Supplementary Appendix

This appendix has been provided by the authors to give readers additional information about their work.

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Tailoring Adjuvant Endocrine Therapy for Premenopausal Breast Cancer

Francis, Pagani et al.

SUPPLEMENTARY MATERIAL

Contents

I. TEXT and SOFT Investigators and the International Breast Cancer Study Group Participants 1

II. Funding: Grant Support for Cooperative Groups 13

III. Supplemental Methods, Figures and Tables 14

III. A. Methods 14

III. B. Efficacy of Ovarian Suppression in SOFT Figures and Tables 18

III. C. Efficacy of Exemestane Compared with Tamoxifen when Treated with Ovarian Suppression Figures and Tables 30

III. D. Confidence Intervals for Targeted Adverse Events 44

III. E. SOFT + TEXT Combined Analysis and ABCSG-12 45

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Kaiser Permanente - Fremont, Fremont, CA; L. Fehrenbacher
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Cooper Hospital University Medical Center, Newark, NJ; D.D. Biggs
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Cancer Institute of New Jersey At Hamilton, Trenton, NJ; D.L. Toppmeyer
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Albert Einstein College/Medicine, Bronx, NY; C.M. Pellegrino
Montefiore Medical Center, Bronx, NY; C.M. Pellegrino
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Ohio State University Hospital, Columbus, OH; C.D. Bloomfield
Cleveland Clinic Foundation, Cleveland, OH; G.T. Budd
Case Western Reserve University, Cleveland, OH; P. Silverman
Fairview Hospital, Cleveland, OH; G.T. Budd
Aultman Hospital, Canton, OH; J.A. Schmotzer
Samaritan North Health Center, Dayton, OH; H.M. Gross
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Chester County Hospital, West Chester, PA; W.E. Luginbuhl

St. Mary Regional Cancer Center, Langhorne, PA; R.E. Reilly
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III. Supplemental Methods, Figures and Tables

III. A. Methods

Patients

Eligibility in each trial required documented premenopausal status, defined by regular menses without exogenous hormones during the prior six months and/or estradiol level in the premenopausal range; patients who had completed chemotherapy prior to entry into SOFT were required to have a premenopausal estradiol level. Inclusion criteria were histologically-proven operable breast cancer confined to the breast and ipsilateral axilla, with the exception of internal-mammary-node involvement detected by means of sentinel-node biopsy, and tumor that expressed estrogen or progesterone receptors in at least 10% of cells, as assessed with the use of immunohistochemical testing. Patients with synchronous bilateral hormone-receptor-positive breast cancer were eligible. Patients had undergone either a total mastectomy with subsequent optional radiotherapy or breast-conserving surgery with subsequent radiotherapy. Either axillary dissection or a negative sentinel-node biopsy was required. Macrometastasis in a sentinel node required axillary dissection or irradiation. All the patients in TEXT and the patients in SOFT who did not receive chemotherapy underwent randomization within 12 weeks after definitive surgery; patients in SOFT who received neoadjuvant or adjuvant chemotherapy underwent randomization within 8 months after completing chemotherapy, once premenopausal level of estradiol was confirmed. Consistent with this design, patients in SOFT, but not in TEXT, were allowed to receive adjuvant oral endocrine therapy before randomization.

Study Design

TEXT was designed to evaluate 5 years of therapy consisting of exemestane plus the gonadotropin-releasing-hormone (GnRH) agonist triptorelin versus tamoxifen plus triptorelin in women who received ovarian-suppression therapy from the start of adjuvant therapy. Eligible women were randomly assigned in a 1:1 ratio to receive oral exemestane (Aromasin, Pfizer), at a dose of 25 mg daily, plus triptorelin (Decapeptyl Depot [triptorelin acetate], Ipsen; or Trelstar Depot [triptorelin pamoate], Debio), at a dose of 3.75 mg administered by means of intramuscular injection every 28 days, or oral tamoxifen at a dose of 20 mg daily plus triptorelin. Bilateral oophorectomy or ovarian irradiation was allowed after at least 6 months of triptorelin. Chemotherapy was optional in TEXT, and if administered, was started concomitantly with triptorelin; oral endocrine therapy was started after the completion of chemotherapy. If chemotherapy was not administered, oral endocrine therapy was started 6 to 8 weeks after the initiation of triptorelin, to allow for a decline in ovarian estrogen production. Randomization was

stratified according to the intended use of adjuvant chemotherapy (yes vs. no) and lymph-node status (negative vs. positive).

SOFT was designed to evaluate 5 years of treatment with tamoxifen versus tamoxifen plus ovarian suppression versus exemestane plus ovarian suppression in women who remained premenopausal after completion of neoadjuvant or adjuvant chemotherapy or in women for whom adjuvant tamoxifen alone (without neoadjuvant or adjuvant chemotherapy) was considered suitable treatment. Eligible women in SOFT were randomly assigned in a 1:1:1 ratio to receive oral tamoxifen at a dose of 20 mg daily, tamoxifen plus ovarian suppression, or oral exemestane at a dose of 25 mg daily plus ovarian suppression. Ovarian suppression was achieved by choice of triptorelin (Decapeptyl Depot [triptorelin acetate], Ipsen; or Trelstar Depot [triptorelin pamoate], Debio) at a dose of 3.75 mg administered by means of intramuscular injection every 28 days, bilateral oophorectomy, or bilateral ovarian irradiation. Patients receiving triptorelin could subsequently opt to undergo oophorectomy or irradiation. Randomization was stratified according to prior use of (neo)adjuvant chemotherapy (yes vs. no), lymph-node status (negative vs. positive), and intended initial method of ovarian suppression, if the woman was assigned to a group that included ovarian-suppression therapy.

In each trial, randomization to open-label treatment was performed by means of the IBCSG internet-based system, with the use of permuted blocks.

In both TEXT and SOFT, protocol-assigned endocrine therapy continued for 5 years from the date of randomization, and the protocols did not address the issue of extended adjuvant endocrine therapy beyond 5 years, except the requirement to record any therapy. Bisphosphonates were not permitted unless indicated for reduced bone density (T-score, -1.5 or lower) or required for participation in a randomized trial of adjuvant bisphosphonate therapy. Adjuvant trastuzumab was allowed, and was not considered as chemotherapy when considering the timing of enrollment relative to chemotherapy completion in SOFT.

Patients were assessed with physical examination, menstrual and medication documentation every three months for the first year, then every six months until year 6 and annually thereafter. Annual mammography and bone densitometry were recommended. Blood tests and additional imaging were performed if medically indicated or according to local practice. All patients were followed according to protocol regardless of the treatment actually taken, unless a patient

explicitly withdrew consent to further trial participation or was lost to follow-up; some of these patients consented to continued submission of survival status from medical records or such updates were obtainable from tumor and vital registries and could be submitted according to the protocol follow-up schedule. We systematically queried for 22 targeted adverse events and collected other grade 3 or higher adverse events using the Common Terminology Criteria for Adverse Events (CTCAE) v3.0, starting at randomization until 12 months after the last dose of any protocol-assigned therapy.

Study Oversight

TEXT (IBCSG 25-02/BIG 3-02; NCT00066703) and SOFT (IBCSG 24-02/BIG 2-02; NCT00066690) were coordinated by the IBCSG, which was responsible for the study design, randomization, collection and management of data, medical review, data analysis, and reporting. The trial was conducted in accordance with the provisions of the Declaration of Helsinki. The IBCSG ethics committee and ethics committees at each center approved the study protocol and all patients provided written informed consent. The IBCSG data and safety monitoring committee reviewed safety data semi-annually.

Pfizer and Ipsen, the respective manufacturers of exemestane and triptorelin, donated the study drugs; neither manufacturer imposed restrictions with respect to the trial data. The manuscript was written solely by the authors, who vouch for the data and analyses reported and fidelity of the study to the protocol. The steering committee (which included employees of Pfizer and Ipsen) reviewed the manuscript and were responsible for the decision to submit it for publication.

Statistical Design

The original statistical designs and sample-size assumptions and the amended plans have been described previously. The steering committee proposed, and the data and safety monitoring committee endorsed, the amended analysis plans without knowledge of the data according to treatment assignment. No interim analyses were performed.

The original statistical analysis plans for SOFT and TEXT were to compare disease-free survival between treatment groups within each trial separately, with a planned secondary combined analysis of exemestane plus ovarian suppression versus tamoxifen plus ovarian suppression. Protocol amendments to the analysis plans were adopted in 2011, designating the test of superiority of tamoxifen plus ovarian suppression over tamoxifen alone as the primary analysis

for SOFT, and the comparison of exemestane plus ovarian suppression with tamoxifen alone became a secondary objective. The amendments designated the combined analysis of data from TEXT and SOFT as the primary analysis of exemestane plus ovarian suppression versus tamoxifen plus ovarian suppression.

At the time of amendment, we calculated that with an estimated 186 events of disease recurrence, second invasive cancer, or death in the tamoxifen plus ovarian suppression and tamoxifen alone groups of SOFT after a median follow-up of 5 years, the study would have at least 80%, 69%, and 52% power to detect reductions in risk of 33.5%, 30%, and 25%, respectively, with tamoxifen plus ovarian suppression versus tamoxifen alone, at a two-sided alpha level of 0.05. For the combined analysis of TEXT and SOFT, we calculated that with an estimated 436 events of disease recurrence, second invasive cancer, or death, the study would have at least 84% power to detect a hazard ratio of 0.75 with exemestane plus ovarian suppression versus tamoxifen plus ovarian suppression in the primary combined analysis, at a two-sided alpha level of 0.05.

Statistical Analysis

The visit cut-off date was December 31, 2016, and the database-lock date for analysis was May 4, 2017.

The primary endpoint, disease-free survival, was defined as the time from randomization to the first appearance of one of the following: invasive recurrence of breast cancer (local, regional or distant), invasive contralateral breast cancer, second (non-breast) invasive cancer, or death without recurrence or second cancer. Censoring of time-to-event endpoints was at the date of last follow-up visit (or date last known alive for overall survival), including for those 378 patients in SOFT (577 patients in the combined analysis of SOFT and TEXT) who during follow-up either withdrew consent or were lost to follow-up (see **Figs. S1, S5**). There were no sensitivity analyses performed with regard to withdrawal of consent/loss to follow-up. P-values and widths of CIs were not adjusted for multiplicity of tests.

Secondary analyses were conducted in the population of patients with HER2-negative disease, on the basis of the clinical relevance of the subgroup as well as the presence of heterogeneity of the treatment effect between HER2-negative and HER2-positive subgroups. These analyses report estimates and CIs only; CI widths were not adjusted for multiplicity and inference about treatment comparisons or heterogeneity of the treatment effect within the HER2-negative population should be viewed as preliminary.

III. B. Efficacy of Ovarian Suppression in SOFT Figures and Tables

Figure S1. SOFT Randomization, Treatment, and Follow-up.

CONSORT flow diagram showing the intention-to-treat population of 3047 patients for the two pairwise comparisons of tamoxifen plus ovarian suppression with tamoxifen alone (SOFT primary analysis comparison; N=2033) and exemestane plus ovarian suppression with tamoxifen alone. During follow-up, 378 of 3047 patients either withdrew consent or were lost to follow-up and were censored at date of last follow-up visit (median time to withdrawal or lost was 3.0 years [interquartile range, 1.1-5.1 years]); for 132 of 378 patients, the patient consented to continued submission of disease-recurrence and survival status from medical records or such updates are obtainable from tumor and vital registries according to protocol follow-up schedule and overall survival is censored at date last known alive (median follow-up 7.4 years [interquartile range, 5.9-9.6 years]).
Abbreviations: ITT denotes intention-to-treat, OS ovarian suppression, SOFT Suppression of Ovarian Function Trial.

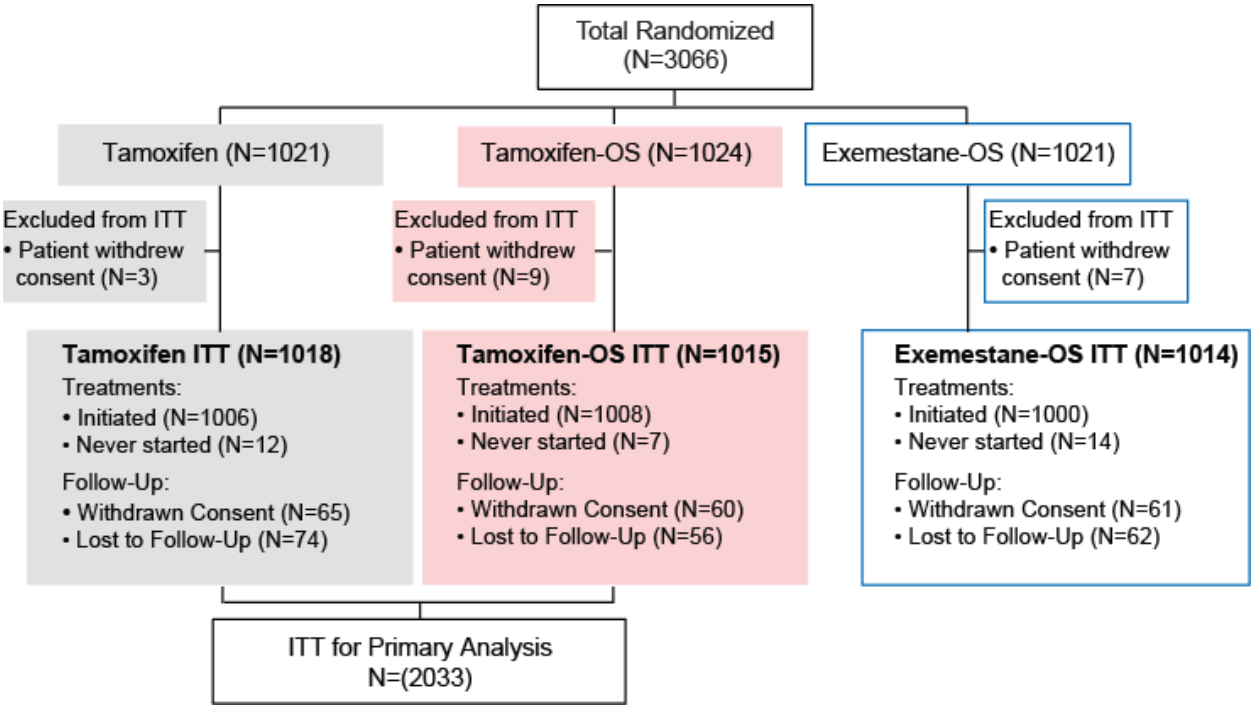
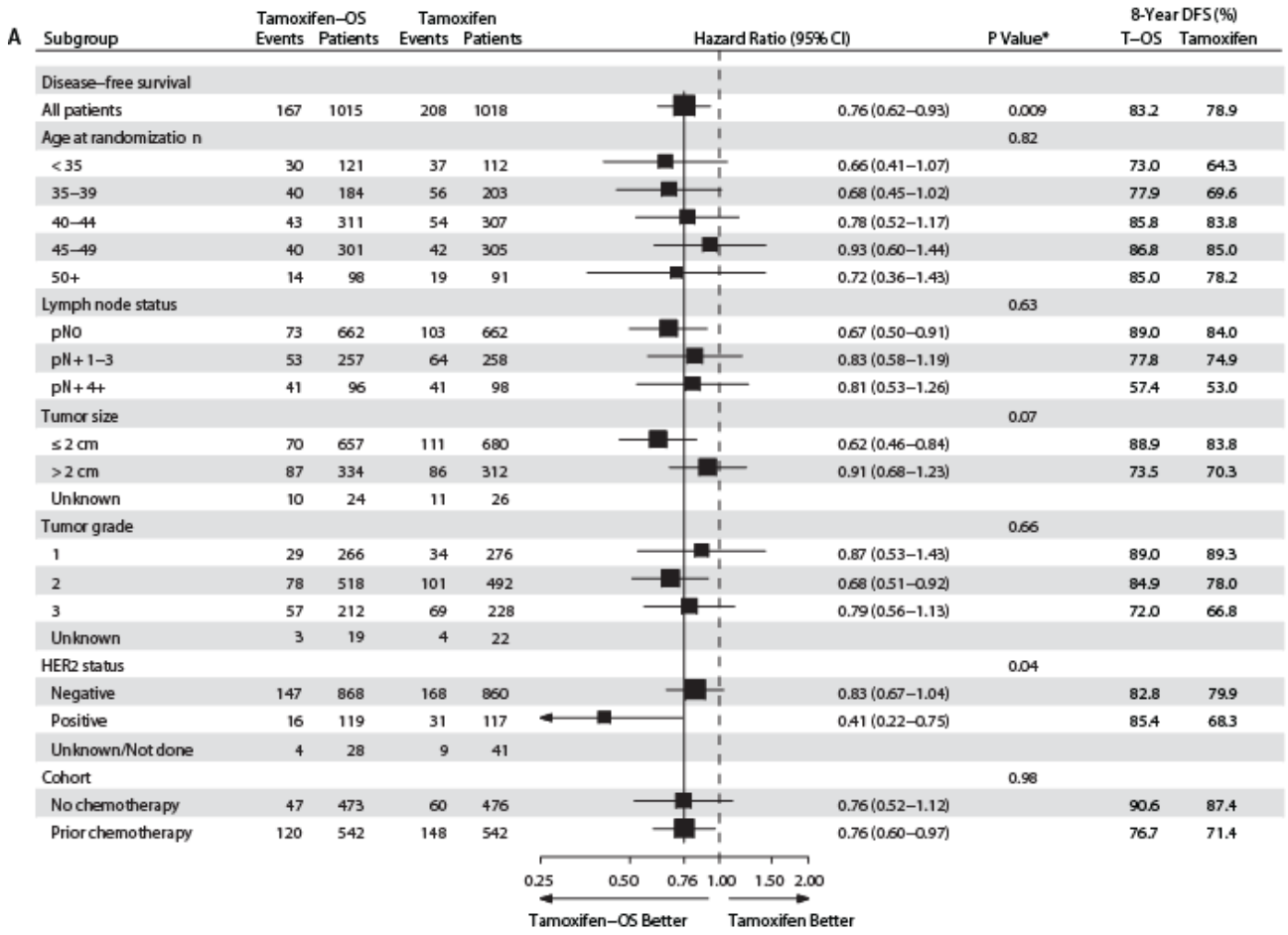


