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The predictive impact of body mass index on the efficacy of extended adjuvant endocrine treatment with anastrozole in postmenopausal patients with breast cancer: an analysis of the randomised ABCSG-6a trial

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Background: We investigated whether body mass index (BMI) can be used as a predictive parameter indicating patients who benefit from extended aromatase inhibitor (AI) treatment.

Methods: The ABCSG-6a trial re-randomised event-free postmenopausal hormone receptor-positive patients from the ABCSG-6 trial to receive either 3 additional years of endocrine therapy using anastrozole *vs* nil. In this retrospective analysis, we investigated the prognostic and predictive impact of BMI on disease outcome and safety.

Results: In all, 634 patients (177 normal weight, 307 overweight, and 150 obese) patients were included in this analysis. Normal weight patients with additional 3 years of anastrozole halved their risk of disease recurrence (disease-free survival (DFS) HR 0.48; $P=0.02$) and death (HR 0.45; $P=0.06$) and had only a fifth of the risk of distant metastases (HR 0.22; $P=0.05$) compared with normal weight patients without any further treatment. In contrast, overweight + obese patients derived no benefit from additional 3 years of anastrozole (DFS HR 0.93; $P=0.68$; distant recurrence-free survival HR 0.91; $P=0.78$; and OS HR 0.9; $P=0.68$). The possible predictive impact of BMI on extended endocrine treatment could be strengthened by a Cox regression interaction model between BMI and treatment ($P=0.07$).

Conclusion: Body mass index may be used to predict outcome benefit of extended AI treatment in patients with receptor-positive breast cancer.

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Aromatase inhibitors (AIs) are standard endocrine treatment for postmenopausal patients with hormone receptor-positive breast cancer. According to the ASCO guidelines 2010, AIs should be offered upfront for 5 years or after 2–3 years of tamoxifen (switch therapy) in the postmenopausal situation (Burstein *et al*, 2010).

However, optimal duration of endocrine therapy is still under intensive investigation. Even after 5 years of endocrine treatment a substantial risk of recurrence has to be taken into account in the follow-up of hormone receptor-positive disease (Saphner *et al*, 1996; EBCTCG, 2005). The MA 17 trial was the first to demonstrate a distinct disease-free survival (DFS) benefit for additional 5 years of letrozole *vs* placebo after 5 years of tamoxifen (Goss *et al*, 2003). The ABCSG-6a trial reported an advantage of additional 3 years of endocrine treatment using anastrozole after 5 years of adjuvant endocrine therapy (Jakesz *et al*, 2007). According to these trials, extended endocrine treatment by an AI can be recommended after 5 years of tamoxifen. The MA17R (NCT00754845), NSABP-B42 (NCT00382070), IDEAL (Netherlands Trial Registry 3077), and ABCSG-16 (SALSA; NCT 00295620) trials will hopefully show whether extended endocrine therapy after 5 years of AI improves disease outcome as well. Despite these encouraging prospects, the accumulation of side effects and perhaps an even worse treatment compliance often complicate this issue in clinical practice (Perez, 2007; Fontein *et al*, 2012). Therefore, the decision to use extended endocrine treatment by AI can not only be driven by prognosis. Predictive parameters indicating patients who will have a distinctive benefit from long-term endocrine therapy should be included in the decision process to outweigh the risk of side effects.

Obesity has an independent prognostic value regarding breast cancer. It has been demonstrated that overweight and obese patients experience a worse outcome regarding distant recurrences and overall survival (OS) (Ewertz *et al*, 2011).

Recently, the predictive value of body mass index (BMI) regarding endocrine therapy has been investigated. Overweight patients seem to derive less benefit from AIs compared with normal weight patients (Sestak *et al*, 2010; Pfeiler *et al*, 2011). It was hypothesised that normal dosages of AIs are not able to fully suppress increased oestrogen serum levels in overweight patients, which impacts on outcome. Taking this into account, BMI might be a predictive parameter whether to use AI-based or tamoxifen-based endocrine treatment. As up to two thirds of the population in developed countries like the United States are overweight and obese, BMI as a prognostic and possibly predictive parameter should be taken into consideration for treatment decision (Flegal *et al*, 2010).

