Tailoring adjuvant therapy for hormone receptor-positive breast cancer

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Chapter 3

Optimal duration of extended adjuvant endocrine therapy for early breast cancer; results of the IDEAL-trial (BOOG 2006-05)

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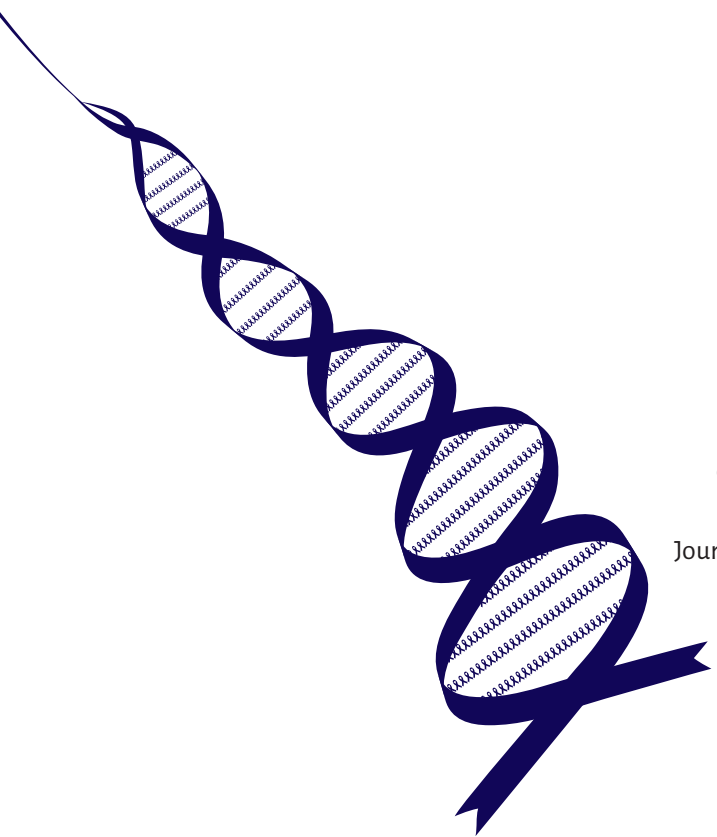

Abstract

Background: The optimal duration of extended endocrine therapy beyond 5 years after initial aromatase inhibitor based adjuvant therapy for postmenopausal women with hormone-receptor positive breast cancer is still unknown. Therefore, we conducted a clinical trial to compare two different extended endocrine therapy durations.

Methods: In the randomized phase III IDEAL trial, postmenopausal patients with hormone-receptor positive breast cancer were randomly allocated to either 2.5 or 5 years of letrozole after the initial 5 years of any endocrine therapy. The primary endpoint was disease free survival (DFS), and secondary endpoints were overall survival (OS), distant metastasis free interval (DMFi), new primary breast cancer, and safety. Hazard ratios (HRs) were determined using Cox regression analysis. All analyses were by intention to treat principle.

Results: 1824 patients were assigned to either 2.5 years (n=909) or 5 years (n=915) of letrozole, with a median follow-up of 6.6 years. A DFS event occurred in 152 patients in the 5-years group, compared to 163 patients in the 2.5 years group (HR 0.92, 95%CI 0.74-1.16). OS (HR 1.04, 95%CI 0.78-1.38) and DMFi (HR 1.06, 95%CI 0.78-1.45) were not different between both groups. A reduction in occurrence of second primary breast cancer was observed with 5 years treatment (HR 0.39, 95% CI 0.19-0.81). Subgroup analysis did not identify patients that benefit from 5 year extended therapy.

Conclusion: This study showed no superiority of 5 years over 2.5 years of extended adjuvant letrozole, after initial 5 years of adjuvant endocrine therapy.

Introduction

Multiple large clinical trials showed superiority of AI-based adjuvant therapy (either upfront or after 2-3 years of tamoxifen) over 5 years tamoxifen monotherapy. [1-4] Just recently, an EBCTCG meta-analysis showed the superiority of AI monotherapy for 5 years over the sequential therapy of tamoxifen followed by an AI, although the absolute benefit was marginal.[5]

