original report

Adding Ovarian Suppression to Tamoxifen for Premenopausal Breast Cancer: A Randomized Phase III Trial

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abstract

PURPOSE The addition of ovarian function suppression (OFS) for 5 years to tamoxifen (TAM) for treatment of premenopausal patients with breast cancer after completion of chemotherapy has beneficial effects on disease-free survival (DFS). This study evaluated the efficacy of adding 2 years of OFS to TAM in patients with hormone receptor–positive breast cancer who remain in a premenopausal state or resume ovarian function after chemotherapy.

PATIENTS AND METHODS We enrolled 1,483 premenopausal women (age ≤ 45 years) with estrogen receptor–positive breast cancer treated with definitive surgery after completing adjuvant or neoadjuvant chemotherapy. Ovarian function was assessed every 6 months for 2 years since enrollment on the basis of follicular-stimulating hormone levels and vaginal bleeding history. If ovarian function was confirmed to be premenopausal at each visit, the patient was randomly assigned to complete 5 years of TAM alone (TAM-only) group or 5 years of TAM with OFS for 2 years that involved monthly goserelin administration (TAM + OFS) group. DFS was defined from the time of enrollment to the time of the first event.

RESULTS A total of 1,293 patients were randomly assigned, and 1,282 patients were eligible for analysis. The estimated 5-year DFS rate was 91.1% in the TAM + OFS group and 87.5% in the TAM-only group (hazard ratio, 0.69; 95% CI, 0.48 to 0.97; $P = .033$). The estimated 5-year overall survival rate was 99.4% in the TAM + OFS group and 97.8% in the TAM-only group (hazard ratio, 0.31; 95% CI, 0.10 to 0.94; $P = .029$).

CONCLUSION The addition of 2 years of OFS to TAM significantly improved DFS compared with TAM alone in patients who remained premenopausal or resumed ovarian function after chemotherapy.

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ASSOCIATED CONTENT

Appendix

Data Supplement

Author affiliations and support information (if applicable) appear at the end of this article.

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Written on behalf of the Korean Breast Cancer Study Group.

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INTRODUCTION

Five-year adjuvant tamoxifen (TAM) therapy has been a standard treatment of premenopausal women with hormone receptor–positive breast cancer. The benefit of TAM on disease-free survival (DFS) and overall survival (OS) is well established.[1-3] By contrast, although ovarian function suppression (OFS) in breast cancer has been studied for decades and has been used widely in clinical practice, evidence for the benefits of adding OFS to standard adjuvant TAM treatment is insufficient.[4-7] The Suppression of Ovarian Function Trial (SOFT; ClinicalTrials.gov identifier: NCT00066690) has shown that the addition of OFS to TAM provides a survival benefit for premenopausal women with hormone receptor–positive breast cancer, particularly for those who receive adjuvant chemotherapy.[8,9] However, studies for the optimal use of OFS for premenopausal women, particularly after completing chemotherapy, are limited.

One of the challenges of an OFS trial is the selection of appropriate patients because the definition of premenopause often is complicated in women who have received chemotherapy and are receiving adjuvant TAM. After chemotherapy, a large proportion of premenopausal patients experience a period of chemotherapy-induced amenorrhea. The rate and pattern of ovarian function recovery after amenorrhea vary widely dependent on patient age and type of chemotherapy. Serum follicle-stimulating hormone (FSH) levels, serum estradiol (E2) levels, and vaginal bleeding history are complementary factors for assessing the resumption of ovarian function in patients who have completed chemotherapy.[10,11]

Accordingly, serum FSH levels, serum E2 levels, and vaginal bleeding history are assumed to need longitudinal monitoring to decide whether to suppress ovarian function after adjuvant chemotherapy.

In South Korea, approximately 50% of patients with newly diagnosed breast cancer in 2015 were premenopausal.[12] Hence, implementation of a precision endocrine therapy strategy for premenopausal women is important. In 2008, the Korean Breast Cancer Study Group launched the Addition of Ovarian Suppression to Tamoxifen in Young Women With Hormone-Sensitive Breast Cancer Who Remain Premenopausal or Regain Vaginal Bleeding After Chemotherapy (ASTRRA; ClinicalTrials.gov identifier: NCT00912548) study. We report the results of the primary analysis in ASTRRA that compares 5-year TAM with 2-years OFS with 5-year TAM alone after a median follow-up of 63 months. This study evaluated the efficacy of adding OFS to TAM in patients with hormone receptor–positive breast cancer who remain in a premenopausal state or resume ovarian function after chemotherapy.

PATIENTS AND METHODS

Patients and Study Design

ASTRRA was an investigator-initiated, open-label, prospective, randomized, multicenter, phase III trial. The patients were enrolled from 35 institutions in South Korea. Full details of the study method, including randomization, have been reported previously.[13] Briefly, premenopausal women age 45 years or younger with estrogen receptor–positive, stage I to III, primary invasive breast cancer were eligible for enrollment if they had been treated with definitive surgery and chemotherapy. Patients were required to have a WHO performance status of 0, 1, or 2 and adequate hematologic, hepatic, and renal function. Premenopausal status was defined as having a regular vaginal bleeding history at the time of diagnosis. Estrogen receptor positivity was defined as an estrogen receptor level of more than 10 fmol/mg cytosol protein or more than 10% positive tumor cells on the basis of each institution's immunohistochemistry report.[13] Exclusion criteria were other primary malignancies within the past 5 years except adequately treated in situ carcinoma of the cervix, basal cell carcinoma, or squamous cell carcinoma of the skin. Any standard chemotherapy regimens were allowed except cyclophosphamide, methotrexate, and fluorouracil regimen. Radiotherapy and human epidermal growth factor receptor 2 (HER2)–targeted therapy were conducted according to the policy of each institution on the basis of the current treatment guideline. Data on adverse events were not collected.

The patients were enrolled within 3 months after the final dose of chemotherapy. Oral TAM had been prescribed for all patients at the time of enrollment. Ovarian function was evaluated at the time of enrollment on the basis of serum FSH levels. The ovarian function of patients with a serum FSH level of 30 mIU/mL or more was evaluated every 6 months for 2 years. Resumption of ovarian function was defined as a serum FSH level of less than 30 mIU/mL or any evidence of vaginal bleeding within 6 months of each visit. Patients who continued to have chemotherapy-induced amenorrhea for 2 years from the time of enrollment were categorized into the permanent menopause group (group A) and were excluded from the survival analysis. Once the patients were evaluated as having resumed ovarian function, they were randomly assigned to complete 5 years of TAM alone (group B) or 5 years of TAM with OFS for 2 years (group C) at the time of each visit. If the FSH level was less than 30 mIU/mL at the time of enrollment, ovarian function was regarded as being maintained, and these patients were randomly assigned either to complete 5 years of TAM alone (group D) or 5 years of TAM with OFS for 2 years (group E) in a 1:1 ratio (Fig 1). The patients of groups B and D were classified into a TAM-only group (TAM-only), and the patients of groups C and E were classified into a TAM plus OFS (TAM + OFS) group. OFS was induced through a 3.6-mg subcutaneous injection of goserelin (Zoladex [D-Ser6(But)Azgly10 luteinizing hormone–releasing hormone]; AstraZeneca, Cambridge, United Kingdom) every 28 days. Oral TAM was provided at a dose of 20 mg daily. Randomization was stratified according to lymph node status. To minimize the bias caused by the difference of each institution's policy, randomization also was stratified by institution. Among patients treated with neoadjuvant chemotherapy, each physician defined lymph node involvement according to the clinical stage.

The study protocol was approved by the institutional review board at each site.[13] All patients provided written informed consent. This study was conducted by the Korean Breast Cancer Study Group and was registered with ClinicalTrials.gov (NCT00912548).

Primary and Secondary End Points

The primary end point was to compare the difference in 5-year DFS between the T plus OFS group and the TAM-only group. DFS was defined as the time from enrollment to the time of the first event (invasive local recurrence, regional recurrence, distant recurrence, invasive contralateral breast cancer, secondary malignancy, or death as a result of any reason). The secondary end point was OS rate between the two groups. Survival was censored at the date of last contact of patients without events. We also compared DFS and OS between the two groups as defined from the time of random assignment to the time of events. Additional subgroup analyses according to time of random assignment and patient characteristics were conducted, although they were not preplanned.

