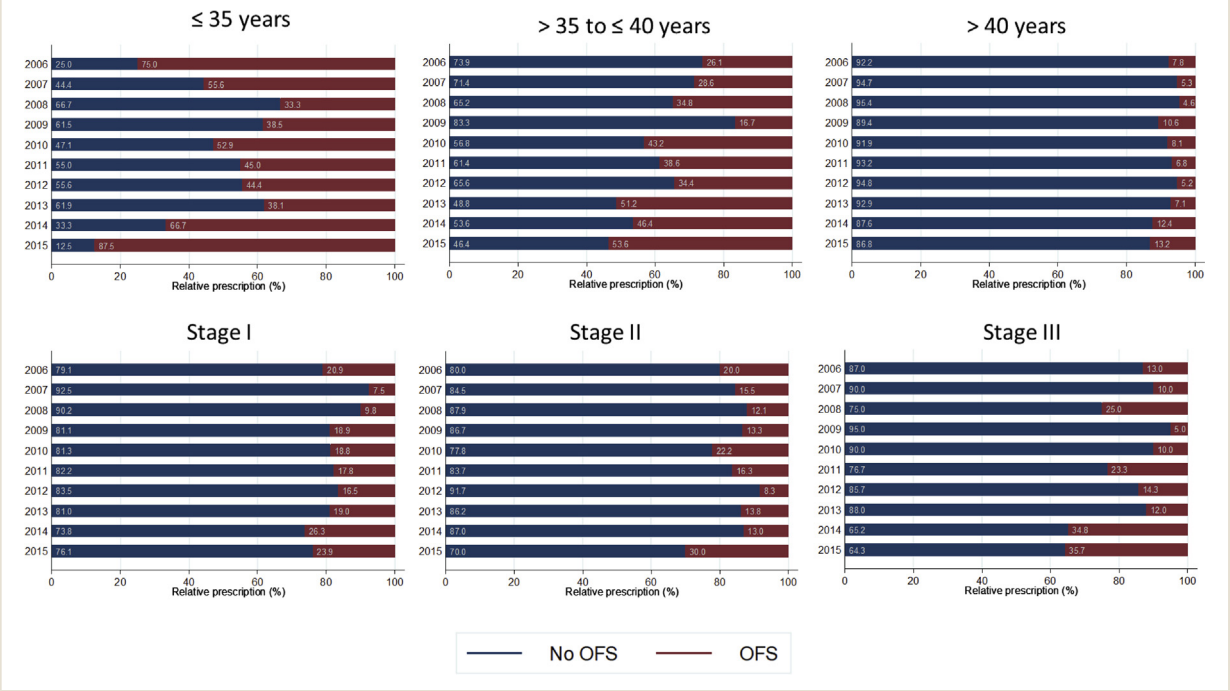
Figure 1 Patterns of Prescription of Adjuvant Endocrine Therapy Over Time



Abbreviations: AI = aromatase inhibitor; OFS = ovarian function suppression.

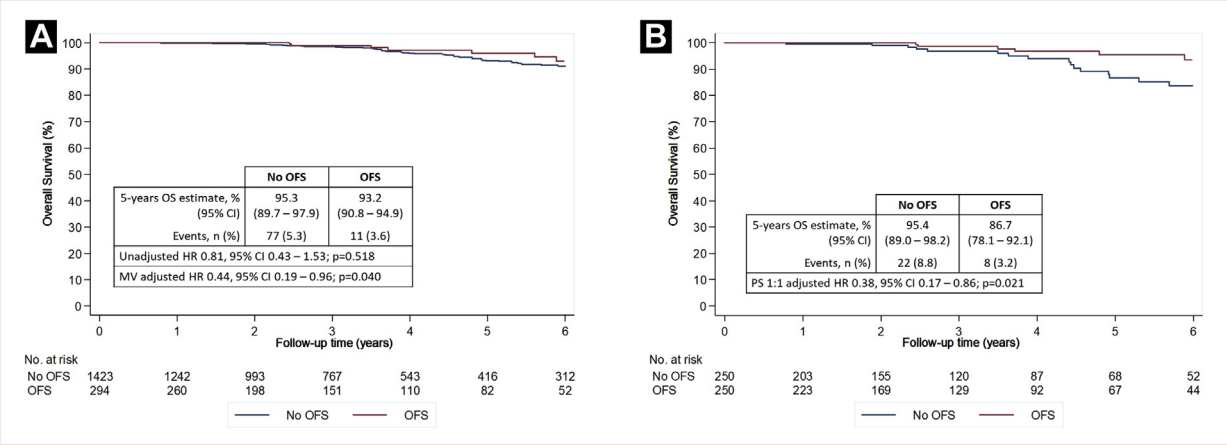
Among patients treated with OFS and with available date of treatment status, approximately 6% were still receiving OFS at the time of analysis. In those with available date of treatment completion (35.2%), the median duration of OFS was of approximately 25 months (IQR, 20-27 months) (Table 3).

