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ORIGINAL REPORT

Treatment Efficacy, Adherence, and Quality of Life Among Women Younger Than 35 Years in the International Breast Cancer Study Group TEXT and SOFT Adjuvant Endocrine Therapy Trials

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ABSTRACT

Purpose
To describe benefits and toxicities of adjuvant endocrine therapies in women younger than 35 years with breast cancer (n = 582) enrolled in the Suppression of Ovarian Function Trial (SOFT) and Tamoxifen and Exemestane Trial (TEXT).

Methods
In SOFT, women still premenopausal after surgery with or without chemotherapy were randomly assigned to tamoxifen alone, tamoxifen plus ovarian function suppression (OFS), or exemestane plus OFS. In TEXT, all received OFS with or without concomitant chemotherapy and were randomly assigned to exemestane plus OFS or tamoxifen plus OFS. We summarize treatment efficacy, quality of life, and adherence of the cohort of women younger than 35 years in SOFT and TEXT, alongside data from the cohort of older premenopausal women.

Results
For 240 human epidermal growth factor receptor 2–negative patients younger than 35 years enrolled in SOFT after receiving chemotherapy, the 5-year breast cancer–free interval (BCFI) was 67.1% (95% CI, 54.6% to 76.9%) with tamoxifen alone, 75.9% with tamoxifen plus OFS (95% CI, 64.0% to 84.4%), and 83.2% with exemestane plus OFS (95% CI, 72.7% to 90.0%). For 145 human epidermal growth factor receptor 2–negative patients younger than 35 years in TEXT, 5-year BCFI was 79.2% (95% CI, 66.2% to 87.7%) with tamoxifen plus OFS and 81.6% (95% CI, 69.8% to 89.2%) with exemestane plus OFS. The most prominent quality of life symptom for patients younger than 35 years receiving OFS was vasomotor symptoms, with the greatest worsening from baseline at 6 months (on the order of 30 to 40 points), but loss of sexual interest and difficulties in becoming aroused were also clinically meaningful (≥ 8-point change). The level of symptom burden was similar in older premenopausal women. A total of 19.8% of women younger than 35 years stopped all protocol-assigned endocrine therapy early.

Conclusion
In women younger than 35 years with hormone receptor–positive breast cancer, adjuvant OFS combined with tamoxifen or exemestane produces large improvements in BCFI compared with tamoxifen alone. Menopausal symptoms are significant but are not worse than those seen in older premenopausal women.

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ASSOCIATED CONTENT

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Appendix
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Data Supplement
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INTRODUCTION

Women younger than 35 years with breast cancer have historically had poor outcomes, with increased rates of both local and distant recurrence.[1-5] Although women younger than 35 years have higher rates of triple-negative breast cancer, it is paradoxically in the hormone receptor (HR)–positive subgroup that the most significantly worse outcomes have been observed. Some data[6] come from earlier trials,

in which premenopausal women with HR-positive tumors received chemotherapy but no endocrine therapy, and the authors suggested that differences in outcomes were related to differential likelihood of undergoing chemotherapy-induced ovarian function suppression (OFS). However, age-related differences in outcomes persist in the face of endocrine therapy. In the US Intergroup INT0101 trial for node-positive HR-positive disease, women younger than 40 years treated with chemotherapy plus OFS (goserelin) with or without tamoxifen had 9-year disease-free survivals of 64% and 55%, versus 69% and 62% for premenopausal women age 40 years or older.[7] It has also been hypothesized that the difference in outcomes is related to a greater ratio of luminal B to luminal A cancers in women younger than 35 years.[8] Yet, a recent large analysis of US National Comprehensive Cancer Network data on women presenting with breast cancer between January 2000 and December 2007, when endocrine therapy was standard for all women with HR-positive disease, found significantly worse outcomes among women ≤ 40 years old specifically for the group with luminal A tumors.[9]

The Suppression of Ovarian Function Trial (SOFT) and Tamoxifen and Exemestane Trial (TEXT) have recently demonstrated that for premenopausal women with HR-positive breast cancer and high-risk clinicopathologic factors, treatment with OFS plus exemestane can produce an absolute improvement of 10% to 15% in 5-year breast cancer–free interval (BCFI).[10] In SOFT and TEXT, HR-positive/human epidermal growth factor receptor 2 (HER2)–negative women younger than age 35 years had a 5-year BCFI of 79%, versus 95% for women age 45 to 49 years.[10] Symptom-specific quality of life (QoL; focusing on symptoms related to endocrine therapy) was worse with the addition of OFS.[11,12] We hypothesized that women younger than 35 years would report more endocrine-related symptoms. We present a summary of benefits and risks of endocrine therapy that includes OFS specific to women younger than 35 years to help facilitate joint decision making.

METHODS

The designs and conduct of the TEXT and SOFT phase III trials have been described.[13-15] Ethics committees at participating centers approved the protocols, and all patients provided written informed consent. In both trials, eligible premenopausal women with surgically resected, invasive early-stage breast cancer with ≥ 10% estrogen receptor (ER)– and/or progesterone receptor (PR)-expressing cells were randomly assigned between November 2003 and March 2011.

TEXT enrolled 2,660 women in the intention-to-treat (ITT) population within 12 weeks after definitive surgery and randomly assigned them to 5 years of exemestane plus OFS or 5 years of tamoxifen plus OFS. OFS was achieved by gonadotropin-releasing hormone (GnRH) agonist triptorelin, bilateral oophorectomy, or ovarian irradiation. Chemotherapy was optional and, when administered, was started concurrently with triptorelin.

SOFT randomly assigned 3,047 women in the ITT population to 5 years of exemestane plus OFS or tamoxifen plus OFS or tamoxifen alone. Patients who did not receive chemotherapy were enrolled within 12 weeks after definitive surgery; those patients who received (neo)adjuvant chemotherapy were enrolled within 8 months after the final dose of chemotherapy, after a premenopausal estradiol level was confirmed.

The trial end points were: disease-free survival (DFS), defined as the time from random assignment to the first appearance of: invasive recurrence of breast cancer (local, regional, or distant), invasive contralateral breast cancer, second nonbreast invasive cancer, or death; BCFI, from random assignment to the recurrence of invasive breast cancer or invasive contralateral breast cancer; distant recurrence-free interval (DRFI), from random assignment to recurrence at a distant site; overall survival, from random assignment to death from any cause. Overall survival is not yet mature after a median follow-up of 6 years in TEXT and 5.6 years in SOFT.

