Extended adjuvant aromatase inhibition after sequential endocrine therapy (DATA): a randomised, phase 3 trial

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Summary

Background **The effect of extended adjuvant aromatase inhibition in hormone receptor-positive breast cancer after sequential endocrine therapy of tamoxifen followed by an aromatase inhibitor for a 5-year treatment period still needs clarification. To address this issue, we began the DATA study to assess different durations of anastrozole therapy after tamoxifen.**

Methods **DATA was a prospective, randomised, open-label, multicentre, phase 3 study done in 79 hospitals in the Netherlands. We randomly assigned postmenopausal women with hormone receptor-positive early breast cancer with no signs of disease recurrence after 2–3 years of adjuvant tamoxifen to either 3 or 6 years of anastrozole treatment (1 mg orally once a day) in a 1:1 ratio. We used TENALEA (Trans European Network for Clinical Trials Services) for the randomisation procedure. Stratification factors were nodal status, hormone receptor status, HER2 status, and tamoxifen treatment duration. The primary study endpoint of this analysis was disease-free survival starting beyond 3 years after randomisation (adapted disease-free survival). Here we report the final analysis from the DATA trial, which is registered with ClinicalTrials.gov, number NCT00301457.**

Findings **Between June 28, 2006, and Aug 10, 2009, we screened 1912 patients of whom 955 were assigned to the 3-year group and 957 to the 6-year anastrozole treatment group. 1860 patients were eligible (931 in the 6-year group and 929 in the 3-year group) and 1660 were disease free 3 years after randomisation. The 5-year adapted disease-free survival was 83·1% (95% CI 80·0–86·3) in the 6-year group and 79·4% (76·1–82·8) in the 3-year group (hazard ratio [HR] 0·79 [95% CI 0·62–1·02]; p=0·066). Patients in the 6-year treatment group had more adverse events than those in the 3-year treatment group, including all-grade arthralgia or myalgia (478 [58%] of 827 in the 6-year treatment group *vs* 438 [53%] of 833 in the 3-year treatment group) and osteopenia or osteoporosis (173 [21%] *vs* 137 [16%]).**

Interpretation **We cannot recommend the use of extended adjuvant aromatase inhibition after 5 years of sequential endocrine therapy in all postmenopausal women with hormone receptor-positive breast cancer.**

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Introduction

Breast cancer treatment has changed substantially in recent decades, leading to improved survival over time. In Europe, the 5-year age-standardised relative survival rate for breast cancer increased from 78% in patients diagnosed from 1999–2001 to 82% in patients diagnosed from 2005–07.[1] Since then, further improvements, including refinements in adjuvant endocrine therapy, have been made.

Adjuvant endocrine therapy with aromatase inhibitors in postmenopausal women either after initial diagnosis (upfront therapy) or after 2–3 years of tamoxifen (sequential therapy), for a total treatment period of 5 years, has been shown to reduce the proportion of patients having a recurrence by about 30% compared with 5 years of tamoxifen alone.[2] Extended treatment with tamoxifen or aromatase inhibitors after 5 years of tamoxifen also led to an improved outcome.[3–7] Consequently, the American Society of Clinical Oncology and the European Society for Medical Oncology recommended that postmenopausal women with hormone receptor-positive early breast cancer use either aromatase inhibitors or sequential tamoxifen followed by an aromatase inhibitor for a total duration of 5 years, or extended adjuvant endocrine therapy for a total of 10 years in patients initially treated with 5 years of tamoxifen.[8,9]

Some physicians already prescribe extended aromatase inhibitor therapy after 5-years of sequential endocrine therapy, in view of the steadily increased risk of disease recurrence in hormone receptor-positive breast cancer for years 5–10 by 5%, and for years 10–20 by 2% if node-negative and by 3% if node-positive disease at diagnosis.[10] However, there are currently no data on the importance of extended aromatase inhibitor use beyond a total duration of 5 years for patients treated with sequential endocrine therapy, and earlier introduction of aromatase inhibitors might make prolonged treatment beyond 5 years redundant by increasing the chance of cure. In order to clarify this issue, we began the DATA study, a prospective randomised, open-label, multicentre, phase 3 study to assess different durations of anastrozole therapy after 2–3 years of tamoxifen as adjuvant therapy in postmenopausal women with hormone receptor-positive breast cancer.

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Research in context

Evidence before this study

For many years, the standard endocrine adjuvant treatment for breast cancer in postmenopausal women with a hormone receptor-positive tumour was 5 years of treatment with the anti-oestrogen treatment tamoxifen. More than a decade ago, two major studies (ATAC and BIG-98), which compared 5 years of adjuvant tamoxifen with 5 years of adjuvant aromatase inhibitor, showed that use of an aromatase inhibitor led to an improved relapse-free survival. Three other studies showed that switching to an aromatase inhibitor after 2–3 years of tamoxifen, for a total adjuvant treatment of 5 years, also gave an improved relapse-free survival. Moreover, two studies have shown that switching patients to an aromatase inhibitor after an initial 5 years of adjuvant tamoxifen gave an improved outcome. The Early Breast Cancer Trialists' Collaborative Group showed a small improvement in recurrence-free survival but not a breast cancer specific survival benefit for 5 years of aromatase inhibitor versus sequential tamoxifen or aromatase inhibitor use. Consequently, international guidelines recommended the use of either aromatase inhibitors or sequential tamoxifen followed by an aromatase inhibitor for a total duration of 5 years, or extended adjuvant endocrine therapy for a total of 10 years in postmenopausal women with hormone receptor-positive early breast cancer initially treated with 5 years of tamoxifen. However, there were no data on the benefit of extended aromatase inhibitor use beyond a total duration of 5 years for patients treated with sequential endocrine therapy.

Added value of this study

In an attempt to clarify this issue, we initiated the DATA study, a prospective randomised, open-label, multicentre, phase 3 study to assess different durations of anastrozole therapy after 2–3 years of tamoxifen as adjuvant therapy in postmenopausal women with hormone receptor-positive breast cancer. By contrast with what was expected, extended aromatase inhibition after 5 years of sequential endocrine therapy did not significantly improve disease-free survival in the total population of postmenopausal women with hormone receptor-positive breast cancer. However, our exploratory analyses suggest that patients with high-risk characteristics might yet benefit from extended therapy and that tumours expressing both oestrogen and progesterone receptors might drive the benefits seen in this study.

