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CLINICAL TRIAL

Symptoms of endocrine treatment and outcome in the BIG 1-98 study

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Abstract There may be a relationship between the incidence of vasomotor and arthralgia/myalgia symptoms and treatment outcomes for postmenopausal breast cancer patients with endocrine-responsive disease who received adjuvant letrozole or tamoxifen. Data on patients randomized into the monotherapy arms of the BIG 1-98 clinical trial who did not have either vasomotor or arthralgia/myalgia/carpal tunnel (AMC) symptoms reported at baseline, started protocol treatment and were alive and disease-free at the 3-month landmark ($n = 4{,}798$) and at the 12-month landmark ($n = 4{,}682$) were used for this report. Cohorts of patients with vasomotor symptoms, AMC symptoms, neither, or both were defined at both 3 and 12 months from randomization. Landmark analyses were performed for disease-free survival (DFS) and for breast cancer free interval (BCFI), using regression analysis to estimate hazard ratios (HR) and 95 % confidence intervals (CI). Median follow-up was 7.0 years. Reporting of AMC symptoms was associated with better outcome for both the 3- and 12-month landmark analyses [e.g., 12-month landmark, HR (95 % CI) for DFS = 0.65 (0.49–0.87), and for BCFI = 0.70 (0.49–0.99)]. By contrast, reporting of vasomotor symptoms was less clearly associated with DFS [12-month DFS HR (95 % CI) = 0.82 (0.70–0.96)] and BCFI (12-month DFS HR (95 % CI) = 0.97 (0.80–1.18). Interaction tests indicated no effect of treatment group on associations between symptoms and outcomes. While reporting of AMC symptoms was clearly associated with better DFS and BCFI, the association between vasomotor symptoms and outcome was

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less clear, especially with respect to breast cancer-related events.

Keywords Aromatase inhibitor · Side effects · Breast cancer · Endocrine therapy

Background

Adjuvant treatments that suppress or block estrogens are effective for hormone-sensitive breast cancer, resulting in better relapse free and overall survival [1]. For several decades, the standard treatment has been tamoxifen. Recent studies have shown that the use of aromatase inhibitors (AIs) is associated with a better outcome compared to tamoxifen in postmenopausal breast cancer patients [2–4]. Tamoxifen blocks the estrogen receptor, while AIs suppress estrogen levels by inhibiting the enzyme responsible for conversion of androgens to estrogens in the peripheral tissue. The *CYP19A1* gene encodes the aromatase enzyme, and polymorphisms in this gene may impact estrogen levels [5, 6]. Tamoxifen is converted in vivo mainly by the cytochrome p450 enzyme CYP2D6 to endoxifen in order to exert adequate receptor blockade [7]. This metabolic capacity is genetically determined and can additionally be influenced by concomitant medication [8, 9].

Adverse events of AIs and tamoxifen differ significantly in incidence, most likely as a result of their specific mechanism of action. Adverse events more commonly seen with AIs include arthralgia, musculoskeletal disorders, osteoporosis, vaginal dryness, and dyspareunia. Adverse events more frequently observed with tamoxifen include thromboembolic events, endometrial disorders, and hot flushes [10]. Although many of these adverse events do not threaten the safety of the patient, short and long term inconvenience may lead to treatment discontinuation [11]. However, not every patient develops treatment-emergent endocrine side effects, and the appearance of these adverse events may reflect the degree of estrogen blockade or estrogen suppression in the individual patient, as well as characterizing the host hormonal environment. Thus, the occurrence of side effects frequently associated with endocrine therapies, along with other known factors, may help predict the efficacy of hormonal therapy.

For some drugs, there is evidence that the occurrence of specific side effects may predict the likelihood of treatment success. In HER1/EGFR-targeted agents, treatment efficacy was linked to the occurrence of acneiform skin rash [12]. In some trials, the appearance of hypertension was an indicator of response to treatment with the angiogenesis inhibitor bevacizumab [13]. Currently available evidence of the association of endocrine-related side effects and efficacy in patients who received hormonal treatment is, however, conflicting and inconclusive.

In this retrospective analysis of prospectively-collected data of adverse events, we evaluated disease-related outcomes of patients from the BIG 1-98 trial treated with 5 years of letrozole or tamoxifen according to the incidence of vasomotor and arthralgia/myalgia/carpal tunnel (AMC) symptoms reported within 3 and 12 months following randomization.

Patients and methods

Study design

The BIG 1-98 trial [2] is an international randomized multicenter double-blind phase 3 trial that enrolled 8,010 postmenopausal patients with hormone receptor-positive early breast cancer. Patients were randomized to monotherapy with 5 years tamoxifen (20 mg daily p.o), or 5 years letrozole (Femara, Novartis, Basel, Switzerland, 2.5 mg daily p.o), or to sequential treatment with tamoxifen for 2 years followed by 3 years of letrozole or the reverse. The monotherapy arms, used in this analysis,

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included 4,922 patients. At a median follow-up of 8.7 years, letrozole monotherapy was associated with a significantly better DFS, breast cancer free interval (BCFI), and OS than tamoxifen monotherapy [2].