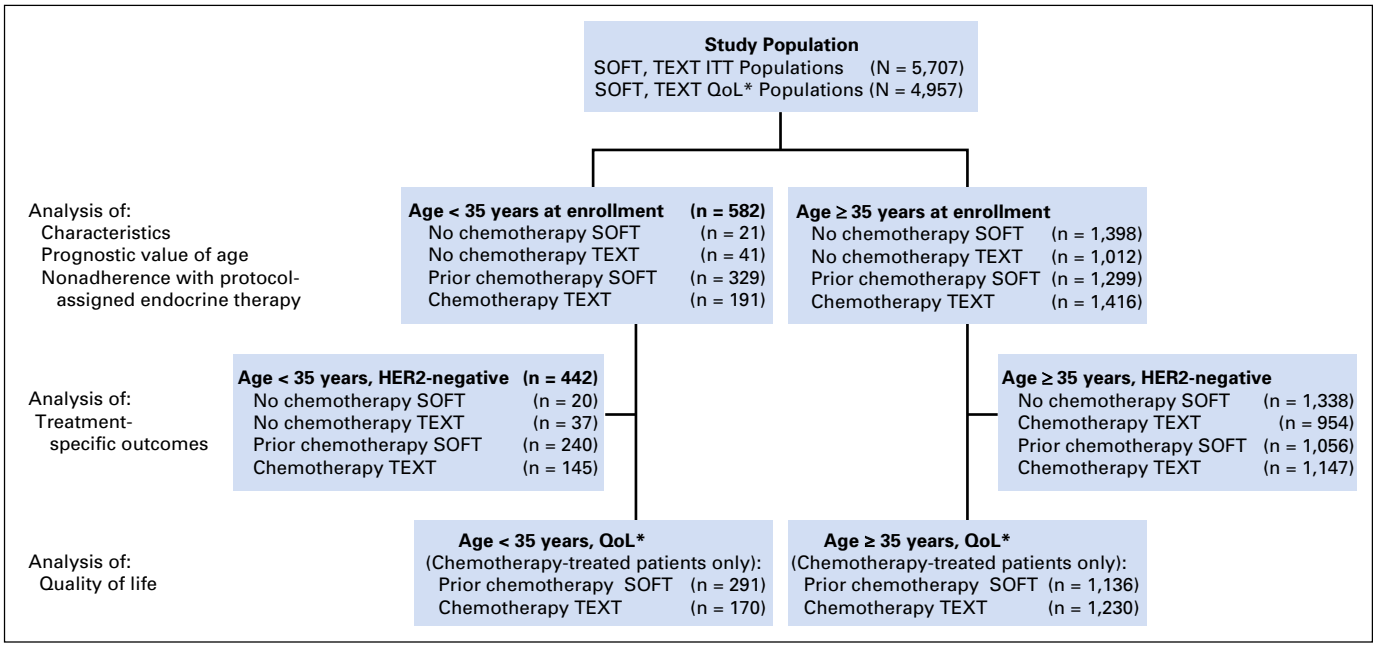

Fig 1. Flow diagram of analysis populations. (*) Quality-of-life (QoL) populations were 87% of the intention-to-treat (ITT) populations, after exclusion of patients having eligibility exemption and of patients at centers not compliant with QoL submission.[11,12] HER2, human epidermal growth factor receptor 2; SOFT, Suppression of Ovarian Function Trial; TEXT, Tamoxifen and Exemestane Trial.

Table 1. Patient, Tumor, and Treatment Characteristics According to Age at Random Assignment in the SOFT and TEXT Randomized Trials

Characteristic	Age at Random Assignment			
	< 35 Years		≥ 35 Years	
	No.	%	No.	%
No. patients	582	100.0	5,125	100.0
Trial/chemotherapy cohort				
No chemotherapy TEXT	41	7.0	1,012	19.7
No chemotherapy SOFT	21	3.6	1,398	27.3
Chemotherapy TEXT	191	32.8	1,416	27.6
Prior chemotherapy SOFT	329	56.5	1,299	25.3
Age at random assignment, years				
< 25	13	2.2	—	—
25-29	128	22.0	—	—
30-34	441	75.8	—	—
35-39	—	—	995	19.4
40-44	—	—	1,830	35.7
45-49	—	—	1,803	35.2
≥ 50	—	—	497	9.7
Race/ethnicity				
Other	14	2.4	117	2.3
Asian	29	5.0	144	2.8
Black/African American	16	2.7	143	2.8
Hispanic/Latino/South American native	71	12.2	250	4.9
White	452	77.7	4,471	87.2
BMI, kg/m^2				
Unknown	17	2.9	119	2.3
Normal (< 25)	341	58.6	2,699	52.7
Overweight (25 to < 30)	124	21.3	1,293	25.2
Obese (≥ 30)	100	17.2	1,014	19.8
Ever pregnant				
Unknown	5	0.9	33	0.6
No	221	38.0	789	15.4
Yes	356	61.2	4,303	84.0
Pregnant at diagnosis				
Unknown	5	0.9	31	0.6
No	563	96.7	5,073	99.0
Yes	14	2.4	21	0.4
Menstruation status at random assignment				
Unknown	8	1.4	90	1.8
Normal	381	65.5	3,643	71.1
Irregular (cycles continuing)	128	22.0	729	14.2
Persistent amenorrhea*	65	11.2	663	12.9
Hormone receptor status				
ER-positive/PR-positive	455	78.2	4,574	89.2
ER-positive/PR-negative	101	17.4	396	7.7
ER-negative/PR-positive	18	3.1	86	1.7
Other†	8	1.4	69	1.3
HER2 status				
Negative	442	75.9	4,495	87.7
Positive	140	24.1	630	12.3
Ki-67 expression by CPR				
Unknown (no tissue for CPR)	120	20.6	980	19.1
< 20%	166	28.5	2,440	47.6
≥ 20%	296	50.9	1,705	33.3
No. nodes positive				
Unknown	—	—	29	0.6
N0	259	44.5	3,096	60.4
N-positive 1-3	203	34.9	1,443	28.2
N-positive 4-9	86	14.8	405	7.9
N-positive ≥ 10	34	5.8	152	3.0
Tumor size, cm				
≤ 2	289	49.7	3,306	64.5
> 2-5	237	40.7	1,561	30.5
> 5	37	6.4	176	3.4
Unknown	19	3.3	82	1.6

