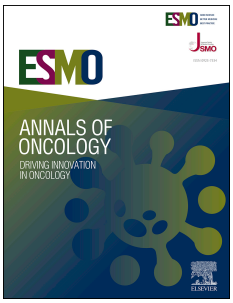

Final outcomes of the SOFT and TEXT phase III trials in premenopausal hormone receptor-positive early breast cancer

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Final outcomes of the SOFT and TEXT phase III trials in premenopausal hormone receptor-positive early breast cancer

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ABSTRACT

Background: The SOFT trial found adding ovarian function suppression (OFS) to tamoxifen (T) reduced breast cancer recurrence, and exemestane (E)+OFS further reduced recurrence. SOFT and TEXT combined analysis showed a significant reduction in distant recurrence with E+OFS versus T+OFS. We now report final 15-year outcomes.

Patients and methods: Premenopausal women with hormone receptor-positive early breast cancer were enrolled, with 3047 in SOFT and 2660 in TEXT intention-to-treat populations. SOFT randomized to 5 years of T versus T+OFS versus E+OFS. TEXT randomized to 5 years of T+OFS versus E+OFS. Chemotherapy was optional, prior to SOFT entry with subsequent premenopausal oestradiol, or concurrent with OFS in TEXT. Endpoints included disease-free survival, breast cancer-free interval (BCFI), distant recurrence-free interval (DRFI) and overall survival. 15-year Kaplan-Meier estimates, hazard ratios (HR) and 95% confidence intervals (CI) are reported.

Results: In SOFT, escalating endocrine therapy (ET) continued to reduce recurrence with 15-year BCFI 78.6% for E+OFS, 75.7% for T+OFS and 72.1% for T; T+OFS versus T, HR 0.82 (CI 0.69-0.98) P=0.03. In the SOFT no-chemotherapy cohort, OFS reduced breast cancer events at 15 years, while DRFI and overall survival remained high regardless of ET assignment. After prior chemotherapy for HER2-negative tumours (n=1257), SOFT 15-year overall survival was 81.0% with E+OFS versus 77.1% with T+OFS versus 76.8% with T. In women under age 35 with HER2-negative tumours (n=241), 15-year overall survival was 82.5% with E+OFS, 77.9% with T+OFS and 68.1% with T. In combined SOFT and TEXT analysis, among those with HER2-negative tumours (n=4035), E+OFS versus T+OFS reduced distant recurrence HR 0.75 (CI 0.63-0.90), with a smaller reduction in deaths HR 0.89 (CI 0.74-1.06), with absolute survival benefits largest with high-risk features, particularly young age or high-grade tumours.

Conclusion: Meaningful overall survival benefit in hormone receptor-positive, HER2-negative breast cancer from adjuvant exemestane and/or OFS compared with tamoxifen alone is limited to high-risk premenopausal subgroups. Tamoxifen-based ET may not result in optimal outcomes in premenopausal high-grade HER2-negative tumours.

HIGHLIGHTS

- Ovarian function suppression (OFS) plus tamoxifen reduces ER+ breast cancer recurrence at 15 years compared with tamoxifen
- Further reduction in recurrence, including distant recurrence, is seen with exemestane plus OFS compared with tamoxifen
- Adjuvant OFS is particularly beneficial for improving outcomes in ER+ HER2- breast cancer in very young women under age 35
- Exemestane plus OFS results in significantly improved freedom from distant recurrence compared with tamoxifen plus OFS
- Meaningful survival benefit from exemestane plus OFS vs. tamoxifen plus OFS or tamoxifen is limited to high-risk subgroups

REGISTRATION: The SOFT and TEXT trials were registered at ClinicalTrials.gov, NCT00066690 and NCT00066703, respectively.

KEYWORDS: premenopausal breast cancer, endocrine therapy, ovarian function suppression

INTRODUCTION

In 2022, there were an estimated 2.3 million women diagnosed with breast cancer and 670,000 deaths worldwide.[1] A higher proportion of breast cancer in low and middle-income countries is diagnosed in premenopausal women and these countries also bear a disproportionate number of breast cancer deaths.[2] Strategies to reduce breast cancer deaths in young women are important. While hormone receptor-positive (HR-positive) cancer is considered a favourable subtype, it is associated with a higher risk of late distant recurrence.[3] This subtype also has a heightened risk of recurrence in women diagnosed very young (< 35 years),[4,5] who are less likely to experience chemotherapy-induced amenorrhoea. Randomized trials show survival benefits from adjuvant endocrine therapy (ET) emerge late and may increase after 10-years,[6] therefore extended follow-up is needed for mature distant recurrence and overall survival (OS) outcomes, and to assess any effect on non-breast cancer mortality. Extended follow-up of ovarian function suppression (OFS) trials is important because older premenopausal women randomized to no OFS may undergo menopause during follow-up, while younger women assigned OFS may have ovarian function recovery following gonadotropin releasing hormone agonist (GnRHa) therapy cessation.

Adjuvant ovarian ablation, tamoxifen and chemotherapy each provide a durable reduction in recurrence of premenopausal HR-positive breast cancer,[6,7] but when these treatments should be combined has been less clear. When the Suppression of Ovarian Function Trials (SOFT) and Tamoxifen and Exemestane Trial (TEXT) premenopausal trials were designed,[8] the value of adding OFS by GnRHa to adjuvant tamoxifen, or to chemotherapy plus tamoxifen was uncertain.[9] Aromatase inhibitors (AI) reduced cancer recurrence more than tamoxifen in postmenopausal women,[10,11] and it was hoped that these improved outcomes would also apply to premenopausal women receiving OFS.