Figure S2A. Results of Cox Proportional-hazards Models for the Disease-free Survival (DFS) Treatment Comparison of Tamoxifen plus Ovarian Suppression vs. Tamoxifen Alone in the SOFT Primary Analysis, among All Patients and According to Subgroups.

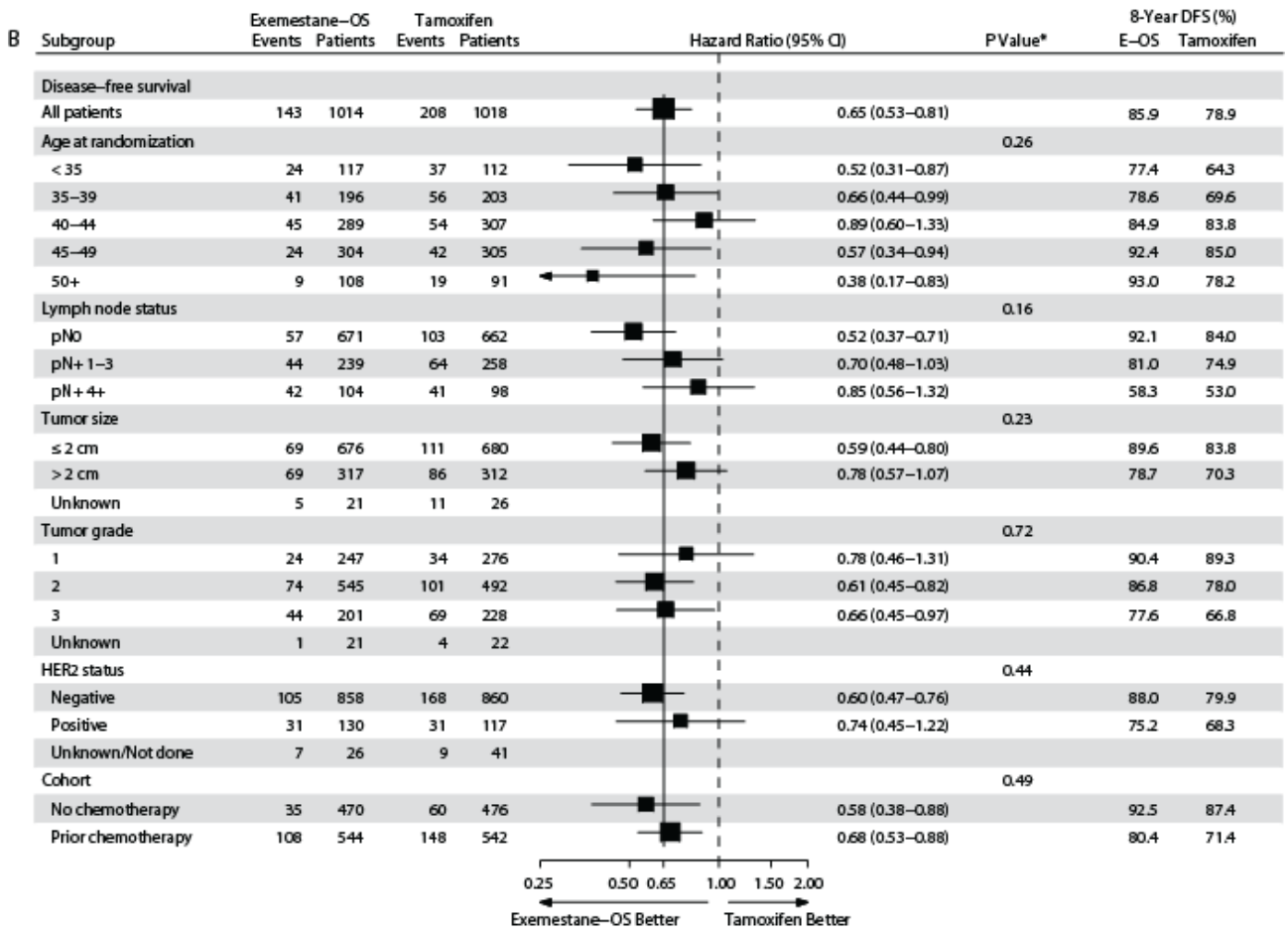
Median follow-up in SOFT was 8 years. The solid vertical line is placed at 0.76, the hazard-ratio estimate for all patients. The x-axis is scaled according to the natural logarithm of the hazard ratio. The size of the square is inversely proportional to the standard error of the hazard ratio.



*P-Value for “All patients” is the stratified log-rank test; for other variables, P-Value is test of heterogeneity of the treatment effect across subgroups, using test of treatment-by-variable interaction from stratified Cox model, with “Unknown” or “Unknown/Not done” group omitted from the test. Abbreviations: CI denotes confidence interval, T tamoxifen, OS ovarian suppression.

Figure S2B. Results of Cox Proportional-hazards Models for the Disease-free Survival (DFS) Treatment Comparison of Exemestane Plus Ovarian Suppression vs. Tamoxifen Alone in SOFT, among All Patients and According to Subgroups.

Median follow-up in SOFT was 8 years. The solid vertical line is placed at 0.65, the hazard-ratio estimate for all patients. The x-axis is scaled according to the natural logarithm of the hazard ratio. The size of the square is inversely proportional to the standard error of the hazard ratio.



*P-Values are for test of heterogeneity of the treatment effect across subgroups, using test of treatment-by-variable interaction from stratified Cox model, with “Unknown” or “Unknown/Not done” group omitted from the test.

Abbreviations: CI denotes confidence interval, E exemestane, OS ovarian suppression.

Figure S3A. Kaplan-Meier Estimates of Freedom from Breast Cancer after a Median Follow-up of 8 Years in the SOFT Population.

The estimates for the primary analysis population and the exemestane-ovarian suppression group of SOFT are summarized for all patients (Panel A) and according to chemotherapy cohort (Panels B and C). The 8-year values are based on Kaplan-Meier estimates of the time to an event. The hazard ratios are for recurrence. OS denotes ovarian suppression, T tamoxifen, E exemestane, HR hazard ratio, CI confidence interval.

Figure S3B. Kaplan-Meier Estimates of Freedom from Recurrence of Breast Cancer at a Distant Site and Overall Survival after a Median Follow-up of 8 Years in the SOFT Population.

The estimates for the primary analysis population and the exemestane-ovarian suppression group of SOFT are summarized for all patients (Panels A and B) and according to chemotherapy cohort (Panels C through F). The 8-year values are based on Kaplan-Meier estimates of the time to an event. The hazard ratios in Panels A,C,E are for recurrence of breast cancer at a distant site; the hazard ratios in Panel B,D,F are for death. OS denotes ovarian suppression, T tamoxifen, E exemestane, HR hazard ratio, CI confidence interval.

Figure S3A

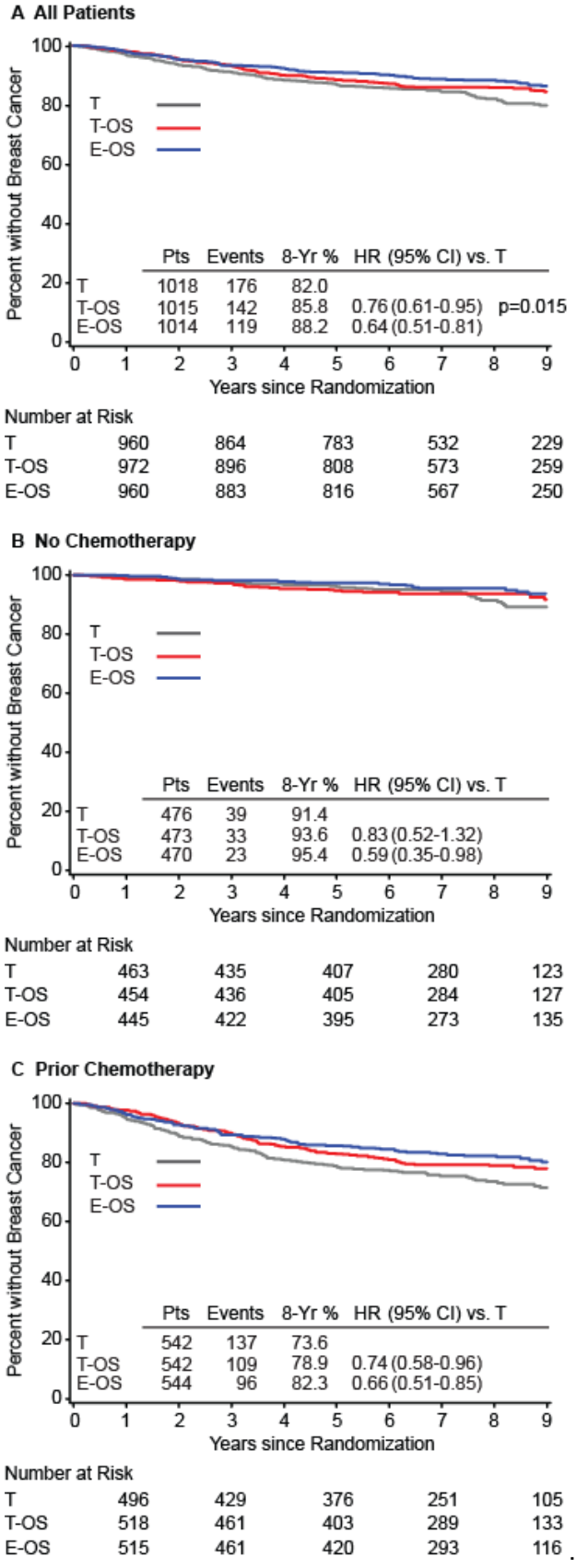

A All Patients
Percent without Breast Cancer
100
80
60
40
20
0
T
T-OS
E-OS
Pts Events 8-Yr % HR (95% CI) vs. T
T 1018 176 82.0
T-OS 1015 142 85.8 0.76 (0.61-0.95) p=0.015
E-OS 1014 119 88.2 0.64 (0.51-0.81)
0 1 2 3 4 5 6 7 8 9
Years since Randomization
Number at Risk
T 960 864 783 532 229
T-OS 972 896 808 573 259
E-OS 960 883 816 567 250
B No Chemotherapy
Percent without Breast Cancer
100
80
60
40
20
0
T
T-OS
E-OS
Pts Events 8-Yr % HR (95% CI) vs. T
T 476 39 91.4
T-OS 473 33 93.6 0.83 (0.52-1.32)
E-OS 470 23 95.4 0.59 (0.35-0.98)
0 1 2 3 4 5 6 7 8 9
Years since Randomization
Number at Risk
T 463 435 407 280 123
T-OS 454 436 405 284 127
E-OS 445 422 395 273 135
C Prior Chemotherapy
Percent without Breast Cancer
100
80
60
40
20
0
T
T-OS
E-OS
Pts Events 8-Yr % HR (95% CI) vs. T
T 542 137 73.6
T-OS 542 109 78.9 0.74 (0.58-0.96)
E-OS 544 96 82.3 0.66 (0.51-0.85)
0 1 2 3 4 5 6 7 8 9
Years since Randomization
Number at Risk
T 496 429 376 251 105
T-OS 518 461 403 289 133
E-OS 515 461 420 293 116

