original reports

Absolute Improvements in Freedom From Distant Recurrence to Tailor Adjuvant Endocrine Therapies for Premenopausal Women: Results From TEXT and SOFT

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abstract

PURPOSE The Tamoxifen and Exemestane Trial (TEXT)/Suppression of Ovarian Function Trial (SOFT) showed superior outcomes for premenopausal women with hormone receptor (HR)–positive breast cancer treated with adjuvant exemestane plus ovarian function suppression (OFS) or tamoxifen plus OFS versus tamoxifen alone. We previously reported the magnitude of absolute improvements in freedom from any recurrence across a continuous, composite measure of recurrence risk to tailor decision making. With longer follow-up, we now focus on distant recurrence.

METHODS The TEXT/SOFT HR-positive/human epidermal growth factor receptor 2 (HER2)–negative analysis population included 4,891 women stratified by predetermined chemotherapy use. Kaplan-Meier estimates of 8-year freedom from distant recurrence were analyzed using subpopulation treatment effect pattern plot (STEPP) methodology across subpopulations defined by the continuous composite measure of recurrence risk. For each patient, the composite risk value was obtained from a Cox model that incorporated age; nodal status; tumor size; grade; and estrogen receptor, progesterone receptor, and Ki-67 labeling index expression levels.

RESULTS The overall rate of 8-year freedom from distant recurrence was 91.1% and ranged from approximately 100% to 63% across lowest to highest composite risks. TEXT patients who received chemotherapy had an average absolute improvement with exemestane plus OFS versus tamoxifen plus OFS of 5.1%, and STEPP analysis showed improvements from less than 1% to more than 15% from lowest to highest composite risks. SOFT patients who remained premenopausal after chemotherapy had an average 5.2% absolute improvement with exemestane plus OFS versus tamoxifen and reached 10% across composite risks; for tamoxifen plus OFS versus tamoxifen, the maximum improvement was approximately 3.5%. Women who did not receive chemotherapy had a more than 97% rate of 8-year freedom from distant recurrence, and improvements with exemestane plus OFS ranged from 1% to 4%.

CONCLUSION Premenopausal women with HR-positive/HER2-negative breast cancer and high recurrence risk, as defined by clinicopathologic characteristics, may experience a 10% to 15% absolute improvement in 8-year freedom from distant recurrence with exemestane plus OFS versus tamoxifen plus OFS or tamoxifen alone. The potential benefit of escalating endocrine therapy versus tamoxifen alone is minimal for those at low recurrence risk.

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ASSOCIATED CONTENT

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

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INTRODUCTION

Adjuvant endocrine therapy recommendations for premenopausal women with hormone receptor (HR)–positive breast cancer have changed on the basis of the 5-year results of the Tamoxifen and Exemestane Trial (TEXT) and the Suppression of Ovarian Function Trial (SOFT; ClinicalTrials.gov identifiers: NCT00066703 and NCT00066690, respectively).[1,2] Tamoxifen alone remains the standard of care in women at low risk of relapse, as defined by clinical and pathologic features, and by genomic parameters, when available. Ovarian function suppression (OFS) should be proposed to patients at higher risk for recurrence in addition to oral endocrine therapy with either tamoxifen or an aromatase inhibitor.[3-6]

A secondary analysis of the women enrolled in TEXT and SOFT with HR-positive/human epidermal growth factor receptor 2 (HER2)–negative cancers estimated

absolute improvements in 5-year freedom from breast cancer (including invasive locoregional, distant, or contralateral breast cancer) according to recurrence risk defined from clinicopathologic characteristics. The women at high recurrence risk experienced absolute improvements of 10% to 15% with exemestane plus OFS versus tamoxifen plus OFS and versus tamoxifen alone, and improvements were of at least 5% for women at intermediate risk.[7] In contrast, improvement was minimal for women at lowest risk. Such estimates of the absolute magnitude of improvement can help clinicians to weigh benefits against adverse effects in treatment decisions with individual patients.

Recent updates of TEXT and SOFT after a median follow-up of 9 and 8 years, respectively, demonstrated significant improvement in disease-free and overall survival with the addition of OFS to tamoxifen in the SOFT population.[8] The combined analysis of TEXT and SOFT demonstrated sustained improvements with exemestane plus OFS versus tamoxifen plus OFS in disease-free survival, freedom from breast cancer, and freedom from distant recurrence but not from overall survival.[8] Among the patients with HR-positive/HER2-negative tumors, the rate of freedom from distant recurrence was improved by 3.6% with the use of exemestane plus OFS versus tamoxifen and by 3.5% with exemestane plus OFS versus tamoxifen plus OFS.

Distant recurrence in a premenopausal woman has personal, economic, and social costs of greater impact than locoregional recurrence.[9] Greater toxicity may be acceptable in prevention of distant recurrence, which generally portends premature death as a result of breast cancer. With extended follow-up, we are now able to refine the estimates of absolute treatment effects in preventing distant recurrence across the spectrum of recurrence risk in the subgroup of women with HR-positive/HER2-negative cancers.

METHODS

Study Designs

The designs and conduct of the trials have been described previously.[1,2] In both trials, eligible premenopausal women had invasive early breast cancer assessed as 10% or greater estrogen receptor (ER)– and/or progesterone receptor (PgR)–expressing cells by local determination. The ethics committee at each participating center approved the study protocols, and all patients provided written informed consent for trial participation and mandatory tissue collection for central pathology assessment. Central review of histopathologic features and expression of ER, PgR, HER2, and Ki-67 labeling index (Ki-67) was conducted for 84% of trial patients in the International Breast Cancer Study Group Central Pathology Office.[10]

In TEXT, all women received OFS by gonadotropin-releasing hormone agonist triptorelin from the start of adjuvant therapy; after at least 6 months of triptorelin, patients could opt for bilateral oophorectomy or ovarian irradiation. Chemotherapy was optional and if administered, was started concurrently with triptorelin. Between November 2003 and March 2011, 2,672 premenopausal women were randomly assigned to 5 years of exemestane plus OFS or tamoxifen plus OFS. Randomization was stratified according to intended use of adjuvant chemotherapy and lymph node status.

SOFT was designed to determine the value of adding OFS to tamoxifen and the role of exemestane plus OFS in two cohorts of premenopausal women: those who remained premenopausal after completion of (neo)adjuvant chemotherapy and those for whom adjuvant tamoxifen without chemotherapy was considered suitable treatment. Between December 2003 and January 2011, 3,066 women were randomly assigned to 5 years of exemestane plus OFS or tamoxifen plus OFS or tamoxifen alone. Randomization was stratified according to prior use of chemotherapy, lymph node status, and intended initial method of OFS (if randomly assigned to OFS).

End Point and Statistical Considerations

The analysis population was previously defined and included 4,891 patients with tumors centrally assessed as HR positive/HER2 negative[7] (Appendix Fig A1, online only). Distant recurrence–free interval (DRFI) was defined as the duration of time from random assignment until first appearance of invasive breast cancer recurrence at a distant site; in the absence of a distant recurrence, DRFI was censored at date of last follow-up. The median follow-up was 9 years in TEXT and 8 years in SOFT.[8]

While following the approach previously described,[7] the composite measure of recurrence risk (hereafter referred to as composite risk) was determined for the entire HR-positive/HER2-negative analysis population by fitting a Cox proportional hazards regression model for DRFI, stratified by cohort (defined by trial and chemotherapy use) and treatment assignment. This use of a stratified model provided the same risk scale for the two trials, which do not share a common control group. Prognostic factors included in the model and their groupings were specified a priori, and there was no intention to optimize the model on the basis of model selection procedures (Table 1; Appendix Table A1, online only). For tumor grade and ER and PgR expression, the centrally determined values were used when available, and locally determined values were used otherwise; Ki-67 expression was available only from central assessment. Unknown categories were used to avoid systematic exclusion of patients without centrally assessed tumor features. After estimating the model parameters, the composite risk value was calculated for each trial patient by summing the model parameter estimates corresponding to her observed values of clinicopathologic factors.

Nonparametric sliding window subpopulation treatment effect pattern plot (STEPP) methodology[11,12] was used to

TABLE 1. Clinicopathologic Characteristics of the HR-Positive/HER2-Negative Analysis Population of TEXT and SOFT

Characteristic	Patients, %					Model		
	TEXT Chemotherapy (n = 1,276)	SOFT Prior Chemotherapy (n = 1,271)	TEXT No Chemotherapy (n = 991)	SOFT No Chemotherapy (n = 1,353)	All Patients (N = 4,891)	Parameter Estimate	SE	Hazard Ratio (95% CI)
Age at random assignment, years								
< 35	11.1	18.3	3.7	1.5	8.8	0.77	0.17	2.2 (1.6 to 3.0)
35-39	17.3	29.5	11.4	7.6	16.6	0.62	0.15	1.9 (1.4 to 2.5)
40-44	34.6	32.0	34.4	27.3	31.9	0.17	0.15	1.2 (0.9 to 1.6)
45-49	31.6	16.8	38.8	46.2	33.2	0 (ref)		
≥ 50	5.4	3.5	11.6	17.4	9.5	0.06	0.26	1.1 (0.6 to 1.8)
No. of positive nodes								
0	31.4	41.5	78.3	91.3	60.1	0 (ref)		
1-3	44.0	40.1	21.5	8.6	28.6	0.54	0.13	1.7 (1.3 to 2.2)
≥ 4	24.6	18.4	0.2	0.1	11.3	1.38	0.14	4.0 (3.0 to 5.2)
Tumor size, cm								
Unknown	1.6	3.9	0.3	0.7	1.7	0.89	0.26	2.4 (1.5 to 4.0)
≤ 2	46.5	49.6	79.8	85.9	64.9	0 (ref)		
> 2	51.9	46.5	19.9	13.5	33.4	0.58	0.11	1.8 (1.4 to 2.2)
ER expression, %								
Unknown	1.8	1.3	1.7	1.0	1.5	−0.20	0.62	0.8 (0.2 to 2.8)
< 50	5.1	5.9	2.0	2.7	4.0	0.14	0.18	1.2 (0.8 to 1.7)
≥ 50	93.1	92.8	96.3	96.3	94.5	0 (ref)		
PgR expression, %								
Unknown	2.0	1.8	1.9	1.6	1.8	1.17	0.53	3.2 (1.1 to 9.1)
< 20	12.8	18.3	5.9	4.1	10.4	0.44	0.13	1.6 (1.2 to 2.0)
20-49	10.4	10.3	7.1	4.9	8.2	0.29	0.15	1.3 (1.0 to 1.8)
≥ 50	74.8	69.6	85.2	89.4	79.6	0 (ref)		
Tumor grade								
1	12.9	15.7	25.4	37.3	22.9	0 (ref)		
2	56.8	57.4	59.2	53.5	56.5	0.81	0.23	2.3 (1.4 to 3.5)
3	30.3	27.0	15.3	9.2	20.6	0.78	0.26	2.2 (1.3 to 3.6)
Ki-67 expression, %								
Unknown	18.8	20.9	19.1	20.0	19.7	−0.08	0.20	0.9 (0.6 to 1.4)
< 14	15.6	19.5	27.1	37.4	25.0	0 (ref)		
14-19	23.0	23.8	26.4	23.9	24.2	−0.10	0.20	0.9 (0.6 to 1.3)
20-25	18.3	17.0	13.6	11.2	15.1	0.26	0.20	1.3 (0.9 to 1.9)
≥ 26	24.3	18.7	13.7	7.5	16.0	0.49	0.21	1.6 (1.1 to 2.5)

NOTE. Characteristics are overall and according to cohort defined by trial and chemotherapy use, and parameter estimates of the Cox proportional hazards regression model define the composite measure of recurrence risk (n = 4,891). Values of grade and ER and PgR expression were centrally determined if available and locally determined otherwise; Ki-67 expression was available only by central determination.

Abbreviations: ER, estrogen receptor; HER2, human epidermal growth factor receptor 2; HR, hormone receptor; Ki-67, labeling index Ki-67; PgR, progesterone receptor; ref, referent group; SOFT, Suppression of Ovarian Function Trial; TEXT, Tamoxifen and Exemestane Trial.

investigate patterns in absolute treatment effects as measured by Kaplan-Meier estimates of 8-year freedom from distant recurrence (*y*-axis) across the continuum of composite risk values (*x*-axis). The STEPP of the overall analysis population had a window size of 500 and was slid by 300 patient values to form each subpopulation. For

SOFT and TEXT, the size of windows were 420 and 300, respectively, and slid by 120 and 150 patient values, respectively. With this approach, most composite risk values are represented in more than one subpopulation.

RESULTS

Among the 4,891 patients in the HR-positive/HER2-negative analysis population, the clinicopathologic characteristics across the four trial cohorts reflected the selection of adjuvant chemotherapy use and whether OFS would be received by all patients (TEXT) or by random assignment (SOFT; Table 1; Appendix Table A1). Poor prognostic features were more frequent on average among the cohorts who received chemotherapy. The distribution of age (youngest among patients in SOFT who received chemotherapy before enrollment) reflected the SOFT eligibility criteria that patients remain premenopausal after chemotherapy.

The relationship of each of the seven clinicopathologic characteristics individually with DRFI is shown in Figure 1. The estimated 8-year freedom from distant recurrence rates are shown for each characteristic by treatment group, along with the relative treatment effects, in Figure 2 and Appendix Figures A2 and A3 (online only) and listed in Appendix Tables A2-A6 (online only).