Assessments

Medical histories and physical examinations were done at baseline, twice per year for the first 5 years and yearly thereafter. Hematological and blood chemical measurements and mammograms were obtained at baseline and additionally when medically indicated. Data on adverse events were obtained using pre-specified check-boxes for vasomotor symptoms and text field responses for AMC symptoms. Date of onset and severity of these adverse events were recorded and rated by the investigators using the National Cancer Institute Common Toxicity Criteria, version 2.0. For this analysis, only patients with at least one dose of study medication without a DFS event during the first 3 months or any known vasomotor or AMC symptoms prior to the start of study treatment were evaluated (Fig. 1). Vasomotor symptoms included hot flushes, night sweats, and vaginal dryness of any grade; AMC symptoms included arthralgia, myalgia, and carpal tunnel syndrome of any grade. Endpoints were DFS and BCFI for newly-occurring symptoms at the 3 and 12 month time points. In addition, we analyzed the incidence of endocrine side effects for tamoxifen and letrozole at 3 and 12 months follow-up. A DFS event was defined as the occurrence of any invasive breast cancer event, second malignancy, and death. A BCFI event was defined as any invasive breast cancer event, with all other events (e.g., other-cause death, second malignancy) treated as competing risks.

Statistical analysis

Adverse event data were used to determine the occurrence of AMC symptoms and vasomotor symptoms within 3 and 12 months of randomization using date of onset, as the basis for landmark analysis at these two time points [14]. Adverse event occurrence was categorized as follows: AMC symptoms only, vasomotor symptoms only, neither symptom, and both symptoms. In addition, the analysis considered the occurrence of AMC symptoms with or without vasomotor symptoms, vasomotor symptoms with or without AMC symptoms, either symptom alone (AMC or vasomotor symptoms but not both) and both symptoms. Adverse event rates were compared using Fisher's exact test [15]. Logistic regression was used to assess the association between baseline characteristics and incidence of AMC and/or vasomotor symptoms. The percent of patients discontinuing study treatment within 4.5 years for reasons other than disease recurrence was estimated using competing risk analysis.

Analyses of DFS and BCFI were performed using standard methods for time-to-event data. DFS was analyzed using the Kaplan–Meier product limit method [16], with comparisons based on the log-rank test [17]. BCFI was analyzed using methods for competing risks. The cumulative incidence of BCFI was compared using the method of Gray [18].

The 3-month analysis excluded patients who experienced disease recurrence, new cancer, or death during the first 3 months following randomization. DFS and BCFI were then analyzed by evaluating outcomes from the 3-month time point forward. The 12-month analysis was similarly performed after excluding patients who experienced disease recurrence, new cancer, or death during the first 12 months following randomization.

