

## Quality of Life in the Intergroup Exemestane Study: A Randomized Trial of Exemestane Versus Continued Tamoxifen After 2 to 3 Years of Tamoxifen in Postmenopausal Women With Primary Breast Cancer

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### A B S T R A C T

#### Purpose

To compare and describe the quality of life (QOL) of women allocated to tamoxifen or exemestane within the Intergroup Exemestane Study (IES).

#### Patients and Methods

Postmenopausal women with primary breast cancer who were disease free after 2 to 3 years were randomly assigned to switch from tamoxifen to exemestane or continue with tamoxifen until 5 years of treatment were completed. A subset of IES centers participated in a QOL substudy. The Functional Assessment of Cancer Therapy–Breast (FACT-B) and endocrine subscale (ES) were administered before random assignment and at predefined follow-up times. The primary end point was the FACT-B composite Trial Outcome Index (TOI). Secondary end points included total FACT-B+ES score, total ES score, and severity of individual endocrine symptoms. This analysis reports QOL up to 24 months.

#### Results

Five hundred eighty-two patients from eight countries were enrolled onto the substudy. Completion and return of questionnaires was excellent, with 85% available for analysis. QOL was generally good and stable over 2 years, with no clinically meaningful differences found between groups in TOI or ES. Prevalence of severe endocrine symptoms at trial entry was high for vasomotor complaints and sexual problems, which persisted for both groups during the study. No significant differences between groups were seen for any endocrine symptoms apart from vaginal discharge, which was more pronounced with tamoxifen ( $P < .001$ ).

#### Conclusion

The switch from tamoxifen to exemestane neither increased nor decreased endocrine symptoms present after 2 to 3 years of tamoxifen; the switch also did not initiate significant reports of new symptoms. Results indicate that the clinical benefits of exemestane over tamoxifen are achieved without significant detrimental effect on QOL.

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### INTRODUCTION

For many years, tamoxifen was the primary adjuvant endocrine therapy for postmenopausal women with early-stage, hormone receptor–positive breast cancer. Five years of treatment improved overall survival and reduced recurrences and the development of contralateral breast cancer by approximately 50%.<sup>1</sup> However tamoxifen has rare but serious adverse effects, including thromboembolic disease and endometrial cancer, and is associated with vasomotor, gynecologic, and sexual problems; these can have a deleterious impact on the quality

of patients' lives and affect compliance with tablet taking.<sup>2</sup> Hence, efforts have been made to develop better endocrine agents such as the aromatase inhibitors (AIs).<sup>3,4</sup> Early results from trials, such as the Arimidex, Tamoxifen, Alone or in Combination (ATAC) and MA-17 trials, have reported disease-free survival (DFS) benefits without compromising short-term quality of life (QOL).<sup>5,6</sup>

The Intergroup Exemestane Study (IES), which was coordinated by the International Collaborative Cancer Group and run under the auspices of the Breast International Group, also showed significant DFS benefits.<sup>7</sup> In this double-blind study, 4,724 postmenopausal women with primary breast cancer

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who were disease free after 2 to 3 years of tamoxifen were randomly assigned to switch to exemestane or continue with tamoxifen until 5 years of treatment were completed. The most recent results, after a median follow-up of 37 months, showed significantly fewer recurrences, less contralateral breast cancer, and superior DFS in patients who were switched to exemestane compared with patients remaining on tamoxifen (hazard ratio = 0.73; 95% CI, 0.62 to 0.86;  $P = .0001$ ).<sup>8</sup> Physician-reported adverse effects showed more thromboembolic and gynecologic symptoms and muscle cramps with tamoxifen and more joint symptoms and diarrhea with exemestane.<sup>7</sup>

Several adjuvant AI trials are ongoing; of these trials that have reported to date, only the Arimidex, Tamoxifen, Alone or in Combination and MA-17 trials have published QOL data.<sup>5,6</sup> However, these trials are not directly comparable with each other or with IES because of differences in trial design, particularly the time at which AI treatment commenced. At entry to IES, patients were well past primary surgery and chemotherapy, which may impact on QOL,<sup>9,10</sup> and had already received 2 to 3 years of tamoxifen. There is evidence that the peak of endocrine-related symptoms occurs within the first 12 weeks of treatment, and thereafter, the symptoms decrease slightly or remain stable.<sup>5,11</sup> Arguably, women participating in IES were those most able to tolerate or adapt to any menopausal-type symptoms associated with endocrine therapy; alternatively, they might be women attempting to reduce symptoms by switching to a different treatment.

