clinical trial updates

Adjuvant Exemestane With Ovarian Suppression in Premenopausal Breast Cancer: Long-Term Follow-Up of the Combined TEXT and SOFT Trials

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abstract

Clinical trials frequently include multiple end points that mature at different times. The initial report, typically based on the primary end point, may be published when key planned co-primary or secondary analyses are not yet available. Clinical Trial Updates provide an opportunity to disseminate additional results from studies, published in JCO or elsewhere, for which the primary end point has already been reported.

The combined analysis of SOFT-TEXT compared outcomes in 4,690 premenopausal women with estrogen/progesterone receptor–positive (ER/PgR+) early breast cancer randomly assigned to 5 years of exemestane + ovarian function suppression (OFS) versus tamoxifen + OFS. After a median follow-up of 9 years, exemestane + OFS significantly improved disease-free survival (DFS) and distant recurrence-free interval (DRFI), but not overall survival, compared with tamoxifen + OFS. We now report DFS, DRFI, and overall survival after a median follow-up of 13 years. In the intention-to-treat (ITT) population, the 12-year DFS (4.6% absolute improvement, hazard ratio [HR], 0.79; 95% CI, 0.70 to 0.90; $P < .001$) and DRFI (1.8% absolute improvement, HR, 0.83; 95% CI, 0.70 to 0.98; $P = .03$), but not overall survival (90.1% *v* 89.1%, HR, 0.93; 95% CI, 0.78 to 1.11), continued to be significantly improved for patients assigned exemestane + OFS over tamoxifen + OFS. Among patients with human epidermal growth factor receptor 2-negative tumors (86.0% of the ITT population), the absolute improvement in 12-year overall survival with exemestane + OFS was 2.0% (HR, 0.85; 95% CI, 0.70 to 1.04) and 3.3% in those who received chemotherapy (45.9% of the ITT population). Overall survival benefit was clinically significant in high-risk patients, eg, women age < 35 years (4.0%) and those with > 2 cm (4.5%) or grade 3 tumors (5.5%). These sustained reductions of the risk of recurrence with adjuvant exemestane + OFS, compared with tamoxifen + OFS, provide guidance for selecting patients for whom exemestane should be preferred over tamoxifen in the setting of OFS.

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ASSOCIATED CONTENT

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Video Abstract

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

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INTRODUCTION

The SOFT-TEXT combined analysis assessed the role of the aromatase inhibitor (AI) exemestane versus tamoxifen in premenopausal women with ER/PgR+ early breast cancer receiving ovarian function suppression (OFS). The most recent analysis after a 9-year median follow-up (MFU)[1] showed sustained improvements with exemestane + OFS versus tamoxifen + OFS in disease-free survival (DFS; hazard ratio [HR], 0.77; 95% CI, 0.67 to 0.90) and distant recurrence-free interval (DRFI) but not overall survival (HR, 0.98; 95% CI, 0.79 to 1.22). Given the potential late recurrences of ER/PgR+ breast cancer[2,3] and late-emergent survival benefit of adjuvant AIs versus tamoxifen in postmenopausal women,[4] we report the 12-year SOFT-TEXT late treatment effects on DRFI and overall survival and benefits in women with human epidermal growth factor receptor 2 (HER2)-negative tumors and in those at high risk of disease relapse.

METHODS

The SOFT-TEXT designs and conduct have been described previously.[5,6] Patients were randomly assigned 1:1 to receive 5 years of tamoxifen + OFS or exemestane + OFS, stratified by the use of adjuvant chemotherapy and lymph node status.

The present report focused on DRFI and time from random assignment until first appearance of invasive breast cancer recurrence at a distant site and overall survival and time from random assignment until death from any cause. Statistical analyses followed previous reports[5]; HRs were also estimated in time

intervals 0 to < 5, 5 to < 10, and ≥ 10 years (or 0 to < 5 and ≥ 5 years for the cohorts; Data Supplement, online only).