Despite the success of adjuvant endocrine therapy, still 50% of all recurrences occur after the first 5 years, especially in HR-positive breast cancer.[6] Randomized trials showed that 10 years of adjuvant tamoxifen was superior over 5 years, although the benefit on overall survival was not observed.[7-9] The MA.17 study investigated extended endocrine therapy with an AI after 5 years of tamoxifen, by randomly assigning patients to 5 years of letrozole or placebo. At interim-analysis after 2.4 years it was observed that letrozole was superior, leading to early closure and cross-over which hampered the power for long-term follow-up.[10] Although this trial was broadly interpreted as evidence for 5 years therapy extension, the actual evidence before cross-over is only until 2.4 years. The actual benefit of 5 years vs placebo, or the difference in effect between 2.5 and 5 years has never been shown, except for extrapolated subgroup analyses.[10-13]

Until now, all evidence for extended endocrine therapy was obtained in clinical trials that included patients who received tamoxifen monotherapy during the first 5 years of adjuvant therapy. As shown recently in the EBCTCG meta-analysis, adjuvant therapy containing AIs in the first 5 years of adjuvant therapy is superior to tamoxifen monotherapy.[5] However, limited evidence is available for extending AI-based adjuvant therapy beyond 5 years of AI-containing therapy, in particular for the optimal duration of therapy.[14]

We report the results of the phase 3 open label multicenter trial: **I**nvestigation on the **D**uration of **E**xtended **A**djuvant **L**etrozole treatment (IDEAL) trial, which randomly assigned patients to either 2.5 or 5 year letrozole, after receiving any adjuvant endocrine therapy for 5 years. The aim of this trial is to determine the optimal duration of extended endocrine therapy, in particular after receiving AI-based adjuvant therapy.

Materials & Methods

Patients and study design

Postmenopausal women who completed 5 years (± 3 months) of any adjuvant endocrine therapy for early stage hormone-receptor positive (ER and/or PR positive in ≥10% of the nuclei) early breast cancer, were randomized between extending treatment with either 2.5 or 5 years of letrozole (2.5mg daily) (**Figure 1**). Other inclusion criteria were no evidence of breast cancer recurrence at time of randomization, a WHO performance status of 0 or 1, and the initial adjuvant endocrine therapy should be completed for no longer than 2 years. Details on trial design were reported earlier.[15]

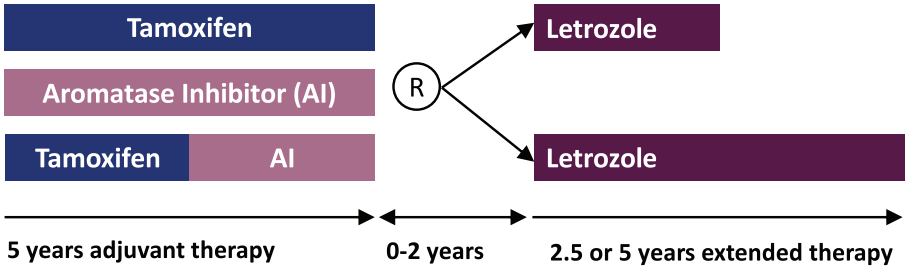

Figure 1: An overview of the trial design.

This study was conducted in 73 hospitals in the Netherlands. Data were collected by the LUMC Datacenter Department of Surgery. The data safety and monitoring board, constituted by an independent statistician, surgeon, and medical oncologist monitored the efficacy endpoints halfway through the trial. Central ethical approval was provided by the ethical committee of the LUMC. All patients provided written informed consent, and were excluded from analysis when consent was withdrawn.

This trial is registered in the Netherlands with the Netherlands Trial Register, NTR3077, the Dutch Breast Cancer Research Group (BOOG 2006-05) and Eudra-CT 2006-003958-16. The study was conducted in compliance with the guidelines of the Declaration of Helsinki, International Conference on Harmonisation and Good Clinical Practice.

Randomization and masking

Randomization was performed by the LUMC Datacenter Department of Surgery in a 1:1 ratio using ALEA software, stratified for prior endocrine therapy regime (5 years

tamoxifen, 5 years AI, or 2-3 years of tamoxifen followed by an AI), time after completion of treatment (0-6 months vs 6-12 months vs 12-24 months), nodal status and the use of adjuvant chemotherapy. All stratification factors were weighted similarly. Pocock's minimisation strategy was used to ensure similar factors in both arms.[16]

Data collection

After providing informed consent, baseline records concerning medical history (including the earlier endocrine therapy), physical examination, mammography, and bone densitometry were collected. Follow-up was conducted annually for at least 5 years with an evaluation of adverse events, disease status, a physical examination, and mammography, with extra visits at 6 and 30 months (latter only for patients in 2.5 year arm to stop allocated therapy).