Implications of all the available evidence

Two other studies (NSABP-B42 and IDEAL), which were presented at the 2016 San Antonio Breast Cancer Symposium and that assessed extended use of aromatase inhibitors in hormone receptor-positive postmenopausal patients also failed to meet their primary endpoints. There were, however, significant improvements in breast cancer-free interval events in the NSABP-B42 trial. Considering all studies together, benefit might be seen from extended use of aromatase inhibitors in subgroups of patients who were initially treated with tamoxifen, as was the case in the DATA study. Any benefit, however, comes at a price; shown by the continuous decline in treatment compliance over time in all three new trials. Hence, careful assessment of potential benefits and risks is required before recommending extended aromatase inhibitor therapy.

Methods

Study design and participants

The DATA study is an open-label, multicentre, phase 3 trial, done in 79 hospitals in the Netherlands. Postmenopausal women with hormone receptor-positive early breast cancer were eligible if they had received 2–3 years of tamoxifen treatment and had no signs of recurrence of disease. Chemotherapy, radiotherapy, or both therapies, before or after surgical treatment at diagnosis were allowed; trastuzumab was not yet standard care during recruitment. Postmenopausal status was defined as age 55 years or older and natural amenorrhoea, a bilateral oophorectomy irrespective of age, or age 45–54 years and follicle stimulating hormone or oestradiol concentrations within the postmenopausal range. Hormone receptor positivity was defined as positive nuclear staining of the oestrogen receptor or the progesterone receptor in at least 10% of tumour cells.

Exclusion criteria included history of invasive breast cancer within 10 years before the breast cancer that the patient was currently included for; other invasive malignancies within the last 5 years other than squamous or basal cell carcinoma of the skin or carcinoma in situ of the cervix; treatment with a non-approved drug; Karnofsky performance score of less than 60%; and being unlikely to comply with the trial regimen.

The protocol was approved by the ethics committee of the Radboud University Medical Center (Nijmegen, Netherlands). All patients provided written informed consent. The trial was done in accordance with the principles of the Declaration of Helsinki and the International Conference on Harmonization Good Clinical Practice Guidelines. The protocol is available online.

The investigator-initiated trial was sponsored by AstraZeneca until November, 2016, and thereafter by the Maastricht University Medical Center (Maastricht, Netherlands). The investigators and the associated research team were jointly responsible for the study design and interpretation of the data, which were compiled and maintained by an independent central data office (Netherlands Comprehensive Cancer Organisation, IKNL). An independent data safety monitoring board monitored the quality and progression of the study protocol.

For the **trial protocol** see https://clinicaltrials.gov/ProvidedDocs/57/NCT00301457/Prot_000.pdf

Randomisation and masking

Patients were randomly assigned (1:1) to receive either 6 years (extended treatment group) or 3 years (control group) of adjuvant anastrozole after 2–3 years of adjuvant tamoxifen (appendix). The local investigator enrolled participants. Randomisation was done by a centralised service (Trans European Network for Clinical Trials Services [TENALEA]) and it was not possible for the investigators to know the allocation sequence in advance. Stratification factors were nodal status (positive *vs* negative), hormone receptor status (oestrogen and progesterone receptor-positive *vs* oestrogen receptor-positive and progesterone receptor-negative *vs* oestrogen receptor-negative and progesterone receptor-positive), HER2 status (positive *vs* negative *vs* unknown), and tamoxifen duration (≤2·5 years *vs* >2·5 years). No one in the study was masked to treatment assignment.

Procedures

The participants' baseline characteristics were recorded at randomisation. The tumour characteristics were based on the postoperative pathology reports. For patients who received neoadjuvant chemotherapy, the clinical T status and N status at diagnosis were reported if more advanced than the pathological status.

Adjuvant anastrozole was given at a dose of 1 mg orally once a day after 2–3 years of adjuvant tamoxifen. Consequently, patients received either a total of 8–9 years or a total of 5–6 years of adjuvant endocrine therapy. Dose reductions were not allowed. Shorter or longer duration of tamoxifen treatment was considered a minor protocol violation. Specific reasons for discontinuing a patient from this study were voluntary discontinuation by the patient, safety reasons, severe non-compliance to the protocol as judged by the responsible physician, incorrect enrolment (ie, the patient did not meet the required inclusion or exclusion criteria), and patients who were lost to follow up.

Follow-up visits were scheduled every 6 months until 6 years after randomisation, and once a year thereafter. Patients were reviewed for recurrence of breast cancer at all visits during treatment and follow-up by history and physical examination. A mammogram was done once a year during treatment and follow-up, according to Dutch guidelines. The primary endpoint was not centrally reviewed.

Adverse events were recorded until 6 years after randomisation, or until diagnosis of recurrence or early definitive cessation of treatment, whichever was first. We obtained data for predefined adverse events: arthralgia or myalgia, osteopenia or osteoporosis, bone fractures, and cardiovascular events. Additionally, adverse events of particular clinical importance or leading to discontinuation of anastrozole were documented. All adverse events were graded by use of the Common Terminology Criteria for Adverse Events (CTCAE) version 3.0.

Outcomes

The primary endpoint was adapted disease-free survival, defined as the disease-free survival beyond 3 years after randomisation, because all patients initiated anastrozole therapy for 3 years. Events ending a period of disease-free survival included non-invasive and invasive breast cancer recurrences (local, regional, or distant), second primary non-invasive and invasive breast and other cancers other than basal-cell or squamous-cell carcinoma of the skin and carcinoma in situ of the cervix, and death from any cause.[11] Secondary endpoints were adapted overall survival (beyond 3 years after randomisation), incidence of secondary breast cancer, and adverse events. Other secondary endpoints were: the assessment of regional differences in the initial treatment of breast cancer; cost-effectiveness of 3 additional years of adjuvant anastrozole therapy; and the assessment of patterns of care in prevention, detection, and treatment of osteoporosis in postmenopausal women with breast cancer treated with adjuvant anastrozole; and its relation with distant (bone) recurrences. These endpoints will be analysed separately and are not reported in this paper.