RESULTS

The ITT population included 4,690 premenopausal women randomly assigned from November 2003-April 2011 to exemestane + OFS or tamoxifen + OFS (Table 1 and Data Supplement). Most patients (86.0%) had HER2-negative tumors. At database lock (May 2021), the MFU was 13 years.

Deaths were reported for 473 patients, 85.6% after a breast cancer event, 6.8% after second (nonbreast) malignancy, and few in the absence of any cancer event (0.4% of all patients, including four cardiovascular deaths in the chemotherapy cohorts; Data Supplement). Patients assigned exemestane + OFS did not have a significantly different hazard of death compared with tamoxifen + OFS (90.1% *v* 89.1% 12-year overall survival, HR, 0.93; 95% CI, 0.78 to 1.11; $P = .43$; Fig 1C). The hazard of death was higher for exemestane + OFS versus tamoxifen + OFS during years 0-5 (HR, 1.34; 95% CI, 0.98 to 1.84) and then lowered with longer follow-up (HR, 0.72; 95% CI, 0.54 to 0.95 years 5-10 and HR, 0.88; 95% CI, 0.61 to 1.28 ≥ 10 years).

DFS continued to be significantly improved with exemestane + OFS versus tamoxifen + OFS (80.5% *v* 75.9%, 4.6% [95% CI, 2.0% to 7.2%] absolute improvement, HR, 0.79; 95% CI, 0.70 to 0.90; Fig 1A). Of 953 DFS events (Data Supplement), 52.0% were distant recurrences (61.0% of events during 0-5 years and 42.7% > 5 years). Patients assigned exemestane + OFS experienced a 1.8% (95% CI, −0.3% to 3.8%) absolute improvement in 12-year DRFI compared with those assigned tamoxifen + OFS (88.4% *v* 86.6%; HR, 0.83; 95% CI, 0.70 to 0.98; $P = .03$; Fig 1B). The estimated DFS and DRFI benefits were strongest during years 0-5 and attenuated during years 5-10 and ≥ 10 years (Fig 1 and Data Supplement).

Clinicopathologic characteristics and patterns of recurrence differed between patients who received or did not receive chemotherapy and by trial; only 81 of 544 distant recurrences and 79 of 473 deaths were in the no-chemotherapy cohorts. Modest absolute 12-year DRFI benefits were evident in the no-chemotherapy cohorts (each HR, 0.67; 1.8% in SOFT, 1.4% in TEXT), ranging from 93.8% to 97.7% (Data Supplement). The 12-year overall survival was > 95% in both treatment groups in the no-chemotherapy cohorts, with no excess deaths reported among patients assigned exemestane + OFS compared with tamoxifen + OFS (Data Supplement).

In the chemotherapy cohorts, the DRFI benefit was homogeneous across trials (each HR, 0.86; 12-year DRFI absolute benefit 1.9% SOFT; 2.4% TEXT; Data Supplement). The differences in 12-year overall survival were −0.7% in SOFT (HR, 1.06; 95% CI, 0.79 to 1.43) and +2.6% in TEXT (HR, 0.85; 95% CI, 0.65 to 1.11; Data Supplement). For both cohorts, as compared with years 0-5 (each HR > 1), there was a consistent reduction in hazard of death for exemestane + OFS versus tamoxifen + OFS after ≥ 5 years (SOFT HR, 0.84; 95% CI, 0.57 to 1.22; TEXT HR, 0.74; 95% CI, 0.53 to 1.03).