(continued on following page)

Table 1. Patient, Tumor, and Treatment Characteristics According to Age at Random Assignment in the SOFT and TEXT Randomized Trials (continued)

Characteristic	Age at Random Assignment			
	< 35 Years		≥ 35 Years	
	No.	%	No.	%
Tumor grade				
1	63	10.8	1,181	23.0
2	266	45.7	2,756	53.8
3	243	41.8	1,107	21.6
Unknown	10	1.7	81	1.6
Vessel invasion (lymphatics and/or blood vessels)				
No	300	51.5	3,409	66.5
Yes	253	43.5	1,423	27.8
Not assessed/unknown	29	4.9	293	5.8
Primary invasive histology				
Ductal	537	92.3	4,259	83.1
Lobular	15	2.6	598	11.7
Other	30	5.2	268	5.2
Locoregional treatment				
Mastectomy, no radiotherapy	124	21.3	1,262	24.6
Mastectomy with radiotherapy	174	29.9	793	15.5
Other‡	16	2.7	64	1.2
BCS with radiotherapy	268	46.0	3,006	58.7
Axillary lymph node dissection				
Unknown	1	0.2	3	0.1
No (sentinel lymph node biopsy only)	158	27.1	2,134	41.6
Yes	423	72.7	2,988	58.3

NOTE. The distributions of all factors were significantly different according to age at random assignment ($P < .001$ by Fisher's exact tests).
Abbreviations: BCS, breast-conserving surgery; BMI, body mass index; CPR, central pathology review; ER, estrogen receptor; HER2, human epidermal growth factor receptor 2; PR, progesterone receptor; SOFT, Suppression of Ovarian Function Trial; TEXT, Tamoxifen and Exemestane Trial.
*Persistent amenorrhea was primarily among patients in SOFT who had received prior chemotherapy: 59 of 65 (91%) younger than 35 years and 564 of 663 (85%) age ≥ 35 years.
†Other includes ER-unknown and PR-unknown, or ER-negative and PR-negative (who were ineligible).
‡Other includes BCS without radiotherapy, or radiotherapy unknown; radiotherapy was required after BCS and optional after mastectomy.

The trials used the International Breast Cancer Study Group QoL core form and a symptom-specific module focusing on symptoms related to endocrine therapy at baseline, 6, 12, 18, and 24 months, and annually during years 3 to 6. All indicators were in the linear analog self-assessment format and ranged from 0 to 100, with higher numbers indicating a better QoL. A clinically significant change was conservatively defined as ≥ 8-point difference.[11,12]

Statistical Considerations

Comparisons of characteristics between age groups used Fisher's exact tests. The association of age younger than 35 years at random assignment with end points used Cox proportional hazard modeling, stratified by trial, chemotherapy receipt, and lymph node status and adjusted for other prognostic and treatment characteristics (number of positive lymph nodes, tumor size, grade, receptor status, HER2 status/therapy, local therapy) and treatment assignment. The distributions of time-to-event end points among patients with HER2-negative tumors were estimated using the Kaplan-Meier method. Adherence to protocol-assigned therapy was estimated from cumulative incidence of cessation, with competing risk of a DFS event, and compared between age groups using Gray's test. Changes in QoL indicators from baseline were summarized as mean and 95% CI, estimated using mixed-effects models (of all time points) adjusting for treatment assignment, with focus on estimates at the 6-, 24-, and 60-month time points among the chemotherapy cohorts.[11,12]

RESULTS

Study Population

A total of 5,707 women were enrolled in the SOFT and TEXT ITT populations (Fig 1). Of these, 582 (10.2%) were younger than 35 years at random assignment and form the basis of this analysis. This includes 11.5% and 8.7% of the SOFT and TEXT ITT populations, respectively.

Characteristics of the Cohort of Women Younger Than Age 35 Years

Although ER and/or PR positivity was only required to be ≥ 10% for enrollment, the vast majority of patients had strongly ER-positive/PR-positive tumors.[16] However, in the population younger than 35 years there was a higher percentage of women with ER-positive/PR-negative tumors (17.4% *v* 7.7% in premenopausal women ≥ 35 years old by local assessment). Overall, the women younger than 35 years enrolled had higher-risk tumor characteristics than the older premenopausal women (Table 1): 47.1% had a tumor > 2 cm versus 33.9% of women age ≥ 35 years, 55.5% (*v* 39.3%) had node-positive disease, 41.8% (*v* 21.6%) had grade 3 histology, 43.5% (*v* 27.8%) had lymphovascular invasion, and 50.9% (*v* 33.3%) had Ki-67 levels ≥ 20% on central pathology review. The majority of women younger than 35 years were treated with chemotherapy: 329 (94%) of 350 in SOFT and 191 (82%) of 232 in TEXT.

Independent Prognostic Value of Age

In the study population, age younger than 35 years at random assignment was associated with higher risk of a breast cancer event (hazard ratio [HR], 1.53; 95% CI, 1.24 to 1.88 *v* age ≥ 35 years), distant recurrence (HR, 1.52; 95% CI, 1.21 to 1.91), and DFS event

(HR, 1.43; 95% CI, 1.18 to 1.74) even after controlling for treatment and disease characteristics (which included HER2 status).

Treatment-Specific Outcomes of Women Younger Than 35 Years With HER2-Negative Disease

TEXT and SOFT began enrollment before the widespread use of adjuvant trastuzumab for patients with HER2-positive breast cancer. Because women enrolled in these trials with HER2-positive disease did not all receive anti-HER2 therapy according to current standards, we chose to exclude HER2-positive disease from the efficacy analysis for this report.

Four hundred forty-two women younger than 35 years had HER2-negative disease. After a median follow-up of 6.0 and 5.6 years in TEXT and SOFT, respectively, 102 (23%) had invasive breast cancer events (v 384 [8.5%] of 4,495 for ≥ 35 years of age). Recurrence at a distant site was reported in 81 patients (18.3%). Death was reported in 50 patients (11.3%); 49 of these deaths occurred in women who had received chemotherapy.