The clinicopathologic characteristic with the greatest contribution to the multivariable model for the composite measure of recurrence risk, relative to the complementary reference category, was four or more positive nodes followed by tumor grade 2 or 3 and younger age (Table 1); one to three positive nodes, tumor size greater than 2 cm, PgR less than 20%, and Ki-67 of 26% or more contributed similarly. ER less than 50% had a very small contribution possibly because only 4% of patients had low ER expression described.[10] The distribution of resulting composite risks is illustrated for the overall population in Figure 3 and summarized by each characteristic subgroup in Appendix Table A7 (online only).

Overall, for the 4,891 patients, 433 distant recurrences were reported, and the 8-year freedom from distant recurrence rate was 91.1% (95% CI, 90.2% to 92.0%). When the clinicopathologic features were integrated as a composite measure of recurrence risk (median, 1.42; interquartile range [IQR], 0.81-2.15), the 8-year freedom from distant recurrence rate varied markedly across patient populations, ranging from approximately 100% to 63% among patients in the subpopulations with lowest composite risks to highest composite risks, respectively (Fig 3). As expected, the majority of distant recurrences occurred among patients who received chemotherapy (Fig 4).

Patients for Whom Chemotherapy Was Part of Adjuvant Therapy

The patients who received chemotherapy, whether in TEXT or SOFT, had similar distributions of composite risk values (Figs 5A and 5B), with a median composite risk of 2.02 (IQR, 1.43-2.71) and 2.00 (IQR, 1.42-2.68), respectively. TEXT patients who received chemotherapy after enrollment had an average 8-year freedom from distant recurrence rate of 87.5% (159 distant recurrences among 1,276 patients after a median follow-up of 9 years). The average absolute improvement in freedom from distant recurrence with exemestane plus OFS versus tamoxifen plus OFS was 5.1% (90.0% *v* 84.9%; Fig 4A). The STEPP analysis showed a distinct pattern of increasing magnitude of improvement with exemestane plus OFS as composite risk increased and reached more than 15% in the subpopulation with the highest composite risks (Fig 5A).

Patients enrolled in SOFT who remained premenopausal after chemotherapy had an 8-year freedom from distant recurrence rate of 82.5% (216 distant recurrences among 1,271 patients after a median follow-up of 8 years). The average absolute improvement with exemestane plus OFS versus tamoxifen was 5.2% (86.2% *v* 81.0%; Fig 4B). The STEPP analysis suggested that all patients across composite risks benefited from exemestane plus OFS versus tamoxifen, with the maximum absolute improvement of approximately 10% (Fig 5B). The absolute improvement with tamoxifen plus OFS versus tamoxifen alone ranged from 0 to at most approximately 3.5% for the subpopulations with the highest composite risks.

Patients for Whom Endocrine Therapy Alone Was Planned as Adjuvant Therapy

In contrast to the patients who received chemotherapy, those who received only adjuvant endocrine therapy had lower composite risks. In TEXT, the median composite risk was 1.13 (IQR, 0.72-1.56), and in SOFT, the median was 0.81 (IQR, 0.17-1.27; Fig 5).

Among the 991 patients in TEXT who did not receive chemotherapy, 35 experienced a distant recurrence after a median follow-up of 9 years, and the overall 8-year freedom from distant recurrence rate was 97.0%. The overall absolute improvement in 8-year freedom from distant recurrence with exemestane plus OFS versus tamoxifen plus OFS was less than 1% (97.4% *v* 96.5%; Fig 4C). The STEPP analysis showed absolute improvement with exemestane plus OFS only in the subpopulations with the highest composite risks, for a maximum magnitude of improvement in the range of 2.5% to 4% (Fig 5C).

The 1,353 patients in SOFT who did not receive chemotherapy had the lowest composite risks, 23 patients experienced a distant recurrence after a median follow-up of 8 years. The overall 8-year freedom from distant recurrence rate was 98.5%, and for exemestane plus OFS, tamoxifen plus OFS, and tamoxifen, the rate was 99.3%, 98.3%, and 98.0%, respectively (Fig 4D). The absolute improvement in 8-year freedom from distant recurrence with exemestane plus OFS versus tamoxifen ranged from approximately 1% to 2.5%, and the improvement with

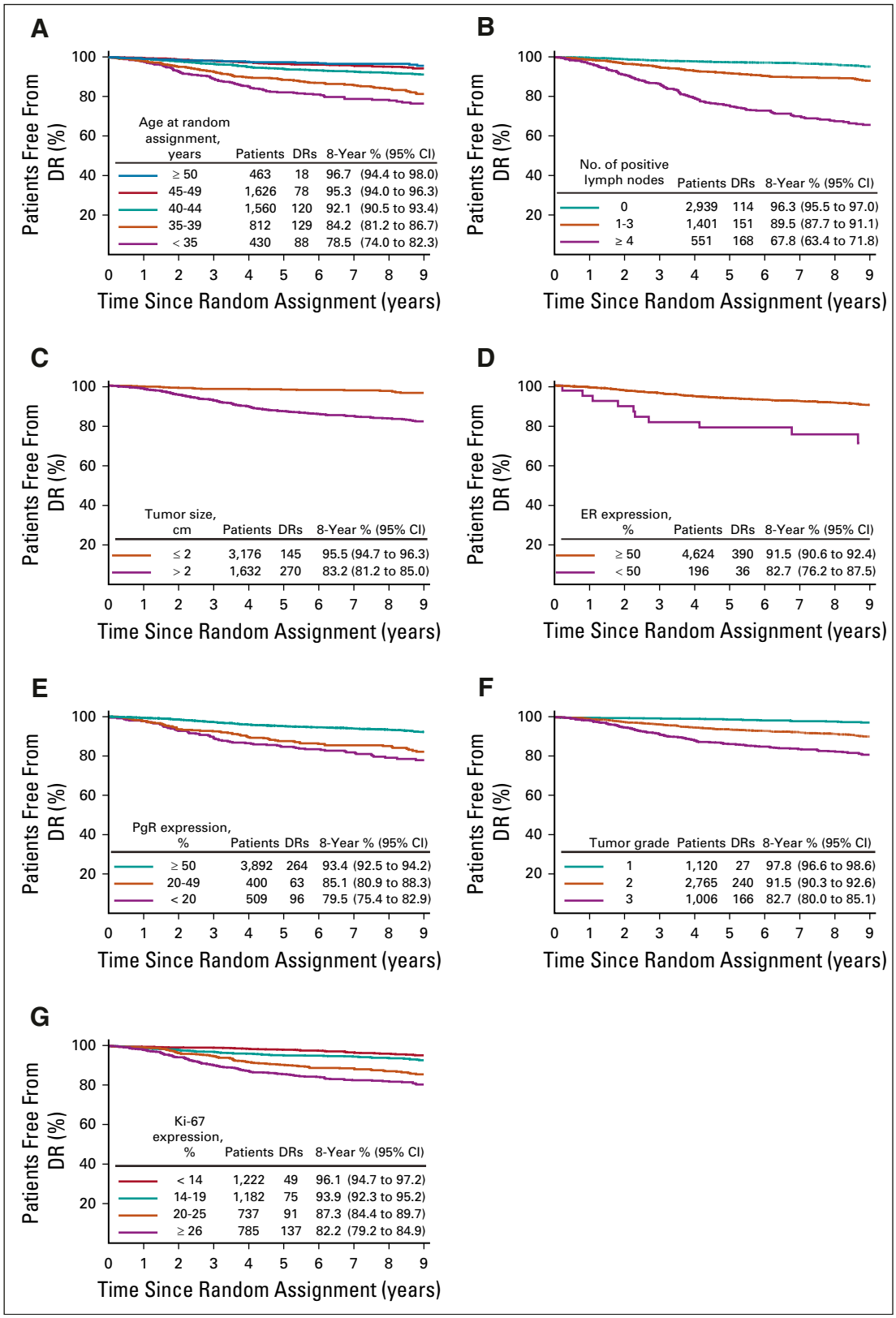

FIG 1. Kaplan-Meier estimates of distant recurrence (DR)–free interval in the overall hormone receptor–positive/human epidermal growth factor receptor 2–negative analysis population according to seven clinicopathologic characteristics. (A) Age at random assignment, (B) number of positive lymph nodes, (C) tumor size, (D) estrogen receptor (ER) expression, (E) progesterone receptor (PgR) expression, (F) tumor grade, and (G) labeling index Ki-67 (Ki67) expression. Unknown values are omitted.

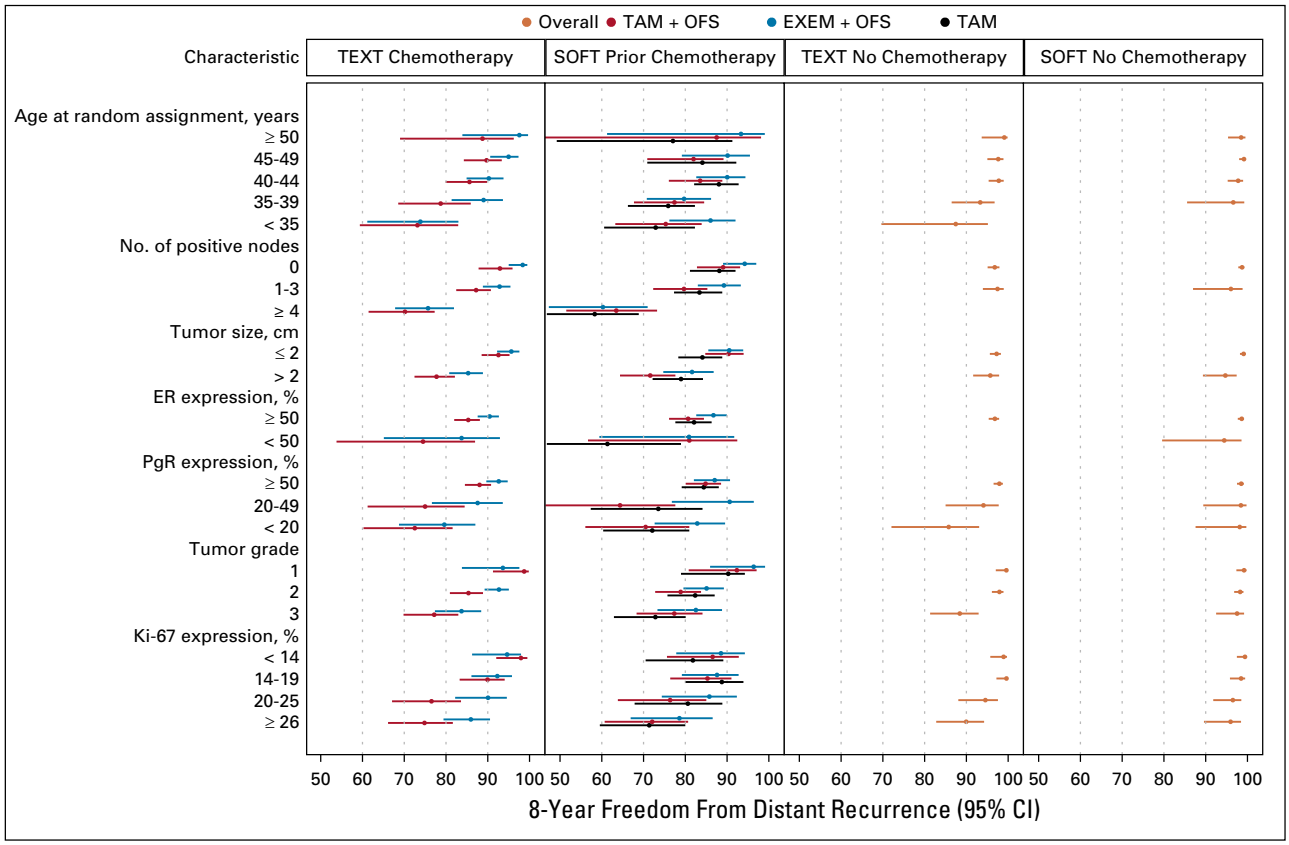

FIG 2. Kaplan-Meier estimates of 8-year freedom from distant recurrence in seven clinicopathologic subgroups in the four patient cohorts defined by trial and chemotherapy use according to treatment assignment. The values are listed in Appendix Tables A3 and A6. Unknown values are omitted. ER, estrogen receptor; EXEM, exemestane; Ki-67, Ki-67 labeling index; OFS, ovarian function suppression; PgR, progesterone receptor; SOFT, Suppression of Ovarian Function Trial; TAM, tamoxifen; TEXT, Tamoxifen and Exemestane Trial.

tamoxifen plus OFS versus tamoxifen was at most 1% (Fig 5D).

DISCUSSION

After 5 years of adjuvant endocrine therapy, breast cancer recurrences steadily occur up to 20 years. In an Early Breast Cancer Trialists' Collaborative Group meta-analysis (62,923 patients disease free after 5 years of endocrine therapy), the risk of distant recurrence was strongly correlated with stage (13% and 41% in T1N0 and T2N2 disease, respectively) and tumor grade (10% and 17% for low-grade T1N0 and high-grade disease, respectively).[13] In the absence of predictive biomarkers, standard clinicopathologic characteristics continue to provide meaningful prognostic information about risk of distant recurrence and guide treatment decision making. We put these features together into a composite measure of recurrence risk, which allows clinicians to better understand and estimate the magnitude of benefit of escalating adjuvant endocrine therapy in premenopausal women with HR-positive/HER2-negative breast cancer.