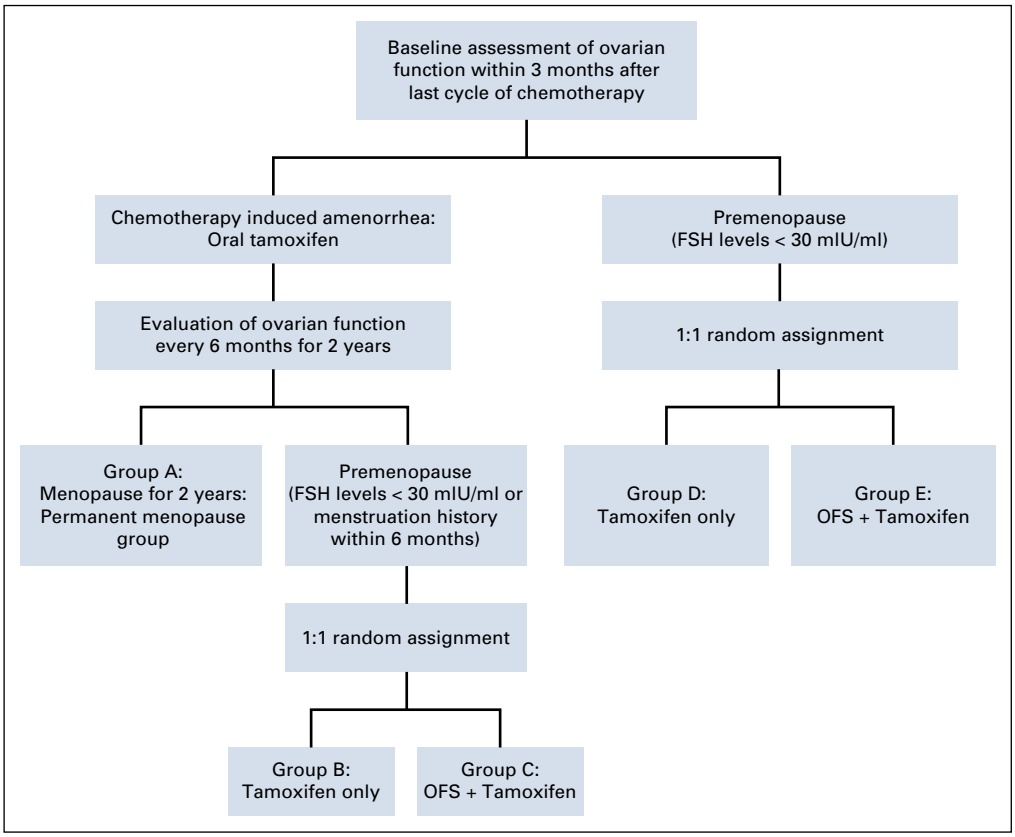

FIG 1. Study design. FSH, follicle-stimulating hormone; OFS, ovarian function suppression. Reprinted with permission from Kim et al.[13]

Procedure and Statistical Analysis

The hypothesis of the study was that the DFS of the TAM + OFS group (groups C and E) would be better than that of the TAM-only group (groups B and D). The original target number of each random assignment was 1,234 patients. We estimated that the study with this sample size would have more than 85% power (two-sided α of 5%) to detect a 7% reduction in hazard in the TAM + OFS group versus the TAM-only group.[13] The expected 5-year DFS in the TAM-only group was 70%. Because patients who remained amenorrheic for 2 years since enrollment and those who experienced recurrence before random assignment were excluded from the survival analysis, the initial target enrollment was 1,580 patients.

In 2010, the protocol was amended to extend the accrual period from 2 years to 5 years because enrollment rates were slower than expected. The recruitment was closed in March 2014. The interim analysis was planned until the time when 187 DFS events occurred. However, because the number of events was smaller than we initially anticipated, the median follow-up period was extended to 5 years before 187 events had occurred. Therefore, the steering committee conducted a final analysis without an interim analysis. Data were locked on October 27, 2017. Kaplan-Meier method was used to present survival curves. Log-rank test was performed to compare the treatment groups. Cox proportional hazards regression was used to estimate hazard ratios (HRs) and 95% CIs.

RESULTS

Patients

A total of 1,483 patients were enrolled between March 2009 and March 2014. Although this number was smaller than the original target of 1,580, the targeted number of randomly assigned patients was achieved because the proportion of patients with resumed ovarian function was higher than we expected. Among these patients, 1,293 were randomly assigned to either the TAM + OFS group or the TAM-only group. Eleven patients were excluded because of inadequate data or consent withdrawal. Finally, 1,282 patients were included in this intention-to-treat analysis. Of these patients, 635 were assigned to the TAM + OFS group and 647 to the TAM-only group (Fig 2). The two groups were well balanced in terms of demographics and baseline disease (Table 1; Appendix Tables A1 and A2, online only). The median age of the patients was 40 years (range, 24 to 45 years). Overall, 705 patients (55.0%) had node-positive disease. There were 176 patients (13.8%) with HER2-positive disease. The type of surgical treatment and chemotherapy regimens was well balanced in both groups. A total of 736 patients (57.5%) were treated with taxane-based chemotherapy regimens. Among patients

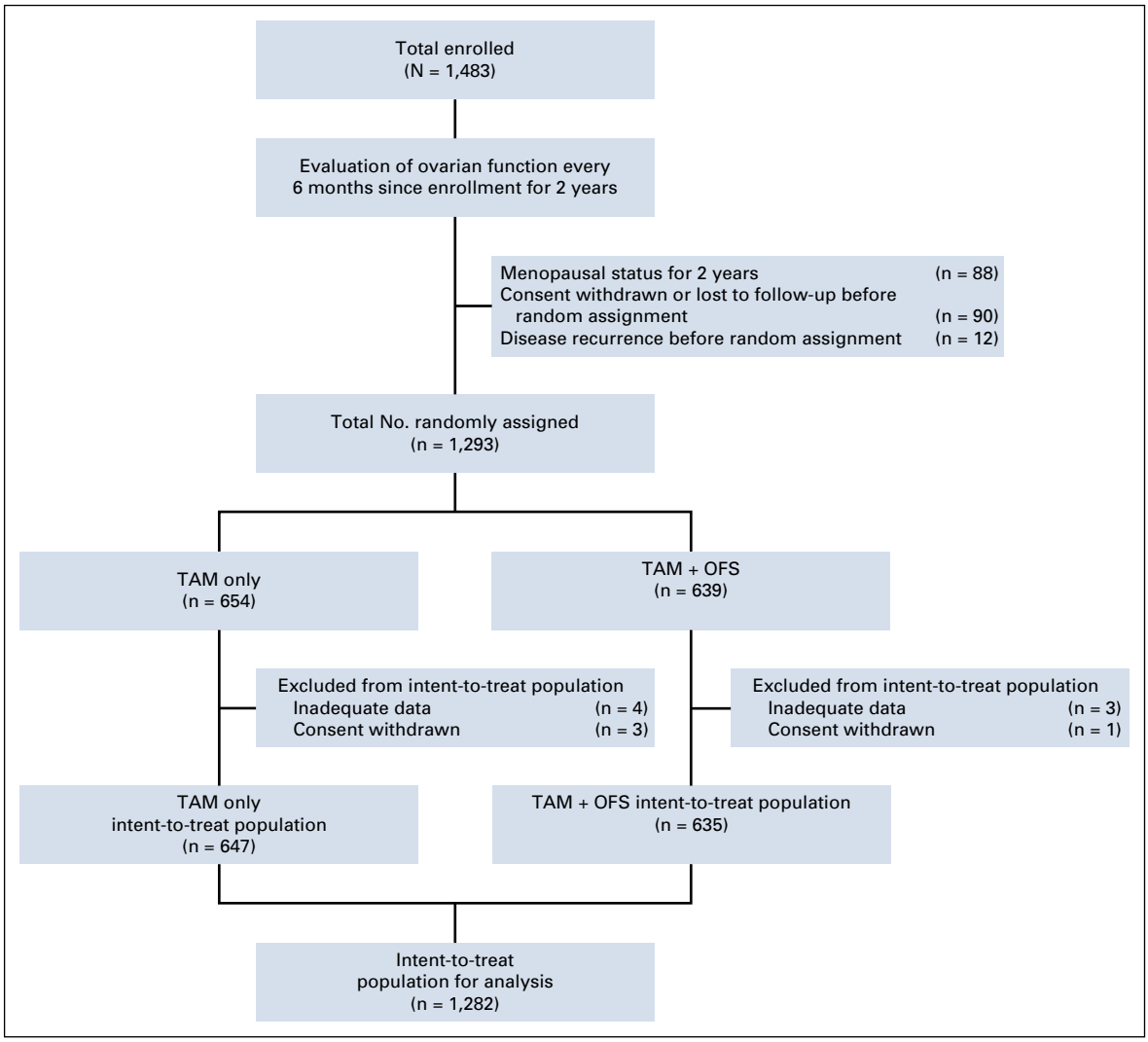

FIG 2. CONSORT diagram.TAM + OFS, tamoxifen plus ovarian function suppression group; TAM only, tamoxifen-only group.

who had been randomly assigned to the TAM + OFS group, the rate of early discontinuation of OFS without recurrence was 25.9% (165 of 635 patients; Appendix Table A3, online only).

