Tailoring endocrine therapy in early breast cancer

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Prolonged duration and potential drawbacks

I.E.G. van Hellemond

Endocrine therapy in early breast cancer: Prolonged duration and potential drawbacks

Cover design and layout © evelienjagtman.com
Printed by Ridderprint | www.ridderprint.nl

ISBN 978-94-6375-438-5

Publication of this thesis was financially supported by:
Maastricht University Medical Centre +
Integraal Kankercentrum Nederland (IKNL)

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PROEFSCHRIFT

ter verkrijging van de graad van doctor
aan de Universiteit Maastricht,
op gezag van Rector Magnificus, Prof. dr. Rianne M. Letschert,
volgens het besluit van het Collega van Decanen,
in het openbaar te verdedigen
op donderdag 31 oktober 2019 om 14:00 uur

door

Irene Elisabeth Gerarda van Hellemond

Geboren te Breda op 31 mei 1986

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The first wealth is health

-

Ralph Waldo Emerson

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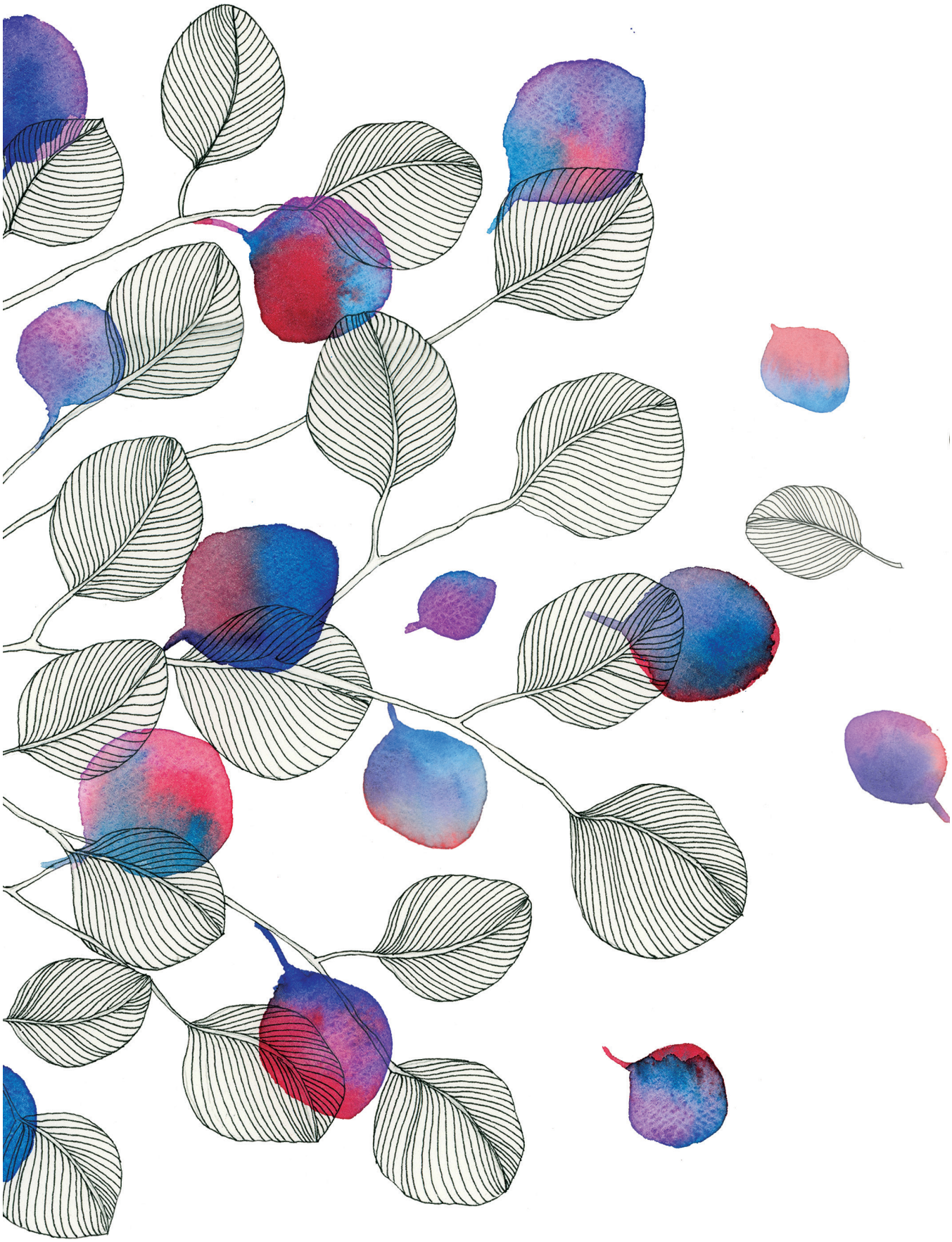

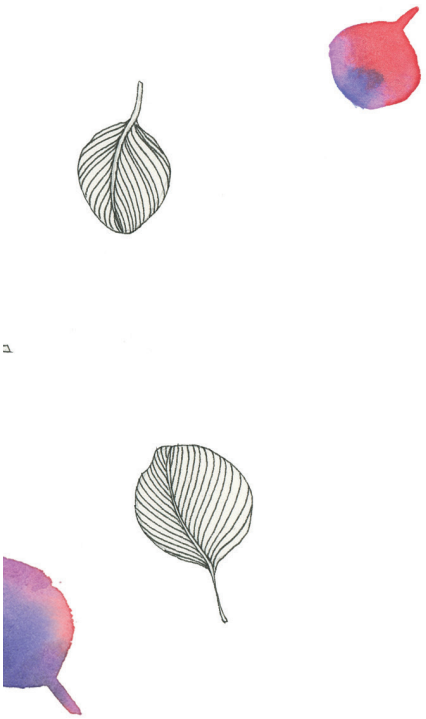

Chapter 1

General introduction and outline of the thesis

General introduction

Cancer is the second leading cause of death globally, and is responsible for an estimated 9.6 million deaths in 2018.[1] Globally, about 1 in 6 deaths is due to cancer. Breast cancer is the most common type of cancer in women with 2.09 million new cases worldwide in 2018 and it is the leading cause of cancer death in women.[1]

In early detected disease lesions, the chance of loco-regional cure is high. However, microscopic disease may already have spread before loco-regional therapy was applied. If this microscopic disease remains untreated, it could develop into a life-threatening clinical recurrence. Although the risk of recurrence is greatest during the first years after diagnosis, it is still substantial in the following decade, especially in patients with hormone receptor positive tumours (figure 1).

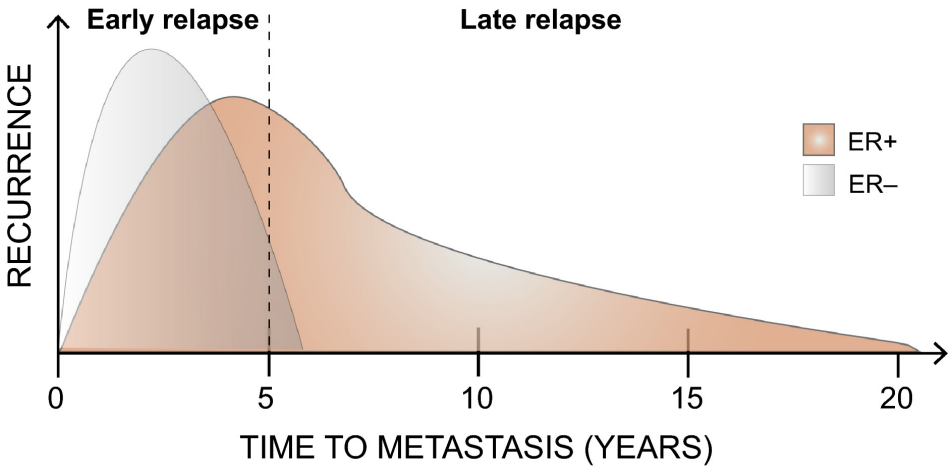

Figure 1. The temporal course of breast cancer metastasis. The oestrogen receptor negative (ER−) breast cancer subtype metastases typically occur within 5 years after primary tumour diagnosis (grey) whereas oestrogen receptor positive (ER+) breast cancer can relapse early (before 5 years) or late, up to decades after the initial diagnosis (orange). The dashed line indicates the clinical threshold for early and late relapse. Reproduced with permission from Gomis, Molecular oncology 2017.[2]

During the last three decades the prognosis of women with breast cancer has improved significantly. Whereas the 10-year overall survival of women with breast cancer diagnosed in the Netherlands was only 61% in the period 1981 to 1990, it improved to 79% in the period from 2006 to 2010 (figure 2).[3]

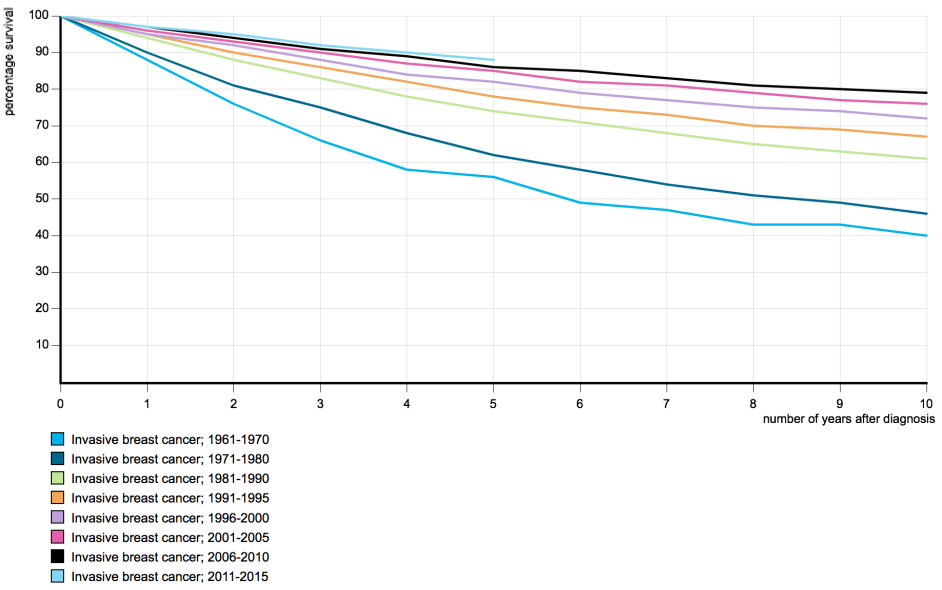

Figure 2. The survival of invasive breast cancer by period of diagnosis. Reproduced with permission from the Nederlandse Kankerregistratie (NKR), IKNL.[3]

One of the reasons for this improvement is the introduction of the national screening programme, which started in the Netherlands in 1990, and the introduction of multidisciplinary care which is associated with an improved survival and a reduced variation in survival among hospitals.[4] And last but not least, the development of several systemic therapies increased the chances for curation and a longer survival.

The dependency of 60 to 70% of the breast cancers on oestrogens for their continued growth has already long been recognised. This led to the development of several systemic endocrine therapies such as tamoxifen, which antagonizes the effects of oestrogen on the tumour, AIs which reduce the circulating concentration of oestrogens in postmenopausal women, and ovarian ablation either chemical or by oophorectomy causing a lower concentration of circulating oestrogens in premenopausal women.

For years, tamoxifen has been the standard adjuvant endocrine treatment of hormone receptor-positive breast cancer in both pre- and postmenopausal women. Later on, third generation aromatase inhibitors (AI) were developed, offering an alternative strategy to tamoxifen in the adjuvant treatment of postmenopausal women with hormone receptor-positive early breast cancer. AIs were found to be superior to tamoxifen in terms of disease-free survival and overall survival.[5,6] At the same time, several studies were performed to investigate the effect of sequenced treatment, using different approaches, but all comparing with 5 years of tamoxifen.[7-12]

Except for one trial, all showed an improvement in disease-free survival and overall survival for sequential endocrine therapy in comparison with 5 years of tamoxifen. In addition, both the BIG 1-98 and the TEAM trial addressed the switch to an AI after 2–3 years of tamoxifen in comparison with AI monotherapy for a total of 5 years.[6,7,13] Neither study found a preference for either strategy after a median follow-up of 8.1 and 9.8 years, respectively, which was confirmed by the results of a meta-analysis of the Early Breast Cancer Trialists Group (EBCTCG).[14]

Nevertheless, the data from the Oxford overview in 2005 showed that there were as many breast cancer recurrences after primary surgery during the years 6 through 15 in patients treated with tamoxifen as between years 1 through 5 in controls.[15] The risk of recurrence was estimated approximately 4% per year for patients with node positive disease and approximately 2% per year for women with node negative disease.[15] These results were recently confirmed by another EBCTCG meta-analysis, in which 63% had been assigned to receive tamoxifen, 17% an AI, and 20% some sequence of tamoxifen and an AI (figure 3).[16]

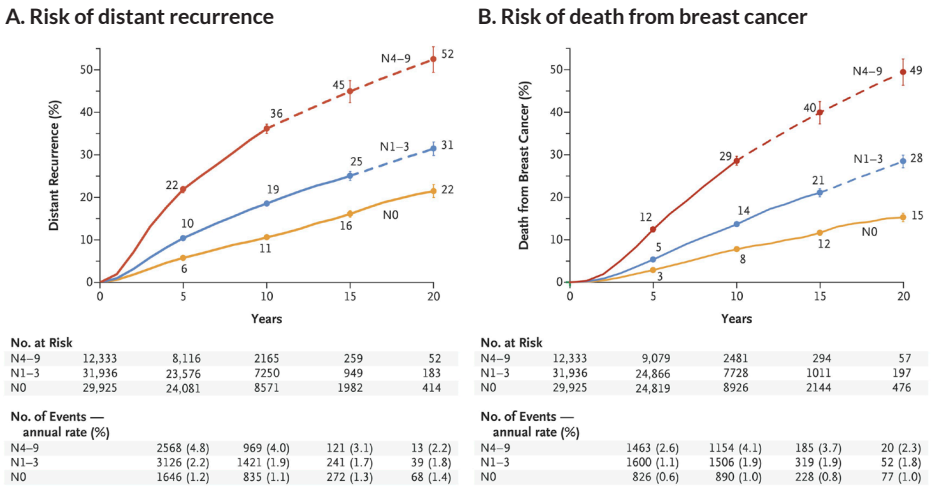

Figure 3. The 20-year risk of distant breast cancer recurrence according to the patients' pathological nodal status at the time of diagnosis: N0, N1–3, or N4–9. The number of events and annual rate are shown for the preceding period (e.g., data for years 0 to 4 are shown at 5 years). The I bars indicate the 95% confidence intervals. The dashed lines indicate that the event rate is for the whole 5-year period, rather than for individual years, as is otherwise shown. Reproduced with permission from Pan, NEJM 2017, Copyright Massachusetts Medical Society.[16]

If the risk of recurrence remained that high during that many years it seemed logical to explore possibilities for extending the duration of endocrine therapy. The first trial investigating the efficacy of a longer duration of adjuvant endocrine therapy was the NSABP-B14 trial.[17] Unexpectedly, their results showed no benefit for extending adjuvant tamoxifen for more than 5

years. A possible explanation for the initial negative results might be the relatively small sample size, besides a hypothesized occurrence of tamoxifen resistance with longer treatment. Based on these data, it was recommended worldwide to limit the use of adjuvant tamoxifen treatment to 5 years until the final results of the larger ATLAS and aTTom trials were presented.[18,19]

Since earlier trials showed AIs to be beneficial after tamoxifen resistance, this led to the start of several trials investigating the effect of the use of AIs after tamoxifen showing an improved disease-free survival.[20,21] However, neither the optimal timing nor the optimal duration of adjuvant AI therapy were established. That was the rationale for initiating the DATA study, comparing the efficacy and safety of 6 vs 3 years of adjuvant anastrozole subsequent tot 2-3 years of tamoxifen treatment in postmenopausal women with hormone receptor positive breast cancer.

Aims and outline of this thesis

Although treatment options in present-day oncology are ever expanding, the only justification of any treatment is relieving symptoms or improving prognosis without too much toxicity. Subsequently, it remains important to further explore the potential of existing therapies. In this thesis we aimed to guide treatment decisions in adjuvant endocrine therapy for patients with hormone receptor positive breast cancer, focussing on the optimal duration and its potential drawbacks.

Part I contains the results of the primary analysis of the DATA trial, a randomised controlled trial investigating the efficacy and safety of 6 vs 3 years of adjuvant anastrozole in the setting of postmenopausal women with hormone receptor positive breast cancer (**chapter 2**), followed by a review article which puts these results in perspective to other research on extended adjuvant endocrine therapy (**chapter 3**).

Part II is about the subgroup of women with chemotherapy-induced ovarian function failure. These women were premenopausal at breast cancer diagnosis, but became postmenopausal after the administration of chemotherapy. This subgroup is interesting because they cannot be treated in the same way postmenopausal women are since they are at risk of ovarian function recovery (OFR), especially if treated with AIs. AIs are not effective in the presence of active ovarian function and thus this situation should be prevented. Moreover, OFR results in high oestrogen levels which potentially leads to stimulation of growth of hormone receptor positive breast cancer cells that were not resected by surgery or destroyed by adjuvant radio- and/or chemotherapy. **Chapter 4** considers the incidence of OFR in the DATA trial during the adjuvant treatment with AIs in women with chemotherapy-induced ovarian function failure. Moreover, it describes the trend of oestrogen levels during treatment with AIs in patients who experienced OFR vs those who did not. **Chapter 5** discusses the consequences of OFR on breast cancer survival in the DATA study.

Part III concerns the bone health of postmenopausal women with early breast cancer. Reduction of the bone mineral density (BMD) is a well-known side effect of AIs which can lead to osteoporosis and consequently invalidating fractures. **Chapter 6** describes the assessment and management of bone health in women with early breast cancer receiving endocrine therapy in the DATA study. Moreover, it reports on the trend of BMD over time during and after cessation of anastrozole treatment. Previously published studies observed that a reduced BMD was associated with a lower risk of developing breast cancer.[22,23] We were therefore interested whether a reduced BMD, in women who already had a diagnosis of breast cancer, was related to a lower risk of distant breast cancer recurrences. This is described in **chapter 7**.

Part IV summarizes and discusses the results of these studies in respect to the available relevant literature and speculates on areas of future research on adjuvant therapy in hormone receptor positive breast cancer (**chapter 8**).