Figure 2 Patterns of Prescription of Adjuvant Endocrine Therapy Over Time and According to Age at Diagnosis and International Union Against Cancer/American Joint Committee on Cancer TNM Staging



Abbreviation: OFS = ovarian function suppression.

Figure 3 Overall Survival in the Overall Cohort (A) and Propensity Score Matching (1:1 Matching) Cohort (B). Variables Included Both in the Multivariate CM and PS Matching Included: Age at Diagnosis, Stage, Histologic Grade, Human Epidermal Growth Factor Receptor 2 Status, Use of (Neo)Adjuvant Chemotherapy, Type of Surgery, and Year of Diagnosis



Abbreviations: CI = confidence interval; CM = Cox model; HR = hazard ratio; MV = multivariate; OFS = ovarian function suppression; OS = overall survival; PS = propensity score.

Effectiveness of OFS

After a median follow-up of 38.3 months (IQR, 19.6-66.4 months; minimum-maximum, 1.8-125 months), 88 deaths were registered, 11 (3.6%) in the OFS cohort and 77 (5.3%) in the no-OFS cohort. The median follow-up is balanced between treatment cohorts, with 38.9 months (IQR, 20.5-67.7 months) in the no-OFS cohort and 36.5 months (IQR, 15.9-62.6 months) in the OFS cohort ($P = .231$). The proportion of patients alive at 5 years was 95.3% (95% CI, 89.7%-97.9%) in the OFS cohort and 93.2% (95% CI, 90.8%-94.9%) in the no-OFS cohort (Figure 3A). In a multivariate model controlling for age at diagnosis, stage, histologic grade, HER2 status, use of (neo)adjuvant chemotherapy, type of surgery, and year of diagnosis, patients receiving adjuvant OFS had a 56% decrease in the risk of death (hazard ratio, 0.44; 95% CI, 0.19-0.96; $P = .04$). Similar results were observed when performing a sensitivity analysis including only patients alive at 1 year (adjusted hazard ratio, 0.44; 95% CI, 0.20-0.97) and with a minimum follow-up of 3 years (adjusted hazard ratio, 0.43; 95% CI, 0.18-1.01) and 5 years (adjusted hazard ratio, 0.39; 95% CI, 0.12-1.23). With a 2.1% absolute difference in survival at 5 years, the number needed to treat to avoid 1 death was 48.

The PS matching cohort results were consistent with those of the Cox proportional hazards multivariate analysis (Figure 3B). Although 8 patients died in the OFS cohort (3.2%), 22 died in the no-OFS cohort (8.8%). The proportion of patients alive at 5 years was 95.4% (95% CI, 89.0%-98.2%) in the OFS cohort and 86.7% (95% CI, 78.1%-92.1%) in the no-OFS cohort. Patients receiving adjuvant OFS had a 62% decrease in the risk of death (hazard ratio, 0.38; 95% CI, 0.17-0.86; $P = .021$).

Discussion

In this large real-world cohort of premenopausal women with BC receiving adjuvant ET, we observed an increment in the use of OFS in recent years. Moreover, young age at diagnosis ($\leq$ 35 years old) was strongly associated with the use of adjuvant OFS. Albeit with a short follow-up time, treatment with OFS combined with either tamoxifen or AI improved short-term OS.

Over the past decades, several randomized trials and meta-analyses examined the impact of adding OFS to backbone ET (see Supplemental Table 2 in the online version). Overall, it emerged from these trials that specific populations, such as premenopausal women with enough risk of recurrence to be eligible for adjuvant chemotherapy, as well as younger women, may derive benefit from adding OFS to ET.[5,6,11-15] In addition, the most recent SOFT trial results further revealed an overall survival advantage for the combination OFS-T.[6]

The first results of the combined analysis of SOFT and TEXT trials in 2014, suggesting the benefit of OFS in some populations, led to the incorporation of this recommendation in several BC treatment guidelines.[3,4] In fact, in the present study, although there is evidence of utilization of OFS since 2006, there was a substantial increment of its use after 2014. As expected, in this study of patients with HRe^{+} tumors diagnosed between 2006 and 2015, of whom more than 70% treated with (neo)adjuvant chemotherapy, we observed that patients at a higher risk of relapse receive OFS more frequently. We further observed that adjuvant OFS added to tamoxifen or AI led to a statistically significant reduction in the risk of death, with an absolute magnitude in line with previous achievements in adjuvant ET and to the updated results of the SOFT trial. Although these results might be influenced by unmeasured confounders, short median follow-up, and time bias (given the increase in use of OFS over time), the treatment effect was consistently present when using different methods to deal with confounding. Thus, this study adds real-world evidence to clinical trial data, supporting the decision of patients and physicians to incorporate OFS in the ET of premenopausal women at higher risk of recurrence.