Because the modes of action of tamoxifen and exemestane differ (tamoxifen is a selective estrogen response modulator, whereas exemestane is a nonreversible steroidal AI), it was possible that the patients randomly assigned to exemestane might experience a flare of endocrine symptoms and/or develop new ones associated with lowered estrogen after tamoxifen withdrawal. In this article, we report the IES QOL results with 24 months of follow-up after random assignment.

## PATIENTS AND METHODS

### Study Design

In IES, 4,724 women were recruited, and preliminary results have already been reported.<sup>7,8</sup> Between March 2000 and January 2002, all eligible IES patients at participating QOL centers were asked to complete baseline questionnaires before random assignment. Subsequent questionnaires were administered before follow-up clinic visits at 3, 6, 9, 12, 18, 24, 30, 36, 48, and 60 months, at suspected recurrence or withdrawal from study treatment, and 1 month after recurrence. In the United Kingdom, questionnaires were posted directly to patients. In other countries, patients completed the questionnaires in clinic before clinical consultations, without assistance from clinical staff. All questionnaires were collated centrally by the Cancer Research UK Psychosocial Oncology Group, who remained blind to treatment allocation before analysis. Analysis of QOL data was undertaken jointly with the independent statisticians at the Institute of Cancer Research and the International Collaborative Cancer Group Data Center. The sponsor had no access to the QOL database or any role in the analysis. The institutional review board of each participating center approved the study protocol, and all patients gave written informed consent. The study was overseen by an independent data monitoring committee and conducted in accordance with the principles of the Good Clinical Practice Guidelines.

### Patients

Women were postmenopausal with early-stage, operable invasive breast cancer, had completed their primary treatment (surgery  $\pm$  radiotherapy  $\pm$  chemotherapy) according to local practice, and had received 2 to 3 years of adjuvant tamoxifen before enrollment. At participating centers, all patients

who consented to the main IES were eligible for the QOL substudy unless the investigator determined that they would be unable to complete questionnaires for psychological or literacy reasons.

### QOL Measures

QOL was measured using the Functional Assessment of Cancer Therapy–Breast (FACT-B)<sup>12</sup> questionnaire (version 3), together with an endocrine symptom subscale (ES) questionnaire (FACT-B+ES).<sup>11</sup> The FACT-B is a 38-item questionnaire with six subscales assessing physical (seven items), social (seven items), emotional (six items), and functional (seven items) well-being, relationship with doctor (two items), and additional concerns more specific to women with breast cancer (nine items). The ES was designed for use with the FACT-B and comprises 18 items. Four other items (sleep, fatigue, nervousness, and nausea) are already included in the FACT-B. Validated translations were available where relevant. Patients indicated how true a statement had been for them over the past 7 days using a 5-point scale as follows: 0, not at all; 1, a little bit; 2, somewhat; 3, quite a bit; and 4, very much. All items receive equal weighting.

### Study End Points

The primary end point was the Trial Outcome Index (TOI) of the FACT-B questionnaire; TOI is the sum of the scores from the 23 items that make up the physical and functional well-being and the breast cancer subscales. The TOI is a familiar and validated end point frequently used in clinical trials.<sup>13,14</sup> Higher TOI scores are associated with better QOL, and a change of 5 points is considered clinically meaningful.<sup>15</sup>

Secondary end points were the total FACT-B+ES (reflecting overall QOL) and ES (reflecting burden of endocrine symptoms) scores. ES items are negatively framed; thus, scores were reversed for analysis so that high scores equate to a good QOL. Additional analyses examining the proportion of patients reporting severe individual endocrine symptoms (reflecting symptoms that might trigger a clinical action, such as a prescription for pain relief or a vaginal lubricant or referral to a psychologist, and corresponding to endorsement of the quite a bit or very much response categories) were also conducted. Specific items of particular clinical interest were specified a priori in the protocol.