Frequency and Pattern of Ovarian Function Recovery

The patients who showed disease relapse before random assignment and those with inadequate data were excluded from the analysis of ovarian function recovery pattern. Of the 1,370 patients who had been categorized into each group, 155 (11.3%) remained premenopausal at the time of enrollment. A total of 745 patients (54.4%) resumed ovarian function within 6 months of completing chemotherapy. Of note, 381 (27.9%) resumed ovarian function slowly between 6 and 24 months after finishing chemotherapy (Fig 3; Appendix Table A4, online only). Only 88 patients (6.4%) had chemotherapy-induced amenorrhea for 2 years after enrollment.

DFS and OS

At a median follow-up of 63 months, 156 of 1483 enrolled patients had DFS events. The 5-year DFS rate for all enrolled patients was 89.0%. Twelve patients experienced DFS events in the state of chemotherapy-induced menopause before random assignment.

The 1,282 patients who were randomly assigned and included for survival analysis were associated with 132 DFS events (10.3%), including 28 locoregional recurrences, 84 distant metastases, eight contralateral breast cancers, 11 other primary cancers, and one death without recurrence. Eighty and 52 DFS events developed in the TAM-only and TAM + OFS groups, respectively (Table 2). The 5-year DFS rate was 91.1% in the TAM + OFS group and 87.5% in the TAM-only group (HR, 0.69; 95% CI, 0.48 to 0.97; $P = .033$; Fig 4A). This difference was statistically significant. We also compared 5-year DFS between the two groups as defined

TABLE 1. Patient Characteristics

	Treatment Assignment				
	TAM Only (n = 647)		TAM + OFS (n = 635)		
Characteristic	**No.**	**%**	**No.**	**%**	***P***
Age at enrollment, years					.519
< 35	83	12.8	89	14.0	
35-39	194	30.0	173	27.2	
40-45	370	57.2	373	58.7	
Lymph node status					.805
Negative	289	44.7	288	45.4	
Positive	358	55.3	347	54.6	
Tumor size, cm					.877
< 2	310	47.9	307	48.3	
≥ 2	337	52.1	328	51.7	
Tumor grade					.114
1	89	13.8	117	18.4	
2	349	53.9	314	49.4	
3	157	24.6	148	23.3	
Unknown	52	8.0	56	8.8	
Histology					.741
Invasive ductal carcinoma	570	88.1	564	88.8	
Invasive lobular carcinoma	33	5.1	27	4.3	
Other	40	6.2	42	6.6	
Unknown	4	0.6	2	0.3	
HER2 status					.792
Negative	386	59.7	390	61.4	
Positive	92	14.2	84	13.2	
Unknown	169	26.1	161	25.4	
Chemotherapy regimen					.804
Anthracycline plus cyclophosphamide	186	28.7	192	30.2	
Anthracycline plus cyclophosphamide followed by taxane	330	51.0	322	50.7	
Anthracycline plus taxane	29	4.5	29	4.6	
Anthracycline plus cyclophosphamide and taxane	9	1.4	4	0.6	
Fluorouracil, anthracycline, and cyclophosphamide	74	11.4	74	11.7	
Other taxane-based regimens	7	1.1	6	0.9	
Other nontaxane-based regimens	5	0.8	4	0.6	
Unknown	7	1.1	4	0.6	
Surgery					.804
Total mastectomy	260	40.2	244	38.4	
Breast-conserving surgery	370	57.2	373	58.7	
Unknown	17	2.6	18	2.8	
Radiotherapy at time of enrollment					
Done	368	56.9	352	55.4	.613
Not done	279	43.1	283	44.6	

Abbreviations: HER2, human epidermal growth factor receptor 2; TAM + OFS, tamoxifen plus ovarian function suppression group; TAM only, tamoxifen-only group.

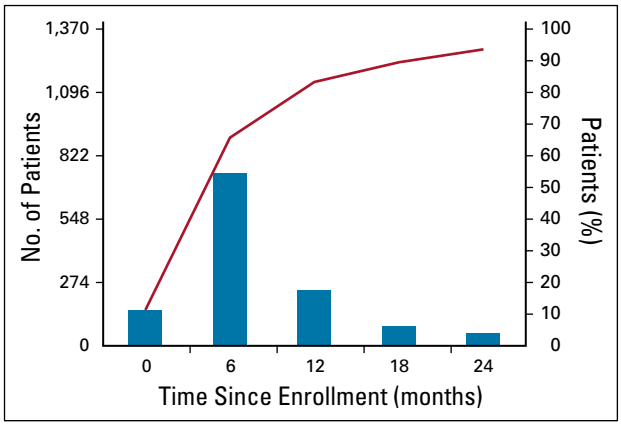

FIG 3. Pattern and frequency of ovarian function resumption for patients randomly assigned to each group.

from the time of random assignment to the time of the first event. The median follow-up since random assignment for all patients was 56 months (TAM-only group, 56.5 months; TAM + OFS group, 55.8 months). In this analysis, the 5-year DFS rate was 89.8% in the TAM + OFS group and 87.3% in the TAM-only group (HR, 0.69; 95% CI, 0.49 to 0.98; P = .036; Fig 4 B).

Next, we evaluated the HR and estimates of DFS defined as the time interval either from enrollment or from random assignment to the first event between the two groups according to the time of random assignment 0, 6, 12, 18, and 24 months after enrollment. The results are shown in Figure 5.

In OS analysis, although the number of events was quite small, the patients in the TAM + OFS group showed significantly better survival than those in the TAM-only group (HR, 0.31; 95% CI, 0.10 to 0.94; P = .029; Appendix Fig A1, online only). The number of events of OS was four in the TAM + OFS group and 14 in the TAM-only group. No death as a result of another primary cancer occurred.

Additional unplanned analysis was performed to evaluate recurrence-free interval and breast cancer–free interval. The differences in recurrence-free interval (HR, 0.68; 95% CI, 0.47 to 0.999; P = .05; Appendix Fig A2A, online only) and breast cancer–free interval (HR, 0.70; 95% CI, 0.49 to 1.01; P = .06; Appendix Fig A2B) between the two groups were consistent with the results of DFS. No heterogeneity of treatment effect of OFS was found according to the mode of detection of the resumption of ovarian function (Appendix Fig A3, online only). In another unplanned subgroup analysis according to patient characteristics, we found no heterogeneity of treatment effect of OFS (Appendix Fig A4, online only).

TABLE 2. Sites of First Disease-Free Survival Events in the Intention-to-Treat Analysis Population

	TAM Only		TAM + OFS		Overall	
Event	**No.**	**%**	**No.**	**%**	**No.**	**%**
Locoregional recurrence	20	25.0	8	15.4	28	21.2
Distant metastasis						
Bone and/or soft tissue only	19	23.8	17	32.7	36	27.3
Visceral metastasis	26	32.5	18	34.6	44	33.3
Unknown	3	3.8	1	1.9	4	3.0
Contralateral breast cancer	4	5.0	4	7.7	8	6.1
Death without recurrence	0		1	1.9	1	0.8
Other primary cancer						
Endometrial	2	2.5			2	1.5
Stomach	2	2.5			2	1.5
Colorectal	2	2.5			2	1.5
Thyroid			2	3.8	2	1.5
Leukemia			1	1.9	1	0.8
Liposarcoma	1	1.3			1	0.8
Kidney	1	1.3			1	0.8
Total	80	100	52	100	132	100

Abbreviations: TAM + OFS, tamoxifen plus ovarian function suppression group; TAM only, tamoxifen-only group.

DISCUSSION

With a median follow-up of 63 months, we found that the addition of OFS for 2 years to TAM in an adjuvant setting resulted in better DFS and OS compared with TAM alone for patients who remained premenopausal or resumed ovarian function after completing chemotherapy. The result is concordant with that of SOFT, which showed a DFS benefit by adding adjuvant OFS to TAM in premenopausal women with breast cancer.

The ASTRRA study showed similar results with a shorter follow-up period and smaller number of patients, which can be explained by the difference in the characteristics of patients in each study. The participants in ASTRRA had a relatively higher risk of disease recurrence than those in SOFT. The subgroup analysis of SOFT showed that most of the survival benefit from the addition of OFS was attributed to the patients who received chemotherapy.[9] Of note, the characteristics of the chemotherapy-treated subgroup in SOFT were similar to those of ASTRRA, such as median age (40 years in both trials), ratio of lymph node positivity (55.0% in ASTRRA *v* 57.3% in SOFT), tumor grade 2 to 3 (75.5% in ASTRRA *v* 82.7% in SOFT), and HER2 positivity (13.7% in ASTRRA *v* 18.1% in SOFT).[14] Therefore, the results of ASTRRA confirm the findings of SOFT that the addition of OFS to TAM provides survival benefits for women at sufficient risk for recurrence to receive adjuvant chemotherapy and who remain in a premenopausal state after chemotherapy.