Outcomes According to HER2 Status

In the predominant HER2-negative subgroup (4,035 patients, 53.3% received chemotherapy), a reduction in hazard of death with exemestane + OFS versus tamoxifen + OFS was apparent (HR, 0.85; 95% CI, 0.70 to 1.04; Fig 1D), with a 2.0% improvement in the 12-year overall survival (90.8% exemestane + OFS *v* 88.8% tamoxifen + OFS). The greatest absolute improvements in overall survival were achieved in patients at higher risk of relapse, ie, women age < 35 years (+4.0%) and those with tumors > 2 cm (+4.5%) and grade 3 tumors (+5.5%; Fig 2). In both chemotherapy cohorts, there was a 3.3% absolute overall survival improvement (84.4% *v* 81.1% in SOFT; 86.8% *v* 83.5% in TEXT; Fig 2 and Data Supplement). Overall, the observed hazards of death were low but higher for exemestane + OFS versus tamoxifen + OFS (HR, 1.24; 95% CI, 0.87 to 1.76) during years 0-5; after year 5, exemestane + OFS showed substantially lower hazard versus tamoxifen + OFS (years 5-10 HR, 0.64; 95% CI, 0.47 to 0.86; ≥ 10 years HR, 0.87; 95% CI, 0.59 to 1.29; Data Supplement). In patients with HER2-positive disease, outcomes continued to favor tamoxifen + OFS versus exemestane + OFS (Fig 2).

DISCUSSION

The updated analysis of SOFT-TEXT after a 13-year MFU confirmed a sustained reduction in recurrence with adjuvant exemestane + OFS compared with tamoxifen + OFS in premenopausal women with ER/PgR+ breast cancer. In the ITT population, absolute improvements were retained in both 12-year DFS (+4.6%) and DRFI (+1.8%). Treatment effects on recurrence tended to attenuate over time, being strongest in years 0-5 with no further improvement after ≥ 10 years. Overall survival was excellent with both treatments, not improved by exemestane + OFS (90.1% *v* 89.1% in patients assigned tamoxifen + OFS); the lack of survival benefit from exemestane + OFS is at least in part attributable to early emergent, persistent favorable outcomes with tamoxifen + OFS in the HER2-positive subgroup. Deaths without breast cancer or second (nonbreast) cancer (Data Supplement) were rare and not higher with exemestane. Similar findings, reported in the postmenopausal meta-analysis of adjuvant AIs versus tamoxifen,[4] contrast data of increased cardiovascular deaths in premenopausal women undergoing oophorectomy[7,8] and are reassuring for the safety of 5-year AI + OFS in premenopausal patients. The EBCTCG meta-analysis[9] showed that in premenopausal women receiving OFS, AIs versus tamoxifen

TABLE 1. Characteristics of Patients in the ITT Analysis Population, Overall and in Cohorts Defined According to Trial and Receipt of Chemotherapy

Characteristic	Cohort[a]				
	SOFT No Chemotherapy, No. (%)	SOFT Prior Chemotherapy, No. (%)	TEXT No Chemotherapy, No. (%)	TEXT Chemotherapy, No. (%)	Overall ITT, No. (%)
No. of patients	943 (100.0)	1,087 (100.0)	1,053 (100.0)	1,607 (100.0)	4,690 (100.0)
Age at random assignment, years					
Median	46	40	45	43	43
< 35	14 (1.5)	224 (20.6)	41 (3.9)	191 (11.9)	470 (10.0)
35-39	68 (7.2)	312 (28.7)	123 (11.7)	289 (18.0)	792 (16.9)
40-49	690 (73.2)	515 (47.4)	768 (72.9)	1,048 (65.2)	3,021 (64.4)
≥ 50	171 (18.1)	36 (3.3)	121 (11.5)	79 (4.9)	407 (8.7)
Lymph node status (stratum)					
Negative	865 (91.7)	470 (43.2)	835 (79.3)	542 (33.7)	2,712 (57.8)
Positive	78 (8.3)	617 (56.8)	218 (20.7)	1,065 (66.3)	1,978 (42.2)
Tumor size, cm					
≤ 2	800 (84.8)	534 (49.1)	846 (80.3)	738 (45.9)	2,918 (62.2)
> 2	140 (14.8)	512 (47.1)	204 (19.4)	846 (52.6)	1,702 (36.3)
Unknown	3 (0.3)	41 (3.8)	3 (0.3)	23 (1.4)	70 (1.5)
Tumor grade					
1	360 (38.2)	153 (14.1)	270 (25.6)	189 (11.8)	972 (20.7)
2	512 (54.3)	552 (50.8)	652 (61.9)	825 (51.3)	2,541 (54.2)
3	62 (6.6)	352 (32.4)	121 (11.5)	590 (36.7)	1,125 (24.0)
Unknown	9 (1.0)	30 (2.8)	10 (0.9)	3 (0.2)	52 (1.1)
HER2 status[b]					
Negative	892 (94.6)	835 (76.8)	991 (94.1)	1,317 (82.0)	4,035 (86.0)
Positive	30 (3.2)	219 (20.1)	53 (5.0)	276 (17.2)	578 (12.3)
Unknown/not done	21 (2.2)	33 (3.0)	9 (0.9)	14 (0.9)	77 (1.6)
Months from surgery to enrollment					
Median	1.8	8.0	1.5	1.2	1.6