SOFT was designed to assess the role of adjuvant OFS and of adjuvant AI therapy for women who remained premenopausal after chemotherapy, or for whom adjuvant tamoxifen alone following surgery was a reasonable option. In the first analysis, the addition of OFS to tamoxifen did not significantly improve 5-year disease-free survival (DFS).[12] However, in those remaining premenopausal after prior chemotherapy, the improvements observed in freedom from breast cancer (BCFI) with OFS led to changes in treatment guidelines for premenopausal women at higher risk of recurrence.[13,14] The 8-year SOFT outcomes reported a significant improvement in DFS and OS from the addition of OFS to tamoxifen, albeit with

a small absolute OS improvement, with 8-year OS of 93.3% with tamoxifen plus OFS compared with 91.5% with tamoxifen.[15]

TEXT was designed to assess the role of AI therapy in premenopausal women who received OFS from the start of adjuvant therapy. A combined analysis of SOFT and TEXT in women undergoing OFS, compared the AI exemestane with tamoxifen and previously found that those assigned exemestane plus OFS had a significant improvement in DFS, BCFI and freedom from distant recurrence (DRFI) but not a significant improvement in OS.[15-17] The current analysis reports the final 15-year outcomes of the SOFT and TEXT trials.

METHODS

Study design and patients

SOFT (ClinicalTrials.gov NCT00066690) and TEXT (ClinicalTrials.gov NCT00066703) are phase III, randomized, controlled, open-label trials conducted across 510 sites and 27 countries. Detailed methods were previously published.[12,16] Eligible patients were premenopausal women with resected breast cancer with oestrogen or progesterone receptors in at least 10% of cells. Chemotherapy was optional and if given, was commenced after randomization concurrent with OFS in TEXT. In SOFT, if chemotherapy was given, it was prior to enrolment and women could undergo randomization within 8 months of completing chemotherapy, after confirmation of a premenopausal oestradiol level. The study protocol and amendments were approved by the institutional review board or ethics committee at each site. All patients provided written informed consent before trial enrolment.

Treatment

Women in SOFT were randomly allocated 1:1:1 to tamoxifen 20 mg daily, or tamoxifen plus OFS, or exemestane 25 mg daily plus OFS. Assigned ET was for 5 years from randomization. OFS was administered by choice of triptorelin 3.75 mg IM injection every 4 weeks, bilateral oophorectomy, or ovarian irradiation. Patients receiving triptorelin could subsequently undergo oophorectomy or ovarian irradiation. Randomization was stratified according to receipt of previous (neo)adjuvant chemotherapy (yes versus no), lymph-node status (negative versus positive), and intended initial OFS method if allocated (triptorelin versus oophorectomy versus irradiation).

Women in TEXT were randomly allocated 1:1 to exemestane plus triptorelin or tamoxifen plus triptorelin for 5 years. Bilateral oophorectomy or ovarian irradiation was permitted after

6 months of triptorelin. Randomization was stratified according to intended use of adjuvant chemotherapy (yes versus no) and lymph-node status (negative versus positive).

In SOFT and TEXT, the protocols did not address extended ET beyond 5 years, except the requirement to record any therapy.

Endpoints

The primary endpoint in both trials was DFS, defined as time from randomization to the first appearance of invasive breast cancer recurrence (local, regional, or distant), invasive contralateral breast cancer, second non-breast invasive cancer, or death. In the absence of an event, DFS was censored at the date of last follow-up for disease status. Secondary endpoints included: BCFI, time from randomization to the recurrence of invasive breast cancer or invasive contralateral breast cancer; DRFI, time from randomization until first appearance of invasive breast cancer recurrence at a distant site; OS, time from randomization until death from any cause. OS was censored at the date last known alive.

Assessments

After year 6, assessment was limited to annual physical examination and otherwise according to local and/or national standards. Data collection included selected late adverse events and use of ET or bisphosphonates for prevention of breast cancer recurrence; from 2022 through 2024, collection was limited to disease and vital status updates. Patients were followed regardless of ET taken, unless they withdrew consent for any further data submission. Considering international heterogeneity of oncological follow-up beyond 10 years, annual follow-up data may have been obtained by clinic visit, contacting the patient, other doctors or medical records, or from tumour and vital status registries.

Statistical analysis

The last-patient last-visit for SOFT was 6 November 2024 and 31 October 2024 for TEXT. The analyses used an intention-to-treat approach. Kaplan-Meier estimates of time-to-event endpoints and 15-year estimates with pointwise 95% confidence intervals (CIs) were reported. Stratified proportional-hazards regression estimated hazard ratios and 95% CIs. For SOFT, the two pairwise comparisons with tamoxifen alone were estimated; the comparison of tamoxifen plus OFS versus tamoxifen alone also reported a stratified log-rank test. The comparison of exemestane plus OFS versus tamoxifen plus OFS was from the combined SOFT and TEXT analysis,[8] including hypothesis testing. Secondary analyses were conducted

in the subgroup of patients with HER2-negative disease, based on the clinical relevance and presence of heterogeneity of the treatment effect between HER2-negative and HER2-positive subgroups; these analyses report hazard ratios and CIs only.

RESULTS

Patients

In SOFT, between December 2003 and January 2011, 1021 premenopausal women were randomly allocated to tamoxifen alone, 1024 to tamoxifen plus OFS, and 1021 to exemestane plus OFS. The intention-to-treat population included 3047 women after exclusions (Supplementary Figure S1). Before randomization in SOFT, 1628 women (53.4%) had received (neo)adjuvant chemotherapy (Table 1). The cancer was node-positive in 34.5% and HER2-negative in 84.9%. Among those assigned OFS, 91% chose triptorelin as their initial method.