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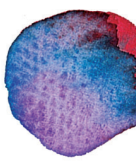
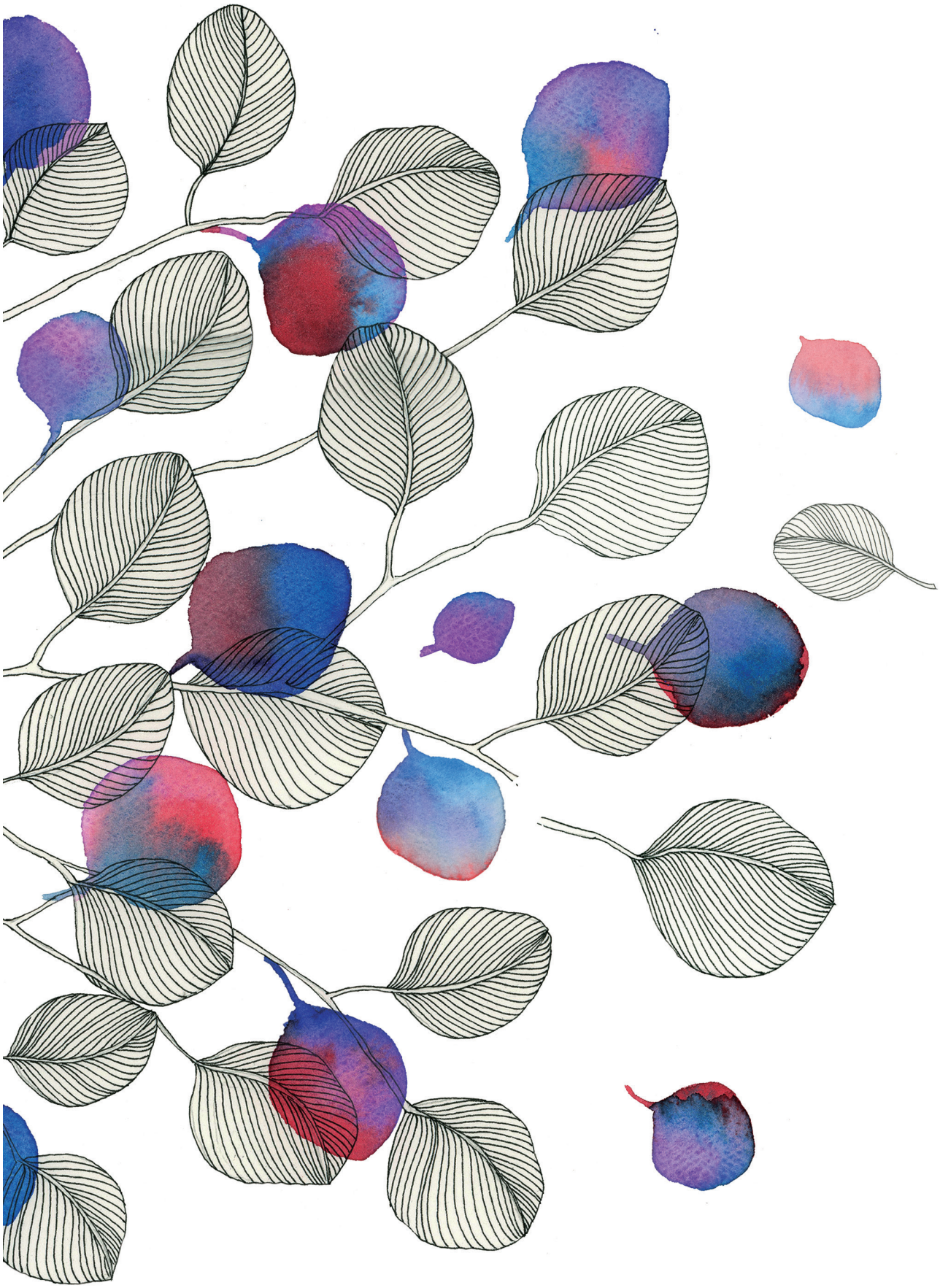
Extended adjuvant endocrine therapy in breast cancer



Part I



Chapter 2

Extended Adjuvant Aromatase Inhibition After Sequential Endocrine Therapy (DATA): a randomised phase 3 trial

Vivianne C.G. Tjan-Heijnen, Irene E.G. van Hellemond, Petronella G.M Peer, Astrid C.P. Swinkels, Carolien H. Smorenburg, Maurice J.C. van der Sangen, Judith R. Kroep, Hiltje De Graaf, Aafke H. Honkoop, Frans L.G. Erdkamp, Franchette W.P.J. van den Berkmortel, Maaike de Boer, Wilfred K. de Roos, Sabine C. Linn, Alexander L.T. Imholz, Caroline Seynaeve, on behalf of the Dutch Breast Cancer Research Group (BOOG).

The Lancet oncology. 2017;18(11):1502-11.

Abstract

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.

Funding

AstraZeneca.

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.

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 Centre (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 Centre (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.

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 figure S1). 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 (i.e., 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.

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.[3,4,5] 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 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 August 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 (figure S4 and S5).

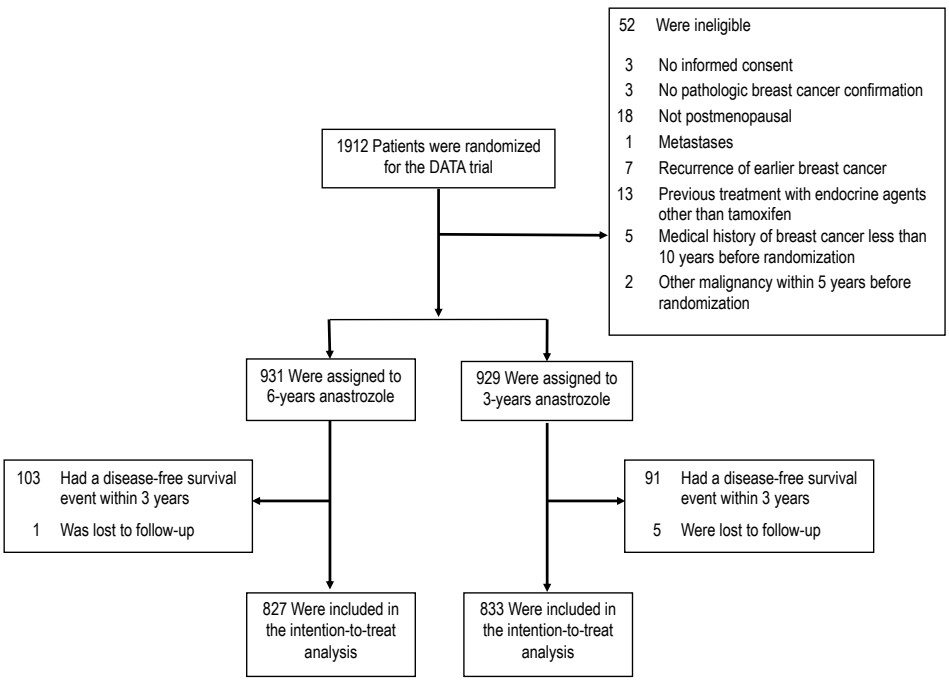


Figure 1. Trial profile

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.

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

Characteristic	6-year Anastrozole (N=827)	3-year Anastrozole (N=833)
Median age at randomisation - years	57.7 (51.9–64.3)	57.6 (51.2–64.5)
Age at randomisation – no. (%)		
< 49 years	141 (17.0)	160 (19.2)
50-59 years	342 (41.4)	328 (39.4)
≥ 60 years	344 (41.6)	345 (41.4)
Tumour status – no. (%)		
pT1	376 (45.5)	383 (46.0)
pT2	392 (47.4)	382 (45.9)
pT3/4	58 (7.0)	67 (8.0)
TX	1 (0.1)	1 (0.1)
Nodal status – no. (%)		
pN0 / pN0(i+)	266 (32.2)	282 (33.8)
pN1	434 (52.5)	457 (54.9)
pN2 / pN3	127 (15.3)	94 (11.3)
Histological grade – no. (%)		
Grade I	139 (16.8)	158 (19.0)
Grade II	430 (52.0)	415 (49.8)
Grade III	229 (27.7)	238 (28.6)
Unknown	29 (3.5)	22 (2.6)
Hormone-receptor status – no. (%)		
ER and PR positive	627 (75.8)	633 (76.0)
ER or PR positive	200 (24.2)	200 (24.0)
HER2 status – no. (%)		
Positive	18 (2.2)	22 (2.6)
Negative	745 (90.1)	748 (89.8)
Unknown	64 (7.7)	63 (7.6)
Histology		
Lobular	154 (18.6)	140 (16.8)
Other	673 (81.4)	693 (83.2)
Type of breast surgery – no. (%)		
Breast-conserving surgery	433 (52.4)	408 (49.0)
Mastectomy	394 (47.6)	425 (51.0)

Table 1. Continued

Characteristic	6-year Anastrozole (N=827)	3-year Anastrozole (N=833)
Type of axillary surgery – no. (%)		
Sentinel node only	226 (27.3)	209 (25.1)
Sentinel node plus axillary lymph node dissection	370 (44.7)	386 (46.3)
Axillary lymph node dissection	218 (26.4)	230 (27.6)
None	13 (1.6)	8 (1.0)
Radiotherapy – no. (%)		
Local	235 (28.4)	233 (28.0)
Local and regional lymph nodes	315 (38.1)	291 (34.9)
Regional lymph nodes	21 (2.5)	14 (1.7)
None/unknown	256 (31.0)	295 (35.4)
Prior (neo)adjuvant chemotherapy – no. (%)		
Anthracycline- and taxane-containing regimen	45 (5.4)	59 (7.1)
Anthracycline-containing regimen without taxane	507 (61.3)	495 (59.4)
Taxane-containing regimen without anthracycline	4 (0.5)	2 (0.2)
Regimen without anthracycline or taxane	9 (1.1)	14 (1.7)
No chemotherapy	262 (31.7)	263 (31.6)
Prior HER2-targeted therapy – no. (%)		
Yes	3 (0.4)	3 (0.4)
Previous duration of tamoxifen – no. (%)		
Median and range (years)	2.3 (1.6 - 3.2)	2.3 (1.4 – 3.8)

* There were no statistically significant differences between the groups in baseline characteristics
TX: size of tumour could not be assessed. ER: Oestrogen Receptor. PR: Progesterone Receptor. HER2: human epidermal growth factor receptor 2.

At the data cut-off 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 vs 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% vs 69.2% if also having a larger tumour size (≥T2; n=429; HR 0.53 (0.53–0.82), p=0.0031; appendix figure S2).

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).

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 anastrozole 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).

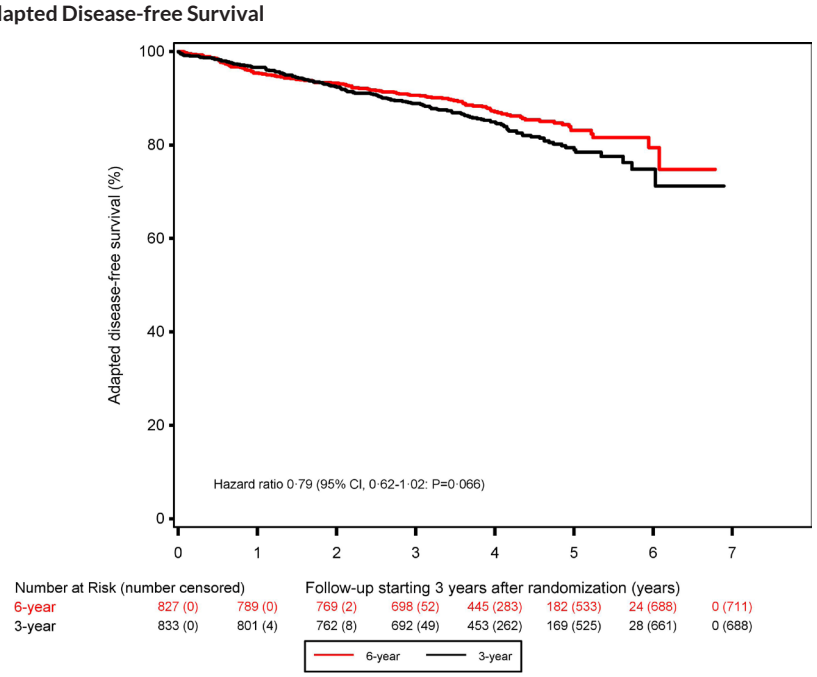
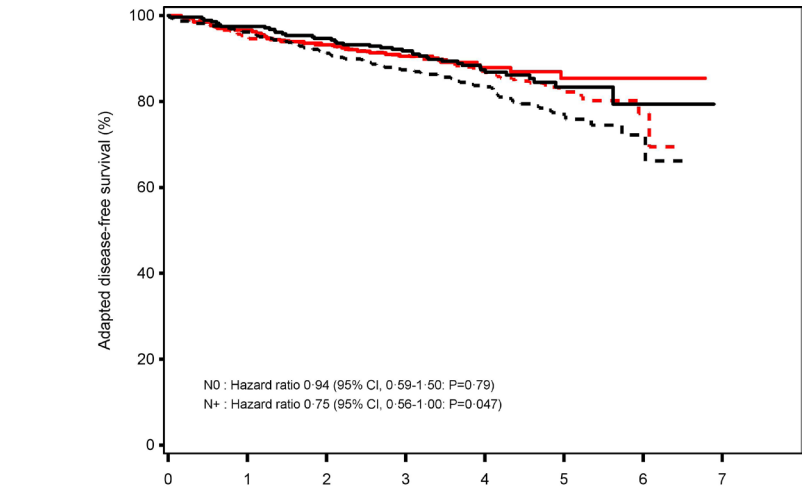


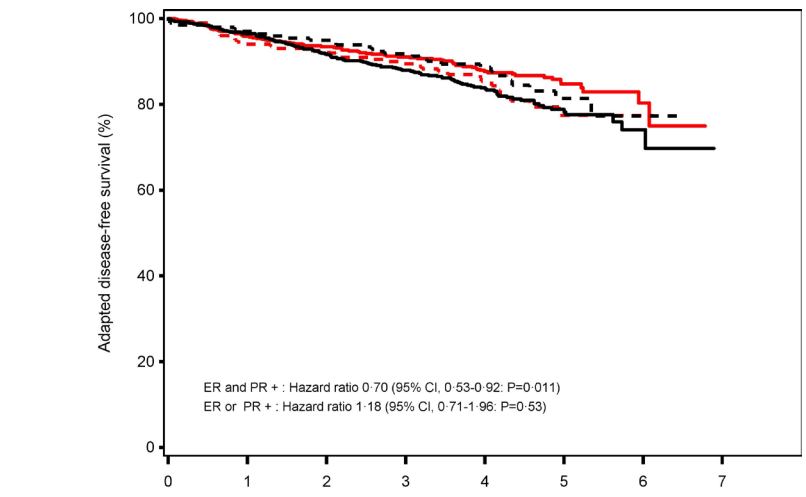
Figure 2. Kaplan-Meier estimates of the primary and secondary endpoint and subgroup analyses. Adapted disease-free survival (A), adapted disease-free survival for both treatment groups subdivided by patients with node-positive and node-negative disease (B), adapted disease-free survival for both treatment 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.

B. Adapted Disease-free Survival subdivided by nodal status



Number at Risk (number censored)			Follow-up starting 3 years after randomization (years)					
6-year N0	266 (0)	257 (0)	247 (1)	224 (17)	128 (108)	50 (184)	9 (225)	0 (234)
6-year N+	561 (0)	532 (0)	522 (1)	474 (35)	317 (175)	132 (349)	15 (463)	0 (477)
3-year N0	282 (0)	275 (0)	264 (3)	243 (16)	156 (93)	64 (180)	12 (231)	0 (243)
3-year N+	551 (0)	526 (4)	498 (5)	449 (33)	297 (169)	105 (345)	16 (430)	0 (445)

C. Adapted Disease-free Survival subdivided by hormone receptor status



Number at Risk (number censored)			Follow-up starting 3 years after randomization (years)					
6-year ER and PR +	627 (0)	601 (0)	585 (1)	533 (38)	345 (210)	149 (399)	21 (524)	0 (544)
6-year ER or PR +	200 (0)	188 (0)	184 (1)	165 (14)	100 (73)	33 (134)	3 (164)	0 (167)
3-year ER and PR +	633 (0)	611 (0)	577 (3)	529 (28)	343 (193)	132 (389)	22 (495)	0 (516)
3-year ER or PR +	200 (0)	190 (4)	185 (5)	163 (21)	110 (69)	37 (136)	6 (166)	0 (172)

Figure 2. Continued.

D. Adapted Overall Survival

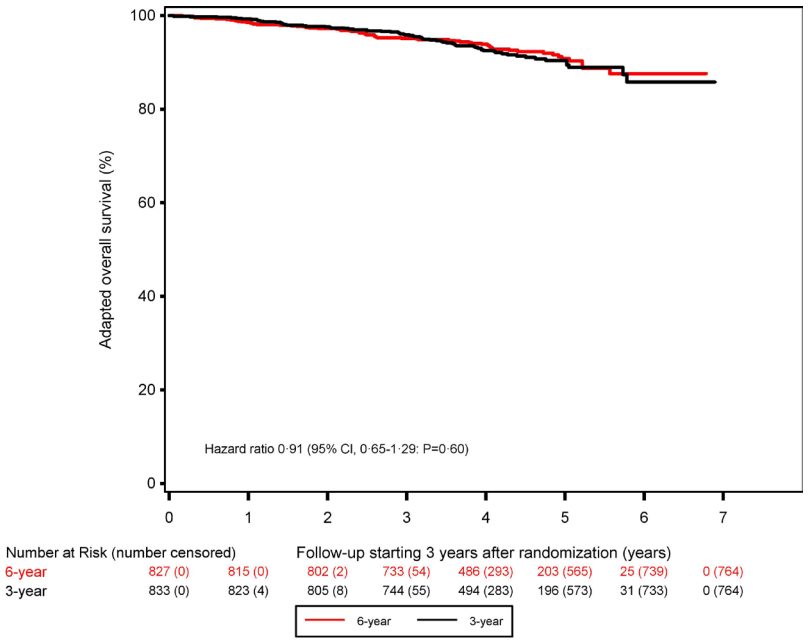


Figure 2. Continued.

16 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 table S2).

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.