Abbreviations: HER2, human epidermal growth factor receptor 2; ITT, intention-to-treat.

[a]In both trials, eligible premenopausal women had resected invasive early breast cancer with ≥ 10% estrogen receptor- and/or progesterone receptor-expressing cells by local determination. In SOFT, patients who did not receive chemotherapy were enrolled within 12 weeks after definitive surgery; those who received prior (neo)adjuvant chemotherapy were enrolled within 8 months after the final dose of chemotherapy, after a premenopausal estradiol level was documented. In TEXT, all patients were randomly assigned within 12 weeks after definitive surgery, and if chemotherapy was prescribed, it was initiated concurrently with ovarian function suppression.

[b]Eighty-six percent of patients with HER2-positive disease received chemotherapy, whereas the use of adjuvant HER2-targeted therapy became standard during trial conduct: 52.9% of patients with HER2-positive tumors received HER2-targeted therapy (47.4% and 60.2% in TEXT and SOFT, respectively, because of enrollment patterns over time).

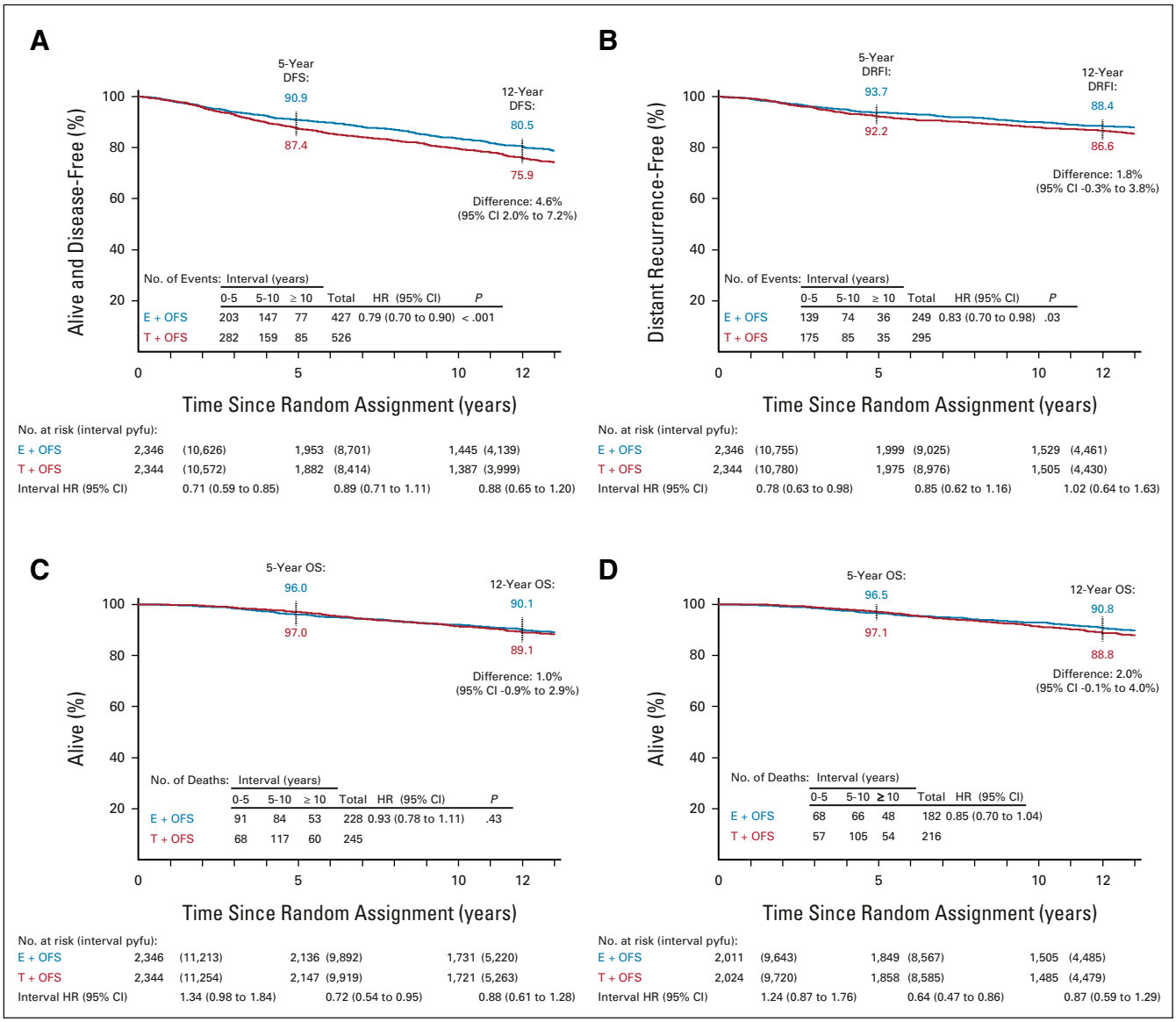