The combined analysis of TEXT/SOFT, without regard to tumor HER2 status, showed an average 2.1% absolute improvement in freedom from distant recurrence at 8 years in premenopausal women treated with an aromatase inhibitor versus tamoxifen with OFS.[8] This benefit is comparable to that observed for postmenopausal women in the Early Breast Cancer Trialists' Collaborative Group meta-analysis, wherein 5 years of aromatase inhibitors were associated with a 2% absolute 10-year reduction in distant recurrence compared with 5 years of tamoxifen (16.3% *v* 14.3%, respectively).[14]

We focused on the predominant subgroup with HR-positive/HER2-negative cancers. As previously highlighted,[15] SOFT/TEXT data suggest differential relative treatment efficacy by HER2 status and show lesser benefit of aromatase inhibitors and greater benefit from adding OFS to tamoxifen for HER2-positive than for HER2-negative cancers. Secondary analyses from the Hormonal Adjuvant Treatment Bone Effects (HOBOE)[16] and Adjuvant Lapatinib and/or Trastuzumab Treatment Optimization (ALTTO)[17] trials were consistent with this observation. A closer analysis of the HER2-positive subgroup is planned.

Among women with HR-positive/HER2-negative tumors who received chemotherapy (on average, a higher-risk group), an average 5% absolute improvement was

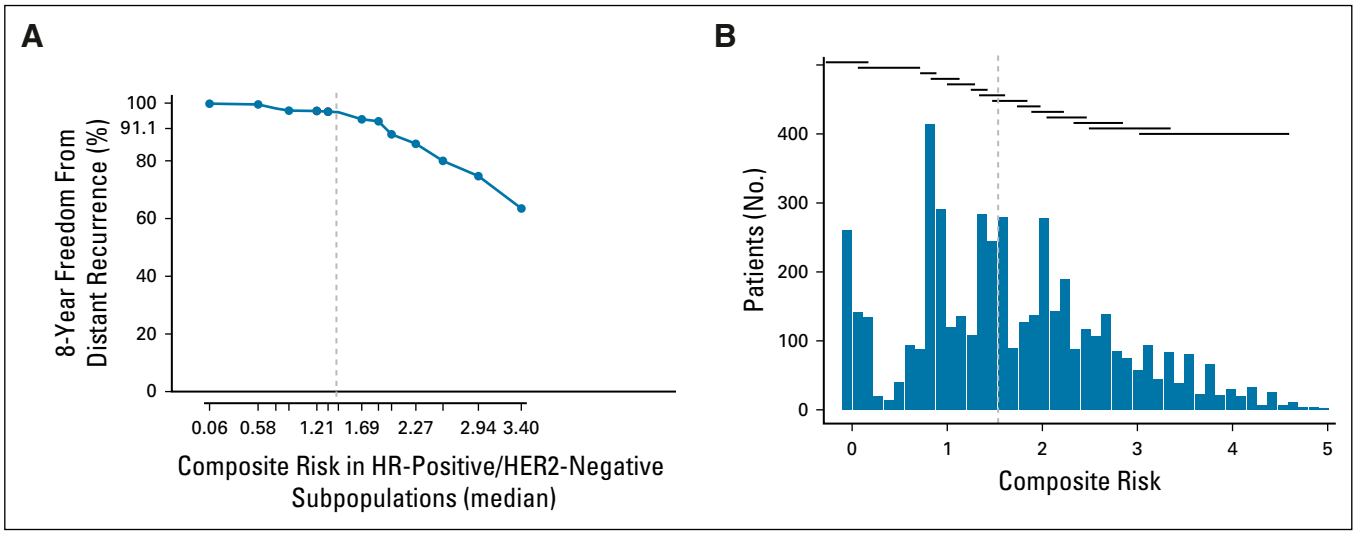

FIG 3. (A) Subpopulation treatment effect pattern plot of 8-year freedom from distant recurrence according to median composite risk in subpopulations and (B) histogram of the composite risk distribution in the overall hormone receptor (HR)–positive/human epidermal growth factor receptor 2 (HER2)–negative analysis population. The horizontal lines above the histogram indicate the ranges of composite risks in subpopulations that are plotted at the subpopulation median value. The overall 8-year freedom from distant recurrence rate of 91.1% also is indicated on the *y*-axis. The overall median composite risk of 1.42 is indicated by the vertical dashed lines.

achieved by escalating endocrine therapy to exemestane plus OFS in both TEXT and SOFT. In the STEPP analysis, the composite risk for a high-risk scenario (eg, 35 to 39 years of age, grade 3, pT2pN1a, ER and PgR of 50% or greater, Ki-67 26% or greater; composite risk, 3.00; Appendix Fig A4A, online only) was represented in subpopulations that had an absolute improvement greater than the average (range, 7% to 10%). The magnitude of

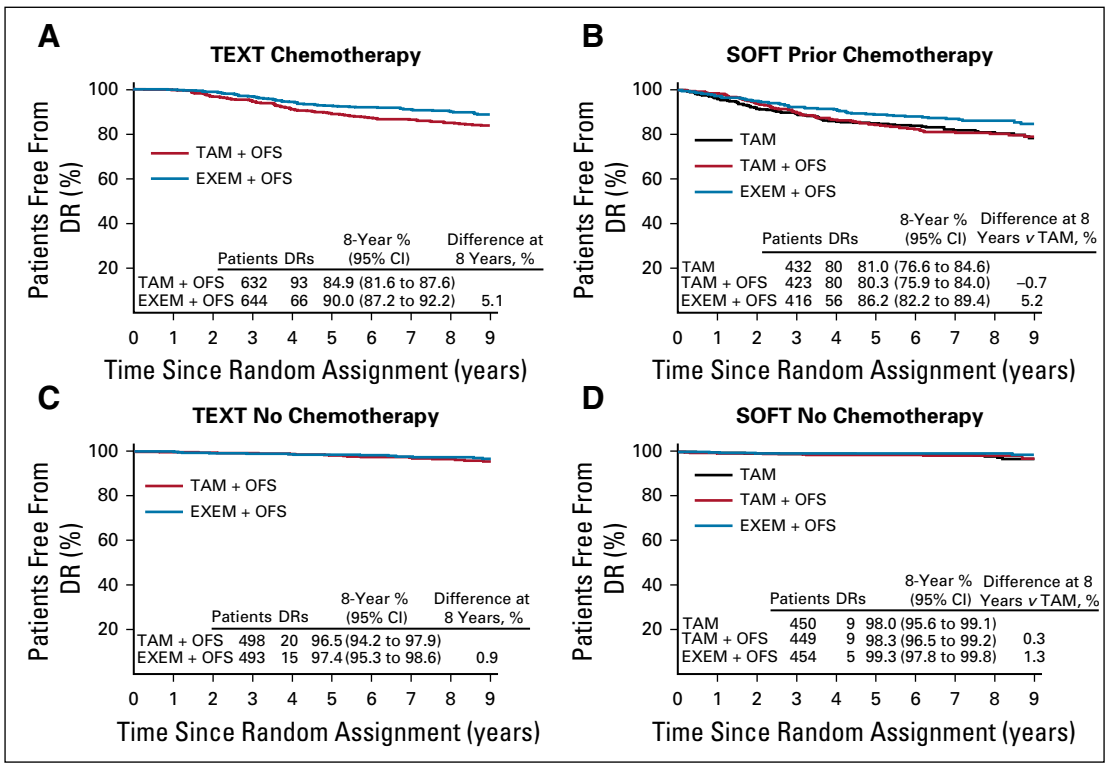

FIG 4. Kaplan-Meier estimates of distant recurrence (DR)–free interval in the four patient cohorts defined by trial and chemotherapy use according to treatment assignment. (A) Tamoxifen and Exemestane Trial (TEXT) chemotherapy, (B) Suppression of Ovarian Function Trial (SOFT) prior chemotherapy, (C) TEXT no chemotherapy, and (D) SOFT no chemotherapy. EXEM, exemestane; OFS, ovarian function suppression; TAM, tamoxifen.

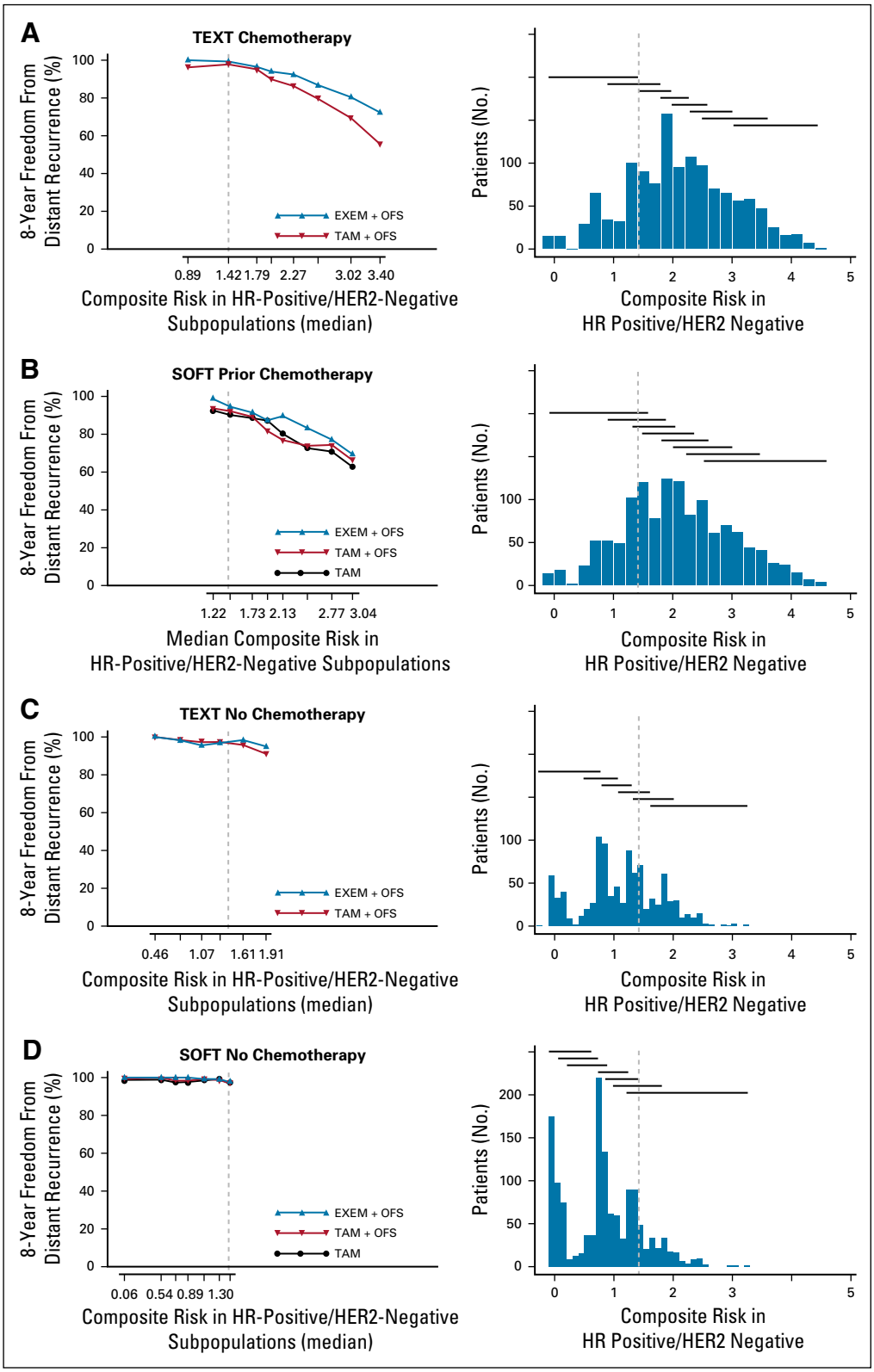

FIG 5. Subpopulation treatment effect pattern plots of 8-year freedom from distant recurrence according to median composite risk in subpopulations and histograms of the composite risk distributions for each of the four cohorts in the hormone receptor (HR)–positive/human epidermal growth factor receptor 2 (HER2)–negative analysis population according to treatment assignment. (A) Tamoxifen and Exemestane Trial (TEXT) chemotherapy, (B) Suppression of Ovarian Function Trial (SOFT) prior chemotherapy, (C) TEXT no chemotherapy, and (D) SOFT no chemotherapy. The horizontal lines above each histogram indicate the ranges of composite risks in subpopulations that are plotted at the subpopulation median composite risk value. The vertical dashed lines indicate the median composite risk of 1.42 in the overall HR-positive/HER2-negative analysis population. EXEM, exemestane; OFS, ovarian function suppression; TAM, tamoxifen.

improvement with exemestane plus OFS versus tamoxifen with or without OFS was larger in TEXT than in SOFT high-risk patients, but improvement was consistently observed in both cohorts. In contrast, in low-risk patients (Appendix Fig A4C) who did not receive chemotherapy, the 8-year freedom from distant recurrence was improved on average by approximately 1% in patients who received exemestane plus OFS compared with tamoxifen alone or tamoxifen plus