In TEXT, between November 2003 and April 2011, 1338 premenopausal women were randomly allocated to exemestane plus OFS and 1334 to tamoxifen plus OFS. The intention-to-treat population included 2660 women after exclusions. After randomization in TEXT, 1607 women (60.4%) received chemotherapy (Table 1). After exclusions, 4690 women were included in the combined SOFT and TEXT intention-to-treat population for the comparison between exemestane plus OFS versus tamoxifen plus OFS (Supplementary Figure S1). In this combined population, 42.2% had node-positive tumours and 86.0% had HER2-negative tumours (Table 1).

The median follow-up was 15 years for SOFT, 17 years for TEXT, and 16 years for the combined analysis. For these updated analyses, 79.4% of surviving patients in SOFT and 81.3% of surviving patients in TEXT had final follow-up during or subsequent to 2020, and for 68.2% and 72.7% respectively this was during 2023-2024.

Use of non-protocol extended oral ET of any type (continuing beyond year 6) in women free from BCFI events at 5 years in follow-up is detailed in Supplementary Table S1. In SOFT this occurred in 10.4% in the no-chemotherapy cohort and 30.4% in the prior chemotherapy cohort and was approximately twice as frequent in those assigned tamoxifen as their oral therapy as in those assigned exemestane. In TEXT extended oral ET occurred in 11.3% of no-chemotherapy cohort and 26.4% of chemotherapy cohort and was similarly more frequent in the tamoxifen plus OFS group than in the exemestane plus OFS group.

Efficacy of OFS in SOFT

In this final SOFT analysis, there were 815 DFS events reported, of these 655 (80.4%) were breast cancer events (Supplementary Table S2A). A moderate DFS benefit persisted for tamoxifen plus OFS versus tamoxifen [HR, 0.85 (95% CI 0.72-1.00) P=0.05]. DFS events were further reduced with exemestane plus OFS as compared with tamoxifen [HR, 0.73 (95% CI 0.61-0.86)]. The 15-year DFS was 73.5% with exemestane plus OFS, 70.5% with tamoxifen plus OFS and 67.0% with tamoxifen (Figure 1A; Supplementary Figures S2A and S2B). Local, regional or contralateral breast events constituted 34.8% of first DFS events. Among first DFS events, one in seven were non-breast 2nd malignancies, with endometrial, melanoma, thyroid and lung the most frequent (Supplementary Table S3A). Acute myeloid leukemia was rare with 1 case in the prior chemotherapy cohort (0.06%) in which 91.8% received doxorubicin or epirubicin.

Invasive breast cancer events continued throughout follow-up and were significantly reduced with the addition of OFS to tamoxifen [HR, 0.82 (0.69-0.98) P=0.03]. BCFI was highest in women assigned exemestane plus OFS, with a 30% relative reduction in breast cancer events compared with tamoxifen [HR, 0.70 (95% CI 0.58-0.84)], with 15-year BCFI 78.6% with exemestane plus OFS, 75.7% with tamoxifen plus OFS and 72.1% with tamoxifen (Figure 1B). Estimated relative and absolute treatment effects in subgroups for DFS and BCFI are consistent with earlier analyses (Supplementary Figures S3, S4 and S5) with persisting evidence of treatment effect heterogeneity in subgroups defined by HER2 status. Although most BCFI events (69.8%) occurred in the prior chemotherapy cohort (Supplementary Figure S2D), in the no-chemotherapy cohort the number of BCFI events at 15 years had more than doubled compared with at 8 years,[15] and larger absolute differences in BCFI were observed in this cohort for those assigned OFS compared with tamoxifen alone (Supplementary Figures S2C and S5). In the no-chemotherapy cohort with HER2-negative tumours (n=1329), 15-year BCFI was 87.8% with exemestane plus OFS, 84.9% with tamoxifen plus OFS, and 79.4% with tamoxifen (Figure 2A). In those who received prior chemotherapy for HER2-negative tumours (n=1257), 15-year BCFI rates were 71.8% with exemestane plus OFS, 65.7% with tamoxifen plus OFS and 66.1% with tamoxifen (Figure 2B).

After 15 years median follow-up there were 423 DRFI events, with 306 previously reported at 8 years.[15] After 15 years, the addition of OFS to tamoxifen did not significantly reduce distant recurrence [HR, 0.93 (95% CI 0.75-1.17) P=0.56] (Figure 1C) while DRFI was

improved with exemestane plus OFS compared with tamoxifen [HR, 0.78 (95% CI 0.62-0.99)]. The 15-year DRFI was 86.4% with exemestane plus OFS, 83.6% with tamoxifen plus OFS and 83.5% with tamoxifen. In the SOFT no-chemotherapy cohort, 15-year DRFI remained high, exceeding 94%, regardless of ET assignment (Supplementary Figure S2E and Figure 2C). Most DRFI events (86.8%) occurred in the prior chemotherapy cohort (Supplementary Figure S2F). In those who received prior chemotherapy for HER2-negative tumours, 15-year DRFI was 78.8% with exemestane plus OFS, 71.9% with tamoxifen plus OFS and 73.4% with tamoxifen (Figure 2D) with an absolute improvement of 5.5% observed with exemestane plus OFS versus tamoxifen.