FIG 1. Outcomes after a 13-year median follow-up. Kaplan-Meier estimates of (A) DFS, (B) DRFI, (C) OS distributions in the ITT population, and (D) OS in the predominant subgroup with HER2-negative cancers. Reported are 5- and 12-year event-free percentages and 12-year difference (E + OFS minus T + OFS; with 95% CI). Stratified HRs with 95% CIs are reported, with log-rank *P* values in the ITT population only. In addition, numbers of events, pyfu, and HRs are provided for time intervals of 0 to < 5 years, ≥ 5 to < 10 years, and ≥ 10 years. DFS, disease-free survival; DRFI, distant recurrence-free interval; E, exemestane; HER2, human epidermal growth factor receptor 2; HR, hazard ratio; ITT, intention-to-treat; OFS, ovarian function suppression; OS, overall survival; pyfu, patient-years of follow-up; T, tamoxifen.

reduced the relative risk of recurrence by 21% and of distant recurrence by 17%; no significant difference in breast cancer mortality or overall survival was found, but follow-up beyond 10 years was extremely limited.

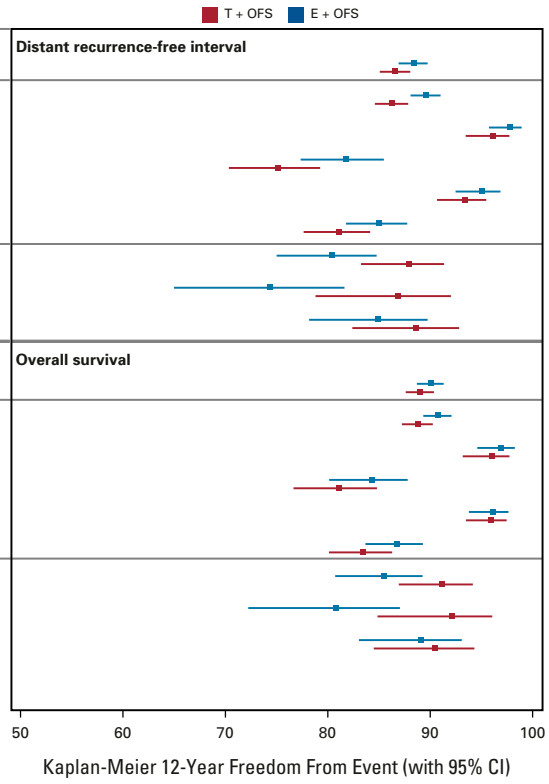
Distinct outcomes persisted long term according to the baseline risk of recurrence and the choice to administer chemotherapy or not. The 12-year overall survival > 95% in women selected not to receive adjuvant chemotherapy confirmed that premenopausal patients at lower risk of relapse have excellent long-term outcomes with risk-adapted endocrine therapy even in the presence of node-positive disease (8.3% in SOFT and 20.7% in TEXT).