These results must be put in context of the tolerability implications of OFS. In the SOFT trial, patients randomized to tamoxifen plus OFS more frequently had hot flashes, loss of sexual interest, and sleep disturbance, as well as vaginal dryness, with early

Table 2 Patient and Tumor Features Associated With OFS Prescription

Variable List	Predictors of OFS Prescription		
	OR	95% CI	*P* Value
Univariate analysis			
Age at diagnosis, y			
<35	14.5	10.1-20.8	<.001
35 to <40	6.2	4.5-8.5	
40 to <50	Reference	Reference	
Year of diagnosis (for each added year since 2006)	1.08	1.03-1.13	.002
Year of diagnosis			
Before 2014	Reference	Reference	<.001
In or after 2014	1.84	1.38-2.45	
Pathologic staging			
Stage I	Reference	Reference	.920
Stage II	0.91	0.69-1.20	
Stage III	1.04	0.71-1.52	
Histology			
Invasive carcinoma of NST	Reference	Reference	.039
Invasive lobular carcinoma	0.47	0.26-0.84	
Other	0.74	0.40-1.35	
Histologic grade			
Grade 1	Reference	Reference	.001
Grade 2	1.21	0.84-1.73	
Grade 3	1.95	1.28-2.95	
HER2 status			
Negative	Reference	Reference	.059
Positive	1.38	1.99-1.94	
Type of surgery			
Breast conserving surgery	Reference	Reference	.013
Mastectomy	1.39	1.07-1.80	
Radiotherapy			
No	Reference	Reference	.053
Yes	0.76	0.58-1.00	
(Neo)adjuvant chemotherapy			
No	Reference	Reference	.029
Yes	1.40	1.04-1.90	
Multivariate model (full model shown)			
Age at diagnosis, y			
≤35	14.7	9.74-22.1	<.001
>35 to ≤40	6.12	4.32-8.67	
>40 to ≤50	Reference	Reference	
Year of diagnosis			
Before 2014	Reference	Reference	<.001
In or after 2014	1.89	1.34-2.67	
Histology			
Invasive carcinoma of NST	Reference	Reference	.171
Invasive lobular carcinoma	0.75	0.39-1.43	
Other	0.63	0.27-1.43	

Table 2 Continued

Variable List	Predictors of OFS Prescription		
	OR	95% CI	*P* Value
Histologic grade			
Grade 1	Reference	Reference	.156
Grade 2	1.04	0.68-1.59	
Grade 3	1.44	0.85-2.43	
HER2 status			
Negative	Reference	Reference	.969
Positive	0.99	0.66-1.48	
Type of surgery			
Breast conserving surgery	Reference	Reference	.526
Mastectomy	1.11	0.78-1.56	
Radiotherapy			
No	Reference	Reference	.399
Yes	0.85	0.58-1.24	
(Neo)adjuvant chemotherapy			
No	Reference	Reference	.243
Yes	0.79	0.53-1.18	

Abbreviations: CI = confidence interval; HER2 = human epidermal growth factor receptor 2; HG = histologic grade; NST = no special type; OFS = ovarian function suppression; OR = odds ratio.

discontinuation of oral ET close to 20%.[16] Interestingly, after 6 months of therapy, symptom-specific treatment differences were less evident in those patients previously treated with chemotherapy. Other studies further showed a detrimental effect of OFS in self-reported health-related quality of life.[17] However, no particular changes in global cognitive function, nor depression or anxiety scores were noted.[18,19]

The use of OFS further opens the possibility of using AIs in premenopausal women. The incremental efficacy of OFS and AI (vs. OFS-T) is not definitely established (see Supplemental Table 2 in the online version). Although the ABCSG-12 trial did not document any DFS advantage of OFS-AI over OFS-T and even found a statistically significant detrimental impact of OFS-AI compared with OFS-T (of note, this trial also tested the role of adjuvant zoledronic acid), the analyses of the SOFT and TEXT trials showed that patients treated with chemotherapy who remained premenopausal and those who were < 35 years (higher risk patients) are the ones obtaining the most benefit from AIs (absolute BC-free interval reduction ranging from 5% to 15%).[20-22] However, no OS differences were noted in the overall SOFT/TEXT cohort (hazard ratio, 0.98; 95% CI, 0.79-1.22). In terms of tolerability, both the toxicity profile and its evolution over time differ: patients taking tamoxifen plus OFS had more hot flashes and sweats that improved over time, whereas those on exemestane plus OFS had more vaginal dryness, greater loss of sexual interest, and difficulties becoming aroused that persisted over time.[23] No major differences in quality of life over time were captured with the instruments used. Of note, current guidelines consider both AI and tamoxifen reasonable alternatives when added to OFS, even though American Society of Clinical Oncology guidelines favor the use of AI in women < 35 years.[3,4]

Table 3 Adjuvant Endocrine Treatment Description

	Overall, n (%)	Before 2014, n (%)	In or After 2014, n (%)	*P* Value (<2014 vs. ≥2014)
Receiving OFS	294 (17.1)	210 (15.2)	84 (24.9)	<.001
Concomitant therapy to OFS				<.001
Tamoxifen	261 (88.8)	204 (97.1)	57 (67.9)	
Aromatase inhibitor	33 (11.2)	6 (2.9)	27 (32.1)	
Time on OFS[a]			NR	NA
Median, mo	24.7	24.9		
P25-P75	20.4-26.9	21.5-26.9		
Min-max	1.6-65.9	1.6-65.9		
Date of completion available	99 (33.6)	78 (43.8)		
Ongoing treatment	17 (5.8)	4 (2.2)		

Abbreviations: NA = not available; NR = not reported; OFS = ovarian function suppression.
[a]Time on OFS excludes patients with ongoing treatment with goserelin at time of data cutoff and those with prescription in of after 2013.

