Exemestane Plus Ovarian Function Suppression Is the Best Adjuvant Treatment of Premenopausal Women With Endocrine-Responsive Breast Cancer at Higher Risk of Relapse and With HER2-Negative Tumors

TO THE EDITOR:

In their recent article in *Journal of Clinical Oncology*, Pan et al¹ highlighted that in the Suppression of Ovarian Function Trial (SOFT), both the tamoxifen-plus-ovarian-function-suppression (OFS) and the exemestane-plus-OFS arms significantly improved the primary study end point of disease-free survival (DFS) compared with tamoxifen alone. However, only tamoxifen plus OFS significantly increased overall survival (OS).² The authors argued that the absence of OS improvement in the exemestane arm could be a result of the selection of more aggressive recurrent tumors after adjuvant treatment with aromatase inhibitors.¹ Such considerations led the authors to conclude that tamoxifen plus OFS represents “a prudent approach for the management of premenopausal women with early-stage, estrogen receptor-positive breast cancer.”¹

We disagree with this conclusion. The characteristics of the patients enrolled in SOFT differ from those anticipated in the trial design.^{2,3} An unanticipated enrollment of lower-risk, older premenopausal patients led to lower-than-expected event rates.³ As a consequence, the initial protocol of SOFT was modified, the primary objective was revised to testing the superiority of tamoxifen plus OFS over tamoxifen alone, and any other comparisons became secondary objectives.³

SOFT is therefore underpowered to assess outcome differences between the tamoxifen-plus-OFS and the exemestane-plus-OFS arms, especially for the OS that was a secondary end point.³ With a median follow-up of 8 years, only 76 of 1,014 patients in the exemestane-plus-OFS arm died and 61 of 1,015 patients in the tamoxifen-plus-OFS arm died. Because of the small number of deaths, it is not possible to draw reliable conclusions.²

On the contrary, the preplanned joint analysis of the Tamoxifen and Exemestane Trial (TEXT) and SOFT had adequate power to assess differences between the exemestane-plus-OFS and the tamoxifen-plus-OFS arms.² After a median follow-up of 9 years, the combined analysis confirmed that exemestane plus OFS significantly improved DFS and the distant recurrence-free interval (DRFI).² There was no significant

difference in the risk of death between the two arms: 320 patients (6.8%) died (158 in the exemestane arm and 162 in the tamoxifen arm).² The rate of OS at 8 years was 93.4% among patients assigned to receive exemestane plus OFS and 93.3% among those assigned to receive tamoxifen plus OFS (hazard ratio, 0.98; 95% CI, 0.79 to 1.22; $P = .84$).²

In subgroup analyses, the only heterogeneity-of-treatment effect was according to human epidermal growth factor receptor 2 (HER2) status (Table 1).² Patients with HER2-negative disease who were assigned to the exemestane-plus-OFS arm obtained a significant and large improvement of DFS and DRFI and also showed a trend for OS improvement (hazard ratio, 0.86; 95% CI, 0.68 to 1.10).²

On the contrary, in the HER2-positive group there was a nonsignificant trend for DFS and DRFI improvement and a significant improvement in OS in favor of the tamoxifen-plus-OFS arm.² The higher number of deaths observed in SOFT for the exemestane-plus-OFS arm compared with tamoxifen-plus-OFS arm was totally driven by the subgroup of HER2-positive tumors, whereas no difference was observed between the two treatment arms in the subgroup with HER2-negative tumors.²

A significant interaction between HER2 tumor status and the efficacy of an aromatase inhibitor versus tamoxifen was also recently reported in the Hormonal Bone Effects-2 (HOBEO-2) trial. This three-arm randomized controlled trial compared tamoxifen plus OFS with letrozole plus OFS with letrozole plus OFS plus zoledronic acid in premenopausal women with endocrine-responsive early-stage breast cancers.⁴ A significant improvement in DFS in the zoledronic-acid-plus-letrazole arm compared with tamoxifen has been reported in all the subgroups explored, apart from the small subgroup of women with HER2-positive tumors who showed greater benefit with tamoxifen (interaction $P = .002$).⁴ Because the data were derived from subgroup analyses, the finding of an interaction between HER2 status and the efficacy of aromatase inhibitors versus tamoxifen should be considered as hypothesis generating only and needs to be further validated.