See Online for appendix

Statistical analysis

Because all patients received the same therapy for 3 years after randomisation, we only expected differences between the treatment groups to appear after this timepoint. 3 years after randomisation, we expected 91% of all participants in both groups to be disease free.[12] We assumed that 6 years after randomisation, the 3-year adapted disease-free survival rate would be 90% in the 3-year treatment group. We designed this study to detect an increase in the 3-year adapted disease-free survival to 94% in the 6-year anastrozole group, corresponding with a hazard ratio (HR) of 0·60, based on previous studies with aromatase inhibitors.[12,13] Originally, we designed the trial with one planned interim analysis. A statistical power of 80% and a two-sided α level of 0·05 (spending 0·01 at the interim analysis and 0·04 for the final analysis) required 770 disease-free participants in each group to start the extended treatment or control part of the trial, which required 850 randomly assigned participants in each group. Accounting for about a 10% dropout, 950 participants per group had to be included. By protocol amendment 4 (dated Oct 30, 2014), the interim analysis was skipped because the difference in treatment duration between the study groups was minimal at the time and a disease-free survival difference was only expected after a longer follow-up period.[3–5] Therefore, the final analysis could be assessed at a significance level of 0·05, increasing the power to 82·5%.

We analysed the primary and secondary endpoints in all eligible patients, excluding patients with a disease-free event or who were lost to follow-up during the first 3 years after randomisation. Because of the intention-to-treat design of the study, the patients who had prematurely stopped anastrozole treatment in the first

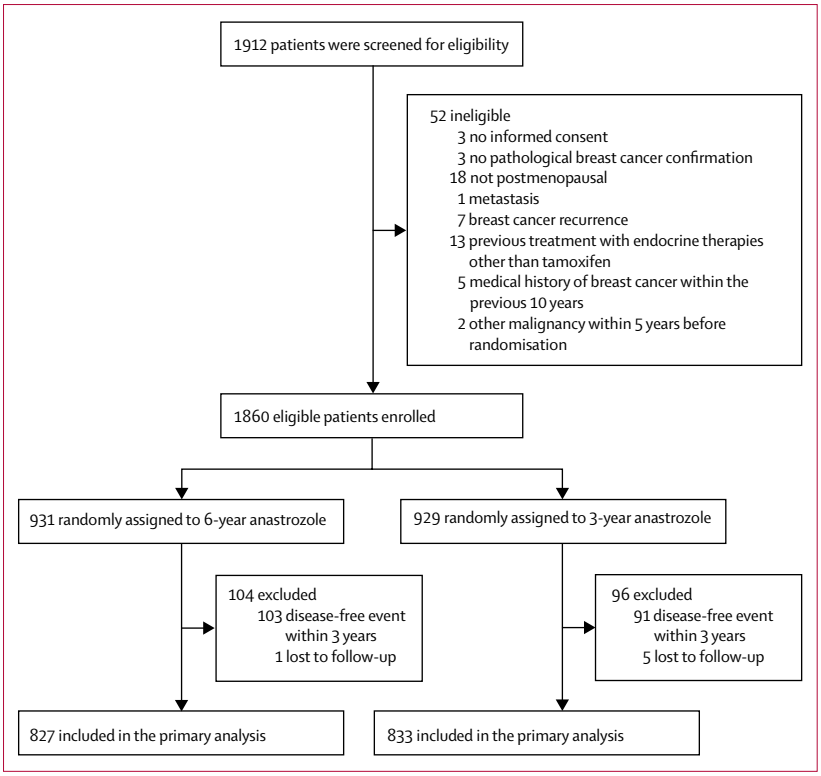

Figure 1: **Trial profile**

3 years, without having a disease-free survival event, were included in the analysis.

Here, we report the final analysis, which was planned after the last patient randomly assigned to treatment had reached a minimum follow-up of 6 years after randomisation, corresponding with an adapted follow-up of 3 years. The median follow-up time was calculated from the Kaplan-Meier curve with reversed censoring. A further follow-up analysis is planned when all patients have reached a minimum adapted follow-up of 9 years. Kaplan-Meier survival curves were used to show the primary and secondary survival endpoints. Differences between the two treatment groups were tested with the stratified log-rank test. HRs and the corresponding 95% CIs were estimated with stratified Cox regression analyses. The test for interaction of treatment with a risk factor was assessed in a stratified Cox regression model with the risk factor as an additional stratum variable. The risk factors were the stratification factors (nodal status, oestrogen or progesterone receptor status, HER2 status, and tamoxifen treatment duration), additional prognostic factors (age, tumour size, histology, and grade), and use of previous adjuvant or neoadjuvant chemotherapy (yes or no). The proportionality assumption for treatment was addressed by extending the Cox model with an interaction term for treatment and time, allowing for a monotonous increase or decrease in treatment effect over time.

For the safety analysis, we reported the number of patients with specific adverse events by period of occurrence: years 0–3 and years 0–6 after randomisation. For the compliance analysis, we assessed the proportion of patients still on treatment at 33 months and 69 months after randomisation as a minimum requirement for 3-year and 6-year treatment durations. Treatment duration was censored at the time of a primary event. We used SAS (version 9.4) for the statistical analyses.

This study is registered with ClinicalTrials.gov, number NCT00301457 (other study ID numbers: D5392NL003 and EUDRACT 2005–006167–31).

Role of the funding source

AstraZeneca was involved in the trial design and monitoring of the trial conduct. The sponsor had no role in data collection, data analysis, data interpretation, or writing of the report. The corresponding author had full access to all the data in the study and final responsibility for the decision to submit for publication.

Results

Between June 28, 2006, and Aug 10, 2009, we screened 1912 patients from 79 hospitals in the Netherlands, of whom 955 were assigned to the 3-year anastrozole treatment group and 957 to the 6-year anastrozole treatment group. Of these, 1860 patients (931 in the 6-year group *vs* 929 in the 3-year group) were eligible (figure 1). Here, we report the results of the primary endpoint analysis in 1660 patients who were disease free at 3 years after randomisation; the results of all 1860 eligible patients are presented in the appendix (pp 10–12).