OFS in both SOFT and TEXT. The STEPP analysis suggested that this low-risk scenario (eg, 40 to 44 years of age, grade 2, pT1pN0, ER and PgR of 50% or greater, Ki-67 of 14% to 19%; composite risk, 0.89) was well characterized by the average improvement of approximately 1%. Most intermediate-risk patients in SOFT and TEXT received chemotherapy. In this patient scenario (eg, 40 to 44 years of age, grade 2, pT1pN1a, ER and PgR of 50% or greater, Ki-67 of 20% to 25%; composite risk, 1.78; Appendix Fig A4B), the absolute improvement with exemestane plus OFS was estimated to be less than the average improvement of 5%. Of note, intermediate-risk patients in TEXT who did not receive chemotherapy were estimated to have an improvement with exemestane plus OFS that exceeded 4%; these patients also achieved approximately 10% improvement in freedom from any breast cancer recurrence at 5 years with exemestane plus OFS.[7]

TEXT and SOFT results may encourage physicians to reconsider the indication for adjuvant chemotherapy in intermediate-risk premenopausal women with HR-positive/HER2-negative breast cancer. The patient selection for chemotherapy differed in SOFT and TEXT. The knowledge that all patients would receive OFS in TEXT, whereas OFS was administered by random assignment in SOFT, possibly prompted the prescription of chemotherapy for some SOFT patients. For instance, more patients younger than 40 years of age (47.8% and 28.4%) and with node-negative disease (41.5% and 31.4%) received chemotherapy in SOFT than in TEXT. This also can be inferred by the higher median composite risk in TEXT patients in the no-chemotherapy cohorts (eg, 21.5% of patients who received endocrine therapy alone in TEXT had one to three positive nodes; Fig 4) compared with 8.6% in SOFT. These different clinical characteristics of women who received adjuvant chemotherapy in SOFT and TEXT might partly explain the slightly different absolute improvements. Premenopausal women represented approximately 30% of patients in the clinical trials that addressed the added benefit of adjuvant chemotherapy over endocrine therapy[18-20] in HR-positive/HER2-negative breast cancer. Tamoxifen was the standard of care in premenopausal women when these trials were designed and conducted, and the additional benefit of adjuvant chemotherapy in this age-group cannot be extrapolated to women treated with combined endocrine therapy as in TEXT and SOFT. The Rx for Positive Node, Endocrine Responsive Breast Cancer (RxPONDER) trial (ClinicalTrials.gov identifier: NCT01272037) enrolled patients with one to three positive nodes between 2011 and 2015 who may have received combined endocrine therapy and could provide additional insight for intermediate-risk patients.

Several gene expression assays also have been developed for postmenopausal women[21] to estimate better the risk of early (0 to 5 years) and late (5 to 10 years) distant recurrence[22-24] of patients with HR-positive early breast cancer and tailor their adjuvant endocrine treatment. None of these tests was developed to select which endocrine therapy is more appropriate according to genomic risk. The prognostic information provided by these assays should not be interpreted automatically as a prediction of treatment benefit.[25] Although the risk of late distant recurrence is seemingly similar across age-groups,[13] the different algorithms cannot be applied to premenopausal patients without further validation because most of the data derive from postmenopausal women.

The 5% to 15% absolute improvement in freedom from distant recurrence from escalating endocrine therapy to tamoxifen plus OFS or exemestane plus OFS needs to be integrated in the clinical situation of each individual patient. The results in patients at higher risk of recurrence who received chemotherapy are of particular clinical relevance. A retrospective cohort study of 1,616 women showed that the median time to all-cause mortality was significantly longer in women with locoregional recurrence than in those with distant metastases (6.4 *v* 3.4 years, respectively).[26] Moreover, the 10-year survival rate of 101 women with local recurrence was 56% compared with 9% in those with distant recurrence.[27] In patients with HER2-negative disease who did not receive adjuvant chemotherapy, the majority with a lower risk of recurrence, after 8 to 9 years median follow-up in SOFT and TEXT, very few distant recurrences (23 and 35, respectively) occurred. In these patients, the benefit of treatment escalation is derived largely from locoregional and contralateral breast cancer reduction.[7] Given the impact on patients' quality of life from escalating endocrine therapy,[28] clinicians need to weigh the risk of recurrence and the expected absolute improvement in disease outcomes carefully against the added adverse effects.

With all women beyond the 5-year treatment period, the toxicity profiles of exemestane plus OFS and tamoxifen plus OFS are similar to postmenopausal women, and no new toxicity signal has emerged.[8] Nonadherence and early discontinuation of oral adjuvant endocrine therapy is frequent among young women[29] and associated with reduced overall survival.[30] In TEXT/SOFT, early discontinuation of all assigned endocrine therapy was approximately 20% in each treatment group, which is in line with published data.[29] Several demographic and clinical characteristics can help physicians to identify patients at risk for nonpersistence/adherence.[31] By better quantifying treatment benefits in the individual patient, our results may allow for a more-tailored risk/benefit discussion and an increase in women's motivation, particularly those at highest risk of distant recurrence, to follow treatment prescriptions.

Given the potential for late recurrences of HR-positive breast cancer, conclusions about overall survival remain premature. In postmenopausal women, the benefit of aromatase inhibitors versus tamoxifen on breast cancer mortality only emerged at 10 years[14] (2.1% absolute gain, 14.2% *v* 12.1%, respectively).

The current results add to our earlier study[7] to assist physicians and patients with estimating the individual risk-based benefit of escalating endocrine therapy. A recent survey showed that practicing US medical oncologists underestimated the absolute improvement in 5-year freedom from breast cancer with the use of aromatase inhibitors plus OFS versus tamoxifen for high-risk patients (physician estimate, 5.9%) compared with our previous study findings of 10% to 15%.[7,32] An online tool is in development to assist clinicians with using SOFT/TEXT in their daily practice risk/benefit calculations in premenopausal women with HR-positive/HER2-negative breast cancer.

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CLINICAL TRIAL INFORMATION

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

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AUTHORS' DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST

Absolute Improvements in Freedom From Distant Recurrence to Tailor Adjuvant Endocrine Therapies for Premenopausal Women: Results From TEXT and SOFT

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APPENDIX

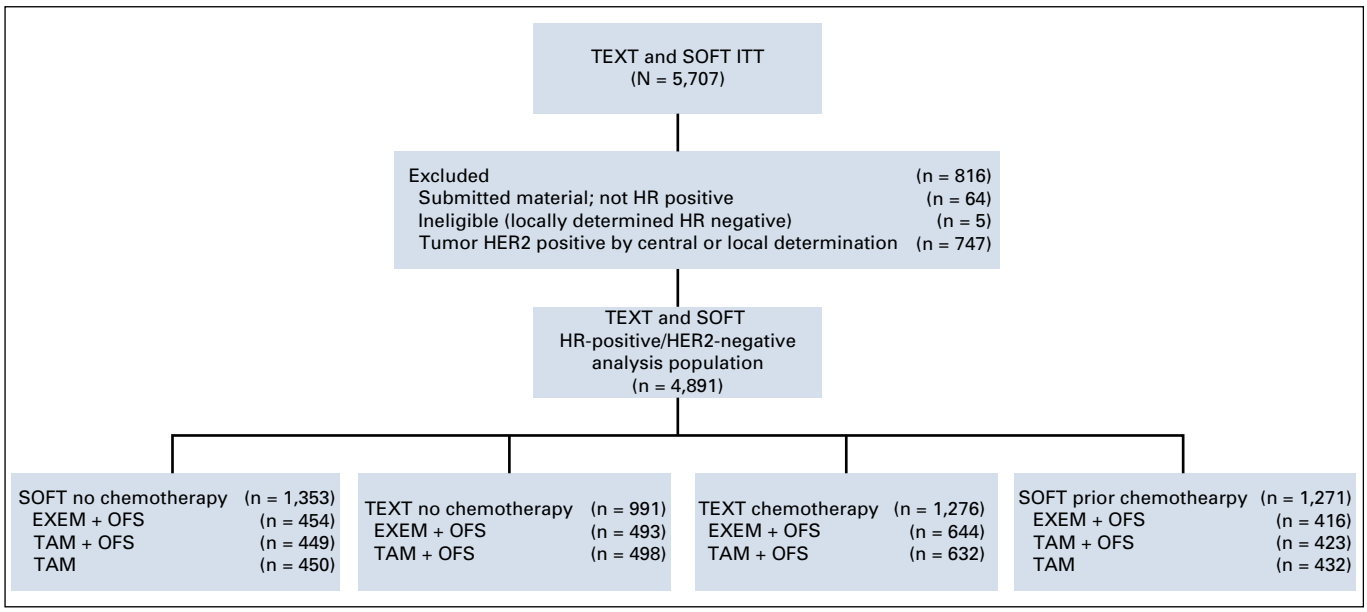

FIG A1. Flow diagram of the 4,891 patients included in the Suppression of Ovarian Function Trial (SOFT) and the Tamoxifen and Exemestane Trial (TEXT) hormone receptor (HR)–positive/human epidermal growth factor receptor 2 (HER2)–negative analysis population. EXEM, exemastane; ITT, intent to treat; OFS, ovarian function suppression; TAM, tamoxifen.

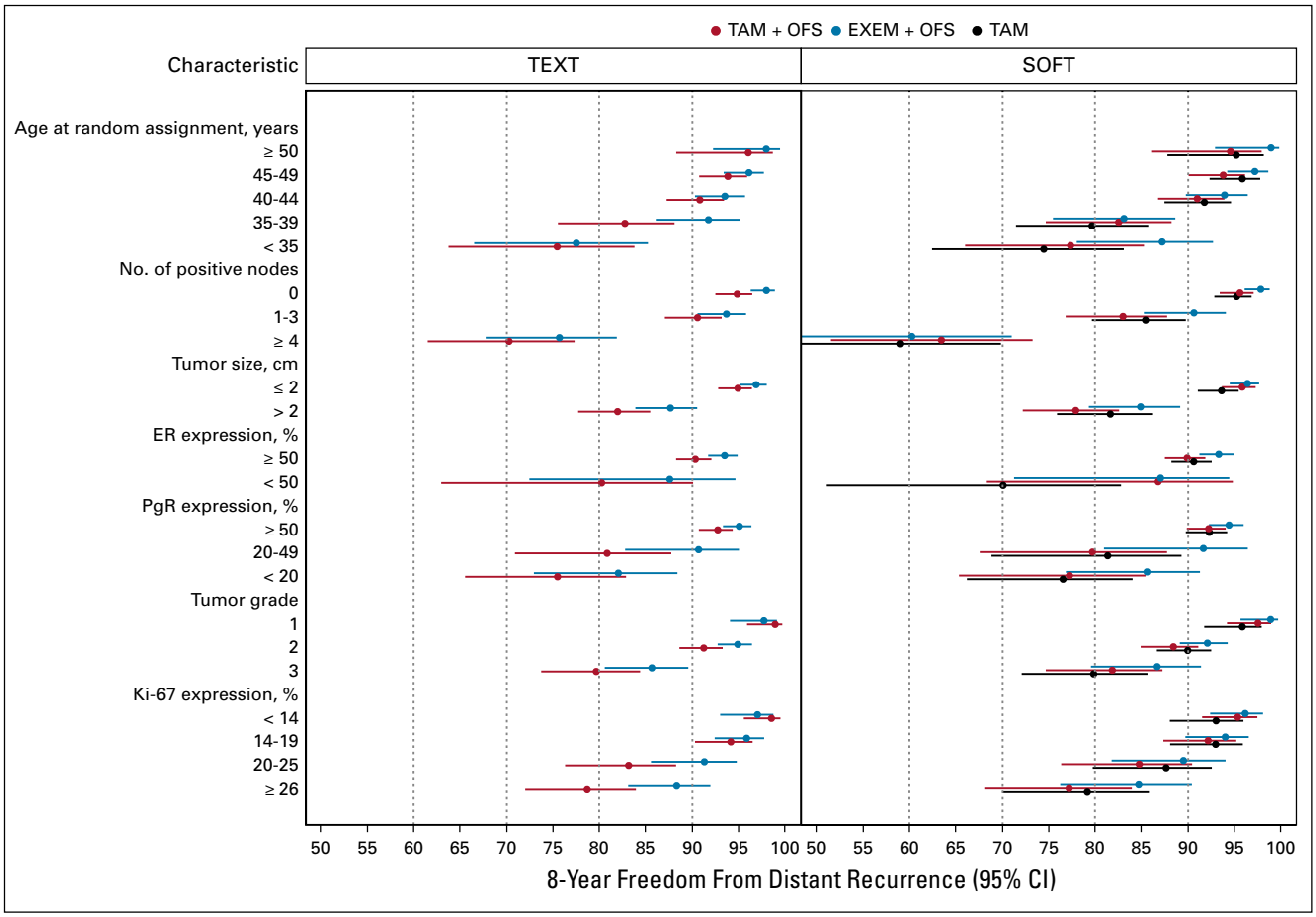

FIG A2. Kaplan-Meier estimates of 8-year freedom from distant recurrence in seven clinicopathologic subgroups, according to treatment assignment, separately by trial. The plotted values are provided in Tables A2 and A5. Unknown values are omitted. ER, estrogen receptor; EXEM, exemestane; Ki-67, Ki-67 labeling index; PgR, progesterone receptor; OFS, ovarian function suppression; SOFT, Suppression of Ovarian Function Trial; TAM, tamoxifen; TEXT, Tamoxifen and Exemestane Trial.