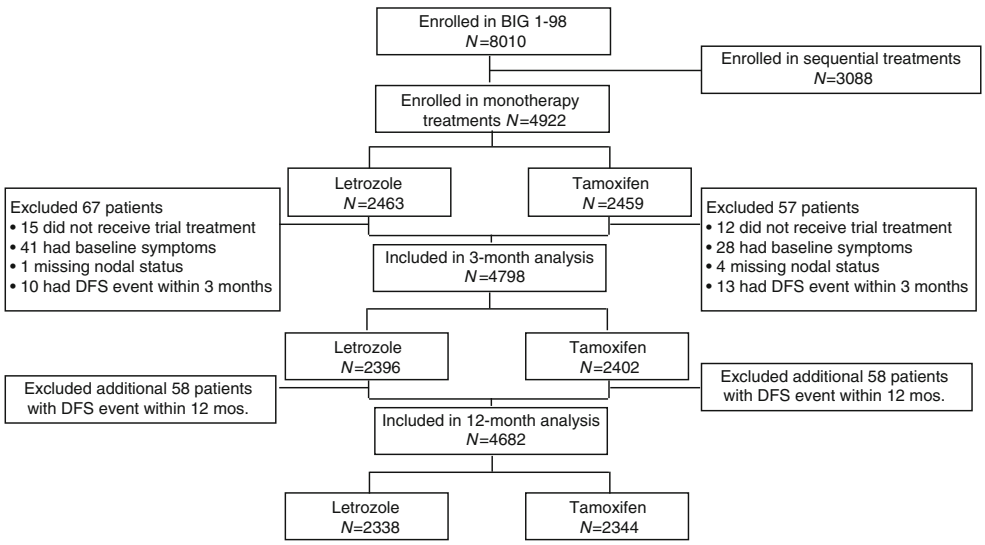


Fig. 1 Consort diagram showing the patient population for this analysis

Table 1 Baseline characteristics

	Letrozole ($N = 2,396$)		Tamoxifen ($N = 2,402$)		Total ($N = 4,798$)	
	number (%)					
Menopausal category						
Postmenopausal before chemotherapy, if received	2,321	(97)	2,313	(97)	4,634	(97)
Postmenopausal only after chemotherapy	47	(2)	53	(2)	100	(2)
Other	28	(1)	36	(1)	64	(1)
Tumor size						
≤2 cm	1,486	(62)	1,468	(61)	2,954	(62)
>2 cm	892	(37)	913	(38)	1,805	(38)
Unknown or missing	18	(<1)	21	(<1)	39	(<1)
Nodal status						
Negative	1,383	(58)	1,406	(59)	2,789	(58)
1–3 positive nodes	714	(30)	700	(29)	1,414	(29)
≥4 positive nodes	299	(12)	296	(12)	595	(12)
ER and PgR status						
Positive/positive	1,485	(62)	1,464	(61)	2,949	(61)
Positive/negative or negative/positive	547	(23)	571	(24)	1,118	(23)
Other	364	(15)	367	(15)	731	(15)
Adjuvant or neoadjuvant chemotherapy						
Yes	586	(24)	613	(26)	1,199	(25)
No	1,810	(76)	1,789	(74)	3,599	(75)
Tumor grade						
I	594	(25)	644	(27)	1,238	(26)
II	1,146	(48)	1,118	(47)	2,264	(47)
III	295	(12)	307	(13)	602	(13)
Unknown or missing	361	(15)	333	(14)	694	(14)
Prior HRT use						
No	1,562	(65)	1,517	(63)	3,079	(64)
Yes, within last 3 months	398	(17)	444	(18)	842	(18)
Yes, >3 months and <5 years ago	304	(13)	313	(13)	617	(13)
Yes, ≥5 years ago	132	(6)	127	(5)	259	(5)
Unknown or missing	0	(0)	1	(<1)	1	(<1)
Body mass index, kg/m^2						
<18.5	36	(2)	28	(1)	64	(1)
18.5–24.9	889	(37)	902	(38)	1,791	(37)
25–29.9	846	(35)	837	(35)	1,683	(35)
≥30	535	(22)	544	(23)	1,079	(22)
Missing or unknown	90	(4)	91	(4)	181	(4)
Median (range)						
Age, years	61	(38–88)	61	(39–84)	61	(38–88)
Weight, kg	68	(40–135)	68	(38–155)	68	(38–155)
Body mass index, kg/m^2	26.0	(15.8–47.9)	26.1	(14.8–59.8)	26.1	(14.8–59.8)
Adjuvant chemotherapy	569	(24)	581	(24)	1,150	(24)
CMF	208	(9)	218	(9)	426	(9)
AC or EC	121	(5)	151	(6)	272	(6)
FEC	114	(5)	106	(4)	220	(5)
Taxane	8	(< 1)	6	(< 1)	14	(< 1)
Other adjuvant chemotherapy	118	(5)	100	(4)	218	(5)

Table 1 continued

	Letrozole ($N = 2,396$)		Tamoxifen ($N = 2,402$)		Total ($N = 4,798$)	
	number (%)					
Neoadjuvant chemotherapy	51	(2)	65	(3)	116	(2)
Anthracycline based	27	(1)	40	(2)	67	(1)
Anthracycline/taxane based	13	(< 1)	9	(< 1)	22	(< 1)
Other neoadjuvant chemotherapy	11	(< 1)	16	(< 1)	27	(< 1)

CMF cyclophosphamide+methotrexate+5-fluorouracil, *AC* doxorubicin+cyclophosphamide, *EC* epirubicin+cyclophosphamide, *FEC* 5-fluorouracil+epirubicin+cyclophosphamide

Regression analysis was used to evaluate DFS and BCFI following adjustment for baseline covariates. Proportional hazards regression [19] stratified by randomization option (2-arm vs. 4-arm) and chemotherapy use was used for DFS, and the method of Fine and Gray [20] was used for BCFI. Adjustment factors were treatment group, age quartile, body mass index quartile, prior HRT use (yes or no), nodal status (node-negative, 1–3 involved nodes, and ≥4 involved nodes), tumor grade (I, II, III, and unknown), tumor size (≤2 cm, >2 cm, and unknown), and cooperative clinical trial group. Indicator variables were included for the occurrence of AMC symptoms, the occurrence of vasomotor symptoms, and the occurrence of both AMC and vasomotor symptoms. Results were converted to hazard ratios (along with 95 % confidence intervals and *p*-values) relative to patients who experienced neither symptom. Linear combinations of the regression-parameter estimates were used to estimate hazard ratios corresponding to the occurrence of vasomotor symptoms with or without AMC symptoms, the occurrence of AMC symptoms with or without vasomotor symptoms, and the occurrence of either symptom. Coefficients for these linear combinations were based on the proportions of patients in each adverse event group in the regression model. We also investigated whether the association between adverse event occurrence and outcome was modified by treatment assignment. This analysis consisted of adding treatment-by-adverse event interaction terms to the model. A wald test [21] was used to determine whether any significant effect modification was present. For all statistical tests, a two-sided *p* value less than 0.05 was considered statistically significant.