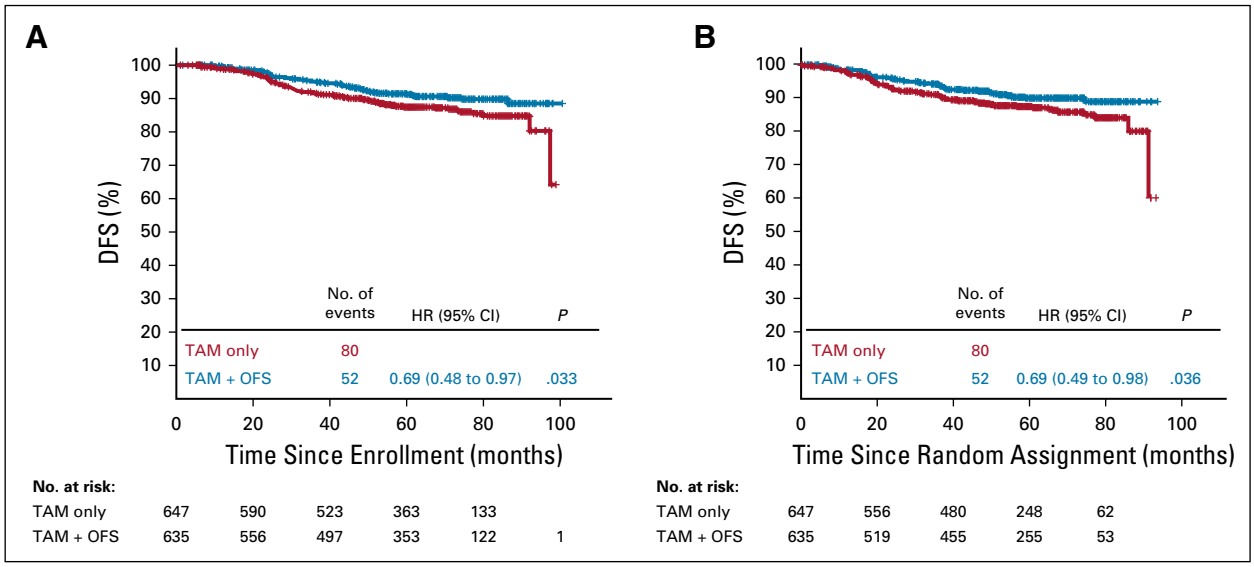

FIG 4. Kaplan-Meier estimates of disease-free survival (DFS) as defined (A) since the time of enrollment and (B) since the time of random assignment to the time of first event. HR, hazard ratio; TAM + OFS, tamoxifen plus ovarian function suppression group; TAM only, tamoxifen-only group.

Although SOFT and ASTRRA have many similarities, they differ in several aspects. First, SOFT enrolled all premenopausal women without limiting age, whereas ASTRRA excluded women older than 45 years. Most older premenopausal women who are in their late 40s at the time of starting adjuvant endocrine therapy experience natural and spontaneous menopause during the 5-year course of treatment. We assumed that spontaneous menopause might obscure the effect of OFS and might affect the results of the study. Thus, to minimize the effect of natural menopause, we set the age limit as 45 years or younger. Second, in ASTRRA, we evaluated ovarian function according to serum FSH level or menstrual bleeding history every 6 months for 2 years since enrollment. Meanwhile, ovarian function in SOFT was assessed within 8 months after completing chemotherapy on the basis of serum E2 level. In this study, we found that the resumption of ovarian function had occurred continuously for 2 years, and approximately 30% of patients resumed ovarian function slowly after 6 months since completion of chemotherapy. This is consistent with the current international consensus guideline, which stresses that caution must be taken in defining menopausal status after chemotherapy.[11,15,16] Finally, the duration of OFS was 2 years in ASTRRA, whereas it was 5 years in SOFT. Although the addition of OFS to TAM generally is accepted to provide survival benefit for premenopausal women with hormone receptor–positive breast cancer, uncertainty still exists about patient selection, the best timing, and optimal duration. A long-term duration of OFS in young women inevitably is accompanied by toxicities.[17-19] This study suggests that the use of OFS for 2 years from the point of resumption of ovarian function could be an option. The overall adherence rate with OFS for patients assigned to the TAM + OFS group was 74.1%. Given that younger premenopausal women are less adherent to endocrine therapy than older premenopausal women, it is speculated that the adherence rate in this study was not lower than that in real-world practice.[18,19]

In this study, we tried to reflect the real-world practice pattern as much as possible. Thus, the time of randomization varied from the point of enrollment to 24 months after enrollment. Initially, we set the primary end point as DFS defined from the time of enrollment to the time of the first event. We acknowledge that this might have incorporated selection bias. However, because this study was designed to determine the value of OFS in women with intact ovarian function and the comparisons were made between the two groups in the same conditions, the events that occurred in the state of chemotherapy-induced amenorrhea were not likely to affect the evaluation of OFS efficacy. Moreover, we observed homogeneous difference in DFS as defined either from enrollment or from randomization to the time of the first event between the two groups. We also evaluated the HR and estimates of DFS within each pair according to the time of ovarian function recovery. Although these subset analyses were not preplanned and any inference from these comparisons are preliminary, we found that the trend was more pronounced in patients who had been randomly assigned at 6 months after completing chemotherapy.

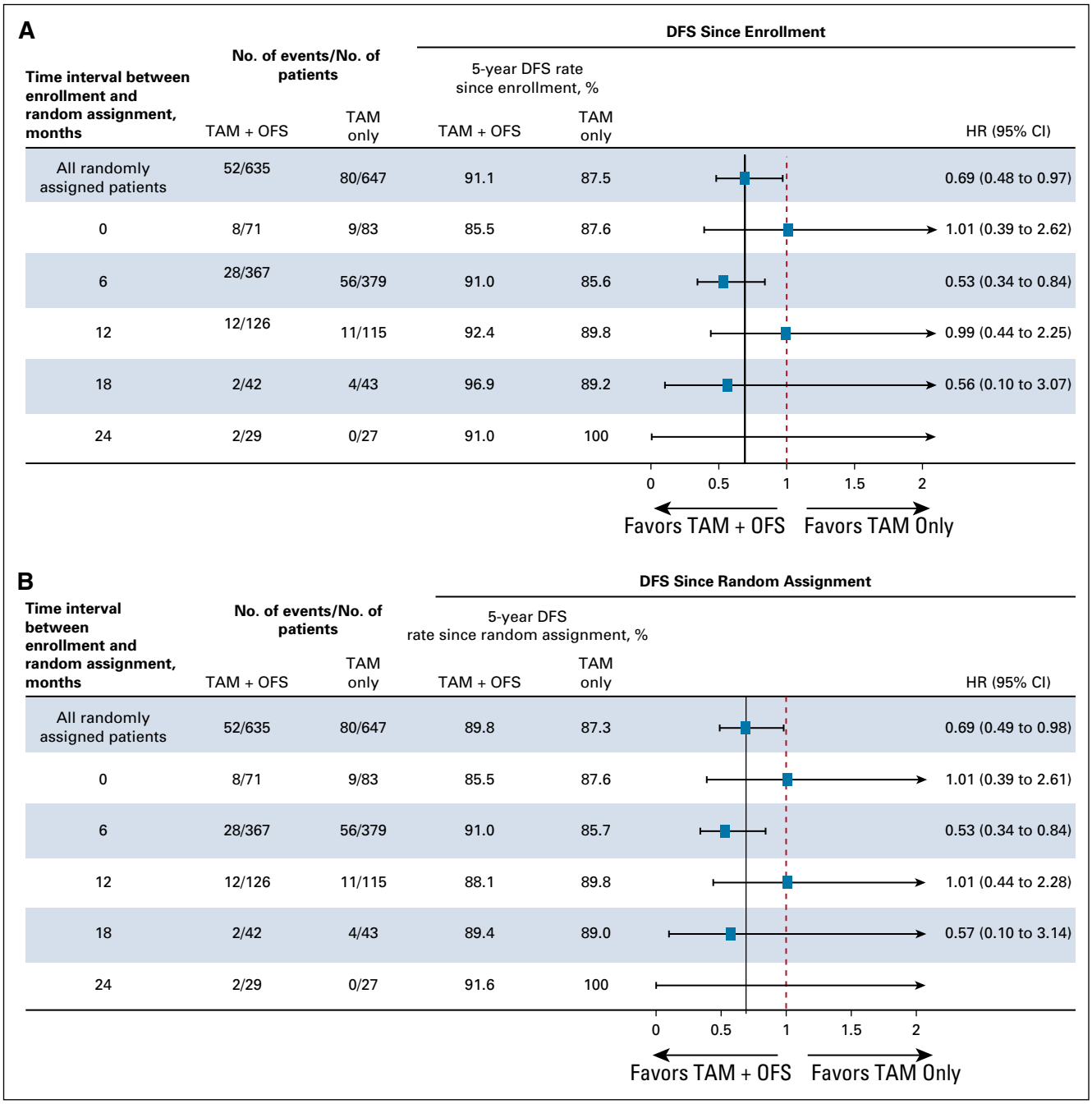

FIG 5. Hazard ratio (HR) and estimates of disease-free survival (DFS) as defined (A) since the time of enrollment and (B) since the time of random assignment to the time of the first event according to time interval between enrollment and random assignment. TAM + OFS, tamoxifen plus ovarian function suppression group; TAM only, tamoxifen-only group.

