Adjuvant Systemic Treatment of Premenopausal Women With Hormone Receptor–Positive Early Breast Cancer: Lights and Shadows

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Background

Research has shown premenopausal women with hormone receptor–positive (HR+) early breast cancer who experience chemotherapy-induced amenorrhea (CIA) have reduced risk of recurrence compared with those who have no CIA, whether treated with adjuvant chemotherapy alone or followed by tamoxifen.[1,2] Younger premenopausal women, in particular those younger than 35 years, are less likely to experience CIA and have increased risk of recurrence.[3] The Suppression of Ovarian Function Trial (SOFT) tested whether women with HR+ breast cancer who remained premenopausal after chemotherapy, and those never receiving chemotherapy, benefit from adding ovarian function suppression (OFS) to 5 years of tamoxifen treatment, or from use of the aromatase inhibitor (AI) exemestane with OFS.[4] The companion Tamoxifen and Exemestane Trial (TEXT) tested the benefit of exemestane versus tamoxifen for women receiving adjuvant OFS, with or without chemotherapy.[4]

The first results of SOFT, after a median follow-up of approximately 5 years, showed clinically meaningful improvement in outcomes with the addition of OFS to tamoxifen[5] for women who remained premenopausal after chemotherapy, and the results of SOFT and TEXT showed greater benefit with exemestane plus OFS.[5,6] Equally as important, women at low risk of recurrence who received endocrine therapy without chemotherapy had excellent outcomes with tamoxifen alone and therefore minimal potential gain from escalating therapy to include OFS, with or without AI.[5] Treatment guidelines subsequently recommended OFS with either tamoxifen or AI for women at higher risk of recurrence, and omission of OFS for women at low risk of recurrence.[7-9] Recently updated results of SOFT and TEXT, after a median follow-up of 8 and 9 years, respectively,[10] strengthened evidence of reduced recurrence with either tamoxifen plus OFS or exemestane plus OFS versus tamoxifen alone for premenopausal women. An overall survival benefit has emerged for the addition of OFS to tamoxifen, but not for exemestane versus tamoxifen with OFS.

Despite the consistent evidence of improved efficacy of escalating endocrine therapy, adjuvant endocrine therapy must be tailored for the individual patient, considering the known early and potential long-term treatment adverse effects. Many questions arise when translating results of SOFT and TEXT, which were launched in 2003, into clinical care.

What Have We Learned From SOFT and TEXT About Adjuvant Endocrine Therapy for Premenopausal Women With HR+/HER2+ Disease?

Overall, approximately 700 patients (12%) with locally determined human epidermal growth factor receptor 2–positive (HER2+) disease were enrolled in SOFT and TEXT, most of whom received chemotherapy: 313 of the patients (19%) remaining premenopausal after chemotherapy in SOFT, and 276 (17%) of those initiating OFS at start of adjuvant chemotherapy in TEXT. Notably, the use of adjuvant HER2-targeted therapy began during trial conduct (69% and 53% of patients with HER2+ disease received trastuzumab with chemotherapy, respectively), and it is possible that now, SOFT and TEXT would not have enrolled patients with HER2+ disease or that a separate analysis of this patient subgroup would have been planned.

The trials suggest potentially greater benefit from using OFS for women with HR+/HER2+ disease than for the HER2-negative (HER2−) subgroup; the signal of differential relative efficacy persists from the initial report to longer follow-up,[5,6,10] and regardless of HER2-targeted therapy use (unpublished data). A recent analysis of data from the Adjuvant Lapatinib and/or Trastuzumab Treatment Optimization trial found premenopausal patients with HR+/HER2+ tumors who developed treatment-related amenorrhea had better outcomes than patients who did not, consistent with our findings.[11]

The most efficacious oral endocrine therapy for patients with HR+/HER2+ disease is unclear from the trials, because results of SOFT versus TEXT were heterogeneous. This could result from patient, disease, or chemotherapy differences between trials, and/or timing of enrollment and OFS initiation

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

Accepted on January 21, 2019 and published at jco.org on February 27, 2019: DOI https://doi.org/10.1200/JCO.18.02433

sequentially or concurrently with chemotherapy. A recent observational study reported heterogeneity between AI and tamoxifen efficacy by age in women with HR+/HER2+ tumors.[12] Closer investigation of the HR+/HER2+ subgroup of SOFT and TEXT, and of premenopausal women in other adjuvant trials, is warranted to better inform their care.