Endpoints

The primary endpoint of this trial was disease free survival (DFS), defined as the time from randomization to recurrence (either local, regional or distant), new primary breast tumors (DCIS or invasive) or death due to any cause, whichever comes first. Similar to most adjuvant endocrine therapy trials, but in contrast to the definitions defined by Hudis *et al*, second primary non-breast cancer was not included in the definition of DFS.[1, 3, 4, 10, 17] Secondary endpoints were overall survival (OS), distant metastasis free interval (DMFi), new primary breast malignancies (contralateral or new ipsilateral breast cancer), and safety. For safety analysis, adverse events were recorded during active treatment of the patients.

Statistics

It was expected that recurrence rates would be similar in both AI containing arms during the first 2.5 years after randomization, and therefore the power calculations were based on the period after these initial 2.5 years. The objective was to detect an annual decrease of 3.3% in DFS rate in the control arm and 2.0 % in the extended treatment arm (hazard ratio (HR) = 0.60), with a two-sided type I error of 0.05 and power of 80%. Allowing for an annual 2% dropout rate due to loss to follow-up, 126 events, and therefore 1276 patients, were required to detect this difference. Since these 1276 patients needed to be disease free and on treatment after 2.5 years, and with an expected dropout of 30% during the first 2.5 years (due to patients stopping therapy or having a DFS-event in the first 2.5 years after randomization), a number of 1823 patients was required to be randomized.

Despite the fact that the power analysis was performed based on follow-up starting at 2.5 years, it cannot be ruled out that randomization had an influence on either the patient or treating physician during the first 2.5 years since the trial was not blinded. Therefore, all analyses were performed in two parallel ways; the primary analysis starting with all randomized patients on intention-to-treat principle, and the secondary analysis starting at 2.25 years (2.5 years with 10% margin) post-randomization with patients being disease free and on therapy at that time point, after which the treatment arms diverge. Kaplan-Meier analyses were performed for DFS and OS, using stratified log-rank test to determine the level of statistical significance. For DMFi and new primary breast malignancies cumulative incidence curves were estimated, accounting for death as competing risk. Furthermore, for all endpoints, univariate stratified Cox regression analysis was used to determine the hazard ratio (HR). The proportional hazards assumption for treatment (the only variable for which proportional hazards was assumed) was checked using Schoenfeld residuals. Stratified Cox regression within subgroups was used to perform subgroup analysis. For analyses of the adverse events, chi-square tests were used to assess which AE occurs more frequently in which treatment arm, applying Bonferroni correction to correct for multiple testing. All analyses were performed using SPSS 23.0, data visualization was performed using GraphPad Prism 6.05 and R 3.2.2.

All statistical tests were two-sided and a P-value of less than 0.05 was considered statistically significant.

Results

Study population

As planned, 1824 patients were randomized between April 2007 and November 2011 in 73 participating hospitals in the Netherlands (909 patients in 2.5 years group, 915 patients in 5 years group). The median follow-up of these patients was 6.6 year (inter quartile range (IQR) 5.3-7.5 years). Of these, 3 patients withdrew their consent and were excluded for the primary analysis starting at randomization, leaving 908 patients in the 2.5 years group and 913 patients in the 5 years group (**Figure 2**). All other patients were included in the intention-to-treat analysis. Furthermore, 482 patients encountered a DFS event or stopped with therapy before they reached 2.25 year, leaving 1339 patients for the secondary analysis after 2.25 years. In this secondary analysis, the median follow-up was 6.6 years (IQR 5.2-7.5 years)