In conclusion, results of the preplanned combined analyses of TEXT and SOFT are more appropriate than those of SOFT only for drawing conclusions regarding which is the better adjuvant treatment for premenopausal women with endocrine-responsive early-stage breast cancer. In accordance with these results, exemestane plus OFS should be considered the best treatment option, especially for patients at higher risk of relapse who benefit the most from this treatment approach. Available data suggest that the small

TABLE 1. Analyses of SOFT and TEXT

End Point and HER2 Status	SOFT											Joint Analysis of SOFT and TEXT											
	Tamoxifen Plus OFS						Exemestane Plus OFS					Tamoxifen Plus OFS						Exemestane Plus OFS					
	No. of Events	No. of Patients	8-Year Rate (%)	95% CI	HR	95% CI*	No. of Events	No. of Patients	8-Year Rate (%)	95% CI	HR	95% CI*	No. of Events	No. of Patients	8-Year Rate (%)	95% CI	No. of Events	No. of Patients	8-Year Rate (%)	95% CI	HR	95% CI†	P‡
DFS																							.014
Overall	167	1,015	83.2	80.5 to 85.4	0.76	0.62 to 0.93	143	1,014	85.9	83.4 to 88.1	0.65	0.53 to 0.81	402	2,344	82.8	81.1 to 84.3	318	2,346	86.8	85.3 to 88.2	0.77	0.67 to 0.9	
HER2 negative	147	868	82.8	80.0 to 85.3	0.83	0.67 to 1.04	105	858	88.0	85.5 to 90.2	0.60	0.47 to 0.76	350	2,024	82.7	80.9 to 84.4	250	2,022	88.1	86.5 to 89.6	0.70	0.60 to 0.83	
HER2 positive	16	119	85.4	77.3 to 90.8	0.41	0.22 to 0.75	72	411	75.2	66.4 to 82.0	0.74	0.45 to 1.22	47	280	82.9	77.6 to 87.0	60	298	79.7	74.4 to 84.0	1.18	0.80 to 1.73	
OS																							.015
Overall	61	1,015	93.3	91.4 to 94.8	0.67	0.48 to 0.92	76	1,014	92.1	90.0 to 93.7	0.85	0.62 to 1.15	162	2,344	93.3	92.1 to 94.3	158	2,346	93.4	92.2 to 94.4	0.98	0.79 to 1.22	
HER2 negative	53	868	93.4	91.3 to 95.0	NA		53	858	93.4	91.3 to 95.0	NA		142	2,024	93.4	92.1 to 94.5	120	2,011	94.1	92.9 to 95.1	0.86	0.68 to 1.10	
HER2 positive	5	119	95.1	88.5 to 97.9	NA		19	130	85.9	77.7 to 91.2	NA		16	280	93.7	89.9 to 96.1	34	298	89.5	85.1 to 92.7	1.91	1.05 to 3.46	

Abbreviations: DFS, disease-free survival; HER2, human epidermal growth factor receptor; HR, hazard ratio; NA, not available; OFS, ovarian function suppression; OS, overall survival; SOFT, Suppression of Ovarian Function Trial; TEXT, Tamoxifen and Exemestane Trial.

*Hazard ratio experimental arm v tamoxifen alone.

†Hazard ratio exemestane plus OFS v tamoxifen plus OFS.

‡Interaction between treatment efficacy and HER2 status. *P* values have not been corrected for multiple testing.

subgroup of HER2-positive/hormone receptor-positive tumors could derive more benefit from tamoxifen plus OFS, but additional validation is needed. Data on the interaction between treatment effect and tumor HER2 status from the Austrian Breast Cancer Study Group 12 (ABCSG-12; Tamoxifen Versus Anastrozole, Alone or in Combination With Zoledronic Acid) trial would be of great interest.

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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.19.00559>.

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