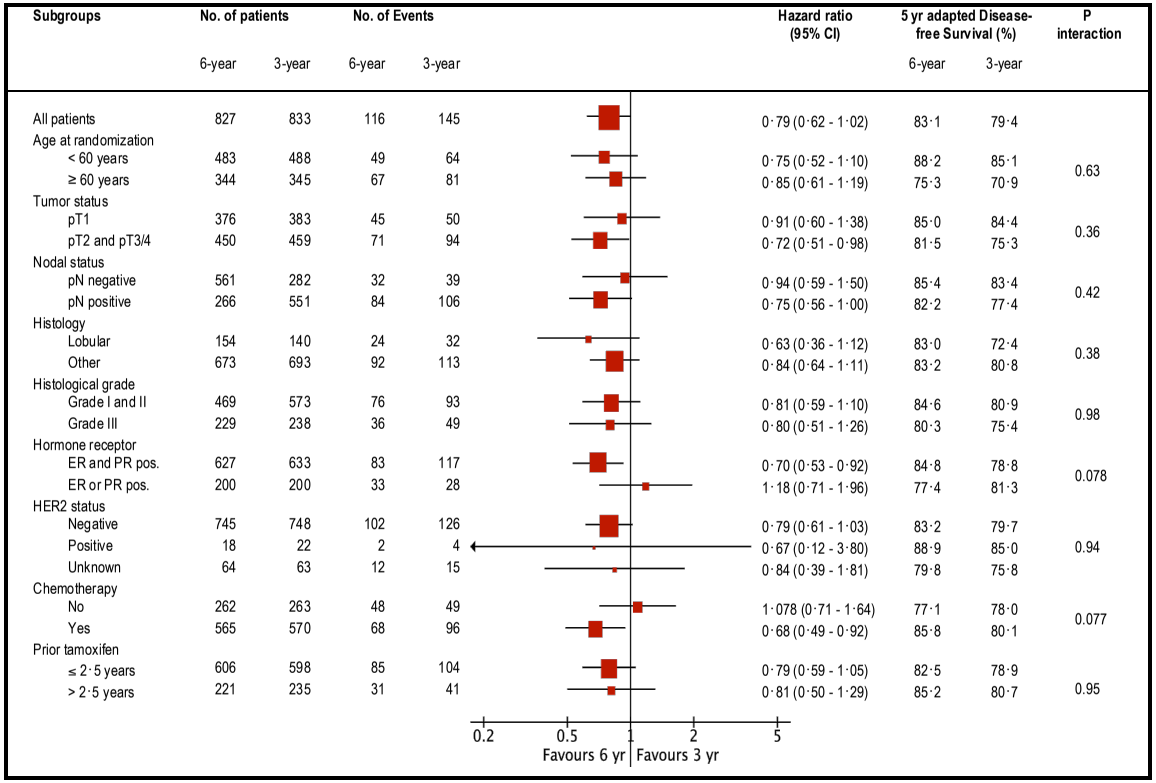


Figure 3. Cox proportional-hazards model results of adapted disease-free survival by 6-year anastrozole compared with 3-year anastrozole. Adapted disease-free survival implies the disease-free survival time beyond 3 years after randomisation. The disease-free survival events include: local, regional, 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.

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 table S2). According to protocol, treatment duration was censored at a disease event, resulting in non-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 figure S3).

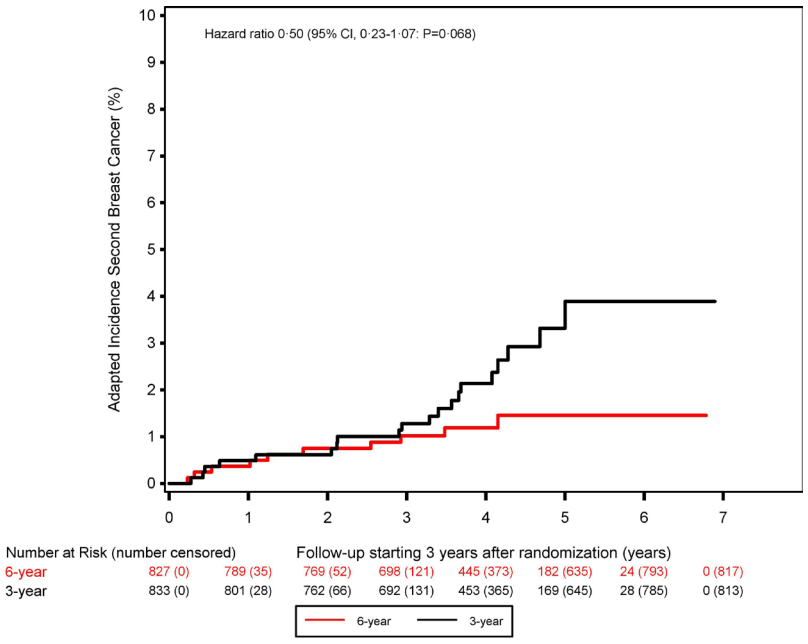


Figure 4. Kaplan-Meier estimates of adapted cumulative incidence of second breast cancer
Adapted incidence implies the incidence beyond 3 years after randomisation. The p value was calculated with the two-sided log-rank test.

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

Event	6-year Anastrozole (N=827)	3-year Anastrozole (N=833)
	Number of patients (%)	
Primary End Point		
Adapted Disease-free Survival event *	116	145
Local recurrence	12 (10.3)	7 (4.8)
Regional recurrence	10 (8.6)	14 (9.7)
Distant recurrence #	48 (41.4)	52 (35.9)
Visceral	29	38
Bone	26	30
Soft tissue	5	3
Other	6	3
Second, (non-)invasive breast cancer	10 (8.6)	23 (15.9)
Ipsilateral invasive	3	4
Ipsilateral DCIS	0	1
Contralateral invasive	4	15
Contralateral DCIS	3	3
Second, non-breast cancer §	27 (23.3)	45 (31.0)
Death without prior breast cancer event	20 (17.2)	18 (12.4)
Secondary end points		
Death from any cause	63	69
Breast cancer related	30 (47.6)	32 (46.4)
Not breast cancer related	33 (52.4)	37 (53.6)
Second primary malignancy	10	16
Cardiovascular disease	6	5
Other	17	16

* Patients may have had multiple disease-free survival events at the same moment

In some patients multiple locations of recurrences were reported

§ See appendix table S3.

Table 3. Adverse events by treatment group

	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 for 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.

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 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 table S3). 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.[3,15,16,17] 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 locoregional 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.[19,20,21,22] 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.[23,24,25] 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.

Acknowledgments

We would like to thank all the patients and their families who participated in this phase 3 study, the members of the Independent Safety Data Monitoring Committee (C.J.A. Punt (chairperson, Academic Medical Centre, Amsterdam), A. Voogd (Maastricht University Medical Centre, Maastricht), Prof.dr. J. Klijn (Erasmus Medical Centre, Rotterdam; retired), L. Beex (Radboud University Medical Centre, Nijmegen; retired), M. Bontenbal (Erasmus Medical Centre, Rotterdam; retired), the members of the steering committee (J. R. Kroep (Leiden University Medical Centre, Leiden), M.J.C. van der Sangen (Catharina Hospital, Eindhoven), C. Seynaeve (Erasmus Medical Centre Daniel den Hoed Cancer Centre, Rotterdam), C.H. Smorenburg (Antoni van Leeuwenhoek Hospital, Amsterdam) and the principal Data Manager (A. Swinkels). We thank the specialists who also contributed to the recruitment, treatment, and follow-up of patients as trial site principal investigators. The results of the trial were first presented in part at the San Antonio Breast Cancer Symposium, December 7–10, 2016. Additionally, we would like to acknowledge the contributions from Wim Lemmens and Bianca Schalk (Radoud University Medical Centre, the Netherlands), who helped PGMP with the statistical analyses.

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Supplementary appendix

Table S1. List of participating centres, local principal investigators and number of patients recruited.

Recruiting site	Patients recruited
Medisch Centrum Leeuwarden : H. de Graaf	67
Noordwest Ziekenhuisgroep, locatie Alkmaar: C. Smorenburg (S. Vrijaldenhoven)	61
Isala Clinics : A.H. Honkoop	59
Zuyderland, locatie Sittard-Geleen : F.L.G. Erdkamp	59
Zuyderland, locatie Heerlen : F.W.P.J. van den Berkmortel	56
Albert Schweitzer Ziekenhuis,locatie Dordwijk: J.J.E.M. Kitzen	54
Maastricht University Medical Centre : M. De Boer	48
Ziekenhuis Gelderse Vallei : W.K. de Roos	48
Antoni van Leeuwenhoek : S.C. Linn	47
Deventer Ziekenhuis : A.L.Th. Imholz	47
Canisius-Wilhelmina Ziekenhuis : L.J.A. Strobbe	40
ZGT Almelo : E.A. Kouwenhoven	40
Diakonessenhuis Utrecht : T. van Dalen	39
Meander Medisch Centrum : A.J. van Overbeeke	38
Amphia Ziekenhuis, locatie, Molengracht: J.K.S. Nuytinck	37
Bravis Ziekenhuis Roosendaal : I.E. Arntz	35
Rijnstate Arnhem : R.J.B. Blaisse	35
Spaarne Gasthuis loc. Haarlem-Zuid : H.B.A.C. Stockmann	35
VieCuri Medisch Centrum locatie, Venlo: P.H.A. Nijhuis	35
Antonius Ziekenhuis Sneek : G.J. Veldhuis	34
Medisch Spectrum Twente - Enschede : W.J.B. Mastboom	34
ETZ Elisabeth : J.M.G.H. van Riel	32
Havenziekenhuis : J.H. van Dam	32
Laurentius Ziekenhuis : M.O. den Boer	32
St Antonius Ziekenhuis, locatie Nieuwegein: M.J. Agterof	32
Ziekenhuis Rivierenland : M.A.J. de Roos	32
Máxima Medisch Centrum Veldhoven : R.M.H. Roumen	31
Radboudumc : J.J.M. van der Hoeven	29
Spaarne Gasthuis loc. Hoofddorp : A. Beeker	28
St Antonius Ziekenhuis, locatie Nieuwegein: R. Koelemij	28
Zaans Medisch Centrum : A. van Bochove	27
Gelre Apeldoorn : G.S. Madretsma	23
ZGT Hengelo : E.J.M. Siemerink	23
Ziekenhuis Bronovo : O.R. Guicherit	23

Table S1. Continued.

Recruiting site	Patients recruited
Ziekenhuis Bernhoven : A.H. Vos	22
Catharina Ziekenhuis : G.A.P. Nieuwenhuijzen	21
IJsselland Ziekenhuis : D.F.S. Kehrer	21
Bravis Ziekenhuis Bergen op Zoom : F.A.A. Valster	20
Groene Hart Ziekenhuis : B.C. Tanis	20
Rijnstate Ziekenhuis Zevenaar : T. van Voorthuizen	19
Tergooi (afdeling interne), locatie Hilversum: A.M.T. van der Velden	19
Admiraal De Ruyter Ziekenhuis, locatie Goes: R.A. Hellingman	18
Alrijne Ziekenhuis Leiden : R. Vree	18
Franciscus Vlietland : Q. van Rossum-Schornagel	18
OLVG, locatie Oost : J.M. Meerum Terwogt	18
BovenIJ ziekenhuis : W.G. van Leeuwen-Breuk	17
Leids Universitair Medisch Centrum : J.R. Kroep	17
Treant zorggroep locatie Bethesda : J.G. Haasjes	17
Rivas Zorggroep Beatrix Ziekenhuis : M.A. Davidis-van Schoonhoven	16
Tergooi (afdeling chirurgie), locatie Hilversum: E.J.C. Vriens	16
Röpcke Zweers Ziekenhuis : M. Jagers	15
Slingeland Ziekenhuis : E.W. Muller	15
Streekziekenhuis Koningin Beatrix : P.P.J.B.M. Schiphorst	15
Ziekenhuis Amstelland : C.J. van Groeningen	15
ZorgSaam Zeeuws-Vlaanderen, locatie Terneuzen: M.A. van Dijk	15
Admiraal De Ruyter Ziekenhuis, locatie Vlissingen: E. Janssens- van Vliet	14
St. Anna Ziekenhuis : E.E.M. Schepers	14
HagaZiekenhuis, loc. Sportlaan : J.W.S. Merkus	13
Ziekenhuis Bernhoven : N.G.J. van Diemen	13
Zuwe Hofpoort Ziekenhuis : R.C. van Doorn	13
Jeroen Bosch Ziekenhuis : K. Bosscha	12
Spijkenisse Medisch Centrum : R. den Toom	12
Van Weel-Bethesda Ziekenhuis : P.C. van der Velden	12
Jeroen Bosch Ziekenhuis : C.T.A.M. van Rossum	11
Medisch Centrum Haaglanden, Antoniushove: H.M. Oosterkamp	11
UMC Utrecht, locatie AZU: R. van Hillegersberg	11
LangeLand Ziekenhuis : B. Jas	10
Treant zorggroep locatie Scheper : E.E.M. Weernink	10
Gelre Zutphen : J.M.A. Ketel	9
Treant zorggroep locatie Refaja : J.J. Jansen	9

Table S1. Continued.

Recruiting site	Patients recruited
ETZ TweeSteden : J.K. Maring	7
Westfriesgasthuis : M.J.P.M. Govaert	7
Maasziekenhuis Pantein : Y.J.L. Kamm	6
Waterlandziekenhuis : M.M. Vleugel	6
Ziekenhuis Nij Smellinghe : S. Hovenga	5
Ziekenhuis Tjongerschans : J. de Boer	5
Ommelander Ziekenhuis Groningen, locatie Lucas: H. Potthoff	4
Flevoziekenhuis : D.W. Sommeijer	3
MC Slotervaart : E.J. van Dulken	3

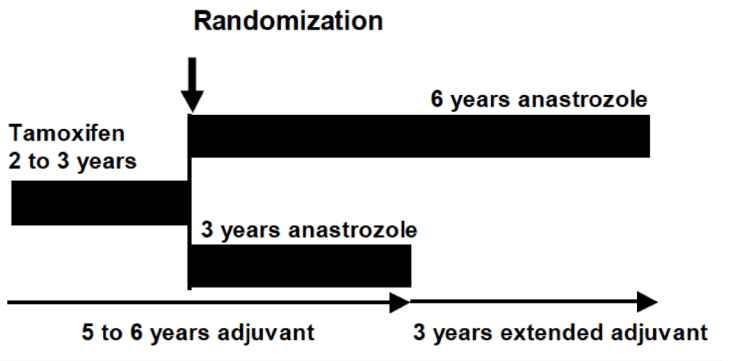


Figure S1. Design of the trial.

A. Adapted disease-free survival for patients with ER *and* PR positive, node-positive early breast cancer (N= 849)

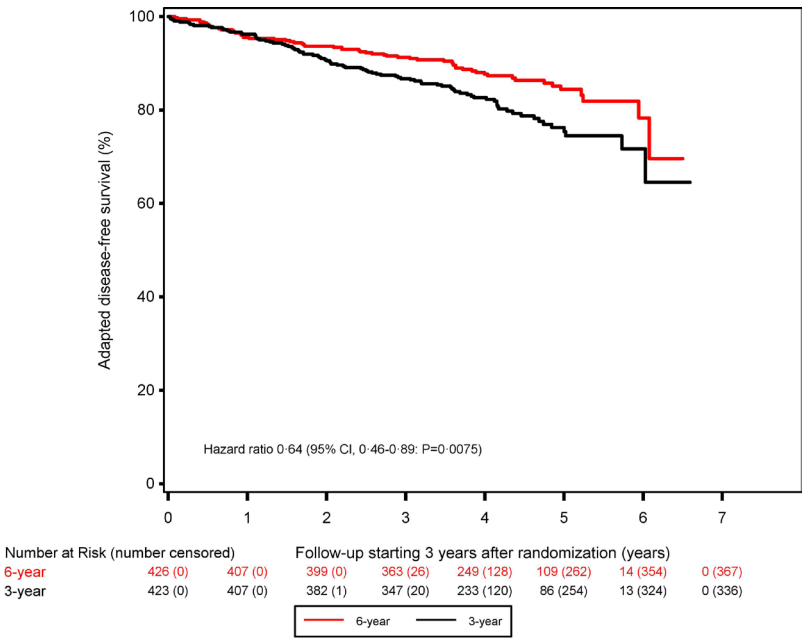


Figure S2. Adapted disease-free survival for patients with ER *and* PR positive, node-positive early breast cancer (N=849; Panel A), and for patients with ER *and* PR positive, node-positive and ≥T2 early breast cancer (N= 429; Panel B). In Panel A the 5-year adapted disease-free survival was 84.4% in the 6-year and 76.2% in the 3-year group, and in Panel B the 5-year adapted disease-free survival was 82.7% in the 6-year and 69.2% in the 3-year group.

B. Adapted disease-free survival for patients with ER and PR positive, node-positive and ≥T2 early breast cancer (N= 429)

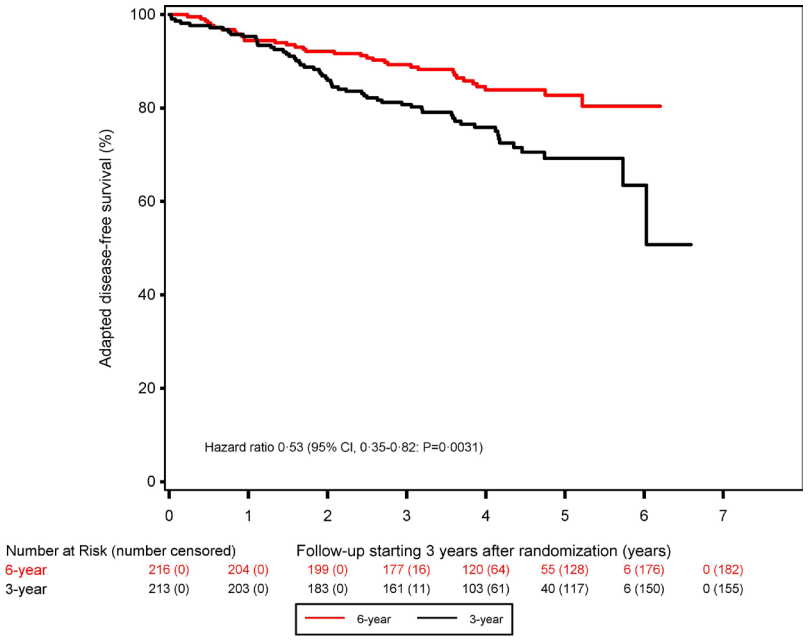


Figure S2. Continued.

Table S2. Termination of study treatment of all eligible patients.

	6-year Anastrozole (N=827)	**3-year Anastrozole (N=833)**
	N (%)	N (%)
Total number of patients with early treatment termination	304	131
Not due to primary disease-event		
Adverse events	201 (66.1)	118 (90.1)
Patient refusal	43 (14.1)	4 (3.1)
Protocol violation	13 (4.3)	5 (3.8)
Other	11 (3.6)	4 (3.1)
Due to primary disease event	36 (11.8)	0 (0.0)

As patients who had a primary event within the first 3 years beyond randomisation were excluded, no patients in the 3-year treatment group prematurely stopped treatment due to an event. Because of the longer treatment duration, more patients stopped treatment in the 6-year group compared to the 3-year group. Note, that the numbers are not synonymous for non-compliance. For calculating treatment compliance rates, treatment duration was censored at the time of a primary disease-free survival event, see also Figure S4.