To investigate whether BMI can be used as a predictive parameter regarding long-term endocrine treatment with an AI we re-analysed the ABCSG-6a trial, which investigated additional 3 years of anastrozole *vs* no further treatment in a randomised manner.

PATIENTS AND METHODS

The ABCSG-6a trial (NCT00300508) re-randomised event-free patients from the ABCSG-6 trial to receive either 3 additional years of endocrine therapy using anastrozole *vs* nil (Jakesz *et al*, 2007). In the ABCSG-6 trial postmenopausal, hormone-receptor positive patients with breast cancer were randomised to receive either tamoxifen for 5 years (40 mg for 2 years and 20 mg for 3 years) or tamoxifen for 5 years (40 mg for 2 years and 20 mg for 3 years) together with aminoglutethimide for the first 2 years (Schmid *et al*, 2003). Patients with primary unilateral stage I or II breast cancer with or without lymph-node involvement were included. At the end of ABCSG-6 trial, 1135 patients were event free (according to chest X-rays, abdominal ultrasound, mammography, and other investigations if clinically indicated) and eligible for participation in the ABCSG-6a trial. In all, 854 postmenopausal, hormone receptor-positive patients with breast cancer were randomised in ABCSG-6a (anastrozole for 3 years *vs* nil). In the anastrozole arm, 210 (54.3%) patients had received 5 years of tamoxifen only and 177 (45.7%) patients had received tamoxifen + aminoglutethimide, which is comparable to the group of patients without extended endocrine treatment. Extended endocrine therapy was initiated within 6 weeks after completing 5 years of adjuvant endocrine therapy in the ABCSG-6 trial. The primary end point of ABCSG-6a was recurrence-free survival and secondary end points were OS and tolerability. Details of the protocol have been reported elsewhere (Jakesz *et al*, 2007). This study has been approved by regulatory and ethics committees for all participating centres. Written informed consent was signed by all participating patients.

This retrospective analysis aimed to test for a prognostic and predictive effect of BMI on the end point DFS, distant recurrence-free survival (DRFS), OS, and safety. The primary hypothesis of this reanalysis was that patients with a BMI above the normal range derive less benefit from additional 3 years of anastrozole than normal weight patients. Data on height and weight at baseline of ABCSG-6a were used to calculate BMI classes according to WHO criteria with BMI values ranging from 18.5 to 24.9 $kg\,m^{-2}$ for normal weight, from 25 to 29.9 $kg\,m^{-2}$ for overweight, and with BMI values $\geqslant 30\,kg\,m^{-2}$ for obese patients. Patients without information on height or weight as well as underweight patients with a BMI of $<18.5\,kg\,m^{-2}$ were excluded from these analyses.

Disease-free survival was defined as the time from randomisation to the first occurrence of any of the following events: locoregional recurrence, distant metastasis, cancer in contralateral breast, second primary cancer, or death from any cause. For DRFS, subjects who have died without distant metastases were censored at the time of death. Disease-free survival, DRFS, and OS were analysed according to the BMI subgroups as well as the two study arms (anastrozole *vs* nihil).

Statistical analyses. Hazard ratios with confidence intervals and test statistics for the group comparisons were obtained from Cox proportional hazards regression models. Kaplan–Meier plots with log-rank tests were used for selected comparisons. To adjust for effects of demographic and additional prognostic factors on DFS, distant recurrence survival and OS, tumour stage, nodal stage, grade, ER, PR, and age were included in multivariate Cox regression models for the comparison of overweight/obese *vs* normal weight patients. A Cox regression interaction model was used to describe any interaction between BMI and treatment regarding disease outcome. Demographic data and side effects were compared using Fisher's exact test and Kruskal–Wallis test when appropriate. All analyses were performed at a two-sided significance level of 0.05.

