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Specific Adverse Events Predict Survival Benefit in Patients Treated With Tamoxifen or Aromatase Inhibitors: An International Tamoxifen Exemestane Adjuvant Multinational Trial Analysis

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ABSTRACT

Purpose
Specific adverse events (AEs) associated with endocrine therapy and related to depletion or blocking of circulating estrogens may be related to treatment efficacy. We investigated the relationship between survival outcomes and specific AEs including vasomotor symptoms (VMSs), musculoskeletal adverse events (MSAEs), and vulvovaginal symptoms (VVSs) in postmenopausal patients with breast cancer participating in the international Tamoxifen Exemestane Adjuvant Multinational (TEAM) trial.

Patients and Methods
Primary efficacy end points were disease-free survival (DFS), overall survival (OS), and distant metastases (DM). VMSs, MSAEs, and VVSs arising in the first year of endocrine treatment were considered. Patients who did not start or who discontinued their allocated therapy and/or had an event (recurrence/death) within 1 year after randomization were excluded. Landmark analyses and time-dependent multivariate Cox proportional hazards models assessed survival differences up to 5 years from the start of treatment.

Results
A total of 9,325 patients were included. Patients with specific AEs (*v* nonspecific or no AEs) had better DFS and OS (multivariate hazard ratio [HR] for DFS: VMSs, 0.731 [95% CI, 0.618 to 0.866]; MSAEs, 0.826 [95% CI, 0.694 to 0.982]; VVSs, 0.769 [95% CI, 0.585 to 1.01]; multivariate HR for OS: VMSs, 0.583 [95% CI, 0.424 to 0.803]; MSAEs, 0.811 [95% CI, 0.654 to 1.005]; VVSs, 0.570 [95% CI, 0.391 to 0.831]) and fewer DM (VMSs, 0.813 [95% CI, 0.664 to 0.996]; MSAEs, 0.749 [95% CI, 0.601 to 0.934]; VVSs, 0.687 [95% CI, 0.436 to 1.085]) than patients not reporting these symptoms. Increasing numbers of specific AEs were also associated with better survival outcomes. Outcomes were unrelated to treatment allocation.

Conclusion
Certain specific AEs are associated with superior survival outcomes and may therefore be useful in predicting treatment responses in patients with breast cancer treated with endocrine therapy.

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INTRODUCTION

Since the 1980s, adjuvant endocrine therapy by means of tamoxifen, a selective estrogen receptor modulator, has been a beneficial agent for patients with breast cancer, being most effective in hormone-sensitive breast cancer.[1,2] Later, 5 years of tamoxifen therapy became the gold standard for adjuvant endocrine treatment. Over the last 15 years, several studies have been performed to assess the value of third-generation aromatase inhibitors, showing benefit in terms of overall survival (OS), disease-free survival (DFS), distant disease-free survival, and contralateral breast cancer recurrence in postmenopausal patients with breast cancer who have hormone receptor–positive disease when compared with tamoxifen.[3-5] Other studies showed beneficial effects of a sequential treatment regimen consisting

of 2 to 3 years of tamoxifen followed by 2 to 3 years of an aromatase inhibitor when compared with tamoxifen alone.[3,4,6,7]

Both tamoxifen and aromatase inhibitors are associated with inconvenient and sometimes debilitating adverse effects resembling menopausal symptoms and which may be related to lower levels of peripherally circulating estrogens or blocking of the estrogen receptor (ER) in particular tissues, depending on the type of endocrine therapy used.[8-11] Some relevant and commonly reported adverse events (AEs) associated with adjuvant endocrine therapy for early breast cancer comprise vasomotor symptoms (VMSs), musculoskeletal and joint symptoms (MSAEs), and vulvovaginal symptoms (VVSs). After menopause, estrogen production is derived from peripheral tissues including adipose tissue, muscle, liver, skin, brain, bone marrow, and breast tissue.[12,13] VMSs are a well-known adverse effect of estrogen deprivation, occurring both naturally during menopause and artificially in relation to chemotherapy and endocrine therapy administered in patients with early breast cancer.[11] Estrogen is considered a factor that affects temperature regulation by promoting vasodilation, which influences blood flow to the skin.[14] Through decreased estrogen levels associated with endocrine therapy, the body lacks the ability to maintain normal body temperatures.[15] Estrogen deprivation has also been linked to the development of MSAEs in patients on endocrine therapy.[9] Estrogen has antinociceptive effects that influence the body's sensitivity to pain in articular structures as well as increased levels of proinflammatory cytokines, which is thought to be associated with MSAEs.[9,16] With respect to VVSs, aromatase inhibitors (further) lower postmenopausal estrogen levels, causing vaginal atrophy, and possibly resulting in vaginal dryness and dyspareunia.[17,18] Tamoxifen, however, has known agonist effects on the uterus.[19,20]