### Statistical Methods

The TOI was used to determine sample size for the QOL substudy. It was estimated that, to ensure an analysis with 95% power at a two-sided 5% significance level to conclude a treatment difference of 5 points or more, at least 235 patients per group were required.

The primary QOL substudy analysis was based on the intent to treat (ITT) and included all available questionnaires. Sensitivity analyses conducted using treatment received and excluding 22 protocol violators produced similar results (data not shown). All analyses were conducted using STATA version 8.2 (STATA Corp, College Station, TX).

For QOL scores, change from baseline to each time point was calculated for all patients with valid baseline questionnaires. Analysis of covariance was also used to compare QOL scores between treatment groups at each time point. This gave similar results (data not shown). Comparisons between randomly assigned treatment groups were based on two-sample *t* tests of mean change scores. Changes within treatment groups over time were assessed using one-sample *t* tests. To allow for multiple testing,  $P < .01$  was considered significant. To incorporate the longitudinal nature of the data, a repeated-measures multivariate analysis using generalized estimating equations (GEE)<sup>16</sup> was also performed. GEE can estimate the correlation of responses within an individual and assume incomplete data are missing at random. For these data, the models assumed an unstructured correlation and included terms for allocated treatment, baseline score, days from random assignment, and the a priori specified prognostic factors of estrogen receptor (ER) status (ER negative *v* ER positive), nodal status (node negative, one to three positive nodes, or  $\geq$  four positive nodes), chemotherapy use (yes *v* no), and hormone replacement therapy use before random assignment (yes *v* no). GEE models that did not include these prognostic factors gave similar results (data not shown). The estimate of the treatment term provides an overall measure of treatment difference in terms of QOL for the time period of 3 to 24 months. Neither an interaction between treatment effect and days from random

**Table 1.** Baseline Demographic and Clinical Characteristics

Characteristic	Exemestane (n = 289)		Tamoxifen (n = 293)		Total (N = 582)	
	No. of Patients	%	No. of Patients	%	No. of Patients	%
<b>Age</b>						
< 55 years	46	15.9	36	12.3	82	14.1
55-59 years	55	19.0	59	20.1	114	19.6
60-64 years	84	29.1	73	24.9	157	27.0
65-69 years	45	15.6	54	18.4	99	17.0
70+ years	59	20.4	71	24.2	130	22.3
<b>Tumor size</b>						
< 2 cm	150	51.9	165	56.3	315	54.1
2-5 cm	124	42.9	118	40.3	242	41.6
> 5 cm	12	4.2	9	3.1	21	3.6
Unknown	3	1.0	1	0.3	4	0.7
<b>Nodal status</b>						
Negative	162	56.1	167	57.0	329	56.5
1-3 positive nodes	78	27.0	69	23.5	147	25.3
≥ 4 positive nodes	37	12.8	42	14.3	79	13.6
Unknown	12	4.2	15	5.1	27	4.6
<b>Hormone receptor status</b>						
ER positive and/or PgR positive	269	93.1	266	90.8	535	91.9
ER negative and PgR negative	0	0.0	1	0.3	1	0.2
ER/PgR unknown	20	6.9	26	8.9	46	7.9
<b>Histologic type</b>						
Infiltrating ductal	216	74.7	237	80.9	453	77.8
Infiltrating lobular	50	17.3	39	13.3	89	15.3
Other	23	8.0	17	5.8	40	6.9
<b>Histologic grade</b>						
Grade 1	56	19.4	60	20.5	116	19.9
Grade 2	130	45.0	141	48.1	271	46.6
Grade 3	56	19.4	49	16.7	105	18.0
Grade 4	2	0.7	3	1.0	5	0.9
Grade X	0	0.0	2	0.7	2	0.3
Unknown/missing	45	15.6	38	13.0	83	14.3
<b>Primary location</b>						
Left	159	55.0	151	51.5	310	53.3
Right	130	45.0	142	48.5	272	46.7
<b>Surgery type</b>						
Mastectomy	141	48.8	138	47.1	279	47.9
BCT	146	50.5	155	52.9	301	51.7
Unknown	2	0.7	0	0.0	2	0.3
<b>Chemotherapy</b>						
Yes	130	45.0	125	42.7	255	43.8
No	159	55.0	168	57.3	327	56.2
<b>Radiotherapy</b>						
Yes	199	68.9	193	65.9	392	67.4
No	90	31.1	99	33.8	189	32.5
Unknown	0	0.0	1	0.3	1	0.2
<b>Use of HRT</b>						
Yes	139	48.1	136	46.4	275	47.3
No	145	50.2	154	52.6	299	51.4
Unknown	5	1.7	3	1.0	8	1.4
<b>Duration of tamoxifen before random assignment, months (interquartile range)</b>						
Median	26.8		27.8		27.3	
Interquartile range	24.9-31.0		25.1-32.0		25.0-31.8	
<b>Duration of randomly assigned treatment, months</b>						
Median	26.4		26.7		26.7	
Interquartile range	17.8-33.7		18.1-31.9		17.9-32.9	