What Are the Results From SOFT and TEXT for the Women With HR+/HER2− Disease?

The overall conclusions of SOFT and TEXT are consistent for the majority subgroup (88%) of patients with HR+/HER2− disease (Fig 1). In SOFT, patients experienced reduced hazards of recurrence and death with the addition of OFS to tamoxifen. The absolute improvement in 8-year overall survival was 2.5% among women who remained premenopausal after chemotherapy. Reductions in recurrence, including distant recurrences, were greater with exemestane plus OFS versus tamoxifen alone, with absolute improvement in 8-year overall survival of 3.5% among patients who received chemotherapy.

For patients who received OFS in the combined SOFT and TEXT cohorts, the improvement in 8-year freedom from distant recurrence to 93.0% with exemestane plus OFS versus 89.6% with tamoxifen plus OFS has not yielded an overall survival benefit (hazard ratio, 0.86; 95% CI, 0.68 to 1.10; 8-year absolute improvement, 0.7%). The improvement percentages were greater among women who received chemotherapy (8-year absolute improvements: distant recurrence, 7.0% SOFT and 5.0% TEXT; overall survival, 1.0% SOFT, 1.9% TEXT). Extended follow-up is required for HR+/HER2− disease.

Are There Patient or Disease Features or Tools to Guide Endocrine Therapy Selection?

In the HR+/HER2− subgroup, the relative treatment effects (hazard ratios) are consistent according to patient age; tumor size, grade, and lymph node status[10]; and PgR and Ki67 expression, determined by central pathology review.[13] Because younger age, lower PgR expression, and higher Ki67 expression are each poor prognostic factors, there was greater absolute improvement from escalating endocrine therapy in these subgroups. The ABCSG-12 trial that compared 3 year of tamoxifen plus OFS versus anastrozole plus OFS reported high body mass index to be a poor prognostic factor and potentially predictive of lesser benefit of anastrozole plus OFS[14]; this has not yet been assessed in SOFT and TEXT.

In the absence of predictive markers of benefit, the greater absolute improvements in outcomes among patients with poorer prognostic features motivate escalation of endocrine