Figure S3B

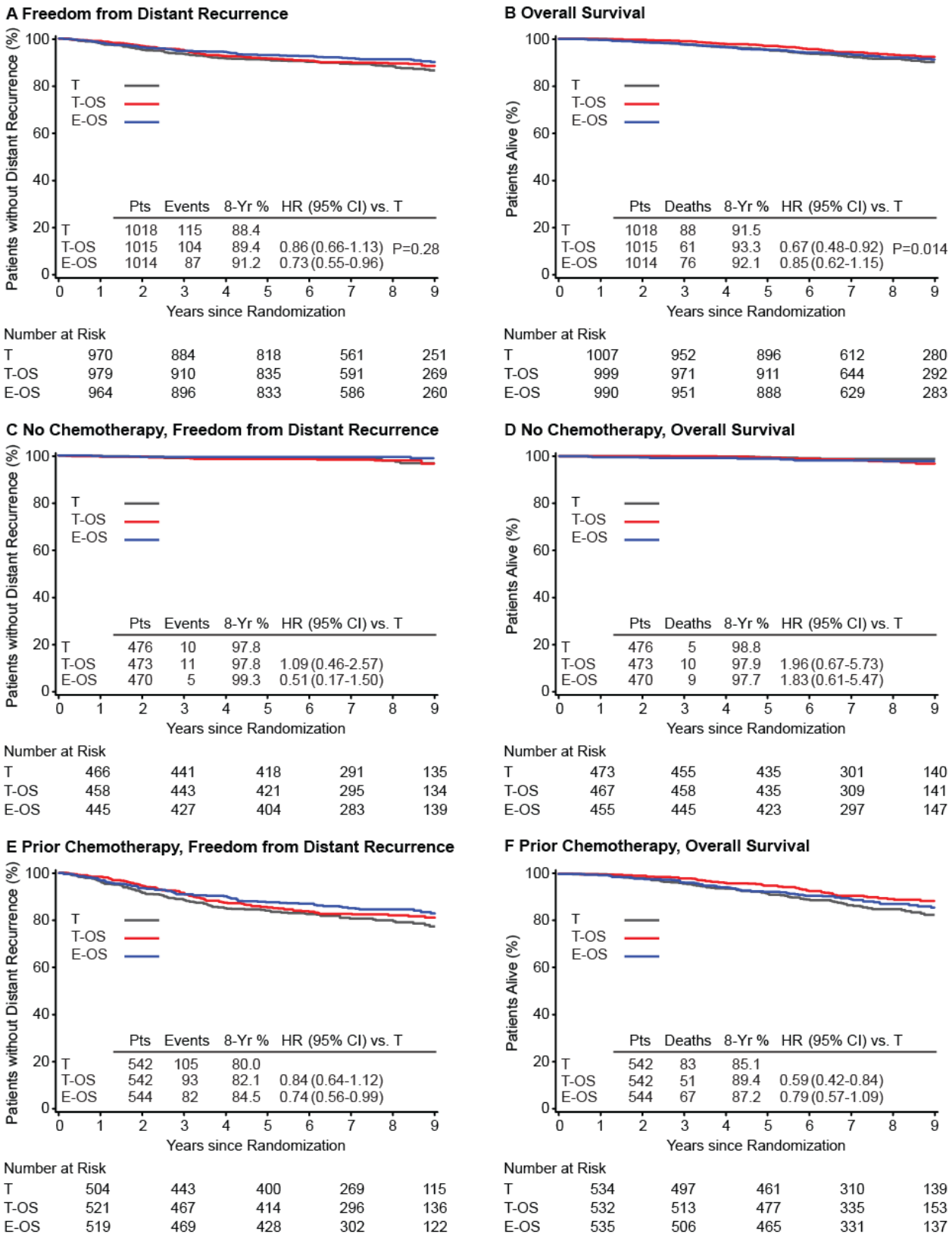

A Freedom from Distant Recurrence
Patients without Distant Recurrence (%)
T
T-OS
E-OS
Pts Events 8-Yr % HR (95% CI) vs. T
T 1018 115 88.4
T-OS 1015 104 89.4 0.86 (0.66-1.13) P=0.28
E-OS 1014 87 91.2 0.73 (0.55-0.96)
Years since Randomization
Number at Risk
T 970 884 818 561 251
T-OS 979 910 835 591 269
E-OS 964 896 833 586 260
B Overall Survival
Patients Alive (%)
Pts Deaths 8-Yr % HR (95% CI) vs. T
T 1018 88 91.5
T-OS 1015 61 93.3 0.67 (0.48-0.92) P=0.014
E-OS 1014 76 92.1 0.85 (0.62-1.15)
Years since Randomization
Number at Risk
T 1007 952 896 612 280
T-OS 999 971 911 644 292
E-OS 990 951 888 629 283
C No Chemotherapy, Freedom from Distant Recurrence
Patients without Distant Recurrence (%)
Pts Events 8-Yr % HR (95% CI) vs. T
T 476 10 97.8
T-OS 473 11 97.8 1.09 (0.46-2.57)
E-OS 470 5 99.3 0.51 (0.17-1.50)
Years since Randomization
Number at Risk
T 466 441 418 291 135
T-OS 458 443 421 295 134
E-OS 445 427 404 283 139
D No Chemotherapy, Overall Survival
Patients Alive (%)
Pts Deaths 8-Yr % HR (95% CI) vs. T
T 476 5 98.8
T-OS 473 10 97.9 1.96 (0.67-5.73)
E-OS 470 9 97.7 1.83 (0.61-5.47)
Years since Randomization
Number at Risk
T 473 455 435 301 140
T-OS 467 458 435 309 141
E-OS 455 445 423 297 147
E Prior Chemotherapy, Freedom from Distant Recurrence
Patients without Distant Recurrence (%)
Pts Events 8-Yr % HR (95% CI) vs. T
T 542 105 80.0
T-OS 542 93 82.1 0.84 (0.64-1.12)
E-OS 544 82 84.5 0.74 (0.56-0.99)
Years since Randomization
Number at Risk
T 504 443 400 269 115
T-OS 521 467 414 296 136
E-OS 519 469 428 302 122
F Prior Chemotherapy, Overall Survival
Patients Alive (%)
Pts Deaths 8-Yr % HR (95% CI) vs. T
T 542 83 85.1
T-OS 542 51 89.4 0.59 (0.42-0.84)
E-OS 544 67 87.2 0.79 (0.57-1.09)
Years since Randomization
Number at Risk
T 534 497 461 310 139
T-OS 532 513 477 335 153
E-OS 535 506 465 331 137

Figure S4. Kaplan-Meier Estimates of Freedom from Recurrence of Breast Cancer and Freedom from the Recurrence of Breast Cancer at a Distant Site, among Women Younger than 35 Years of Age at Randomization in the SOFT Population.

Panel A shows Kaplan-Meier estimates of freedom from recurrence of breast cancer, and Panel B shows freedom from recurrence of breast cancer at a distant site. The 8-year values are based on Kaplan-Meier estimates of the time to an event. The median follow-up in SOFT was 8 years. OS denotes ovarian suppression, T tamoxifen, E exemestane.

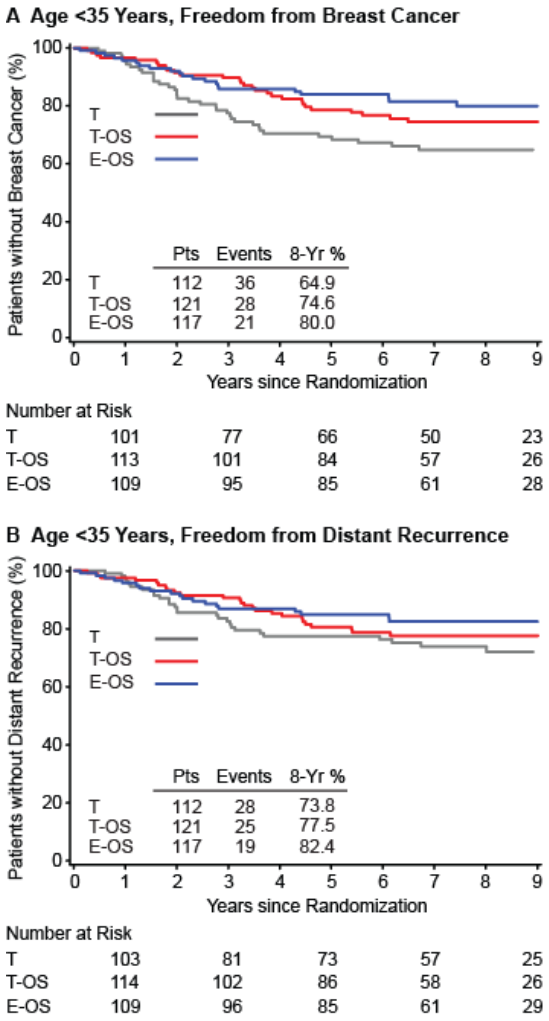


Table S1. Kaplan-Meier estimates of 8-year end point rates with 95% confidence intervals, according to treatment assignment in SOFT, overall and by HER2 status and chemotherapy stratum. Bold values are those reported in the manuscript text.

			Tamoxifen					Tamoxifen-OS					Exemestane-OS				
			N Pts	N Events	8-yr Rate (%)	95% Lower CI	95% Upper CI	N Pts	N Events	8-yr Rate (%)	95% Lower CI	95% Upper CI	N Pts	N Events	8-yr Rate (%)	95% Lower CI	95% Upper CI
	HER2	**Chemo stratum**															
DFS	**Overall**	**Overall**	**1018**	**208**	**78.9**	**75.9**	**81.6**	**1015**	**167**	**83.2**	**80.5**	**85.4**	**1014**	**143**	**85.9**	**83.4**	**88.1**
		No Chemo	476	60	87.4	83.4	90.4	473	47	90.6	87.3	93.0	470	35	92.5	89.3	94.8
		Prior Chemo	**542**	**148**	**71.4**	**67.0**	**75.4**	**542**	**120**	**76.7**	**72.7**	**80.2**	**544**	**108**	**80.4**	**76.6**	**83.7**
	Negative	Overall	860	168	79.9	76.7	82.7	868	147	82.8	80.0	85.3	858	105	88.0	85.5	90.2
		No Chemo	437	55	87.7	83.5	90.8	445	42	91.3	88.1	93.7	447	33	92.7	89.5	95.0
		Prior Chemo	**423**	**113**	**71.9**	**66.8**	**76.3**	**423**	**105**	**73.9**	**69.1**	**78.0**	**411**	**72**	**83.1**	**78.8**	**86.5**
	Positive	Overall	117	31	68.3	57.5	76.9	119	16	85.4	77.3	90.8	130	31	75.2	66.4	82.0
		No Chemo	23	3	-	-	-	17	3	-	-	-	13	0	-	-	-
		Prior Chemo	94	28	-	-	-	102	13	-	-	-	117	31	-	-	-
	Unknown/Not done	Overall	41	9	-	-	-	28	4	-	-	-	26	7	-	-	-
		No Chemo	16	2	-	-	-	11	2	-	-	-	10	2	-	-	-
		Prior Chemo	25	7	-	-	-	17	2	-	-	-	16	5	-	-	-
BCFI	**Overall**	**Overall**	1018	176	82.0	79.2	84.5	1015	142	85.8	83.3	87.9	1014	119	88.2	85.9	90.2
		No Chemo	**476**	**39**	**91.4**	**87.8**	**94.0**	**473**	**33**	**93.6**	**90.9**	**95.6**	**470**	**23**	**95.4**	**92.8**	**97.1**
		Prior Chemo	542	137	73.6	69.3	77.4	542	109	78.9	75.0	82.3	544	96	82.3	78.6	85.4
	Negative	Overall	860	138	83.4	80.4	86.0	868	126	85.3	82.7	87.6	858	85	90.3	87.9	92.2
		No Chemo	437	35	91.8	88.0	94.4	445	30	93.9	91.1	95.9	447	22	95.5	92.8	97.2
		Prior Chemo	423	103	74.7	69.8	78.9	423	96	76.3	71.7	80.3	411	63	84.8	80.6	88.1
	Positive	Overall	117	31	68.3	57.5	76.9	119	13	88.1	80.4	93.0	130	28	77.5	68.8	84.0
		No Chemo	23	3	-	-	-	17	2	-	-	-	13	0	-	-	-
		Prior Chemo	94	28	-	-	-	102	11	-	-	-	117	28	-	-	-
	Unknown/Not done	Overall	41	7	-	-	-	28	3	-	-	-	26	6	-	-	-
		No Chemo	16	1	-	-	-	11	1	-	-	-	10	1	-	-	-
		Prior Chemo	25	6	-	-	-	17	2	-	-	-	16	5	-	-	-
DRFI	**Overall**	**Overall**	**1018**	**115**	**88.4**	**86.0**	**90.3**	**1015**	**104**	**89.4**	**87.2**	**91.2**	**1014**	**87**	**91.2**	**89.2**	**92.9**
		No Chemo	476	10	97.8	95.6	99.0	473	11	97.8	95.7	98.9	470	5	99.3	97.9	99.8
		Prior Chemo	**542**	**105**	**80.0**	**76.0**	**83.3**	**542**	**93**	**82.1**	**78.3**	**85.2**	**544**	**82**	**84.5**	**81.0**	**87.5**
	Negative	Overall	860	89	89.6	87.1	91.6	868	91	89.3	86.9	91.3	858	58	93.2	91.2	94.8
		No Chemo	437	9	97.9	95.5	99.0	445	9	98.3	96.4	99.2	447	5	99.3	97.8	99.8
		Prior Chemo	**423**	**80**	**80.8**	**76.4**	**84.5**	**423**	**82**	**79.8**	**75.3**	**83.5**	**411**	**53**	**86.8**	**82.8**	**89.9**
	Positive	Overall	117	22	78.6	69.2	85.4	119	11	89.6	81.9	94.2	130	25	79.9	71.4	86.1
		No Chemo	23	1	-	-	-	17	2	-	-	-	13	0	-	-	-
		Prior Chemo	94	21	-	-	-	102	9	-	-	-	117	25	-	-	-
	Unknown/Not done	Overall	41	4	-	-	-	28	2	-	-	-	26	4	-	-	-
		No Chemo	16	0	-	-	-	11	0	-	-	-	10	0	-	-	-
		Prior Chemo	25	4	-	-	-	17	2	-	-	-	16	4	-	-	-
OS	**Overall**	**Overall**	**1018**	**88**	**91.5**	**89.4**	**93.2**	**1015**	**61**	**93.3**	**91.4**	**94.8**	**1014**	**76**	**92.1**	**90.0**	**93.7**
		No Chemo	476	5	98.8	97.1	99.5	473	10	97.9	95.7	98.9	470	9	97.7	95.6	98.8
		Prior Chemo	**542**	**83**	**85.1**	**81.5**	**88.1**	**542**	**51**	**89.4**	**86.1**	**91.9**	**544**	**67**	**87.2**	**83.8**	**90.0**
	Negative	Overall	860	68	92.2	89.9	93.9	868	53	93.4	91.3	95.0	858	53	93.4	91.3	95.0
		No Chemo	437	4	99.0	97.4	99.6	445	7	98.7	97.0	99.5	447	9	97.7	95.5	98.8
		Prior Chemo	**423**	**64**	**85.2**	**81.0**	**88.5**	**423**	**46**	**87.7**	**83.7**	**90.8**	**411**	**44**	**88.7**	**84.8**	**91.7**
	Positive	Overall	117	16	86.0	77.4	91.5	119	5	95.1	88.5	97.9	130	19	85.9	77.7	91.2

			Tamoxifen					Tamoxifen-OS					Exemestane-OS				
			N Pts	**N Events**	**8-yr Rate (%)**	**95% Lower CI**	**95% Upper CI**	**N Pts**	**N Events**	**8-yr Rate (%)**	**95% Lower CI**	**95% Upper CI**	**N Pts**	**N Events**	**8-yr Rate (%)**	**95% Lower CI**	**95% Upper CI**
		No Chemo	23	0	-	-	-	17	1	-	-	-	13	0	-	-	-
		Prior Chemo	94	16	-	-	-	102	4	-	-	-	117	19	-	-	-
	Unknown/Not done	Overall	41	4	-	-	-	28	3	-	-	-	26	4	-	-	-
		No Chemo	16	1	-	-	-	11	2	-	-	-	10	0	-	-	-
		Prior Chemo	25	3	-	-	-	17	1	-	-	-	16	4	-	-	-

Table S2. Sites of first disease-free survival (DFS) event after a median follow-up in SOFT of 8 years, overall and according to chemotherapy cohort and treatment assignment. (A) denominator is all patients; (B) denominator is patients who had a DFS event. (C) Deaths without preceding cancer event.

A	**Chemotherapy Cohort**				**Treatment Assignment**							
	No Chemo		**Prior Chemo**		**Tamoxifen**		**Tamoxifen-OS**		**Exemestane -OS**		**Overall**	
	N	%	N	%	N	%	N	%	N	%	N	%
No. of patients	*1419*	*100.0*	*1628*	*100.0*	*1018*	*100.0*	*1015*	*100.0*	*1014*	*100.0*	*3047*	*100.0*
DFS event												
No	1277	90.0	1252	76.9	810	79.6	848	83.5	871	85.9	2529	83.0
Yes	142	10.0	376	23.1	208	20.4	167	16.5	143	14.1	518	17.0
Site of first DFS event												
No failure	1277	90.0	1252	76.9	810	79.6	848	83.5	871	85.9	2529	83.0
Local	23	1.6	41	2.5	29	2.8	17	1.7	18	1.8	64	2.1
Contralateral breast ± above	33	2.3	18	1.1	25	2.5	14	1.4	12	1.2	51	1.7
Regional ± above	14	1.0	27	1.7	19	1.9	15	1.5	7	0.7	41	1.3
Soft tissue/ distant LN ± above	1	0.1	5	0.3	3	0.3	2	0.2	1	0.1	6	0.2
Bone ± above	11	0.8	113	6.9	40	3.9	40	3.9	44	4.3	124	4.1
Viscera ± above	13	0.9	136	8.4	59	5.8	54	5.3	36	3.6	149	4.9
Second (non-breast) malignancy	40	2.8	30	1.8	25	2.5	24	2.4	21	2.1	70	2.3
Death without preceding cancer event	6	0.4	3	0.2	6	0.6	1	0.1	2	0.2	9	0.3
Death, recurrence suspected	1	0.1	2	0.1	1	0.1	-	-	2	0.2	3	0.1
Death, no recurrence information	-	-	1	0.1	1	0.1	-	-	-	-	1	0.0

B	**Chemotherapy Cohort**				**Treatment Assignment**							
	No Chemo		**Prior Chemo**		**Tamoxifen**		**Tamoxifen -OS**		**Exemestane -OS**		**Overall**	
	N	%	N	%	N	%	N	%	N	%	N	%
No. of patients having DFS events	*142*	*100.0*	*376*	*100.0*	*208*	*100.0*	*167*	*100.0*	*143*	*100.0*	*518*	*100.0*
Site of first DFS event												
Local	23	16.2	41	10.9	29	13.9	17	10.2	18	12.6	64	12.4
Contralateral breast ± above	33	23.2	18	4.8	25	12.0	14	8.4	12	8.4	51	9.8
Regional ± above	14	9.9	27	7.2	19	9.1	15	9.0	7	4.9	41	7.9
Soft tissue/ distant LN ± above	1	0.7	5	1.3	3	1.4	2	1.2	1	0.7	6	1.2
Bone ± above	11	7.7	113	30.1	40	19.2	40	24.0	44	30.8	124	23.9
Viscera ± above	13	9.2	136	36.2	59	28.4	54	32.3	36	25.2	149	28.8
Second (non-breast) malignancy	40	28.2	30	8.0	25	12.0	24	14.4	21	14.7	70	13.5
Death without preceding cancer event	6	4.2	3	0.8	6	2.9	1	0.6	2	1.4	9	1.7
Death, recurrence suspected	1	0.7	2	0.5	1	0.5	-	-	2	1.4	3	0.6
Death, no recurrence information	-	-	1	0.3	1	0.5	-	-	-	-	1	0.2

OS denotes ovarian function suppression; LN denotes lymph nodes.