Abbreviations: ER, estrogen receptor; PgR, progesterone receptor; BCT, breast-conserving therapy; HRT, hormone replacement therapy.

**Table 2.** Reasons for Missing Questionnaires

Reason Missing	Exemestane (No. of patients)	Tamoxifen (No. of patients)
Patient attrition	175	207
Administrative error	61	64
Patient choice	1	6
Reason unknown	53	33
Total	290	310

assignment nor adding polynomial effects improved the fit of the model. In addition, using an alternative correlation structure, such as exchangeable or autoregressive, did not impact on the results.

Analyses of individual ES items, using all available data, were performed by creating a binary variable differentiating severe or significant complaints (see Study End Points) from lesser or no complaint for each symptom. Proportions of patients reporting clinically significant symptoms at any time point are reported. GEEs were used to calculate odds ratios (ORs). Results of this analysis are presented graphically as Forrest plots (with 95% CIs), where ORs less than 1 imply a better QOL for exemestane compared with tamoxifen. The box size for each symptom on the Forrest plots is calculated using 1 SE of the treatment covariate. Symptoms are shown in four conceptually meaningful clinical categories. Rationale for this categorization and display has been described previously.<sup>5</sup>

## RESULTS

### Demographics

Five hundred eighty-two patients from eight countries were enrolled onto the QOL substudy; the majority of patients was from the United States ( $n = 280$ ) and the United Kingdom ( $n = 173$ ). Other countries included Spain ( $n = 50$ ), Argentina ( $n = 40$ ), Italy ( $n = 25$ ), Australia ( $n = 8$ ), the Netherlands ( $n = 4$ ), and New Zealand ( $n = 2$ ). Baseline demographic and clinical characteristics are listed in Table 1. Twenty-two patients in the QOL substudy were subsequently found to be ineligible for the main trial (inadequate primary treatment,  $n = 8$ ; uncertain menopausal status,  $n = 7$ ; previous osteoporotic fractures,  $n = 3$ ; ER negative,  $n = 2$ ; other reason,  $n = 2$ ) but are included in all analyses on an ITT basis.

### Attrition and Questionnaire Completion

Five hundred sixty-two of the 582 enrolled patients returned valid baseline questionnaires. Of those who did not return baseline

questionnaires, five patients subsequently returned follow-up forms. Overall patient attrition during the 2-year period was low, with a total of 90 patients (15.5%) withdrawn (exemestane,  $n = 38$ ; tamoxifen,  $n = 52$ ). Reasons for withdrawal included death/recurrence (exemestane,  $n = 3$ ; tamoxifen,  $n = 18$ ), adverse event (exemestane,  $n = 16$ ; tamoxifen,  $n = 14$ ), and other/consent withdrawn (exemestane,  $n = 19$ ; tamoxifen,  $n = 18$ ). During the 2-year follow-up period, a total of 3,474 (85.3%) of 4,074 questionnaires were returned from 582 enrolled patients and were available for analysis. The reasons for questionnaires missing are listed in Table 2.