The number of women younger than 35 years with HER2-negative disease who did not receive chemotherapy was small (n = 57; SOFT = 20, TEXT = 37); these women seem to have low-risk tumors (94% node-negative, 84% ≤ 2 cm, and 23% grade 1). In this cohort, eight patients (14%) had invasive breast cancer events, including three distant recurrences and one death.

In the cohort of women younger than age 35 years who had received chemotherapy before SOFT enrollment, 5-year BCFI was 67.1% (95% CI, 54.6% to 76.9%) for tamoxifen alone, 75.9% (95% CI, 64.0% to 84.4%) for tamoxifen plus OFS, and 83.2% (95% CI, 72.7% to 90.0%) for exemestane plus OFS (Fig 2; Appendix, online only). Their 5-year DRFI was 74.6% (95% CI, 62.7% to 83.2%) for tamoxifen alone, 77.3% (95% CI, 65.5% to 85.5%) for tamoxifen plus OFS, and 84.4% (95% CI, 74.0% to 90.9%) for exemestane plus OFS (Appendix Fig A1, online only).

For women younger than 35 years enrolled in TEXT who received chemotherapy, the 5-year BCFI was 79.2% (95% CI, 66.2% to 87.7%) with tamoxifen plus OFS and 81.6% (95% CI, 69.8% to 89.2%) with exemestane plus OFS. Their 5-year DRFI was 80.9% (95% CI, 68.1% to 89.0%) for tamoxifen plus OFS and 81.0% (95% CI, 68.8% to 88.8%) with exemestane plus OFS (Appendix Fig A1, online only).

QoL

Most patients younger than 35 years are likely to receive chemotherapy as part of adjuvant treatment, and 94% and 82% of women younger than 35 years enrolled in SOFT and TEXT did receive chemotherapy and are the focus of QoL analysis. In TEXT, the

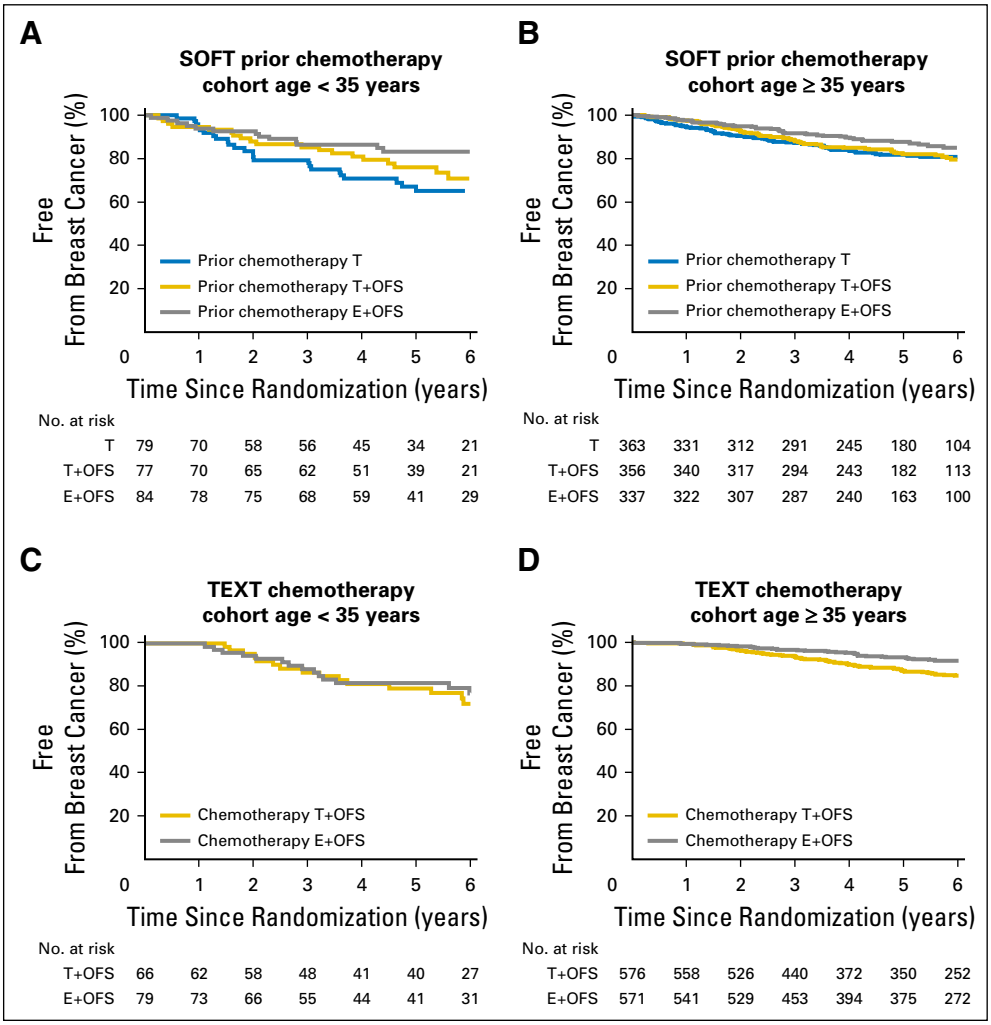

Fig 2. Kaplan-Meier estimates of breast cancer–free interval (BCFI) among patients with human epidermal growth factor receptor 2–negative disease in the chemotherapy cohorts of the Suppression of Ovarian Function Trial (SOFT) and Tamoxifen and Exemestane Trial (TEXT), according to age at random assignment and treatment assignment. Median follow-up was 5.6 years in SOFT and 6.0 years in TEXT. (A, B) SOFT prior chemotherapy, age younger than 35 years and ≥ 35 years. (C, D) TEXT chemotherapy, age younger than 35 years and ≥ 35 years. E, exemestane; OFS, ovarian function suppression; T, tamoxifen.

baseline QoL assessment occurred before adjuvant chemotherapy. In SOFT, the baseline QoL assessment occurred after chemotherapy (median, 3.5 months from last dose of chemotherapy); approximately 40% had also received tamoxifen before enrollment.