The baseline characteristics were well balanced between the groups (table 1). The median age at randomisation was 57·7 years (IQR 51·9–64·3) in the 6-year group and 57·6 years (51·2–64·5) in the 3-year group. Two-thirds of patients had node-positive disease and three-quarters had oestrogen and progesterone receptor-positive disease at diagnosis. The median duration of previous adjuvant tamoxifen was 2·3 years (IQR 2·1–2·5) in both the 6-year group and the 3-year group.

At the data cutoff date on July 14, 2016, the median adapted follow-up was 4·2 years (IQR 3·7–5·0). The adapted disease-free survival at 3 years was 90·7% (95% CI 88·7–91·0) in the 6-year anastrozole group and 88·9% (86·7–91·0) in the 3-year group; the adapted disease-free survival at 5 years was 83·1% (95% CI 80·0–86·3) and 79·4% (76·1–82·8) respectively, giving a curve with an HR of 0·79 (95% CI 0·62–1·02; p=0·066; figure 2A). The proportionality of hazards assumption was not violated (p=0·22).

Post-hoc analyses by stratified subgroups (by nodal and oestrogen and progesterone receptor status) are shown in figures 2B and 2C. Figure 3 presents the HRs for all stratified and non-stratified subgroups. In a post-hoc exploratory subgroup analysis, extended treatment was

associated with an improved 5-year adapted disease-free survival irrespective of chemotherapy use of 84·4% in the 6-year group versus 76·2% in the 3-year group in patients with oestrogen receptor and progesterone receptor-positive expression having node-positive disease (n=849; HR 0·64 [95% CI 0·46–0·89], p=0·0075); and of 82·7% versus 69·2% if also having a larger tumour size (≥T2; n=429; HR 0·53 [0·53–0·82], p=0·0031; appendix p 5).

The number of patients who achieved 5-year adapted overall survival did not differ between the treatment groups (90·8% [95% CI 83·3–93·3] in the 6-year group *vs* 90·4% [88·1–92·8] in the 3-year treatment group; HR 0·91 [95% CI 0·65–1·29]; p=0·60; figure 2D).

	6-year anastrozole (n=827)	3-year anastrozole (n=833)
Median age at randomisation, years	57·6 (51·6–64·4)	57·6 (51·6–64·4)
<49 years	141 (17%)	160 (19%)
50–59 years	342 (41%)	328 (39%)
≥60 years	344 (42%)	345 (41%)
Tumour status		
pT1	376 (46%)	383 (46%)
pT2	392 (47%)	382 (46%)
pT3/4	58 (7%)	67 (8%)
TX	1 (<1%)	1 (<1%)
Nodal status		
pN0 / pN0(i+)	266 (32%)	282 (34%)
pN1	434 (53%)	457 (55%)
pN2 / pN3	127 (15%)	94 (11%)
Histological grade		
1	139 (17%)	158 (19%)
2	430 (52%)	415 (50%)
3	229 (28%)	238 (29%)
Unknown	29 (4%)	22 (3%)
Hormone receptor status		
ER and PR positive	627 (76%)	633 (76%)
ER or PR positive	200 (24%)	200 (24%)
HER2 status		
Positive	18 (2%)	22 (3%)
Negative	745 (90%)	748 (90%)
Unknown	64 (8%)	63 (8%)
Histology		
Lobular	154 (19%)	140 (17%)
Other	673 (81%)	693 (83%)
Type of breast surgery		
Breast-conserving surgery	433 (52%)	408 (49%)
Mastectomy	394 (48%)	425 (51%)
Type of axillary surgery		
Sentinel node only	226 (27%)	209 (25%)
Sentinel node plus axillary lymph node dissection	370 (45%)	386 (46%)
Axillary lymph node dissection	218 (26%)	230 (28%)
None	13 (2%)	8 (1%)

(Table 1 continues in next column)

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	6-year anastrozole (n=827)	3-year anastrozole (n=833)
Radiotherapy		
Local	235 (28%)	233 (28%)
Local and regional lymph nodes	315 (38%)	291 (35%)
Regional lymph nodes	21 (3%)	14 (2%)
None/unknown	256 (31%)	295 (35%)
Prior (neo)adjuvant chemotherapy		
Anthracycline-containing and taxane-containing regimen	45 (5%)	59 (7%)
Anthracycline-containing regimen without taxane	507 (61%)	495 (59%)
Taxane-containing regimen without anthracycline	4 (1%)	2 (<1%)
Regimen without anthracycline or taxane	9 (1%)	14 (2%)
No chemotherapy	262 (32%)	263 (32%)
Previous HER2-targeted therapy	3 (<1%)	3 (<1%)
Median previous duration of tamoxifen, years	2·3 (1·6–3·2)	2·3 (1·4–3·8)

Data are median (IQR) or n (%). TX=size of tumour could not be assessed. ER=oestrogen receptor. PR=progesterone receptor.

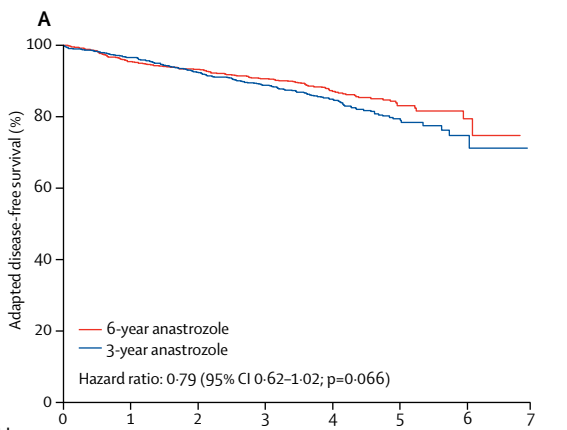
Table 1: **Baseline characteristics of the patients who were disease free at 3 years after randomisation**

The number of patients who had an adapted cumulative 5-year incidence of a secondary breast cancer was 1·5% (95% CI 0·5–2·4) in the 6-year anastozole group and 3·3% (1·7–4·9) in the 3-year anastrozole group (HR 0·50 [95% CI 0·23–1·07]; p=0·068; figure 4).