One of the limitations of this study is that the safety and adverse event data were not included. Because OFS has been used widely in clinical practice for decades and the adverse effects of relatively short-term use of OFS for 2 years were considered to be well understood in previous studies, we focused on the oncologic efficacy of OFS in the current study.[4,20,21]

In conclusion, ovarian function needs to be monitored longitudinally for at least 2 years in premenopausal patients who have been administered chemotherapy. For those who remain in a premenopausal state or resume ovarian function after chemotherapy, the addition of OFS for 2 years to standard TAM treatment significantly improves DFS compared with TAM alone.

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AUTHORS' DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST AND DATA AVAILABILITY STATEMENT

Disclosures provided by the authors and data availability statement (if applicable) are available with this article at DOI https://doi.org/10.1200/JCO.19.00126.

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AUTHORS' DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST

Adding Ovarian Suppression to Tamoxifen for Premenopausal Breast Cancer: A Randomized Phase III Trial

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APPENDIX

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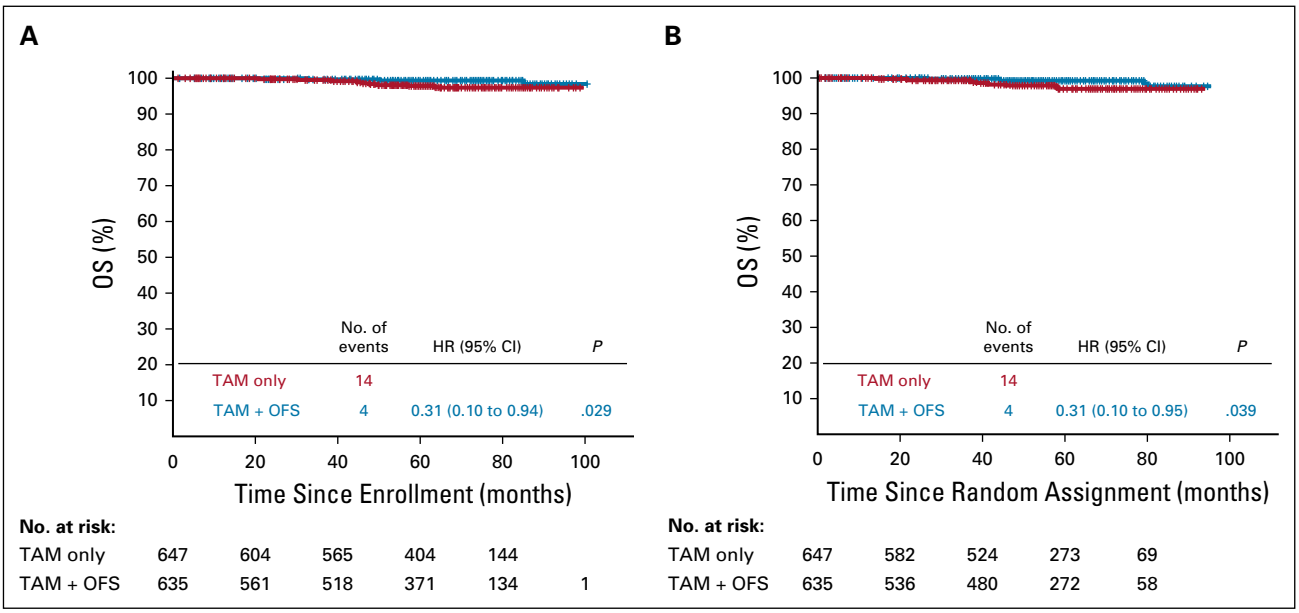

FIG A1. Kaplan-Meier estimates of overall survival (OS) as defined (A) since the time of enrollment and (B) since the time of random assignment to death. HR, hazard ratio; TAM + OFS, tamoxifen plus ovarian function suppression group; TAM only, tamoxifen-only group.

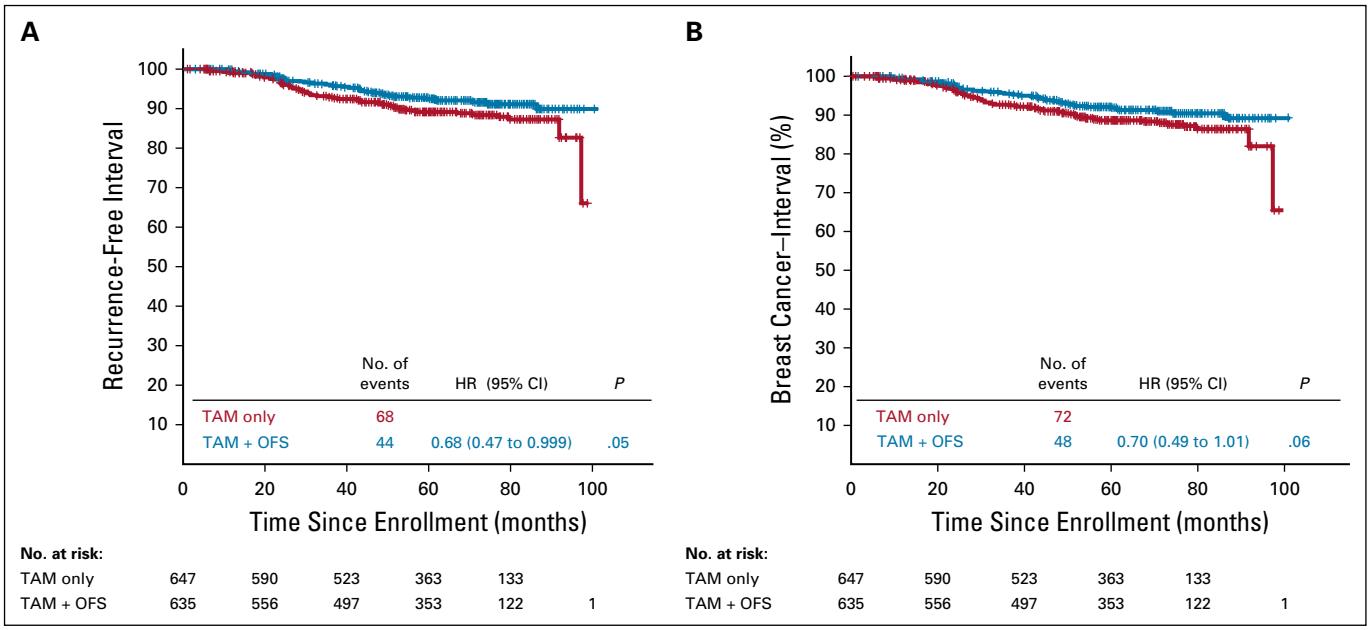

FIG A2. The differences in (A) recurrence-free interval and (B) breast cancer–free interval. The events for recurrence-free interval were local recurrence, regional recurrence, distant recurrence, or death as a result of breast cancer as the first event. The events for breast cancer–free interval were local recurrence, regional recurrence, distant recurrence, contralateral breast cancer, or death as a result of breast cancer as the first event. HR, hazard ratio; TAM + OFS, tamoxifen plus ovarian function suppression group; TAM only, tamoxifen-only group.