Adverse effects during long-term treatment can significantly impact quality of life as well as treatment compliance. Earlier studies on adjuvant breast cancer therapy recognized that noncompliance is largely attributable to the presence of adverse effects.[21-25] Furthermore, treatment outcomes can be compromised when adjuvant endocrine treatment is not taken for the full prescribed duration.[26]

In earlier reports, the relationship between vasomotor as well as musculoskeletal symptoms and breast cancer recurrence in patients treated with adjuvant endocrine therapy was investigated.[27,28] The presence of both symptoms was predictive of fewer breast cancer recurrences. Recently, we reported results of Dutch and Belgian exemestane-only patients and found a significant relapse-free survival (RFS) benefit in patients who reported VMSs and MSAEs.[29] Similarly, a recent investigation by Huober et al[30] in the Breast International Group 1-98 trial found associations between arthralgia, myalgia, and vasomotor symptoms and improved DFS. Stearns et al,[31] however, also investigated the association between endocrine symptoms and RFS in the MA27 trial, but did not find a benefit in patients who reported VMSs and/or MSAEs. Another issue is that patients treated with either tamoxifen or aromatase inhibitors commonly complain of VVSs. Vaginal dryness was addressed in the study by Huober et al,[30] categorized as one of the VMSs. To the author's knowledge, no other reports exist on the relationship between VVSs and breast cancer recurrence.

In the present analysis, we investigated the relationship between specific AEs (VMSs, MSAEs, and VVSs) arising in the first year of endocrine therapy and treatment efficacy in postmenopausal patients with early breast cancer enrolled in the Tamoxifen Exemestane Adjuvant Multinational (TEAM) trial. In addition, the influence of early treatment discontinuation within the 5-year treatment period in relation to outcome in patients with and without specific AEs was assessed.

PATIENTS AND METHODS

TEAM Trial

The TEAM trial is a randomized, phase III, multinational, open-label study conducted in postmenopausal women with ER and/or progesterone receptor–positive breast cancer and who were eligible for adjuvant endocrine treatment. Patients were randomly assigned to receive either exemestane 25 mg once daily for 5 years or tamoxifen 20 mg once daily for 2.5 to 3 years, followed by exemestane 25 mg once daily for 2.5 to 2 years (sequential regimen).[6] Participants were enrolled in 599 hospitals in nine countries worldwide (Belgium, France, Germany, Greece, Japan, the Netherlands, United Kingdom and Ireland, and the United States).[6] Similar trial protocols were used in all countries, with minor differences to accommodate the regional treatment guidelines; the TEAM trial protocols were approved by the regulatory and ethics authorities of all participating centers in all participating countries.[6] All patients provided written informed consent, and additional consent was obtained from patients using tamoxifen for the switch to exemestane. The study was conducted in compliance with the guidelines of the Declaration of Helsinki, International Conference on Harmonisation, and Good Clinical Practice. Appropriate approvals from the ethical committee were obtained.[6] Data collection was performed locally by case report forms and regularly transferred to a local data center, after which the Central Statistical and Data Center collected and analyzed the pooled data. Follow-up was carried out every 3 months in the first year and twice yearly until year 5 (end of randomized therapy), with yearly mammography. Details of eligibility criteria have been published in earlier reports.[6]

In the TEAM trial, 9,766 patients were allocated to 5 years of exemestane or to a sequential treatment with tamoxifen followed by exemestane for a total of 5 years in the TEAM trial. For the current analyses, we excluded patients who did not start the randomized treatment, who discontinued their allocated therapy within the first year, or who had an event (recurrence or death) within the first year of starting endocrine therapy.

AEs

All AEs reported in the first year of starting adjuvant endocrine therapy were included in the analyses. AEs were obtained from patient responses during follow-up visits, and a standard symptom checklist was not used. Severity of AEs was assessed using the National Cancer Institute Common Toxicity Criteria and were centrally recoded using the Medical Dictionary for Regulatory Activities (version 12.1).[6] VMSs were defined as a subjective and transient sensation of heat, including hot flashes and night sweats. MSAEs were all accounts of arthralgia, arthritis, arthrosis, myalgia, and bone pain. For the current analysis, osteoporosis was not considered an MSAE due to the fact that osteoporosis is a long-term process, likely to take more than 1 year to become evident. VVSs included all accounts of vaginal dryness/itching, vaginal discharge, dyspareunia, and endometrial and libido disorders.