### Primary End Point (TOI)

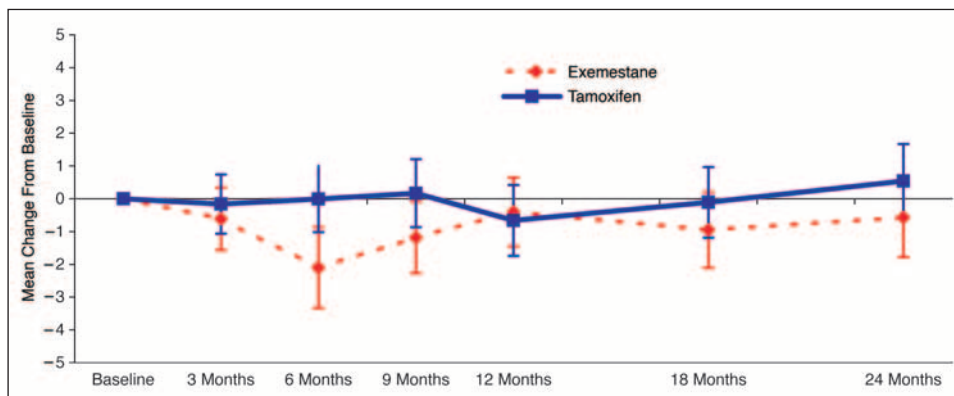
There were no significant treatment differences in TOI scores over the total time period from 3 to 24 months (GEE: mean TOI score for patients allocated to tamoxifen was 0.89 points higher than the score for patients in the exemestane group; 95% CI,  $-0.22$  to  $1.99$ ). When changes in baseline at each time point were examined, the TOI change at 6 months for patients in the exemestane group was statistically significantly different from the TOI change for patients in the tamoxifen group (mean difference in change scores [exemestane – tamoxifen] =  $-2.10$ ; 95% CI,  $-3.67$  to  $-0.52$ ;  $P = .009$ ). This difference is not clinically meaningful and arises from a modest, short-term reduction in TOI within the exemestane group ( $-2.10$ ; 95% CI,  $-3.32$  to  $-0.89$ ;  $P = .001$ ) and, as might be expected, no change in the tamoxifen group ( $-0.01$ ; 95% CI,  $-1.01$  to  $0.99$ ;  $P = .99$ ; Fig 1). At all other time points, there was no evidence to suggest a difference in TOI change scores between the groups.

There were no significant within-group changes in TOI for patients in the tamoxifen arm. Neither group displayed clinically meaningful mean changes at any time point, and the repeated-measures analysis suggested that, irrespective of treatment, TOI did not change significantly with time.

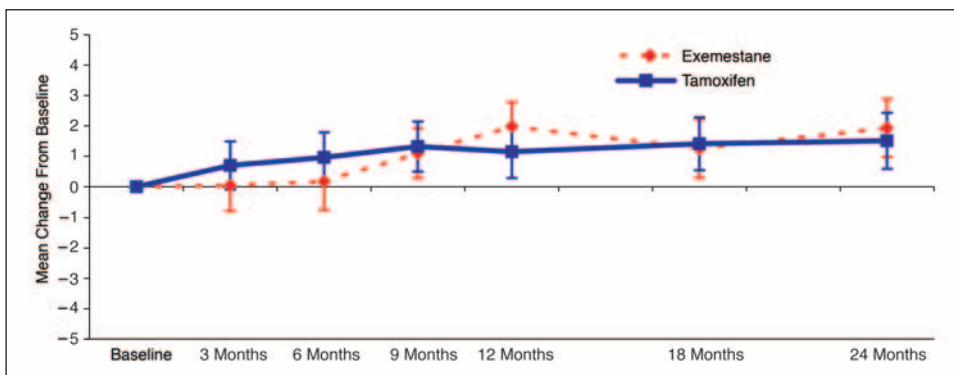
The proportions of patients who maintained a clinically meaningful TOI point increase from baseline at all time points and, thus, had a sustained improvement were 3.9% (95% CI, 2.0% to 6.9%) for exemestane and 4.7% (95% CI, 2.5% to 7.9%) for tamoxifen ( $P = .64$ ). The proportions of patients who had a clinically meaningful sustained decrease at each time point compared with baseline were 2.5% (95% CI, 1.0% to 5.1%) for exemestane and 3.6% (95% CI, 1.8% to 6.6%) for tamoxifen ( $P = .43$ ).