OFS is also being increasingly used as an approach to reduce the likelihood of chemotherapy-induced ovarian insufficiency and thus as a complementary strategy to improve future fertility without impacting survival.[24-26] Such use is reflected in current international guidelines.[27-29] Although we had access to the exact date of OFS initiation, in our cohort, the date of (neo)adjuvant chemotherapy introduction was not thoroughly available beyond the knowledge of its administration before or after surgery. This limited the possibility of describing the use of OFS as a fertility preservation strategy in our cohort of premenopausal women.

Despite the large sample size and the methodological rigor, this study has limitations. It is a retrospective observational study, thus susceptible to residual confounding. ROR-S does not collect menopausal status, both at diagnosis and after primary treatment, which was estimated for local patterns. Also, ROR-S does not accurately collect comorbidities, educational level, type of (neo)adjuvant chemotherapy, patients' preferences, or Ki67 that can be unbalanced between arms; nevertheless, we used different modeling strategies to address confounding with consistent findings. Therapy administration was measured by drug prescription, not actual drug administration, and a substantial proportion of patients did not have information available concerning treatment stop date. Also, the median follow-up is short for a HRe^+ population, and a time bias might exist associated with an increase in use of OFS over time. The follow-up is impacted by the inclusion of patients up to the date of censoring, but this was done to extract the most information possible from the analysis focusing on the patterns of use of OFS. In addition, the sensitivity analysis restricted to patients with 5 or more years of follow-up showed consistent results. Moreover, the follow-up is balanced between the 2 groups. Although unexpected, the fact that the use of OFS was present since the beginning of the cohort, that the increased uptake of OFS is predominantly achieved in the very later years of the cohort, and that the overall absolute number of patients receiving OFS is lower than those not receiving this treatment explain the balanced follow-up and add to the robustness of the analysis. Finally, treatment effectiveness was measured as OS, not cancer-specific survival, and DFS was not available. Although cancer-specific survival could add some extra robustness to our study, the relatively young age of this group of patients might increase the likelihood of the identification of mostly cancer-specific deaths. Although ROR-S exhaustively collects OS through its electronic connection to the national death certificates database, as a population-based registry, recurrence events need to be proactively reported by contributing centers, leading to a relevant proportion of patients with missing DFS status and thus rendering this outcome not useful for clinical research at this point in time.

Conclusion

Now that intensification of ET with OFS in pre-menopausal women with HRe^+ BC at high risk of relapse is becoming standard of care, this large cohort of premenopausal women receiving adjuvant ET shows real-world evidence that supports these guidelines. Since 2014, one-quarter of patients were treated with adjuvant OFS, of which more than 30% were treated in combination with an AI. The use of adjuvant OFS showed an OS benefit.

Clinical Practice Points

- The real-world use and effectiveness of OFS as adjuvant treatment for premenopausal women with early BC is poorly understood.
- In this retrospective cohort study of 1717 premenopausal women with stage I to III HRe^+ BC diagnosed from 2006 to 2015, the use of adjuvant OFS increased after 2014 from 16% to 25% of patients.
- AIs are the combination of choice in more than 30% of cases.
- OFS improved short-term OS in this real-world setting study, providing a real-world layer of evidence supporting its use and allowing a more informed discussion between patients and physicians.

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Disclosure

Dr Passos-Coelho reports an advisory role with Roche, Novartis, Astrazeneca, Jansen, and Astellas and research funding from BMS. Dr Brito reports an advisory role with Roche, Pfizer, and Astrazeneca. The remaining authors have stated that they have no conflicts of interest.

Supplemental Data

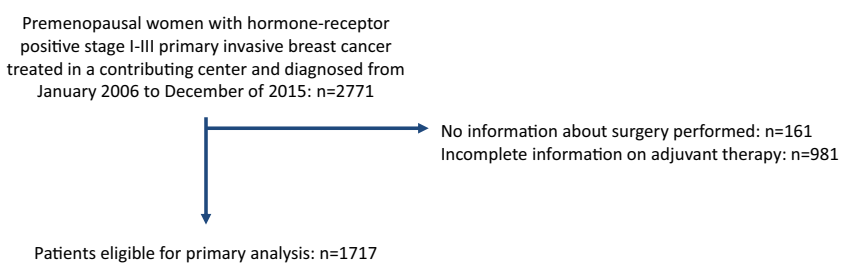
Supplemental data accompanying this article can be found in the online version at https://doi.org/10.1016/j.clbc.2019.06.003.