After 15 years median follow-up, there were 388 deaths reported in SOFT. There was no significant OS benefit for tamoxifen plus OFS versus tamoxifen [HR, 0.87 (95% CI 0.68-1.10)] (Figure 1D) or exemestane plus OFS versus tamoxifen [HR, 0.85 (95% CI 0.67-1.08)] with 15-year OS of 86.9% with exemestane plus OFS, 86.7% with tamoxifen plus OFS, and 85.3% with tamoxifen. There was no excess of deaths without a prior breast cancer event observed in those assigned OFS (Supplementary Tables S2A and S4A). Estimated relative and absolute treatment effects in subgroups for DRFI and OS are consistent with earlier analyses (Supplementary Figures S6 and S7). In the no-chemotherapy cohort, 15-year OS rates exceeded 94% in all treatment arms (Supplementary Figure S2G and Figure 2E). Most deaths (82.0%) occurred in the prior chemotherapy cohort (Supplementary Figure S2H). In those who received prior chemotherapy for HER2-negative tumours, 15-year OS was 81.0% for exemestane plus OFS, 77.1% for T+OFS, and 76.8% for tamoxifen, resulting in a 4.3% absolute OS improvement with exemestane plus OFS versus tamoxifen (Figure 2F).

In those with HER2-negative tumours in SOFT (Supplementary Table S5), younger women had higher rates of recurrence (Supplementary Figure S8). Among those with HER2-negative tumours randomised under age 35 (n=241), 51.3% assigned tamoxifen remained free from recurrence at 15 years, with improved BCFI rates in this subgroup of 69.6% with exemestane plus OFS and 64.1% with tamoxifen plus OFS (Figure 3A). In this subgroup 92.5% had prior chemotherapy and 15-year OS was 82.5% with exemestane plus OFS, 77.9% with tamoxifen plus OFS, and 68.1% with tamoxifen (Figure 3B and Supplementary Table S6).

Exemestane plus OFS vs Tamoxifen plus OFS

In the final combined analysis of SOFT and TEXT, there were 1180 DFS events reported (Supplementary Tables S2B and S3B). A significant DFS benefit persisted for exemestane plus OFS versus tamoxifen plus OFS [HR, 0.82 (95% CI 0.73-0.92) P<0.01] with 15-year DFS of 74.9% and 71.3% respectively (Figure 4A). With 946 BCFI events reported, there remained a significant BCFI benefit for exemestane plus OFS versus tamoxifen plus OFS [HR, 0.79 (95% CI 0.70-0.90) P<0.01] (Figure 4B). There were 626 DRFI events reported and a significant reduction in distant recurrence persisted for exemestane plus OFS versus tamoxifen plus OFS [HR, 0.83 (95% CI 0.71-0.97) P=0.02] with 15-year DRFI of 86.5% and 83.9% respectively (Figure 4C). With 573 deaths reported (Supplementary Table S4B) there was not a significant OS benefit seen for exemestane plus OFS versus tamoxifen plus OFS [HR, 0.94 (95% CI 0.80-1.11) P=0.48] with 15-year OS of 87.8% and 87.0% respectively (Figure 4D and Supplementary Table S7).

In the combined SOFT and TEXT analysis, 47.1% with HER2 positive tumours did not receive HER2-targeted therapy (Table 1). Focusing on women with HER2-negative tumours (n=4035; Supplementary Table S5), there was a 25% relative reduction in the risk of distant recurrence with exemestane plus OFS versus tamoxifen plus OFS [HR, 0.75 (95% CI 0.63-0.90)] with 15-year DRFI of 87.6% and 83.7% respectively, translating to a 3.9% absolute DRFI improvement (Supplementary Figure S9A). Subgroup analysis suggested consistent relative treatment effect across subgroups (Supplementary Figure S10). The absolute DRFI improvement with exemestane plus OFS was larger in cohorts who received chemotherapy (Supplementary Figure S9B). In those with HER2-negative tumours there was an 11% relative reduction in the risk of death with exemestane plus OFS versus tamoxifen plus OFS [HR, 0.89 (95% CI 0.74-1.06)] with 15-year OS of 88.5% and 86.9% respectively (Supplementary Figure S9C). The absolute improvement in 15-year OS seen in HER2-negative cohorts with exemestane plus OFS versus tamoxifen plus OFS was larger in those who received chemotherapy, at 3.9% in SOFT and 2.5% in TEXT (Supplementary Figure S9D).

In the combined analysis in women with HER2-negative tumours, distant metastasis and deaths were more frequent in women under age 40. Larger absolute benefits were seen in these younger women when assigned exemestane plus OFS versus tamoxifen plus OFS, in

the range of 7.4-7.6% increase in DRFI and 3.6-3.8% increase in OS respectively at 15 years (Supplementary Figure S11).

In the context of current premenopausal trials, we assessed in the combined analysis outcomes for the 289 women (median age 45 years), with node-positive HER2-negative disease selected not to receive chemotherapy and assigned endocrine therapy plus OFS. This subgroup had estimated rates of 15-year DRFI and OS of 93.1% and 94.2% respectively, with 15-year BCFI of 84.1%.

Late Adverse Events

Among patients in follow-up without DFS events at 6 years, the cumulative incidence over the subsequent 9 years of late cardiovascular or cerebrovascular adverse events was 1.8% in SOFT tamoxifen group, 2.7% in SOFT tamoxifen plus OFS group, 2.6% in SOFT exemestane plus OFS group, and 2.1% in combined SOFT (OFS-assigned) and TEXT groups (Supplementary Methods). Cumulative late fracture incidence was 4.2% in SOFT tamoxifen group, 6.6% in SOFT tamoxifen plus OFS group and 6.8% in SOFT exemestane plus OFS group.

DISCUSSION

Long term follow-up of SOFT shows a sustained, significant, 18% relative reduction in the risk of breast cancer recurrence at 15 years with tamoxifen plus OFS versus tamoxifen. Further reduction is seen with exemestane plus OFS compared with tamoxifen, with a 30% relative reduction in BCFI events and a 22% relative reduction in DRFI events [HR, 0.78 (95% CI 0.62-0.99)]. OS in the SOFT ITT population was not significantly improved with either tamoxifen plus OFS or exemestane plus OFS compared with tamoxifen at 15 years. Non-breast cancer mortality does not appear to be adversely impacted by assignment to OFS for 5 years in premenopausal women.