### Secondary End Points

ES. There was no significant difference between treatment groups in ES change scores over time. At individual time points, no



**Fig 1.** Mean (95% CI) Trial Outcome Index score changes from baseline.



**Fig 2.** Mean (95% CI) endocrine subscale score changes from baseline.

difference was seen at 6 months (mean difference [exemestane – tamoxifen] =  $-0.79$ ; 95% CI,  $-2.02$  to  $0.44$ ;  $P = .21$ ) or at any other time point. Irrespective of treatment, mean ES scores increased (ie, endocrine symptoms decreased) over time. Patients in the exemestane and tamoxifen arms had significantly higher ES scores compared with baseline (ie, fewer endocrine symptoms) at 9, 12, 18, and 24 months (all  $P \leq .01$ ; Fig 2).

**Total FACT-B+ES.** No significant differences in total FACT-B+ES scores were seen by treatment group or over time after adjustment for baseline score and known prognostic factors. There were no significant differences between treatment groups at 6 months (mean difference [exemestane – tamoxifen] =  $-3.08$ ; 95% CI,  $-6.10$  to  $-0.06$ ;  $P = .05$ ) or at any other time point. The only statistically significant within-treatment group change was seen at 6 months for patients in the exemestane arm, although this change was not clinically meaningful (mean change =  $-3.12$ ; 95% CI,  $-5.37$  to  $-0.87$ ;  $P = .007$ ; Fig 3).

### Severity of Individual Endocrine Symptoms

**Vasomotor symptoms.** Vasomotor complaints did not differ by randomly assigned treatment group (Fig 4A), although a considerable proportion of patients in each group reported that, at some point, hot flashes, cold and night sweats, and sleeping difficulties had affected them quite a bit or very much. The most commonly reported endocrine symptom in both groups was hot flashes (exemestane, 46%; tamoxifen, 45%); this symptom decreased over time in both groups.

**Neuropsychological symptoms.** Problems grouped under neuropsychological symptoms were common ( $> 10\%$  reporting quite a bit or very much) but did not differ significantly between treatment arms

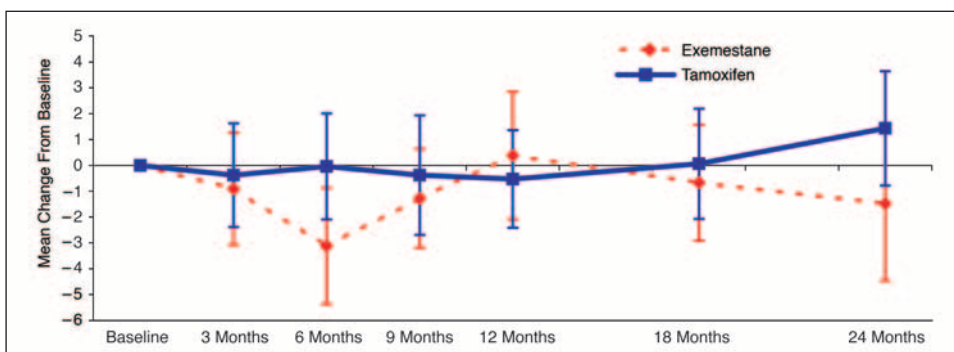
(Fig 4B). In particular, a lack of energy was reported at some point by 38% of exemestane patients and 34% of tamoxifen patients.

**GI symptoms.** There were no significant differences in GI symptoms between treatment groups (Fig 4C). Patients rarely reported nausea, vomiting, or diarrhea as severe ( $< 8\%$ ), whereas weight gain was reported at some point by at least 47% of patients.