End Points

The efficacy end points of the present investigation were DFS, OS, and distant metastases (DM), starting as of the second year of therapy. DM comprised all cases of metastases of the skeleton, skin, liver, lung, brain, and contralateral lymph nodes and excluded locoregional recurrences (including ipsilateral breast cancer, ipsilateral lymph nodes, ipsilateral chest wall recurrences), contralateral breast cancer, and new primary tumors. DFS was defined as the time on treatment to the earliest documentation of disease relapse or death (all causes) or end of follow-up, whichever came first. OS was defined as the time on treatment to the date of death.

The relationship between the occurrence of specific AEs (VMSs, MSAEs, and VVSs) and survival and recurrence outcomes was assessed. Furthermore, we evaluated the relationship between outcome measures and the sum of the different kinds of specific AEs reported per patient.

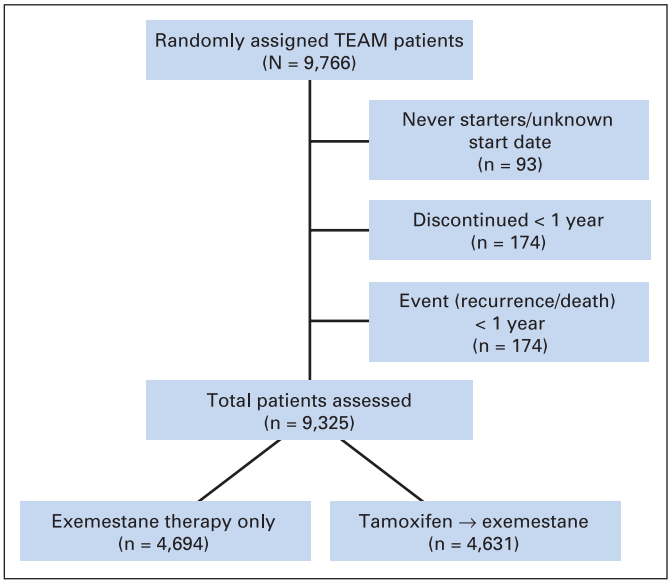

Fig 1. CONSORT diagram. Patients included in the analyses of adverse events and breast cancer outcomes. TEAM, Tamoxifen Exemestane Adjuvant Multinational.

Statistical Analysis

Statistical analyses were performed using SPSS 17.0 (SPSS, Chicago, IL). It was possible to combine the patients in the two treatment groups, as the primary efficacy analysis found no differences in outcome between the two treatment arms.[6] Landmark analyses were conducted, with follow-up starting at 1 year after randomization. Accounts of specific AEs reported in the first year after randomization were used to classify patients into the yes/no cohorts for VMSs, MSAEs, and VVSs. Kaplan-Meier curves were plotted for time to event. Early treatment discontinuation is an important factor in patients who experience AEs of endocrine treatment, as shorter time on treatment may negatively influence outcomes.[26] Multivariate time-dependent Cox proportional hazards models with specific adverse event (yes/no), on treatment (yes/no), and their interaction assessed differences in survival with respect to the presence or absence of VMSs, MSAEs, and VVSs, in relation to time on treatment. All multivariate analyses were adjusted for age at diagnosis, country, histologic grade, tumor size, nodal stage, most extensive surgery, radiotherapy, and chemotherapy. Interaction terms between adverse symptoms and all previously mentioned adjusted variables were incorporated in the Cox model to test for the presence of effect modification.

RESULTS

Study Population

In total, 9,325 patients (95%) were included in the current analyses; reasons for exclusion are shown in Figure 1. We excluded patients who never started treatment or who had an unknown start date (n = 93) and patients who discontinued their allocated therapy (n = 174) or who had an event (recurrence or death) within the first year of treatment (n = 174). A total of 4,694 patients were allocated to receive 5 years of exemestane, and 4,631 patients were allocated to receive the sequential treatment regimen. Median follow-up was 5.13 years (range, 0.01 to 9.23 years), and median age was 63.8 years (range, 34.9 to 96.1 years). Baseline characteristics were similar between the two treatment groups.[6]