C Treatment Assignment	Chemotherapy Stratum	Oral ET Duration (mos)	Ovarian Suppression (mos)	Overall Survival (mos)	Cause of Death
Tamoxifen	No chemo	32	--	32	Myocardial infarction
Tamoxifen	No chemo	60	--	75	Myocardial infarction
Tamoxifen	Prior chemo	57	--	129	Cardiogenic shock
Tamoxifen	No chemo	45	--	69	Multiple sclerosis
Tamoxifen	Prior chemo	20	--	20	Other-mixed drug intoxication
Tamoxifen	Prior chemo	4	--	4	Unknown cause (confirmed)
Tamoxifen-OS	No chemo	0	0	64	Unknown cause (confirmed)
Exemestane-OS	No chemo	22	22	23	Cirrhosis
Exemestane-OS	No chemo	6	7	8	Unknown cause (confirmed)

Notes: ET denotes endocrine therapy; OS ovarian function suppression. The 3 patients assigned to OS had GnRH agonist triptorelin as only method of OS. In cases of unknown cause (confirmed) of death, the absence of preceding cancer event was confirmed.

Table S3. Status of death relative to site of first disease-free survival (DFS) event, according to chemotherapy cohort and treatment assignment, after a median follow-up in SOFT of 8 years.

	Chemotherapy Cohort				Treatment Assignment							
	No chemo		Prior chemo		Tamoxifen		Tamoxifen -OS		Exemestane -OS		Overall	
	N	%	N	%	N	%	N	%	N	%	N	%
N Patients who died	*24*	*100.0*	*201*	*100.0*	*88*	*100.0*	*61*	*100.0*	*76*	*100.0*	*225*	*100.0*
Status of Death												
After breast cancer event	12	50.0	188	93.5	78	88.6	58	95.1	64	84.2	200	88.9
After second (non-breast) malignancy	5	20.8	7	3.5	2	2.3	2	3.3	8	10.5	12	5.3
Without preceding cancer event	6	25.0	3	1.5	6	6.8	1	1.6	2	2.6	9	4.0
Incomplete information	1	4.2	3	1.5	2	2.3	-	-	2	2.6	4	1.8

Table S4. Final status of protocol-assigned treatment in SOFT, overall and according to chemotherapy cohort and treatment assignment.

Status of Protocol-assigned Treatment	Chemotherapy Cohort				Treatment Assignment						Overall	
	No Chemo		Prior Chemo		Tamoxifen		Tamoxifen -OS		Exemestane -OS			
	N	%	N	%	N	%	N	%	N	%	N	%
No. of Patients	*1419*	*100.0*	*1628*	*100.0*	*1018*	*100.0*	*1015*	*100.0*	*1014*	*100.0*	*3047*	*100.0*
Status of protocol-assigned treatment overall												
Last known on protocol-assigned treatment	8	0.6	11	0.7	6	0.6	7	0.7	6	0.6	19	0.6
Completed protocol treatment as assigned	1119	78.9	1314	80.7	771	75.7	864	85.1	798	78.7	2433	79.8
Stopped all protocol-assigned treatment early	277	19.5	285	17.5	229	22.5	137	13.5	196	19.3	562	18.4
Never started protocol-assigned treatment	15	1.1	18	1.1	12	1.2	7	0.7	14	1.4	33	1.1
Status of protocol-assigned oral ET												
Last know on assigned oral ET	8	0.6	10	0.6	6	0.6	7	0.7	5	0.5	18	0.6
Completed assigned oral ET	1060	74.7	1228	75.4	771	75.7	812	80.0	705	69.5	2288	75.1
Stopped assigned oral ET early	332	23.4	367	22.5	229	22.5	188	18.5	282	27.8	699	22.9
Never started assigned oral ET	19	1.3	23	1.4	12	1.2	8	0.8	22	2.2	42	1.4
Status of induced ovarian suppression												
Last known on GnRH agonist	6	0.4	11	0.7	-	-	8	0.8	9	0.9	17	0.6
Completed OS	697	49.1	849	52.1	-	-	764	75.3	782	77.1	1546	50.7
Stopped GnRH agonist early	216	15.2	214	13.1	-	-	223	22.0	207	20.4	430	14.1
OS never started	24	1.7	12	0.7	-	-	20	2.0	16	1.6	36	1.2
N/A (SOFT tam alone)	476	33.5	542	33.3	1018	100.0	-	-	-	-	1018	33.4

Notes: ET denotes endocrine therapy.
OS: ovarian function suppression was GnRH agonist (triptorelin) intramuscular injection every 28 days, bilateral oophorectomy or bilateral ovarian irradiation; the choice of GnRH agonist, bilateral oophorectomy or bilateral ovarian irradiation was by patient preference and patients who began with GnRH agonist could opt to undergo ovarian surgery or irradiation at any time. In total 369/2029 (18.2%) of patients assigned to OS opted to undergo bilateral oophorectomy or bilateral ovarian irradiation at some point during adjuvant therapy.
For patients randomized to exemestane-OS, exemestane was to begin 6 to 8 weeks after initiation of OS to allow a decline in ovarian estrogen production, and patients who had been taking tamoxifen at the time of randomization were permitted to continue tamoxifen until exemestane was initiated.
Tamoxifen was to start at randomization and continue for 5 years from date of randomization.
Protocol-assigned endocrine therapy continued for 5 years from the date of randomization, and the protocol did not address the issue of extended adjuvant endocrine therapy beyond 5 years.

III. C. Efficacy of Exemestane Compared with Tamoxifen when Treated with Ovarian Suppression Figures and Tables

Figure S5. Randomization, Treatment and Follow-up for the Combined SOFT and TEXT Population.

CONSORT flow diagram showing the intention-to-treat population of 4717 patients included in the analysis. During follow-up, 577 of 4717 patients either withdrew consent or were lost to follow-up and were censored at date of last follow-up visit (median time to withdrawal or lost was 3.0 years [interquartile range, 1.0-5.5 years]); for 198 of 577 patients, the patient consented to continued submission of disease-recurrence and survival status from medical records or such updates were obtainable from tumor and vital registries according to protocol follow-up schedule and overall survival is censored at date last known alive (median follow-up 8.6 years [interquartile range, 6.4-9.9 years]).

SOFT denotes Suppression of Ovarian Function Trial, TEXT Tamoxifen and Exemestane Trial, E exemestane, T tamoxifen, OS ovarian suppression, ITT intention-to-treat.

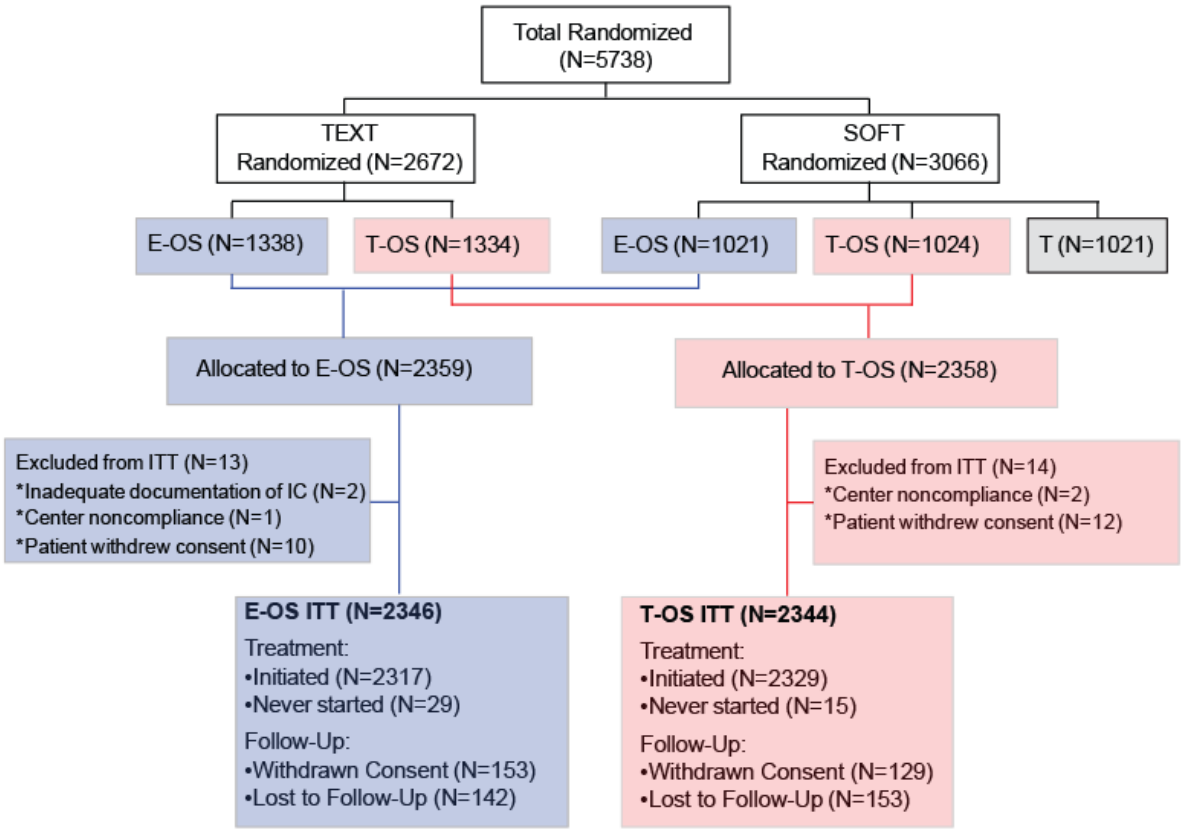
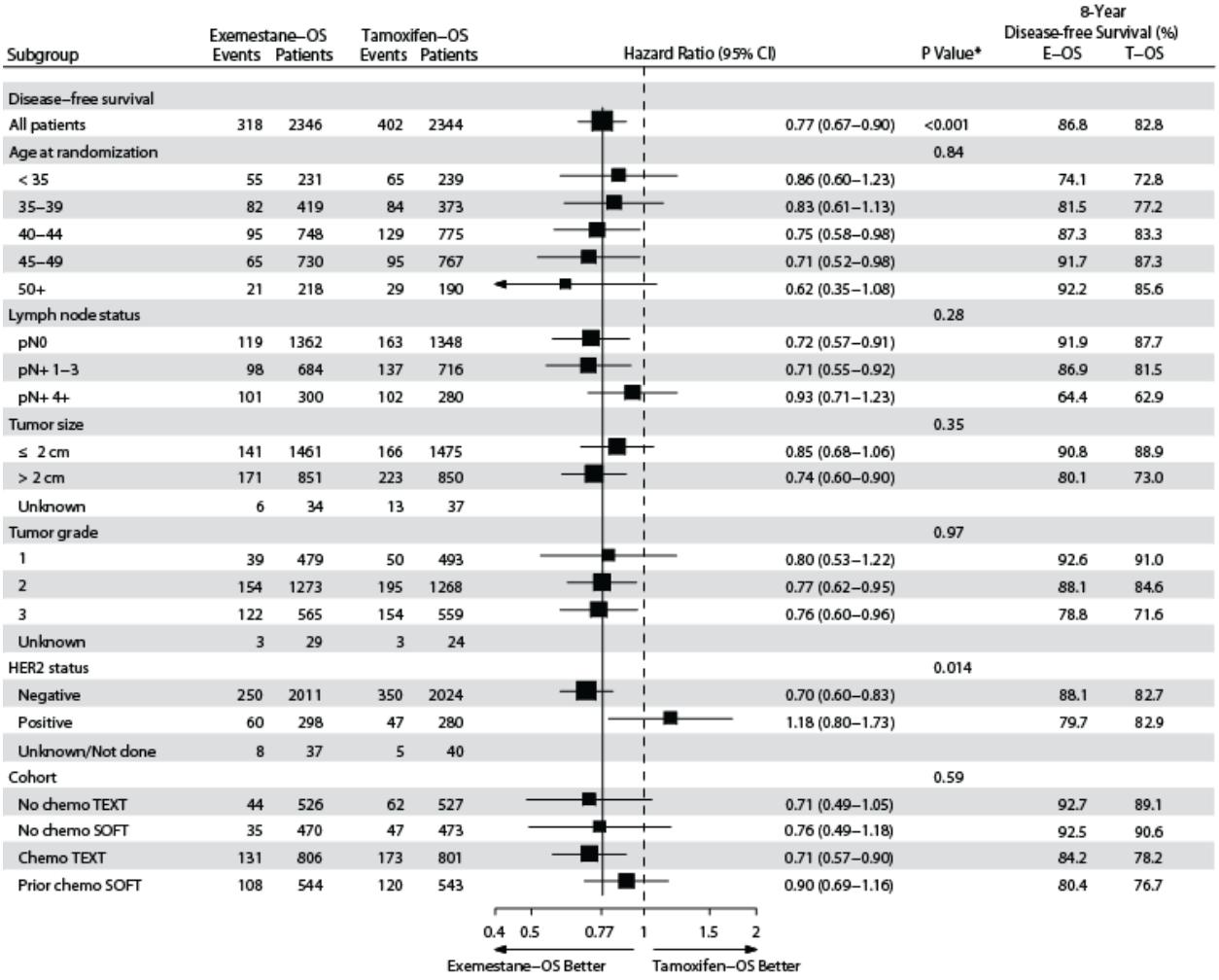


Figure S6. Results of Cox Proportional-hazards Models for the Disease-free Survival (DFS) Treatment Comparison of Exemestane Plus Ovarian Suppression vs. Tamoxifen Plus Ovarian Suppression, among All Patients and According to Subgroups in the Combined SOFT and TEXT Population.

The solid vertical line at 0.77 indicates the overall hazard-ratio estimate (the hazard ratio is for disease recurrence, second invasive cancer, or death). The 8-year values are Kaplan-Meier estimates of DFS. The x-axis is scaled according to the natural logarithm of the hazard ratio. The size of the squares is inversely proportional to the standard error of the hazard ratio. The median follow-up was 9 years.