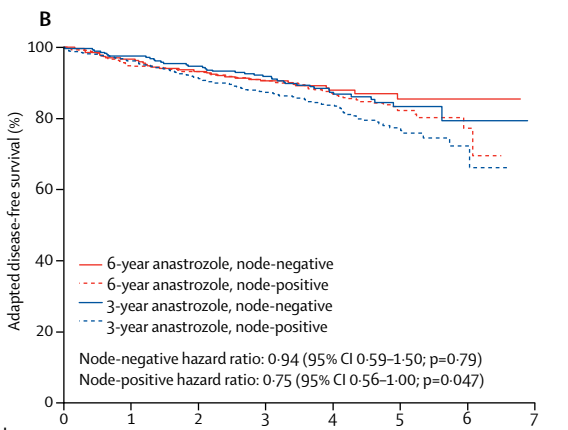
116 disease-free survival events occurred in the 6-year treatment group and 145 events occurred in the 3-year treatment group (table 2), with little difference in locoregional or distant events, and the main driver a reduction in contralateral invasive breast cancers and secondary non-breast cancers (appendix p 8).

As expected, there was no difference between groups in the adverse event rate in the first 3 years after randomisation (table 3). However, for the entire observation period (0–6 years), the occurrence of all-grade arthralgia or myalgia (478 [58%] of 827 in the 6-year treatment group *vs* 438 [53%] of 833 in the 3-year treatment group) and osteopenia or osteoporosis (173 [21%] *vs* 137 [16%]) were higher in the 6-year compared with the 3-year treatment group. Grade 3–4 events were similar between groups for arthralgia or myalgia (75 [9%] of 827 in the 6-year group *vs* 72 [9%] of 833 in the 3-year treatment group) and osteopenia or osteoporosis (12 [2%] *vs* 7 [1%]). No difference in cardiovascular adverse events was seen. The observed adverse events were mainly grade 1–2 and no toxic deaths were observed.

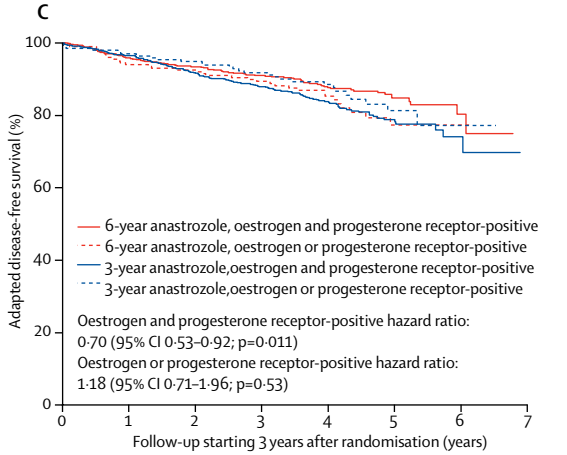
A substantial number of patients in the 6-year and 3-year anastrozole treatment groups discontinued their treatment early because of adverse events or patient refusal, and in the 6-year group also for a primary disease event (appendix p 6). According to protocol, treatment duration was censored at a disease event, resulting in non-



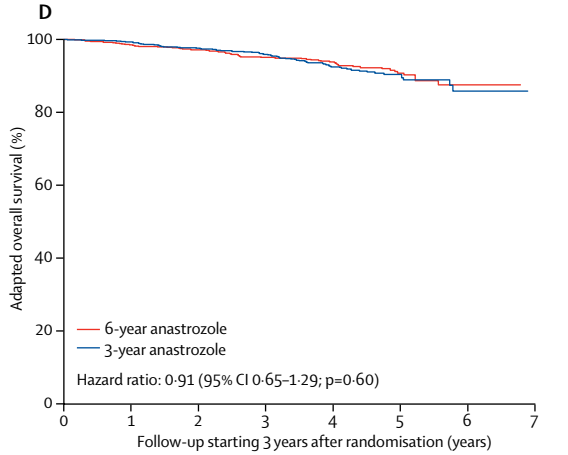
Number at risk (number censored)								
6-year anastrozole	827 (0)	789 (0)	769 (2)	698 (52)	445 (283)	182 (533)	24 (688)	0 (711)
3-year anastrozole	833 (0)	801 (4)	762 (8)	692 (49)	453 (262)	169 (525)	28 (661)	0 (688)



Number at risk (number censored)								
6-year anastrozole, node-negative	266 (0)	257 (0)	247 (1)	224 (17)	128 (108)	50 (184)	9 (225)	0 (234)
6-year anastrozole, node-positive	561 (0)	532 (0)	522 (1)	474 (35)	317 (175)	132 (349)	15 (463)	0 (477)
3-year anastrozole, node-negative	282 (0)	275 (0)	264 (3)	243 (16)	156 (93)	64 (180)	12 (231)	0 (243)
3-year anastrozole, node-positive	551 (0)	526 (4)	498 (5)	449 (33)	297 (169)	105 (345)	16 (430)	0 (445)



Number at risk (number censored)								
6-year anastrozole, oestrogen and progesterone receptor-positive	627 (0)	601 (0)	585 (1)	533 (38)	345 (210)	149 (399)	21 (524)	0 (544)
6-year anastrozole, oestrogen or progesterone receptor-positive	200 (0)	188 (0)	184 (1)	165 (14)	100 (73)	33 (134)	3 (164)	0 (167)
3-year anastrozole, oestrogen and progesterone receptor-positive	633 (0)	611 (0)	577 (3)	529 (28)	343 (193)	132 (389)	22 (495)	0 (516)
3-year anastrozole, oestrogen or progesterone receptor-positive	200 (0)	190 (4)	185 (5)	163 (21)	110 (69)	37 (136)	6 (166)	0 (172)



Number at risk (number censored)								
6-year anastrozole	827 (0)	815 (0)	802 (2)	733 (54)	486 (293)	203 (565)	25 (739)	0 (764)
3-year anastrozole	833 (0)	823 (4)	805 (8)	744 (55)	494 (283)	196 (573)	31 (733)	0 (764)

Figure 2: **Kaplan-Meier estimates of the primary and secondary endpoint and subgroup analyses**
Adapted disease-free survival (A), adapted disease-free survival for both treatment groups subdivided by patients with node-positive and node-negative disease (B), adapted disease-free survival for both treatment groups subdivided by hormone-receptor status (oestrogen and progesterone receptor-positive *vs* oestrogen or progesterone receptor-positive) (C), and adapted overall survival (D). Adapted survival implies the survival time beyond 3 years after randomisation. p values were calculated with the two-sided stratified log-rank test.