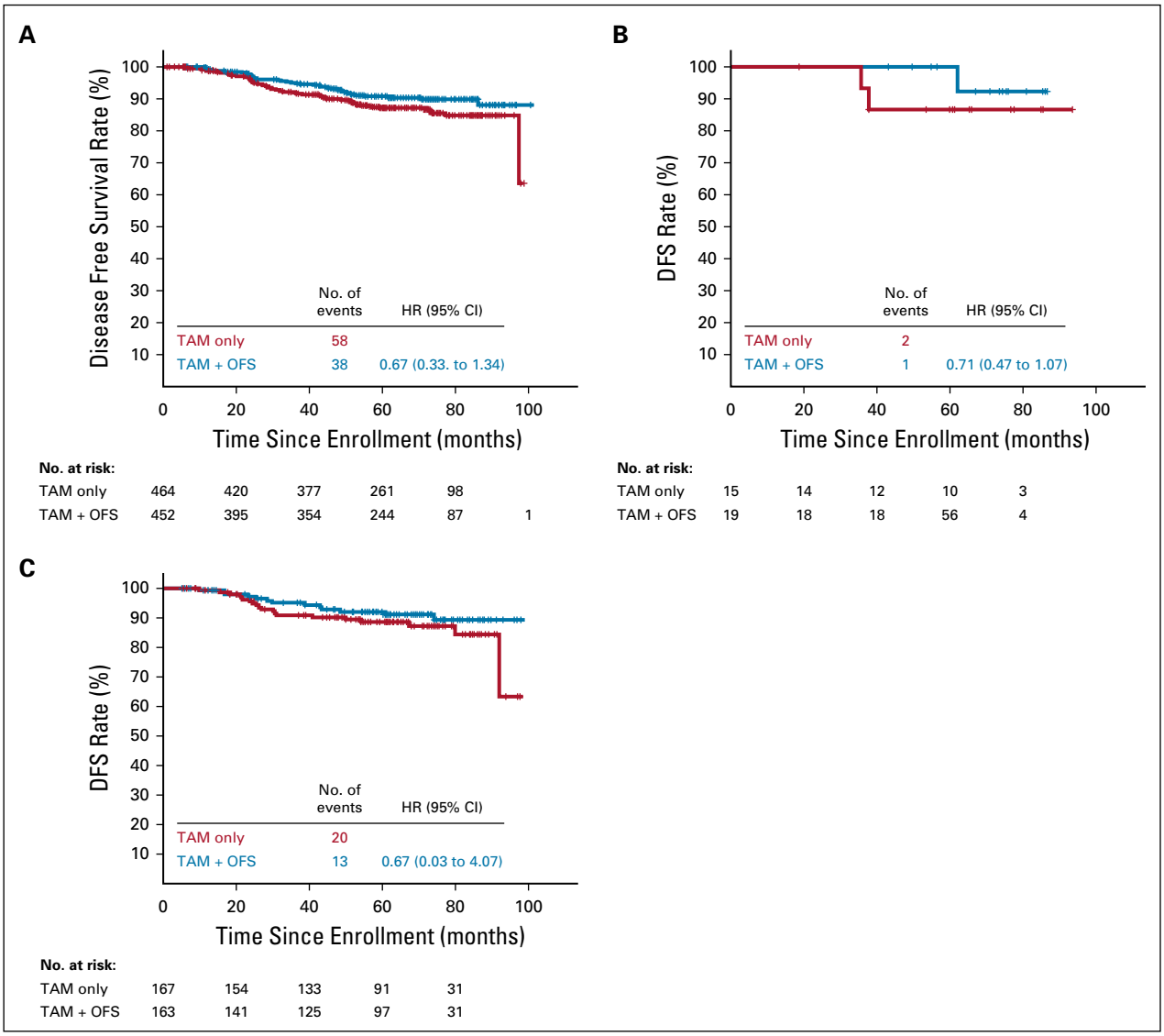

FIG A3. Disease-free survival (DFS) rate on the basis of on the mode of detection of the resumption of ovarian function. (A) DFS of patients who were randomly assigned by follicle-stimulating hormone level. (B) DFS of patients who were randomly assigned by vaginal bleeding history. (C) DFS of patients who were randomly assigned by both follicle-stimulating hormone and the history of vaginal bleeding. HR, hazard ratio; TAM + OFS, tamoxifen plus ovarian function suppression group; TAM only, tamoxifen-only group.

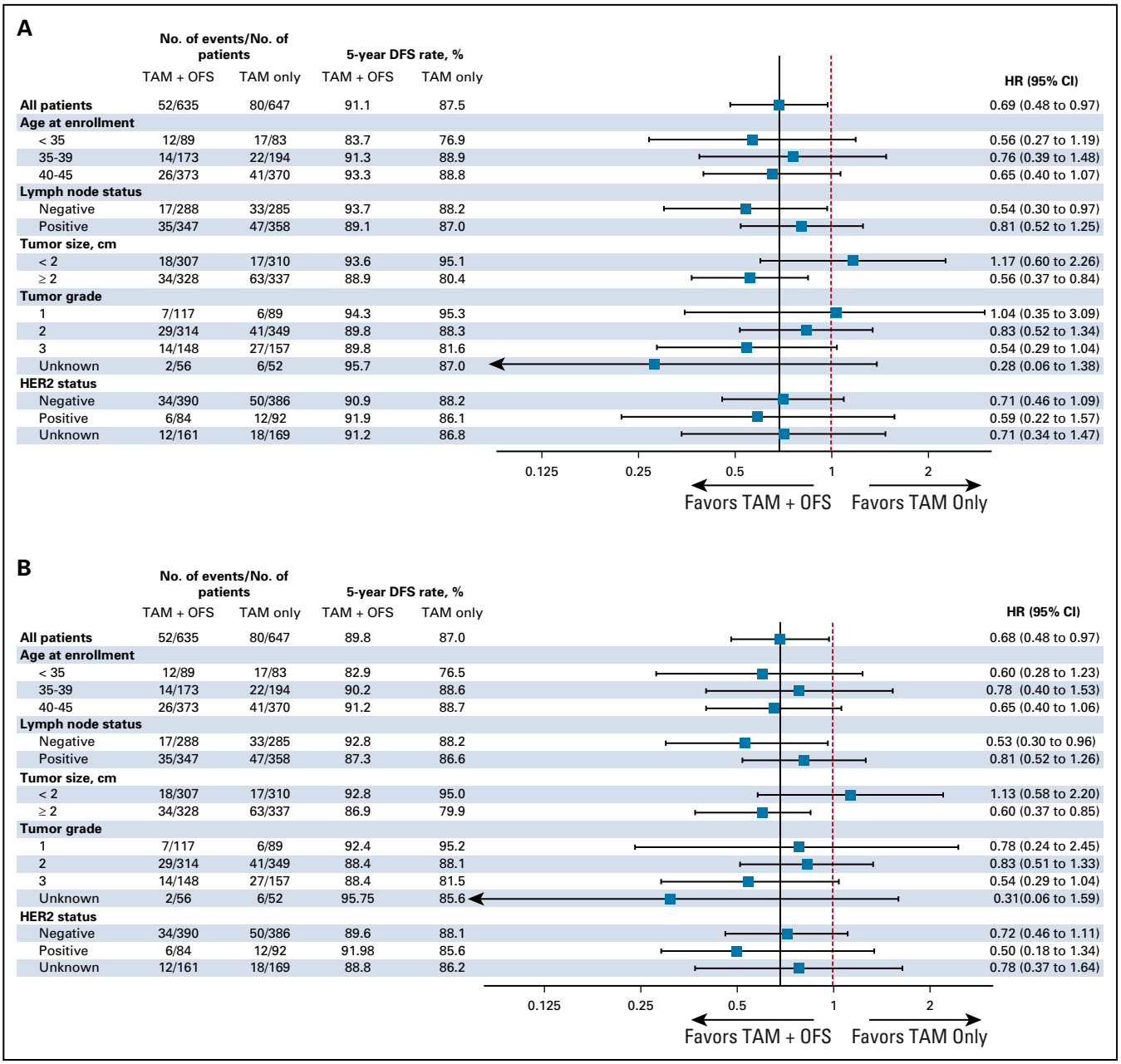

FIG A4. Subgroup analysis of disease-free survival (DFS) since (A) the time of enrollment and (B) since the time of random assignment adjusted by visits. HER2, human epidermal growth factor receptor 2; HR, hazard ratio; TAM + OFS, tamoxifen plus ovarian function suppression group; TAM only, tamoxifen-only group.