Subgroup	Exemestane–OS Events	Exemestane–OS Patients	Tamoxifen–OS Events	Tamoxifen–OS Patients	Hazard Ratio (95% CI)	P Value*	8-Year Disease-free Survival (%) E–OS	8-Year Disease-free Survival (%) T–OS
Disease–free survival								
All patients	318	2346	402	2344	0.77 (0.67–0.90)	<0.001	86.8	82.8
Age at randomization						0.84		
< 35	55	231	65	239	0.86 (0.60–1.23)		74.1	72.8
35–39	82	419	84	373	0.83 (0.61–1.13)		81.5	77.2
40–44	95	748	129	775	0.75 (0.58–0.98)		87.3	83.3
45–49	65	730	95	767	0.71 (0.52–0.98)		91.7	87.3
50+	21	218	29	190	0.62 (0.35–1.08)		92.2	85.6
Lymph node status						0.28		
pN0	119	1362	163	1348	0.72 (0.57–0.91)		91.9	87.7
pN+ 1–3	98	684	137	716	0.71 (0.55–0.92)		86.9	81.5
pN+ 4+	101	300	102	280	0.93 (0.71–1.23)		64.4	62.9
Tumor size						0.35		
≤ 2 cm	141	1461	166	1475	0.85 (0.68–1.06)		90.8	88.9
> 2 cm	171	851	223	850	0.74 (0.60–0.90)		80.1	73.0
Unknown	6	34	13	37				
Tumor grade						0.97		
1	39	479	50	493	0.80 (0.53–1.22)		92.6	91.0
2	154	1273	195	1268	0.77 (0.62–0.95)		88.1	84.6
3	122	565	154	559	0.76 (0.60–0.96)		78.8	71.6
Unknown	3	29	3	24				
HER2 status						0.014		
Negative	250	2011	350	2024	0.70 (0.60–0.83)		88.1	82.7
Positive	60	298	47	280	1.18 (0.80–1.73)		79.7	82.9
Unknown/Not done	8	37	5	40				
Cohort						0.59		
No chemo TEXT	44	526	62	527	0.71 (0.49–1.05)		92.7	89.1
No chemo SOFT	35	470	47	473	0.76 (0.49–1.18)		92.5	90.6
Chemo TEXT	131	806	173	801	0.71 (0.57–0.90)		84.2	78.2
Prior chemo SOFT	108	544	120	543	0.90 (0.69–1.16)		80.4	76.7

*P-value for “All Patients” is the stratified log-rank test; for other variables, P-value is test of heterogeneity of the treatment effect across subgroups, using test of treatment-by-variable interaction from stratified Cox model, with “Unknown” or “Unknown/Not done” group omitted from the test.

Abbreviations: CI denotes confidence interval, E exemestane, T tamoxifen, OS ovarian suppression.

Figure S7A. Kaplan-Meier Estimates of Disease-free Survival, Freedom from Recurrence of Breast Cancer, Freedom from Recurrence of Breast Cancer at a Distant Site, and Overall Survival after a Median Follow-up of 9 Years in the Combined SOFT and TEXT Population.

The hazard ratio in Panel A is for disease recurrence, second invasive cancer, or death. In Panels B and C the hazard ratios are for recurrence of breast cancer and recurrence of breast cancer at a distant site, respectively. The hazard ratio in Panel D is for death. The 8-year values are based on Kaplan-Meier estimates of the time to an event.

Figure S7B. Kaplan-Meier estimates of (A,B) disease-free survival, (C,D) freedom from breast cancer, (E,F) freedom from breast cancer at a distant site, and (G,H) overall survival, according to treatment assignment, among cohorts of patients who were selected to receive chemotherapy.

Figure S7C. Kaplan-Meier estimates of (A,B) disease-free survival, (C,D) freedom from breast cancer, (E,F) freedom from breast cancer at a distant site, and (G,H) overall survival, according to treatment assignment, among cohorts of patients who did not receive chemotherapy.

Abbreviations: CI denotes confidence interval, E exemestane, HR hazard ratio, OS ovarian suppression, pts patients, T tamoxifen.

Figure S7A

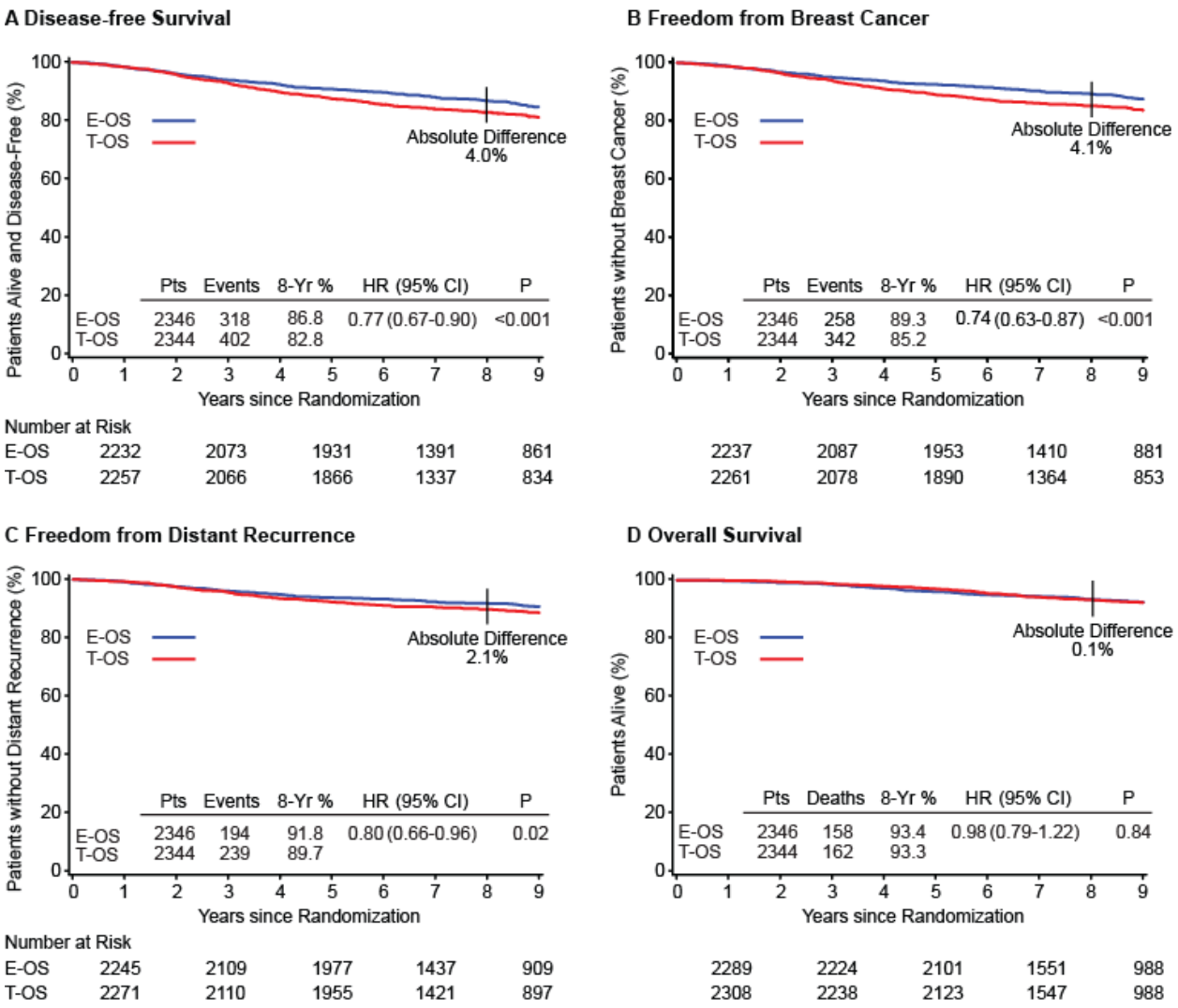

A Disease-free Survival
Patients Alive and Disease-Free (%)
E-OS
T-OS
Absolute Difference
4.0%
Pts Events 8-Yr % HR (95% CI) P
E-OS 2346 318 86.8 0.77 (0.67-0.90) <0.001
T-OS 2344 402 82.8
Years since Randomization
Number at Risk
E-OS 2232 2073 1931 1391 861
T-OS 2257 2066 1866 1337 834
B Freedom from Breast Cancer
Patients without Breast Cancer (%)
E-OS
T-OS
Absolute Difference
4.1%
Pts Events 8-Yr % HR (95% CI) P
E-OS 2346 258 89.3 0.74 (0.63-0.87) <0.001
T-OS 2344 342 85.2
Years since Randomization
2237 2087 1953 1410 881
2261 2078 1890 1364 853
C Freedom from Distant Recurrence
Patients without Distant Recurrence (%)
E-OS
T-OS
Absolute Difference
2.1%
Pts Events 8-Yr % HR (95% CI) P
E-OS 2346 194 91.8 0.80 (0.66-0.96) 0.02
T-OS 2344 239 89.7
Years since Randomization
Number at Risk
E-OS 2245 2109 1977 1437 909
T-OS 2271 2110 1955 1421 897
D Overall Survival
Patients Alive (%)
E-OS
T-OS
Absolute Difference
0.1%
Pts Deaths 8-Yr % HR (95% CI) P
E-OS 2346 158 93.4 0.98 (0.79-1.22) 0.84
T-OS 2344 162 93.3
Years since Randomization
2289 2224 2101 1551 988
2308 2238 2123 1547 988

Figure S7B

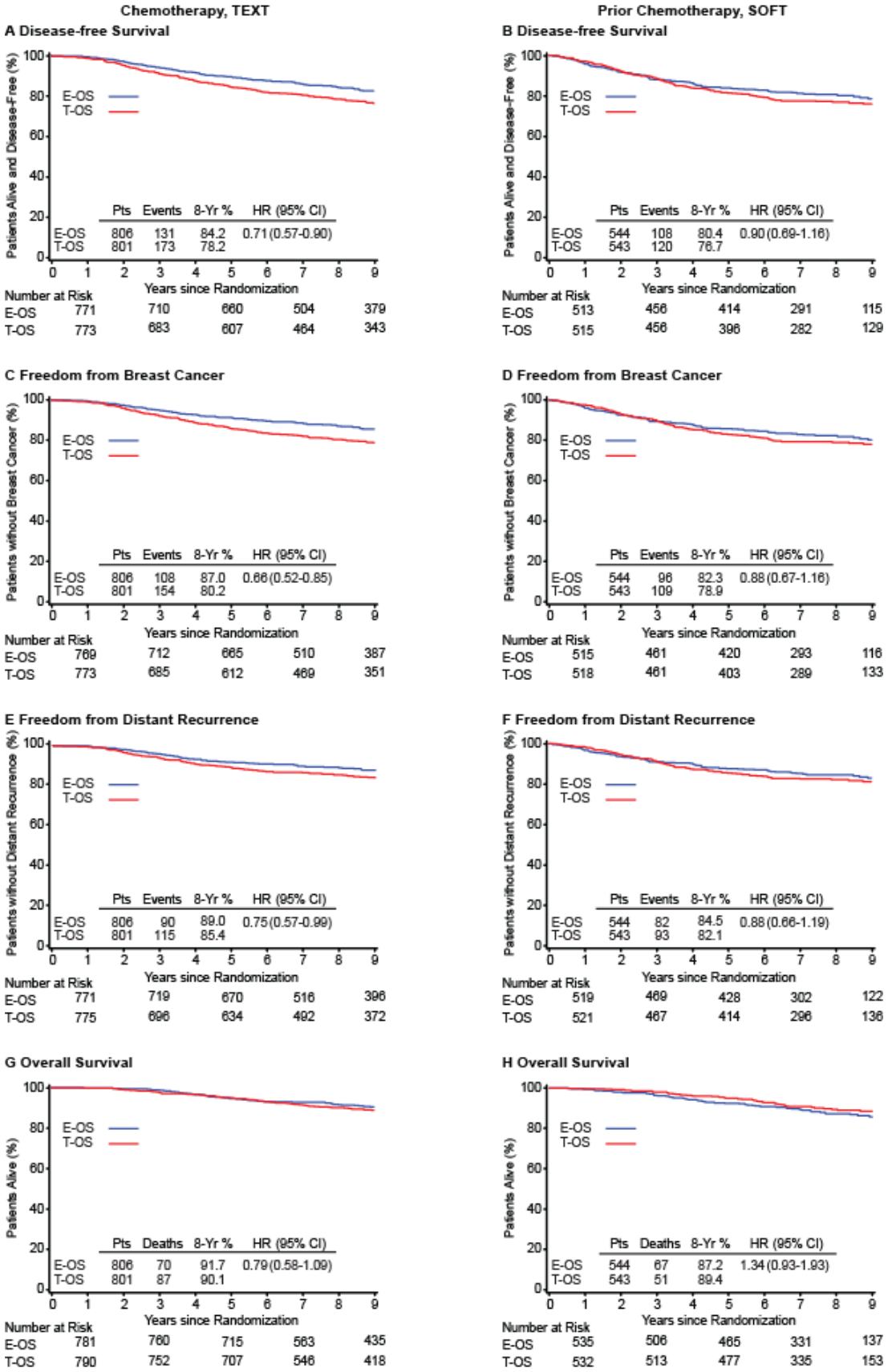

Chemotherapy, TEXT
A Disease-free Survival
Patients Alive and Disease-Free (%)
E-OS
T-OS
Pts Events 8-Yr % HR (95% CI)
E-OS 806 131 84.2 0.71 (0.57-0.90)
T-OS 801 173 78.2
Years since Randomization
Number at Risk
E-OS 771 710 660 504 379
T-OS 773 683 607 464 343
Prior Chemotherapy, SOFT
B Disease-free Survival
Patients Alive and Disease-Free (%)
E-OS
T-OS
Pts Events 8-Yr % HR (95% CI)
E-OS 544 108 80.4 0.90 (0.69-1.16)
T-OS 543 120 76.7
Years since Randomization
Number at Risk
E-OS 513 456 414 291 115
T-OS 515 456 396 282 129
C Freedom from Breast Cancer
Patients without Breast Cancer (%)
E-OS
T-OS
Pts Events 8-Yr % HR (95% CI)
E-OS 806 108 87.0 0.66 (0.52-0.85)
T-OS 801 154 80.2
Years since Randomization
Number at Risk
E-OS 769 712 665 510 387
T-OS 773 685 612 469 351
D Freedom from Breast Cancer
Patients without Breast Cancer (%)
E-OS
T-OS
Pts Events 8-Yr % HR (95% CI)
E-OS 544 96 82.3 0.88 (0.67-1.16)
T-OS 543 109 78.9
Years since Randomization
Number at Risk
E-OS 515 461 420 293 116
T-OS 518 461 403 289 133
E Freedom from Distant Recurrence
Patients without Distant Recurrence (%)
E-OS
T-OS
Pts Events 8-Yr % HR (95% CI)
E-OS 806 90 89.0 0.75 (0.57-0.99)
T-OS 801 115 85.4
Years since Randomization
Number at Risk
E-OS 771 719 670 516 396
T-OS 775 696 634 492 372
F Freedom from Distant Recurrence
Patients without Distant Recurrence (%)
E-OS
T-OS
Pts Events 8-Yr % HR (95% CI)
E-OS 544 82 84.5 0.88 (0.66-1.19)
T-OS 543 93 82.1
Years since Randomization
Number at Risk
E-OS 519 469 428 302 122
T-OS 521 467 414 296 136
G Overall Survival
Patients Alive (%)
E-OS
T-OS
Pts Deaths 8-Yr % HR (95% CI)
E-OS 806 70 91.7 0.79 (0.58-1.09)
T-OS 801 87 90.1
Years since Randomization
Number at Risk
E-OS 781 760 715 563 435
T-OS 790 752 707 546 418
H Overall Survival
Patients Alive (%)
E-OS
T-OS
Pts Deaths 8-Yr % HR (95% CI)
E-OS 544 67 87.2 1.34 (0.93-1.93)
T-OS 543 51 89.4
Years since Randomization
Number at Risk
E-OS 535 506 465 331 137
T-OS 532 513 477 335 153