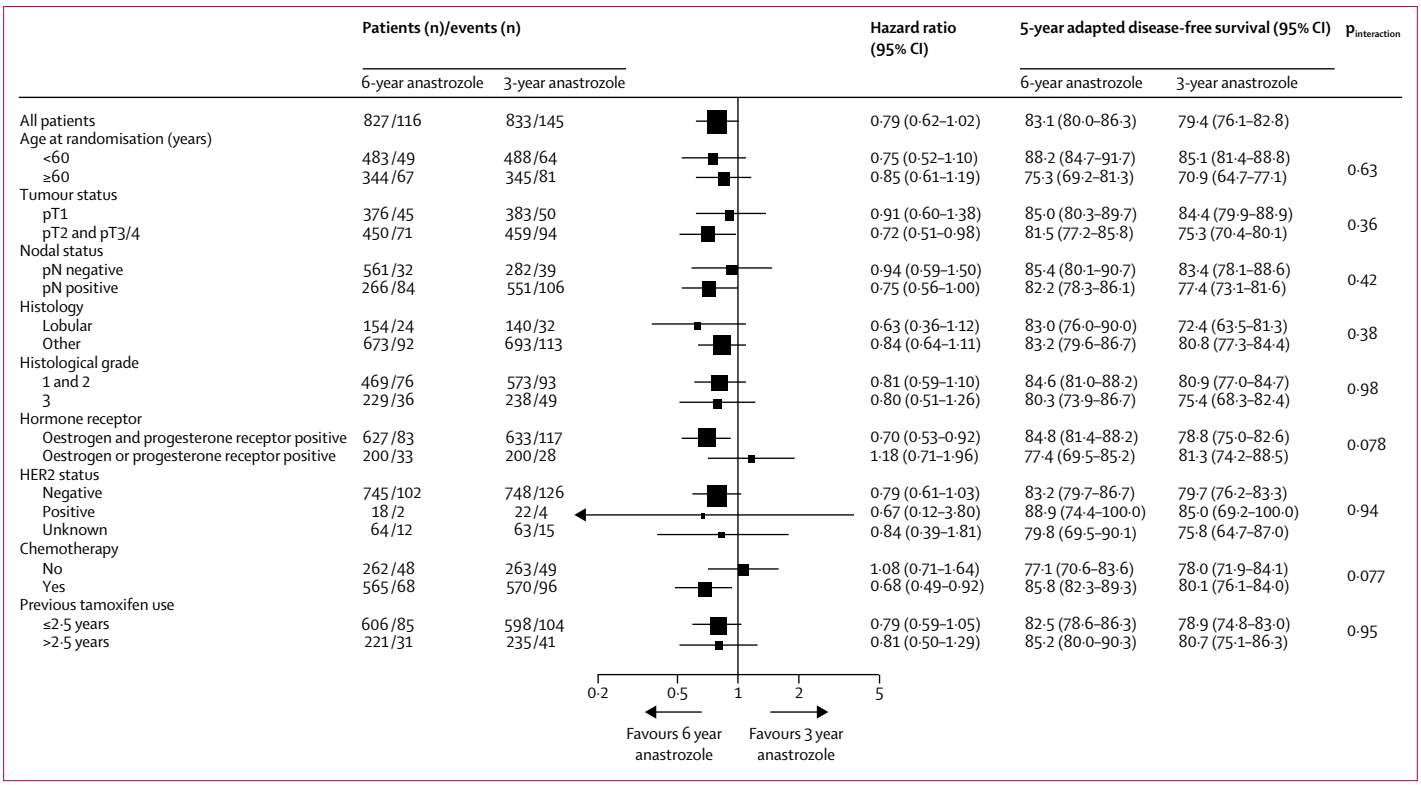


Figure 3: **Cox proportional-hazards model results of adapted disease-free survival by 6-year anastrozole compared with 3-year anastrozole**
Adapted disease-free survival implies the disease-free survival time beyond 3 years after randomisation. The disease-free survival events include: local, regional, and distant disease recurrences; contralateral invasive breast cancer; ductal carcinoma in situ; any second (non-breast) cancer; or death without a previous cancer event. The size of the boxes is inversely proportional to the standard error of the natural logarithm of the hazard ratio.

compliance in 268 (34%) of 827 participants in the 6-year treatment group and 131 (16%) of 833 participants in the 3-year group. Treatment compliance decreased over time at a constant rate in both groups (appendix p 7).

Discussion

In our study, we addressed the question of whether extended adjuvant aromatase inhibition after 5 years of sequential endocrine therapy (tamoxifen followed by an aromatase inhibitor) would improve the outcome of postmenopausal women with hormone receptor-positive breast cancer. We found that extended use of anastrozole for 3 years beyond 5 years of sequential therapy did not significantly improve disease-free and overall survival in the total study population. However, our study results suggest benefit in particular subgroups of patients.

Our exploratory subgroup analyses suggested that extended treatment appeared to be associated with a non-significant improvement in the 5-year adapted disease-free survival from 78·8% to 84·8% in patients with primary tumours having both oestrogen and progesterone receptor expression. The MA.17R trial has reported a larger benefit of extended aromatase inhibitor treatment in patients who had previous chemotherapy and those with node positive disease,[14] implying that patients with worse tumour characteristics