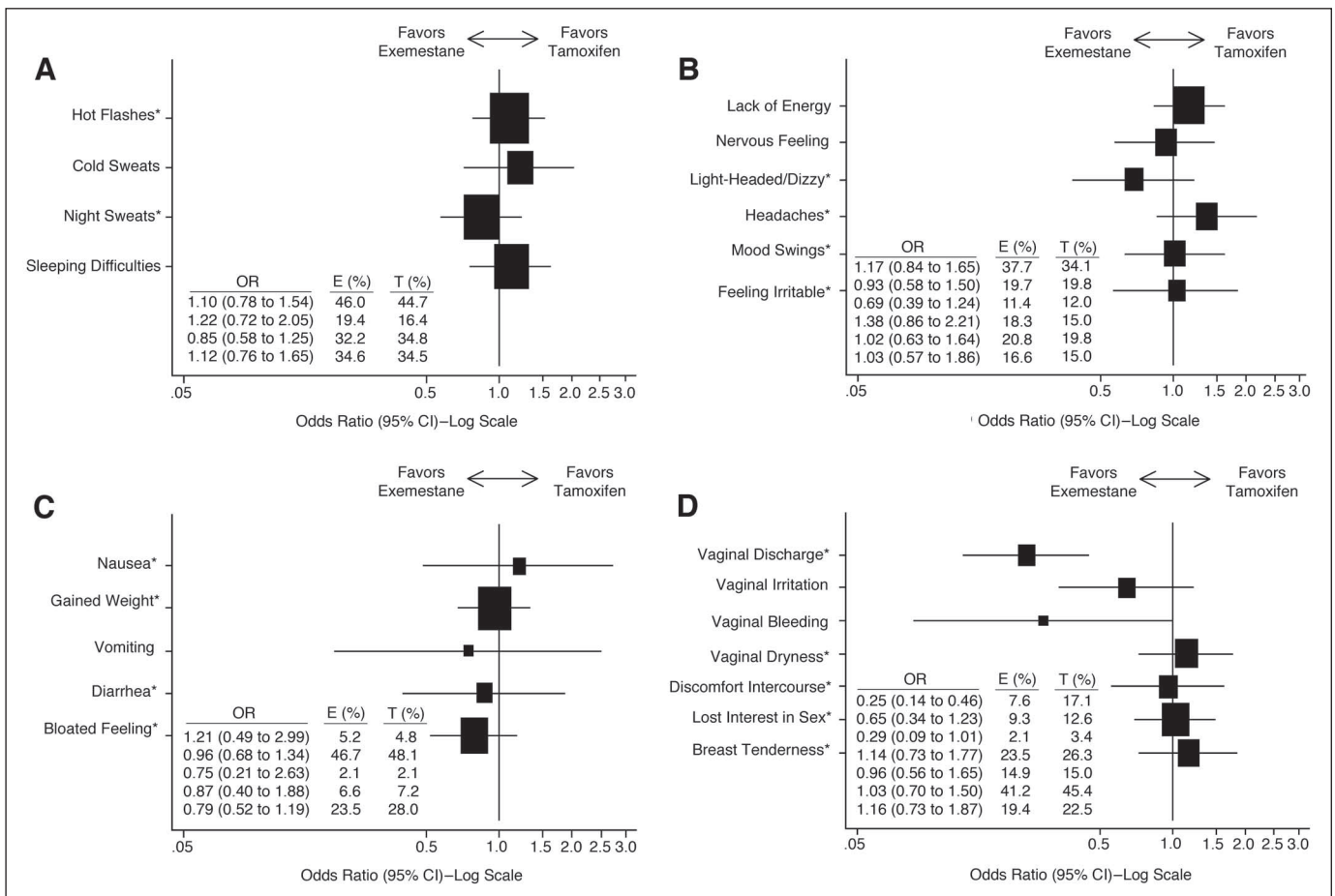
**Gynecologic symptoms.** Vaginal discharge was reported less frequently in the exemestane group (odds ratio [OR] =  $0.25$ ; 95% CI,  $0.14$  to  $0.46$ ;  $P < .001$ ; Fig 4D). The proportion of patients reporting that vaginal discharge affected them quite a bit or very much at some point was 7.6% in the exemestane group and 17.1% in the tamoxifen group. Vaginal bleeding was rarely reported (exemestane, 2.1% of patients; tamoxifen, 3.4% of patients), although there was a suggestion that, over time, this was a less frequent symptom in the exemestane group (OR =  $0.29$ ; 95% CI,  $0.9$  to  $1.01$ ;  $P = .052$ ). Loss of libido was common and did not differ between treatment groups (exemestane, 41.2% of patients; tamoxifen, 45.4% of patients). No significant differences were seen for vaginal dryness, discomfort with intercourse, and vaginal irritation.