References

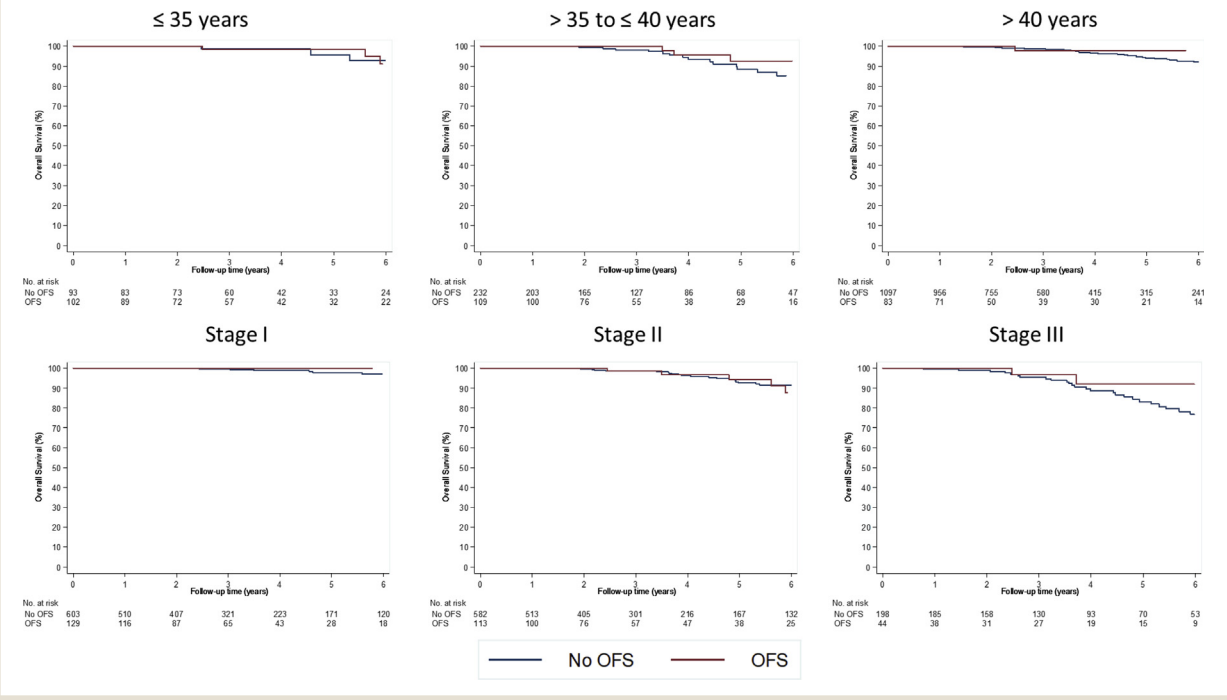
1. Ferlay J, Steliarova-Foucher E, Lortet-Tieulent J, et al. Cancer incidence and mortality patterns in Europe: estimates for 40 countries in 2012. *Eur J Cancer* 2013; 49:1374-403.
2. Early Breast Cancer Trialists' Collaborative Group (EBCTCG), Davies C, Godwin J, Gray R, et al. Relevance of breast cancer hormone receptors and other factors to the efficacy of adjuvant tamoxifen: patient-level meta-analysis of randomised trials. *Lancet* 2011; 378:771-84.
3. Burstein HJ, Lacchetti C, Anderson H, et al. Adjuvant endocrine therapy for women with hormone receptor-positive breast cancer: American Society of Clinical Oncology Clinical Practice Guideline Update on Ovarian Suppression. *J Clin Oncol* 2016; 34:1689-701.
4. Curigliano G, Burstein HJ, P Winer E, et al. De-escalating and escalating treatments for early-stage breast cancer: the St. Gallen International Expert Consensus Conference on the Primary Therapy of Early Breast Cancer 2017. *Ann Oncol* 2017; 28:1700-12.
5. Francis PA, Regan MM, Fleming GF, et al, SOFT Investigators, International Breast Cancer Study Group. Adjuvant ovarian suppression in premenopausal breast cancer. *N Engl J Med* 2015; 372:436-46.
6. Francis PA, Pagani O, Fleming GF, et al, SOFT and TEXT Investigators and the International Breast Cancer Study Group. Tailoring adjuvant endocrine therapy for premenopausal breast cancer. *N Engl J Med* 2018; 379:122-37.
7. Pagani O, Regan MM, Walley BA, et al, TEXT and SOFT Investigators, International Breast Cancer Study Group. Adjuvant exemestane with