Results

Patient characteristics and incidence of treatment-emergent adverse events

After exclusions, 4,798 patients were included in the 3-month analysis and 4,682 patients in the 12-month analysis (Fig. 1). Baseline characteristics were similar across the two treatment groups as were the chemotherapies received (Table 1). Almost 60 % of patients had node-negative disease, and a minority of tumors were poorly differentiated. Prior use of hormone replacement therapy (HRT) was recorded in 36 % of the patients with 18 % using HRT in the last 3 months before randomization. The median age was 61 years, median BMI was 26, and median weight 68 kg. The occurrence of AMC and/or vasomotor symptoms was associated with treatment group, age quartile, and prior HRT use in multivariable logistic regression analysis (data not shown). Differences in the occurrence of the adverse events according to treatment were, as expected, observed for vasomotor and AMC symptoms within 3 and 12 months of randomization (Table 2). The median follow-up for this analysis was 7.0 years.

Duration of study treatment

Treatment discontinuation within 4.5 years for reasons other than disease recurrence was higher for patients with AMC symptoms compared with other groups. Considering patients included in the 3-month landmark analysis, percents (standard error) were 37.6 (4.4) and 38.4 (5.7) for the group of patients reporting AMC symptoms alone and those with both AMC and vasomotor symptoms, respectively, compared with 18.2 (1.3) and 16.4 (0.6) for patients with vasomotor alone and those with neither symptom ($p < 0.0001$, comparing all four groups). Similar results were seen considering the 12-month landmark population.

Outcome—DFS and BCFI

Figure 2a, b shows the cumulative incidence of DFS events over time for the four adverse event groups in the 3-month analysis (Fig. 2a) and the 12-month analysis (Fig. 2b), both showing a significant difference among the adverse event groups ($p = 0.001$ and $p < 0.0001$ for the 3- and 12-month analyses, respectively). Results of the multivariable analyses of DFS and BCFI are illustrated in Fig. 3. Table 3 shows adjusted DFS hazard ratios comparing each adverse event group versus the group of patients experiencing

Table 2 Occurrence of adverse events within 3 and 12 months of randomization

Adverse event(s)	Letrozole		Tamoxifen		Total		*P*-value
	Number (%)						
Within 3 months of randomization[a]							
Neither side effect	1,843	(77)	1,826	(76)	3,669	(76)	0.47
Vasomotor symptoms (with or without AMC symptoms)	459	(19)	545	(23)	1,004	(21)	0.0029
Vasomotor symptoms only	406	(17)	525	(22)	931	(19)	<0.0001
AMC symptoms (with or without vasomotor symptoms)	147	(6)	51	(2)	198	(4)	<0.0001
AMC symptoms only	94	(4)	31	(1)	125	(3)	<0.0001
Either side effect (but not both)	500	(21)	556	(23)	1,056	(22)	0.060
Both side effects	53	(2)	20	(<1)	73	(2)	<0.0001
Within 12 months of randomization[b]							
Neither side effect	1,457	(62)	1,442	(62)	2,899	(62)	0.59
Vasomotor symptoms (with or without AMC symptoms)	685	(29)	803	(34)	1,488	(32)	0.0003
Vasomotor symptoms only	543	(23)	732	(31)	1,275	(27)	<0.0001
AMC symptoms (with or without vasomotor symptoms)	338	(14)	170	(7)	508	(11)	<0.0001
AMC symptoms only	196	(8)	99	(4)	295	(6)	<0.0001
Either side effect (but not both)	739	(32)	831	(35)	1,570	(34)	0.0059
Both side effects	142	(6)	71	(3)	213	(5)	<0.0001

[a] Percentages are based on the total sample size of 4,798 (2,396 in the letrozole group and 2,402 in the tamoxifen group

[b] Percentages are based on the 4,682 patients who had no DFS event within 12 months of randomization (2,338 in the letrozole group and 2,344 in the tamoxifen group)