Figure S7C

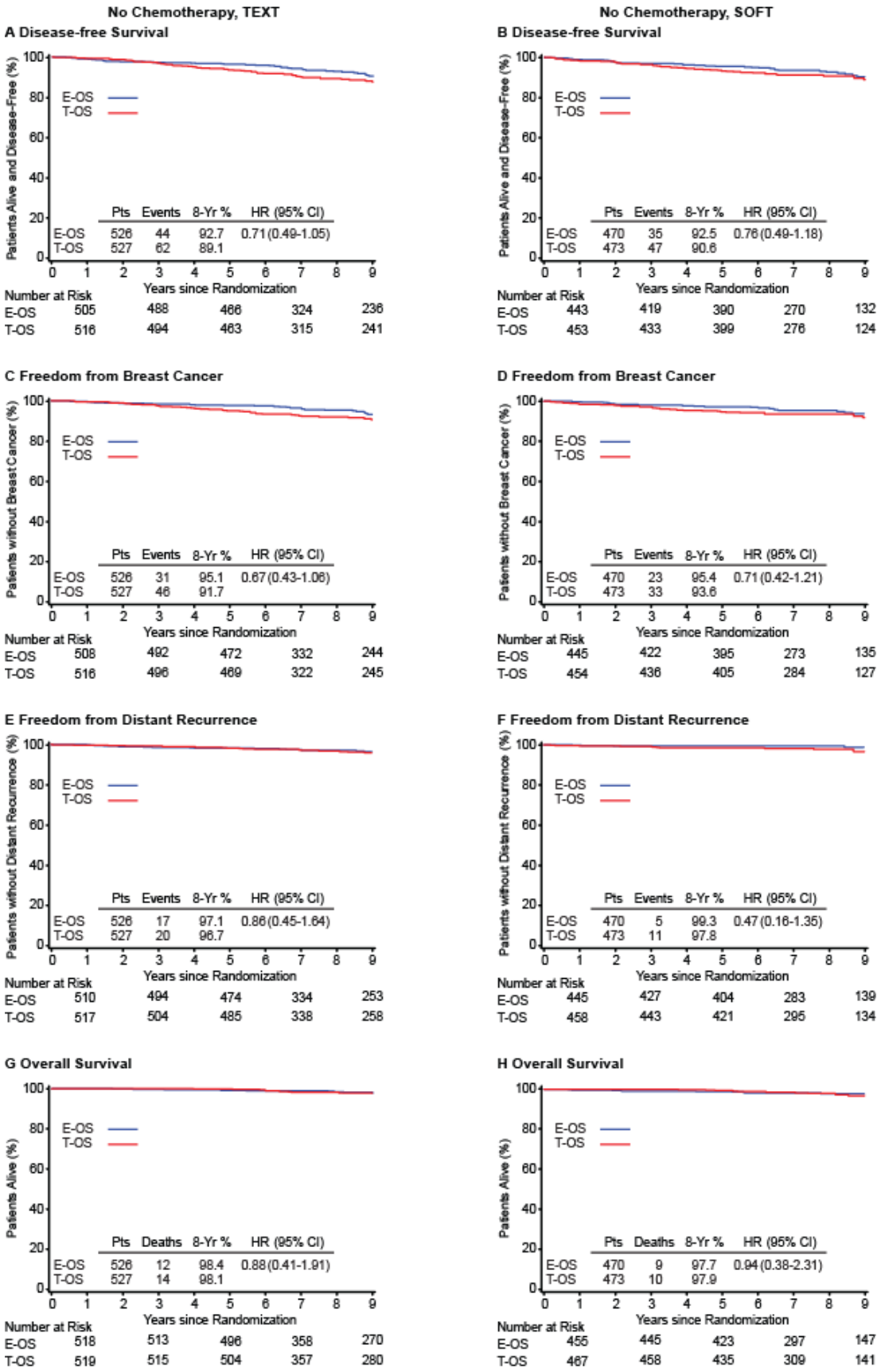
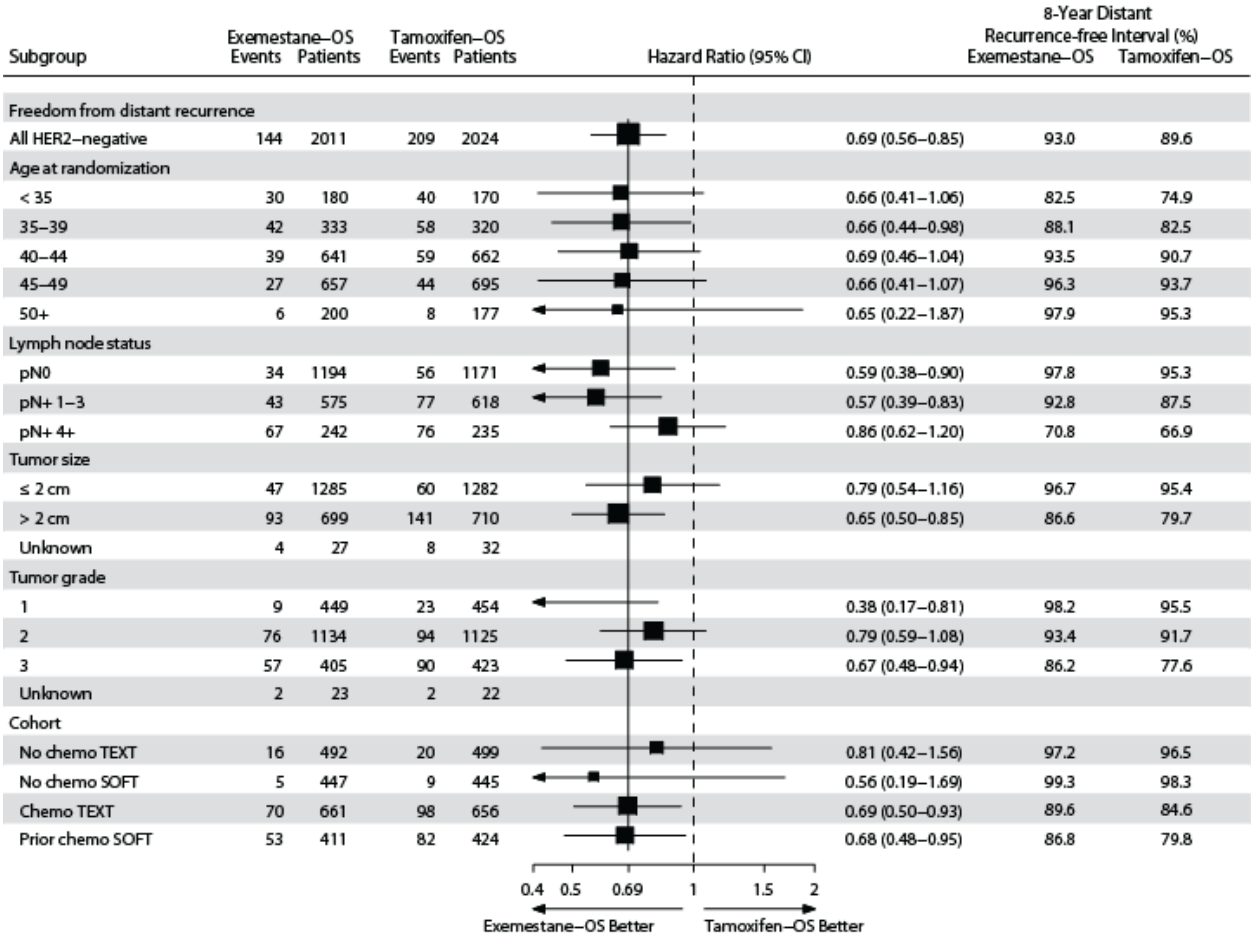

No Chemotherapy, TEXT
A Disease-free Survival
Patients Alive and Disease-Free (%)
E-OS
T-OS
Pts Events 8-Yr % HR (95% CI)
E-OS 526 44 92.7 0.71 (0.49-1.05)
T-OS 527 62 89.1
Years since Randomization
Number at Risk
E-OS 505 488 466 324 236
T-OS 516 494 463 315 241
No Chemotherapy, SOFT
B Disease-free Survival
Patients Alive and Disease-Free (%)
E-OS
T-OS
Pts Events 8-Yr % HR (95% CI)
E-OS 470 35 92.5 0.76 (0.49-1.18)
T-OS 473 47 90.6
Years since Randomization
Number at Risk
E-OS 443 419 390 270 132
T-OS 453 433 399 276 124
C Freedom from Breast Cancer
Patients without Breast Cancer (%)
E-OS
T-OS
Pts Events 8-Yr % HR (95% CI)
E-OS 526 31 95.1 0.67 (0.43-1.06)
T-OS 527 46 91.7
Years since Randomization
Number at Risk
E-OS 508 492 472 332 244
T-OS 516 496 469 322 245
D Freedom from Breast Cancer
Patients without Breast Cancer (%)
E-OS
T-OS
Pts Events 8-Yr % HR (95% CI)
E-OS 470 23 95.4 0.71 (0.42-1.21)
T-OS 473 33 93.6
Years since Randomization
Number at Risk
E-OS 445 422 395 273 135
T-OS 454 436 405 284 127
E Freedom from Distant Recurrence
Patients without Distant Recurrence (%)
E-OS
T-OS
Pts Events 8-Yr % HR (95% CI)
E-OS 526 17 97.1 0.86 (0.45-1.64)
T-OS 527 20 96.7
Years since Randomization
Number at Risk
E-OS 510 494 474 334 253
T-OS 517 504 485 338 258
F Freedom from Distant Recurrence
Patients without Distant Recurrence (%)
E-OS
T-OS
Pts Events 8-Yr % HR (95% CI)
E-OS 470 5 99.3 0.47 (0.16-1.35)
T-OS 473 11 97.8
Years since Randomization
Number at Risk
E-OS 445 427 404 283 139
T-OS 458 443 421 295 134
G Overall Survival
Patients Alive (%)
E-OS
T-OS
Pts Deaths 8-Yr % HR (95% CI)
E-OS 526 12 98.4 0.88 (0.41-1.91)
T-OS 527 14 98.1
Years since Randomization
Number at Risk
E-OS 518 513 496 358 270
T-OS 519 515 504 357 280
H Overall Survival
Patients Alive (%)
E-OS
T-OS
Pts Deaths 8-Yr % HR (95% CI)
E-OS 470 9 97.7 0.94 (0.38-2.31)
T-OS 473 10 97.9
Years since Randomization
Number at Risk
E-OS 455 445 423 297 147
T-OS 467 458 435 309 141

Figure S8. Results of Cox Proportional-hazards Models for the Treatment Comparisons of Freedom from Recurrence of Breast Cancer at a Distant Site, among All Patients with HER2-negative Disease and According to Subgroups in the Combined SOFT and TEXT Population.

The solid vertical line at 0.69 indicates the overall hazard-ratio estimate for recurrence of breast cancer at a distant site for all patients having HER2-negative disease. The 8-year values are based on Kaplan-Meier estimates of freedom from distant recurrence. The x-axis is scaled according to the natural logarithm of the hazard ratio. The size of the squares is inversely proportional to the standard error of the hazard ratio. The median follow-up was 9 years.

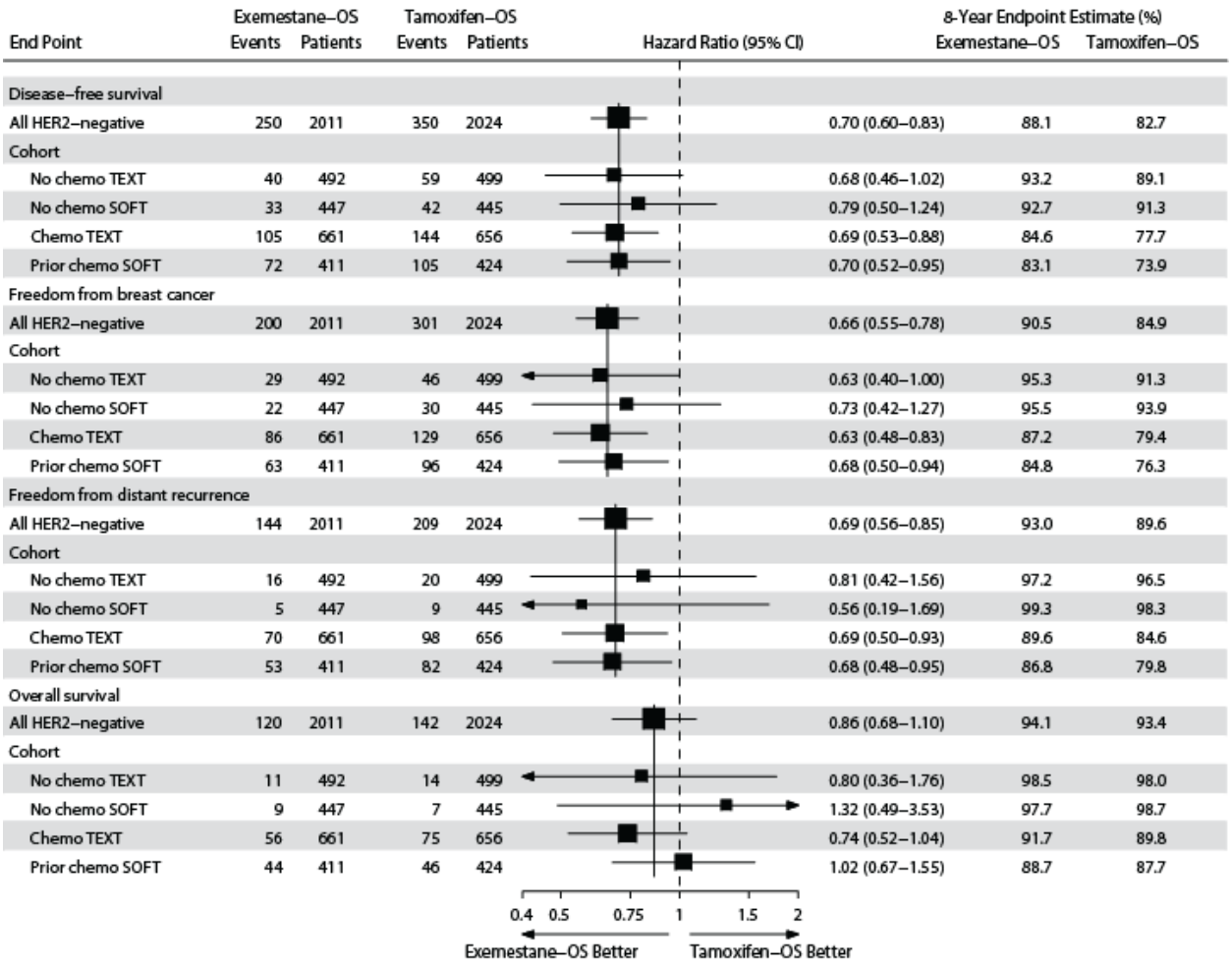


Note: Tests of heterogeneity of the treatment effect across subgroups were not performed within this subgroup of patients having HER2-negative disease. Widths of CIs were not adjusted for multiplicity of testing. Inference from these analyses should be viewed as preliminary.

Abbreviations: OS denotes ovarian suppression, CI confidence interval.

Figure S9. Results of Cox Proportional-hazards Models for the Treatment Comparisons of Four End Points, among Patients in the Combined SOFT and TEXT Population with HER2-negative Disease, Overall and According to Cohort.

The solid vertical lines at 0.70, 0.66, 0.69, and 0.86 indicate the overall hazard-ratio estimates for the four endpoints of disease-free survival (hazard ratio for disease recurrence, second invasive cancer, or death), freedom from recurrence of breast cancer (hazard ratio for recurrence), freedom from recurrence of breast cancer at a distant site (hazard ratio for recurrence), and overall survival (hazard ratio for death), respectively. The 8-year values are based on Kaplan-Meier estimates of the time to an event. The x-axis is scaled according to the natural logarithm of the hazard ratio. The size of the squares is inversely proportional to the standard error of the hazard ratio. The median follow-up was 9 years in the combined SOFT and TEXT population.