Baseline characteristics of the patients who reported specific AEs versus none or nonspecific AEs are shown in Table 1. Overall, there was no difference in the presence of specific versus none or nonspecific AEs between randomized treatments. Assessed separately, patients allocated sequential treatment reported fewer VMSs and MSAEs, but more VVSs (χ^2 $P < .001$ for all comparisons). Younger patients were more likely to report specific AEs, whereas older patients were more likely to report nonspecific AEs (< 60/60 to <75/≥ 75 years: 16.3%/22.2%/31.5% nonspecific AEs reported, respectively). In addition, patients who reported specific AEs more frequently had well-differentiated and low-grade tumors, had node-negative disease, underwent breast-conserving surgery, and had adjuvant radiotherapy

Table 1. Baseline Characteristics for Specific Versus None or Nonspecific Adverse Events

Characteristic	None or Nonspecific AEs No.	%	Specific AEs No.	%	*P*
Age, years					
Median	65.5		62.1		
Range	34.9-92.5		35.8-96.1		
Randomized treatment					.270
Exemestane	2,389	50.9	2,305	49.8	
Tamoxifen → exemestane	2,304	49.1	2,327	50.2	
Age at diagnosis, years					< .001
< 60	1,352	28.8	1,823	40.5	
60-69	1,778	37.9	1,789	38.6	
≥ 70	1,563	33.3	970	20.9	
Grade, BR					< .001
Well (G1)	713	15.2	888	19.2	
Moderate (G2)	2,339	49.8	2,262	48.8	
Poor (G3,G4)	1,276	27.2	1,034	22.3	
Unknown (Gx)	365	7.8	448	9.7	
T stage					< .001
1 (≤ 2 cm)	2,519	53.7	2,974	64.2	
2 (> 2-≤ 5 cm)	1,906	40.6	1,478	31.9	
3 and 4 (> 5 cm)	257	5.5	168	3.6	
IS, 0	3	0.1	3	0.1	
Tx (unknown)	8	0.2	9	0.2	
N stage					< .001
Node negative	2,223	47.4	2,704	58.4	
Node positive	2,470	52.6	1,928	41.6	
ER status					.195
Positive	4,606	98.1	4,558	98.4	
Negative	87	1.9	72	1.6	
Not performed	0	0	2	0	
PR status					< .001
Positive	3,412	72.7	3,578	77.2	
Negative	825	17.6	796	17.2	
Not performed	456	9.7	258	5.6	
Most extensive surgery					< .001
Mastectomy	2,170	46.2	1,921	41.5	
Breast-conserving surgery	2,519	53.7	2707	58.4	
No resection/unknown	4	0.1	4	0.1	
Adjuvant radiotherapy					< .001
Yes	3,139	67.4	3,298	72.0	
No	1,521	32.6	1,284	28.0	
Unknown					
Adjuvant chemotherapy					< .001
Yes	1,466	31.3	1,890	40.8	
No	3,223	68.7	2,742	59.2	

Abbreviations: AEs, adverse events; BR, Bloom & Richardson; ER, estrogen receptor; PR, progesterone receptor.

Table 2. Survival Outcomes and Distant Metastases for Vasomotor Symptoms, Musculoskeletal Adverse Events, and Vulvovaginal Symptoms

Survival Outcome	Univariate HR	95% CI	*P*	Multivariate HR*	95% CI	*P*	Interaction AE and Time on Treatment (*P*)
Disease-free survival							
Vasomotor symptoms							
Yes	0.591	0.502 to 0.697	< .001	0.731	0.618 to 0.866	< .001	.398
No	1	Ref		1	Ref		
Musculoskeletal AEs							
Yes	0.678	0.575 to 0.80	< .001	0.826	0.694 to 0.982	.030	.233
No	1	Ref		1	Ref		
Vulvovaginal symptoms							
Yes	0.566	0.437 to 0.733	< .001	0.769	0.585 to 1.01	.058	.134
No	1	Ref		1	Ref		
Overall survival							
Vasomotor symptoms							
Yes	0.460	0.372 to 0.570	< .001	0.583	0.424 to 0.803	.001	.19
No	1	Ref		1	Ref		
Musculoskeletal AEs							
Yes	0.621	0.506 to 0.762	< .001	0.811	0.654 to 1.005	.055	.802
No	1	Ref		1	Ref		
Vulvovaginal symptoms							
Yes	0.40	0.279 to 0.575	< .001	0.570	0.391 to 0.831	.003	.016
No	1	Ref		1	Ref		
Distant metastases							
Vasomotor symptoms							
Yes	0.664	0.545 to 0.809	< .001	0.813	0.664 to 0.996	.046	.183
No	1	Ref		1	Ref		
Musculoskeletal AEs							
Yes	0.615	0.498 to 0.760	< .001	0.749	0.601 to 0.934	.010	.063
No	1	Ref		1	Ref		
Vulvovaginal symptoms							
Yes	0.639	0.471 to 0.866	.004	0.687	0.435 to 1.085	.107	.870
No	1	Ref		1	Ref		

Abbreviations: AEs, adverse events; HR, hazard ratio; Ref, reference.
*Multivariate analyses were adjusted for age, country, histologic grade, tumor size, nodal stage, most extensive surgery, radiotherapy, and chemotherapy.

and chemotherapy when compared with patients who did not report specific AEs.