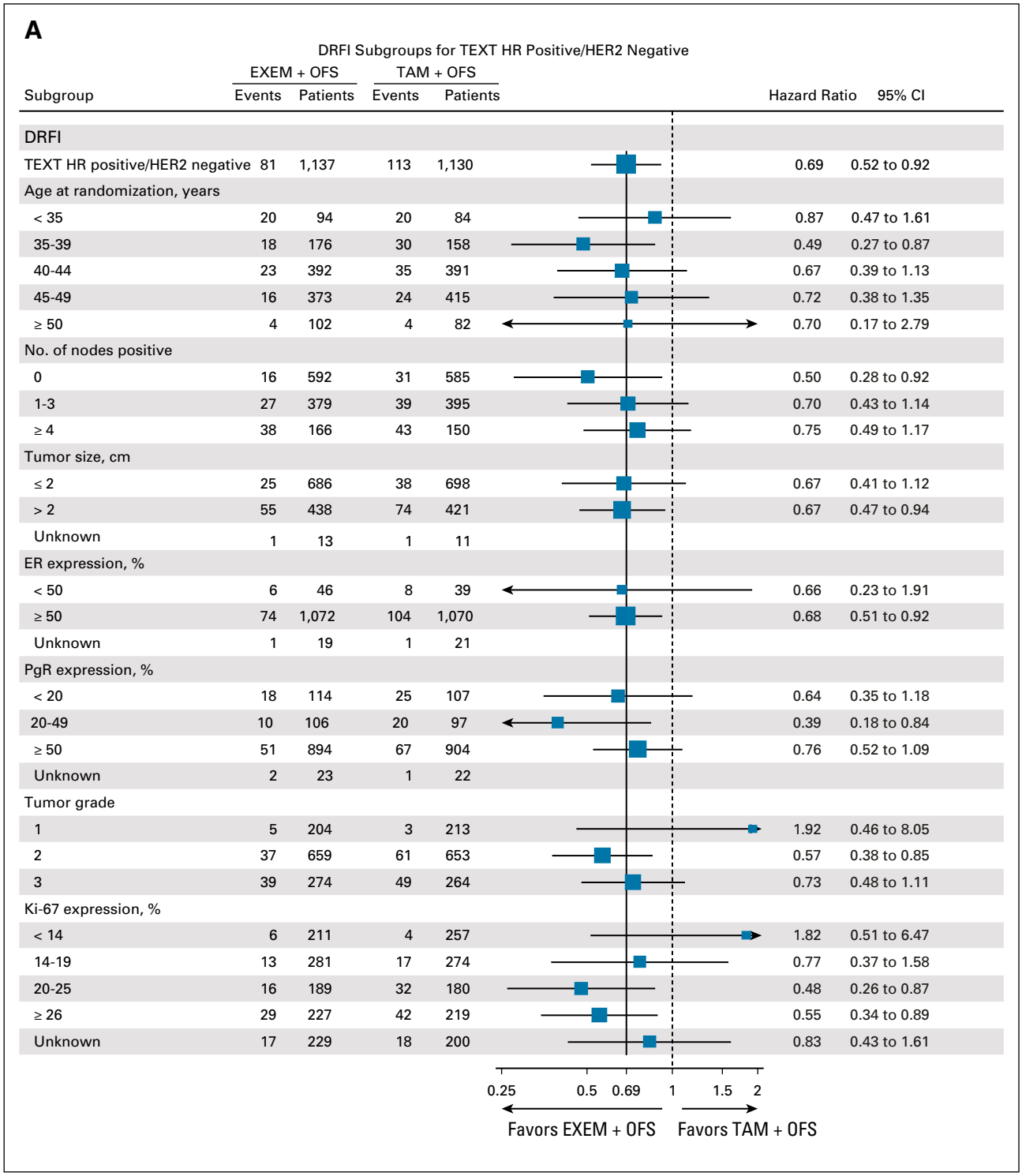

FIG A3. Estimated relative treatment effects on distance recurrence–free interval (DRFI) overall and according to seven clinicopathologic subgroups for the hormone receptor (HR)–positive/human epidermal growth factor receptor (HER2)–negative analysis population. The hazard ratios were estimated from Cox proportional hazards models stratified by cohort. Estimates not provided for unknown groups of < 50 patients. Estimates in subgroups having few events should be interpreted with caution. (A) The Tamoxifen and Exemestane Trial (TEXT) cohorts comparing exemestane (EXE) + ovarian function suppression (OFS) versus tamoxifen (TAM) + OFS. (B) Combined TEXT and Suppression of Ovarian Function Trial (SOFT) cohorts comparing EXE + OFS versus TAM + OFS. (C) SOFT cohorts comparing EXE + OFS versus TAM. (D) SOFT cohorts comparing TAM + OFS versus TAM. ER, estrogen receptor; Ki-67, Ki67 labeling index; PgR, progesterone receptor.

B

DRFI Subgroups for Combined SOFT + TEXT HR Positive/HER2 Negative

Subgroup	EXEM + OFS Events	EXEM + OFS Patients	TAM + OFS Events	TAM + OFS Patients	Hazard Ratio	95% CI
DRFI						
HR positive/HER2 negative	142	2,007	202	2,002	0.69	0.55 to 0.85
Age at randomization, years						
< 35	31	183	37	166	0.72	0.45 to 1.16
35-39	43	333	56	312	0.66	0.44 to 0.99
40-44	38	633	58	659	0.69	0.46 to 1.04
45-49	25	654	43	692	0.62	0.38 to 1.02
≥ 50	5	204	8	173	0.46	0.15 to 1.41
No. of nodes positive						
0	32	1,192	56	1,165	0.55	0.36 to 0.85
1-3	44	575	73	606	0.60	0.42 to 0.88
≥ 4	66	240	73	231	0.89	0.64 to 1.25
Tumor size, cm						
≤ 2	47	1,297	60	1,277	0.78	0.53 to 1.14
> 2	91	682	134	691	0.65	0.50 to 0.84
Unknown	4	28	8	34	0.54	0.16 to 1.79
ER expression, %						
< 50	13	88	12	71	0.91	0.41 to 1.99
≥ 50	127	1,889	186	1,896	0.67	0.54 to 0.84
Unknown	2	30	4	35	0.58	0.11 to 3.19
PgR expression, %						
< 20	32	222	42	190	0.59	0.37 to 0.94
20-49	18	171	33	165	0.43	0.24 to 0.76
≥ 50	88	1,575	123	1,610	0.75	0.57 to 0.98
Unknown	4	39	4	37	1.06	0.26 to 4.23
Tumor grade						
1	7	435	9	445	0.81	0.30 to 2.17
2	77	1,154	114	1,137	0.65	0.48 to 0.86
3	58	418	79	420	0.72	0.51 to 1.01
Ki-67 expression, %						
< 14	16	478	17	508	0.99	0.50 to 1.96
14-19	27	494	32	476	0.85	0.51 to 1.41
20-25	27	299	50	308	0.55	0.35 to 0.88
≥ 26	45	337	69	333	0.59	0.40 to 0.86
Unknown	27	399	34	377	0.72	0.44 to 1.20

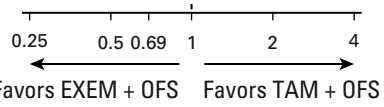

FIG A3. (Continued).

C

DRFI Subgroups for SOFT HR Positive/HER2 Negative

Subgroup	EXEM + OFS Events	EXEM + OFS Patients	TAM Events	TAM Patients	Hazard Ratio	95% CI
DRFI						
SOFT HR positive/HER2 negative	61	870	89	882	0.68	0.49 to 0.95
Age at randomization, years						
< 35	11	89	20	81	0.45	0.22 to 0.94
35-39	25	157	30	167	0.79	0.46 to 1.34
40-44	15	241	24	268	0.74	0.39 to 1.41
45-49	9	281	10	280	0.87	0.35 to 2.14
≥ 50	1	102	5	86	0.18	0.02 to 1.56
No. of nodes positive						
0	16	600	26	582	0.58	0.31 to 1.08
1-3	17	196	34	220	0.54	0.30 to 0.97
≥ 4	28	74	29	80	0.95	0.56 to 1.59
Tumor size, cm						
≤ 2	22	611	38	602	0.56	0.33 to 0.94
> 2	36	244	45	259	0.84	0.54 to 1.30
Unknown	3	15	6	21	0.46	0.12 to 1.84
ER expression, %						
< 50	7	42	11	37	0.43	0.17 to 1.11
≥ 50	53	817	77	839	0.70	0.49 to 0.99
Unknown	1	11	1	6		
PgR expression, %						
< 20	14	108	22	97	0.50	0.26 to 0.99
20-49	8	65	12	64	0.58	0.24 to 1.43
≥ 50	37	681	53	707	0.74	0.49 to 1.13
Unknown	2	16	2	14		
Tumor grade						
1	2	231	11	240	0.19	0.04 to 0.87
2	40	495	49	474	0.77	0.50 to 1.16
3	19	144	29	168	0.71	0.40 to 1.27
Ki-67 expression, %						
< 14	10	267	16	236	0.52	0.24 to 1.15
14-19	14	213	16	212	0.89	0.43 to 1.82
20-25	11	110	14	130	0.80	0.36 to 1.76
≥ 26	16	110	23	115	0.76	0.40 to 1.44
Unknown	10	170	20	189	0.54	0.25 to 1.14

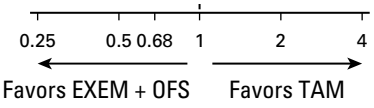

FIG A3. (Continued).

D

DRFI Subgroups for SOFT HR Positive/HER2 Negative

Subgroup	TAM + OFS Events	TAM + OFS Patients	TAM Events	TAM Patients	Hazard Ratio	95% CI
DRFI						
SOFT HR positive/HER2 negative	89	872	89	882	1.00	0.74 to 1.34
Age at randomization, years						
< 35	17	82	20	81	0.81	0.42 to 1.54
35-39	26	154	30	167	0.89	0.53 to 1.51
40-44	23	268	24	268	0.99	0.56 to 1.76
45-49	19	277	10	280	1.71	0.80 to 3.68
≥ 50	4	91	5	86	0.91	0.24 to 3.39
No. of nodes positive						
0	25	580	26	582	0.96	0.55 to 1.66
1-3	34	211	34	220	1.08	0.67 to 1.73
≥ 4	30	81	29	80	0.84	0.50 to 1.39
Tumor size, cm						
≤ 2	22	579	38	602	0.59	0.35 to 0.99
> 2	60	270	45	259	1.33	0.91 to 1.96
Unknown	7	23	6	21	0.83	0.28 to 2.47
ER expression, %						
< 50	4	32	11	37	0.30	0.10 to 0.95
≥ 50	82	826	77	839	1.07	0.79 to 1.47
Unknown	3	14	1	6		
PgR expression, %						
< 20	17	83	22	97	0.88	0.47 to 1.66
20-49	13	68	12	64	1.24	0.57 to 2.72
≥ 50	56	706	53	707	1.00	0.69 to 1.46
Unknown	3	15	2	14		
Tumor grade						
1	6	232	11	240	0.62	0.23 to 1.68
2	53	484	49	474	1.02	0.69 to 1.51
3	30	156	29	168	1.04	0.62 to 1.73
Ki-67 expression, %						
< 14	13	251	16	236	0.74	0.36 to 1.54
14-19	15	202	16	212	0.96	0.47 to 1.94
20-25	18	128	14	130	1.18	0.59 to 2.37
≥ 26	27	114	23	115	1.18	0.68 to 2.07
Unknown	16	177	20	189	0.90	0.46 to 1.73

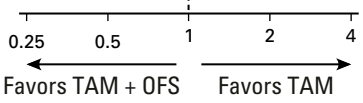

FIG A3. (Continued).