AMC arthralgia, myalgia, carpal tunnel syndrome

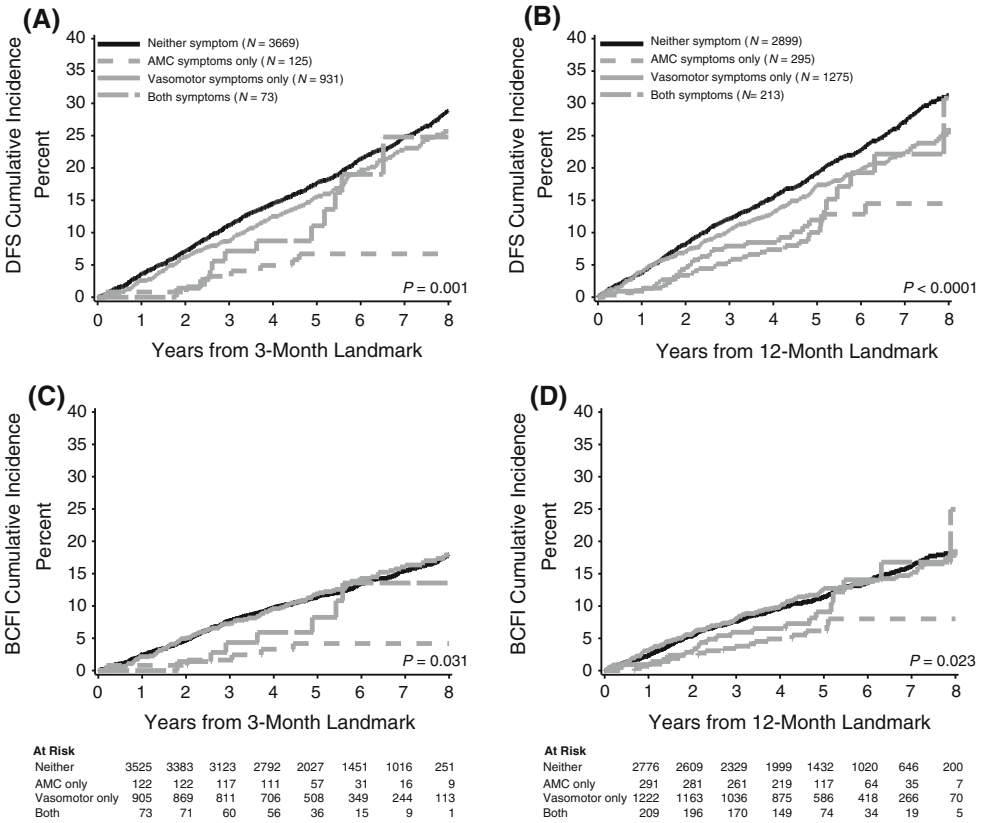
neither AMC symptoms nor vasomotor symptoms. DFS was significantly better in patients with AMC symptoms only (hazard ratio [HR] = 0.36, 95 % confidence interval [CI] 0.18–0.73; HR = 0.57, 95 % CI 0.39–0.84 for the 3- and 12-month analyses, respectively) and also in patients experiencing AMC symptoms with or without vasomotor symptoms (HR = 0.52, 95 % CI 0.32–0.86; HR = 0.65, 95 % CI 0.49–0.87 for the 3- and 12-month analyses, respectively). By contrast, the occurrence of vasomotor symptoms was less strongly associated with DFS, with a significant association observed only in the 12-month analysis in patients who experienced vasomotor symptoms only (HR = 0.83, 95 % CI 0.70–0.97) and in patients who experienced vasomotor symptoms with or without AMC symptoms (HR = 0.82, 95 % CI 0.70–0.96).

Figure 2c, d illustrates BCFI, showing a significant difference in the cumulative incidence of events over time for the four adverse event groups in the 3-month (Fig. 2c) and 12-month analysis (Fig. 2d), with $p = 0.031$ and $p = 0.023$, respectively. Adjusted BCFI hazard ratios comparing each adverse event group versus patients experiencing neither AMC symptoms nor vasomotor symptoms are shown in Table 4. BCFI was significantly better in patients with AMC symptoms only (HR = 0.35, 95 % CI 0.14–0.86; HR = 0.57, 95 % CI 0.35–0.91 for the 3- and 12-month analyses, respectively) and also in patients experiencing AMC symptoms with or without vasomotor symptoms (HR = 0.49, 95 % CI 0.26–0.92; HR = 0.70, 95 % CI 0.49–0.99 for the 3- and 12-month analyses, respectively). The occurrence of vasomotor symptoms, either alone or in combination with AMC symptoms, was not significantly associated with BCFI. We found no significant interaction between treatment group and adverse event occurrence when predicting DFS (p for interaction = 0.24 and 0.73 for the 3- and 12-month analyses, respectively) or BCFI (p for interaction = 0.34 and 0.71 for the 3- and 12-month analyses, respectively).

Discussion

In our analysis of the monotherapy arms of BIG 1-98 trial, patients reporting newly-occurring AMC symptoms at 3 and at 12 months follow-up had both significantly better DFS and BCFI compared to those patients without these reported side effects. This outcome was observed in both tamoxifen-treated and letrozole-treated women, irrespective of whether AMC symptoms were reported alone or together with vasomotor symptoms.

In contrast, for newly-reported vasomotor symptoms without AMC symptoms, no significant difference in BCFI was observed at either time point. Our findings were not affected by treatment group, age, BMI, prior HRT use, nodal status, tumor grade, tumor size, or cooperative clinical trial group.