RESULTS

In all, 854 postmenopausal patients with breast cancer without disease recurrence after 5 years of endocrine treatment participated in the ABCSG-6a trial. For this analysis, 217 patients (92 patients from the anastrozole arm and 125 patients from the control arm) were excluded due to unavailable data on height, weight or both. Complete patient information was available in 637 patients (75%). Furthermore, three underweight patients (one from the anastrozole arm and two from the control arm) were excluded due to small numbers and for biological reasons. Therefore, 634 patients (294 patients in the anastrozole arm and 340 patients in the control arm) were included in this analysis (Figure 1).

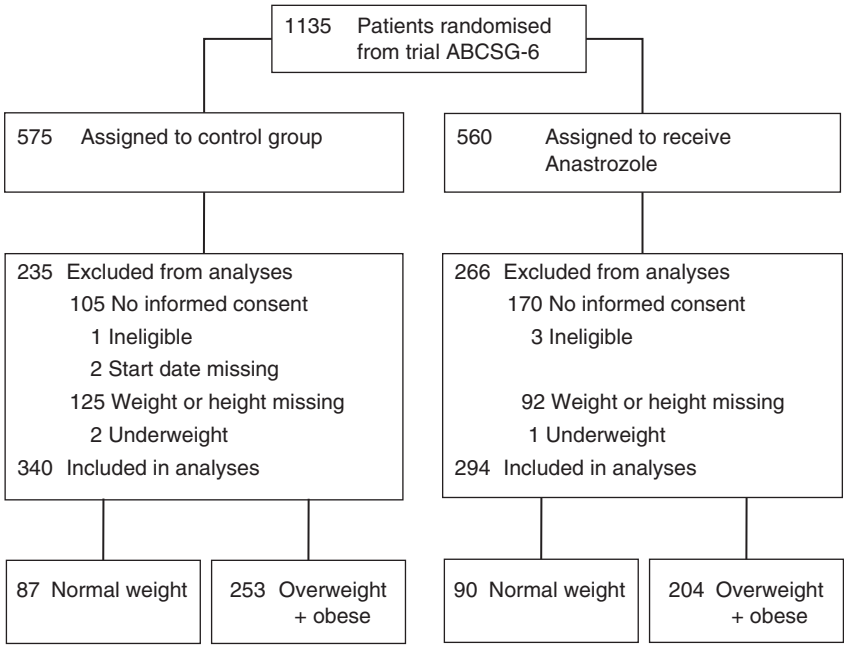

Figure 1. Consort diagram.

Less than one third of these patients (28%, 177 patients) were normal weight, and more than two thirds were overweight (48%, 307 patients) or obese (24%, 150 patients). Patient and tumour characteristics of the anastrozole and the control arm according to BMI category are shown in Table 1. Patient and tumour characteristics were well balanced between the four groups.

Efficacy. This analysis reports on a median follow-up of 73.2 months. In all, 218 events including 94 deaths are included in this analysis (Table 2). Comparing the whole group of overweight + obese patients ($n = 457$) with the whole group of normal weight patients ($n = 177$), no difference in DFS (hazard ratio 1.05; 95% CI, 0.75–1.49, $P = 0.76$) and OS (hazard ratio 1.05; 95% CI, 0.67–1.64, $P = 0.83$) could be observed. This missing impact of BMI on disease outcome was also true with regard to distant metastases. Overweight + obese patients had the same risk for distant metastases compared with normal weight patients in the univariate (hazard ratio 1.45; 95% CI, 0.74–2.84, $P = 0.27$) as well as in the multivariate analysis, which included age, tumour stage, nodal stage, tumour grade, ER and PR expression (hazard ratio 1.29; 95% CI, 0.61–2.76, $P = 0.49$). Additional multivariate analyses are shown in Tables 3 and 4.

Overweight *vs* normal weight according to treatment arm. Analysing patients only with no further adjuvant treatment after 5 years of endocrine therapy (control group), no difference between overweight + obese and normal weight patients with regard to DFS (hazard ratio 0.79; 95% CI, 0.52–1.23, $P = 0.3$), DRFS (hazard ratio 0.91; 95% CI, 0.42–1.98, $P = 0.81$) and OS (hazard ratio 0.81; 95% CI, 0.47–1.4, $P = 0.45$) could be observed.