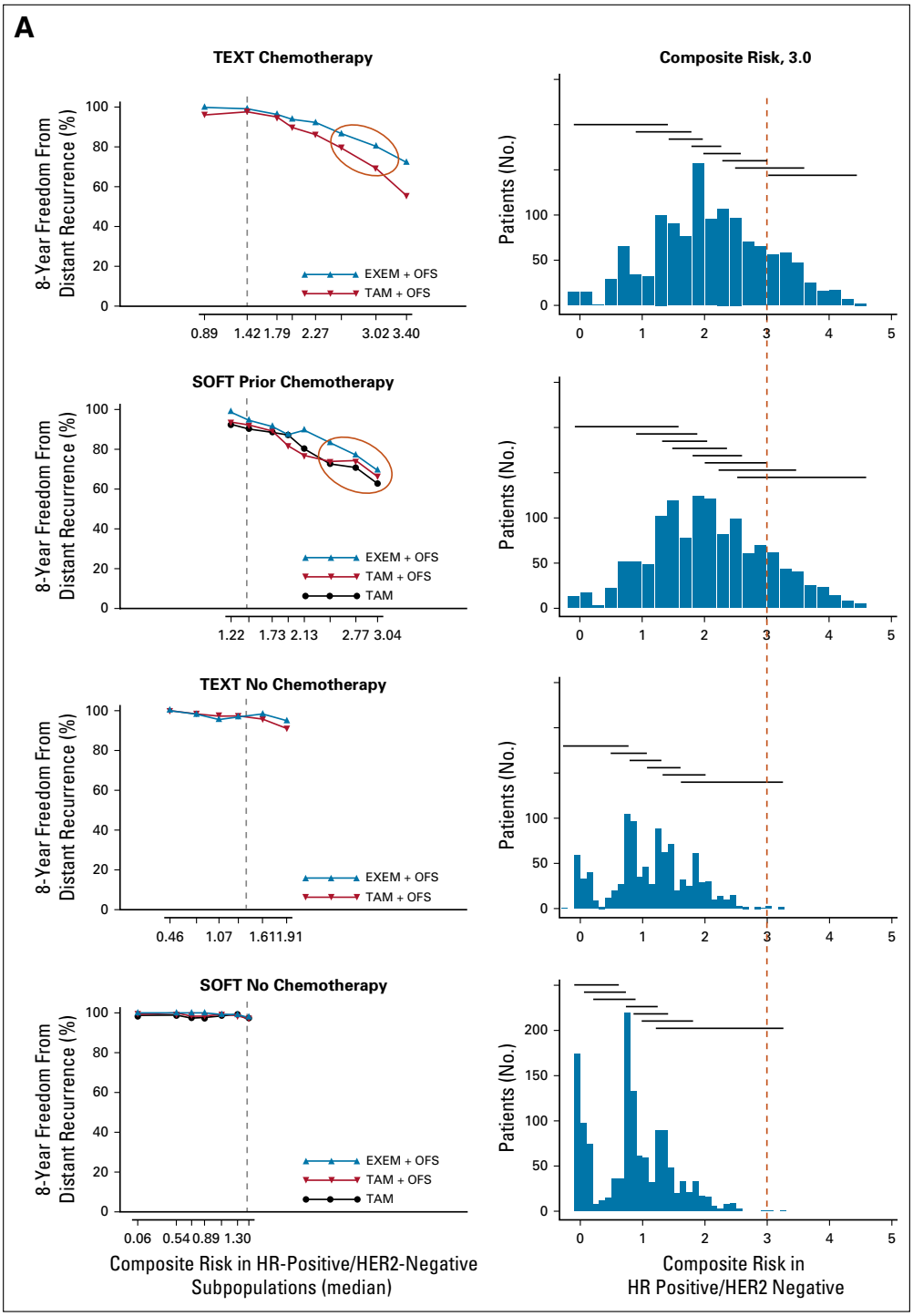

FIG A4. Subpopulation treatment effect pattern plots (STEPP) of 8-year freedom from distant recurrence (*y*-axis) according to median composite risk in subpopulations (*x*-axis) and histograms of the composite risk distributions for each of (continued on following page)the four cohorts in the hormone receptor (HR)–positive/human epidermal growth factor receptor 2 (HER2)–negative analysis population according to treatment assignment. The horizontal lines above each histogram indicate the ranges of composite risks in subpopulations that are plotted at the subpopulation median composite risk value in each corresponding STEPP. The red vertical line on the histograms indicates the selected composite risk, and intersects one or more subpopulations in which the composite risk value is represented. The dark orange circles on the STEPPs indicate the corresponding subpopulations in which the selected composite risk is represented. The black vertical dashed lines indicate the median composite risk of 1.42 in the overall HR-positive/HER2-negative analysis population. Three scenarios are presented: (A) A high-risk scenario (composite risk = 3.00; 35-39 years of age, pT2pN1a, grade 3, estrogen receptor [ER] ≥ 50%, progesterone receptor [PgR] ≥ 50% and Ki-67 labeling index [Ki-67] ≥ 26%). In this scenario, there are no circles on the Tamoxifen and Exemestane Trial (TEXT) no chemotherapy and Suppression of Ovarian Function Trial (SOFT) no chemotherapy STEPPs because there were too few patients with the same or similar composite risk values.

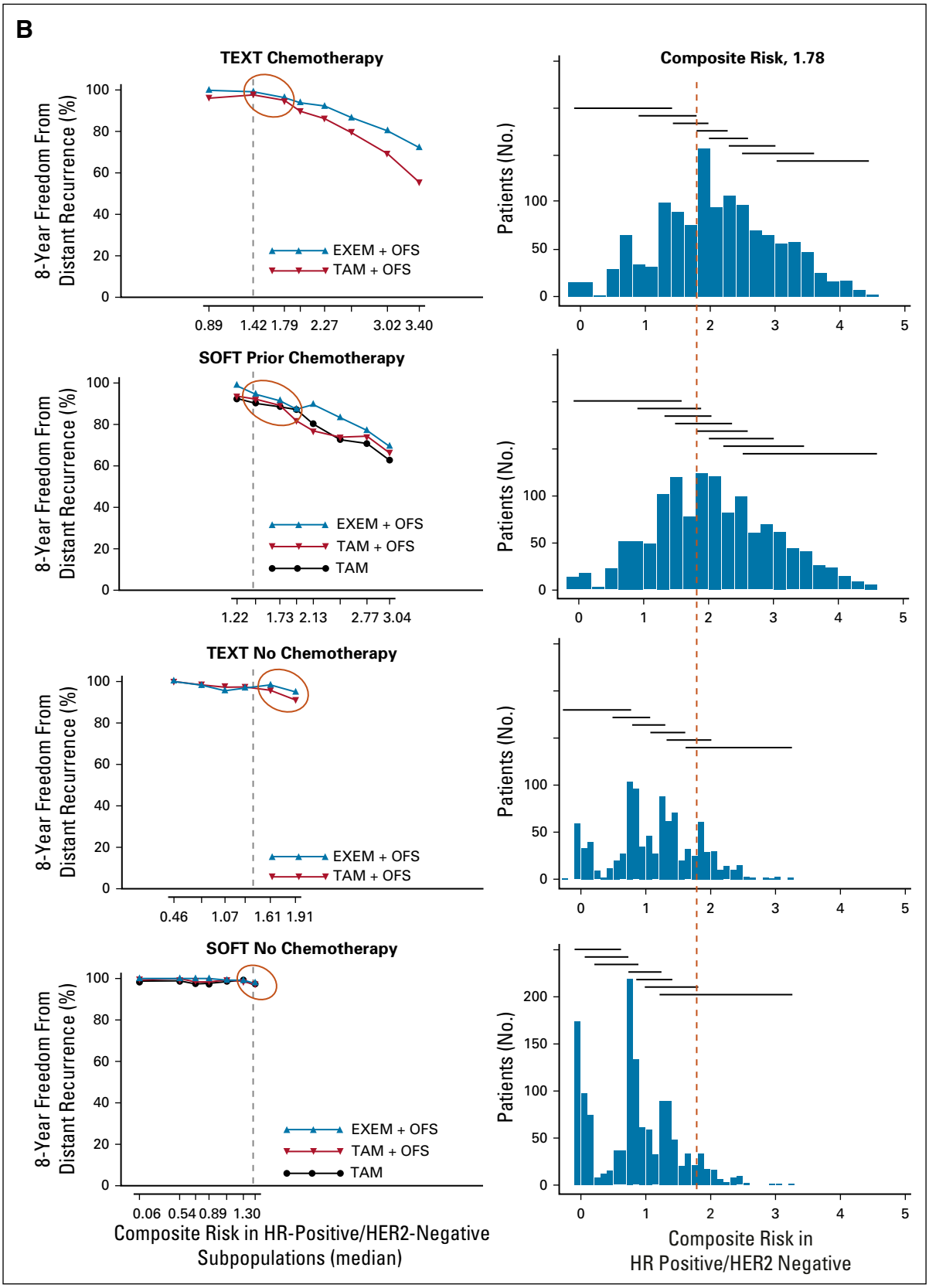

FIG A4. (Continued). (B) An intermediate-risk scenario (composite risk = 1.78; 40-44 years of age, pT1pN1a, grade 2, ER ≥ 50%, PgR ≥ 50%, and Ki-67 20-25%).

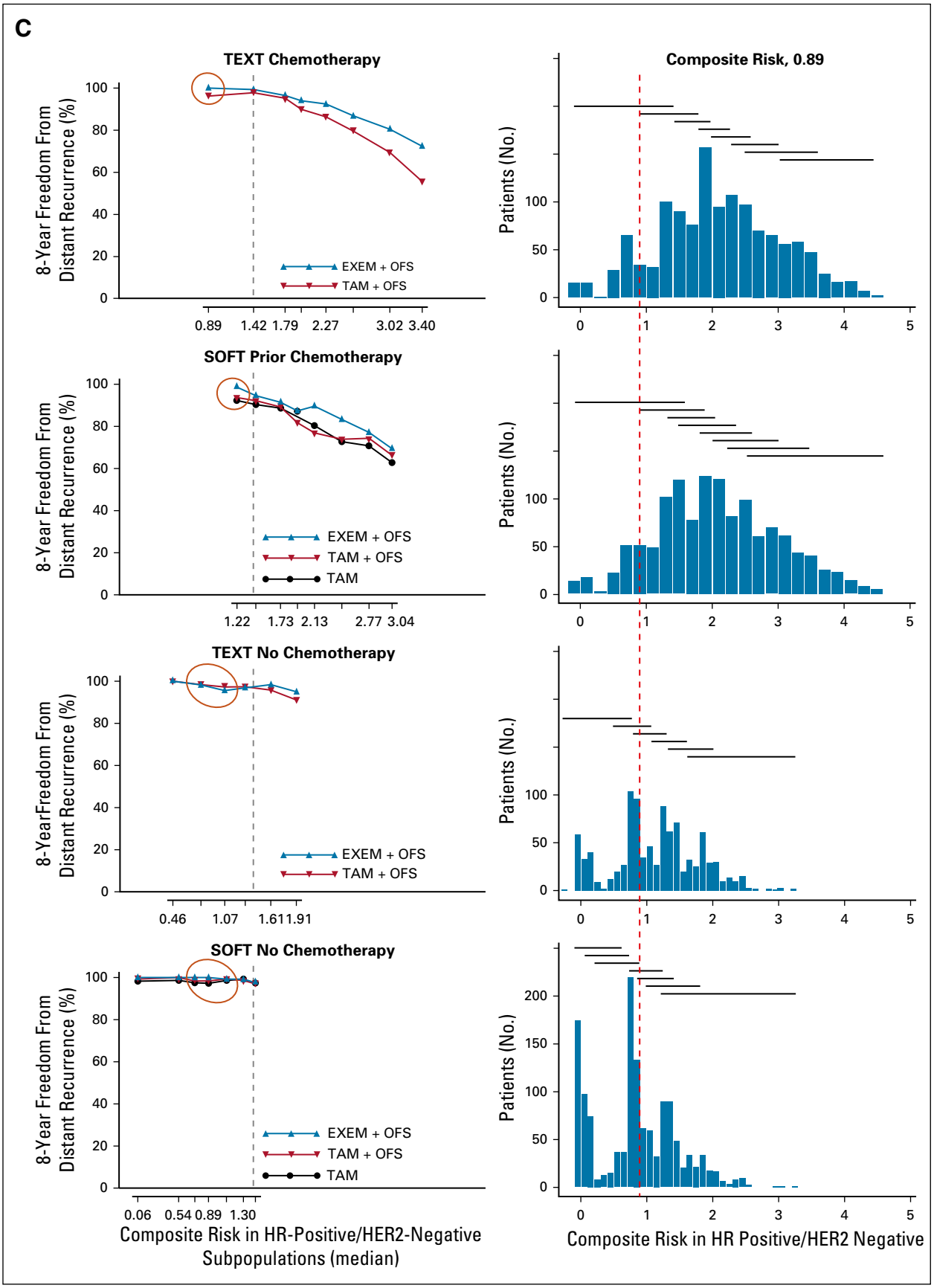

FIG A4. (Continued). (C) A low-risk scenario (composite risk = 0.89; 40-44 years of age, pT1pN0, grade 2, ER ≥ 50%, PgR ≥ 50%, and Ki-67 14-19%).