Meaningful 12-year overall survival improvements in the predominant HER2-negative subgroup were now observed after a 13-year MFU, as high as 3.3% in both chemotherapy cohorts; ongoing follow-up will provide a better assessment of any additional survival benefit. Women with HER2-negative tumors with high-risk clinicopathologic characteristics experienced the greatest absolute improvements in 12-year overall survival when treated with exemestane + OFS compared with tamoxifen + OFS, ranging 4.0% to 5.5%.

A

		No. of Events/ No. of Patients	T + OFS	E + OFS	Difference (95% CI)
Distant recurrence-free interval					
Overall		544/4,690	86.6	88.4	1.8 (-0.3 to 3.8)
HER2–		451/4,035	86.3	89.6	3.3 (1.2 to 5.5)
HER2–	SOFT no chemotherapy	25/892	96.1	97.9	1.7 (-0.8 to 4.2)
	SOFT prior chemotherapy	165/835	75.1	81.8	6.7 (0.7 to 12.7)
	TEXT no chemotherapy	52/991	93.5	95.1	1.6 (-1.5 to 4.8)
	TEXT chemotherapy	209/1,317	81.1	85.0	3.9 (-0.5 to 8.3)
HER2+		86/578	87.9	80.4	-7.5 (-13.8 to 1.2)
HER2+	SOFT	44/249	86.9	74.4	-12.5 (-23.0 to 2.0)
	TEXT	42/329	88.7	84.9	-3.7 (-11.4 to 3.9)
Overall survival					
Overall		473/4,690	89.1	90.1	1.0 (-0.9 to 2.9)
HER2–		398/4,035	88.8	90.8	2.0 (-0.1 to 4.0)
HER2–	SOFT no chemotherapy	29/892	96.1	96.9	0.9 (-1.9 to 3.7)
	SOFT prior chemotherapy	137/835	81.1	84.4	3.3 (-2.3 to 8.9)
	TEXT no chemotherapy	45/991	95.9	96.2	0.2 (-2.4 to 2.9)
	TEXT chemotherapy	187/1,317	83.5	86.8	3.3 (-0.9 to 7.4)
HER2+		66/578	91.2	85.6	-5.7 (-11.2 to 0.2)
HER2+	SOFT	32/249	92.2	80.9	-11.3 (-20.3 to 2.3)
	TEXT	34/329	90.5	89.1	-1.4 (-8.3 to 5.4)

HER2-unknown omitted (patients: 77; events: 7 DR, 8 OS)