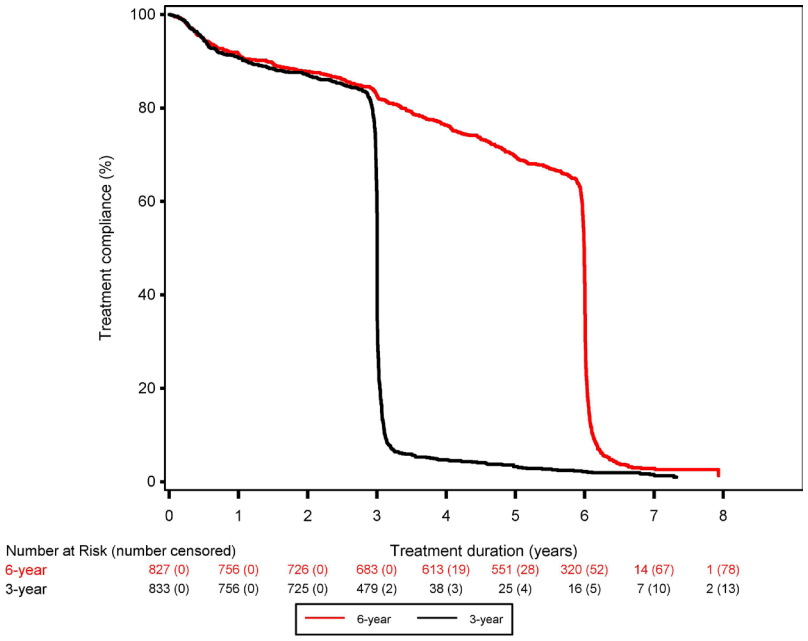


Figure S3. Treatment compliance (N=1660).
The figure shows the proportion of patients using anastrozole over time (since randomisation), calculated by the Kaplan-Meier method. The duration of treatment is calculated from the start of treatment to date of stop treatment. Patients should stop treatment after a primary event. When patients stopped treatment before having a primary event, it was a stop-event at the stop-date. For the compliance analysis we assessed the rate of patients still on treatment at 69 months and 33 months after randomisation as a minimal requirement for 6-year and 3-year treatment duration. Treatment duration was censored at the time of a primary event. Non-compliance rates were 34% at 6-year and 16% at 3-year.

Table S3. Total number of patients with a secondary non-breast cancer per tumour type and treatment group.

	6-year Anastrozole (N=827)	**3-year Anastrozole (N=833)**
	N	N
Multiple myeloma	2	1
Acute Myelocyte Leukaemia	1	0
Colorectal carcinoma	3	8
Endometrial carcinoma	1	2
Lung cancer	3	11
Melanoma	4	9
Non-Hodgkin Lymphoma	0	1
Ovarian carcinoma	2	2
Renal cell carcinoma	1	1
Small Cell Lung Cancer	2	0
Stomach carcinoma	2	0
Adenocarcinoma (liver)	0	1
Adenocarcinoma (mesentery)	1	0
Cholangiocarcinoma	0	1
Oesophageal carcinoma	2	1
Leiomyosarcoma	1	0
Meningioma	0	2
Pancreatic carcinoma	0	1
Head and Neck carcinoma	2	1
Urothelial cell carcinoma	0	2
Waldenstrom's disease	0	1

Hereafter, the results of all eligible patients (N=1860) are presented.

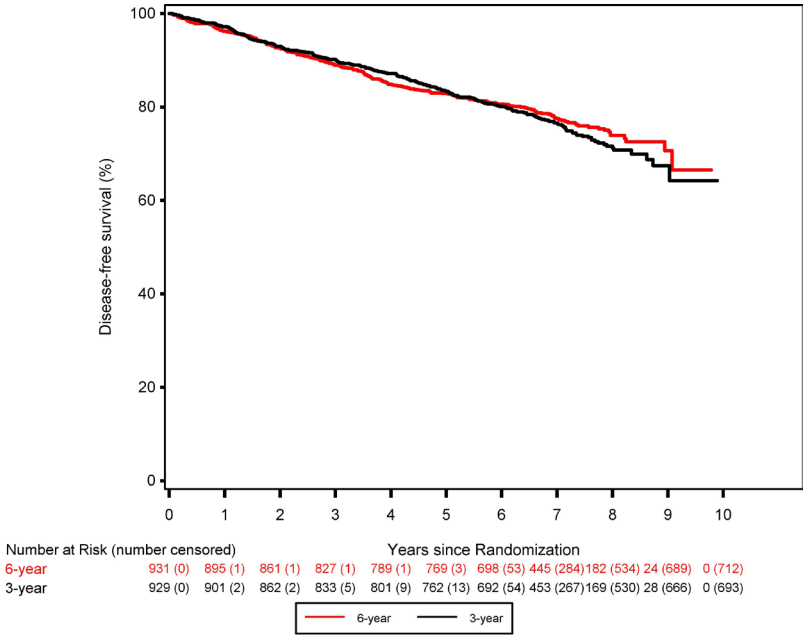


Figure S4. Ten-year disease-free survival for all 1860 eligible patients starting from randomisation.

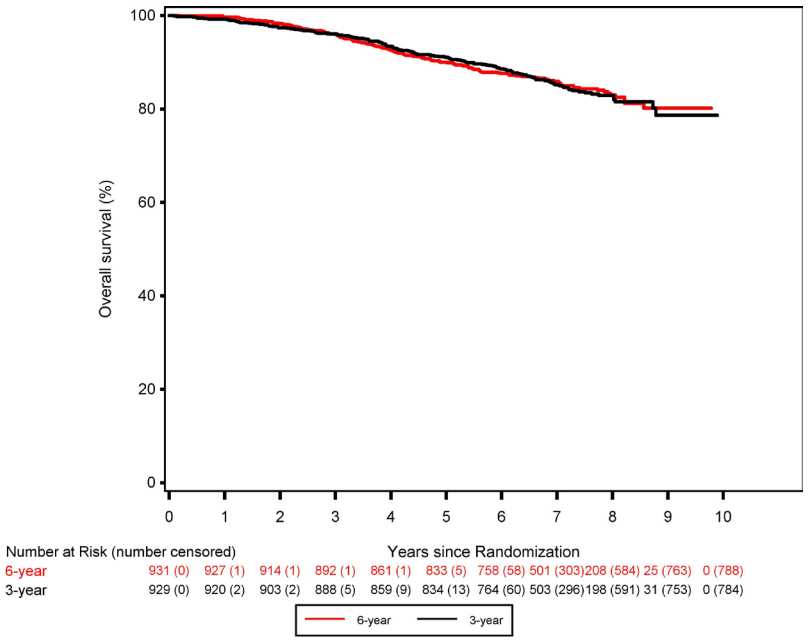
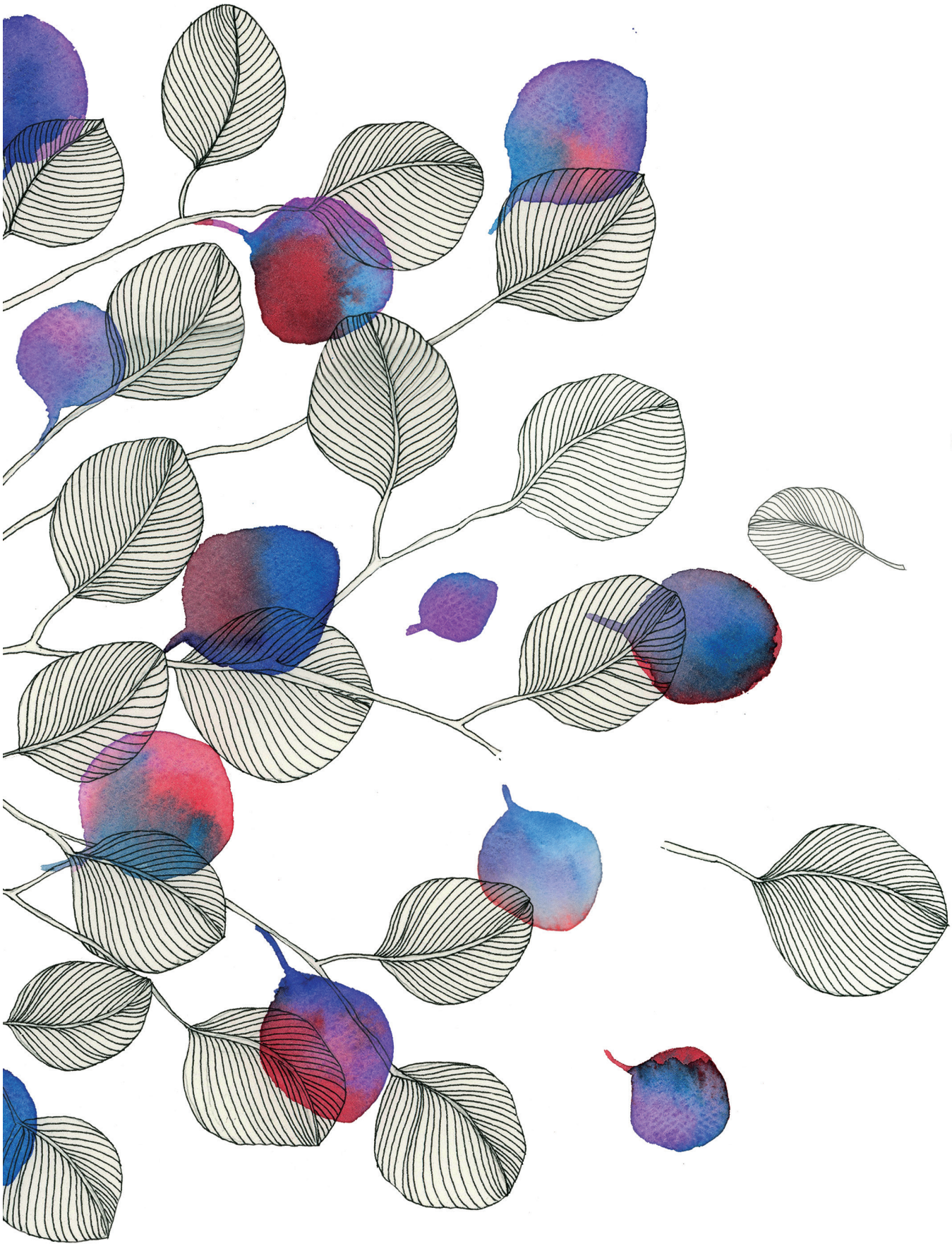
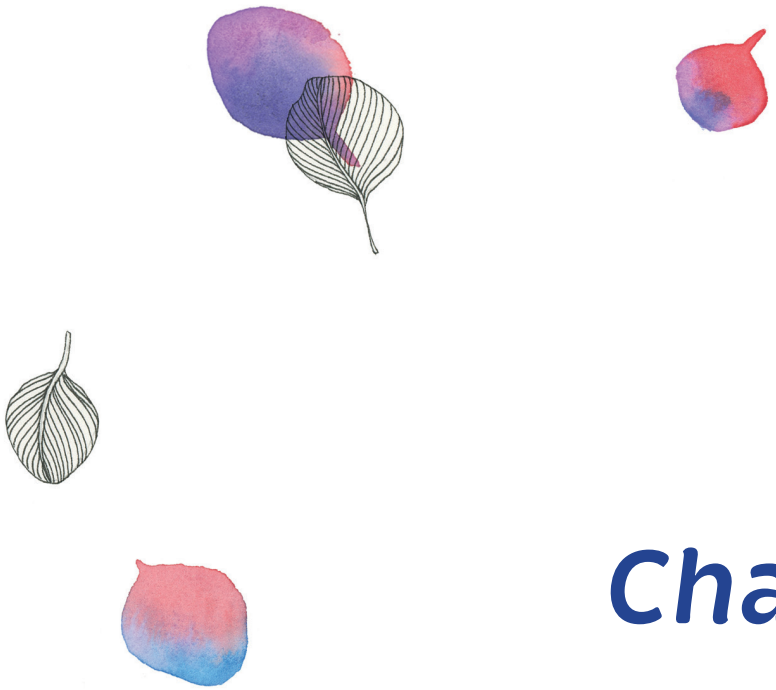


Figure S5. Ten-year overall survival for all eligible patients starting from randomisation.





Chapter 3

Current Status of Extended Adjuvant Endocrine Therapy in Early Stage Breast Cancer

Irene E.G. van Hellemond, Sandra M.E. Geurts, Vivianne C.G. Tjan-Heijnen.

Current Treatment Options in Oncology 2018;19:26.

Opinion statement

In the past decade several endocrine treatment regimens have been developed for the adjuvant treatment of postmenopausal women with hormone receptor positive early breast cancer, including tamoxifen, aromatase inhibitors (AI) or a combination of these. The standard duration of adjuvant endocrine treatment has been five years for a long time. Nevertheless, the high number of recurrences occurring after 5 years, suggested that extended endocrine therapy could further improve outcome, which led to the start of several randomised clinical trials investigating the effects of extended use of endocrine therapy. The extended duration of tamoxifen has been shown to improve disease-free survival and overall survival in the ATLAS and aTTom trials. However, in postmenopausal women, AIs have been shown to be more effective when compared with tamoxifen. Based hereon, it is recommended that adjuvant endocrine therapy in postmenopausal women with early breast cancer should include an AI. Recently, the DATA, IDEAL and NSABP B42 trials showed that extended adjuvant endocrine therapy with AIs beyond five years in postmenopausal women with early breast cancer did reduce the occurrence of secondary breast tumours, but had no or only a small impact on distant metastasis free survival. Furthermore, toxicity of adjuvant AIs led to gradually decreasing compliance rates and long-term toxicities to non-breast cancer related deaths. Therefore, we suggest considering extended adjuvant treatment only in women with high-risk early breast cancer who tolerate treatment well.

Introduction

For years, tamoxifen has been the standard adjuvant endocrine treatment of hormone receptor-positive breast cancer in both pre- and postmenopausal women. In the past decade, several other treatment regimens have been developed, using tamoxifen, aromatase inhibitors (AIs), or a combination of these.

The latest ASCO guideline regarding adjuvant endocrine therapy provides clear recommendations on extended tamoxifen treatment for premenopausal women with hormone receptor-positive early breast cancer.[1] However, for postmenopausal patients, a choice remains between four different treatment regimens; AI monotherapy for 5 years, sequenced treatment with tamoxifen and AIs for 5 years, extended tamoxifen monotherapy for 10 years, or tamoxifen followed by extended AIs for 10 years. To determine which 5-year schedule showed the highest efficacy, the Early Breast Cancer Trialist's Cooperative Group (EBCTCG) has compared three treatment strategies in the adjuvant setting of early breast cancer in postmenopausal women: continuous AI vs tamoxifen monotherapy, sequential tamoxifen and AI vs tamoxifen monotherapy, and sequential tamoxifen and AI vs continuous AI monotherapy.[2] Their meta-analysis showed that 5-year adjuvant endocrine treatment including AIs was more effective than tamoxifen monotherapy in preventing recurrence and breast cancer death in either continuous or sequential regimens.

Recently, a number of trials have been published where the efficacy and tolerability of extended endocrine therapy with AIs beyond 5 years were studied.[3,4,5,6] In this present review, we aim to summarize published randomised controlled trials on the efficacy and tolerability of different regimens of adjuvant endocrine therapy in postmenopausal women with hormone receptor-positive early breast cancer. In particular, the available evidence in terms of efficacy and tolerability of extended adjuvant endocrine treatment beyond 5 years. Moreover, we discuss potential difficulties and consequences of extending endocrine treatment in daily practice in subgroups of postmenopausal women with early breast cancer.

Methods

A detailed search strategy was used to search the PubMed database, consisting of numerous MeSH heading and text word combinations, "breast cancer," "endocrine therapy," "tamoxifen," "aromatase inhibitors," "exemestane," "anastrozole," "letrozole," "adjuvant," "extended," and "postmenopausal." Publications of randomised clinical phase III trials published before December 2017 in English language were included in our analysis. Abstracts of the yearly conferences of the San Antonio Breast Cancer Symposium (SABCS) and the American Society of Clinical Oncology (ASCO) were searched for relevant trials (and substituted by full papers if published before December 2017). Furthermore, we scanned the references of relevant trials, existing meta-analyses and guidelines for additional important trials. We categorized the studies by treatment regimen (tamoxifen, AI, or sequential) and duration (up to 5 years or more than 5 years). Studies concerning locally advanced and/or metastatic disease were excluded.

Hazard ratios (HR) were used to assess the treatment effects in each trial. If available, the HRs were directly obtained from the published article or conference presentation. If the trials did not provide HRs, they were calculated using the available methods of Tierney and colleagues.[7] When the results of the included trials were published at multiple points in time, the results with the longest follow-up duration were included.

Efficacy of treatment up to 5 years

The first randomised trials of adjuvant endocrine treatment for early breast cancer started in the mid-1970s and compared 1 to 2 years of tamoxifen with no endocrine treatment showing a reduction in breast cancer recurrences in the tamoxifen treatment groups.[8,9,10] The observation that these recurrences seemed to occur mostly after the adjuvant treatment period, with a median follow-up of 44–66 months, led to the hypothesis that a longer duration of treatment would further improve outcome.

In the early 1980s, a multicentre randomised trial demonstrated the superiority of 5 years of adjuvant tamoxifen over 2 years in the treatment of postmenopausal women with hormone receptor-positive early breast cancer.[11] This additional benefit in terms of breast cancer recurrence and mortality was confirmed by later trials and meta-analyses.[12,13,14]

Later on, AIs were developed, offering an alternative strategy to tamoxifen in the adjuvant treatment of postmenopausal women with hormone receptor-positive early breast cancer by preventing the production of endogenous oestrogens. The ATAC trial and the BIG 1-98 trial were the first large trials comparing adjuvant AIs with tamoxifen each for a duration of 5 years in postmenopausal women.[15,16] Anastrozole was used in the ATAC trial and letrozole in the BIG 1-98 trial. AIs were found to be superior to tamoxifen in terms of disease-free survival (DFS), recurrence-free survival (RFS), and overall survival (OS).

Thereafter, several studies were performed to investigate the effect of sequenced treatment, using different approaches, but all comparing with 5 years of tamoxifen.[17,18,19,20,21] The ABCSG-8 trial randomised patients between sequential tamoxifen followed by AIs or continuous tamoxifen therapy immediately after the primary breast cancer treatment (surgery, chemotherapy, and/or radiation therapy) and showed a statistically significant improvement in DFS for patients treated with AIs (HR 0.78 (95% CI 0.60–1.00)). Moreover, OS improved, although not statistically significant (HR 0.87 (95% CI 0.64–1.16)).[22] Other trials randomised patients after the initial treatment with tamoxifen, thus selecting a subpopulation of patients with possibly better prognosis and higher endocrine sensitivity.[18,19,20,21] Study findings should therefore be interpreted with caution. With the exception of the Japanese NSAS BC03 trial, all trials showed a statistically significant improvement in terms of DFS for sequential endocrine therapy in comparison with 5 years of tamoxifen. After a median follow-up varying between 30 and 128 months, all trials showed an improved OS, but these results were only statistically significant in the IES and ITA trials.