ovarian suppression in premenopausal breast cancer. *N Engl J Med* 2014; 371:107-18.
8. R Ferreira A, Palha A, Correia L, et al. Variation in type of adjuvant chemotherapy received among patients with stage I breast cancer: A multi-institutional Portuguese cohort study. *Breast* 2016; 29:68-73.
9. Lucas R, Azevedo A, Barros H. Self-reported data on reproductive variables were reliable among postmenopausal women. *J Clin Epidemiol* 2008; 61:945-50.
10. Leuven E, Sianesi B. PSMATCH2: Stata module to perform full Mahalanobis and propensity score matching, common support graphing, and covariate imbalance testing, version 4.0.11, IDEAS. Available at: https://ideas.repec.org/c/boc/bocode/s432001.html 2003. Accessed: October 1, 2017.
11. Cuzick J, Ambroisine L, Davidson N, Jakesz R, Kaufmann M, Regan M. Use of luteinising-hormone-releasing hormone agonists as adjuvant treatment in premenopausal patients with hormone-receptor-positive breast cancer: a meta-analysis of individual patient data from randomised adjuvant trials. *Lancet* 2007; 369:1711-23.
12. Zhang P, Li C-Z, Jiao G-M, et al. Effects of ovarian ablation or suppression in premenopausal breast cancer: a meta-analysis of randomized controlled trials. *Eur J Surg Oncol* 2017; 43:1161-72.
13. Noh WC, Lee JW, Nam SJ, et al. Role of adding ovarian function suppression to tamoxifen in young women with hormone-sensitive breast cancer who remain premenopausal or resume menstruation after chemotherapy: the ASTRRA study. *J Clin Oncol* 2018; 36(15 Suppl):502.
14. Qiu L, Fu F, Huang M, et al. Evaluating the survival benefit following ovarian function suppression in premenopausal patients with hormone receptor positive early breast cancer. *Sci Rep* 2016; 6:26627.
15. Yan S, Li K, Jiao X, Zou H. Tamoxifen with ovarian function suppression versus tamoxifen alone as an adjuvant treatment for premenopausal breast cancer: a meta-analysis of published randomized controlled trials. *Onco Targets Ther* 2015; 8:1433-41.
16. Ribi K, Luo W, Bernhard J, et al. Adjuvant tamoxifen plus ovarian function suppression versus tamoxifen alone in premenopausal women with early breast cancer: patient-reported outcomes in the Suppression of Ovarian Function Trial. *J Clin Oncol* 2016; 34:1601-10.
17. Tevaarwerk AJ, Wang M, Zhao F, et al. Phase III comparison of tamoxifen versus tamoxifen plus ovarian function suppression in premenopausal women with node-negative, hormone receptor-positive breast cancer (E-3193, INT-0142): a trial of the Eastern Cooperative Oncology Group. *J Clin Oncol* 2014; 32:3948-58.
18. Phillips K-A, Regan MM, Ribi K, et al. Adjuvant ovarian function suppression and cognitive function in women with breast cancer. *Br J Cancer* 2016; 114: 956-64.
19. Yi H, Nam S, Kim S, et al. Depression and anxiety after adjuvant ovarian function suppression in premenopausal breast cancer patients. *Cancer Res* 2016; 76(4 Suppl) (abstract P1-11-01).
20. Regan MM, Francis PA, Pagani O, et al. Absolute benefit of adjuvant endocrine therapies for premenopausal women with hormone receptor-positive, human epidermal growth factor receptor 2-negative early breast cancer: TEXT and SOFT Trials. *J Clin Oncol* 2016; 34:2221-31.
21. Saha P, Regan MM, Pagani O, et al, SOFT, TEXT Investigators, International Breast Cancer Study Group. Treatment efficacy, adherence, and quality of life among women younger than 35 years in the International Breast Cancer Study Group TEXT and SOFT adjuvant endocrine therapy trials. *J Clin Oncol* 2017; 35: 3113-22.
22. Gnant M, Mlineritsch B, Stoeger H, et al, Austrian Breast and Colorectal Cancer Study Group, Vienna, Austria. Zoledronic acid combined with adjuvant endocrine therapy of tamoxifen versus anastrozol plus ovarian function suppression in premenopausal early breast cancer: final analysis of the Austrian Breast and Colorectal Cancer Study Group Trial 12. *Ann Oncol* 2015; 26:313-20.
23. Bernhard J, Luo W, Ribi K, et al. Patient-reported outcomes with adjuvant exemestane versus tamoxifen in premenopausal women with early breast cancer undergoing ovarian suppression (TEXT and SOFT): a combined analysis of two phase 3 randomised trials. *Lancet Oncol* 2015; 16:848-58.
24. Lambertini M, Moore HCF, Leonard RCF, et al. Gonadotropin-releasing hormone agonists during chemotherapy for preservation of ovarian function and fertility in premenopausal patients with early breast cancer: a systematic review and meta-analysis of individual patient–level data. *J Clin Oncol* 2018; 36: 1981-90.
25. Lambertini M, Horicks F, Del Mastro L, Partridge AH, Demeestere I. Ovarian protection with gonadotropin-releasing hormone agonists during chemotherapy in cancer patients: from biological evidence to clinical application. *Cancer Treat Rev* 2019; 72:65-77.
26. Regan MM, Walley BA, Francis PA, et al. Concurrent and sequential initiation of ovarian function suppression with chemotherapy in premenopausal women with endocrine-responsive early breast cancer: an exploratory analysis of TEXT and SOFT. *Ann Oncol* 2017; 28:2225-32.
27. Paluch-Shimon S, Pagani O, Partridge AH, et al. ESO-ESMO 3rd international consensus guidelines for breast cancer in young women (BCY3). *Breast* 2017; 35: 203-17.
28. Oktay K, Harvey BE, Partridge AH, et al. Fertility preservation in patients with cancer: ASCO Clinical Practice Guideline Update. *J Clin Oncol* 2018; 36:1994-2001.
29. Lambertini M, Cinquini M, Moschetti I, et al. Temporary ovarian suppression during chemotherapy to preserve ovarian function and fertility in breast cancer patients: a GRADE approach for evidence evaluation and recommendations by the Italian Association of Medical Oncology. *Eur J Cancer* 2017; 71:25-33.