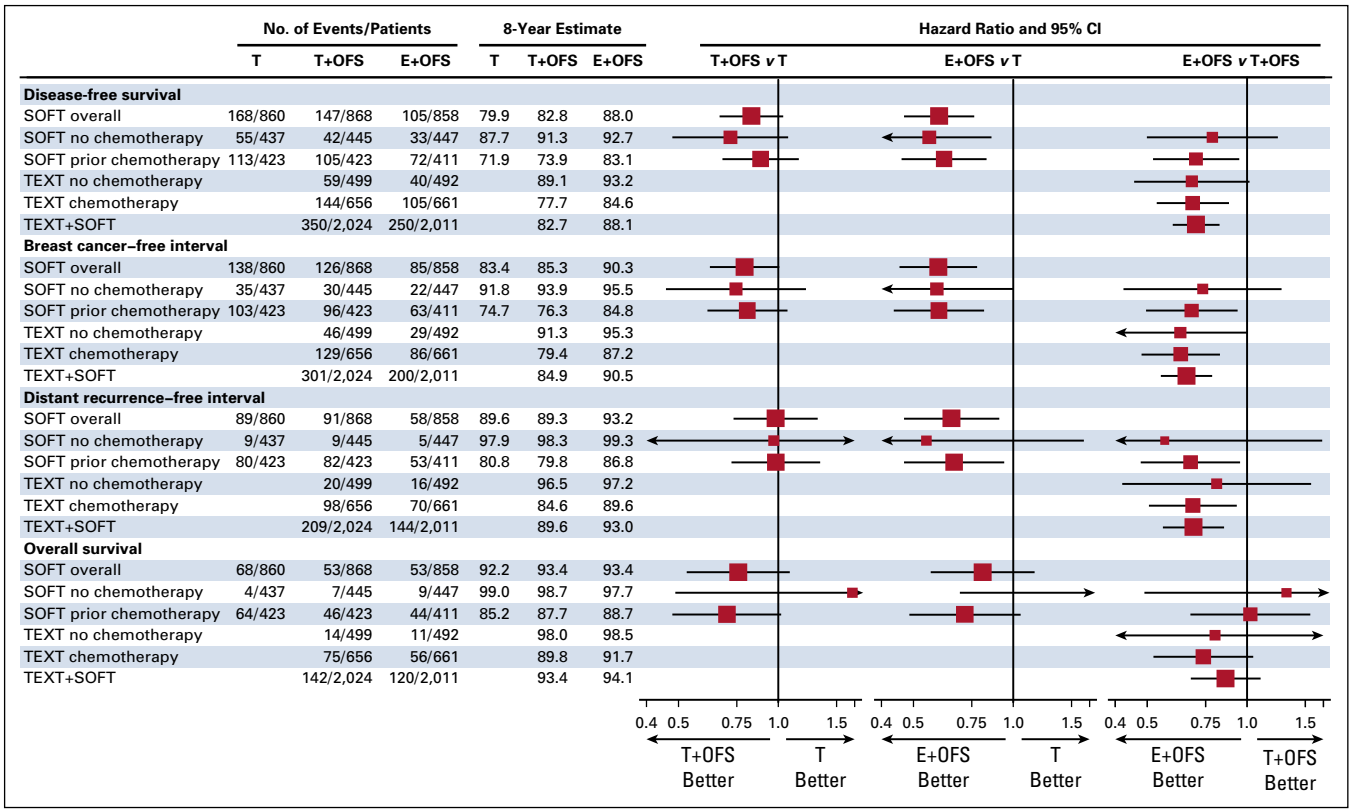

FIG 1. Treatment effect hazard ratios (95% CIs) and Kaplan-Meier estimates of 8-year times to event for four end points in the HR+/HER2− subgroups of SOFT and TEXT, for the two primary analysis populations (ie, SOFT overall and combined TEXT plus SOFT) and by cohort (defined by trial and chemotherapy use).[10] The median follow-up was 8 and 9 years in SOFT and TEXT, respectively. E+OFS, exemestane plus ovarian function suppression; SOFT, Suppression of Ovarian Function Trial; T, tamoxifen; TEXT, Tamoxifen and Exemestane Trial; T+OFS, tamoxifen plus ovarian function suppression.

therapy beyond tamoxifen alone. After the first analyses of data from SOFT and TEXT, we combined traditional clinicopathologic features (ie, patient age; tumor size, grade, and lymph node status; and ER, PgR, and Ki67 expression) into a single continuous value called "composite risk."[15,16] We calculated the absolute improvements in 5-year freedom from breast cancer across the spectrum of composite risk within each of the SOFT and TEXT cohorts defined by chemotherapy use. Absolute improvements of 10% to 15% with exemestane plus OFS versus tamoxifen plus OFS or tamoxifen alone were seen for women at high recurrence risk, at least 5% for women at intermediate risk, and minimal improvement for those at lowest risk (5-year freedom from breast cancer was approximately 96% across all treatment groups).[15] With longer follow-up, the 8-year freedom from distant recurrence has exhibited similar patterns.[16] Development of a Web application is in progress.

Multigene assays should not be used for OFS or oral endocrine therapy selection, because their ability to predict benefit of OFS or of AI versus tamoxifen among premenopausal patients with HR+/HER2− disease has not been studied. SOFT and TEXT have an extensive tissue bank, and investigation of these assays is warranted.

Can SOFT and TEXT Provide Guidance on Use of Chemotherapy, or Selection of OFS Versus Chemotherapy, for HR+/HER2− Disease?

No, they cannot. In SOFT and TEXT, physicians and patients determined use of chemotherapy and, as expected, there were clear differences in patient and clinicopathologic features of women who did and did not receive chemotherapy.[5,6,10,15] In the SOFT no-chemotherapy cohort, greater than 30% of patients had pT1N0 grade 1 tumors. The TEXT cohort receiving combined OFS and oral endocrine therapy without chemotherapy had greater diversity of patients enrolled, greater than 20% had one to three positive lymph nodes, and less than 20% had pT1N0 grade 1 tumors. In the SOFT and TEXT no-chemotherapy cohorts, respectively, the 8-year freedom from distant recurrence was approximately 98% and greater than 96%, with, respectively, 23 of 1,329 and 36 of 991 distant recurrences over median follow-up of 8 and 9 years, respectively (Fig 1).