TABLE A1. Clinicopathologic Characteristics of the HR-Positive/HER2-Negative Analysis Population of TEXT and SOFT Overall and According to Cohort Defined by Trial and Chemotherapy Use

	TEXT Chemotherapy		SOFT Prior Chemotherapy		TEXT No Chemotherapy		SOFT No Chemotherapy		All Patients	
Characteristic	**No.**	**%**	**No.**	**%**	**No.**	**%**	**No.**	**%**	**No.**	**%**
No. of patients	1,276	100	1,271	100	991	100	1,353	100	4,891	100
Age at random assignment, years										
< 35	141	11.1	232	18.3	37	3.7	20	1.5	430	8.8
35-39	221	17.3	375	29.5	113	11.4	103	7.6	812	16.6
40-44	442	34.6	407	32.0	341	34.4	370	27.3	1,560	31.9
45-49	403	31.6	213	16.8	385	38.8	625	46.2	1,626	33.2
≥ 50	69	5.4	44	3.5	115	11.6	235	17.4	463	9.5
No. of positive nodes										
0	401	31.4	527	41.5	776	78.3	1,235	91.3	2,939	60.1
1-3	561	44.0	510	40.1	213	21.5	117	8.6	1,401	28.6
≥ 4	314	24.6	234	18.4	2	0.2	1	0.1	551	11.3
Tumor size, cm										
Unknown	21	1.6	50	3.9	3	0.3	9	0.7	83	1.7
≤ 2	593	46.5	630	49.6	791	79.8	1,162	85.9	3,176	64.9
> 2	662	51.9	591	46.5	197	19.9	182	13.5	1,632	33.4
ER expression, %										
Unknown	23	1.8	17	1.3	17	1.7	14	1.0	71	1.5
< 50	65	5.1	75	5.9	20	2.0	36	2.7	196	4.0
≥ 50	1,188	93.1	1,179	92.8	954	96.3	1,303	96.3	4,624	94.5
PgR expression, %										
Unknown	26	2.0	23	1.8	19	1.9	22	1.6	90	1.8
< 20	163	12.8	233	18.3	58	5.9	55	4.1	509	10.4
20-49	133	10.4	131	10.3	70	7.1	66	4.9	400	8.2
≥ 50	954	74.8	884	69.6	844	85.2	1,210	89.4	3,892	79.6
Tumor grade										
1	165	12.9	199	15.7	252	25.4	504	37.3	1,120	22.9
2	725	56.8	729	57.4	587	59.2	724	53.5	2,765	56.5
3	386	30.3	343	27.0	152	15.3	125	9.2	1,006	20.6
Ki-67 expression, %										
Unknown	240	18.8	266	20.9	189	19.1	270	20.0	965	19.7
< 14	199	15.6	248	19.5	269	27.1	506	37.4	1,222	25.0
14-19	293	23.0	303	23.8	262	26.4	324	23.9	1,182	24.2
20-25	234	18.3	216	17.0	135	13.6	152	11.2	737	15.1
≥ 26	310	24.3	238	18.7	136	13.7	101	7.5	785	16.0

Abbreviations: ER, estrogen receptor; HER2, human epidermal growth factor receptor 2; HR, hormone receptor; Ki-67, Ki-67 labeling index; PgR, progesterone receptor; SOFT, Suppression of Ovarian Function Trial; TEXT, Tamoxifen and Exemestane Trial.

TABLE A2. TEXT: Kaplan-Meier Estimates of 8-Year Freedom From DR in Clinicopathologic Subgroups According to Treatment Assignment

Characteristic	Patients	DRs	Exemestane Plus OFS, 8-Year % (95% CI)	Tamoxifen Plus OFS, 8-Year % (95% CI)
All patients	2,267	194	93.2 (91.5 to 94.6)	90.1 (88.0 to 91.8)
Age at random assignment, years				
< 35	178	40	77.5 (66.6 to 85.3)	75.5 (63.8 to 83.8)
35-39	334	48	91.7 (86.1 to 95.1)	82.8 (75.5 to 88.1)
40-44	783	58	93.5 (90.3 to 95.7)	90.8 (87.2 to 93.4)
45-49	788	40	96.1 (93.4 to 97.7)	93.8 (90.7 to 95.9)
≥ 50	184	8	98.0 (92.2 to 99.5)	96.1 (88.2 to 98.7)
No. of positive nodes				
0	1,177	47	98.0 (96.3 to 98.9)	94.9 (92.5 to 96.5)
1-3	774	66	93.7 (90.6 to 95.8)	90.6 (87.0 to 93.2)
≥ 4	316	81	75.7 (67.8 to 81.9)	70.2 (61.5 to 77.3)
Tumor size, cm				
≤ 2	1,384	63	96.9 (95.1 to 98.1)	94.9 (92.8 to 96.4)
> 2	859	129	87.6 (83.9 to 90.5)	82.0 (77.7 to 85.5)
Unknown	24	2		
ER expression, %				
< 50	85	14	87.5 (72.4 to 94.7)	80.3 (63.0 to 90.1)
≥ 50	2,142	178	93.5 (91.7 to 94.9)	90.3 (88.2 to 92.1)
Unknown	40	2		
PgR expression, %				
< 20	221	43	82.1 (72.9 to 88.4)	75.5 (65.6 to 82.9)
20-49	203	30	90.7 (82.8 to 95.0)	80.9 (70.9 to 87.7)
≥ 50	1,798	118	95.1 (93.3 to 96.4)	92.8 (90.7 to 94.4)
Unknown	45	3		
Tumor grade				
1	417	8	97.8 (94.1 to 99.2)	99.0 (95.9 to 99.7)
2	1,312	98	94.9 (92.7 to 96.5)	91.2 (88.6 to 93.3)
3	538	88	85.7 (80.6 to 89.6)	79.7 (73.7 to 84.4)
Ki-67 expression, %				
< 14	468	10	97.1 (93.0 to 98.8)	98.6 (95.6 to 99.5)
14-19	555	30	95.9 (92.4 to 97.8)	94.2 (90.3 to 96.5)
20-25	369	48	91.3 (85.6 to 94.8)	83.2 (76.3 to 88.2)
≥ 26	446	71	88.3 (83.1 to 92.0)	78.7 (72.0 to 84.0)
Unknown	429	35	93.1 (88.5 to 95.9)	91.7 (86.6 to 94.9)

NOTE. Estimates not provided for unknown groups of < 50 patients. Estimates in subgroups that had few events should be interpreted with caution.

Abbreviations: DR, distant recurrence; ER, estrogen receptor; Ki-67, Ki-67 labeling index; OFS, ovarian function suppression; PgR, progesterone receptor; TEXT, Tamoxifen and Exemestane Trial.

TABLE A3. TEXT: Kaplan-Meier Estimates of 8-Year Freedom From DR in Clinicopathologic Subgroups According to Chemotherapy Use and Treatment Assignment

Characteristic	Chemotherapy				No Chemotherapy		
	Patients	DRs	Exemestane Plus OFS, 8-Year % (95% CI)	Tamoxifen Plus OFS, 8-Year % (95% CI)	Patients	DRs	8-Year % (95% CI)
All patients	1,276	159	90.0 (87.2 to 92.2)	84.9 (81.6 to 87.6)	991	35	97.0 (95.5 to 97.9)
Age at random assignment, years							
< 35	141	36	73.9 (61.2 to 83.0)	73.2 (59.4 to 82.9)	37	4	87.5 (69.7 to 95.2)
35-39	221	37	89.0 (81.3 to 93.6)	78.7 (68.6 to 85.9)	113	11	93.3 (86.5 to 96.8)
40-44	442	49	90.3 (84.9 to 93.8)	85.6 (79.9 to 89.8)	341	9	97.8 (95.3 to 98.9)
45-49	403	31	95.0 (90.6 to 97.4)	89.7 (84.3 to 93.4)	385	9	97.6 (95.0 to 98.9)
≥ 50	69	6	97.6 (83.9 to 99.7)	88.7 (69.0 to 96.2)	115	2	99.1 (93.7 to 99.9)
No. of positive nodes							
0	401	20	98.4 (95.0 to 99.5)	92.9 (87.8 to 95.9)	776	27	96.8 (95.1 to 97.9)
1-3	561	58	92.8 (88.8 to 95.4)	87.2 (82.4 to 90.7)	213	8	97.5 (93.9 to 98.9)
≥ 4	314	81	75.7 (67.8 to 81.9)	70.2 (61.5 to 77.3)	2	0	
Tumor size, cm							
≤ 2	593	38	95.6 (92.2 to 97.6)	92.6 (88.5 to 95.2)	791	25	97.2 (95.6 to 98.3)
> 2	662	119	85.3 (80.8 to 88.8)	77.7 (72.5 to 82.1)	197	10	95.7 (91.6 to 97.8)
Unknown	21	2			3	0	—
ER expression, %							
< 50	65	13	83.7 (65.1 to 92.9)	74.5 (53.8 to 87.0)	20	1	
≥ 50	1,188	144	90.4 (87.6 to 92.7)	85.3 (82.0 to 88.1)	954	34	96.8 (95.3 to 97.8)
Unknown	23	2			17	1	—
PgR expression, %							
< 20	163	36	79.6 (68.7 to 87.0)	72.5 (60.2 to 81.6)	58	7	85.8 (72.1 to 93.1)
20-49	133	25	87.6 (76.6 to 93.6)	75.0 (61.2 to 84.5)	70	5	94.1 (85.0 to 97.7)
≥ 50	954	95	92.6 (89.7 to 94.8)	88.0 (84.5 to 90.8)	844	23	97.9 (96.5 to 98.7)
Unknown	26	3			19	0	—
Tumor grade							
1	165	6	93.6 (83.8 to 97.6)	98.7 (91.2 to 99.8)	252	2	99.6 (97.0 to 99.9)
2	725	81	92.7 (89.2 to 95.0)	85.4 (80.9 to 88.9)	587	17	97.9 (96.1 to 98.9)
3	386	72	83.7 (77.3 to 88.4)	77.2 (69.8 to 83.0)	152	16	88.4 (81.3 to 92.9)
Ki-67 expression, %							
< 14	199	8	94.6 (86.2 to 98.0)	97.9 (92.0 to 99.5)	269	2	98.9 (95.7 to 99.7)
14-19	293	26	92.3 (86.1 to 95.8)	89.9 (83.3 to 94.1)	262	4	99.6 (97.2 to 99.9)
20-25	234	41	90.1 (82.2 to 94.6)	76.5 (67.1 to 83.6)	135	7	94.5 (88.1 to 97.6)
≥ 26	310	58	86.0 (79.4 to 90.5)	74.9 (66.1 to 81.6)	136	13	90.0 (82.8 to 94.2)
Unknown	240	26	90.0 (82.6 to 94.3)	86.9 (78.5 to 92.2)	189	9	97.1 (93.3 to 98.8)

NOTE. Estimates provided for treatment groups combined in the no-chemotherapy cohort because of a small number of events and were not reported when ≤ 20 patients. Estimates not provided for unknown groups of < 50 patients overall. Estimates in subgroups that had few events should be interpreted with caution.

Abbreviations: DR, distant recurrence; ER, estrogen receptor; Ki-67, Ki-67 labeling index; OFS, ovarian function suppression; PgR, progesterone receptor; TEXT, Tamoxifen and Exemestane Trial.

TABLE A4. Combined SOFT and TEXT Cohorts Treated With Ovarian Suppression: Kaplan-Meier Estimates of 8-Year Freedom From DR in Clinicopathologic Subgroups According to Treatment Assignment

Characteristic	Patients	DRs	Exemestane Plus OFS, 8-Year % (95% CI)	Tamoxifen Plus OFS, 8-Year % (95% CI)
All patients	4,009	344	93.1 (91.8 to 94.2)	89.8 (88.3 to 91.1)
Age at random assignment, years				
< 35	349	68	82.3 (75.5 to 87.4)	76.2 (68.4 to 82.4)
35-39	645	99	87.7 (83.3 to 91.0)	82.7 (77.6 to 86.7)
40-44	1,292	96	93.6 (91.2 to 95.4)	90.8 (88.2 to 92.9)
45-49	1,346	68	96.6 (94.7 to 97.8)	93.8 (91.5 to 95.5)
≥ 50	377	13	98.5 (95.3 to 99.5)	95.3 (90.2 to 97.7)
No. of positive nodes				
0	2,357	88	97.9 (96.8 to 98.7)	95.2 (93.7 to 96.4)
1-3	1,181	117	92.6 (90.0 to 94.6)	88.0 (84.9 to 90.4)
≥ 4	471	139	70.9 (64.2 to 76.6)	67.7 (60.8 to 73.7)
Tumor size, cm				
≤ 2	2,574	107	96.7 (95.4 to 97.6)	95.3 (93.9 to 96.4)
> 2	1,373	225	86.7 (83.7 to 89.1)	80.4 (77.0 to 83.3)
Unknown	62	12	88.4 (68.2 to 96.1)	75.3 (56.6 to 86.8)
ER expression, %				
< 50	159	25	87.3 (77.5 to 93.0)	83.3 (71.9 to 90.4)
≥ 50	3,785	313	93.4 (92.1 to 94.5)	90.1 (88.6 to 91.4)
Unknown	65	6	91.1 (68.8 to 97.7)	86.7 (68.2 to 94.8)
PgR expression, %				
< 20	412	74	83.7 (77.6 to 88.2)	76.2 (69.0 to 82.0)
20-49	336	51	91.0 (85.3 to 94.6)	80.3 (72.9 to 85.8)
≥ 50	3,185	211	94.8 (93.5 to 95.9)	92.5 (91.0 to 93.7)
Unknown	76	8	86.8 (68.4 to 94.8)	87.3 (69.4 to 95.0)
Tumor grade				
1	880	16	98.4 (96.3 to 99.3)	98.2 (96.3 to 99.2)
2	2,291	191	93.7 (92.0 to 95.1)	90.0 (88.0 to 91.7)
3	838	137	86.0 (82.0 to 89.1)	80.5 (76.0 to 84.2)
Ki-67 expression, %				
< 14	986	33	96.6 (94.2 to 98.0)	97.0 (94.8 to 98.2)
14-19	970	59	95.0 (92.5 to 96.7)	93.2 (90.4 to 95.3)
20-25	607	77	90.6 (86.4 to 93.6)	83.9 (78.9 to 87.9)
≥ 26	670	114	87.1 (82.9 to 90.4)	78.2 (73.0 to 82.5)
Unknown	776	61	93.6 (90.4 to 95.8)	90.9 (87.3 to 93.5)

NOTE. Estimates not provided for unknown groups of < 50 patients. Estimates in subgroups that had few events should be interpreted with caution.