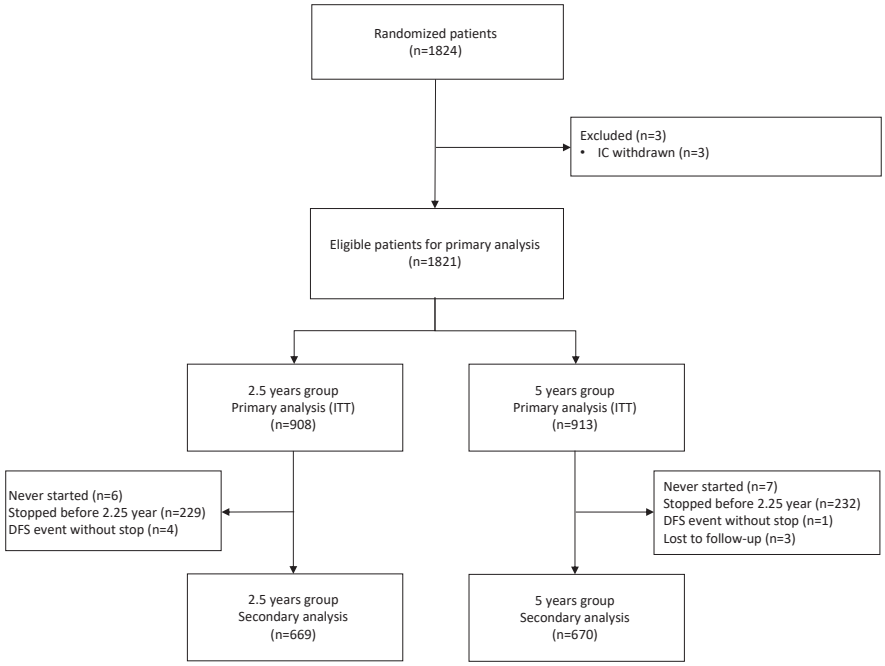

Figure 2: A consort diagram showing the flowchart of the trial.
N:number, IC: informed consent, ITT: intention-to-treat, DFS: disease-free survival

Baseline characteristics for the randomized eligible patients are shown in **Table 1**. There were no statistically significant differences observed between both arms. The majority of patients received AI-based adjuvant therapy, either upfront (28.8%) or after 2-3 years of tamoxifen (59.0%). Only 12.2 percent were AI-naïve and received 5 years of tamoxifen. Most patients (88.6%) continued with extended therapy within 6 months after regular adjuvant endocrine therapy.

Compliance

To assess the capacity of patients to endure extended endocrine therapy, compliance was monitored closely in this trial. A total of 629 patients stopped therapy earlier than planned (34.6%). In the group allocated to 2.5 years, 241 (26.5%) patients stopped early, for which the main reasons were symptoms or adverse events (n=156), a study endpoint (recurrence, new primary tumor or death) (n=30), and treatment refusal (n=24). In the 5-years group 388 patients (42.5%) stopped before 5 years of treatment, for which the main reasons were symptoms or adverse events (n=212), a study endpoint (recurrence, new primary tumor or death) (n=78), and treatment refusal (n=46) (**Figure 3**). Furthermore, 104 patients continued with therapy beyond their allocated treatment

duration with a median overtreatment of 4 months, 13 patients never started therapy and 3 patients withdrew consent, limiting the total compliance to 59.9%.

Table 1. Baseline clinicopathological features of all randomized patients per treatment arm

Subgroups	Treatment Arm			
	2.5 years letrozole		5 years letrozole	
	N	(%)	N	(%)
Age at randomization, y				
<55	250	(27.5%)	260	(28.5%)
55-65	386	(42.5%)	375	(41.1%)
65-75	210	(23.1%)	201	(22.0%)
>75	62	(6.8%)	77	(8.4%)
Nodal status				
pN0	227	(25.0%)	223	(24.4%)
pN0(i+)	10	(1.1%)	12	(1.3%)
pN1(mi)	105	(11.6%)	105	(11.5%)
pN1: 1-3 pos	433	(47.7%)	431	(47.2%)
pN2: 4-9 pos	97	(10.7%)	104	(11.4%)
pN3: >=10 pos	30	(3.3%)	29	(3.2%)
Tumor type				
ductal	683	(75.2%)	732	(80.2%)
mucinous	9	(1.0%)	7	(0.8%)
medullar	3	(0.3%)	4	(0.4%)
lobular	165	(18.2%)	131	(14.3%)
other	47	(5.2%)	39	(4.3%)
Histological grade				
grade 1	156	(17.2%)	130	(14.2%)
grade 2	380	(41.9%)	394	(43.2%)
grade 3	270	(29.7%)	296	(32.4%)
unknown	102	(11.3%)	93	(10.1%)
Progesterone receptor status				
Negative	160	(17.6%)	182	(19.9%)
Positive ≥10%	712	(78.4%)	697	(76.3%)
HER2 status				
0	193	(45.7%)	199	(47.0%)
1+	95	(22.5%)	93	(22.0%)
2+	47	(11.1%)	51	(12.1%)
3+	81	(19.2%)	78	(18.4%)
Performed final surgery				
breast conserving	445	(49.0%)	443	(48.5%)
mastectomy	460	(50.7%)	468	(51.3%)
Prior chemotherapy				
no	291	(32.0%)	287	(31.4%)
yes	617	(68.0%)	626	(68.6%)