Women enrolled in the prior-chemotherapy SOFT cohort generally had worse baseline QoL symptoms but reported better coping than those enrolled in TEXT (Table 2). Other global indicators were similar between these cohorts. This is expected, because patients in SOFT had already received chemotherapy (and possibly tamoxifen). For patients in SOFT with prior chemotherapy, only a few baseline symptom-specific QoL indicators differed by ≥ 8 points between women younger and older than 35 years (hot flushes [mean difference, 10; 95% CI, 6 to 14], sweats [mean difference, 10; 95% CI, 6 to 13], bone or joint pain [mean difference, 9; 95% CI, 5 to 12]), with women younger than 35 years being less affected for all. The greatest difference in baseline global QoL indicators between women younger and older than 35 years in the SOFT prior-chemotherapy cohort was only 5 points (95% CI, 2 to 8 points) for coping effort, and the women younger than 35 years were more affected.

Because of the baseline QoL differences between patients in SOFT and TEXT, and to isolate the added toxicity of OFS combined with oral endocrine therapy from that of chemotherapy, we have focused on the 291 women younger than age 35 years who had received chemotherapy before enrollment in SOFT (Fig 3). The most prominent change in symptom-specific QoL in the women younger than age 35 years in SOFT who had prior chemotherapy was an increase in symptoms seen between baseline and the 6-month time point; in general, symptoms improved over time thereafter. Vasomotor symptoms (hot flushes, sweats) showed the greatest worsening from baseline to 6 months (on the order of 30- to 40-point change with OFS). Thereafter, vasomotor symptoms improved in women younger than 35 years receiving OFS but without reaching baseline, whereas scores worsened over time in patients younger than 35 years receiving tamoxifen alone. Changes in gynecologic symptoms were smaller than for vasomotor symptoms but were clinically meaningful for loss of sexual interest and difficulties in becoming aroused among patients younger than 35 years assigned to OFS and also for vaginal dryness among those receiving exemestane plus OFS; loss of sexual interest and vaginal dryness showed little improvement over time. Women treated with exemestane plus OFS noted increase in bone/joint pain at the 6-month time point that stabilized thereafter. Women younger than 35 years old treated with tamoxifen alone or tamoxifen plus OFS were also found to have an increase in bone/joint pain over time, which was slower in onset but reached a level similar to that of the exemestane plus OFS group by 24 months. Changes in global QoL indicators

Table 2. Quality-of-Life Symptom and Global Indicator Scores at Baseline According to Cohort and Age at Random Assignment

Indicator	Cohort and Age at Random Assignment: Chemotherapy TEXT, < 35 Years, Mean Score ± SD	Chemotherapy TEXT, ≥ 35 Years, Mean Score ± SD	Chemotherapy TEXT, Mean Difference* (95% CI)	Prior Chemotherapy SOFT, < 35 Years, Mean Score ± SD	Prior Chemotherapy SOFT, ≥ 35 Years, Mean Score ± SD	Prior Chemotherapy SOFT, Mean Difference* (95% CI)
No. of patients†	170	1,230		291	1,316	
Symptom indicators						
Vasomotor						
Hot flushes	91 ± 19	92 ± 17	−0 (−3 to 3)	80 ± 27	69 ± 32	10 (6 to 14)
Sweats (including night sweats)	86 ± 22	88 ± 19	−2 (−6 to 1)	83 ± 23	73 ± 29	10 (6 to 13)
Gynecologic or sexual						
Vaginal discharge	85 ± 21	90 ± 16	−6 (−8 to −3)	76 ± 25	80 ± 23	−4 (−7 to −1)
Vaginal dryness	93 ± 15	94 ± 12	−1 (−3 to 1)	81 ± 25	80 ± 26	1 (−3 to 4)
Vaginal itching/irritation	91 ± 16	93 ± 14	−3 (−5 to −0)	87 ± 21	86 ± 22	1 (−2 to 4)
Loss of sexual interest‡	81 ± 25	78 ± 27	3 (−2 to 7)	73 ± 29	66 ± 31	7 (3 to 11)
Difficulty in becoming aroused	87 ± 19	84 ± 20	3 (−1 to 6)	74 ± 27	72 ± 27	2 (−2 to 6)
Musculoskeletal or neurologic pain						
Bone or joint pain	89 ± 15	88 ± 20	2 (−2 to 5)	83 ± 24	74 ± 28	9 (5 to 12)
Headaches	82 ± 23	85 ± 21	−3 (−6 to 0)	82 ± 23	82 ± 23	−1 (−4 to 2)
Constitutional or psychological						
Sleep disturbance	76 ± 25	71 ± 27	5 (1 to 9)	72 ± 29	66 ± 29	6 (2 to 10)
Tiredness	64 ± 27	65 ± 26	−1 (−5 to 3)	56 ± 28	56 ± 26	0 (−3 to 4)
Troubled by weight gain	90 ± 17	88 ± 20	1 (−2 to 5)	72 ± 32	69 ± 31	3 (−1 to 7)
Being irritable	73 ± 23	74 ± 24	−1 (−5 to 3)	70 ± 25	73 ± 24	−3 (−6 to 0)
Global indicators						
Physical well-being	78 ± 20	77 ± 22	0 (−3 to 4)	78 ± 22	77 ± 21	1 (−2 to 4)
Mood	69 ± 24	70 ± 24	−1 (−5 to 3)	74 ± 22	75 ± 22	−1 (−4 to 2)
Coping effort	58 ± 28	60 ± 28	−2 (−6 to 3)	65 ± 27	70 ± 25	−5 (−8 to −2)
Treatment burden	74 ± 25	76 ± 24	−2 (−6 to 2)	71 ± 25	72 ± 24	−2 (−5 to 2)
Health perception	70 ± 21	70 ± 22	−0 (−4 to 3)	72 ± 21	73 ± 21	−1 (−4 to 2)

NOTE. Quality-of-life scores for all indicators range from 0 to 100, with higher scores indicating a better state.
Abbreviations: SD, standard deviation; SOFT, Suppression of Ovarian Function Trial; TEXT, Tamoxifen and Exemestane Trial.
*Because of rounding, the mean difference between age groups may be different from the differences between the mean scores.
†The quality-of-life population was 87% of the intention-to-treat populations. The number of patients who answered each question differs slightly from the overall number of patients in the respective group.
‡Loss of sexual interest was to be answered only by patients who reported that they had been sexually active in the past 6 months (n = 127, 941, 229, 812 in the four groups, respectively).