In contrast, in the group of patients with additional 3 years of anastrozole, overweight + obese patients had a non-significant worse DFS compared with normal weight patients (hazard ratio 1.55; 95% CI, 0.87–2.77, $P = 0.14$). Regarding DRFS in this group of patients, overweight + obese patients had a nearly four-fold non-significant increased risk of distant metastases compared with normal weight patients (hazard ratio 3.85; 95% CI, 0.88–16.75, $P = 0.07$). This non-significant worse DRFS of overweight + obese compared with normal weight patients could also be shown in the multivariate analysis (hazard ratio 3.41; 95% CI, 0.74–15.75, $P = 0.12$). Only a moderate, non-significant worse OS of overweight + obese compared with normal weight patients could be identified in the group of patients with 3 additional years of anastrozole (hazard ratio 1.58; 95% CI, 0.72–3.49, $P = 0.25$).

Anastrozole *vs* Control according to BMI. Comparison of the efficacy of additional 3 years of anastrozole with no further treatment in the group of normal weight patients revealed a significant benefit for the treatment group (Figure 2). Normal weight patients with additional 3 years of anastrozole halved their risk of disease recurrence (DFS hazard ratio 0.48; 95% CI, 0.26–0.89, $P = 0.02$) and had only a fifth of the risk of distant metastases (hazard ratio 0.22; 95% CI, 0.05–1.0, $P = 0.05$) compared with normal weight patients without any further treatment. This could be confirmed in the multivariate analyses, which included age, tumour stage, nodal stage, tumour grade, and ER and PR expression. The significantly decreased risk of disease recurrence in normal weight patients treated with additional 3 years of anastrozole translated into a strong trend for a better OS compared with normal weight patients without further treatment. Normal weight patients with additional 3 years of anastrozole halved their risk of death compared with normal weight patients with no further treatment (hazard ratio 0.45; 95% CI, 0.19–1.04, $P = 0.06$). Again, this could be confirmed in the multivariate analysis, data not shown.

In strong contrast, overweight + obese patients did not benefit from additional 3 years of endocrine treatment with anastrozole (Figure 3). When comparing overweight + obese patients with additional 3 years of anastrozole to overweight + obese patients with no further treatment, no difference regarding DFS (hazard ratio 0.93; 95% CI, 0.63–1.35, $P = 0.68$), DRFS (hazard ratio 0.91; 95% CI, 0.48–1.74, $P = 0.78$), and OS (hazard ratio 0.9; 95% CI, 0.55–1.47, $P = 0.68$) could be observed.

Interaction between BMI and treatment. To concrete the possible impact of BMI on extended endocrine treatment with anastrozole, a Cox regression interaction model between BMI and treatment regarding DFS and OS was performed. The model showed a strong trend for interaction between BMI and treatment regarding DFS (0.07) although this did not reach statistical significance. However, hardly any interaction could be shown between BMI and treatment regarding OS ($P = 0.17$).