Supplemental Figure 1 Patient Flowchart



Supplemental Figure 2 Overall Survival by Treatment Arm in Subgroups Defined by Age at Diagnosis and TNM Staging



Abbreviation: OFS = ovarian suppression function.

Supplemental Table 1 Patient Demographics, Tumor Characteristics, and Type of Concomitant Treatment by Type of Adjuvant Endocrine Therapy in the Matching Samples

Variable List	PS Matching (1:1)		
	No OFS, n (%)	OFS, n (%)	*P* Value (No OFS vs. OFS)
Total patients	250 (50.0)	250 (50.0)	NA
Follow-up, mo			
Median	34.8	36.5	.419
IQR	14.6-63.7	16.1-62.6	
Demographic and clinicopathologic characteristics			
Age, y			
≤35	68 (27.2)	84 (33.6)	.291
>35 to ≤40	103 (41.2)	92 (36.8)	
>40 to ≤50	79 (31.6)	74 (29.6)	
Year of diagnosis			
2006-2009	73 (29.2)	64 (25.6)	.445
2010-2012	67 (26.8)	79 (31.6)	
2013-2015	110 (44.0)	107 (42.8)	
pT (tumor size, pathologic)			
pT0/1	174 (69.6)	168 (67.7)	.103
pT2	71 (28.4)	66 (26.6)	
pT3/4	5 (2.0)	14 (5.7)	
pN (nodes, pathologic)			
Negative	150 (60.0)	148 (59.2)	.948
pN1	66 (26.4)	64 (25.6)	
pN2	23 (9.2)	27 (10.8)	
pN3	11 (4.4)	11 (4.4)	
Simplified TNM staging			
Stage I	115 (46.0)	229 (91.6)	.331
Stage II	98 (39.2)	13 (5.2)	
Stage III	37 (14.8)	8 (3.2)	
Histology			
Invasive ductal carcinoma	225 (90.0)	229 (91.6)	.331
Invasive lobular carcinoma	20 (8.0)	13 (5.2)	
Other	5 (2.0)	8 (3.2)	
Histologic grade			
Grade 1	39 (15.6)	41 (16.4)	.694
Grade 2	155 (62.0)	146 (58.4)	
Grade 3	56 (22.4)	63 (25.2)	
Hormone receptor status			
ER and PR positive	200 (85.5)	202 (86.3)	.791
ER or PR positive	34 (14.5)	32 (13.7)	
HER2 receptor status			
Negative	207 (82.8)	201 (80.4)	.489
Positive	43 (17.2)	49 (19.6)	
Treatment characteristics			
Surgery			
Breast-conserving surgery	120 (48.0)	110 (44.0)	.370
Mastectomy	130 (52.0)	140 (56.0)	

Supplemental Table 1 Continued

Variable List	PS Matching (1:1)		
	No OFS, n (%)	OFS, n (%)	*P* Value (No OFS vs. OFS)
Radiotherapy			
Yes	176 (70.4)	175 (70.0)	.922
No	74 (29.6)	75 (30.0)	
(Neo)adjuvant chemotherapy			
Yes	187 (74.8)	198 (79.2)	.242
No	63 (25.2)	52 (20.8)	

Abbreviations: ER = estrogen receptor; HER2 = human epidermal growth factor receptor 2; IQR = interquartile range; OFS = ovarian function suppression; PR = progesterone receptor.

Supplemental Table 2 Summary of Adjuvant Trials and Meta-analyses Comparing Tamoxifen With or Without OFS and OFS With Either Tamoxifen or an AI[a]