Within the first year of treatment, 3,003 patients (32.2%) reported vasomotor symptoms (with or without other specific or nonspecific adverse effects), 2,635 patients reported musculoskeletal AEs (28.3%), and 1,150 patients reported vulvovaginal symptoms (12.3%).

DFS

DFS outcomes are depicted in Table 2 and Figure 2. Using both univariate and multivariate Cox regression analyses (adjusted for age at diagnosis, country, histologic grade, tumor size, nodal stage, most extensive surgery, radiotherapy, and chemotherapy), patients who reported VMSs or MSAEs had a better DFS than those who did not report these symptoms (multivariate hazard ratio [HR] for VMSs: 0.731 [95% CI, 0.618 to 0.866]; MSAEs: 0.826 [95% CI, 0.694 to 0.982]). DFS was significantly better in patients who reported VVSs after univariate analyses and borderline significant after multivariate analyses (univariate HR: 0.566 [95% CI, 0.437 to 0.733]; multivariate HR: 0.769 [95% CI, 0.585 to 1.01]).

OS

Figure 2 shows OS outcomes for VMSs, MSAEs, and VVSs, respectively. Both univariate and multivariate Cox regression analyses showed that patients who reported VMSs or VVSs had better outcomes in terms of OS than those who did not report these symptoms (multivariate HR for VMSs: 0.583 [95% CI, 0.424 to 0.803[; for VVSs: 0.570 [95% CI, 0.391 to 0.831[). There was a borderline significance for improved OS with respect to MSAEs versus no MSAEs after multivariate analyses (multivariate HR: 0.811 [95% CI, 0.654 to 1.005]; Table 2).

DMs

Further investigations into the occurrence of VMSs and MSAEs in relation to DM revealed that patients who reported these symptoms had fewer accounts of DM than when these symptoms were not reported (multivariate HR for VMSs: 0.813 [95% CI, 0.664 to 0.996[; MSAE: 0.749 [95% CI, 0.601 to 0.934[). VVSs were associated with significantly fewer DMs after univariate analyses, but not for multivariate analyses (Table 2). There was no effect modification for treatment discontinuation and the risk of DM for VMSs, MSAEs, and VVSs (Table 2).

Early Treatment Discontinuation

Time-dependent Cox regression analyses were performed to investigate the relationship between time on treatment and survival outcomes. Pertaining to VMSs and MSAEs, treatment discontinuation did not affect the improved DFS and OS in patients who reported