Table 1. continued

Subgroups	Treatment Arm			
	2.5 years letrozole		5 years letrozole	
	N	(%)	N	(%)
Prior endocrine treatment				
5 years tamoxifen	109	(12.0%)	113	(12.4%)
5 years AI	261	(28.7%)	263	(28.8%)
2-3 years tam-> 3-2 years AI	538	(59.3%)	537	(58.8%)
Time after stop hormonal therapy, mos				
0 to <6	803	(88.4%)	811	(88.8%)
6 to <12	48	(5.3%)	47	(5.1%)
12-27	57	(6.3%)	55	(6.0%)

Endpoints

At the moment of database lock (December 22th, 2016), 315 out of 1821 patients in the primary analysis had encountered a DFS event, of which 163/908 (18.0%) in the 2.5 year arm and 152/913 (16.6%) in the 5 years arm (**Table 2**). The hazard ratio (HR) for DFS was 0.92 (95% CI 0.74-1.16, Log-rank P=0.49) for patients in the 5 year group, compared to the 2.5 year group (**Figure 4A**). A preplanned subgroup analysis showed that there is no individual subgroup which benefits statistically significant from extended adjuvant endocrine therapy up to 5 year (**Figure 5**). The proportional hazards assumption for treatment was not found to be violated.

Furthermore, no statistically significant effect on either overall survival (**Figure 4B**) or distant recurrences (**Figure 4C**) was shown with respective HRs of 1.04 (OS, 95% CI 0.78-1.38, Log-rank P=0.79) and 1.06 (DMFi, 95% CI 0.78-1.45, Log-rank P=0.71). For second primary breast malignancies (**Figure 4D**), 27 (3.1%) events were observed in the 2.5-year group and 10 (1.1%) in the 5-year group, which was statistically significant (HR 0.39, 95% 0.19-0.81, Log-rank P=0.01).

In the secondary analysis (**Figure 6**), in which patients who encountered an event or stopped therapy before 2.25 years were excluded, 86 DFS events were observed during follow-up in the 2.5 year arm, and 74 events in the 5 year arm (HR 0.88, 95% CI 0.64-1.21) (**Table 2**). Of these events, 15 second primary breast malignancies were observed in the 2.5 year arm, and 6 in the 5 year arm (HR 0.42, 95% CI 0.16-1.11).

Table 2. An overview of the number of events in both arms and the subsequent hazard ratio (HR), both for the primary population, and the secondary population who were disease free and on therapy at 2.25 years*

Endpoints	Treatment arm		HR (95% CI)
	5 year letrozole	2.5 year letrozole	
	No. of events	No. of events	
DFS (full population)	152/913	163/908	0.92 (0.74-1.16)
local recurrence	14	12	1.06 (0.49-2.31)
regional recurrence	14	10	1.27 (0.55-2.92)
distant recurrence	86	78	1.06 (0.78-1.45)
2nd primary breast cancer	10	27	0.39 (0.19-0.81)
death any cause	104	96	1.04 (0.78-1.38)
DFS (after 2.25 year)	74	86	0.88 (0.64-1.21)
local recurrence	10	8	1.17 (0.46-2.98)
regional recurrence	6	7	0.92 (0.30-2.76)
distant recurrence	35	47	0.75 (0.48-1.17)
2nd primary breast cancer	6	15	0.42 (0.16-1.11)
death any cause	45	40	1.06 (0.68-1.65)