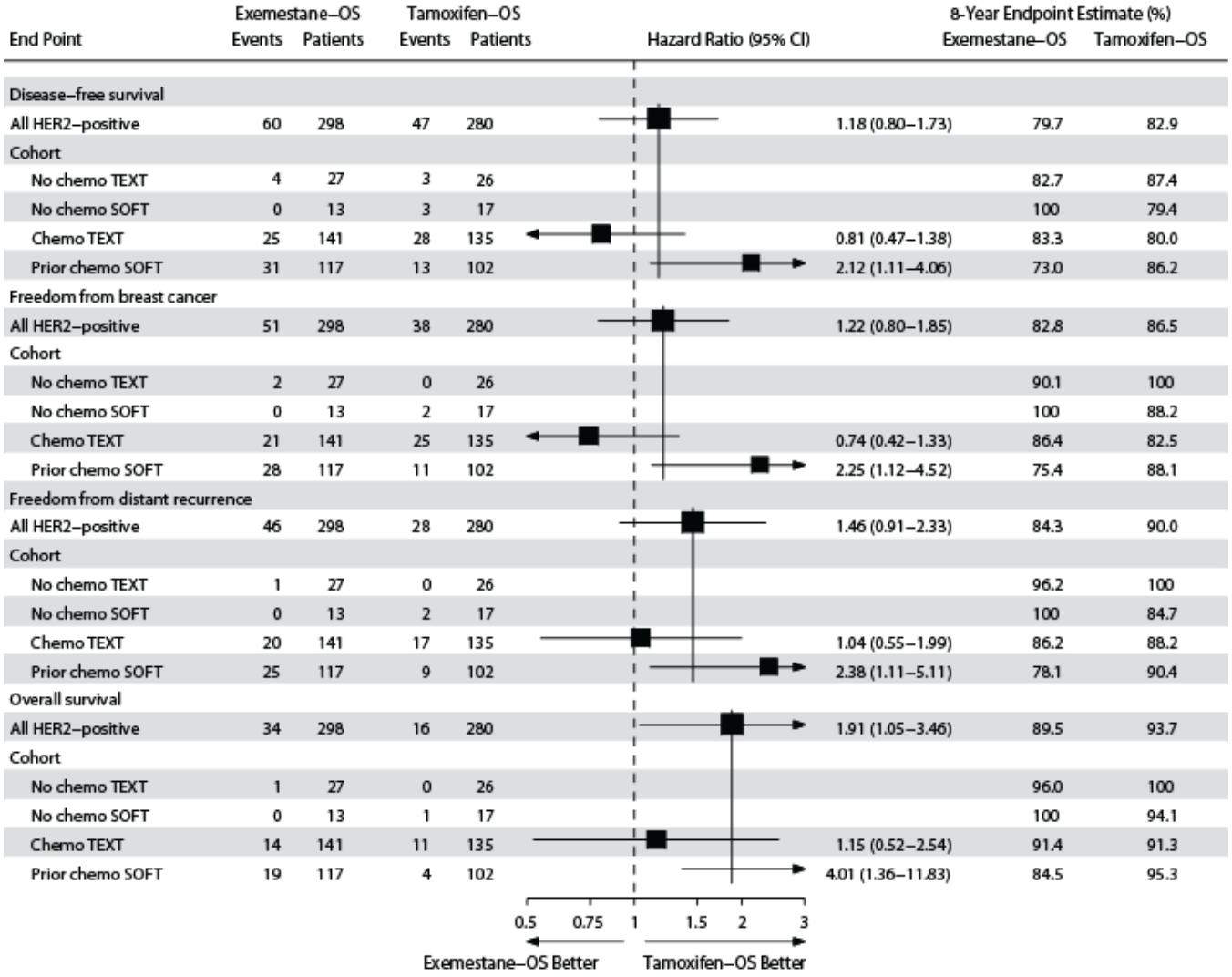


Note: Tests of heterogeneity of the treatment effect across cohorts were not performed within this subgroup of patients having HER2-negative disease. Widths of CIs were not adjusted for multiplicity of testing. Inference from these analyses should be viewed as preliminary.

Abbreviations: OS denotes ovarian suppression, CI confidence interval.

Figure S10. Results of Cox Proportional-hazards Models for the Treatment Comparisons of Four End Points, among 578 Patients in the Combined SOFT and TEXT Population with HER2-positive Disease, Overall and according to Cohort.

The solid vertical lines at 1.18, 1.22, 1.46, and 1.91 indicate the overall hazard-ratio estimates for the four endpoints, respectively. In the analysis of disease-free survival, the hazard ratio is for disease recurrence, second invasive cancer, or death. In the analyses of freedom from recurrence of breast cancer and freedom from recurrence of breast cancer at a distant site, the hazard ratios are for disease recurrence. In the overall survival analysis, the hazard ratio is for death. The 8-year values are based on Kaplan-Meier estimates of the time to an event. The x-axis is scaled according to the natural logarithm of the hazard ratio. The size of the squares is inversely proportional to the standard error of the hazard ratio. The median follow-up was 9 years.



Note: Tests of heterogeneity of the treatment effect across cohorts were not performed within this subgroup of patients having HER2-positive disease. Widths of CIs were not adjusted for multiplicity of testing. Inference from these analyses should be viewed as preliminary.

Abbreviations: OS denotes ovarian suppression, CI confidence interval.

Table S5. Kaplan-Meier estimates of 8-year end point rates with 95% confidence intervals, according to treatment assignment in the combined SOFT & TEXT population, overall and by HER2 status and cohort. Bolded values are those reported in the manuscript text.

			Exemestane-OS					Tamoxifen-OS				
			N Pts	N Events	8-yr Rate (%)	95% Lower CI	95% Upper CI	N Pts	N Events	8-yr Rate (%)	95% Lower CI	95% Upper CI
End point	**HER2**	**Cohort**										
DFS	**Overall**	**Overall**	**2346**	**318**	**86.8**	**85.3**	**88.2**	**2344**	**402**	**82.8**	**81.1**	**84.3**
		No chemo TEXT	526	44	92.7	89.8	94.8	527	62	89.1	85.8	91.6
		No chemo SOFT	470	35	92.5	89.3	94.8	473	47	90.6	87.3	93.0
		Chemo TEXT	806	131	84.2	81.3	86.7	801	173	78.2	75.0	81.1
		Prior chemo SOFT	544	108	80.4	76.6	83.7	543	120	76.7	72.7	80.2
	Negative	Overall	**2011**	**250**	**88.1**	**86.5**	**89.6**	**2024**	**350**	**82.7**	**80.9**	**84.4**
		No chemo TEXT	492	40	93.2	90.2	95.3	499	59	89.1	85.8	91.7
		No chemo SOFT	447	33	92.7	89.5	95.0	445	42	91.3	88.1	93.7
		Chemo TEXT	661	105	84.6	81.3	87.3	656	144	77.7	74.0	80.9
		Prior chemo SOFT	411	72	83.1	78.8	86.5	424	105	73.9	69.1	78.0
	Positive	Overall	298	60	79.7	74.4	84.0	280	47	82.9	77.6	87.0
		No chemo TEXT	27	4	-	-	-	26	3	-	-	-
		No chemo SOFT	13	0	-	-	-	17	3	-	-	-
		Chemo TEXT	141	25	83.3	75.8	88.7	135	28	80.0	71.8	86.1
		Prior chemo SOFT	117	31	73.0	63.6	80.3	102	13	86.2	77.4	91.8
	Unknown/Not done	Overall	37	8	-	-	-	40	5	-	-	-
		No chemo TEXT	7	0	-	-	-	2	0	-	-	-
		No chemo SOFT	10	2	-	-	-	11	2	-	-	-
		Chemo TEXT	4	1	-	-	-	10	1	-	-	-
		Prior chemo SOFT	16	5	-	-	-	17	2	-	-	-
BCFI	**Overall**	**Overall**	2346	258	89.3	87.9	90.6	2344	342	85.2	83.6	86.7
		No chemo TEXT	526	31	95.1	92.6	96.8	527	46	91.7	88.8	93.9
		No chemo SOFT	470	23	95.4	92.8	97.1	473	33	93.6	90.9	95.6
		Chemo TEXT	806	108	87.0	84.2	89.3	801	154	80.2	77.1	83.0
		Prior chemo SOFT	544	96	82.3	78.6	85.4	543	109	78.9	75.0	82.3
	Negative	Overall	2011	200	90.5	89.0	91.8	2024	301	84.9	83.1	86.5
		No chemo TEXT	492	29	95.3	92.7	97.0	499	46	91.3	88.2	93.6
		No chemo SOFT	447	22	95.5	92.8	97.2	445	30	93.9	91.1	95.9
		Chemo TEXT	661	86	87.2	84.2	89.7	656	129	79.4	75.9	82.5
		Prior chemo SOFT	411	63	84.8	80.6	88.1	424	96	76.3	71.7	80.3
	Positive	Overall	298	51	82.8	77.8	86.8	280	38	86.5	81.7	90.1
		No chemo TEXT	27	2	-	-	-	26	0	-	-	-
		No chemo SOFT	13	0	-	-	-	17	2	-	-	-
		Chemo TEXT	141	21	86.4	79.3	91.2	135	25	82.5	74.6	88.1
		Prior chemo SOFT	117	28	75.4	66.2	82.5	102	11	88.1	79.5	93.2
	Unknown/Not done	Overall	37	7	-	-	-	40	3	-	-	-
		No chemo TEXT	7	0	-	-	-	2	0	-	-	-
		No chemo SOFT	10	1	-	-	-	11	1	-	-	-
		Chemo TEXT	4	1	-	-	-	10	0	-	-	-
		Prior chemo SOFT	16	5	-	-	-	17	2	-	-	-
DRFI	**Overall**	**Overall**	**2346**	**194**	**91.8**	**90.5**	**92.9**	**2344**	**239**	**89.7**	**88.3**	**90.9**
		No chemo TEXT	526	17	97.1	95.1	98.3	527	20	96.7	94.6	98.0
		No chemo SOFT	470	5	99.3	97.9	99.8	473	11	97.8	95.7	98.9
		Chemo TEXT	806	90	89.0	86.5	91.1	801	115	85.4	82.6	87.8
		Prior chemo SOFT	544	82	84.5	81.0	87.5	543	93	82.1	78.3	85.2
	Negative	Overall	**2011**	**144**	**93.0**	**91.7**	**94.1**	**2024**	**209**	**89.6**	**88.0**	**90.9**
		No chemo TEXT	492	16	97.2	95.0	98.4	499	20	96.5	94.3	97.9
		No chemo SOFT	447	5	99.3	97.8	99.8	445	9	98.3	96.4	99.2
		Chemo TEXT	661	70	89.6	86.8	91.8	656	98	84.6	81.4	87.3
		Prior chemo SOFT	411	53	86.8	82.8	89.9	424	82	79.8	75.3	83.5
	Positive	Overall	298	46	84.3	79.4	88.1	280	28	90.0	85.6	93.1
		No chemo TEXT	27	1	-	-	-	26	0	-	-	-
		No chemo SOFT	13	0	-	-	-	17	2	-	-	-
		Chemo TEXT	141	20	86.2	79.0	91.1	135	17	88.2	81.2	92.7
		Prior chemo SOFT	117	25	78.1	69.0	84.8	102	9	90.4	82.4	94.9
	Unknown/Not done	Overall	37	4	-	-	-	40	2	-	-	-
		No chemo TEXT	7	0	-	-	-	2	0	-	-	-
		No chemo SOFT	10	0	-	-	-	11	0	-	-	-
		Chemo TEXT	4	0	-	-	-	10	0	-	-	-
		Prior chemo SOFT	16	4	-	-	-	17	2	-	-	-

			Exemestane-OS					Tamoxifen-OS				
			N Pts	**N Events**	**8-yr Rate (%)**	**95% Lower CI**	**95% Upper CI**	**N Pts**	**N Events**	**8-yr Rate (%)**	**95% Lower CI**	**95% Upper CI**
OS	**Overall**	**Overall**	**2346**	**158**	**93.4**	**92.2**	**94.4**	**2344**	**162**	**93.3**	**92.1**	**94.3**
		No chemo TEXT	526	12	98.4	96.7	99.3	527	14	98.1	96.3	99.1
		No chemo SOFT	470	9	97.7	95.6	98.8	473	10	97.9	95.7	98.9
		Chemo TEXT	806	70	91.7	89.4	93.5	801	87	90.1	87.6	92.1
		Prior chemo SOFT	544	67	87.2	83.8	90.0	543	51	89.4	86.1	91.9
	Negative	Overall	**2011**	**120**	**94.1**	**92.9**	**95.1**	**2024**	**142**	**93.4**	**92.1**	**94.5**
		No chemo TEXT	492	11	98.5	96.7	99.4	499	14	98.0	96.1	99.0
		No chemo SOFT	447	9	97.7	95.5	98.8	445	7	98.7	97.0	99.5
		Chemo TEXT	661	56	91.7	89.1	93.6	656	75	89.8	87.0	92.1
		Prior chemo SOFT	411	44	88.7	84.8	91.7	424	46	87.7	83.7	90.8
	Positive	Overall	298	34	89.5	85.1	92.7	280	16	93.7	89.9	96.1
		No chemo TEXT	27	1	-	-	-	26	0	-	-	-
		No chemo SOFT	13	0	-	-	-	17	1	-	-	-
		Chemo TEXT	141	14	91.4	85.0	95.2	135	11	91.3	84.8	95.1
		Prior chemo SOFT	117	19	84.5	75.7	90.3	102	4	95.3	88.0	98.2
	Unknown/Not done	Overall	37	4	-	-	-	40	4	-	-	-
		No chemo TEXT	7	0	-	-	-	2	0	-	-	-
		No chemo SOFT	10	0	-	-	-	11	2	-	-	-
		Chemo TEXT	4	0	-	-	-	10	1	-	-	-
		Prior chemo SOFT	16	4	-	-	-	17	1	-	-	-

Table S6. Sites of first disease-free survival (DFS) event after a median follow-up of 9 years in the combined SOFT and TEXT population. Values are number and percent of patients. (A) denominator is all patients; (B) denominator is patients who had a DFS event. (C) Deaths without preceding cancer event.

A.	**Cohort**								**Treatment Assignment**				**Overall**	
	No chemo TEXT		**No chemo SOFT**		**Chemo TEXT**		**Prior chemo SOFT**		**Exemestane-OS**		**Tamoxifen-OS**			
No. of patients	*1053*	*100.0*	*943*	*100.0*	*1607*	*100.0*	*1087*	*100.0*	*2346*	*100.0*	*2344*	*100.0*	*4690*	*100.0*
DFS event														
No	947	89.9	861	91.3	1303	81.1	859	79.0	2028	86.4	1942	82.8	3970	84.6
Yes	106	10.1	82	8.7	304	18.9	228	21.0	318	13.6	402	17.2	720	15.4
Site of DFS event														
No event	947	89.9	861	91.3	1303	81.1	859	79.0	2028	86.4	1942	82.8	3970	84.6
Local	22	2.1	13	1.4	33	2.1	22	2.0	42	1.8	48	2.0	90	1.9
Contralateral breast ± above	11	1.0	20	2.1	18	1.1	6	0.6	22	0.9	33	1.4	55	1.2
Regional ± above	9	0.9	8	0.8	20	1.2	14	1.3	13	0.6	38	1.6	51	1.1
Soft tissue / distant LN ± above	2	0.2	1	0.1	8	0.5	2	0.2	6	0.3	7	0.3	13	0.3
Bone ± above	17	1.6	6	0.6	71	4.4	78	7.2	81	3.5	91	3.9	172	3.7
Viscera ± above	16	1.5	8	0.8	111	6.9	82	7.5	93	4.0	124	5.3	217	4.6
Second (non-breast) malignancy	27	2.6	22	2.3	30	1.9	23	2.1	52	2.2	50	2.1	102	2.2
Death without preceding cancer event	2	0.2	3	0.3	7	0.4	-	-	4	0.2	8	0.3	12	0.3
Death, recurrence suspected	-	-	1	0.1	-	-	1	0.1	2	0.1	-	-	2	0.0
Death, no recurrence information	-	-	-	-	6	0.4	-	-	3	0.1	3	0.1	6	0.1