Table 1. Patient demographics and tumour characteristics

	Normal weight					Overweight + obese				
	Control		Anastrozole			Control		Anastrozole		
Characteristics	***N***	**%**	***N***	**%**	***P*-value**	***N***	**%**	***N***	**%**	***P*-value**
No. of patients	87		90			253		204		
BMI values					0.6226					0.4307
Median Range	23.2 19.4–25.0		23.4 18.6–25.0			28.3 25.0–50.6		28.4 25.0–46.8		
Age at start of trial-6a					0.1009					0.1414
Median Range	69 51–83		63 52–82			66 52–85		67.5 51–82		
Cancer stage					0.9994					0.9888
pT1 pT2 pT3	55 30 2	63.2 34.5 2.3	57 31 2	63.3 34.5 2.2		150 99 4	59.3 39.1 1.6	120 81 3	58.8 39.7 1.5	
Nodal status					0.8727					0.3244
N0 N1 N2 N3	60 22 4 1	69.0 25.3 4.6 1.1	65 19 4 2	72.2 21.1 4.5 2.2		161 65 21 6	63.6 25.7 8.3 2.4	124 65 13 2	60.8 31.8 6.4 1.0	
Tumour grading					0.3564					0.7276
G1 G2 G3 Gx	19 37 27 4	21.9 42.5 31.0 4.6	17 49 19 5	18.9 54.4 21.1 5.6		43 146 47 17	17.0 57.7 18.6 6.7	34 119 42 9	16.7 58.3 20.6 4.4	
Hormone-receptor status (biochemical)					0.5415					0.245
ER+ PgR+ ER+ PgR− ER− PgR+ ER+ PgR? ER? PgR+ ER− PgR− Not determ. Unknown Missing	11 5 0 0 0 0 0 3 68	12.6 5.8 0.0 0.0 0.0 0.0 0.0 3.4 78.2	14 3 1 0 0 1 2 2 67	15.6 3.3 1.1 0.0 0.0 1.1 2.2 2.2 74.5		51 18 3 0 0 0 5 17 159	20.2 7.1 1.2 0.0 0.0 0.0 2.0 6.7 62.8	54 9 0 1 0 1 2 14 123	26.4 4.4 0.0 0.5 0.0 0.5 1.0 6.9 60.3	
Oestrogen-receptor status					0.6208					0.0719
ER− ER+ ER++ ER+++ Unknown Missing	3 17 36 20 5 6	3.4 19.6 41.4 23.0 5.7 6.9	5 15 29 30 4 7	5.5 16.7 32.2 33.3 4.5 7.8		6 41 75 93 26 12	2.4 16.2 29.6 36.7 10.3 4.7	4 25 77 56 23 19	2.0 12.2 37.7 27.5 11.3 9.3	
Progesterone-receptor status					0.6318					0.1593
PgR− PgR+ PgR++ PgR+++ Unknown Missing	18 15 23 20 5 6	20.7 17.3 26.4 23.0 5.7 6.9	11 22 25 20 4 8	12.2 24.4 27.8 22.2 4.5 8.9		32 50 59 74 26 12	12.7 19.8 23.3 29.2 10.3 4.7	18 32 59 53 23 19	8.8 15.7 28.9 26.0 11.3 9.3	
Type of surgery					0.4830					0.6877
Breast conserving Radically modified	50 37	57.5 42.5	47 43	52.2 47.8		135 118	53.4 46.6	105 99	51.5 48.5	
Histology					0.0424					0.9632
Lobular invasive Ductal invasive Other Unknown	15 62 4 6	17.2 71.3 4.6 6.9	24 63 3 0	26.7 70.0 3.3 0.0		39 190 16 8	15.4 75.1 6.3 3.2	35 151 12 6	17.2 74.0 5.9 2.9	

Abbreviation: BMI = body mass index.

Table 2. Events of normal weight and overweight + obese patients treated with anastrozole *vs* nihil

	Normal weight				Overweight + obese			
	Control		Anastrozole		Control		Anastrozole	
	N	**%**	***N***	**%**	***N***	**%**	***N***	**%**
Number of patients	87		90		253		204	
All events	42	48.3	18	20.0	95	37.5	63	30.9
Locoregional	3	3.5	2	2.2	11	4.3	4	2.0
Distant	9	10.4	2	2.2	22	8.7	16	7.8
Contralateral	5	5.7	2	2.2	6	2.4	4	2.0
Secondary malignant conditions	6	6.9	4	4.4	16	6.3	12	5.9
Death								
All	19	21.8	8	8.9	40	15.8	27	13.2

Table 3. Overweight + obese *vs* normal weight: multivariant analyses including age, tumour stage, nodal stage, tumour grade, and ER and PR expression

	All		3 years Anastrozole		No treatment	
	HR	**95% CI**	**HR**	**95% CI**	**HR**	**95% CI**
DFS						
Overweight + obese *vs* Normal weight	0.89	0.55–1.12	1.27	0.65–2.46	0.68	0.42–1.10
Distant recurrence-free survival						
Overweight + obese *vs* Normal weight	1.29	0.61–2.76	3.41	0.74–15.75	0.79	0.33–1.97
Overall survival						
Overweight + obese *vs* Normal weight	0.77	0.49–1.28	0.71	0.27–1.86	0.67	0.34–1.35

Abbreviations: CI = confidence interval; DFS = disease-free survival; HR = hazard ratio.