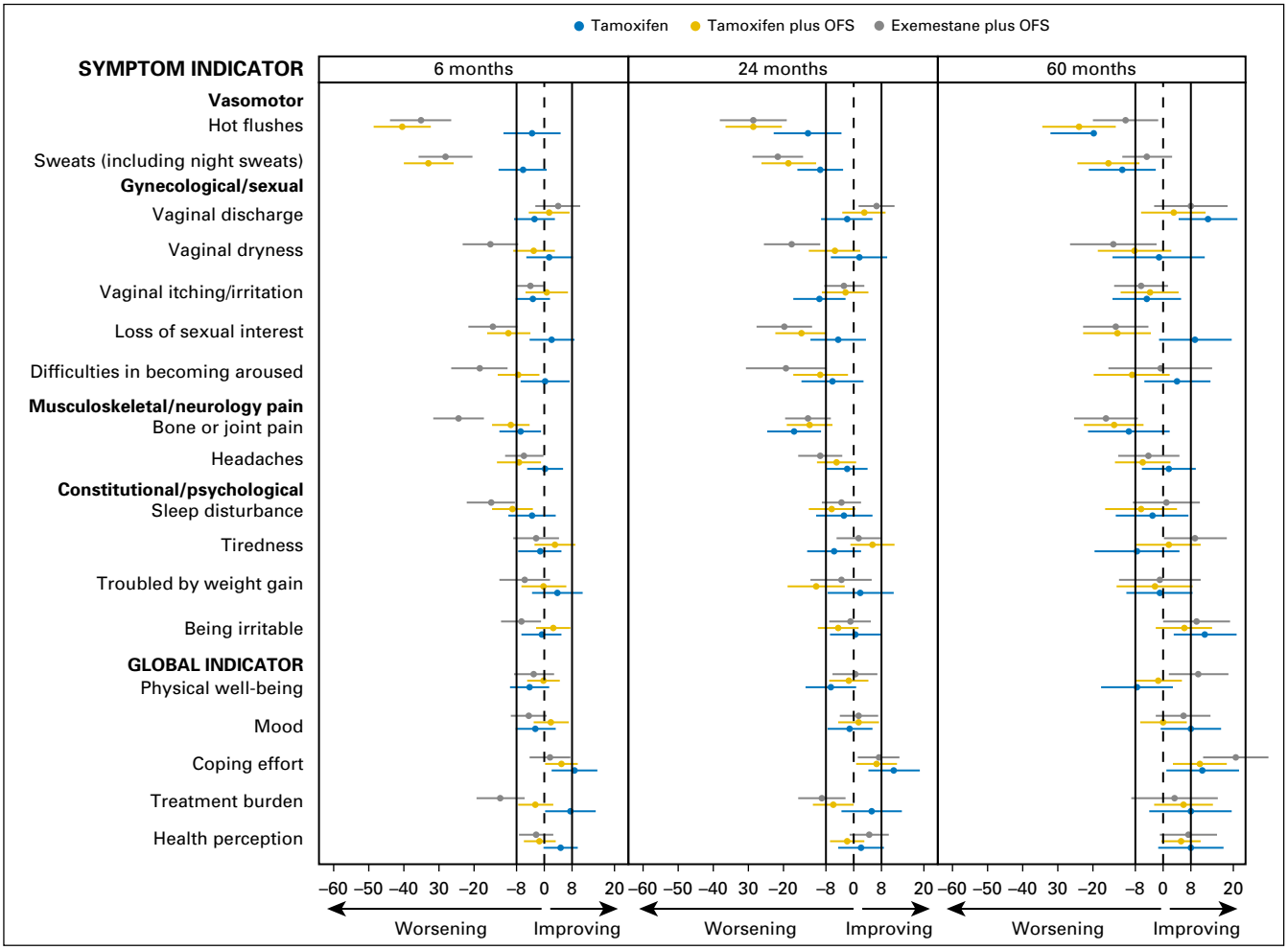

Fig 3. Change in quality-of-life symptom and global indicator scores from baseline (mean with 95% CI), for 291 patients in the Suppression of Ovarian Function Trial who were younger than 35 years at random assignment and had received prior chemotherapy. Plus or minus 8 is the minimal clinical meaningful change of quality-of-life scores, indicated by dashed vertical lines. OFS, ovarian function suppression.

(physical well-being, mood, coping effort, and health perception) were minimal and similar among treatment groups. Treatment burden was greater than baseline at the 6-month time point in women younger than 35 years treated with exemestane plus OFS but improved over time to baseline levels in all treatment groups.

These data are similar to those previously published for all age groups combined.[11,12] The only clinically meaningful difference (defined as ≥ 8-point difference) between the younger than 35 years and ≥ 35 years age groups when adjusted for assigned endocrine therapy was a greater worsening in sweats for women younger than 35 years (eg, −8; 95% CI, −12 to −3 at 6 months), with similar trend in hot flushes (data shown only for younger than 35 years old). This should be viewed in the context of the worse hot flushes and sweats present at baseline for participants in SOFT ≥ 35 years of age than those younger than 35 years (Table 2). In both SOFT and TEXT cohorts treated with chemotherapy, the changes in global QoL indicators were similar for the younger than 35 years and the ≥ 35 years age groups.

Nonadherence to Protocol-Assigned Endocrine Therapy

All women enrolled in SOFT and TEXT, regardless of chemotherapy use and HER2 status, were included in the adherence analysis. Adherence was defined as continuing assigned endocrine therapy for 5 years or until DFS event; women who were switched to an alternate endocrine therapy were considered nonadherent. Women who initially achieved OFS with a GnRH agonist but subsequently decided on a permanent method of ovarian ablation, such as surgery, were considered adherent; whether a woman received every triptorelin dose on the 28-day (±3 days) schedule per protocol was not taken into account.