We have been asked how frequently the OncotypeDX Recurrence Score (RS; Genomic Health, Redwood City, CA) was used to select chemotherapy in SOFT and TEXT, but this information was not collected. We estimate at most 7% could have been tested, on the basis of the percentage of patients enrolled in the United States with node-negative HER2− disease after 2006 (when the NSABP B-20 gene expression study was published[17]).

It has been proposed that the SOFT no-chemotherapy cohort provides an opportunity to validate multigene assays for chemotherapy selection in premenopausal women (eg, as replication of the Trial Assigning Individualized Options for Treatment (TAILORx) low-risk population[18]), but it does not. In TAILORx, all patients having an RS of less than 11 were prospectively assigned to receive endocrine therapy alone without chemotherapy and had excellent outcomes; notably, only 30% of those patients were premenopausal. Even if nearly 100% of the SOFT no-chemotherapy cohort—who were selected on the basis of clinicopathologic features—were determined to have an RS of less than 11, this retrospective analysis would not demonstrate that all young patients in a clinically definable cohort who have an RS of less than 11 will do well on endocrine therapy alone. To establish the clinical utility of a disease feature or marker for chemotherapy decision-making, a trial must include randomization of chemotherapy use, as in TAILORx (intermediate RS, 11 to 25[19]) and the Microarray in Node-Negative and 1 to 3 Positive Lymph Node Disease May Avoid Chemotherapy (MINDACT) study.[20]

TAILORx investigators suggested there was a chemotherapy benefit for women 50 years and younger with an RS of 16 to 25 (see Fig. S8 in reference 19),[19] but it is uncertain whether this would be the case if combined OFS and oral endocrine therapy were used (13% of premenopausal patients received OFS). It would be interesting in the randomly assigned population having an RS of 11 to 25 to examine the chemotherapy treatment effect according to age as a continuous variable. The indirect endocrine effect of chemotherapy would be anticipated to show the chemotherapy benefit is limited to older premenopausal patients who are more likely to experience CIA and diminished among the younger patients, who are least likely to have CIA.

Other trials attempted to test the value of chemotherapy for premenopausal patients who receive combined OFS plus oral endocrine therapy, but without multigene assays defining a population for which there was clinical equipoise, they did not recruit well.[4,21] The Premenopausal Endocrine Responsive Chemotherapy trial (PERCHE), launched with SOFT and TEXT, had identical eligibility to TEXT but randomly assigned the use or not of chemotherapy. PERCHE enrolled 29 patients over 3 years.[22] Previously, IBCSG Trial 11-93 randomly assigned 174 patients, of whom 97% had 1-3 positive lymph nodes, and were receiving OFS plus tamoxifen to chemotherapy or no chemotherapy; no difference in outcome was observed after a median follow-up to 10 years.[21]

When Chemotherapy and OFS Are Given, Do SOFT and TEXT Provide Guidance on Choice of Sequential Use, as in SOFT, or Concurrent Initiation, as in TEXT?

We observed a nearly identical breast cancer-free interval in women with HR+/HER2− disease in SOFT who were premenopausal after chemotherapy and women in TEXT who began chemotherapy and gonadotropin-releasing hormone (GnRH) analog concurrently, overall, and

in women 40 years and younger versus those older than 40 years, after median follow-up of 5 years.[23] This comparative effectiveness, short-term observation supports the sequential approach for older premenopausal women and the concurrent initiation of GnRH analog with chemotherapy for younger women who are unlikely to develop CIA and may desire future pregnancy.[24] A re-examination with longer follow-up is warranted.

When a GnRH Analog Is Used as Ovarian Suppression, Should Estradiol or Follicle-Stimulating Hormone and Luteinizing Hormone Levels be Monitored?