Table 4. Anastrozole *vs* Control: multivariant analyses including age, tumour stage, nodal stage, tumour grade, and ER and PR expression

	Overweight + Obese		Normal weight	
	HR	**95% CI**	**HR**	**95% CI**
DFS				
Anastrozole *vs* Control	0.94	0.62–1.45	0.51	0.26–1.00
Distant recurrence-free survival				
Anastrozole *vs* Control	0.97	0.47–1.99	0.28	0.06–1.46
Overall survival				
Anastrozole *vs* Control	0.90	0.51–1.61	0.52	0.20–1.31

Abbreviations: CI = confidence interval; DFS = disease-free survival; HR = hazard ratio.

Safety and tolerability. Table 5 shows side effects of both treatment arms according to BMI. As shown, using a Cochran–Mantel–Haenszel test stratified by treatment, BMI had no impact on the frequency of side effects. However, normal weight as well as overweight patients with additional 3 years of anastrozole had significant more side effects compared with patients without any further treatment (control group).

DISCUSSION

The ABCSG-6a trial was one of the first to demonstrate an advantage of additional 3 years of endocrine treatment using anastrozole compared with nihil after 5 years of endocrine treatment. The MA 17 trial and the NSABP B-33 reported improvement of disease outcome by long-term endocrine treatment with an AI as well (Goss *et al*, 2003; Mamounas *et al*, 2008). Taken these trials into consideration, extended endocrine treatment with an AI after 5 years of tamoxifen can be recommended and long-term endocrine treatment with an AI for 10 years is reasonable and under intensive investigation. Though patients with long-term endocrine treatment experience a reduction in the risk of recurrence, this goes along with a significant increase in side effects (Goss *et al*, 2008).

Not all patients did benefit from long-term endocrine therapy in the three mentioned prospective randomised trials. Predicitve parameters are needed to distinguish between patients who will and patients who will not benefit from a certain therapy. Predicitve parameters could help to increase the relative efficacy of a treatment and to outweigh the risk of side effects as patients likely to be non-responders can be identified and excluded from treatment.

In this reanalysis of the ABCSG-6a trial, we demonstrate that BMI is a predictive parameter regarding extended endocrine treatment with an AI. Normal weight patients experienced substantial benefit from additional 3 years of anastrozole, which halved their risk of disease recurrence and death from any cause.

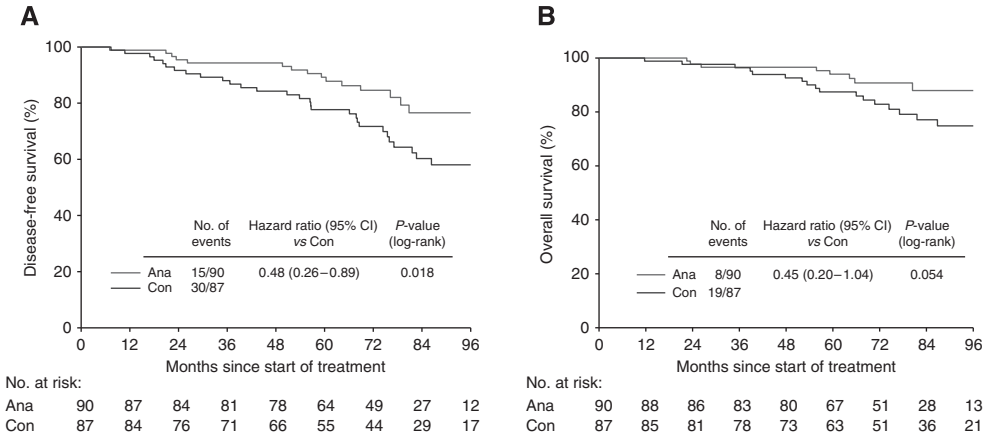

Figure 2. (**A**) DFS: Anastrozole *vs* Control, normal weight patients and (**B**) OS: Anastrozole *vs* Control, normal weight patients.