In addition, both the BIG 1-98 and the TEAM trial addressed the switch to an AI after 2–3 years of tamoxifen in comparison with AI monotherapy for a total of 5 years.[16,17,23] These trials randomised patients directly after primary breast cancer treatment (surgery, radiation therapy, and/or chemotherapy). Neither study showed a preference for either strategy after a median follow-up of 8.1 and 9.8 years, respectively. This was in line with the intention-to-treat patient-level meta-analysis by the EBCTCG showing that both continuous and sequential regimens including AIs are more effective than tamoxifen monotherapy for 5 years in preventing recurrence and breast cancer death.[2] AI monotherapy was associated with a significant 30% reduction in recurrences during the first year of endocrine treatment, when compared with a sequential regimen with tamoxifen followed by an AI. In the years thereafter, the number of recurrences did not differ between the treatment groups. Since it is expected that this benefit during the first year of endocrine therapy will not disappear, it is likely that, with longer follow-up, this benefit will also show in DFS and OS outcomes.

Efficacy of extended treatment duration

Hormone receptor-positive breast cancer is characterised by a very long natural history. As a consequence, some women remain at risk of late recurrence for years, fuelling the discussion to prolong endocrine therapy beyond 5 years. The risk of breast cancer recurrence after 5 years of endocrine therapy was evaluated in a meta-analysis by the EBCTCG.[24] In that meta-analysis, breast cancer recurrences occurred at a steady rate throughout the study period from 5 to 20 years, strongly correlated with the original tumour- and nodal status and tumour grade. Among the patients with stage T1 disease, the risk of distant recurrence in the period from 5 to 20 years was 13% without nodal involvement (T1N0), 20% with N1-3 status, and 34% with N4-9 status; among those with stage T2 disease, the risks were 19% with T2N0, 26% with T2N1-3, and 41% with T2N4-9. The risk of death from breast cancer was similarly dependent on TN status.

Other studies reported an annual rate of distant relapse in excess of 2% for at least 15 years after diagnosis, even after 5 years of tamoxifen.[25] A similar risk remains for at least 10 years for postmenopausal women who have received AIs for 5 years.[15] The Oxford overview analyses likewise show that at least 50% of recurrences occurred more than 5 years after diagnosis.[13] To determine whether there is any outcome advantage in continuing adjuvant endocrine therapy for more than 5 years, and what the optimal duration of adjuvant endocrine treatment is, several strategies have been researched. These trial findings are summarized in Table 1 and are discussed next.

Extended tamoxifen monotherapy

Results from the recent large ATLAS and aTTom trials clearly demonstrated that 10 years of tamoxifen showed an improved RFS and OS in comparison with 5 years of tamoxifen treatment (no data about DFS available).[26,27,28] Also, the smaller ECOG trial showed a benefit for 10 years tamoxifen treatment.[29] In contrast, data from the NSABP B-14 trial and the Scottish trial failed to demonstrate a positive impact of prolonged tamoxifen treatment on RFS and OS.[30,31]

Table 1. Overview of the reported results considering efficacy in the published trials on extended adjuvant endocrine treatment in postmenopausal women with early stage breast cancer.

Trial	Sample size	Median FU (yrs)	Treatment arm	Yrs 1 2 3 4 5
MA.17 [34]	5187	5.3	I	
			C	
NSABP B-33 [33]	1598	2.5	I	
			C	
ABCSG 6a [32]	856	5.2	I	
			C	
ATLAS [26]	6846	7.6	I	
			C	
aTTom [27,28]	6953	~9.0	I	
			C	
MA.17R [6]	1918	6.3	I	
			C	
DATA [3]	1660	4.4	I	
			C	
IDEAL [4]	1824	6.6	I	
			C	
NSABP B-42 [5]	3966	6.9	I	
			C	
SOLE [36]	4884	5.0	I	
			C	

Red: tamoxifen. Grey: aromatase inhibitor. Diagonal lines: either tamoxifen or an aromatase inhibitor.

FU follow-up, *I* intervention arm, *C* control arm, *yrs.* years, *DFS* disease-free survival, *HR* hazard ratio, *CI* confidence interval, *OS* overall survival,

*No data on DFS available, data on RFS reported

§ 9 months per year

	6	7	8	9	10	11	12	13	14	15	DFS HR (95%CI)	OS HR (95%CI)
											0.68 (0.56-0.83)	0.99 (0.79-1.24)
											0.68 (0.45-1.03)	NR
											0.62 (0.40-0.96)*	0.89 (0.53-1.34)
											0.84 (0.76-.93)*	0.87 (0.78-0.97)
											0.86 (0.77-0.96)*	0.94 (0.86-1.03)
											0.80 (0.63-1.01)	0.97 (0.73-1.28)
											0.79 (0.62-1.02)	0.91 (0.65-1.29)
											0.92 (0.74-1.16)	1.04 (0.78-1.38)
											0.85 (0.73-0.99)	1.15 (0.92-1.44)
	Intermittent §										1.08 (0.93-1.26)	0.85 (0.68-1.06)
	Continuous											

Extended sequential regimen

Additionally, there have been studies investigating the use of AIs after 5 years of tamoxifen treatment. The ABCSG-6a, MA.17 and NSABP B33 trials all showed a clear benefit of 5 years AI treatment after an initial 5 years of tamoxifen in DFS.[32,33,34] There was also an improvement in OS, but this was not statistically significant. This may have been caused by a lack of power due to early unblinding of the study. The early interim analysis of the MA.17 trial, after a median of 2.5 years of follow-up, showed an improved DFS for women using letrozole after 5 years of tamoxifen (HR 0.58 (95% CI 0.45–0.76)). After unblinding, 60% of placebo patients crossed over to letrozole, which complicated the efficacy analysis. Due to the results of the MA.17 interim analysis, also the NSABP B33 trial was unblinded early after a median follow-up of 2.5 years.

Several studies investigated the efficacy and safety of additional treatment with AIs after a sequential regimen of tamoxifen and an AI for 5 years.[3,4,5] The DATA trial investigated the effectiveness of 6 vs 3 years of anastrozole after an initial 2–3 year of tamoxifen in patients who were disease-free 3 years after randomisation.[3] The 5-year adapted DFS was not statistical significantly better for the overall study population in the 6-year group (HR 0.79 (95% CI 0.62–1.02); $p = 0.066$). However, in the subgroup of women with high-risk tumours, extended endocrine therapy was associated with an improved adapted DFS. For instance, in women with node positive disease, 5-year DFS was 84% in the 6-year group vs 76% in the 3-year group (HR 0.64 (95% CI 0.46–0.89), $p = 0.0075$); and 83% vs 69% if also having a larger tumour size (≥ T2; HR 0.53 (95% CI 0.53–0.82), $p = 0.0031$). Nevertheless, great care must be taken when interpreting subgroup analyses and should be interpreted as hypothesis generating rather than definitive. The results of a similar trial (GIM-4-LEAD; NCT01064635) are awaited, studying the effect of letrozole for 2–3 years vs 5 years after an initial 2–3 years of tamoxifen.

The IDEAL trial investigated the use of 2.5 vs 5 years of letrozole after an initial 5 years of endocrine treatment.[4] The initial treatment could either be tamoxifen monotherapy, AI monotherapy, or a sequential regimen. Regardless of the initial treatment regimen, no statistically significant benefit on DFS and OS was found for 5 years of extended letrozole treatment in comparison to an extended 2.5 years of AI treatment.

The NSABP B42 study investigated the efficacy of 5 years of letrozole after an initial 5-year of endocrine therapy including an AI.[5] This could be either AI monotherapy, or sequenced with tamoxifen. In the overall analysis, no statistically significant benefit was found for extended letrozole on DFS and OS. However, the results for distant recurrence-free survival (DRFS) and breast cancer-free interval (BCFI) were statistically significantly better for the extended treatment group (DRFS: HR 0.72 (95% CI 0.53–0.97), $p = 0.03$; BCFI: HR 0.71 (95% CI 0.56–0.89), $p = 0.003$).

The MA.17R trial investigated the efficacy of 5 years of letrozole after an initial 10-year treatment with tamoxifen for 5 years followed by AI for 5 years.[6] The 5-year DFS rate was 95% with letrozole and 91% with placebo (HR 0.80 (95% CI 0.63–1.01), $p = 0.06$). The rate of 5-year OS was not different (93 vs 94% for the letrozole and placebo groups respectively). The annual incidence rate of contralateral breast cancer in the letrozole group was 0.21%, and the rate in the placebo group was 0.49% (HR 0.42 (95% CI 0.22–0.81), $p = 0.007$). This suggests that the benefit of extended endocrine therapy in this trial was mainly caused by a reduction in the development of contralateral breast cancer.

In a recent meta-analysis on extended endocrine therapy, including the abovementioned trials, particularly women with a positive nodal status seemed to have more benefit of extended endocrine therapy (node positive HR 0.72 vs node negative HR 0.83).[35] Similarly, a relative larger benefit was seen from extended endocrine therapy in women with a larger tumour size (> 2 cm HR 0.77 vs ≤ 2 cm HR 0.88), and for those with both ER and PR expression vs single receptor expression (HR 0.68 vs 1.01). A greater effect was also seen in patients who received adjuvant chemotherapy compared with those who did not (HR 0.71 vs 0.80). However, as exposure to chemotherapy is probably a surrogate measure for worse disease, this finding could be a reflection of a higher chemotherapy receipt among patients with larger tumours and/or nodal involvement. Even though the differences in effect size of AIs between the higher and lower risk groups were not statistically different, it is yet an intriguing observation as in contrast to these AI studies, extended tamoxifen yielded similar relative benefits for the prognostic subgroups.[26]

Another treatment approach was tested in the SOLE trial, in which it was hypothesized that resistance to letrozole could be reversed by withdrawal and reintroduction of letrozole.[36] Postmenopausal women, previously treated by 5 years of endocrine treatment (tamoxifen, AI, or sequential), were randomised to either 5 years of intermittent letrozole or 5 years of continuous letrozole. Intermittent letrozole use did not improve DFS compared with continuous letrozole use (HR 1.08 (95% CI 0.93–1.26)).

Compliance

Compliance is an important issue in adjuvant endocrine therapy in general because it influences the efficacy. A recent analysis of the BIG 1-98 trial looked at treatment adherence and its impact on DFS in patients on tamoxifen, letrozole, or a sequential regimen for 5 years.[37] Both early cessation and a low compliance score were associated with a reduced DFS. Sequential treatments were associated with higher rates of non-persistence (Tam-Let, 20.8%; Let-Tam, 20.3%; Tam 16.9%; Let 17.6%). In 82.7% of patients, adverse events were the reason for discontinuation. The reason sequential endocrine therapy with tamoxifen and AIs could be preferred over AI monotherapy is diverse. Costs, due to patency, used to play a restricting role in the use of AIs. Nowadays, adverse events like musculoskeletal events and bone loss are frequently the motivation for switching therapies.[38,39] Furthermore, Henry and colleagues reported a 32% discontinuation rate for initial AI therapy within 2 years due to adverse events; 24% of the total study population discontinued specifically because of musculoskeletal symptoms.[40] The high percentage of discontinuation in the women taking tamoxifen might be explained by a younger age. A large cohort study published by Hershman and colleagues reported that women aged under 40 years had the highest risk of discontinuation in comparison with older aged women (HR 1.51 (95% CI 1.23–1.85).[41] Also, two other studies showed a younger age to be a predictor of premature discontinuation of tamoxifen.[42,43]

For both tamoxifen and AIs, the probability of early termination increases with a longer treatment duration. A systematic, qualitative meta-regression analysis illustrated endocrine treatment discontinuation rates ranging from 31 to 73% over the treatment period.[44] In the women taking tamoxifen, 13.6% discontinued during the first year of treatment, which increased to 47.1% at 5 years. In the women taking AIs, percentages of discontinuation were 11.7% during the first year and 31.3% at 5 years.[44,45] Likewise, another study described increasing discontinuation rates each year of AI treatment, ranging from 14 to 22% in the first year to 21–38% in the third year.[42] Early discontinuation rates in the published trials investigating extended endocrine therapy are as high as 30%.[3,4,5,37]

Tolerability

Each type of endocrine therapy is known for its drug-specific side effects. Tamoxifen inhibits the growth of breast tumours by competitive antagonism of oestrogen at its receptor site. Its actions are complex and it also has partial oestrogen agonist effects. These partial agonist effects can be beneficial, since they may help prevent bone demineralization in postmenopausal women, but also unfavourable, as they are associated with increased risks of uterine cancer and thromboembolism.[38]

AIs suppress plasma and intra-tumoural oestrogen concentrations in postmenopausal women by inhibiting or inactivating aromatase: the enzyme responsible for synthesizing oestrogens from androgenic substrate.[46] Unlike tamoxifen, AIs have no partial agonist activity. AIs have side effects that are predominantly predictable consequences of oestrogen deprivation.[38] Musculoskeletal events (e.g. arthralgia and myalgia), bone loss and cardiovascular events have been reported frequently during AI use.[39] In contrast to tamoxifen, follow-up of the adjuvant AI trials is relatively short- and the long-term consequences of adjuvant AI use have yet to be fully determined.

A meta-analysis including seven trials comprising 16,349 patients analysed the reported toxicity of extended endocrine treatment with AIs.[47] Longer treatment with AIs was associated with increased odds of cardiovascular events (odds ratio (OR) = 1.18, $p = 0.05$, number needed to harm (NNH) = 122), bone fractures (OR = 1.34, $p < .001$, NNH = 72), and cessation of treatment due to adverse events (OR = 1.45, $p < 0.001$, NNH = 21). Extended use of AIs did not influence the odds of a second malignancy (OR = 0.93, $p = 0.56$), but a numerical excess of deaths without breast cancer recurrence was found with prolonged AI (OR = 1.11, $p = 0.34$). Even though the increase of deaths without breast cancer recurrence was not statistically significant, this might change when future results of these trials with a longer follow-up duration are published. The updated results of the TEAM trial, comparing 5 years of anastrozole with a 5-year sequenced regimen with tamoxifen and anastrozole with a median follow-up of 9.8 years, showed that the potential beneficial effect of exemestane on breast cancer-specific mortality might be counterbalanced by an increase in non-breast cancer-related mortality (12 vs 10%), leading to a similar overall survival between the treatment groups.[23]

Postmenopausal due to prior chemotherapy

AIs are contraindicated in premenopausal women. Noteworthy, AIs are also contraindicated in women with chemotherapy-induced ovarian function failure because of the possibility of ovarian function recovery.[48,49] Therefore, we advise against using AIs in women with chemotherapy-induced ovarian function failure, and also advise caution even when used in combination with gonadotropin-releasing hormone (GnRH) agonists. GnRH agonists do not suppress the ovarian function completely in all patients, as was observed in the SOFT-EST trial.[50] During 12 months of follow-up, 34.2% of the patients had inadequately suppressed E2 levels, at least once, indicating incomplete ovarian function suppression.[50] This might be the underlying reason that the combination of AI/GnRH agonist has not shown to improve overall survival in comparison with tamoxifen monotherapy or the combination of tamoxifen/GnRH.[51,52] Hence, for women who became postmenopausal due to prior chemotherapy, extended adjuvant endocrine treatment with tamoxifen can be used in case of high-risk tumours.

Future perspectives

Future research needs to identify the subgroup of women that will have benefit of extended endocrine treatment. In designing a therapeutic strategy to prevent disease recurrence, it is necessary to not only have knowledge about the total risk of relapse but also to ascertain when recurrence is most likely to occur and when this risk becomes minimal. For this purpose, annual hazard rates could be used. Annual hazard rates describe the changes in the risk of recurrence over time. Instead of simply estimating the overall course of disease, they emphasize when a relapse occurs. When looking at the annual hazard rate curves of women with hormone receptor-positive breast cancer, it comes across that recurrences occur even more than 10 years after the initial diagnosis. Dignam and colleagues presented the annual recurrence hazard for women with node negative early breast cancer that had undergone surgery without subsequent systemic adjuvant treatment.[53] The annual hazard rate for patients with hormone receptor negative tumours reached a peak around 18 months and diminished rapidly afterwards. In the hormone receptor-positive group, this peak appeared slightly later but had a less rapid decrease and did not diminish totally during a follow-up of 12 years. Considering an annual risk of distant recurrence remains 1–2% for at least 15–20 years after diagnosis of hormone receptor-positive breast cancer, even after 5 years of endocrine therapy, extended adjuvant therapy may seem a logical approach.[24] However, from the trials on extended adjuvant endocrine therapy, it is suggested that these have in general a larger impact on secondary breast cancers and loco-regional recurrences than on distant recurrences. Moreover, it is debated whether the effect size might be larger for extended adjuvant endocrine therapy in those who received initially tamoxifen than in those who received initially AIs. Hence, extending endocrine therapy seems not to be the solution for the observed late distant recurrences.

Moreover, many women are treated with endocrine agents who will never develop metastases. Consequently, they unnecessarily suffer from side effects that influence their quality of life. Therefore, it is important to identify those women with a high risk of relapse and who will have maximum benefit from extended endocrine treatment. For this purpose, several strategies could be used. Firstly, clinical studies investigating endocrine therapy should divide women with hormone receptor-positive breast cancer in luminal A and luminal B subgroups. Luminal B breast cancer has been reported to have lower expression of hormone receptors, higher expression of proliferation markers, and higher histologic grade than luminal A, all exhibiting to a worse prognosis.[54] Furthermore, luminal B breast cancer has a distinct profile of response to endocrine therapy and chemotherapy.[54]

The use of several molecular risk scores was approved for use in decision-making concerning adjuvant chemotherapy, however, if these scores can also be used to guide decisions on extended endocrine therapy is not sufficiently clear yet.[55] Nevertheless, the TransATAC trial showed promising results in predicting which women had a low risk of developing distant recurrences 5 to 10 years after breast cancer diagnosis, thereby identifying the women in who extended therapy is not justified.[56,57]

Furthermore, several studies are now combining endocrine therapy with a targeted drug, such as mTOR inhibition or CDK 4/6 inhibition. Much is expected from these combinations, although toxicity is like significantly worse which again can compromise compliance and indirectly efficacy. For that reasons, most studies have chosen to select only high-risk patients based on tumour size, nodal status, and/or histological grade. The on-going trials on the adjuvant endocrine treatment in postmenopausal women with early breast cancer are presented in Table 2.

Table 2. On-going trials on the djuvant endocrine treatment in postmenopausal women with early breast cancer.