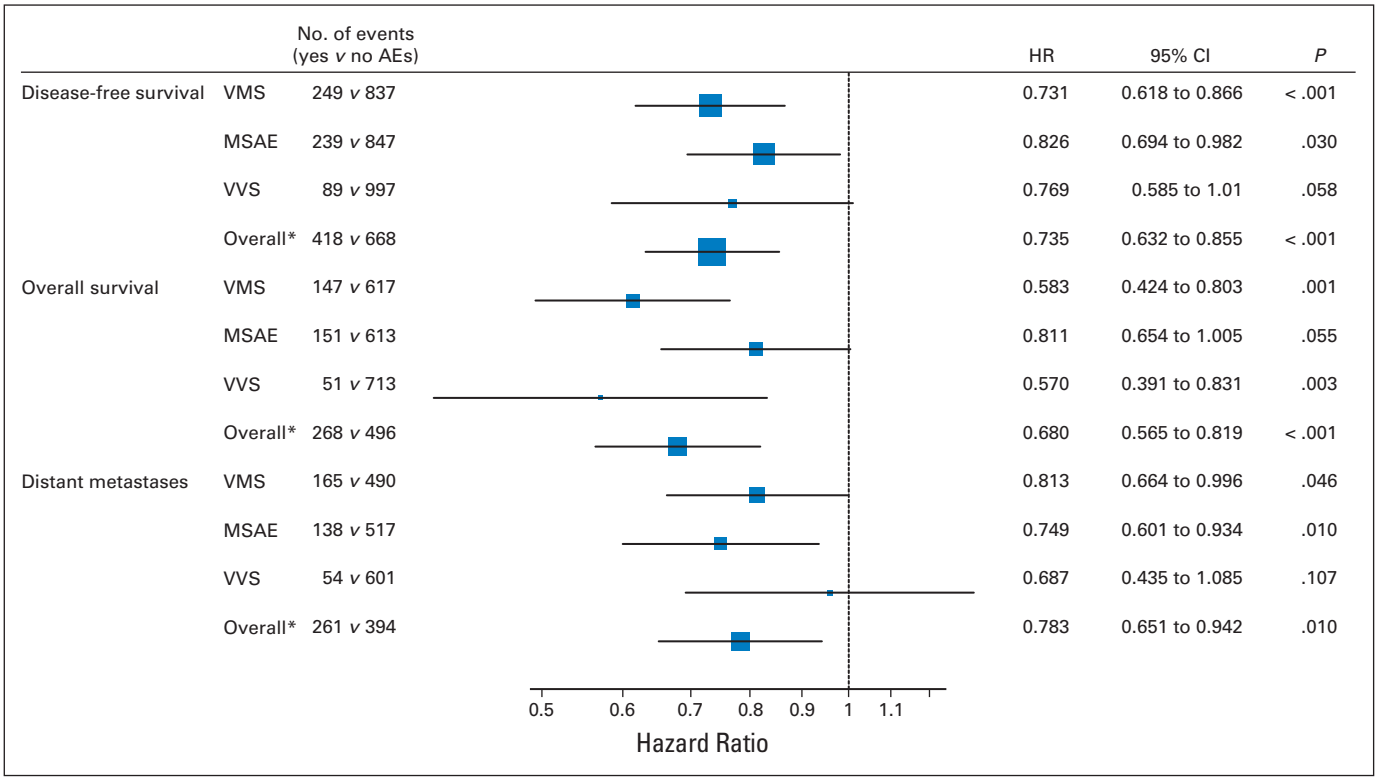

Fig 2. Outcomes for disease-free survival, overall survival, and distant metastases in relation to specific adverse events (AEs). HR, hazard ratio; MSAE, musculoskeletal adverse events; VMS, vasomotor symptoms; VVS, vulvovaginal symptoms.

these specific AEs. Therefore, even if patients discontinued treatment before the predesignated stop date (which was 5 years after the start of randomized therapy), a survival benefit persisted in those who reported specific AEs. This was also the case for DFS in relation to VVSs, but not for OS (P for interaction = .016; Table 2).

Sum of Specific AEs

A patient could have a maximum of three types of specific AEs, which was the sum of VMSs, MSAEs, and VVSs (yes/no outcome). Improved outcomes for DFS, OS, and DM were found for increasing numbers of specific AEs reported (Table 3; Fig 3).

Table 3. Outcome Based on the Number of Specific Adverse Events Reported

No. of Specific AEs	No. of Patients	Univariate HR	95% CI	P	Multivariate HR*	95% CI	P
Disease-free survival							
0	4,658	1	Ref	< .001	1	Ref	.001
1	2,825	0.647	0.551 to 0.760		0.769	0.651 to 0.909	
2	1,384	0.501	0.396 to 0.634		0.668	0.522 to 0.853	
3	373	0.432	0.273 to 0.683		0.624	0.388 to 1.004	
Overall survival							
0	4,740	1	Ref	< .001	1	Ref	< .001
1	2,862	0.587	0.483 to 0.713		0.744	0.608 to 0.910	
2	1,402	0.405	0.299 to 0.548		0.579	0.423 to 0.794	
3	374	0.189	0.084 to 0.423		0.296	0.130 to 0.673	
Distant metastases							
0	4,689	1	Ref	< .001	1	Ref	.049
1	2,832	0.694	0.57 to 0.845		0.805	0.657 to 0.987	
2	1,389	0.554	0.417 to 0.734		0.762	0.568 to 1.024	
3	374	0.358	0.191 to 0.672		0.563	0.294 to 1.079	

Abbreviations: AEs, adverse events; HR, hazard ratio; Ref, reference.
*Multivariate analyses were adjusted for age, country, histologic grade, tumor size, nodal stage, most extensive surgery, radiotherapy and chemotherapy.