## DISCUSSION

These results are encouraging and suggest that the clinical benefits already reported for switching to exemestane compared with continuation of tamoxifen are achieved without a detrimental effect on QOL. Although considerable proportions of patients recorded certain endocrine symptoms as severe during the study, overall QOL, as measured



**Fig 3.** Mean (95% CI) Functional Assessment of Cancer Therapy–Breast plus endocrine subscale score changes from baseline.



**Fig 4.** Odds ratios (ORs) with 95% CIs and proportions of patients reporting clinically significant symptoms at any time point. \* Indicates items that were identified a priori to be of clinical importance. (A) Vasomotor symptoms; (B) neuropsychological symptoms; (C) GI symptoms; and (D) gynecologic symptoms. E, exemestane; T, tamoxifen.

using the total FACT-B+ES and TOI, showed no clinically meaningful or statistically significant differences between treatment groups or significant changes from baseline (irrespective of treatment) over 24 months of follow-up.

No statistically significant differences were seen in ES change scores between treatments, with both groups showing a gradual lessening of endocrine symptoms over time. Patients were all 2 to 3 years after primary treatment at enrollment, so it would have been surprising to see a sudden adverse affect of tamoxifen on QOL. However, it was possible that the sudden switch to exemestane, a steroidal AI with a different molecular structure and biochemical profile, might have produced a flare or increase in endocrine symptoms. There was little evidence of this. In addition, there were no significant differences between groups in terms of severity of individual endocrine symptoms apart from vaginal discharge, which was greater in tamoxifen patients. Overall, there was a suggestion that several other gynecologic symptoms, including bleeding and irritation, were reported less frequently by patients taking exemestane, especially as time went on, but because prevalence of these symptoms was low, they were not shown to be significantly different between groups. Despite clinician reports of an association of diarrhea with exemestane,<sup>17</sup> GI problems and, specifically, diarrhea were reported as severe infrequently with exemestane and applied equally to women taking tamoxifen.

The prevalence of menopausal symptoms experienced by many patients as severe, irrespective of treatment, highlights the price paid for efficacious adjuvant hormone therapy. In common with other reports, vasomotor symptoms, especially hot flashes, sweating, and sleep disturbance, were frequent complaints that merit better ameliorative interventions.

Some comment is needed regarding the proportions of patients ever reporting severe symptoms. Prevalence was often similar and, for certain symptoms, high in both groups. Some of the ORs from the GEEs imply that the odds of reporting a severe symptom (the cumulative incidence) differ, albeit not statistically. This could be interpreted as symptoms disappearing more quickly in the exemestane group. Such an interpretation is consistent with a short carryover effect of tamoxifen; in other words, the number of patients with severe symptoms may be similar because all patients reported them at 3 months (the first assessment after the switch). Thereafter, symptoms more likely to be associated with tamoxifen seem to be reported less often by the exemestane group, whereas any reduction in the tamoxifen group may merely reflect a general reduction of symptoms over time. As an indication of the contribution of the carryover effect of tamoxifen, the bone substudy indicated that this was likely to last for less than 6 months because the decrease in bone mineral density was apparent at the 6-month time point, which is consistent with

the known half-life of tamoxifen and its active metabolite (4 and 9 days, respectively).<sup>18</sup>

The QOL instrument used in this study was developed specifically for research with women having endocrine treatment. Clinical reports of troublesome arthralgia and joint pains have only recently emerged as a problem associated with AIs. Newer versions of the

FACT-B+ES include this item and should be used in the future. Results from this study may encourage clinicians to offer patients a switch from tamoxifen to exemestane knowing that the superior clinical efficacy in terms of a reduced incidence of thromboembolic disorders, improved DFS, fewer recurrences, and less contralateral breast cancer may be achieved without compromising overall QOL.

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## Appendix

The Appendix is included in the full-text version of this article, available online at [www.jco.org](http://www.jco.org). It is not included in the PDF (via Adobe® Acrobat Reader®) version.

## Authors' Disclosures of Potential Conflicts of Interest and Author Contributions

Although all authors completed the disclosure declaration, the following authors or their immediate family members indicated a financial interest. No conflict exists for drugs or devices used in a study if they are not being evaluated as part of the investigation. For a detailed description of the disclosure categories, or for more information about ASCO's conflict of interest policy, please refer to the Author Disclosure Declaration and the Disclosures of Potential Conflicts of Interest section in Information for Contributors.

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