At Risk

Neither	3525	3383	3123	2792	2027	1451	1016	251
AMC only	122	122	117	111	57	31	16	9
Vasomotor only	905	869	811	706	508	349	244	113
Both	73	71	60	56	36	15	9	1

At Risk

Neither	2776	2609	2329	1999	1432	1020	646	200
AMC only	291	281	261	219	117	64	35	7
Vasomotor only	1222	1163	1036	875	586	418	266	70
Both	209	196	170	149	74	34	19	5

Fig. 2 Cumulative incidence according to occurrence of adverse events within 3 months (**a, c**) and within 12 months (**b, d**) of randomization for disease-free survival (DFS) (**a, b**) and breast cancer-free interval (BCFI) (**c, d**). Non-breast cancer events are considered as competing risks in the analysis of BCFI. (AMC: arthralgia, myalgia, carpal tunnel syndrome)

In our analysis, we included patients without a DFS event during the first 3 months and without any known vasomotor or AMC symptoms prior to treatment. We chose to measure endocrine symptoms at 3 months follow-up to exclude confounding factors such as non-adherence to endocrine treatment or treatment discontinuation for other reasons. Adherence to treatment within 3 months was good in BIG 1-98, with only 159 patients never starting or stopping treatment within the first 3 months. Since the cumulative incidence of adverse events occurring in the course of 12 months of treatment may better reflect the individual response of the host to endocrine therapy, we were also interested in results at the 12-month time point. The increasing cumulative number of side effects after a longer follow-up period may facilitate detecting differences between these groups; however, those patients suffering from estrogen deprivation side effects—frequently severe—may be more likely to discontinue treatment early and thereby lose the benefit of DFS and BCFI risk reduction.

Side effects and efficacy have been reported in other large hormonal treatment trials for postmenopausal women. The ATAC trial compared anastrozole to tamoxifen over 5 years in postmenopausal women with early breast cancer. A retrospective analysis of the hormone receptor-positive population of this trial showed that both anastrozole- and tamoxifen-treated patients had a significantly lower recurrence rates when new joint symptoms and vasomotor symptoms of all grades were reported after 3 months follow-up [22]. However, these differences were only significant when joint symptoms were considered with vasomotor symptoms. In patients with vasomotor symptoms only, breast cancer recurrence rates were not significantly lower compared to those patients without occurrence of these symptoms (HR 0.84,95 %CI 0.68–1.03; $p = 0.09$). These results are similar to ours, highlighting that the occurrence of joint symptoms is primarily associated with an improved outcome.

The TEAM trial compared 5 years of exemestane with 2.5–3 years of tamoxifen followed by 2–2.5 years of exemestane [23]. A retrospective analysis of the German cohort (1,502 women) investigating vasomotor and joint symptoms of any grade occurring during the 5 year treatment showed that arthralgia/myalgia and menopausal symptoms during endocrine treatment were significantly associated with longer OS and DFS than in those patients not reporting these symptoms [24]; however, the effect on OS was irrespective of study treatment given. A recent report including the whole study population of the TEAM trial showed a better outcome in terms of DFS and OS for those with vasomotor-musculoskeletal and vulvovaginal symptoms arising in the first year of endocrine treatment compared to those not reporting these symptoms [25].