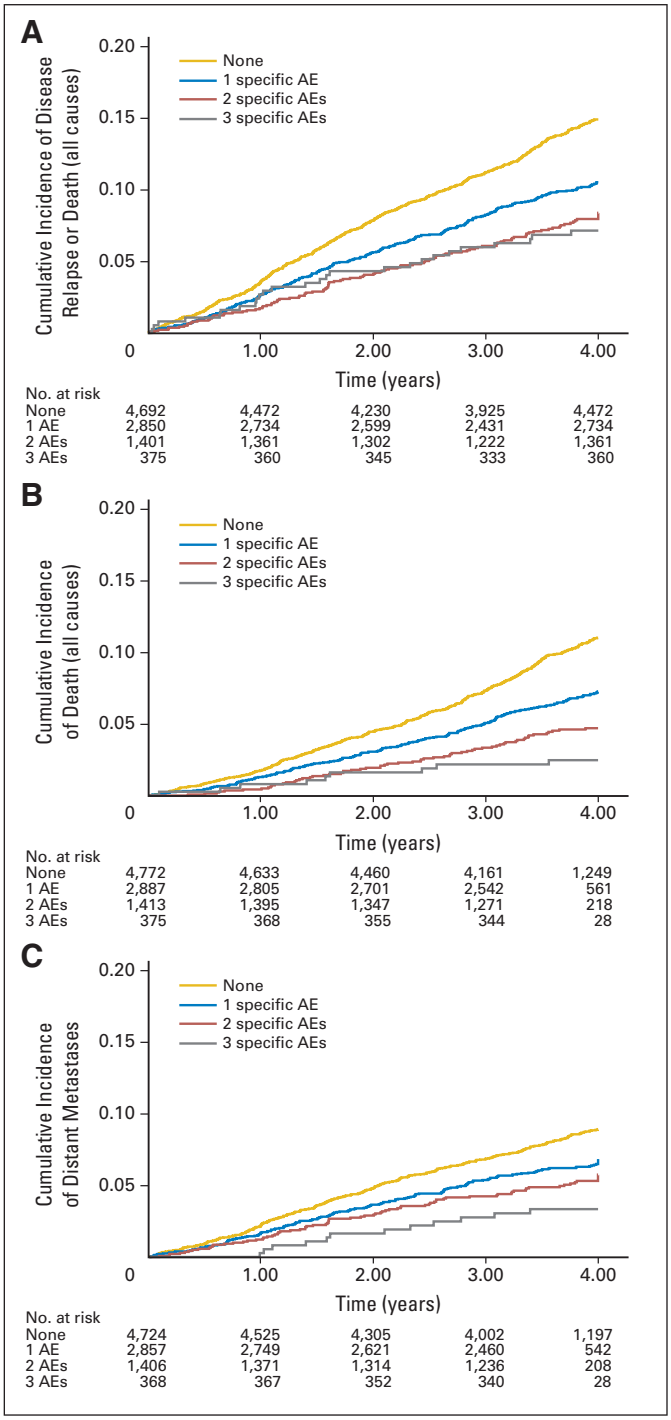

Fig 3. Outcomes for (A) disease-free survival, (B) overall survival, and (C) distant metastases based on the number of specific adverse events (AEs) reported.

Adjuvant Chemotherapy in Relation to Specific AEs

Patients who received adjuvant chemotherapy more frequently reported specific AEs when compared with patients who had not been treated with adjuvant chemotherapy (56.3% *v* 43.7%; $P < .001$). There is a known relationship between adjuvant chemotherapy and menopausal symptoms, although the relation with late-onset symptoms has not been fully investigated.[32] We tested for effect modification by chemotherapy for VMSs and VVSs and MSAEs. No effect could be demonstrated (data not shown).

DISCUSSION

The present analyses showed that postmenopausal patients with breast cancer who received at least 1 year of adjuvant endocrine therapy and who reported one or more treatment-related AEs during the first year of treatment had better subsequent outcomes in terms of DFS and OS and fewer DMs than patients who do not report these symptoms. The strongest effect on distant recurrence and survival outcomes was observed for VMSs. A decreasing incidence of distant metastases, disease relapse, and death was noted in patients reporting increasing numbers of different specific AEs. Furthermore, even if patients who reported specific AEs were not on treatment for the full duration, they still had better outcomes than patients who were on treatment for longer, but did not experience specific AEs. No difference in effect was found between the two TEAM trial treatment arms.