*CI=confidence interval; DFS=Disease free survival

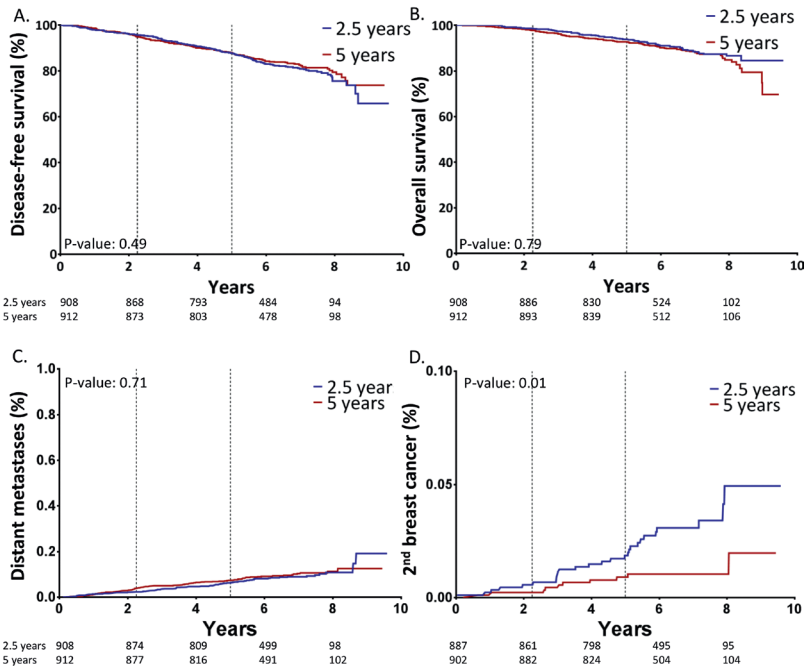

Figure 4: Kaplan Meier analysis. Results are shown for (A) disease free survival (DFS), (B) overall survival (OS), (C) distant metastasis free interval (DMFi), and (D) new primary breast cancer, including all randomized patients based on intention-to-treat principle. Log-rank tests were used to assess the differences between groups within each graph (reported as p-value).

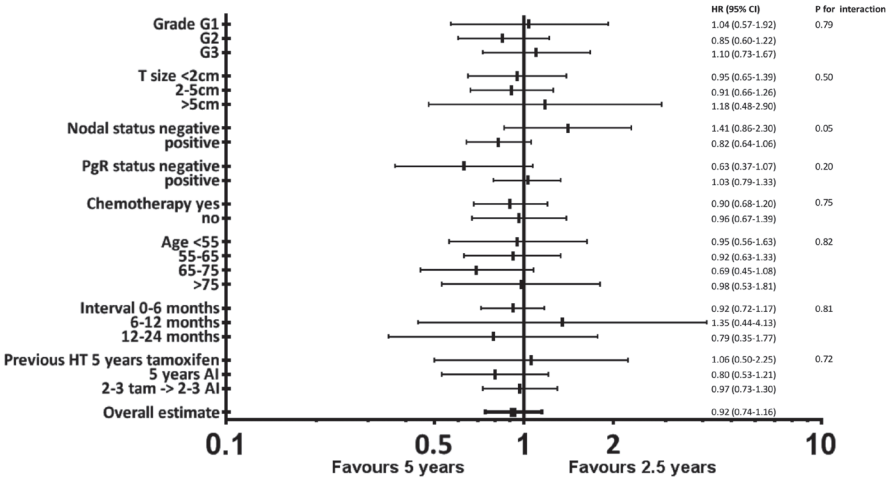

Figure 5: A pre-planned subgroup analysis. All values were determined using two-sided Cox-regression analysis. Error bars represent 95% confidence intervals.
HR: hazard ratio, CI: confidence interval, T size: tumor size, PgR: progesterone receptor, HT: hormonal therapy, AI: aromatase inhibitor, tam: tamoxifen

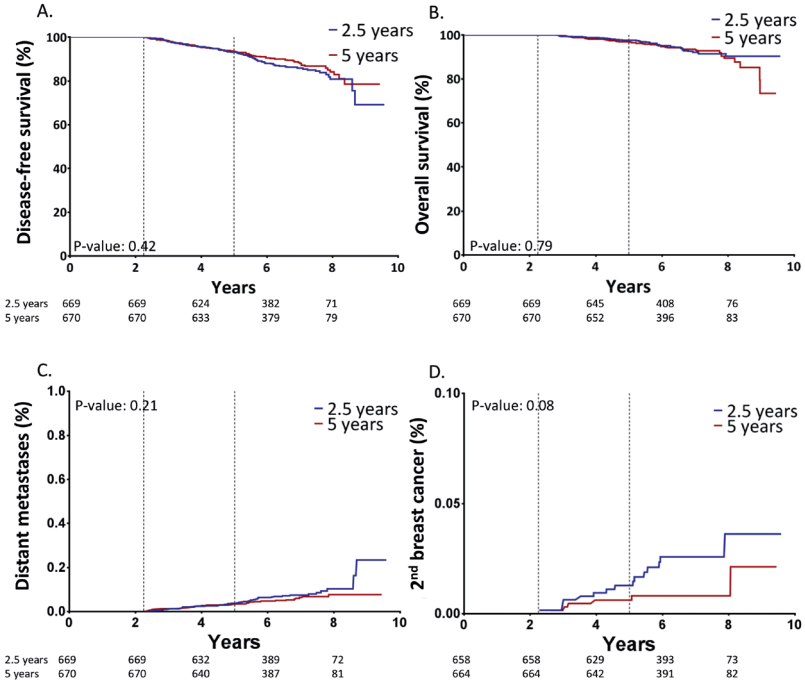

Figure 6: Secondary analysis. Results are shown for (A) disease free survival (DFS), (B) overall survival (OS), (C) distant metastasis free interval (DMFi), and (D) new primary breast cancer, including all patients that were disease free and on therapy at 2.25 years. Log-rank tests were used to assess the differences between groups within each graph (reported as p-value).