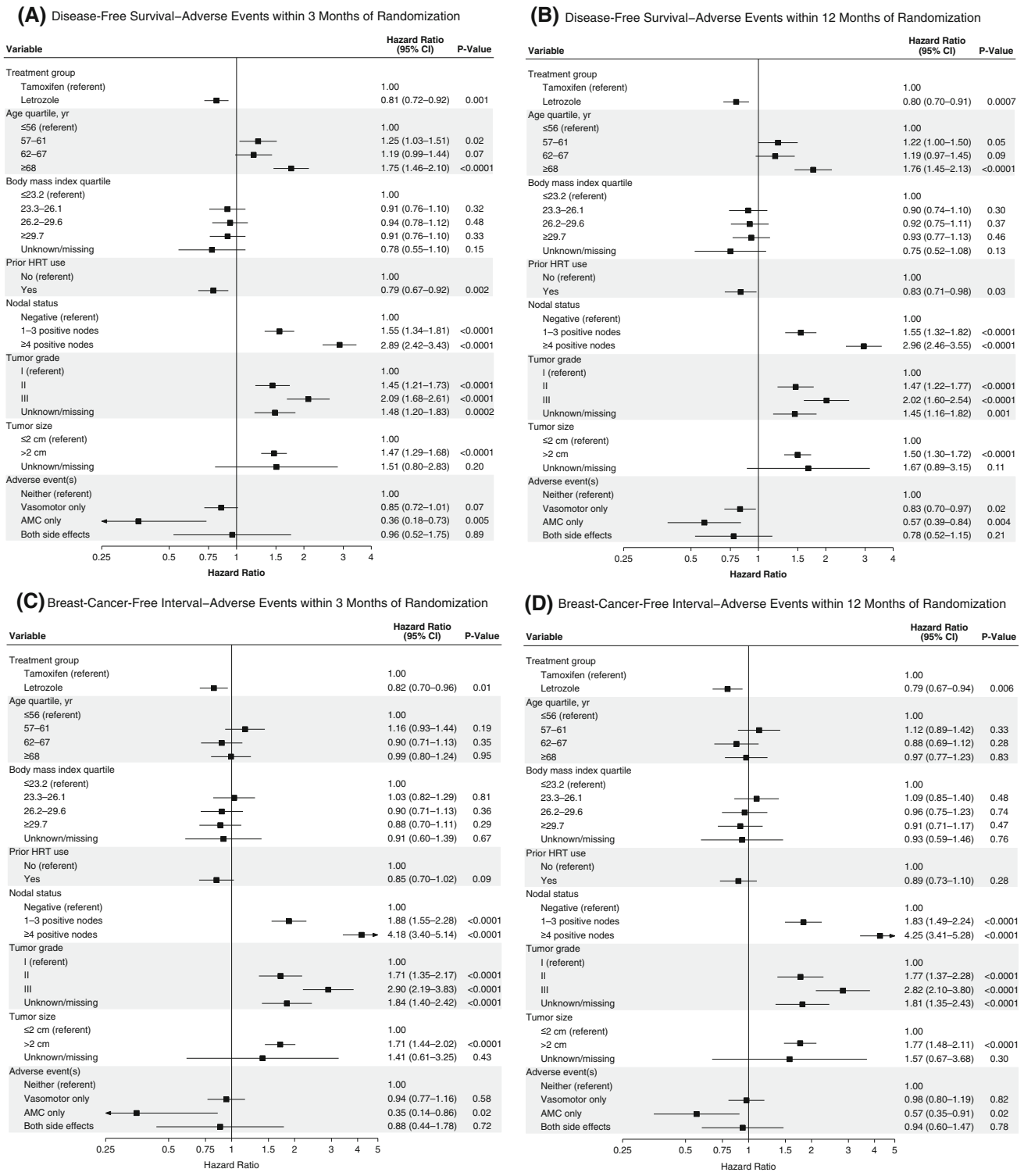


Fig. 3 Multivariable analysis results according to occurrence of adverse events within 3 months (**a, c**) and within 12 months (**b, d**) of randomization for disease-free survival (DFS) based on proportional hazards regression (**a, b**) and breast cancer-free interval (BCFI) based on competing-risks regression (**c, d**). Hazard ratios are based on a multivariable model including all variables listed as well as cooperative trial group. Proportional hazards regression of DFS was stratified by randomization option (2-arm vs. 4-arm) and chemotherapy use. For each variable included, a hazard ratio less than 1.0 indicates lower hazard than the referent group, and a hazard ratio greater than 1.0 indicates higher hazard than the referent group. Hazard ratios are shown with 95 % CIs.

Table 3 Disease-free survival (DFS) according to occurrence of adverse events

Adverse event(s)	n/wy	(Annual rate, %)	Hazard ratio[a]	95 % CI	*p*-value
Within 3 months of randomization					
Neither side effect	820/20,137	(4.1)	1.00		
Vasomotor symptoms (with or without AMC symptoms)	192/5,477	(3.5)	0.86	0.73–1.02	0.084
Vasomotor symptoms only	181/5,106	(3.5)	0.85	0.72–1.01	0.073
AMC symptoms (with or without vasomotor symptoms)	19/1,038	(1.8)	0.52	0.32–0.86	0.011
AMC symptoms only	8/666	(1.2)	0.36	0.18–0.73	0.0047
Either side effect	189/5,773	(3.3)	0.77	0.65–0.92	0.0043
Both side effects	11/371	(3.0)	0.96	0.52–1.75	0.89
Within 12 months of randomization					
Neither side effect	633/14,221	(4.5)	1.00		
Vasomotor symptoms (with or without AMC symptoms)	253/7,107	(3.6)	0.82	0.70–0.96	0.014
Vasomotor symptoms only	226/6,160	(3.7)	0.83	0.70–0.97	0.023
AMC symptoms (with or without vasomotor symptoms)	56/2,340	(2.4)	0.65	0.49–0.87	0.0031
AMC symptoms only	29/1,393	(2.1)	0.57	0.39–0.84	0.0039
Either side effect	255/7,553	(3.4)	0.77	0.66–0.90	0.0013
Both side effects	27/947	(2.9)	0.78	0.52–1.15	0.21

[a] Proportional hazards regression stratified by randomization option (2-arm vs. 4-arm) and chemotherapy use. Hazard ratios are adjusted for treatment group, age quartile, body mass index quartile, prior HRT use, nodal status, tumor grade, tumor size, and cooperative clinical trial group

AMC arthralgia, myalgia, or carpal tunnel syndrome, *n* number of DFS events, *wy* woman years of follow-up, *CI* confidence interval

Contrary to these results are emerging data from the MA.27 trial—a study of 7,576 women with hormone receptor-positive early breast cancer randomized to receive 5 years of endocrine treatment with anastrozole or exemestane. The effect of early onset new or worsening vasomotor or joint symptoms on relapse free survival was investigated. At 3, 6, and 12 months, no significant improvement of RFS could be observed regardless of whether or not there was a prior history of vasomotor or joint symptoms [26, 27]. Similarly musculoskeletal symptoms at 6 months in a retrospective analysis of the Intergroup Exemestane Study were not associated with better outcome when adjusted for possible confounding factors [28].