TABLE A1. Patient Characteristics by Treatment Group According to the Timing of Random Assignment and Total Patient Characteristics Stratified by Visit

	Treatment Assignment						
	TAM Only		TAM + OFS		Total		
Characteristic	No.	%	No.	%	No.	%	*P*
Visit 1							
Age at enrollment, years							
< 35	18	21.7	27	38.0	45	29.2	.053
35-39	40	48.2	23	32.4	63	40.9	
40-45	25	30.1	21	29.6	46	29.9	
Lymph node status							
Negative	59	71.1	52	73.2	111	72.1	.858
Positive	24	28.9	19	26.8	42	27.9	
Tumor size, cm							
< 2	50	60.2	50	70.4	100	64.9	.236
≥ 2	33	39.8	21	29.6	54	35.1	
Tumor grade							
1	9	10.8	15	21.1	24	15.6	.100
2	47	56.6	36	50.7	83	53.9	
3	15	18.1	16	22.5	31	20.1	
Unknown	12	14.5	4	5.6	16	10.4	
Histology							
Invasive ductal carcinoma	74	89.2	63	88.7	137	89.0	.626
Invasive lobular carcinoma	2	2.4	1	1.4	3	1.9	
Other	6	7.2	7	9.9	13	8.4	
Unknown	1	1.2			1	0.6	
HER2 status							
Negative	43	51.8	42	59.2	85	55.2	.408
Positive	12	14.5	12	16.9	24	15.6	
Unknown	28	33.7	17	23.9	45	29.2	
Chemotherapy regimen							
Anthracycline plus cyclophosphamide	42	50.6	37	52.1	79	51.3	.455
Anthracycline plus cyclophosphamide followed by taxane	19	22.9	21	29.6	40	26.0	
Anthracycline plus taxane	2	2.4	0		2	1.3	
Anthracycline plus cyclophosphamide and taxane	0		0		0		
Fluorouracil, anthracycline, and cyclophosphamide	13	15.7	8	11.3	21	13.6	
Other taxane-based regimen	1	1.2	2	2.8	3	1.9	
Other nontaxane-based regimen	2	2.4	2	2.8	4	2.6	
Unknown	4	4.8	1	1.4	5	3.2	
Surgery							
Total mastectomy	27	32.5	20	28.2	47	30.5	.030
Breast-conserving surgery	51	61.4	51	71.8	102	66.2	
Unknown	5	6.0	0		5	3.2	

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TABLE A1. Patient Characteristics by Treatment Group According to the Timing of Random Assignment and Total Patient Characteristics Stratified by Visit (continued)

	Treatment Assignment						
	TAM Only		TAM + OFS		Total		
Characteristic	No.	%	No.	%	No.	%	*P*
Visit 2							
Age at enrollment, years							
< 35	49	12.9	39	10.6	88	11.8	.540
35-39	110	29.0	103	28.1	213	28.6	
40-45	220	58.0	225	61.3	445	59.7	
Lymph node status							
Negative	160	42.2	162	44.1	322	43.2	.605
Positive	219	57.8	205	55.9	424	56.8	
Tumor size, cm							
< 2	176	46.4	167	45.5	343	46.0	.826
≥ 2	203	53.6	200	54.5	403	54.0	
Tumor grade							
1	54	14.2	61	16.6	115	15.4	.449
2	208	54.9	189	51.5	397	53.2	
3	93	24.5	85	23.2	178	23.9	
Unknown	24	6.3	32	8.7	56	7.5	
Histology							
Invasive ductal carcinoma	330	87.1	330	89.9	660	88.5	.556
Invasive lobular carcinoma	22	5.8	17	4.6	39	5.2	
Other	24	6.3	19	5.2	43	5.8	
Unknown	3	0.8	1	0.3	4	0.5	
HER2 status							
Negative	248	65.4	238	64.9	486	65.1	.926
Positive	52	13.7	54	14.7	106	14.2	
Unknown	79	20.8	75	20.4	154	20.6	
Chemotherapy regimen							
Anthracycline plus cyclophosphamide	105	27.7	111	30.2	216	29.0	.627
Anthracycline plus cyclophosphamide followed by taxane	201	53.0	185	50.4	386	51.7	
Anthracycline plus taxane	21	5.5	17	4.6	38	5.1	
Anthracycline plus cyclophosphamide and taxane	2	0.5	2	0.5	4	0.5	
Fluorouracil, anthracycline, and cyclophosphamide	43	11.3	49	13.4	92	12.3	
Other taxane-based regimen	3	0.8	1	0.3	4	0.5	
Other nontaxane-based regimen	2	0.5	2	0.5	4	0.5	
Unknown	2	0.5	0		2	0.3	
Surgery							
Total mastectomy	159	42.0	144	39.2	303	40.6	.425
Breast-conserving surgery	215	56.7	214	58.3	429	57.5	
Unknown	5	1.3	9	2.5	14	1.9	

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TABLE A1. Patient Characteristics by Treatment Group According to the Timing of Random Assignment and Total Patient Characteristics Stratified by Visit (continued)

	Treatment Assignment						
	TAM Only		TAM + OFS		Total		
Characteristic	No.	%	No.	%	No.	%	*P*
Visit 3							
Age at enrollment, years							
< 35	11	9.6	19	15.1	30	12.4	.406
35-39	29	25.2	32	25.4	61	25.3	
40-45	75	65.2	75	59.5	150	62.2	
Lymph node status							
Negative	44	38.3	46	36.5	90	37.3	.791
Positive	71	61.7	80	63.5	151	62.7	
Tumor size, cm							
< 2	50	43.5	57	45.2	107	44.4	.797
≥ 2	65	56.5	69	54.8	134	55.6	
Tumor grade							
1	11	9.6	25	19.8	36	14.9	.135
2	54	47.0	57	45.2	111	46.1	
3	39	33.9	34	27.0	73	30.3	
Unknown	11	9.6	10	7.9	21	8.7	
Histology							
Invasive ductal carcinoma	104	90.4	110	87.3	214	88.8	.559
Invasive lobular carcinoma	5	4.3	5	4.0	10	4.1	
Other	6	5.2	10	7.9	16	6.6	
Unknown	0		1	0.8	1	0.4	
HER2 status							
Negative	64	55.7	73	57.9	137	56.8	.699
Positive	18	15.7	15	11.9	33	13.7	
Unknown	33	28.7	38	30.2	71	29.5	
Chemotherapy regimen							
Anthracycline plus cyclophosphamide	23	20.0	26	20.6	49	20.3	.338
Anthracycline plus cyclophosphamide followed by taxane	70	60.9	75	59.5	145	60.2	
Anthracycline plus taxane	4	3.5	11	8.7	15	6.2	
Anthracycline plus cyclophosphamide and taxane	4	3.5	1	0.8	5	2.1	
Fluorouracil, anthracycline, and cyclophosphamide	11	9.6	10	7.9	21	8.7	
Other taxane-based regimen	3	2.6	2	1.6	5	2.1	
Other nontaxane-based regimen	0		0		0		
Unknown	0		1	0.8	1	0.4	
Surgery							
Total mastectomy	50	43.5	52	41.3	102	42.3	.852
Breast-conserving surgery	61	53.0	68	54.0	129	53.5	
Unknown	4	3.5	6	4.8	10	4.1	

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TABLE A1. Patient Characteristics by Treatment Group According to the Timing of Random Assignment and Total Patient Characteristics Stratified by Visit (continued)

	Treatment Assignment						
	TAM Only		TAM + OFS		Total		
Characteristic	No.	%	No.	%	No.	%	*P*
Visit 4							
Age at enrollment, years							
< 35	4	9.3	2	4.8	6	7.1	.631
35-39	7	16.3	9	21.4	16	18.8	
40-45	32	74.4	31	73.8	63	74.1	
Lymph node status							
Negative	18	41.9	17	40.5	35	41.2	1.000
Positive	25	58.1	25	59.5	50	58.8	
Tumor size, cm							
< 2	17	39.5	19	45.2	36	42.4	.663
≥ 2	26	60.5	23	54.8	49	57.6	
Tumor grade							
1	9	20.9	9	21.4	18	21.2	.732
2	24	55.8	19	45.2	43	50.6	
3	6	14.0	9	21.4	15	17.6	
Unknown	4	9.3	5	11.9	9	10.6	
Histology							
Invasive ductal carcinoma	38	88.4	35	83.3	73	85.9	.737
Invasive lobular carcinoma	2	4.7	2	4.8	4	4.7	
Other	3	7.0	5	11.9	8	9.4	
Unknown	0		0		0		
HER2 status							
Negative	20	46.5	24	57.1	44	51.8	.473
Positive	6	14.0	3	7.1	9	10.6	
Unknown	17	39.5	15	35.7	32	37.6	
Chemotherapy regimen							
Anthracycline plus cyclophosphamide	9	20.9	12	28.6	21	24.7	.382
Anthracycline plus cyclophosphamide followed by taxane	22	51.2	22	52.4	44	51.8	
Anthracycline plus taxane	2	4.7	1	2.4	3	3.5	
Anthracycline plus cyclophosphamide and taxane	2	4.7	0		2	2.4	
Fluorouracil, anthracycline, and cyclophosphamide	7	16.3	6	14.3	13	15.3	
Other taxane-based regimen	0		1	2.4	1	1.2	
Other nontaxane-based regimen	0		0		0		
Unknown	1	2.3	0		1	1.2	
Surgery							
Total mastectomy	15	34.9	20	47.6	35	41.2	.476
Breast-conserving surgery	26	60.5	20	47.6	46	54.1	
Unknown	2	4.7	2	4.8	4	4.7	

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TABLE A1. Patient Characteristics by Treatment Group According to the Timing of Random Assignment and Total Patient Characteristics Stratified by Visit (continued)