Of the women younger than 35 years enrolled in SOFT and TEXT, 19.8% (115 of 582) stopped all protocol-assigned therapy early (19.2% continued receiving protocol-assigned therapy at time of analysis). Nonadherence with assigned oral endocrine therapy was higher in women younger than 35 years (P = .01) than in women ≥ 35 years. The cumulative incidence of nonadherence with oral endocrine therapy in women younger than 35 years at 1 year was 11%, increasing to approximately 17%, 23%, and 25% at 2, 3, and 4 years after random assignment (Fig 4). For those ≥ 35 years old, it was 9%, 14%, 18%, and 21%, respectively. Of 470 women younger than 35 years assigned to OFS, six never started OFS, 45 (9.6%) chose oophorectomy after receiving some GnRH agonist, and five had oophorectomy as the only means of OFS. Nonadherence with

medical OFS, which required monthly injections for 5 years, was significantly higher among patients younger than 35 years ($P = .009$). The cumulative incidence of nonadherence to medical OFS in women younger than 35 years at 1 year was 10%, increasing to approximately 15%, 20%, and 23% at 2, 3, and 4 years after random assignment (Fig 4); for the ≥ 35 years age group it was 8%, 12%, 15%, and 17%, respectively. More women older than 35 years opted for permanent OFS via surgery or radiotherapy.

DISCUSSION

Women younger than 35 years in SOFT and TEXT had worse outcomes overall than older premenopausal women, with 5-year BCFI of only 79% for those younger than 35 years with HER2-negative disease.[8] It may be that recurrence rates will increase by 10 years of follow-up. For women in SOFT with HER2-negative disease who received chemotherapy, outcomes at 5 years were substantially improved by the use of OFS, increasing to a BCFI of 81.6% with the use of exemestane plus OFS from 67.1% for the use of tamoxifen alone. As noted in other studies,[1] there was a higher incidence of HER2 positivity in women younger than 35 years, and the HER2-positive subgroups of SOFT and TEXT will be explored in future analyses.

The number of women younger than 35 years who did not receive adjuvant chemotherapy was small, and the majority of them received OFS. Only six women younger than 35 years were treated with tamoxifen and no chemotherapy in SOFT. Although most guidelines would not suggest the use of OFS in women younger than 35 years with low-risk tumor characteristics, the 5- to 6-year median follow-up is too short for definite conclusions about the value of OFS in this lower-risk group; 50% of recurrences in HR-positive tumors will occur after 5 years.[8,17] A limitation of our study is that genomic testing, which is now widely used to identify women of low risk, was not used in this study.

Benefit from the addition of OFS must be weighed against toxicity. The primary QoL analyses for patients enrolled in TEXT and SOFT have been previously published.[11,12] We had hypothesized that women younger than 35 years might report more severe endocrine symptoms than their older premenopausal counterparts, but that did not seem to be the case. However, all age groups suffered bothersome symptoms. Symptoms overall improved after the 6-month time point, with the exception of bone and joint pain in the tamoxifen-treated groups and vaginal dryness and loss of sexual interest in the OFS groups. Some symptom indicators remained at a level indicating substantial treatment burden necessitating persistent attention to symptom alleviation and supportive care. No data are yet available on patient-reported symptoms at > 5 years from enrollment, when protocol-assigned treatment would have stopped, and future analyses will address the reversibility of treatment-induced menopausal symptoms. Future analyses could also consider protocol-assigned and nonprotocol endocrine therapy actually received to assess whether some of the improvement in symptoms over time resulted from cessation of therapy by patients reporting the worst symptoms.

Women younger than 35 years in SOFT and TEXT had a higher rate of nonadherence than those ≥ 35 years of age. Several observational studies have reported that younger age is associated with lower rates of treatment compliance with endocrine therapy, possibly suggesting the level of toxicity (eg, sexual toxicity) is less acceptable to women younger than 35 years.[18-20] In a large medical and pharmacy insurance claims database, Neugut et al[21] found that patients with breast cancer who were younger than 45 years had an odds ratio of 2.0 of nonadherence to oral endocrine therapy compared with women 55 to 64 years of age. The need to come to a physician's office for injectable hormone therapy might further increase the difficulties of endocrine therapy for women younger than 35 years who have competing responsibilities, such as career and childcare.[22] Finally, a desire for pregnancy may also be relevant; only 10% of women younger than 35 years of age opted for oophorectomy. The POSITIVE (Pregnancy Outcome and Safety of Interrupting Therapy for women with endocrine responsive breast cancer) trial (ClinicalTrials.gov identifier: NCT02308085) is currently enrolling young women who wish to interrupt endocrine therapy to become pregnant.

In summary, in two international randomized trials of endocrine therapy among premenopausal women with HR-positive early breast cancer, women younger than 35 years had higher-risk disease characteristics than their older premenopausal counterparts and were also at increased risk for recurrence

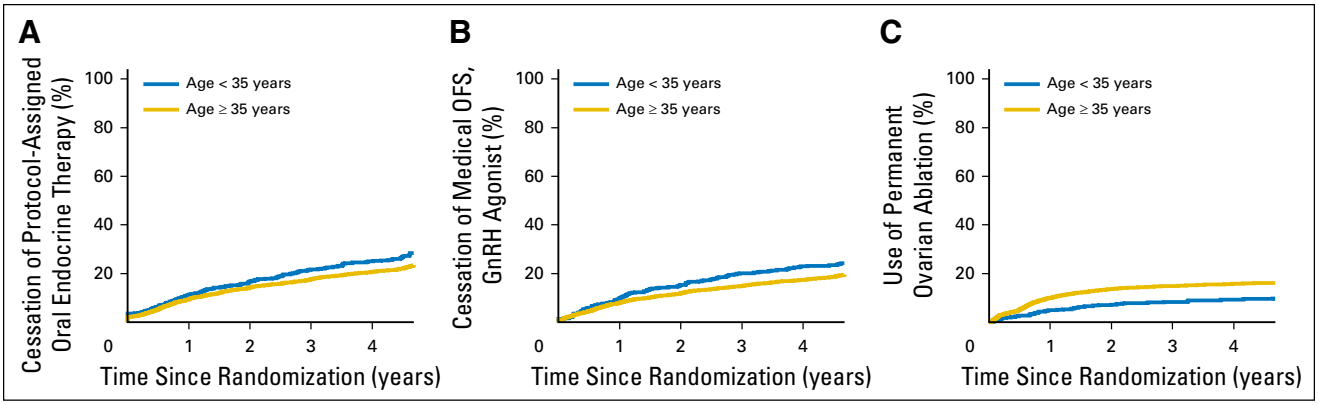

Fig 4. Adherence with protocol-assigned endocrine therapy according to age at random assignment. (A) Cumulative incidence of cessation of assigned oral endocrine therapy (exemestane or tamoxifen). (B) Cumulative incidence of cessation of medical ovarian function suppression (OFS) by gonadotropin-releasing hormone (GnRH) agonist; patients switching to permanent OFS are not considered as having ceased medical OFS. (C) Cumulative incidence of permanent ovarian ablation by bilateral oophorectomy or ovarian irradiation.