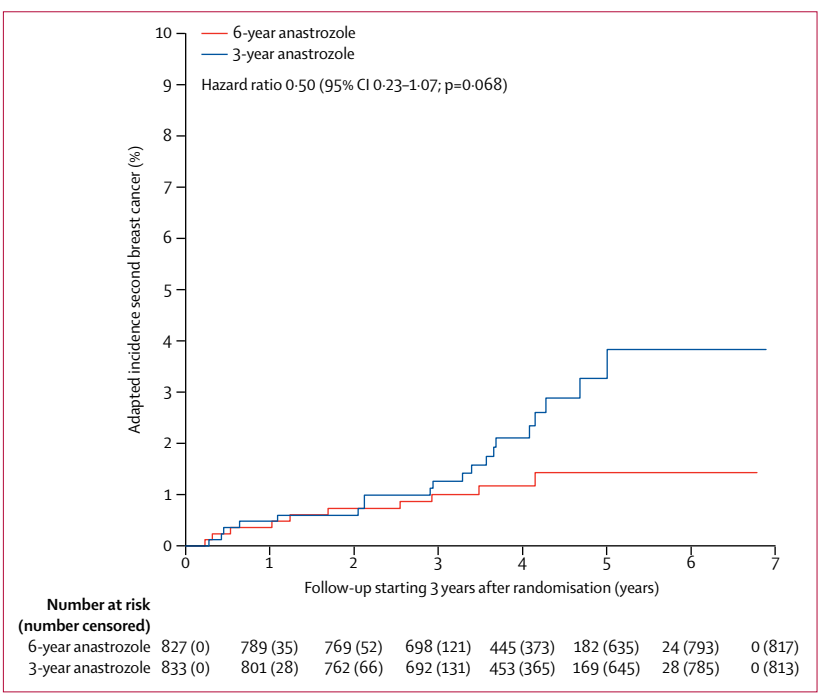


Figure 4: **Kaplan-Meier estimates of adapted cumulative incidence of second breast cancer**
Adapted incidence implies the incidence beyond 3 years after randomisation. The p value was calculated with the two-sided log-rank test.

	6-year anastrozole (n=827)	3-year anastrozole (n=833)
Primary endpoint		
Adapted disease-free survival event*	116	145
Local recurrence	12 (10%)	7 (5%)
Regional recurrence	10 (9%)	14 (10%)
Distant recurrence†	48 (41%)	52 (36%)
Visceral	29 (25%)	38 (26%)
Bone	26 (22%)	30 (21%)
Soft tissue	5 (4%)	3 (2%)
Other	6 (5%)	3 (2%)
Secondary, invasive or non-invasive breast cancer	10 (9%)	23 (16%)
Ipsilateral invasive	3 (3%)	4 (3%)
Ipsilateral DCIS	0	1 (1%)
Contralateral invasive	4 (3%)	15 (10%)
Contralateral DCIS	3 (3%)	3 (2%)
Secondary, non-breast cancer‡	27 (23%)	45 (31%)
Death without previous breast cancer event	20 (17%)	18 (12%)
Secondary endpoints		
Death from any cause	63	69
Breast cancer related	30 (48%)	32 (46%)
Not breast cancer related	33 (52%)	37 (54%)
Second primary malignancy	10 (16%)	16 (23%)
Cardiovascular disease	6 (10%)	5 (7%)
Other	17 (27%)	16 (23%)

Data are number of patients (%). DCIS=ductal carcinoma in situ. *Patients may have had multiple disease-free survival events. †In some patients, multiple locations of recurrences were reported. ‡See appendix p 8.

Table 2: **Efficacy endpoint events in patients who were disease-free at 3 years after randomisation**

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	6-year anastrozole (n=827)			3-year anastrozole (n=833)		
	Grade 1–2	Grade 3	Grade 4	Grade 1–2	Grade 3	Grade 4
Years 0–3						
Arthralgia or myalgia*	361 (44%)	55 (7%)	1 (<1%)	361 (43%)	55 (7%)	1 (<1%)
Bone fractures	38 (5%)	14 (2%)	0	24 (3%)	16 (2%)	0
Osteoporosis†	103 (13%)	5 (1%)	0	104 (13%)	6 (1%)	0
Cardiovascular‡	51 (6%)	19 (2%)	2 (<1%)	47 (6%)	25 (3%)	2 (<1%)
Total years 0–6						
Arthralgia or myalgia*	403 (49%)	74 (10%)	1 (<1%)	366 (44%)	71 (9%)	1 (<1%)
Bone fractures	59 (7%)	24 (3%)	0	39 (5%)	24 (3%)	0
Osteoporosis†	161 (19%)	12 (2%)	0	130 (16%)	7 (1%)	0
Cardiovascular‡	74 (9%)	39 (5%)	6 (1%)	66 (8%)	45 (5%)	5 (1%)

Data are n (%). Adverse events reported include only predefined adverse events (arthralgia or myalgia, bone fractures, osteoporosis, and cardiovascular). When a predefined adverse event was reported multiple times for one patient within one timeframe, only the adverse event with the highest grade was counted. No grade 5 events occurred. CTCAE=Common terminology Criteria ffor Adverse Events. *Arthralgia or myalgia included the CTCAE version 3.0 categories: pain–musculoskeletal, musculoskeletal or soft tissue–arthritis, musculoskeletal or soft tissue–joint function, and musculoskeletal or soft tissue–other–tendinopathy. †Osteoporosis included both osteopenia and osteoporosis (T score <–1·5). ‡Cardiovascular events include the following CTCAE version 3.0 categories: cardiac arrhythmia, cardiac general, and vascular.

Table 3: **Adverse events by treatment group**

have more to gain from extended endocrine treatment. However, we should be aware that the indications for adjuvant or neoadjuvant chemotherapy have changed over time because of new insights.[14] Hence, selecting patients solely on the basis of previous use of chemotherapy might not be correct. Considering this remark, our exploratory subgroup analysis suggested that extended treatment was associated with a significantly improved 5-year adapted disease-free survival irrespective of chemotherapy use in patients with oestrogen and progesterone receptor-positive expression having node-positive disease, and an even larger benefit if they also had a larger tumour size, which might be considered a worthwhile benefit for many of these patients. Nevertheless, we should interpret these data with caution because these data concern trends and subgroups that might not be singly related to the use of previous chemotherapy, and have only a non-significant treatment effect in the entire study population so far.