Study acronym **Trial ID number** **Phase** **Country**	Sample size (*n*)	Purpose	Inclusion criteria
Duration endocrine treatment			
GIM-4-LEAD **NCT01064635** **Phase III** **Italy**	4050	Comparing the efficacy of different regimens of L in postmenopausal women with stage I, II, or III BC previously treated with T	Postmenopausal women with HR+ BC stage I-III. Any nodal stage. No metastases. Completed initial T treatment.
ABCSG 16 SALSA **NCT00295620** **Phase III** **Austria**	3486	Efficacy of a further 2 years *vs* a further 5 years of adjuvant treatment with A after initial 5 years of adjuvant endocrine therapy	Postmenopausal women with HR+ BC Any nodal stage No metastases Completed initial anti-hormonal treatment
SOLE/ **ABCSG 35-07** **NCT00553410** **Phase III** **International**	4800	Continuous Lversus intermittent L in postmenopausal women with BC who received 4-6 years of endocrine therapy	Postmenopausal women with HR+ BC Any nodal stage No metastases Completed initial endocrine treatment < 12 months ago
MINDACT **NCT00433589** **Phase III** **International**	6589	Comparing the efficacy of 7 years of L with 2 years of T followed by 5 years of L	Postmenopausal women with HR+ BC 0-3 Positive lymph nodes No metastases
N-SAS-BC-05 **JPRN-UMIN000000818**	2500	Comparing the efficacy of 5 year A after either 5 years of A or 5 years of sequential therapy with T followed by A	Postmenopausal women with HR+ BC Any nodal stage No metastases

	Endocrine therapy before randomisation (years)	Treatment Arms	Outcome measures	First results expected
	2-3 years T	1) 2-3 years L 2) 5 years L	OS Safety	2015
	5 years of any endocrine therapy	1) 2 years A 2) 5 years A	DFS OS Fracture occurrence Secondary carcinoma Contralateral BC	2019
	4-6 years of any endocrine therapy	1) 5 years L continuously 2) 5 years Intermittent L (4 x 9 months, 1 x 12 months)	DFS OS Distant DFS BC free interval Second malignancies Deaths without prior cancer events Adverse events	2021
	none	1) 7 years L 2) 2 years T- 5 years L	DFS OS Safety	Unknown
	5 years of A or 5 years of sequential therapy (T followed by A)	1) 5 years A 2) no additional endocrine treatment	DFS OS DDFS Adverse events QALY HRQOL	Unknown

Table 2. Continued.

Study acronym **Trial ID number** **Phase** **Country**	Sample size (*n*)	Purpose	Inclusion criteria
Sequenced treatment vs monotherapy			
GIM-3-FATA **NCT00541086** **Phase III** **Italy**	10000	Evaluate the efficacy of sequenced treatment vs AI monotherapy	Postmenopausal women with HR+ BC, stage I-III Any nodal stage No metastases Completed initial endocrine treatment < 2 years ago
Sequential or concurrent with chemotherapy			
GIM-10-CONSENT **NCT02918084** **Phase III**	1000	Concurrent vs sequential AI for a total of 5 years in postmenopausal patients receiving adjuvant chemotherapy for BC	Postmenopausal women with HR+ BC Any lymph node status No metastases
Comparison of aromatase inhibitors			
FACE **NCT00248170** **Phase III** **International**	4160	5 years of adjuvant L vs A in postmenopausal women with HR-positive, node positive BC	Postmenopausal women with HR+ BC Positive lymph nodes No metastases Recently underwent surgery
PHACS **NCT01127295** **Phase IV** **France**	2000	The correlation between pharmacokinetic and pharmacogenetic parameters of adjuvant endocrine BC treatment, during the first 3 years	Postmenopausal women with HR+ BC Any lymph node status No metastases

	Endocrine therapy before randomisation (years)	Treatment Arms	Outcome measures	First results expected
	none	1) 5 years A, E or L monotherapy 2) 2.5 years T- 2.5 years A, E or L	DFS OS DDFS Contralateral BC BC free interval Second malignancy Effects on lipids Toxicity	2018
	none	1) Adjuvant chemotherapy followed by 5 years AI (sequential) 2) Adjuvant chemotherapy and 5 years AI concurrent	DFS OS Genomic analysis	2028
	none	1) 5 years A 2) 5 years L	DFS Safety OS DDFS Cancer specific survival Effect on lipids Bone fractures	2018
	none	1) 5 years T 2) 5 years L 3) 5 years A 4) 5 years E	Correlation pharmacokinetic and pharmacogenetic parameters. Relation plasmatic concentrations, effectivity and adverse events. Polymorphisms and relapses.	2019

Table 2. Continued.

Study acronym **Trial ID number** **Phase** **Country**	Sample size (*n*)	Purpose	Inclusion criteria
Predictive Factors			
PreFace **NCT01908556** **Phase IV** **Germany**	3545	Identification of biomarkers that could predict the efficacy of adjuvant L treatment	Postmenopausal women with HR+ BC Any lymph node status No metastases
Long term follow-up			
LATTE **NCT01745289** **Phase III** **USA**	6000	Evaluate the long-term effects of A (5 years) vs T (5 years) (follow-up ATAC trial)	All women that were included In the ATAC trial which investigated the efficacy of 5 years of A vs T.
Targeted Therapy			
S1207 **NCT01674140** **Phase III** **USA**	1900	Evaluate adjuvant endocrine therapy with or without 1 year of everolimus in high-risk, hormone receptor-positive and HER2/Neu negative BC patients	Pre- and Postmenopausal women with HR+ BC Her2 – N+
UNIRAD **NCT01805271** **Phase III** **France**	1984	Evaluate the benefit of adding everolimus to adjuvant endocrine therapy of early BC	Pre- and postmenopausal women with HR+ BC Her2 - N +
EarLEE-1 **NCT03078751** **Phase III** **USA**	2000	Evaluate eficacy and safety of ribociclib with endocrine therapy as adjuvant treatment of high risk early BC	Pre- and postmenopausal women with HR+ BC Her2 – AJCC prognostic Stage Group III
EarLEE-2 **NCT03081234** **Phase III** **USA**	4000	Evaluate efficacy and safety of ribociclib with endocrine therapy as adjuvant treatment of intermed. risk early BC	Pre- and postmenopausal women with HR+ BC Her2 – AJCC prognostic Stage Group II

	Endocrine therapy before randomisation (years)	Treatment Arms	Outcome measures	First results expected
	none	1) 5 years L	DFS OS Prediction of pharmacogenetic markers on efficacy and side effects	2015
	5 years A or 5 years T	Follow up	Long term RFS	2018
	none	Any endocrine therapy combined with 1) 1 year everolimus 2) 1 year placebo	IDFS DFS OS Toxicity	2022
	1 year of any endocrine therapy	1) 1 year everolimus 2) 1 year placebo	DFS OS EFS DMFS Secondary cancer	2021
	none	Any endocrine therapy combined with 1) 2 years ribociclib 2) 2 years placebo	IDFS RFS OS QoI	2023
	none	Any endocrine therapy combined with 1) 2 years ribociclib 2) 2 years placebo	IDFS RFS OS QoI	2025

Table 2. Continued.

Study acronym **Trial ID number** **Phase** **Country**	Sample size (*n*)	Purpose	Inclusion criteria
monarchE **NCT03155997** **Phase III** **International**	3580	Evaluatie efficacy of abemaciclib combined with standard adjuvant endocrine therapy vs standard adjuvant endocrine therapy alone	Pre- and postmenopausal women with HR+ HER2- BC N+ status and 1 of the following indicating a higher risk of relapse: - 4 or more N+ - Tumour size ≥ 5 cm - Grade 3 histology - Ki67 index of ≥20%
PALLAS **NCT02513394** **Phase III** **USA**	4600	Evaluate efficacy of palbociclib with standard adjuvant endocrine therapy vs standard adjuvant endocrine therapy alone	Pre- and postmenopausal women with HR+ BC Her2 -

	Endocrine therapy before randomisation (years)	Treatment Arms	Outcome measures	First results expected
	none	Standard 5 year adjuvant endocrine treatment with 1) 2 years palbociclib 2) none	IDFS DRFS OS Toxicity	2022
	none	Standard 5 year adjuvant endocrine treatment with 1) 2 years palbociclib 2) none	IDFS DRFS OS LRRFS	2020

Conclusions

Based on the reviewed literature, we believe both the type and duration of adjuvant endocrine treatment should be personalized based on expected efficacy and tolerability. The identification of subgroups of patients who might benefit from extended endocrine treatment is of great significance. Possibly molecular risk scores will offer more insight hereon in the future. Moreover, it is important to consider quality of life during treatment and other long-term toxicities, such as osteoporosis and cardiovascular diseases that might interfere with overall survival outcome. If a patient tolerates the endocrine treatment well, extended use of hormonal therapy, especially if not initially treated with AIs, could be considered in case of a high-risk tumour that is both ER and PR positive (Figure 1). But, more targeted treatment approaches are eagerly waited for from on-going trials.

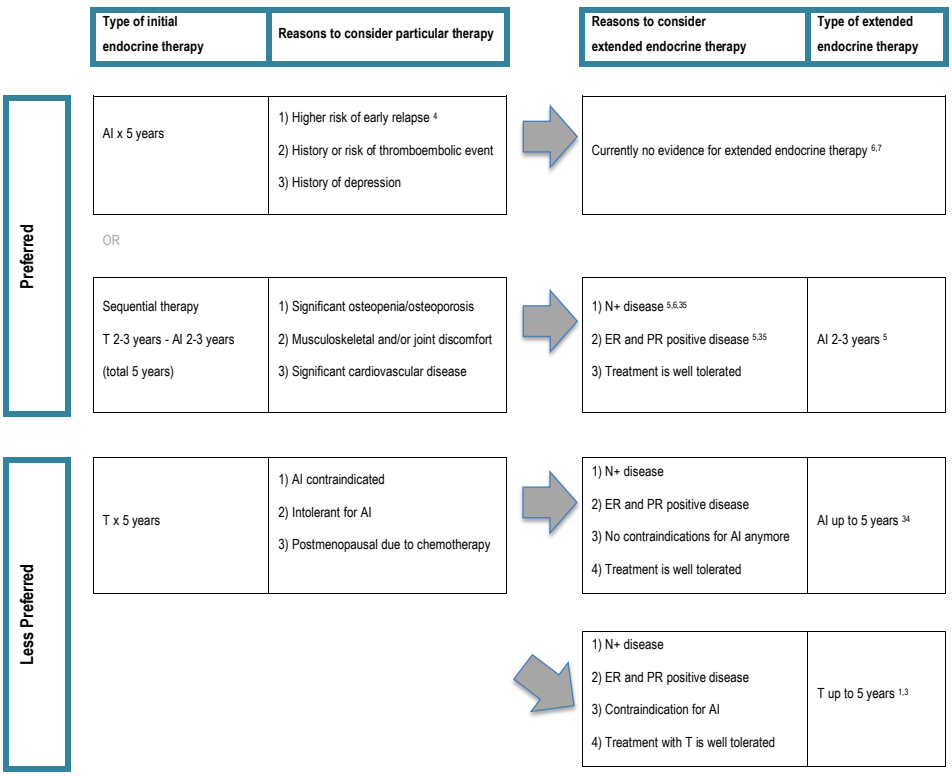


Figure 1. Adjuvant endocrine treatment in postmenopausal women with early stage hormone receptor-positive breast cancer. AI, aromatase inhibitor; T, tamoxifen.

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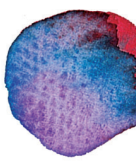
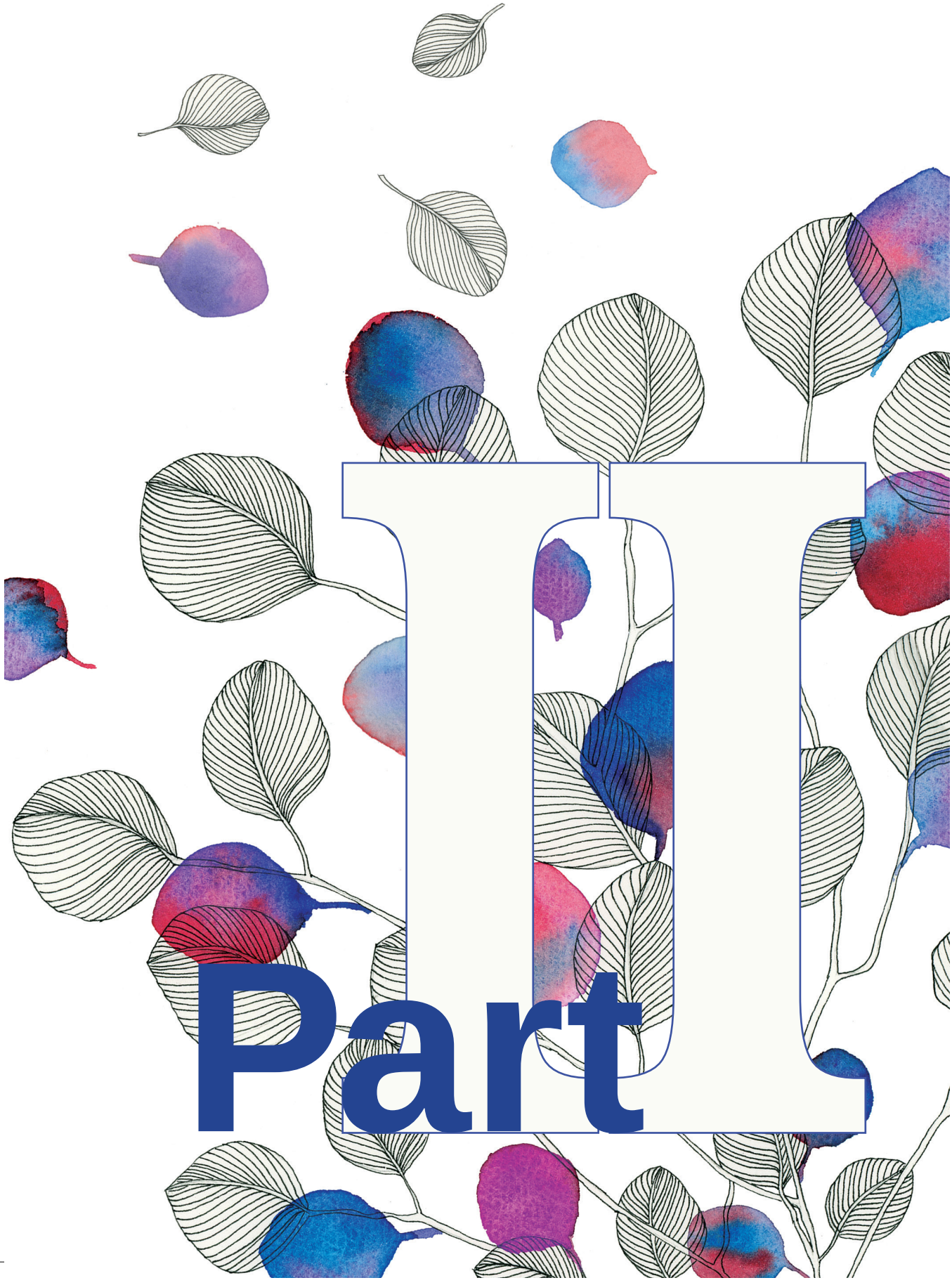
Ovarian function recovery during endocrine therapy

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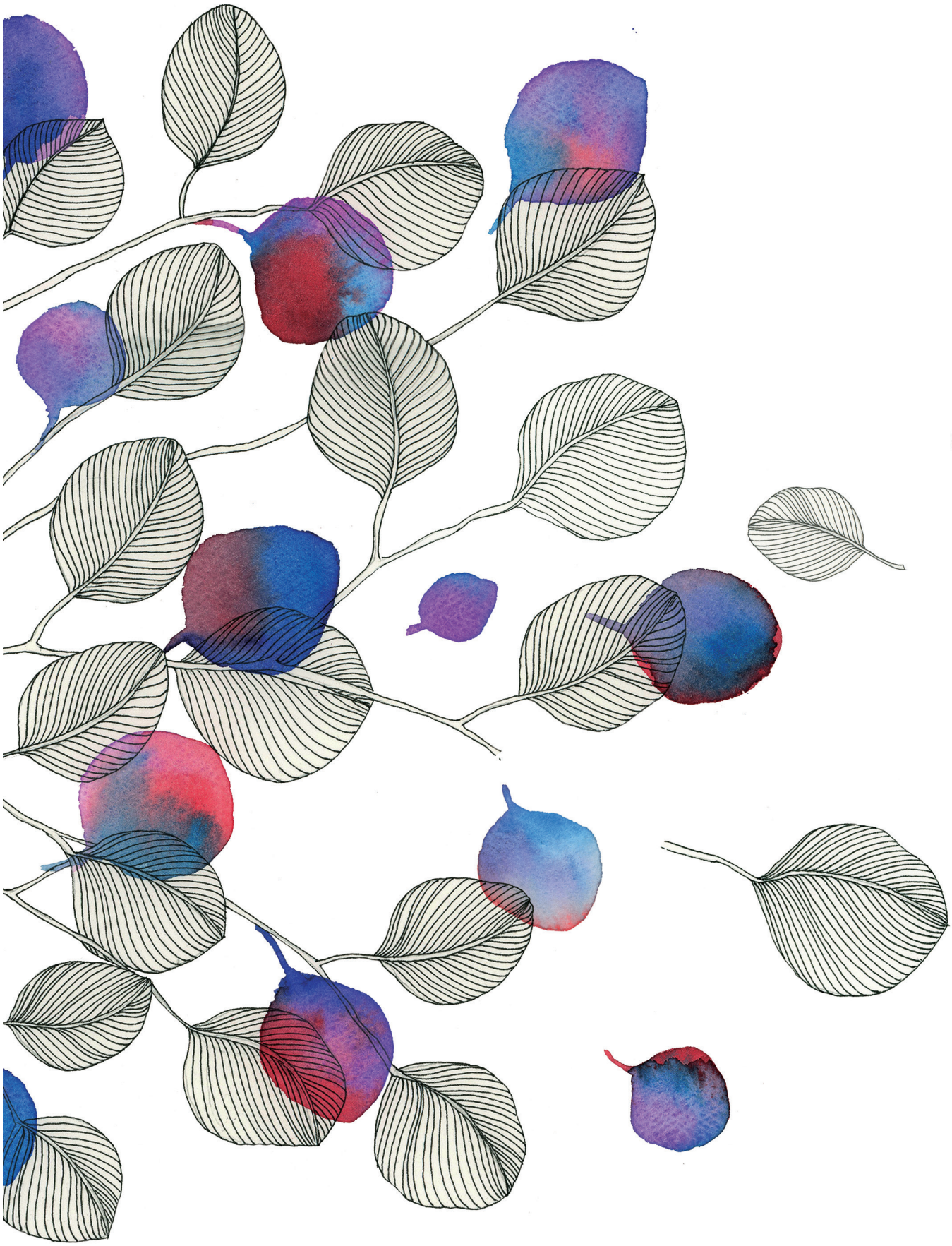





Chapter 4

Ovarian Function Recovery during Anastrozole in Breast Cancer Patients with Chemotherapy-Induced Ovarian Function Failure

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The Journal of the National Cancer Institute 2017;109.