independent of assessed baseline tumor characteristics and treatment. There was a meaningful clinical benefit in breast cancer outcomes with the addition of OFS to tamoxifen and some additional benefit from use of an aromatase inhibitor with OFS. Longer follow-up is critical to clarify potential survival benefits. There were substantial adverse effects from these combined endocrine treatments, but they were not different in the younger and older than 35 years populations. Despite this, rates of nonadherence were slightly higher in women younger than 35 years. Availability of these age-specific data regarding risks and benefits of combined endocrine therapy will support shared decision making regarding OFS among young women at high risk for recurrence and death from breast cancer and, it is hoped, improve adherence among those who select OFS.

AUTHORS' DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST

Disclosures provided by the authors are available with this article at jco.org.

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Treatment Efficacy, Adherence, and Quality of Life Among Women Younger Than 35 Years in the International Breast Cancer Study Group TEXT and SOFT Adjuvant Endocrine Therapy Trials

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Appendix

Supplemental Results

Among 442 women younger than 35 years with human epidermal growth factor receptor 2–negative disease, 111 had luminal A-like tumors, 221 had luminal B-like tumors, and 110 could not be classified because centrally assessed Ki-67 values were not available. Luminal A-like tumors were defined by progesterone receptor $\geq$ 20% and Ki-67 $<$ 20%; luminal B-like tumors were defined by either progesterone receptor $<$ 20% or Ki-67 $\geq$ 20% (or both). The 5-year breast cancer–free interval of women younger than 35 years assigned to ovarian function suppression was 83.6% in those who had luminal A-like tumors (ν 96.2% for $\geq$ 35 years) and 79.2% in luminal B-like tumors (ν 86.4% for $\geq$ 35 years).

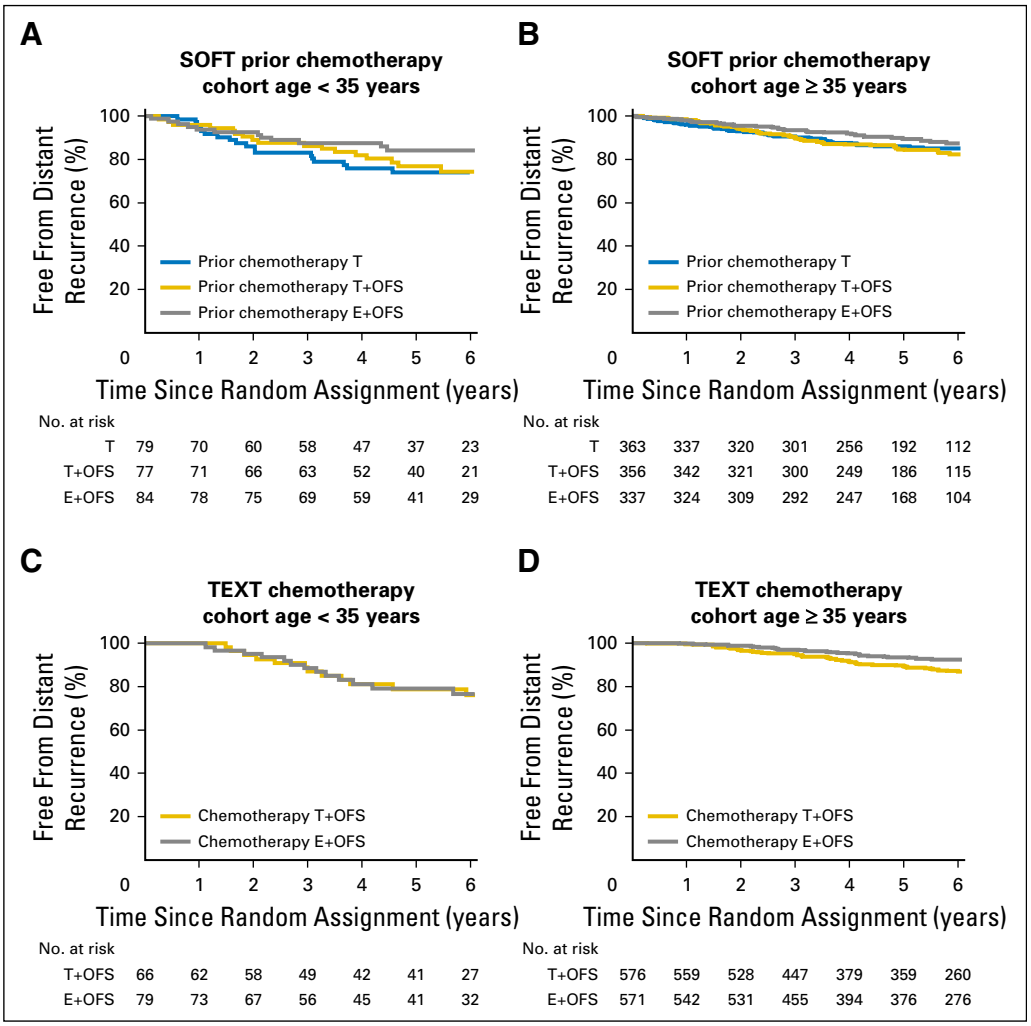

Fig A1. Kaplan-Meier estimates of distant recurrence-free interval among patients with human epidermal growth factor receptor 2–negative disease in the chemotherapy cohorts of the Suppression of Ovarian Function Trial (SOFT) and Tamoxifen and Exemestane Trial (TEXT), according to age at random assignment and treatment assignment. Median follow-up was 5.6 years in SOFT and 6.0 years in TEXT. (A, B) SOFT prior chemotherapy, age younger than 35 years and ≥ 35 years. (C, D) TEXT chemotherapy, age younger than 35 years and ≥ 35 years. E, exemestane; OFS, ovarian function suppression; T, tamoxifen.