Table 3. An overview of the most frequently reported adverse events, stratified per grade and treatment arm*

Adverse events	2.5 year letrozole					5 year letrozole					Total (%)
	Grade 1	Grade 2	Grade 3	Grade 4	Any grade, No. (%)	Grade 1	Grade 2	Grade 3	Grade 4	Any grade, No. (%)	
Arthralgia	72	40	7	0	119 (13.2%)	70	48	13	2	133 (14.7%)	252 (14.0%)
Hot flashes	67	24	5	0	96 (10.5%)	69	40	6	3	118 (13.1%)	214 (11.8%)
Osteoporosis	39	26	3	0	68 (7.5%)	61	54	1	0	116 (12.7%)	184 (10.2%)
Fatigue	46	17	5	0	68 (7.5%)	50	34	3	1	88 (9.7%)	156 (8.6%)
Joint range of motion decreased	43	14	2	0	59 (6.5%)	33	21	2	0	56 (6.2%)	115 (6.4%)
Alopecia	51	6	2	0	59 (6.5%)	45	7	1	1	54 (6.0%)	113 (6.3%)
Depression	34	18	5	0	57 (6.2%)	23	20	4	0	47 (5.2%)	104 (5.8%)
Back pain	30	20	5	0	55 (6.1%)	19	22	2	2	45 (5.0%)	100 (5.5%)
Fracture	2	17	5	1	25 (2.8%)	6	24	14	1	45 (5.0%)	70 (3.9%)
Total	935	496	126	15	1580 (70.1%)	983	681	155	34	1860 (71.8%)	3440 (71.4%)

* All events with a frequency over 5% in one of the arms are shown.

Safety

In all patients who started therapy (n=1806), 3440 adverse events were reported by 1289 patients. Of these events, 1580 were reported by 640 (70.1%) patients in the 2.5 year arm during active treatment, and 1860 were reported by 649 patients (71.8%) in the 5 year arm during treatment. Of all events, 90.3% was graded as 1 or 2, and there was no difference in the proportion of grade 3/4 events between both groups (2.5yr: 8.8%, 5yr: 10.0%, X^2 p=0.43) (data not shown).

A total of 368 patients stopped therapy due to AEs, of which 156 in the 2.5-years arm (17.3%) and 212 in the 5-years arm (23.5%) In patients allocated to 5 years of therapy, the majority of events (n=1481, 79.6%) occurred during the first 2.5 years. In total, 85.8% of the patients (n=182) in the 5 years group that ceased therapy due to side effects, did this before 2.5 years. The frequency of adverse events is reported in **Table 3**, in which all events with a frequency over 5% in one of the arms are shown. Most frequently reported AEs were arthralgia, reported by 252 patients (14.0%) , hot flashes (n=214, 11.8%) and osteoporosis (n=184, 10.2%). The most reported grade 3/4 AEs were arthralgia (n=22) and fractures (n=21).

Discussion

This study has shown that, after receiving any adjuvant endocrine therapy for 5 years, there is no statistically significant difference in disease related outcomes between patients treated with either 2.5 or 5 years of letrozole at a median follow-up of 6.6 years, with the exception of preventing new primary breast malignancies. Subgroup analysis showed that there was no benefit of 5 years of extended therapy regarding DFS for any specific subgroup. Furthermore, no interaction between subgroups was observed.