One of the hallmarks of HR-positive breast cancer is the ongoing propensity for late recurrence. In the SOFT no-chemotherapy cohort, those assigned 5 years of tamoxifen alone, continued to have high 15-year DRFI of 94.7%, but the 8-year BCFI of 91.4%,[15] declined to 15-year BCFI of 79.4%. This SOFT no-chemotherapy cohort with a median age of 46 years had predominantly pT1pN0 grade 1-2 tumours. The high DRFI in this cohort suggests that emerging endocrine approaches are unlikely to meaningfully impact overall survival in such premenopausal patients. However, with long-term follow-up we now observe in this cohort,

that those assigned to receive OFS had fewer invasive BCFI events at 15 years, with absolute improvements of 8.4% with exemestane plus OFS and 5.4% with tamoxifen plus OFS respectively, compared with tamoxifen alone. This was despite a smaller percentage of those assigned OFS using extended ET, which may reduce BCFI events in premenopausal women after 5 years of OFS plus oral ET.[18] OFS had an impact on invasive local, regional and contralateral events given greater reductions in all recurrence than distant recurrence in this low-risk cohort selected by treating physicians not to require chemotherapy. Premenopausal women in whom chemotherapy is not indicated and who have undergone bilateral mastectomy may experience a smaller absolute improvement in long-term BCFI with OFS plus AI versus tamoxifen. More than 10% of SOFT first DFS events involved the contralateral breast. A Cancer Intervention and Surveillance Network (CISNET) model found the estimated number of future contralateral breast cancers per 100 women diagnosed under age 45 years was 16.7, 13.4, 12.5 and 11.7 with no adjuvant ET, tamoxifen for 5 years, tamoxifen plus OFS for 5 years or AI plus OFS for 5 years respectively.[19] While non-distant BCFI events maybe curable, they result in distress, additional surgery, possible chemotherapy, and delay for those who have not completed childbearing. BCI (H/I)-low genomic status might identify premenopausal women with greater BCFI benefit from including OFS in ET.[20]

Meaningful OS improvement with OFS in SOFT appears limited to subgroups at higher risk for recurrence, particularly very young women. In the SOFT subgroup under age 35 with HER2-negative tumours, there are substantial absolute improvements in 15-year OS of 14.4% for exemestane plus OFS and 9.8% for tamoxifen plus OFS respectively, compared with tamoxifen, and only 51.3% of those assigned tamoxifen remained free from BCFI events. A meta-analysis of OFS (including ablation) trials reported a significant reduction in 10-year breast cancer mortality with OFS [RR 0.74 (0.58-0.95) P=0.012] in premenopausal women (no chemotherapy or premenopausal after) receiving tamoxifen when limited to women age < 45 years.[21] Updated 10-year ASTRRA trial outcomes showed significant recurrence reduction with addition of OFS to tamoxifen, but a less pronounced effect in women < 40 years, suggesting 2 years OFS is insufficient in this age group.[22] The combined SOFT-TEXT analysis shows for women under age 40 with HER2-negative tumours assigned exemestane plus OFS versus tamoxifen plus OFS, absolute improvements in DRFI of ~7.5% and ~3.7 % for OS at 15 years.

There remains room for improvement in very young women with HR-positive HER2-negative tumours, as among those under 35 assigned exemestane plus OFS in SOFT, 30.4% experienced BCFI events by 15 years. Considerations for further reducing recurrence include baseline breast MRI, genetic testing (with consideration of bilateral mastectomies in those with highest-risk germline pathogenic mutations and adjuvant olaparib), improved ET adherence,[23] extended ET,[18] adjuvant CDK4/6 inhibitors, and combining immunotherapy with neoadjuvant chemotherapy for high-grade cancers.[24,25]

For some other SOFT subgroups at increased risk of recurrence, such as those who received prior chemotherapy for HER2-negative tumours or those with grade 3 HER2-negative tumours, exemestane plus OFS provides an absolute OS benefit over tamoxifen at 15 years of 4.3% (Figure 2F) and 8.4% (Supplementary Figure S12) respectively. In the combined analysis comparing exemestane plus OFS versus tamoxifen plus OFS, there was a significant reduction in distant recurrence but not OS. However, for those with grade 3 HER2-negative tumours, the differential benefit from exemestane plus OFS over tamoxifen plus OFS appears meaningful, with absolute benefits of 12.1% for BCFI, 9.7% for DRFI and 5.8% for OS at 15 years (Supplementary Figure S13). These results suggest that premenopausal women with high-grade HER2-negative tumours do not achieve optimal outcomes with tamoxifen-based ET. Long-term follow up of the Stockholm STO-5 premenopausal trial testing 2 years of goserelin, tamoxifen, combination, or control, suggested a worse outcome with the addition of tamoxifen to goserelin compared with goserelin alone in genomic (70-gene signature) high-risk tumours.[26] Premenopausal women with high risk HER2-negative breast cancer receiving adjuvant AI plus OFS benefit from adjuvant abemaciclib. In the monarchE trial that permitted a tamoxifen backbone ET, the larger absolute DFS benefit seen with adjuvant abemaciclib in those who commenced ET with tamoxifen, suggest that it may be possible to improve outcomes in the context of a less effective oral ET.[27] However, if adjuvant CDK4/6 inhibitor is not available for premenopausal high grade HER2-negative cancer, the potential differential benefit from ET with an AI plus OFS maybe greater.