Study (Year of Last Results Update)	Treatment Arms	Sample Size	Follow-up	Disease-free Survival	Overall Survival
Clinical trials: tamoxifen vs. tamoxifen + OFS					
SOFT (2018)[5,6]	Tamoxifen alone vs. tamoxifen + OFS (vs. exemestane + OFS)	2033	8.0	HR, 0.76; 95% CI, 0.62-0.93; $P = .009$	HR, 0.67; 95% CI 0.48-0.92; $P = .01$
ASTRRA (2018)[13]	Tamoxifen alone vs. tamoxifen + OFS	1282	5.3	HR, 0.686; 95% CI, 0.48-0.97; $P = .033$	HR, 0.310; 95% CI, 0.10-0.94; $P = .029$
E-3193/INT-0142 (2014)[17]	Tamoxifen alone vs. tamoxifen + OFS	345	9.9	HR, 1.16; 95% CI, 0.64-2.08; $P = .62$	HR, 1.19; 95% CI, 0.52-2.70; $P = .67$
ABC/OAS (2007)[E1]	Tamoxifen alone vs. tamoxifen + OFS/ablation	2144	5.9	HR, 0.95; 95% CI, 0.81-1.12; $P = .56$	HR, 0.94; 95% CI, 0.78-1.13; $P = .44$
ZIPP (2005)[E2]	Tamoxifen alone vs. tamoxifen + OFS	2710	5.5	HR, 0.80; 95% CI, 0.69-0.92; $P = .002$	HR, 0.81; 95% CI, 0.67-0.99; $P = .038$
INT 0101/E5188 (2005)[E3]	CAF vs. CAF + OFS vs. CAF + OFS + tamoxifen	1503	9.6	HR, 0.93; 95% CI, 0.76-1.12; $P = .22$	HR, 0.88; 95% CI, 0.70-1.11; $P = .14$
Meta-analyses: tamoxifen vs. tamoxifen + OFS					
Zhang (2017)[12]	OFS + tamoxifen vs. tamoxifen	7331	NR	HR, 0.94; 95% CI, 0.88-1.01; $P = .09$	HR, 0.92; 95% CI, 0.82-1.03; $P = .13$
Qiu (2016)[14]	OFS + tamoxifen vs. tamoxifen[b]	12,292	NR	RR, 0.86; 95% CI, 0.75-0.96; $P =$ NR	RR, 0.79; 95% CI, 0.70-0.89; $P =$ NR
Yan (2015)[15]	OFS + tamoxifen vs. tamoxifen	6279	NR	RR, 0.87; 95% CI, 0.71-1.06; $P = .16$	RR, 0.84; 95% CI, 0.66-1.07; $P = .16$
Cuzick (2007)[11]	OFS + tamoxifen vs. tamoxifen	1013	NR	HR, 0.85; 95% CI, 0.67-1.09; $P = .20$	HR, 0.84; 95% CI, 0.59-1.19; $P = .33$
Clinical trials: OFS + tamoxifen vs. OFS + AI					
SOFT/TEXT (2018)[6,7]	OFS + tamoxifen vs. OFS + exemestane (vs. tamoxifen alone)	4690	9.0	HR, 0.77; 95% CI, 0.67-0.90; $P < .001$	HR, 0.98; 95% CI, 0.79-1.22; $P = .84$
ABCSG-12 (2015)[22]	OFS + tamoxifen vs. OFS + anastrazol	1803	7.9	HR, 1.13; 95% CI, 0.88-1.45; $P = .335$	HR, 1.63; 95% CI, 1.05-1.45; $P = .030$
HOBOE-2 (2018)[E4]	OFS + tamoxifen vs. OFS + letrozole (vs. OFS + letrozole + ZA)	710[c]	5.4	HR, 0.72; 95% CI, 0.48-1.07; $P = .06$	NR

Abbreviations: AI = aromatase inhibitor; CI = confidence interval; ET = endocrine therapy; HR = hazard ratio; NR = not reported; OFS = ovarian function suppression; RR = relative risk; ZA = zoledronic acid.

[a]NSABP-30 and ABCSG 13-93 studies further showed that patients achieving chemotherapy-induced amenorrhea had improved survival. The 2005 EBCTCG meta-analysis compared adjuvant OFS/ablation to no further ET showing a significant effect of OFS on both DFS and OS.

[b]Tamoxifen or other ET beyond OFS was not provided in all trials included in this meta-analysis.

[c]1065 patients if including the OFS + letrozole + ZA arm.

Supplemental References

E1. The Adjuvant Breast Cancer Trials Collaborative Group. Ovarian ablation or suppression in premenopausal early breast cancer: results from the international Adjuvant Breast Cancer Ovarian Ablation or Suppression randomized trial. *J Natl Cancer Inst* 2007; 99:516-25.

E2. Baum M, Hackshaw A, Houghton J, et al, ZIPP International Collaborators Group. Adjuvant goserelin in pre-menopausal patients with early breast cancer: results from the ZIPP study. *Eur J Cancer* 2006; 42:895-904.

E3. Davidson NE, O'Neill AM, Vukov AM, et al. Chemoendocrine therapy for premenopausal women with axillary lymph node–positive, steroid hormone receptor–positive breast cancer: results from INT 0101 (E5188). *J Clin Oncol* 2005; 23:5973-82.

E4. Perrone F, De Laurentiis M, de Placido S, et al. LBA14_PR The HOBOE-2 multicenter randomized phase III trial in premenopausal patients with hormone-receptor positive early breast cancer comparing triptorelin plus either tamoxifen or letrozole or letrozole + zoledronic acid. *Ann Oncol* 2018; 29(Suppl 8), mdy424.003.