The adapted disease-free survival definition we used[11] includes breast cancer recurrences, secondary breast and non-breast cancers, and death without a previous breast cancer event. The difference in number of disease events was partly due to the occurrence of a variety of non-breast tumours, even though some of these might be suspected to be unidentified metastases of the previous breast tumour (appendix p 8). In our study, the difference in number of events was largely due to the prevention of secondary primary breast cancers by extended aromatase inhibition, which is in agreement with the results seen in other extended endocrine treatment trials.[3,15–17] Yet, the purpose of adjuvant treatment is, by definition, to prevent recurrences from the previous breast cancer, using prognostic nomograms such as Adjuvant! online, in which the prognosticated outcome is related to the primary tumour characteristics.[18] Therefore, we suggest that future adjuvant trials should use recurrence-free survival as a primary endpoint, only including loco-regional and distant breast cancer recurrences. Alternatively, patients at risk of a second breast cancer could benefit from additional treatment, which should be based on other criteria and nomograms. Secondary endpoints of future trials should, therefore, include second breast cancers to assess the primary prevention effect, and death without previous breast cancer events to assess long-term adverse events.

We mentioned the recommendations of international guidelines on the use of sequential tamoxifen followed by an aromatase inhibitor above.[8,9] In 2015, the Early Breast Cancer Trialists' Collaborative Group reported that in the comparison of 5 years of an aromatase inhibitor alone with sequential use of tamoxifen followed by an aromatase inhibitor, there were fewer recurrences with 5 years of aromatase inhibitors (relative risk [RR] 0·90, [95% CI 0·81–0·99]; p=0·045);[2] however, breast cancer mortality was not significantly reduced (RR 0·89,

[0·78–1·03]; p=0·11). We think, therefore, that there is still a role for the sequential treatment approach because aromatase inhibitors are associated with a different spectrum of adverse events and tamoxifen might be able to balance these (at least partly) against the negative effect on bone mineral density.

In our study, extended aromatase inhibition was associated with an increased number of bone, joint, and muscle-related complaints. The substantial non-compliance rate over time indicates that prolonged endocrine treatment is not a feasible option for all patients. Gene-expression profiles might help to identify patients who are at sufficient risk of developing late recurrences to increase efficacy and, indirectly, compliance.[19–22] In our opinion, future studies should also focus on targeting other pathways, such as CDK 4/6 inhibition, instead of increasing the duration of treatment.[23–25] Additionally, the primary use of bisphosphonates and denosumab has been shown to increase the proportion of cured patients and reduce bone mineral density adverse events associated with aromatase inhibition.[26,27] In our study, primary use of these drugs was not yet routinely recommended. Lifestyle interventions (eg, weight control or physical activity) are probably also effective strategies to reduce the number of recurrences.

We decided to randomly assign patients to treatment after the 2–3 years of tamoxifen, rather than after the total 5 years of tamoxifen followed by an aromatase inhibitor, to address the treatment compliance since beginning use of the aromatase inhibitor. We observed that treatment compliance decreased at a constant rate, so it was not associated with the extended use of the aromatase inhibitor. Because of the stratified randomisation design and the same initial treatment, an imbalance in baseline characteristics after the initial 3-year period was not expected. Indeed, the baseline characteristics remained well balanced. Potential limitations of our study are the non-blinded design, potentially affecting treatment decisions. The use of more effective systemic therapies like trastuzumab and taxane-based chemotherapy can influence the effects recorded in the present study. Furthermore, the current follow-up period is still too short to fully appreciate the effect of extended anastrozole treatment on adapted disease-free and overall survival.[3] As specified in the protocol, a second analysis is planned in the year 2021.

Two other studies on the extended use of aromatase inhibitors were presented at the 2016 San Antonio Breast Cancer Symposium.[28,29] The NRG Oncology/NSABP B-42 trial[28] assessed 5 years of letrozole compared with placebo in 3966 patients who had completed 5 years of treatment with an aromatase inhibitor or tamoxifen followed by an aromatase inhibitor. In the IDEAL trial,[29] 1824 patients had received 5 years of adjuvant tamoxifen, aromatase inhibitor, or tamoxifen followed by an aromatase inhibitor, and were randomly assigned to letrozole treatment for 2·5 years or 5 more years of extended therapy. In both studies, the extended use of aromatase inhibitors did not result in an improved disease-free survival, although in the B-42 trial a significant improvement in the breast-cancer-free interval was seen with extended therapy.

In conclusion, we cannot recommend the use of extended adjuvant aromatase inhibition after 5 years of sequential endocrine therapy to all postmenopausal women with hormone receptor-positive breast cancer. However, our exploratory subgroup analyses suggest that patients with high-risk characteristics might benefit from extended therapy, and that tumours expressing both oestrogen and progesterone receptors might drive the benefits we observed. The main conclusion from all three recent trials is that if aromatase inhibitors have already been incorporated as part of the initial adjuvant therapy regimen then there is little benefit to continuing them for beyond 5 years for most patients. Any benefit also comes at a price, as shown by the continuous decline in treatment compliance over time. Hence, careful assessment of potential benefits and risks is required before recommending extended aromatase inhibitor therapy.

Contributors

Development of the study design was supported by the Dutch Breast Cancer Research Group (BOOG), led by VCGT-H, IEGvH, PGMP, and ACPS. The study was supported and completed through the Netherlands Comprehensive Cancer Organisation (IKNL), Nijmegen, Netherlands. PGMP was responsible for the detailed statistical analysis. VCGT-H, IEGvH, PGMP, and ACPS interpreted the data and prepared the initial draft of the report; they also collated changes proposed by all of the authors into the final draft paper before final approval by all of the named coauthors. All authors gave final approval of the version to be published.

Declaration of interests

VCGT-H reports grants from AstraZeneca, during the conduct of the study; grants and non-financial support from Roche, Pfizer, and Novartis; and grants from Eisai outside the submitted work. IEGvH, PGMP, ACPS, WKdR, and ALTI report grants from AstraZeneca during the conduct of the study. JRK reports grants and non-financial support from Amgen and Novartis outside the submitted work. AHH reports grants from the Dutch Breast Cancer Research Group during the conduct of the study and outside the submitted work. MdB reports grants from AstraZeneca during the conduct of the study; grants and non-financial support from Roche, AstraZeneca, Novartis; and grants from Pfizer and Eisai outside the submitted work. SCL reports grants from AstraZeneca during the conduct of the study; grants and non-financial support from AstraZeneca and Roche; other support from Novartis, Cergentis, Philips Health BV, AstraZeneca, and IBM; and grants from Genentech outside the submitted work. SCL has patents WO/2015/080585 and PCT/NL2014/050813 pending. All other authors declare no competing interests.

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