The safe omission of chemotherapy in premenopausal node-positive breast cancer was not demonstrated in RxPONDER or MINDACT genomic assay trials, that underutilized OFS in ET.[28,29] Current premenopausal trials re-examining this question require OFS. While these trials enrol, it is reassuring to note the low 15-year distant recurrence rate among node-positive SOFT and TEXT patients selected not to receive chemotherapy and assigned oral ET plus OFS, albeit with few very young patients in this cohort.

In conclusion, adding OFS to oral ET significantly reduces premenopausal breast cancer recurrence, and more so when combined with an AI. Given high 15-year DRFI and OS rates in the SOFT no-chemotherapy cohort regardless of ET assignment, nuanced discussion regarding OFS and aromatase inhibitors is required in premenopausal women deemed not to require chemotherapy. Most premenopausal women will not derive a long-term OS advantage from intensification of ET, but some, particularly younger premenopausal women, and those with grade 3 HER2-negative tumours can derive meaningful improvements in their risk of distant metastasis or death.

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DATA SHARING

After publication, access to deidentified participant data may be requested by researchers by submitting a proposal (to stat_center@ibcsg.org), which will be reviewed for scientific merit and feasibility in accordance with the Guidelines for Collaborative research (https://www.ibcsg.org/images/Member/Publi/Documents/Guidelines_for_Collaborative_Research_for_ETOP_IBCSG_Partners_Foundation_Dec_2022.pdf) and data sharing policy (https://www.ibcsg.org/images/Member/Publi/Documents/Data_Sharing_Policy_for_IBCSG_Trials_Dec_2022.pdf) for IBCSG trials.

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Table 1. Key characteristics of SOFT and TEXT participants in the intention-to-treat (ITT) analysis populations, overall and by chemotherapy stratum.

Reported values are (%) of patients.

	SOFT			TEXT			Combined Analysis		
	All	**No Chemo**	**Prior Chemo**	**All**	**No Chemo**	**Chemo**	**All**	**No Chemo**	**Chemo**
N. patients in ITT population	*3047*	*1419*	*1628*	*2660*	*1053*	*1607*	*4690*	*1996*	*2694*
Chemotherapy stratum									
No chemotherapy	46.6	100.0	-	39.6	100.0	-	42.6	100.0	-
Chemotherapy*	53.4	-	100.0	60.4	-	100.0	57.4	-	100.0
LN status stratum									
pN0	65.5	91.2	43.1	51.8	79.3	33.7	57.8	85.2	37.6
pN1+	34.5	8.8	56.9	48.2	20.7	66.3	42.2	14.8	62.4
Age at enrollment (years)									
<35	11.5	1.5	20.2	8.7	3.9	11.9	10.0	2.8	15.4
35-39	19.1	7.8	29.1	15.5	11.7	18.0	16.9	9.6	22.3
40-44	29.8	27.7	31.6	34.7	34.4	34.9	32.5	31.1	33.5
45-49	29.9	45.9	15.8	33.6	38.6	30.3	31.9	41.9	24.5
50+	9.7	17.1	3.3	7.5	11.5	4.9	8.7	14.6	4.3
Tumor size									
<=2 cm	66.1	85.5	49.1	59.5	80.3	45.9	62.2	82.5	47.2
>2 cm	31.6	14.1	46.9	39.5	19.4	52.6	36.3	17.2	50.4
Unknown	2.3	0.4	3.9	1.0	0.3	1.4	1.5	0.3	2.4
Tumor grade									
1	25.9	39.7	13.8	17.3	25.6	11.8	20.7	31.6	12.7
2	51.0	52.8	49.5	55.5	61.9	51.3	54.2	58.3	51.1
3	21.1	6.6	33.7	26.7	11.5	36.7	24.0	9.2	35.0
Unknown	2.0	0.9	2.9	0.5	0.9	0.2	1.1	1.0	1.2
HER2 status									
Negative	84.9	93.7	77.2	86.8	94.1	82.0	86.0	94.3	79.9
Positive	12.0	3.7	19.3	12.4	5.0	17.2	12.3	4.2	18.4
HER2-target therapy	60.2	5.7	69.4	47.4	17.0	53.3	52.9	13.3	59.6
Unknown/not done	3.1	2.6	3.5	0.9	0.9	0.9	1.6	1.5	1.7
Surgery									
Mastectomy	41.7	27.7	53.9	41.3	29.1	49.3	41.3	28.2	51.1
Breast-conserving	58.3	72.3	46.1	58.7	70.9	50.7	58.7	71.8	48.9

*Chemotherapy (chemo): SOFT upon enrollment patients were premenopausal after prior chemotherapy; TEXT, premenopausal patients initiated chemotherapy after randomization concurrently with triptorelin.

Figure 1. Kaplan-Meier estimates of (A) disease-free survival (DFS); (B) breast cancer-free interval (BCFI); (C) distant recurrence-free interval (DRFI); and (D) overall survival (OS) after 15 years median follow-up according to treatment assignment in SOFT.

Stratified hazard ratio (HR) for comparisons to tamoxifen, with 95% confidence interval (CI), and 15-year estimates are provided.