Different baseline characteristics of patients as well as differences in methodology to collect, categorize, analyze, and report adverse events between these studies may contribute to divergent findings. The adverse events of tamoxifen were well-known when these trials were started, whereas the less well-known adverse events of AIs were not well-known and probably underreported, especially early in the trials.

The exact mechanism involved in endocrine treatment associated AMC symptoms remains unknown; however, estrogen suppression is hypothesized to play an important pathophysiological role. In our study, the percent of women enrolled based on postmenopausal status following chemotherapy was small and well-balanced across both treatment arms. Recent data in a Korean population suggest [29] that single nucleotide polymorphisms of CYP19A1 are associated with both letrozole efficacy in metastatic breast cancer and adverse events like arthralgia, myalgia, and hot flushes. Similar results were observed in a Caucasian population where functional polymorphisms in the CYP19A1 enzyme were associated with the occurrence of arthralgia and myalgia [30]. A special subtype of CYP19A1 gene polymorphism was found to be associated with both arthralgia/myalgia and lower estrogen levels in postmenopausal women [30]. A report by Ingle et al. [31] identified 4 SNPs on chromosome 14 that were associated with musculoskeletal adverse events. Interestingly one of the SNPs created a functional estrogen response element which influenced the expression of *TCL1A*, the gene closest to the SNPs and possibly associated with cytokine function. A recent study reported that patients receiving tamoxifen and reporting hot flushes were less likely to experience breast cancer recurrence than those without these symptoms. It was suggested that this may be due to greater conversion of tamoxifen to its active metabolite endoxifen because of polymorphisms in the cytochrom p450 complex [32]. However, analyses regarding CYP2D6 polymorphism in the ATAC and BIG 1-98 populations do not support this observation, since CYP2D6 phenotypes of reduced enzyme activity were not associated with worse disease control but, surprisingly, were associated with increased incidence of vasomotor symptoms [33, 34].

Table 4 Breast-cancer-free interval (BCFI) according to the occurrence of adverse events

Adverse event(s)	n/wy	(Annual rate, %)	Hazard ratio[a]	95 % CI	*p*-value
Within 3 months of randomization					
Neither side effect	519/20,531	(2.5)	1.00		
Vasomotor symptoms (with or without AMC symptoms)	139/5,529	(2.5)	0.94	0.76–1.15	0.54
Vasomotor symptoms only	132/5,153	(2.6)	0.94	0.77–1.16	0.58
AMC symptoms (with or without vasomotor symptoms)	12/1,043	(1.2)	0.49	0.26–0.92	0.027
AMC symptoms only	5/667	(0.8)	0.35	0.14–0.86	0.022
Either side effect	137/5,820	(2.4)	0.84	0.68–1.04	0.11
Both side effects	7/376	(1.9)	0.88	0.44–1.78	0.72
Within 12 months of randomization					
Neither side effect	382/14,499	(2.6)	1.00		
Vasomotor symptoms (with or without AMC symptoms)	184/7,178	(2.6)	0.97	0.80–1.18	0.76
Vasomotor symptoms only	163/6,219	(2.6)	0.98	0.80–1.19	0.82
AMC symptoms (with or without vasomotor symptoms)	39/2,369	(1.6)	0.70	0.49–0.99	0.042
AMC symptoms only	18/1,410	(1.3)	0.57	0.35–0.91	0.018
Either side effect	182/7,644	(2.4)	0.88	0.73–1.07	0.20
Both side effects	21/959	(2.2)	0.94	0.60–1.47	0.78

[a] Hazard ratios are adjusted for treatment group, age quartile, body mass index quartile, prior HRT use, nodal status, tumor grade, tumor size, and cooperative trial group

AMC: arthralgia, myalgia, or carpal tunnel syndrome, *n* number of DFS events, *wy* woman years of follow-up, *CI* confidence interval

Limitations of our study include the possible underreporting of AMC symptoms (at baseline and during follow-up) because they were not collected with a pre-defined checkbox. The incidence of arthralgia and myalgia in particular at the 3 months time point (4.1 % of patients) was low. It is possible that this under-reporting of symptoms influenced our results. The side effects reported in randomized trials are frequently lower than seen in clinical practice and patient reported toxicity may more comprehensively capture subjective side effects of therapies than toxicity documented by trial investigators [35, 36]. Despite these limitations, the hazard ratios of all endpoints were consistently decreased both at 3 and at 12 months for both end points for AMC symptoms.

Our data suggest that the occurrence of AMC symptoms at 3 and 12 months is associated with a significantly better DFS and BCFI irrespective of treatment. Our results are consistent with those in the ATAC and TEAM trials. Based on these results, a prospective validation of the influence of treatment-emergent symptoms and long-term outcome with refined assessment of the side effects is warranted. If confirmed, these results may improve adherence to treatment despite these frequently bothersome side effects.

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