Additionally, we observed a statistically significant decrease in second primary breast malignancies in patients treated with 5 years of extended therapy. This observation was in agreement with the MA.17R trial, in which most of the effect of 5 years letrozole after 10 years of earlier therapy was accounted to prevention of contralateral breast cancer.[18] It could be argued that extended endocrine adjuvant therapy with aromatase inhibitors beyond 7.5 years is secondary prevention rather than actual adjuvant therapy preventing relapse of the earlier breast cancer. This preventive effect

has already been shown in multiple clinical trials in healthy women without breast cancer, using both tamoxifen and AIs.[19-25]

This study did not question whether AI-containing adjuvant therapy should be extended beyond the first 5 years. The MA.17 and MA.17R trials already showed that 5 years of letrozole was superior to placebo after the initial 5 years of tamoxifen monotherapy, and that a further extension up to 10 years of AIs led to a further improvement in DFS.[13, 18] However, death from any cause was not included in their definition of DFS, and the statistically significant effect on DFS in MA.17R was mainly attributed to a decrease in second primary breast cancers.[18] Furthermore, the results of both MA.17 and MA.17R are not valid for the majority of patients, who nowadays receive upfront AI as adjuvant endocrine therapy.[26]

The B42 trial, presented recently at SABCS 2016, compared 5 years of letrozole to placebo after initial AI-containing adjuvant therapy. They did not show a benefit on DFS in the overall patient group and subgroups [27]The DATA trial, presented at the same conference, showed that there is no statistically significant benefit of 6 years anastrozole over 3 years anastrozole, after initial 2-3 years of tamoxifen.[28] In contrast to the B42 trial and our results, their subgroup analysis suggested a statistically significant benefit for higher risk patients (node positive, tumor size larger than pT2) and for tumors expressing both ER and PR.

Combining these recent results, there is no evidence for therapy extension for the general hormone receptor positive postmenopausal breast cancer patient after an AI in the first 5 years. Data on high-risk subgroups, reflected by tumor size, nodal status, or hormone receptor subgroups are discordant. It is unclear why, in general, there is a lack of extended therapy effect in the population that received AIs earlier. A possible explanation could be the relative inferiority of tamoxifen during the first 5 years, which leaves a possibility for benefit of extended therapy. A second explanation might be therapy resistance. In metastatic disease, it is well known that mutations in the gene encoding for ER, are associated to resistance against AIs.[29, 30] Although this has not been studied, a similar mechanism could play a role in dormant tumor cells, making them resistant against the adjuvant treatment and causing the extended therapy to have no additional benefit.

A number of clinical trials studying the extension of AI-based adjuvant therapy are still ongoing.[14] In case future studies will show a benefit of extended AI adjuvant therapy, the results of this trial show that the effect is limited to 7.5 years of total treatment duration. However, it cannot be ruled out that there is an effect in a subgroup of patients. For this, future explorative subgroup analyses will be performed, and follow-up will be extended up to 10 years. Furthermore, a translational side study is initiated, to explore biomarkers capable of predicting extended therapy benefit.

The rate of patients reporting AEs is similar in both arms, although the absolute count of AEs is higher in the 5 year group. However, since adverse events were only recorded during active treatment, the frequency of AEs in the 2.5 years group might be underreported since there was no registration of side effects in the second 2.5 years in which there was no therapy. The frequency of specific adverse events, like e.g. hot flashes, is lower than expected based on earlier studies. In the MA.17 trial, 5 year of letrozole was associated to 47% of patients reporting hot flashes, whereas in this trial only 12% of patients reported these symptoms.[31] Most likely, these differences are due to differences in trial design. In the MA.17 trial, all patients where AI-naïve, whereas 88% patients in this trial had earlier received treatment with an AI and were therefore less likely to report the side effects. Furthermore, selection bias might have occurred, since patients that experienced side effects during regular adjuvant therapy, would have been less likely to participate in this trial.

A limitation of this trial is the upfront randomization. After randomization, there was approximately 30% drop-out before the moment that the treatment arms actually diverged, which could have led to additional random differences between both arms. However, this drop-out was accounted for in the sample size calculation, and therefore did not influence the statistical power of the analyses. A second limitation is the open-label design. In combination with the upfront randomization, this could have influenced the patient or clinician in their decisions. However, drop-out was similar in both groups during the first 2.5 years, although a small bias cannot be excluded. In order to prevent an attrition bias during the first 2.5 years, the primary analysis started at randomization and not at the moment that the treatment arms diverged.

In summary, we have shown that the effect on any disease-related outcomes of 5 years of extended letrozole was not superior over 2.5 years of extended therapy with

letrozole, after 5 years of any regular adjuvant endocrine therapy, except for a small difference in the occurrence of new primary breast malignancies. Although this study did not show the added value of extended use of AI-containing adjuvant therapy in itself, it has shown that whenever extended AI-containing adjuvant therapy is considered, extended therapy longer than 2.5 years will not lead to a further reduction in disease free or overall survival.

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