The present investigation only included patients who reported symptoms in the first year of endocrine therapy. Because of the unplanned nature of these analyses, preexisting symptoms were not recorded. The effect observed may therefore be larger when the occurrence of specific AEs over the entire follow-up period is considered. Reporting of AEs may not be uniform across countries or study centers within countries; therefore, it is conceivable that results may be influenced by reporting bias. The incidence of reported specific AEs varied considerably by country, and survival outcomes were better in countries where more specific AEs were reported (Appendix Table A1, online only). These results must be interpreted with caution, as no information was available for individual study centers. All AEs were patient-reported AEs, and no standardized symptom checklist was used. Cultural differences between countries may therefore also reflect differences in reporting of AEs. A symptom checklist that actively inquires about a patient's symptoms and severity thereof will undoubtedly lead to a more accurate assessment and potentially observe a stronger relationship between specific AEs, severity, and improved outcomes. Also of note, characteristics of patients reporting specific versus no or nonspecific AEs revealed that patients with specific AEs were younger, more frequently had lower-grade tumors and node-negative disease, and underwent breast-conserving surgery and adjuvant radiotherapy and chemotherapy. Although it is conceivable that older patients may be less likely than younger patients to report any AE at all, older patients reported more nonspecific AEs than younger patients in our cohort. Nonetheless, even after adjusting for these possible confounders, the correlation between specific AEs and superior outcomes was still present.

Previously, a relationship was found between VMSs and MSAE and disease recurrence in patients with breast cancer participating in the Arimidex, Tamoxifen, Alone or in Combination (ATAC) trial[27] and between hot flashes and outcomes in tamoxifen-treated patients in a study by Mortimer et al.[28] Our earlier manuscript regarding Dutch and Belgian exemestane users reports a relationship between MSAEs and VMSs and disease recurrence.[29] In the current analyses, we aimed to assess whether results varied in a much more heterogeneous population. Minor variations in protocols between countries accommodated regional treatment guidelines. Additionally, in the

context of cultural differences between countries, variations in reporting may exist. Most importantly, however, we address time on treatment in relation to the occurrence of AEs. In contrast to what is generally expected, Cuzick et al[27] noted a better treatment adherence in patients experiencing vasomotor and joint symptoms. However, noncompliance resulting from adverse effects plays an important role in adjuvant endocrine therapy for postmenopausal patients with hormone receptor–positive breast cancer, and several studies have reported that patients who discontinue treatment before the predesignated end date do so largely because of AEs.[21-25] Patients who discontinue the prescribed treatment regimen may not enjoy the full benefit of treatment as a result of shorter time on treatment.[26] Pritchard sharply points out that the reporting of AEs may depend on the kind of patient who reports these symptoms; this may be related to treatment compliance, which would hence explain improved treatment outcomes in these patients.[33] Similarly, patients who do not report specific AEs may not have taken the prescribed treatment. Therefore, we performed a time-dependent Cox regression analysis for time on and off treatment. The positive effect of specific AEs on outcomes did not change for patients who went off treatment. Accordingly, even if patients who experience specific AEs discontinued treatment before the designated stop date, they still had a survival benefit over patients who did not experience specific AEs.

Although our results must be considered hypothesis generating, our findings show an association between specific adverse effects caused by endocrine therapy and outcomes and may thus potentially be a valuable predictor and biomarker of treatment efficacy. Future prospective studies, however, are warranted to advance the personalization of treatment strategies for patients with breast cancer.

AUTHORS' DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST

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Appendix

Table A1. Disease-Free and Overall Survival Outcomes for Specific Adverse Events Versus Nonspecific Adverse Events by Country

Survival Outcome and Country	Specific AEs		No or Nonspecific AEs			Survival* (%)	
	No.	%	No.	%	χ^2 *P*	Specific AEs	No/nonspecific AEs
Disease-free survival							
France	777	65.0	418	35.0	< .001	92.6	91.4
Germany	745	53.0	660	47.0		91.2	88.8
Greece	13	7.0	172	90.0		84.6	87.6
Japan	108	61.7	67	38.3		86.6	87.4
Netherlands/Belgium	1,040	34.2	1,999	65.8		86.6	82.0
United Kingdom/Ireland	361	29.3	873	70.7		87.1	85.6
United States	1,588	75.9	504	24.1		92.4	85.4
Overall survival							
France	782	65.0	422	35.0	< .001	97.2	94.9
Germany	751	52.7	673	47.3		95.3	93.4
Greece	13	6.8	177	93.2		100	93.2
Japan	112	61.9	69	38.1		95.3	94.8
Netherlands/Belgium	1,061	34.2	2,042	65.8		90.3	85.9
United Kingdom/Ireland	364	29.2	884	70.8		91.4	88.4
United States	1,605	75.9	509	24.1		94.5	90.0

Abbreviation: AEs, adverse events.
*Disease-free survival in top portion; overall survival in bottom portion.