Abbreviations: T=Tamoxifen; E=Exemestane; OFS=ovarian function suppression

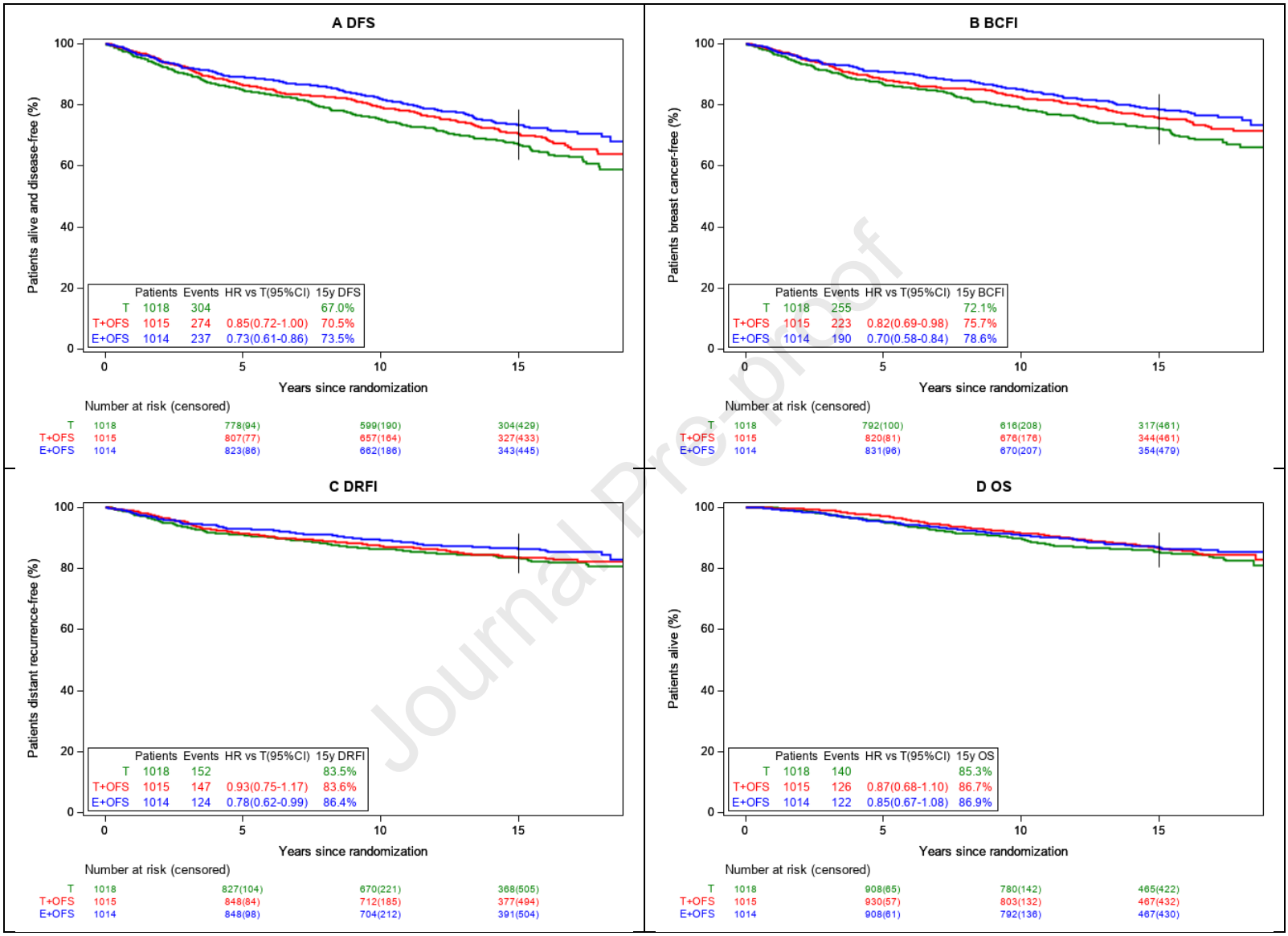

Figure 2. Kaplan-Meier estimates of (A,B) breast cancer-free interval (BCFI); (C,D) distant recurrence-free interval (DRFI); and (E,F) overall survival after 15 years median follow-up, according to chemotherapy stratum among those with HER2-negative tumors in SOFT.

Stratified hazard ratio (HR) for comparisons to tamoxifen, with 95% confidence interval (CI), and 15-year estimates are provided.