	Treatment Assignment						
	TAM Only		TAM + OFS		Total		
Characteristic	No.	%	No.	%	No.	%	*P*
Visit 5							
Age at enrollment, years							
< 35	1	3.7	2	6.9	3	5.4	.675
35-39	8	29.6	6	20.7	14	25.0	
40-45	18	66.7	21	72.4	39	69.6	
Lymph node status							
Negative	8	29.6	11	37.9	19	33.9	.580
Positive	19	70.4	18	62.1	37	66.1	
Tumor size, cm							
< 2	17	63.0	14	48.3	31	55.4	.296
≥ 2	10	37.0	15	51.7	25	44.6	
Tumor grade							
1	6	22.2	7	24.1	13	23.2	.394
2	16	59.3	13	44.8	29	51.8	
3	4	14.8	4	13.8	8	14.3	
Unknown	1	3.7	5	17.2	6	10.7	
Histology							
Invasive ductal carcinoma	24	88.9	26	89.7	50	89.3	.996
Invasive lobular carcinoma	2	2.4	2	6.9	4	7.1	
Other	1	3.7	1	3.4	2	3.6	
Unknown	0		0		0		
HER2 status							
Negative	11	40.7	13	44.8	24	42.9	.045
Positive	4	14.8	0		4	7.1	
Unknown	12	44.4	16	55.2	28	50.0	
Chemotherapy regimen							
Anthracycline plus cyclophosphamide	7	25.9	6	20.7	13	23.2	.349
Anthracycline plus cyclophosphamide followed by taxane	18	66.7	19	65.5	37	66.1	
Anthracycline plus taxane	0		0		0		
Anthracycline plus cyclophosphamide and taxane	1	3.7	1	3.4	2	3.6	
Fluorouracil, anthracycline, and cyclophosphamide	0		1	3.4	1	1.8	
Other taxane-based regimen	0		0		0		
Other nontaxane-based regimen	1	3.7	0		1	1.8	
Unknown	0		2	6.9	2	3.6	
Surgery							
Total mastectomy	9	33.3	8	27.6	17	30.4	.891
Breast-conserving surgery	17	63.0	20	69.0	37	66.1	
Unknown	1	3.7	1	3.4	2	3.6	

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TABLE A1. Patient Characteristics by Treatment Group According to the Timing of Random Assignment and Total Patient Characteristics Stratified by Visit (continued)

	Treatment Assignment						
	TAM Only		TAM + OFS		Total		
Characteristic	No.	%	No.	%	No.	%	*P*
Total							
Age at enrollment, years							.519
< 35	83	12.8	89	14.0	172	13.4	
35-39	194	30.0	173	27.2	367	28.6	
40-45	370	57.2	373	58.7	743	58.0	
Lymph node status							.822
Negative	289	44.7	288	45.4	577	45.0	
Positive	358	55.3	347	54.6	705	55.0	
Tumor size, cm							.911
< 2	310	47.9	307	48.3	617	48.1	
≥ 2	337	52.1	328	51.7	665	51.9	
Tumor grade							.113
1	89	13.8	117	18.4	206	16.1	
2	349	53.9	314	49.4	663	51.7	
3	157	24.6	148	23.3	305	23.8	
Unknown	52	8.0	56	8.8	108	8.4	
Histology							.741
Invasive ductal carcinoma	570	88.1	564	88.8	1134	88.5	
Invasive lobular carcinoma	33	5.1	27	4.3	60	4.7	
Other	40	6.2	42	6.6	82	6.4	
Unknown	4	0.6	2	0.3	6	0.5	
HER2 status							.792
Negative	386	59.7	390	61.4	776	60.5	
Positive	92	14.2	84	13.2	176	13.7	
Unknown	169	26.1	161	25.4	330	25.7	
Chemotherapy regimen							.884
Anthracycline plus cyclophosphamide	186	28.7	192	30.2	378	29.5	
Anthracycline plus cyclophosphamide followed by taxane	330	51.0	322	50.7	652	50.9	
Anthracycline plus taxane	29	4.5	29	4.6	58	4.5	
Anthracycline plus cyclophosphamide and taxane	9	1.4	4	0.6	13	1.0	
Fluorouracil, anthracycline, and cyclophosphamide	74	11.4	74	11.7	148	11.5	
Other taxane-based regimens	7	1.1	6	0.9	13	1.0	
Other nontaxane-based regimens	5	0.8	4	0.6	9	0.7	
Unknown	7	1.1	4	0.6	11	0.9	
Surgery							.804
Total mastectomy	260	40.2	244	38.4	504	39.3	
Breast-conserving surgery	370	57.2	373	58.7	743	58.0	
Unknown	17	2.6	18	2.8	35	2.7	

Abbreviations: HER2, human epidermal growth factor receptor 2; TAM + OFS, tamoxifen plus ovarian function suppression group; TAM only, tamoxifen-only group.

TABLE A2. Characteristics of All Enrolled Patients

Characteristic	Group, No.				Total, No.
	TAM Only	TAM + OFS	Non Randomly Assigned	Randomly Assigned and Excluded From Analysis	
No. of patients	647	635	190	11	1,483
Age at enrollment, years					
< 35	83	89	12	2	186
35-39	194	173	38	3	408
40-45	370	373	140	6	889
Lymph node status					
Negative	289	288	87	2	666
Positive	358	347	103	2	810
Unknown				7	7
Tumor size, cm					
< 2	310	307	94	5	716
≥ 2	337	328	96	1	762
Unknown				5	5
Tumor grade					
1	89	117	28	1	235
2	349	314	94	1	758
3	157	148	44	3	352
Unknown	52	56	24	6	138
Histology					
Invasive ductal carcinoma	570	564	175	6	1,315
Invasive lobular carcinoma	33	27	5	0	65
Other	40	42	10	0	92
Unknown	4	2	0	5	11
HER2 status					
Negative	386	390	84	4	914
Positive	92	84	26		202
Unknown	169	161	80	7	417
Chemotherapy regimen					
Anthracycline plus cyclophosphamide	186	192	50	2	430
Anthracycline plus cyclophosphamide followed by taxane	330	322	93	2	747
Anthracycline plus taxane	29	29	14		72
Anthracycline plus cyclophosphamide and taxane	9	4	2		15
Fluorouracil, anthracycline, and cyclophosphamide	74	74	30	1	179
Other taxane-based regimen	7	6	1		14
Other nontaxane-based regimen	5	4			9
Unknown	7	4		6	17
Surgery					
Total mastectomy	260	244	73	3	580
Breast-conserving surgery	370	373	107	2	852
Unknown	17	18	10	6	51

Abbreviations: HER2, human epidermal growth factor receptor 2; TAM + OFS, tamoxifen plus ovarian function suppression group; TAM only, tamoxifen-only group.

TABLE A3. Completion Rate of Two Years Gonadotropin-Releasing Hormone Agonist Administration

	Randomly Assigned, No. (%)	
Variable	**Group E (initiated)**	**Group C (introduced)**
Completed	56 (78.9)	397 (70.4)
Early discontinuation without recurrence	14 (19.7)	151 (26.8)
Early discontinuation with recurrence	1 (1.4)	16 (2.8)
Total	71 (100)	564 (100)

TABLE A4. Random Assignment at Each Visit on the Basis of FSH and Vaginal Bleeding History

	Group, No. (%)		
Variable	**TAM Only**	**TAM + OFS**	**Total, No. (%)**
Visit 1			
FSH*	71 (100)	83 (100)	154
Visit 2			
FSH	243 (64.1)	238 (64.9)	481 (64.5)
Vaginal bleeding	5 (1.3)	6 (1.6)	11 (1.5)
Both	131 (34.6)	123 (33.5)	254 (34.0)
Visit 3			
FSH	84 (73.0)	92 (73.0)	176 (73.0)
Vaginal bleeding	8 (7.0)	6 (4.8)	14 (5.8)
Both	23 (20.0)	28 (22.2)	51 (21.2)
Visit 4			
FSH	34 (79.1)	31 (73.8)	65 (76.5)
Vaginal bleeding	0	4 (9.5)	4 (4.7)
Both	9 (20.9)	7 (16.7)	16 (18.8)
Visit 5			
FSH	20 (74.1)	20 (69.0)	40 (71.4)
Vaginal bleeding	2 (7.4)	3 (10.3)	5 (8.9)
Both	4 (14.8)	5 (17.2)	9 (16.1)
Ovarian function not resumed (randomization error)	1 (3.7)	1 (3.4)	2 (3.6)
Total			
FSH	464 (71.7)	452 (71.2)	916 (71.5)
Vaginal bleeding	15 (2.3)	19 (3.0)	34 (2.7)
Both	167 (25.8)	163 (25.7)	330 (25.7)
Ovarian function not resumed (randomization error)	1 (0.2)	1 (0.2)	2 (0.2)

Abbreviations: FSH, follicle-stimulating hormone; TAM + OFS, tamoxifen plus ovarian function suppression group; TAM only, tamoxifen-only group.

*On the basis of protocol, there was no record of vaginal bleeding at visit 1.