The SOFT Estrogen Suppression Substudy (SOFT-EST), a prospective SOFT substudy, analyzed estradiol levels in a central laboratory at 0, 3, 6, and 12 months after initiation of the GnRH analog triptorelin. At each time point, at least 17% of patients randomly assigned to exemestane plus triptorelin had estradiol levels above a threshold of 2.72 pg/mL, a level expected in postmenopausal women receiving an AI.[25] Such elevations continued, but less frequently, at 18, 24, 36, and 48 months.[26] The international consensus guidelines for breast cancer in young women[9] suggest hormone levels be checked if there are concerns of inadequate OFS, especially in patients receiving an AI. The guidelines emphasize that estradiol assays are not standardized, and their accuracy and interpretation can be problematic in the presence of very low levels of estradiol.

The International Breast Cancer Study Group–conducted TREND trial compared estradiol suppression in premenopausal patients receiving the GnRH agonist triptorelin or GnRH antagonist degarelix, each with letrozole, for six 28-day neoadjuvant cycles.[27] Patients treated with degarelix had faster time to suppression, and all maintained suppression throughout six cycles. There were increased endocrine symptoms but no other adverse events. The potential for a GnRH antagonist to maintain or improve efficacy and obviate concerns of inadequate OFS should be investigated along with adverse effects and adherence.

Are There Special Considerations for Very Young Patients (Younger Than 35 Years)?

Although the relative efficacies of tamoxifen plus OFS versus tamoxifen and exemestane plus OFS versus tamoxifen with or without OFS are independent of age, younger women have the largest magnitude of absolute improvement in outcomes with OFS.[10,28] Adherence with endocrine therapy can be problematic in very young patients, who more often stopped treatment early in SOFT and TEXT.[28] Surprisingly, the very young women did not report worse quality of life than the older premenopausal women.[28] Monitoring adherence and addressing adverse effects are especially critical in this patient subgroup.

What Is the Future for SOFT and TEXT?

Follow-up of patients in SOFT and TEXT continues, with analysis planned in 2021 after reaching a minimum follow-up of 10 years. The longer follow-up is essential to understand later recurrences and potential late treatment toxicities. In the meantime, analyses of substudies, quality of life, and clinical and translational research questions continue. Fundraising efforts are underway to continue follow-up of these pivotal studies.

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

Disclosures provided by the authors and data availability statement (if applicable) are available with this article at DOI https://doi.org/10.1200/JCO.18.02433.

AUTHOR CONTRIBUTIONS

Manuscript writing: All authors
Final approval of manuscript: All authors
Accountable for all aspects of the work: All authors

ACKNOWLEDGMENT

We thank the patients, physicians, nurses, trial coordinators, and pathologists who participated in the Suppression of Ovarian Function Trial (SOFT) and Tamoxifen and Exemestane Trial (TEXT). The trials were conducted by the International Breast Cancer Study Group (IBCSG) in collaboration with the Breast International Group (BIG), BIG cooperative groups, and US National Cancer Institute National Clinical Trials Network cooperative groups. SOFT and TEXT receive financial support for trial conduct and long-term follow-up from Pfizer, Ipsen, TerSera, Breast Cancer Research Foundation, and IBCSG. Pfizer and Ipsen provided drug supply.

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AUTHORS' DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST

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Consulting or Advisory Role: Merck, Ipsen (Inst)
Research Funding: Veridex (Inst), OncoGenex (Inst), Pfizer (Inst), Ipsen (Inst), Novartis (Inst), Merck (Inst), Ferring (Inst), Celgene (Inst), AstraZeneca (Inst), Pierre Fabre (Inst), Ipsen (Inst), Bayer (Inst), Bristol-Myers Squibb (Inst), Roche (Inst), Astellas Pharma (Inst), Medivation (Inst), Janssen (Inst), Millennium Pharmaceuticals (Inst), Sanofi (Inst), Sotio (Inst), Dendreon (Inst)
Travel, Accommodations, Expenses: Bristol-Myers Squibb

Gini F. Fleming
Research Funding: Corcept Therapeutics (Inst), AbbVie (Inst), Genentech (Inst), Tesaro (Inst), Syndax (Inst), Forty Seven (Inst), Iovance Biotherapeutics (Inst), Syros Pharmaceuticals (Inst), Astex Pharmaceuticals (Inst), Merck (Inst)

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Honoraria: AstraZeneca, Novartis
Travel, Accommodations, Expenses: Pfizer

No other potential conflicts of interest were reported.