Abstract

Background

Aromatase inhibitors (AIs) are given as adjuvant therapy for hormone receptor–positive breast cancer in postmenopausal women, also to those with chemotherapy-induced ovarian function failure. The current analysis reports on endocrine data of patients with chemotherapy-induced ovarian function failure who were included in the phase III DATA study assessing different durations of adjuvant anastrozole after tamoxifen.

Methods

We identified all patients with chemotherapy-induced ovarian function failure. Women who underwent a bilateral ovariectomy or used luteinizing hormone-releasing hormone agonists before random assignment were excluded. Plasma oestradiol and follicle-stimulating hormone levels were monitored until 30 months after random assignment at local laboratories. We aimed to determine the ovarian function recovery (OFR) rate during AI use by the cumulative incidence competing risk method and analysed the trend of oestradiol levels during AI use by a nested case-control approach in which a subset of control subjects were compared with the OFR patients excluding the value at OFR diagnosis.

Results

The 329 eligible patients had a median age of 50.0 years (range = 45–57 years) at random assignment. Thirty-nine patients developed OFR, corresponding with a 30-month recovery rate of 12.4%. Of these, 11 (28.2%) were age 50 years or older at AI initiation. The oestradiol level decreased statistically significantly by 37.8% (95% CI = 27.4% to 46.7%) over the initial 30 months of AI treatment in both groups. However, the oestradiol levels in the women who experienced OFR remained statistically significantly higher (difference = 20.6%, 95% CI = 2.0% to 42.7%) prior to OFR diagnosis compared with those who did not experience OFR.

Conclusions

The risk of OFR during AI treatment in breast cancer patients with chemotherapy-induced ovarian function failure is relevant, even beyond 45 years. Furthermore, women experiencing OFR had statistically significant higher oestradiol levels during AI treatment (before OFR) than those without, with potential consequences regarding efficacy.

Introduction

In early-stage hormone receptor–positive breast cancer, aromatase inhibitors (AIs) are an established component of adjuvant endocrine therapy for postmenopausal women.[1] By inhibiting the aromatase enzyme, the conversion from androgens to oestradiol (E2) is blocked, which leads to E2 deprivation, but only in women without functioning ovaries. In daily practice, AIs are also offered to patients with chemotherapy-induced ovarian function failure. However, the use of AIs in these women has not been studied extensively, and this could be very relevant because it is difficult to determine to what extent their ovaries still function. If AIs are administered to women with functioning ovaries, the gonadotropin secretion is stimulated, which may result in a vigorous increase of E2 levels that abolishes the expected anticancer effect of AIs and subsequently withholds patients from effective breast cancer therapy.[2,3]

Some small studies showed that the recovery of ovarian function (OFR) occurred in 27% to 39% of women with chemotherapy-induced ovarian function failure receiving AI treatment, months to even years after prior adjuvant chemotherapy.[3,4,5,6] However, these studies were small and patients received various prior systemic treatments.

The DATA trial is a large phase III randomised clinical trial assessing the efficacy of three *vs* six years of adjuvant anastrozole in postmenopausal women with hormone receptor–positive breast cancer who previously received two to three years of adjuvant tamoxifen (ClinicalTrials.gov No. NCT00301457).[7] Patients age 45 years or older with chemotherapy-induced ovarian function failure were also eligible for the DATA trial, provided they had E2 levels within the postmenopausal range within the last three months before random assignment. After the publication of Smith and colleagues, which described OFR during AI use in women with chemotherapy-induced amenorrhea, we recommended monitoring plasma E2 and follicle-stimulating hormone (FSH) levels serially at six monthly intervals during the first 30 months.[4] The current analysis reports on the patients with chemotherapy-induced ovarian function failure and aims to assess the frequency and timing of OFR while receiving AIs after prior tamoxifen. Moreover, we analysed the trend of E2 levels during treatment with AIs in patients who experienced OFR *vs* those who did not.

Methods

Patients and Study Design

In the DATA trial, postmenopausal women with stage I to III hormone receptor–positive invasive early breast cancer were randomly assigned, after two to three years of adjuvant tamoxifen, to three or six years of anastrozole 1 mg once daily (ClinicalTrials.gov No. NCT00301457). Eligibility criteria for the DATA trial were the following: no recurrence at random assignment and postmenopausal status at the time of random assignment according to the following criteria: bilateral ovariectomy irrespective of age, age 55 years or older and natural amenorrhea for one or more years, or between age 45 and 54 years with amenorrhea and E2 levels within the postmenopausal range, confirmed by local postmenopausal laboratory values, assessed within the last three months before random assignment, also applicable for those with chemotherapy-induced ovarian function failure. FSH levels were not considered at this point because all women were using tamoxifen until random assignment, which is known to suppress FSH levels (5,8–10).[5,8,9,10] Local postmenopausal reference values for E2 and FSH were gathered for each participating hospital (n = 76) because the hospitals used various assays to measure the E2 levels. Confirmation in a central laboratory was not available. Trained registration clerks reported the laboratory values and the occurrence of menstrual bleeding on electronic case report forms.

The DATA trial protocol was initially dated per July 3, 2006, and it was amended on January 23, 2007, recommending monitoring plasma E2 and FSH levels serially in patients under the age of 55 at six monthly intervals up to the visit at around 30 months (+/− one month) after random assignment. During evaluation, we noticed that there were some patients older than age 55 years whose E2 and FSH levels had been checked regularly. Therefore, for the current sub-analysis, we selected patients from the DATA trial who were age 57 years or younger and were initially pre-/perimenopausal and who developed chemotherapy-induced ovarian function failure after receiving adjuvant chemotherapy that was still persisting at random assignment with E2 measurements within postmenopausal ranges.[11,12] Patients who underwent an ovariectomy or used a luteinizing hormone-releasing hormone (LHRH) agonist prior to random assignment were not eligible for the current analysis. Lastly, we excluded patients who did not have E2/FSH monitoring during follow-up because without data here on we could not determine whether these patients experienced OFR or not.

Patients provided written informed consent before enrolment. The study was conducted in accordance with the Declaration of Helsinki and the principles of Good Clinical Practice. The study was approved by the Ethics Committee of the Radboud University Medical Centre, Nijmegen, the Netherlands, in agreement with the Dutch law code for medical research on humans.

Study End Points

The primary end point for the current analysis was OFR within 30 months after random assignment. OFR was considered when any of the following events occurred: 1) return of menstrual bleeding with premenopausal E2/FSH levels or 2) premenopausal E2/FSH levels only (according to the local reference values in the participating hospitals). The secondary aim was to analyse the evolution of E2 levels during anastrozole use over time in the women whose ovarian function did and did not recover in the period preceding OFR. Furthermore, we aimed to identify baseline risk factors of OFR considering age, E2 values, body mass index (BMI), type of adjuvant chemotherapy, and duration of tamoxifen.

Statistical Analysis

The cumulative risk for OFR was estimated with the cumulative incidence competing risk (CICR) method.[13] The occurrence of a disease-free survival (DFS) event including (non-)invasive breast cancer recurrences (local, regional, distant), second primary (non-)invasive (breast) cancers other than basal cell or squamous cell carcinoma of the skin and carcinoma in situ of the cervix, and death of any cause hindered the observation of an OFR and were therefore considered a competing risk. The time to recovery was censored at the last E2/FSH monitoring date or at an earlier date if recovery could not be assessed because of prior ovariectomy.

Risk factors of OFR were assessed by Cox regression analysis and included age at random assignment, body mass index (BMI), type of previous (neo-)adjuvant chemotherapy, and duration of previous tamoxifen therapy.[5,6,14] They were presented as hazard ratios (HRs) with 95% confidence intervals (CIs).

For the explorative analyses on the trend in E2 levels, we used a nested case-control approach in which a subset of controls were compared with the OFR patients. Because different hospitals used different tests with a wide range of reference values, we could not use the absolute E2 values. The E2 levels were logarithmic-transformed and analysed in a linear mixed model with random effects for hospital and patient, to take into account the dependency of measurements within the same patient and within the same hospital. Hereby, we compared the E2 levels of the women with and without OFR per hospital to overcome the differences in local reference values between the hospitals. A model with linear trend in time and the interaction of the group with time was analysed. The interaction term reflects the difference in trend in E2. Because we were interested in the development of the E2 levels preceding OFR, we did not consider the high E2 levels at the time of OFR diagnosis and thereafter.

The reported P values are calculated with Wald tests. All statistical tests were two-sided, and a P value of less than .05 was considered statistically significant.

Results

Patients

Of the 1860 patients included in the DATA trial, 841 patients were age 45 to 57 years at random assignment (Figure 1). Of them, 51 had not received chemotherapy, 167 had their last menstrual bleeding more than one year before diagnosis and were considered definitely postmenopausal, 104 underwent a bilateral ovariectomy or used LHRH agonists before inclusion, 166 had no baseline or follow-up E2 measurements available, and 24 patients had premenopausal E2 levels at random assignment. Hence, a total of 329 patients were included in the current analysis.

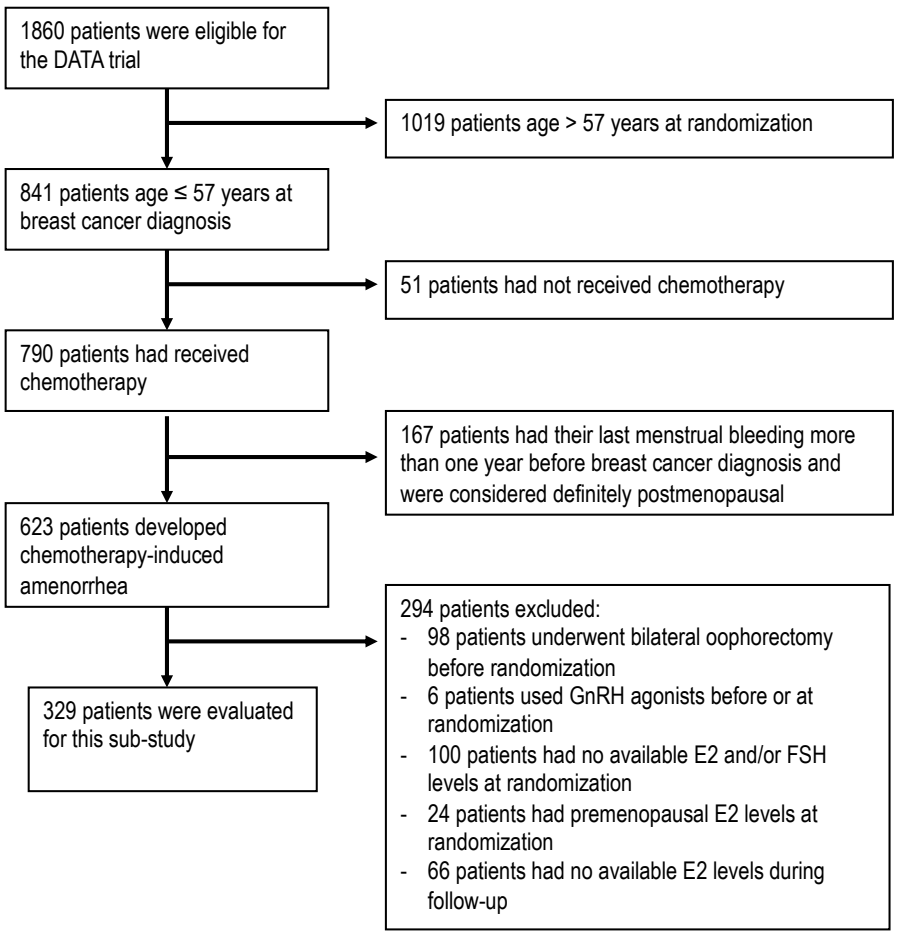


Figure 1. Flow chart about the patient selection in the DATA study. E2 = oestradiol; FSH = follicle-stimulating hormone; GnRH = gonadotropin-releasing hormone; LHRH = luteinizing hormone-releasing hormone.

The baseline characteristics are presented in Table 1. The median age at diagnosis was 48.0 years (range = 41–54 years), and at random assignment the median was 50.0 years (range = 45–57 years). Eighty-three percent had received (neo-)adjuvant chemotherapy consisting of anthracyclines without taxanes prior to study entry (median number of five cycles, range = 3–6 cycles).

Ovarian Function Recovery

Among the 329 included patients, the recovery rate was 8.1% (n = 26) at 12 months after AI initiation; 0.6% had a DFS event. At 30 months, 12.4% (n = 38) had experienced OFR and 4.1% had a DFS event (Figure 2A). The figure implies that this number could have increased even further with longer follow-up. Of the total of 39 patients experiencing OFR, 11 (28.2%) were age 50 years or older at AI initiation. Considering the patients being age 50 years or older (n = 209) at random assignment, the 30-month recovery rate was 5.1%, vs 25.2% for patients younger than age 50 years (Figure 2B). The DFS event rates were 4.7% and 3.0%, respectively, for these age groups. Nineteen out of 39 patients (48.7%) reported vaginal bleeding. Adjuvant endocrine treatment was adjusted in 27 (69.2%) patients: 12 patients received an LHRH agonist combined with AIs, seven underwent an oophorectomy, six switched to tamoxifen (in two patients combined with an LHRH agonist), and two received LHRH agonist monotherapy. In 12 patients, no treatment adjustments were made. In the univariate analysis, age younger than 50 years at AI initiation was the only factor that was related to OFR (HR = 4.85, 95% CI = 2.41 to 9.75, P < .001) (Table 2).

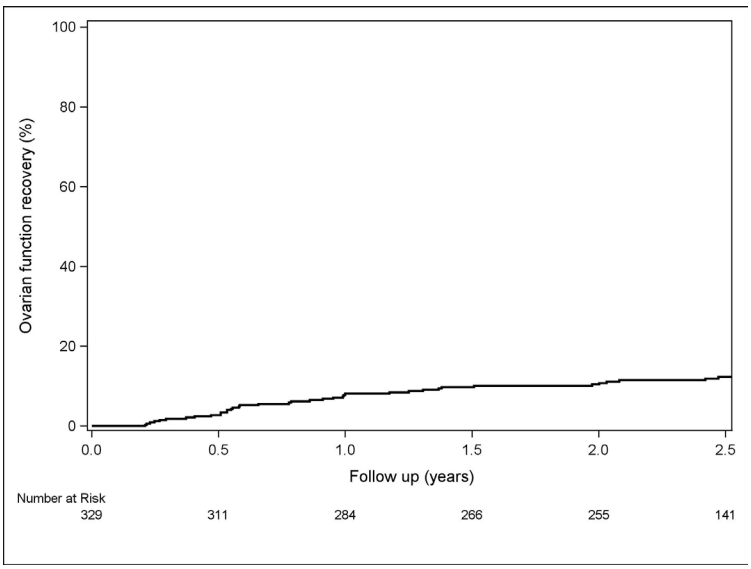
Table 1. Baseline characteristics of the patients with and without ovarian function recovery (OFR) and the total group of patients with chemotherapy-induced ovarian function failure.

Characteristic	
Age at breast cancer diagnosis – median, range	
< 50 years – no. (%)	
50-54 years – no. (%)	
Age at randomisation (AI-initiation) – median, range	
< 50 years – no. (%)	
50-54 years – no. (%)	
Body Mass Index (kg/m^2)	
≤ 24.9	
25.0-29.9	
≥ 30.0	
Missing	
Prior (neo)adjuvant chemotherapy* – no. (%)	
Anthracycline- and taxane-containing regimen	
Anthracycline-containing regimen without taxane	
Taxane-containing regimen without anthracycine	
Regimen without anthracycline or taxane	
Previous duration of tamoxifen – no. (%)	
≤ 2.5 years	
> 2.5 years	
Baseline FSH levels	
Premenopausal according to local reference values	
Postmenopausal according to local reference values	

* All patients received combination chemotherapy including cyclophosphamide. OFR, Ovarian Function Recovery. AI, Aromatase Inhibitor. FSH, Follicle Stimulating Hormone.

	No-OFR (N = 290	OFR (N = 39)	Total chemotherapy-induced ovarian function failure group (N = 329)
	48.0 (41.0 – 54.0)	45.0 (42.0 – 51.0)	48.0 (41.0 – 54.0)
	212 (73.1)	38 (97.4)	250 (76.0)
	78 (26.9)	1 (2.6)	79 (24.0)
	51.0 (45.0 – 57.0)	48.0 (45.0 – 54.0)	50.0 (47.0 – 57.0)
	92 (31.7)	28 (71.8)	120 (36.5)
	198 (68.3)	11 (28.2)	209 (63.5)
	137 (47.3)	23 (59.0)	160 (48.6)
	95 (32.7)	14 (35.9)	109 (33.1)
	46 (15.9)	2 (5.1)	48 (14.6)
	12 (4.1)	0 (0.0)	12 (3.6)
	38 (13.1)	4 (10.3)	42 (12.8)
	239 (82.5)	34 (87.2)	273 (83.0)
	1 (0.3)	0 (0.0)	1 (0.2)
	12 (4.1)	1 (2.5)	13 (4.0)
	201 (69.3)	28 (71.8)	229 (69.6)
	89 (30.7)	11 (28.2)	100 (30.4)
	94 (32.4)	8 (20.5)	102 (31.0)
	196 (67.6)	31 (79.5)	227 (69.0)

A. Total study population



B. Subdivided by age

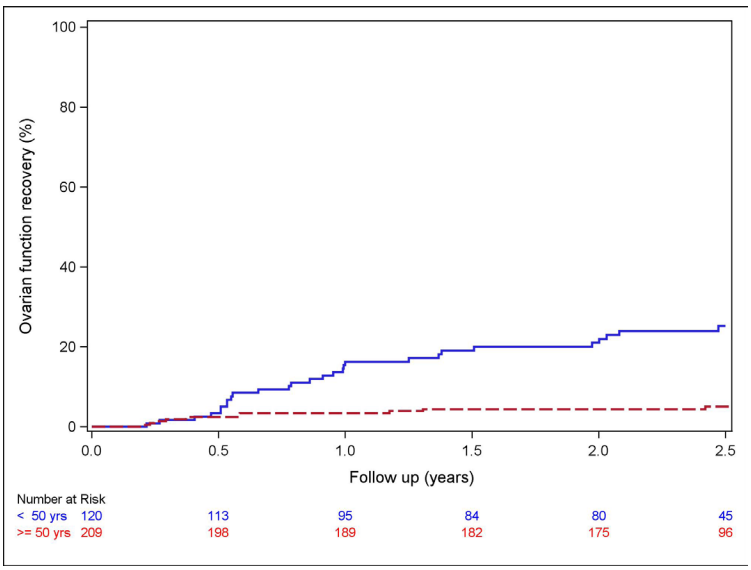


Figure 2. Cumulative percentages of patients experiencing ovarian function recovery. **(A)** Total study population, **(B)** subdivided by age. OFR = ovarian function recovery.