B.	**Cohort**								**Treatment Assignment**				**Overall**	
	No chemo TEXT		**No chemo SOFT**		**Chemo TEXT**		**Prior chemo SOFT**		**Exemestane-OS**		**Tamoxifen-OS**			
No. of patients having DFS events	*106*	*100.0*	*82*	*100.0*	*304*	*100.0*	*228*	*100.0*	*318*	*100.0*	*402*	*100.0*	*720*	*100.0*
Site of first DFS event														
Local	22	20.8	13	15.9	33	10.9	22	9.6	42	13.2	48	11.9	90	12.5
Contralateral breast ± above	11	10.4	20	24.4	18	5.9	6	2.6	22	6.9	33	8.2	55	7.6
Regional ± above	9	8.5	8	9.8	20	6.6	14	6.1	13	4.1	38	9.5	51	7.1
Soft tissue / distant LN ± above	2	1.9	1	1.2	8	2.6	2	0.9	6	1.9	7	1.7	13	1.8
Bone ± above	17	16.0	6	7.3	71	23.4	78	34.2	81	25.5	91	22.6	172	23.9
Viscera ± above	16	15.1	8	9.8	111	36.5	82	36.0	93	29.2	124	30.8	217	30.1
Second (non-breast) malignancy	27	25.5	22	26.8	30	9.9	23	10.1	52	16.4	50	12.4	102	14.2
Death without preceding cancer event	2	1.9	3	3.7	7	2.3	-	-	4	1.3	8	2.0	12	1.7
Death, recurrence suspected	-	-	1	1.2	-	-	1	0.4	2	0.6	-	-	2	0.3
Death, no recurrence information	-	-	-	-	6	2.0	-	-	3	0.9	3	0.7	6	0.8

OS denotes ovarian suppression; LN denotes lymph nodes

C Treatment Assignment	Cohort	Oral ET Duration (mos)	Ovarian Suppression (mos)	Overall Survival (mos)	Cause of Death
Tamoxifen-OS	TEXT No chemo	0	2†	139	Suicide
Tamoxifen-OS	TEXT Chemo	60	6†	88	Suicide
Tamoxifen-OS	TEXT Chemo	11	11	11	Other infection; Surgical complications
Tamoxifen-OS	TEXT Chemo	60	58†	70	Diabetes
Tamoxifen-OS	TEXT No chemo	60	61	61	Accident
Tamoxifen-OS	TEXT Chemo	13	10†	18	Other – Diphenhydramine intoxication
Tamoxifen-OS	SOFT No chemo	0	0	64	Unknown (confirmed)
Tamoxifen-OS	TEXT Chemo	18	22	23	Unknown (confirmed)
Exemestane-OS	TEXT Chemo	24	25	64	Cerebrovascular accident
Exemestane-OS	TEXT Chemo	62	62	103	Congestive heart failure
Exemestane-OS	SOFT No chemo	22	22	23	Cirrhosis
Exemestane-OS	SOFT No chemo	6	7	8	Unknown (confirmed)

Notes: ET denotes endocrine therapy; OS ovarian function suppression. †4 patients underwent oophorectomy after use of triptorelin; each other patient had triptorelin as only method of OS. In cases of unknown cause (confirmed) of death, the absence of preceding cancer event was confirmed.

Table S7. Status of death relative to site of first disease-free survival (DFS) event, according to cohort and treatment assignment, after a median follow-up in the combined SOFT and TEXT population of 9 years.

	Cohort								Treatment Assignment					
	No chemo TEXT		No chemo SOFT		Chemo TEXT		Prior chemo SOFT		Exemestane -OS		Tamoxifen -OS		Overall	
	N	%	N	%	N	%	N	%	N	%	N	%	N	%
N Patients who died	*26*	*100.0*	*19*	*100.0*	*157*	*100.0*	*118*	*100.0*	*158*	*100.0*	*162*	*100.0*	*320*	*100.0*
Status of Death														
After breast cancer event	21	80.8	10	52.6	134	85.4	112	94.9	134	84.8	143	88.3	277	86.6
After second (non-breast) malignancy	3	11.5	5	26.3	11	7.0	5	4.2	16	10.1	8	4.9	24	7.5
Without preceding cancer event	2	7.7	3	15.8	7	4.5	-	-	4	2.5	8	4.9	12	3.8
Incomplete information	-	-	1	5.3	5	3.2	1	0.8	4	2.5	3	1.9	7	2.2

Table S8. Final status of protocol-assigned treatment, overall and according to cohort and treatment assignment, for the combined SOFT and TEXT population.

Status of Protocol-assigned Treatment	Cohort								Treatment Assignment				Overall	
	No chemo TEXT		No chemo SOFT		Chemo TEXT		Prior chemo SOFT		Exemestane -OS		Tamoxifen -OS			
	N	%	N	%	N	%	N	%	N	%	N	%	N	%
No. of Patients	*1053*	*100.0*	*943*	*100.0*	*1607*	*100.0*	*1087*	*100.0*	*2346*	*100.0*	*2344*	*100.0*	*4690*	*100.0*
Status of protocol-assigned treatment overall														
Last known on protocol-assigned treatment	-	-	3	0.3	2	0.1	10	0.9	8	0.3	7	0.3	15	0.3
Completed protocol treatment as assigned	896	85.1	753	79.9	1370	85.3	909	83.6	1901	81.0	2027	86.5	3928	83.8
Stopped all protocol-assigned treatment early	150	14.2	173	18.3	220	13.7	160	14.7	408	17.4	295	12.6	703	15.0
Never started protocol-assigned treatment	7	0.7	14	1.5	15	0.9	8	0.7	29	1.2	15	0.6	44	0.9
Status of protocol-assigned oral ET														
Last know on assigned oral ET	-	-	3	0.3	1	0.1	9	0.8	6	0.3	7	0.3	13	0.3
Completed assigned oral ET	823	78.2	694	73.6	1219	75.9	823	75.7	1716	73.1	1843	78.6	3559	75.9
Stopped assigned oral ET early	211	20.0	228	24.2	326	20.3	242	22.3	555	23.7	452	19.3	1007	21.5
Never started assigned oral ET	19	1.8	18	1.9	61	3.8	13	1.2	69	2.9	42	1.8	111	2.4
Status of induced ovarian suppression														
Last known on GnRH agonist	2	0.2	6	0.6	3	0.2	11	1.0	13	0.6	9	0.4	22	0.5
Completed OS	852	80.9	697	73.9	1321	82.2	849	78.1	1872	79.8	1847	78.8	3719	79.3
Stopped GnRH agonist early	192	18.2	216	22.9	268	16.7	214	19.7	430	18.3	460	19.6	890	19.0
Never started OS	7	0.7	24	2.5	15	0.9	13	1.2	31	1.3	28	1.2	59	1.3

Notes: ET denotes endocrine therapy.
OS: ovarian function suppression was GnRH agonist (triptorelin) intramuscular injection every 28 days, bilateral oophorectomy or bilateral ovarian irradiation. In SOFT the choice of GnRH agonist, bilateral oophorectomy or bilateral ovarian irradiation was by patient preference and patients who began with GnRH agonist could opt to undergo ovarian surgery or irradiation at any time. In TEXT, OS began with GnRH agonist for at least 6 months, after which patients could opt to undergo ovarian surgery or irradiation at any time. In total 16.6% of patients opted to undergo bilateral oophorectomy or bilateral ovarian irradiation at some point during adjuvant therapy.
Protocol-assigned endocrine therapy continued for 5 years from the date of randomization, and the protocol did not address the issue of extended adjuvant endocrine therapy beyond 5 years.

III. D. Confidence Intervals for Targeted Adverse Events

Table S9. Targeted Adverse Events Reported During Treatment, According to Treatment Assignment, with 95% confidence intervals.*

	Tamoxifen (N=1005)						Tamoxifen plus Ovarian Suppression (N=2326)						Exemestane plus Ovarian Suppression (N=2317)					
	Any Event			Grade 3 or 4 Event			Any Event			Grade 3 or 4 Event			Any Event			Grade 3 or 4 Event		
Adverse Event	no. pts	%	(95% CI)	no. pts	%	(95% CI)	no. pts	%	(95% CI)	no. pts	%	(95% CI)	no. pts	%	(95% CI)	no. pts	%	(95% CI)
Allergic reaction or hypersensitivity	35	3.5	(2.4-4.8)	2	0.2	(0.0-0.7)	110	4.7	(3.9-5.7)	9	0.4	(0.2-0.7)	122	5.3	(4.4-6.3)	12	0.5	(0.3-0.9)
Injection-site reaction	4	0.4	(0.1-1.0)	0	0	–	189	8.1	(7.0-9.3)	1	0.0	(0.0-0.2)	174	7.5	(6.5-8.7)	1	0.0	(0.0-0.2)
Hot flushes	808	80.4	(77.8-82.8)	78	7.8	(6.2-9.6)	2175	93.5	(92.4-94.5)	284	12.2	(10.9-13.6)	2141	92.4	(91.2-93.5)	234	10.1	(8.9-11.4)
Depression	476	47.4	(44.2-50.5)	41	4.1	(2.9-5.5)	1195	51.4	(49.3-53.4)	108	4.6	(3.8-5.6)	1197	51.7	(49.6-53.7)	95	4.1	(3.3-5.0)
Sweating	492	49.0	(45.8-52.1)	–		–	1391	59.8	(57.8-61.8)	–		–	1286	55.5	(53.5-57.5)	–		–
Insomnia	470	46.8	(43.6-49.9)	30	3.0	(2.0-4.2)	1383	59.5	(57.4-61.5)	105	4.5	(3.7-5.4)	1375	59.3	(57.3-61.4)	89	3.8	(3.1-4.7)
Fatigue	612	60.9	(57.8-63.9)	34	3.4	(2.4-4.7)	1496	64.3	(62.3-66.3)	70	3.0	(2.4-3.8)	1450	62.6	(60.6-64.6)	75	3.2	(2.6-4.0)
Hypertension	181	18.0	(15.7-20.5)	57	5.7	(4.3-7.3)	550	23.6	(21.9-25.4)	188	8.1	(7.0-9.3)	564	24.3	(22.6-26.1)	168	7.3	(6.2-8.4)
Cardiac ischemia or infarction**	5	0.5	(0.2-1.2)	4	0.4	(0.1-1.0)	10	0.4	(0.2-0.8)	6	0.3	(0.1-0.6)	17	0.7	(0.4-1.2)	7	0.3	(0.1-0.6)
Thrombosis or embolism	22	2.2	(1.4-3.3)	17	1.7	(1.0-2.7)	53	2.3	(1.7-3.0)	47	2.0	(1.5-2.7)	27	1.2	(0.8-1.7)	20	0.9	(0.5-1.3)
Nausea	241	24.0	(21.4-26.7)	0	0	–	692	29.8	(27.9-31.7)	14	0.6	(0.3-1.0)	747	32.2	(30.3-34.2)	17	0.7	(0.4-1.2)
Musculoskeletal symptoms	703	70.0	(67.0-72.8)	67	6.7	(5.2-8.4)	1809	77.8	(76.0-79.4)	132	5.7	(4.8-6.7)	2082	89.9	(88.6-91.1)	263	11.4	(10.1-12.7)
Osteoporosis	138	13.7	(11.7-16.0)	1	0.1	(0.0-0.6)	648	27.9	(26.0-29.7)	7	0.3	(0.1-0.6)	977	42.2	(40.1-44.2)	10	0.4	(0.2-0.8)
Fractures	53	5.3	(4.0-6.8)	8	0.8	(0.3-1.6)	140	6.0	(5.1-7.1)	23	1.0	(0.6-1.5)	179	7.7	(6.7-8.9)	37	1.6	(1.1-2.2)
Vaginal dryness	426	42.4	(39.3-45.5)	–		–	1144	49.2	(47.1-51.2)	–		–	1245	53.7	(51.7-55.8)	–		–
Libido decrease	434	43.2	(40.1-46.3)	–		–	981	42.2	(40.2-44.2)	–		–	1056	45.6	(43.5-47.6)	–		–
Dyspareunia	242	24.1	(21.5-26.8)	16	1.6	(0.9-2.6)	636	27.3	(25.5-29.2)	35	1.5	(1.1-2.1)	733	31.6	(29.7-33.6)	56	2.4	(1.8-3.1)
Urinary incontinence	166	16.5	(14.3-19.0)	6	0.6	(0.2-1.3)	433	18.6	(17.1-20.3)	9	0.4	(0.2-0.7)	317	13.7	(12.3-15.1)	9	0.4	(0.2-0.7)
CNS cerebrovascular ischemia	6	0.6	(0.2-1.3)	4	0.4	(0.1-1.0)	10	0.4	(0.2-0.8)	7	0.3	(0.1-0.6)	6	0.3	(0.1-0.6)	5	0.2	(0.1-0.5)
CNS hemorrhage	15	1.5	(0.8-2.4)	0	0	–	26	1.1	(0.7-1.6)	2	0.1	(0.0-0.3)	19	0.8	(0.5-1.3)	1	0.0	(0.0-0.2)
Glucose intolerance†	18	1.8	(1.1-2.8)	4	0.4	(0.1-1.0)	68	2.9	(2.3-3.7)	23	1.0	(0.6-1.5)	63	2.7	(2.1-3.5)	15	0.6	(0.4-1.1)
Hyperglycemia†	20	2.0	(1.2-3.1)	1	0.1	(0.0-0.6)	92	4.0	(3.2-4.8)	20	0.9	(0.5-1.3)	71	3.1	(2.4-3.8)	14	0.6	(0.3-1.0)
Any targeted adverse event	962	95.7	(94.3-96.9)	247	24.6	(21.9-27.4)	2295	98.7	(98.1-99.1)	721	31.0	(29.1-32.9)	2288	98.7	(98.2-99.2)	748	32.3	(30.4-34.2)

*Data are for patients in the safety populations in SOFT and TEXT who initiated a protocol-assigned treatment, including: 1005 patients who were randomly assigned to receive tamoxifen in SOFT, and 4643 patients who were randomly assigned to receive tamoxifen plus ovarian suppression (2326 patients) or exemestane plus ovarian suppression (2317) in SOFT or TEXT. Data are missing for 4 patients (1 in the tamoxifen group and 3 in the tamoxifen plus ovarian suppression group) who initiated treatment but withdrew consent within 1 month after randomization and for whom no adverse-event data were submitted. Targeted adverse events and other adverse events of grade 3 or higher were categorized according to the Common Terminology Criteria for Adverse Events (CTCAE), version 3.0. CNS denotes central nervous system, and a dash indicates that grade 3 or 4 was not possible grades for the specified AE.

**One patient in the tamoxifen group in SOFT had grade 5 cardiac ischemia or infarction; no other grade 5 targeted AEs were reported.

†Glucose intolerance (diabetes) and hyperglycemia were added as targeted adverse events in 2011 and therefore may be underreported.

III. E. SOFT + TEXT Combined Analysis and ABCSG-12

Table S10. Features of the SOFT+TEXT Combined Analysis Population and ABCSG-12 Trial in Premenopausal Hormone-Receptor Positive Breast Cancer Comparing Adjuvant Aromatase Inhibitor (AI) Plus Ovarian Suppression versus Tamoxifen (Tam) Plus Ovarian Suppression.

	Trial	
Feature	**SOFT+TEXT Combined Analysis**	**ABCSG-12[3]**
Patients in analysis	4,690	1,803
Median age at randomization	43 years	45 years
Young patients	28% < age 40 years AI group 26% < age 40 years Tam group	25% ≤ age 40 years AI group 21% ≤ age 40 years Tam group
Premenopausal status determination	Defined by regular menses without exogenous hormones during the prior 6 months and/or E2 level in the premenopausal range; patients who had completed chemotherapy prior to entry into SOFT were required to have a premenopausal E2 level	Defined by a clinically-estimated regular menstrual cycle or a last menstrual cycle occurring not more than 1 year before study entry; if indeterminate menstrual status (eg, post-hysterectomy), serum FSH and LH were used.
Lymph node negative	58%	67%*
Tumor size ≤ 2 cm	62%	76%
No Chemotherapy	43%	85% ¥
Chemotherapy	57%	5% ¥
Duration trial therapy	5 years	3 years
AI studied	exemestane	anastrozole
GnRH agonist ovarian suppression studied	triptorelin	goserelin
Bisphosphonate therapy	Allowed if T-score ≤ 1.5 or if co-enrolled in randomized trial of bisphosphonate	50% Randomized to zoledronate 50% Randomized to no zoledronate
Median follow-up	9 years	7.9 years
DFS events	720	251
Deaths	320	86

E2 denotes estradiol, FSH follicle-stimulating hormone, LH luteinizing hormone, GnRH gonadotropin-releasing hormone.
*Missing data in 2% of patients; lymph node-positive limited to <10 positive nodes.
¥ Missing data in 9% of patients; all chemotherapy use was pre-operative.