B

Subgroup		No. of Deaths/ No. of Patients	12-Year Overall Survival (%) T + OFS	E + OFS	Difference
Age at random assignment (years)	< 35	67/350	77.6	81.6	4.0 (-5.0 to 12.9)
	35 – 39	98/653	83.0	86.5	3.5 (-2.5 to 9.4)
	40 – 44	114/1,303	90.3	91.5	1.2 (-2.2 to 4.6)
	45 – 49	87/1,352	92.8	94.8	2.0 (-0.8 to 4.8)
	50 +	32/377	88.7	90.8	2.1 (-5.0 to 9.1)
Positive LNs	pN0	117/2,365	94.2	95.8	1.5 (-0.4 to 3.5)
	pN+ 1-3	136/1,193	87.0	89.7	2.6 (-1.3 to 6.6)
	pN+ 4+	145/477	67.4	69.2	1.8 (-7.2 to 10.7)
Tumor size	≤ 2 cm	140/2,567	94.5	94.6	0.2 (-1.8 to 2.1)
	> 2 cm	245/1,409	79.3	83.8	4.5 (0.1 to 8.9)
Tumor grade	1	40/903	94.8	96.6	1.8 (-1.1 to 4.8)
	2	203/2,259	90.5	91.2	0.7 (-1.9 to 3.3)
	3	151/828	78.1	83.6	5.5 (-0.1 to 11.1)

Omitted are 59 unknown T sizes and 45 unknown T grades

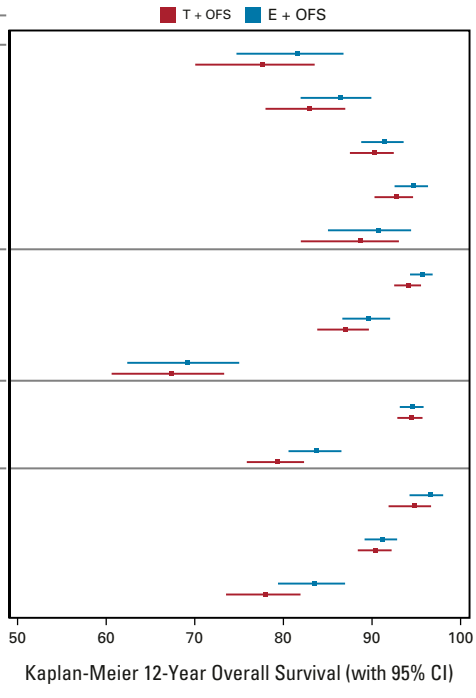


FIG 2. Kaplan-Meier estimates of 12-year outcomes (with 95% CIs) according to treatment assignment. The median follow-up is 13 years. Estimates and difference (exemestane + OFS minus tamoxifen + OFS) are presented for (A) DRFI and overall survival in the ITT population, in HER2 subgroups, and within HER2 status according to the cohort or trial and (B) for overall survival among 4,035 patients who had hormone receptor–positive/HER2-negative cancers in clinicopathologic subgroups. DRFI, distant recurrence-free interval; E, exemestane; HER2, human epidermal growth factor receptor 2; ITT, intention-to-treat; OFS, ovarian function suppression; T, tamoxifen.

The monarchE trial reported significant short-term iDFS and DRFS benefits from adding the CDK4/6 inhibitor abemaciclib to standard adjuvant endocrine therapy in patients at high risk of relapse.[10] It is currently unknown if the impact of abemaciclib in premenopausal women (43% of patients) is independent of the endocrine backbone[11] or limited to women treated with tamoxifen alone, 41% of enrolled premenopausal women despite their high-risk disease characteristics.[12]

In conclusion, with a 13-year MFU, a reduction not only in recurrences but also in mortality emerged for exemestane + OFS versus tamoxifen + OFS in women with HER2-negative disease, most clinically meaningful for those at higher risk of relapse. No overall survival benefit with exemestane + OFS was evident in women at lower risk of relapse not receiving chemotherapy. Given the burden of treatment intensification on quality of life,[13,14] proper selection of women most likely to benefit is paramount.

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EQUAL CONTRIBUTION

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M.M.R. and P.A.F. contributed equally to this work.

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AUTHORS' DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST

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DATA SHARING STATEMENT

After publication, access to deidentified individual participant data may be requested by researchers by submitting a proposal (to stat_center@ibcsg.org), which will be reviewed for scientific merit and feasibility in accordance with IBCSG guidelines for collaborative research and data sharing policy.

AUTHOR CONTRIBUTIONS

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