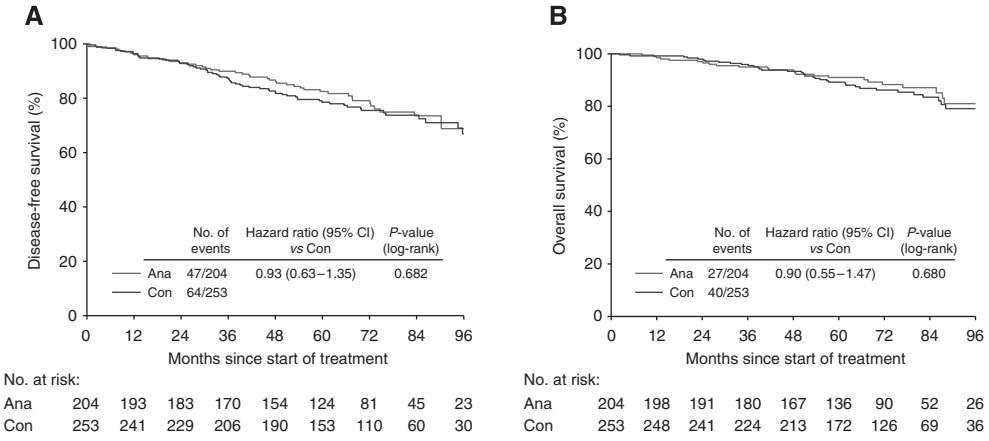

Figure 3. (**A**) DFS: Anastrozole *vs* Control, overweight + obese patients and (**B**) OS: Anastrozole *vs* Control, overweight + obese patients.

Overweight and obese patients did not derive benefit from long-term endocrine treatment with anastrozole.

Recently, it has been suggested that overweight patients derive not the same benefit from AIs as normal weight patients possibly due to increased aromatisation in the fat tissue. The reanalysis of the ABCSG-12 trial demonstrated that overweight premenopausal patients treated with goserelin + anastrozole have a worse outcome compared with overweight premenopausal patients treated with goserelin + tamoxifen (Pfeiler *et al*, 2011). Sestak *et al* (2010) reported that BMI impacts on the efficacy of anastrozole but not tamoxifen in postmenopausal patients with breast cancer. These two publications demonstrate an impact of BMI on the efficacy of AI and are in line with our results reported here. However, in the ABCSG-12 trial as well as in the ATAC trial, all patients received a kind of endocrine treatment (either anastrozole based or tamoxifen based), which allows to report on the relative impact of BMI on endocrine therapy only. In contrast, in ABCSG-6a halve of the patients received no treatment. Therefore, the comparison of anastrozole *vs* nil in normal weight and overweight patients may even better reflect the biological interaction of AI treatment and body weight.

In normal weight patients, 3 additional years of anastrozole halved the risk of disease recurrence and death compared with patients without any further treatment. It is remarkable that a relatively limited duration of endocrine treatment extension leads to a significant reduction in relapse rates (particularly distant metastases).

In contrast, overweight patients derived no benefit from 3 additional years of anastrozole when compared with overweight patients without any further treatment. This indicates that overweight and obese postmenopausal patients with breast cancer are non-responders to long-term endocrine treatment with anastrozole.

A limitation of this study is that because of its retrospective nature, patient and event numbers are somewhat limited. Further, we cannot rule out that healthier lifestyle including more physical activity in leaner patients contributes to our results. For the analyses, we combined overweight and obese patients. As previously shown, the prognostic and predictive impact of BMI is more distinct in obese than in overweight (Sestak *et al*, 2010; Kwan *et al*, 2012; Pfeiler *et al*, 2013). We can therefore not completely exclude that the data presented here are mainly driven by the group of obese patients, and further differentiation between limited weight excess and severe obesity is beyond numerical reason in our trial.

In contrast to other reports, we did not observe a prognostic impact of BMI in these long-term treated patients with breast cancer. Ewertz *et al* (2011) demonstrated a significant impact of BMI on disease outcome especially after 5 years of follow-up. Wolters *et al* (2012) confirmed this long-term prognostic impact of BMI). Recently, Goodwin *et al* (2012) reported on a constant impact of obesity on distant recurrences over time. The missing prognostic impact of BMI in our reanalysis might be due to the fact that we do not report on events after breast cancer diagnosis but after 5 years of endocrine treatment.