Abbreviations: DR, distant recurrence; ER, estrogen receptor; Ki-67, Ki-67 labeling index; OFS, ovarian function suppression; PgR, progesterone receptor; SOFT, Suppression of Ovarian Function Trial; TEXT, Tamoxifen and Exemestane Trial.

TABLE A5. SOFT: Kaplan-Meier Estimates of 8-Year Freedom From DR in Clinicopathologic Subgroups According to Treatment Assignment

Characteristic	Patients	DRs	Exemestane Plus OFS, 8-Year % (95% CI)	Tamoxifen Plus OFS, 8-Year % (95% CI)	Tamoxifen, 8-Year % (95% CI)
All patients	2,624	239	93.0 (90.9 to 94.6)	89.5 (87.2 to 91.5)	89.7 (87.3 to 91.7)
Age at random assignment, years					
< 35	252	48	87.2 (78.0 to 92.7)	77.4 (66.0 to 85.3)	74.5 (62.5 to 83.1)
35-39	478	81	83.1 (75.5 to 88.6)	82.6 (74.7 to 88.2)	79.7 (71.4 to 85.8)
40-44	777	62	93.9 (89.7 to 96.4)	91.0 (86.7 to 93.9)	91.8 (87.4 to 94.6)
45-49	838	38	97.2 (94.2 to 98.7)	93.8 (90.0 to 96.2)	95.9 (92.3 to 97.8)
≥ 50	279	10	99.0 (92.9 to 99.9)	94.6 (86.1 to 98.0)	95.2 (87.7 to 98.2)
No. of positive nodes					
0	1,762	67	97.9 (96.1 to 98.8)	95.6 (93.4 to 97.1)	95.3 (92.8 to 96.9)
1-3	627	85	90.6 (85.3 to 94.1)	83.0 (76.8 to 87.7)	85.5 (79.7 to 89.7)
≥ 4	235	87	60.3 (47.3 to 71.0)	63.5 (51.5 to 73.2)	59.0 (46.0 to 69.8)
Tumor size, cm					
≤ 2	1,792	82	96.4 (94.5 to 97.7)	95.9 (93.6 to 97.3)	93.6 (91.0 to 95.5)
> 2	773	141	84.9 (79.3 to 89.1)	77.9 (72.2 to 82.6)	81.7 (75.9 to 86.2)
Unknown	59	16	85.1 (52.3 to 96.1)	69.6 (46.6 to 84.2)	73.9 (48.2 to 88.2)
ER expression, %					
< 50	111	22	87.0 (71.2 to 94.4)	86.7 (68.3 to 94.8)	70.1 (51.0 to 82.8)
≥ 50	2,482	212	93.3 (91.2 to 94.9)	89.9 (87.5 to 91.9)	90.6 (88.2 to 92.5)
Unknown	31	5			
PgR expression, %					
< 20	288	53	85.6 (76.9 to 91.3)	77.2 (65.4 to 85.5)	76.5 (66.2 to 84.1)
20-49	197	33	91.6 (81.0 to 96.5)	79.7 (67.6 to 87.7)	81.4 (68.8 to 89.3)
≥ 50	2,094	146	94.4 (92.2 to 96.0)	92.2 (89.8 to 94.1)	92.3 (89.7 to 94.2)
Unknown	45	7			
Tumor grade					
1	703	19	98.9 (95.7 to 99.7)	97.6 (94.2 to 99.0)	95.9 (91.7 to 98.0)
2	1,453	142	92.1 (89.1 to 94.3)	88.4 (85.0 to 91.1)	90.0 (86.6 to 92.5)
3	468	78	86.6 (79.6 to 91.4)	81.9 (74.7 to 87.2)	79.9 (72.1 to 85.7)
Ki-67 expression, %					
< 14	754	39	96.2 (92.4 to 98.1)	95.4 (91.5 to 97.5)	93.0 (88.0 to 96.0)
14-19	627	45	94.0 (89.7 to 96.6)	92.2 (87.3 to 95.2)	93.0 (88.0 to 95.9)
20-25	368	43	89.5 (81.8 to 94.0)	84.8 (76.3 to 90.4)	87.6 (79.8 to 92.6)
≥ 26	339	66	84.7 (76.2 to 90.4)	77.2 (68.1 to 84.0)	79.2 (70.0 to 85.8)
Unknown	536	81	94.4 (89.0 to 97.2)	90.0 (84.1 to 93.7)	89.8 (84.3 to 93.5)

NOTE. Estimates not provided for unknown groups of < 50 patients. Estimates in subgroups that had few events should be interpreted with caution.

Abbreviations: DR, distant recurrence; ER, estrogen receptor; Ki-67, Ki-67 labeling index; OFS, ovarian function suppression; PgR, progesterone receptor; SOFT, Suppression of Ovarian Function Trial.

TABLE A6. SOFT: Kaplan-Meier Estimates of 8-Year Freedom From DR in Clinicopathologic Subgroups According to Chemotherapy Use and Treatment Assignment

	Prior Chemotherapy					No Chemotherapy		
Characteristic	Patients	DRs	Exemestane Plus OFS, 8-Year % (95% CI)	Tamoxifen Plus OFS, 8-Year % (95% CI)	Tamoxifen, 8-Year % (95% CI)	Patients	DRs	8-Year % (95% CI)
All patients	1,271	216	86.2 (82.2 to 89.4)	80.3 (75.9 to 84.0)	81.0 (76.6 to 84.6)	1,353	23	98.5 (97.6 to 99.1)
Age at random assignment, years								
< 35	232	48	86.0 (76.2 to 92.0)	75.3 (63.2 to 83.9)	72.9 (60.4 to 82.0)	20	0	
35-39	375	79	79.7 (70.8 to 86.2)	77.4 (67.7 to 84.5)	75.9 (66.2 to 83.2)	103	2	96.6 (85.5 to 99.2)
40-44	407	53	90.0 (82.6 to 94.4)	83.5 (76.1 to 88.9)	88.1 (81.2 to 92.5)	370	9	97.8 (95.3 to 99.0)
45-49	213	29	90.1 (79.2 to 95.5)	82.0 (70.9 to 89.2)	84.1 (70.8 to 91.7)	625	9	99.2 (98.0 to 99.7)
≥ 50	44	7	93.3 (61.3 to 99.0)	87.5 (38.7 to 98.1)	77.0 (49.7 to 90.7)	235	3	98.5 (95.4 to 99.5)
No. of positive nodes								
0	527	47	94.2 (89.0 to 97.0)	89.1 (82.8 to 93.1)	88.2 (81.3 to 92.6)	1,235	20	98.7 (97.8 to 99.2)
1-3	510	82	89.2 (83.0 to 93.3)	79.7 (72.3 to 85.3)	83.4 (76.8 to 88.2)	117	3	96.0 (87.0 to 98.8)
≥ 4	234	87	60.3 (47.3 to 71.0)	63.5 (51.5 to 73.2)	58.3 (45.2 to 69.3)	1	0	
Tumor size, cm								
≤ 2	630	70	90.5 (85.5 to 93.9)	90.4 (84.8 to 94.0)	84.1 (77.7 to 88.8)	1,162	12	99.1 (98.2 to 99.5)
> 2	591	130	81.6 (74.7 to 86.8)	71.6 (64.4 to 77.6)	79.0 (72.3 to 84.2)	182	11	94.7 (89.3 to 97.4)
Unknown	50	16	83.3 (48.2 to 95.6)	66.7 (42.5 to 82.5)	64.6 (34.7 to 83.5)	9	0	—
ER expression, %								
< 50	75	20	80.9 (59.4 to 91.7)	81.0 (56.7 to 92.4)	61.3 (36.4 to 78.9)	36	2	94.4 (79.6 to 98.6)
≥ 50	1,179	191	86.7 (82.6 to 89.9)	80.7 (76.1 to 84.5)	82.1 (77.6 to 85.8)	1,303	21	98.6 (97.7 to 99.2)
Unknown	17	5				14	0	—
PgR expression, %								
< 20	233	52	82.9 (72.7 to 89.5)	70.5 (56.1 to 81.0)	72.1 (60.0 to 81.1)	55	1	98.1 (87.6 to 99.7)
20-49	131	32	90.6 (76.8 to 96.4)	64.4 (46.5 to 77.6)	73.5 (57.2 to 84.5)	66	1	98.4 (89.4 to 99.8)
≥ 50	884	125	87.0 (82.1 to 90.7)	84.9 (80.1 to 88.6)	84.4 (79.2 to 88.4)	1,210	21	98.5 (97.5 to 99.1)
Unknown	23	7				22	0	—
Tumor grade								
1	199	15	96.4 (85.9 to 99.1)	92.3 (80.8 to 97.1)	90.3 (79.5 to 95.5)	504	4	99.2 (97.4 to 99.8)
2	729	127	85.1 (79.5 to 89.2)	78.9 (72.8 to 83.8)	82.4 (76.4 to 86.9)	724	15	98.3 (96.8 to 99.0)
3	343	74	82.5 (73.3 to 88.8)	77.4 (68.3 to 84.1)	72.8 (63.0 to 80.5)	125	4	97.5 (92.5 to 99.2)
Ki-67 expression, %								
< 14	248	33	88.5 (77.8 to 94.3)	86.5 (75.6 to 92.8)	81.8 (69.7 to 89.4)	506	6	99.4 (97.5 to 99.9)
14-19	303	40	87.6 (79.2 to 92.8)	85.3 (76.4 to 91.0)	88.7 (79.9 to 93.8)	324	5	98.5 (95.8 to 99.5)
20-25	216	38	85.8 (74.4 to 92.3)	76.4 (63.8 to 85.0)	80.6 (67.8 to 88.7)	152	5	96.5 (91.8 to 98.5)
≥ 26	238	61	78.6 (66.9 to 86.6)	72.1 (60.7 to 80.7)	71.4 (59.6 to 80.2)	101	5	96.0 (89.6 to 98.5)
Unknown	266	44	88.8 (78.6 to 94.3)	80.3 (69.4 to 87.6)	81.0 (71.1 to 87.7)	270	2	99.1 (96.4 to 99.8)

NOTE. Estimates provided for treatment groups combined in the no-chemotherapy cohort because of the small number of events and not provided when ≤ 20 patients. Estimates not provided for unknown groups of < 50 patients overall (chemotherapy and no-chemotherapy combined). Estimates in subgroups that had a few events should be interpreted with caution.

Abbreviations: DR, distant recurrence; ER, estrogen receptor; Ki-67, Ki-67 labeling index; OFS, ovarian function suppression; PgR, progesterone receptor; SOFT, Suppression of Ovarian Function Trial.

TABLE A7. Distribution of the Composite Measures of Recurrence Risk in Clinicopathologic Subgroups

Measure	Patients	DRs	Composite Risk				
			Median	Quartile 1	Quartile 3	Minimum	Maximum
All HR-positive/HER2-negative	4,891	433	1.42	0.81	2.16	−0.28	4.60
Age at random assignment, years							
< 35	430	88	2.49	1.95	3.16	0.67	4.59
35-39	812	129	2.01	1.49	2.80	0.52	4.60
40-44	1,560	120	1.44	0.89	2.02	0.07	3.84
45-49	1,626	78	1.07	0.72	1.65	−0.28	4.01
≥ 50	463	18	0.79	0.50	1.36	−0.04	3.87
No. of positive nodes							
0	2,939	114	0.98	0.72	1.47	−0.28	3.26
1-3	1,401	151	1.91	1.42	2.43	0.44	3.91
≥ 4	551	168	3.18	2.71	3.59	1.30	4.60
Tumor size, cm							
Unknown	83	18	2.49	2.13	3.15	0.89	4.60
≤ 2	3,176	145	1.07	0.72	1.59	−0.28	4.01
> 2	1,632	270	2.27	1.73	2.92	0.48	4.59
ER expression, %							
Unknown	71	7	1.85	1.61	2.42	−0.28	4.60
< 50	196	36	2.10	1.32	2.96	0.06	4.59
≥ 50	4,624	390	1.39	0.77	2.09	−0.10	4.44
PgR expression, %							
Unknown	90	10	2.14	1.67	2.63	0.90	4.60
< 20	509	96	2.37	1.79	3.03	0.36	4.59
20-49	400	63	2.14	1.40	2.90	0.21	4.32
≥ 50	3,892	264	1.29	0.73	1.89	−0.28	4.03
Tumor grade							
1	1,120	27	0.35	0.06	0.75	−0.28	2.94
2	2,765	240	1.46	0.98	2.10	0.72	4.60
3	1,006	166	2.29	1.75	2.98	0.69	4.59
Ki-67 expression, %							
Unknown	965	81	1.41	0.79	2.11	−0.28	4.60
< 14	1,222	49	0.75	0.17	1.39	0.00	3.82
14-19	1,182	75	1.29	0.77	1.87	−0.10	3.85
20-25	737	91	1.79	1.24	2.42	0.26	4.39
≥ 26	785	137	2.36	1.87	3.00	0.49	4.59

NOTE. Values of grade, ER, and PgR expression were centrally determined if available and locally determined otherwise; Ki-67 expression was available only by central determination.

Abbreviations: DR, distant recurrence; ER, estrogen receptor; HER2, human epidermal growth factor receptor 2; HR, hormone receptor; Ki-67, Ki-67 labeling index; PgR, progesterone receptor.