Abbreviations: T=Tamoxifen; E=Exemestane; OFS=ovarian function suppression

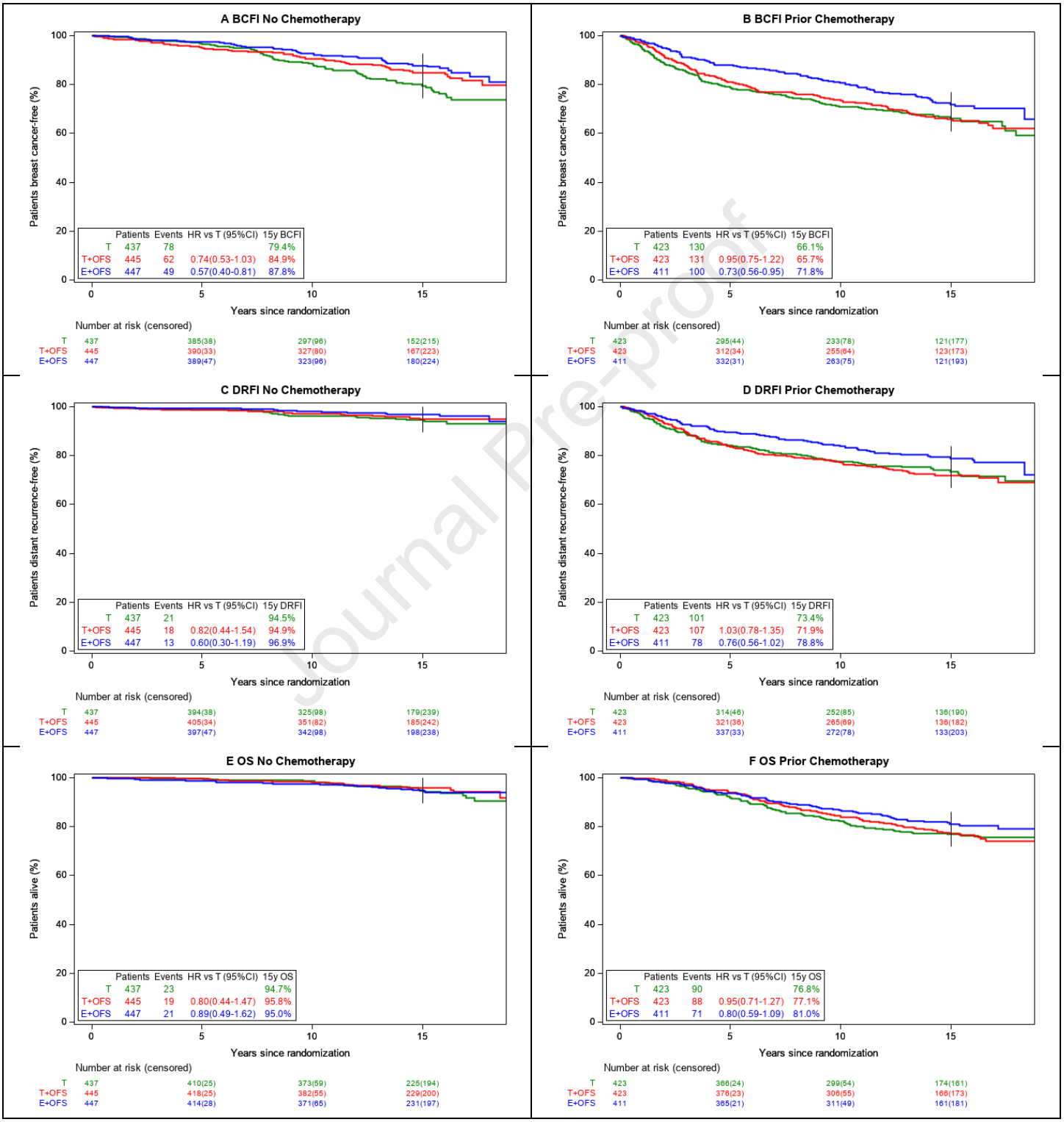

Figure 3. Kaplan-Meier estimates of (A) breast cancer-free interval (BCFI) and (B) overall survival after 15 years median following, among 241 patients <35 years at randomization with HER2-negative tumors in SOFT.

Stratified hazard ratio (HR) for comparisons to tamoxifen, with 95% confidence interval (CI), and 15-year estimates are provided.

Abbreviations: T=Tamoxifen; E=Exemestane; OFS=ovarian function suppression

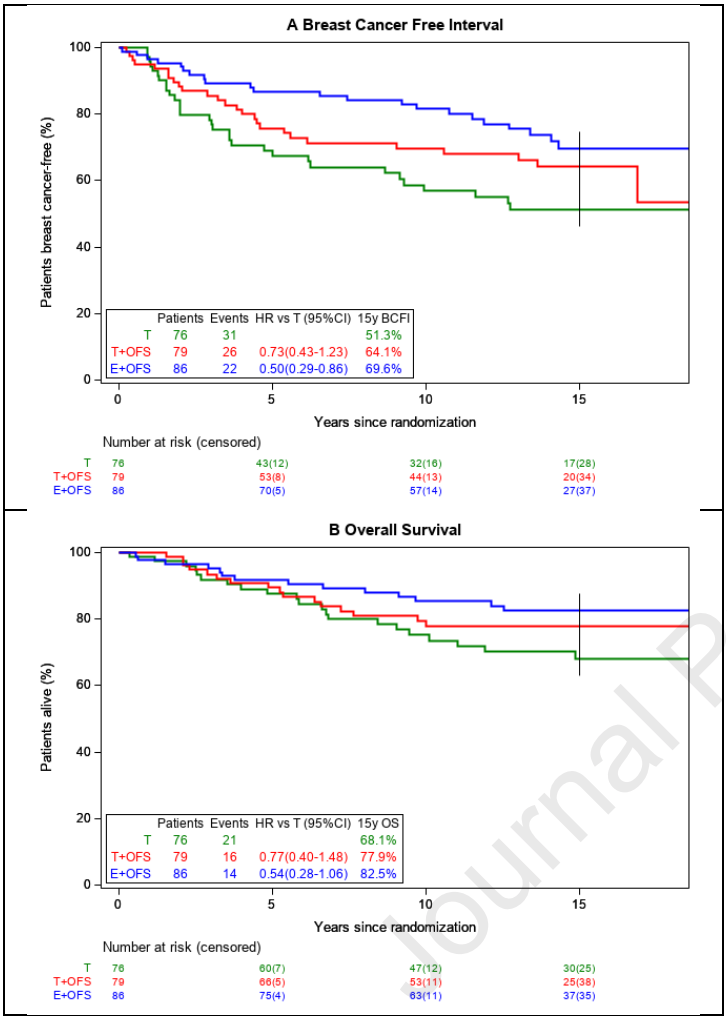

Figure 4. Kaplan-Meier estimates of (A) disease-free survival (DFS); (B) breast cancer-free interval (BCFI); (C) distant recurrence-free interval (DRFI); and (D) overall survival (OS) after 16 years median follow-up according to treatment assignment in the combined SOFT and TEXT population.

Stratified hazard ratio (HR) with 95% confidence interval (CI) and 15-year estimates are provided.
Abbreviations: T=Tamoxifen; E=Exemestane; OFS=ovarian function suppression