In this reanalysis, we did not observe any impact of BMI on the frequency of side effects, which is in line with previous reports (Pfeiler *et al*, 2011, 2013). Overweight patients had the same

Table 5. Comparison of adverse events between BMI categories stratified by treatment

	Control				Anastrozole				
	Norm ($n=87$)		Over ($n=253$)		Norm ($n=90$)		Over ($n=204$)		
Adverse event	***N***	**%**	***N***	**%**	***N***	**%**	***N***	**%**	***P*-value**
Allergy	1	1.1	1	0.4	3	3.3	5	2.5	0.467
Amenorrhoea	85	97.7	245	96.8	84	93.3	192	94.1	0.976
Arrhythmia	3	3.4	3	1.2	4	4.4	8	3.9	0.344
Asthenia	3	3.4	2	0.8	5	5.6	9	4.4	0.211
Bleeding	1	1.1	1	0.4	2	2.2	1	0.5	0.119
Bone aches	25	28.7	50	19.8	26	28.9	57	27.9	0.190
Card disorders	5	5.7	17	6.7	2	2.2	13	6.4	0.222
Cutaneous toxicity	0	0.0	1	0.4	6	6.7	10	4.9	0.647
Depressions	10	11.5	21	8.3	17	18.9	33	16.2	0.319
Diarrhoea	3	3.4	7	2.8	5	5.6	12	5.9	0.918
Eczema	1	1.1	6	2.4	1	1.1	12	5.9	0.058
Fever	1	1.1	4	1.6	3	3.3	5	2.5	0.866
Headache	10	11.5	30	11.9	20	22.2	44	21.6	0.967
Haematuria	0	0.0	2	0.8	1	1.1	3	1.5	0.505
Hair loss	1	1.1	8	3.2	12	13.3	20	9.8	0.746
Hot flushes	18	20.7	61	24.1	42	46.7	82	40.2	0.725
Infections	2	2.3	6	2.4	5	5.6	9	4.4	0.749
Nausea	2	2.3	6	2.4	9	10.0	13	6.4	0.358
Obstipation	2	2.3	9	3.6	8	8.9	14	6.9	0.858
Pericarditis	0	0.0	0	0.0	1	1.1	0	0.0	0.132
Proteinuria	0	0.0	1	0.4	1	1.1	1	0.5	0.866
Somnolence	4	4.6	12	4.7	9	10.0	26	12.7	0.557
Vaginal discharge	6	6.9	5	2.0	5	5.6	16	7.8	0.480
Vaginal dryness	11	12.6	20	7.9	16	17.8	23	11.3	0.045
Vomiting	2	2.3	5	2.0	3	3.3	5	2.5	0.659
Other	28	32.2	82	32.4	42	46.7	78	38.2	0.345

Abbreviation: BMI = body mass index.

frequency of side effects as normal weight patients regarding long-term endocrine therapy with anastrozole. This is of particular importance since overweight patients did not benefit from 3 additional years of anastrozole but significantly more side effects compared with patients without any further treatment.

This observation can be interpreted as the result of a 'minor' reduction in estradiol serum levels in overweight and obese patients by anastrozole, which on the one hand causes noticeable side effects, but on the other hand does not lower estradiol serum levels enough to impact on clinical outcome. Recently, Folkerd *et al* (2012) showed a retrospective analysis of the ALIQUOT study that indeed oestrogen serum levels are lowered in overweight and obese patients but not to the same low level when compared with normal weight patients.

In conclusion, we report that normal weight patients with additional 3 years of anastrozole halve their risk of disease recurrence and death compared with normal weight patients without any further treatment. In contrast, overweight patients derive no benefit from these additional 3 years of endocrine treatment with anastrozole. However, overweight patients treated with anastrozole have the same increased rate of side effects as normal weight patients when compared with patients without any further treatment. According to our reanalysis of the ABCSG-6a, the beneficial effect of extended AI treatment seems to be more pronounced in patients with normal weight compared with patients with increased BMI.

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