Table 2. Univariate Cox regression analysis on the risk of ovarian function recovery (OFR).

Characteristic	No-OFR, N (%) (N = 290)	OFR, N (%) (N = 39)	HR (95% CI)	*P*-value*
Age at randomisation (AI-initiation)				
< 50 years	92 (31.7)	28 (71.8)	4.85 (2.41 - 9.75)	<0.001
50-57 years	198 (68.3)	11 (28.2)	1.00 (reference)	
Body Mass Index, kg/m^2				
<25.0	137 (49.3)	23 (59.0)	1.00 (reference)	
25.0-29.9	95 (34.2)	14 (35.9)	0.92 (0.47 – 1.79)	0.80
>30.0	46 (16.6)	2 (5.1)	0.28 (0.07 – 1.18)	0.08
Prior (neo)adjuvant chemotherapy				
Anthracycline- and taxane-containing regimen	38 (13.1)	4 (10.3)	1.00 (reference)	
Anthracycline-containing regimen without taxane	239 (82.4)	34 (87.2)	1.24 (0.44 – 3.50)	0.68
Regimen without anthracycline or taxane	12 (4.1)	1 (2.5)	0.66 (0.07 – 5.96)	0.72
Previous duration of tamoxifen				
≤ 2.5 years	201 (69.3)	28 (71.8)	1.00 (reference)	
> 2.5 years	89 (30.7)	11 (28.2)	0.87 (0.43 - 1.75)	0.70

* P-values were calculated by two-sided Wald tests. AI = aromatase inhibitor; CI = confidence interval; HR = hazard ratio.

Serial E2 Measurements

The pattern of E2 levels over time of 38 patients with OFR and 102 patients without OFR from 21 hospitals was analysed. The baseline characteristics of these patients were similar to the overall study population. As previously mentioned, the E2 level by which OFR was diagnosed was not included in the analysis. The relative decrease of E2 over time in patients who developed OFR during follow-up did not statistically significantly differ from the relative decrease in patients without OFR (p= .82) (data not shown). Over the 30 months after AI initiation, the E2 levels decreased statistically significantly by 37.8% (95% CI = 27.4% to 46.7%, P < .001) (Figure 3). However, the E2 level in the OFR group, prior to OFR diagnosis, was statistically significantly higher (difference = 20.6%, 95% CI = 2.0% to 42.7%, p= .03) in comparison with the non-OFR group (Figure 3).

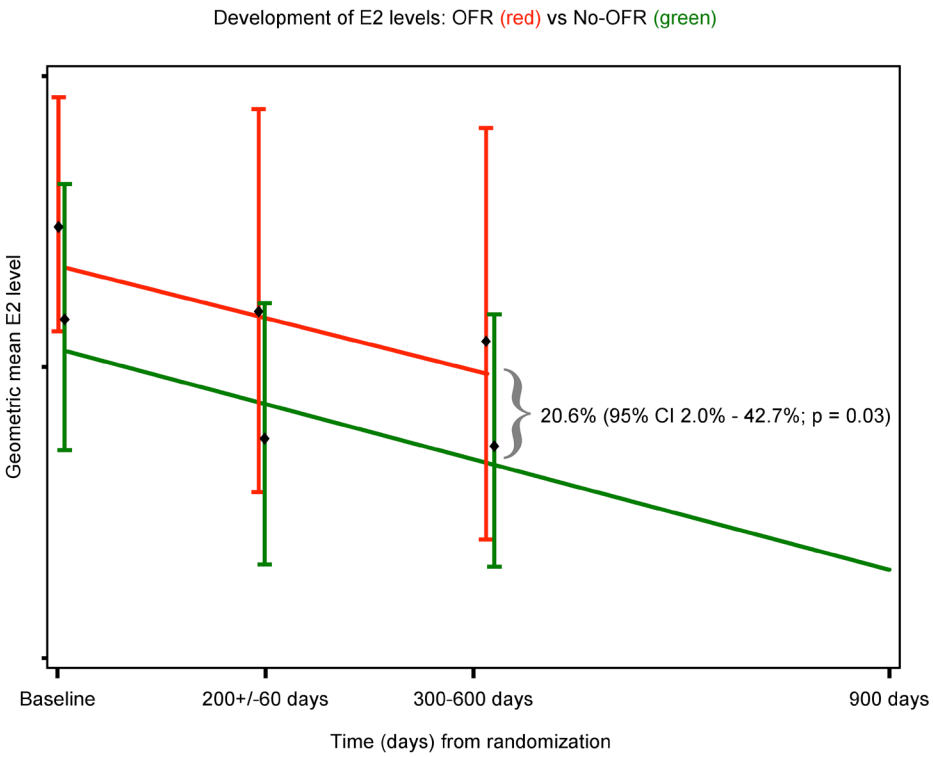


Figure 3. The relative course of the oestradiol (E2) levels over time, within 30 months after the initiation of anastrozole therapy for patients with and without ovarian function recovery (OFR). This figure shows the trend of the geometric mean of the E2 level. The E2 measurements at the time of OFR diagnosis were not included for this analysis. Because various tests with a wide range of reference values for postmenopausal status were used in the included hospitals, no absolute E2 values could be presented. Therefore, we express the E2 trend in time and the difference in E2 levels between the two groups in a relative way and not on an absolute level. The vertical lines represent the 95% confidence intervals. *P*-values were calculated by two-sided Wald tests. CI = confidence interval; E2 = oestradiol; OFR = ovarian function recovery.

Discussion

In the DATA study, a total of 39 out of 329 patients between age 45 and 57 years at random assignment with chemotherapy-induced ovarian function failure experienced OFR while on adjuvant anastrozole after adjuvant tamoxifen. Women under the age of 50 years at AI initiation were at a statistically significantly higher risk of OFR. Yet, of the 39 patients experiencing OFR, 11 (28.2%) were age 50 years or older at AI initiation.

To our knowledge, the current analysis reports on the largest population to date on the occurrence of OFR in a relatively old patient group. Earlier but smaller studies have also reported on OFR during AI use in breast cancer patients with chemotherapy-induced ovarian function failure and reported OFR rates of 27% to 39%.[3,4,5,6] These studies are summarized in Table 3. The outcomes of our study are in line with earlier findings; however, in our study all patients were older than age 45 years at AI initiation, and all received two to three years of prior adjuvant tamoxifen. Moreover, our data underscore that amenorrhea can still be present despite biochemical OFR because only half of the women experiencing OFR in our patient cohort reported menstrual bleeding. Of note, in 12 OFR patients (30.7%), no treatment adjustments were made by the responsible physician. This stresses the need for a guideline on monitoring these patients during AI treatment, a clear definition of OFR, and how treatment should be adjusted in case of OFR.

Monitoring E2 and FSH levels can be challenging because the performances of most E2 assays are poor and diverse tests are used in different laboratories.[15] Additionally, measuring E2 levels in patients receiving steroidal AIs (e.g., exemestane) can be problematic because there is cross-reaction of various metabolites of this drug, even in specialized immunoassays.[16] Guerrero and colleagues showed, however, that different assays when applied to the same patient resulted in a similar incidence of OFR and time to OFR, indicating that one can trust the reference values of the local test.[3] Based on our findings, we suggest monitoring E2 and FSH levels at three-monthly intervals for the first year of AI therapy because OFR occurred in 67% of the patients within the first year, and at six-month intervals during the second and third years of therapy. Furthermore, we suggest as a definition of OFR: “menstrual bleeding confirmed by premenopausal E2/FSH levels or biochemical OFR by premenopausal E2/FSH levels.”

Table 3. Previous studies about ovarian function recovery (OFR) in breast cancer patients with chemotherapy-induced ovarian function failure during adjuvant aromatase inhibitor (AI) treatment. *

First author, year	No. of patients	Age at AI-initiation median (range)	Prior TAM No. (%)	Duration prior TAM
Smith, 2006[4]	45	47 (39-52)	29 (64.4)	1-5 years
Henry, 2013[5]	45	50 (40-56)	28 (62.2)	Unknown
Guerrero, 2013[3]	53	48 (41-55)	53 (100)	Median 2.1 years (Range 1.6-4.3)
Krekow, 2016[6]	177	48 (40-50)	166 (93.8)	Median 18.8 months (Range 2.8-64.5)

CIA, Chemotherapy-Induced Amenorrhea. TAM, Tamoxifen. E2, Oestradiol. FSH, Follicle Stimulating Hormone

***** Of note, we used the term chemotherapy-induced amenorrhea intentionally in this table, since this was the expression used in the references.

In a combined analysis of data from the Tamoxifen and Exemestane Trial (TEXT) and the Suppression of Ovarian Function Trial (SOFT), ovarian function suppression in addition to exemestane resulted in an improved DFS, but not in an overall survival difference.[17,18] However, the results of the SOFT-EST trial,[19] showing that 34.2% of patients had E2 levels above the threshold at least once during 12 months of follow-up, underline the importance of monitoring the extent of ovarian function suppression by gonadotropin-releasing hormone (GnRH) agonists in premenopausal women treated with an AI. In the ABCSG-12 trial, among premenopausal women who received GnRH agonists and either tamoxifen or anastrozole, those who received anastrozole actually had a statistically significantly worse overall survival.[20] The ABCSG investigators hypothesized that the effect might be the result of incomplete E2 level suppression by AIs in overweight women. Therefore, until further results on the survival of these women are known, we would advise performing either a bilateral ovariectomy while continuing an AI or switching to tamoxifen monotherapy.

	Inclusion	Definition OFR used	OFR No. (%)
	CIA > 6 months and post-menopausal E2/ FSH values	Menstrual bleeding and/or premenopausal E2/FSH levels	12 (26.7)
	CIA within 8 weeks of completing chemotherapy, and remained amenorrheic	E2 concentration ≥ 30 pg/ml or return of menses, within 48 weeks of AI-initiation (vaginal spotting only not seen as OFR)	13 (28.9)
	CIA for at least 2 years, and E2 values (by direct assay) in the postmenopausal range (<146 pmol/l)	One of the following events: - Resumption of menses - E2 inconsistent with postmenopausal women on AI (indirect: >8pmol/l; direct: >165 pmol/l) plus premenopausal FSH (<26 IU/l) - Clearly non-postmenopausal E2 (indirect >55 pmol/l; direct >220 pmol/l)	17 (32.1)
	Prior treatment with cyclophospha-mide-based chemotherapy, CIA persisting for > 1 year; and postmenopausal serum E2 levels	Resumption of menses or pre- menopausal E2 levels	67 (37.9)

Moreover, Guerrero and colleagues showed that E2 levels under AI treatment are statistically significantly higher in younger women (mean = 48.1 years, range = 41–55 years) than in women older than age 60 years.[3] We also observed high E2 levels during AI treatment in a substantial number of patients in our study, which may compromise the efficacy of endocrine treatment. However, to what extent the suboptimal E2 suppression influenced breast cancer survival is not known yet. This leads to the more fundamental question of whether a more powerful decrease in E2 levels leads to an improvement in terms of survival. To our understanding, there are few data about the clinical consequences of the extent of E2 reduction during AI treatment. Letrozole has been shown to decrease plasma E2 levels to a greater extent in comparison with anastrozole, although its efficacy in terms of survival has not showed superiority over anastrozole or exemestane.[21,22,23]

In the current study, all patients were treated with tamoxifen for two to three years before they received adjuvant AI treatment. The ovarian response to tamoxifen is not completely understood, and its effect on the incidence of chemotherapy-induced ovarian function failure

is not well defined.[24] Walshe and colleagues reviewed studies focusing on amenorrhea in early breast cancer patients treated with various regimens of adjuvant chemotherapy.[25] Some studies reported no impact of tamoxifen on chemotherapy-induced amenorrhea, whereas larger studies reported higher rates of chemotherapy-induced amenorrhea. A later prospective trial, including 595 patients age 20 to 45 years, showed that adjuvant tamoxifen was less likely associated with monthly menstrual bleeding during the first year following chemotherapy (odds ratio [OR] = 0.50, 95% CI = 0.37 to 0.67).[26] Tamoxifen seemed responsible for the persistence of amenorrhea after adjuvant chemotherapy in 15% of women. A meta-analysis showed that the use of adjuvant tamoxifen statistically significantly increased the incidence of chemotherapy-induced amenorrhea (OR = 1.48, 95% CI = 1.28 to 1.70).[27] The mechanism for this phenomenon remains unclear though. It is thought that tamoxifen has oestrogen-like actions on gonadotropin, which causes a disruption of the hypothalamic ovarian feedback loop, resulting in a decrease in FSH and E2 synthesis.[8,9,10]

Previous studies ascribed the increased probability of OFR in patients with chemotherapy-induced ovarian function failure during AI treatment to the increased secretion of gonadotropin caused by the reduced feedback of oestrogen to the hypothalamus and pituitary.[2,3,4,5,6,28] This seems a logical explanation because AIs additionally proved to be effective in inducing ovulation in women with polycystic ovarian syndrome.[28,29] Nevertheless, OFR could theoretically also be triggered by the discontinuation of tamoxifen itself, rather than solely by AI use. It is thought that by discontinuing tamoxifen, the negative feedback on the hypothalamic ovarian feedback loop diminishes and consequently OFR is more likely to occur.

An important limitation of the current analysis was that the E2 measurements were not standardized between the different hospitals participating in this study. Different assays were used, with different reference values, which made it difficult to compare the measurements. Therefore, the E2 measurements in OFR patients were compared with those in no-OFR patients from the same hospital in a linear mixed model; however, it was not possible to give a recommendation about absolute E2 cut-off values for OFR. Nevertheless, others have showed that different assays when applied to the same patient resulted in a similar incidence of OFR and time to OFR, indicating that one can trust the reference values of the local test.[3]

The results of this study show that we need to be aware of the risk of OFR during AI treatment in early breast cancer patients with chemotherapy-induced ovarian function failure, even in women older than age 45 years. Furthermore, women with (*vs* without) OFR had statistically significantly higher E2 levels during AI treatment, which has potential consequences regarding the optimal efficacy. Overall, AIs should be used with caution in women with chemotherapy-induced ovarian function failure. When considering AIs in these women, the hormone levels should be monitored closely.

Funding

Funded by AstraZeneca NL.

Notes

The funder had no role in the design of the study; the collection, analysis, or interpretation of the data; the writing of the manuscript; or the decision to submit the manuscript for publication. We thank Wim A. J. G. Lemmens for his assistance with performing the statistical analyses.

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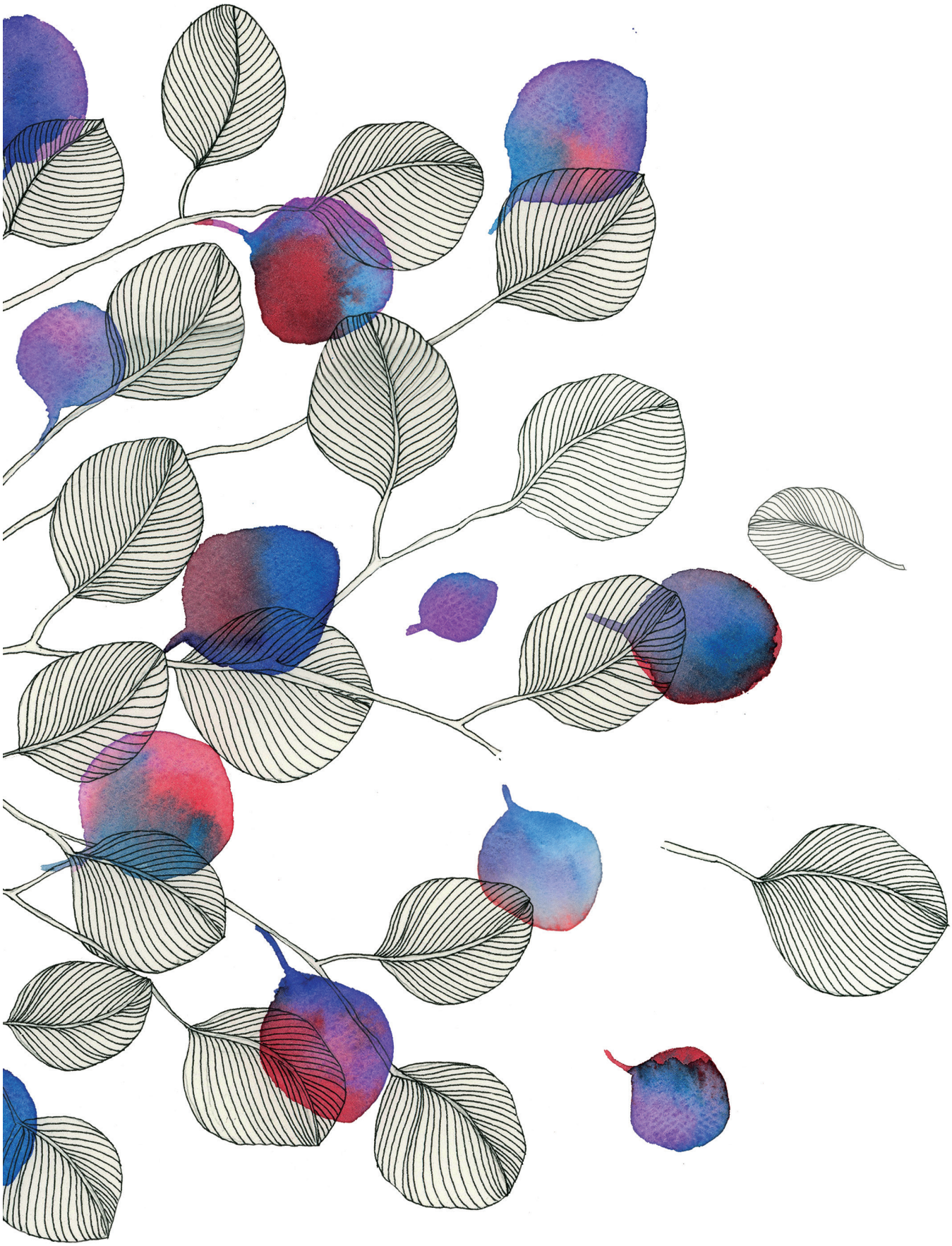

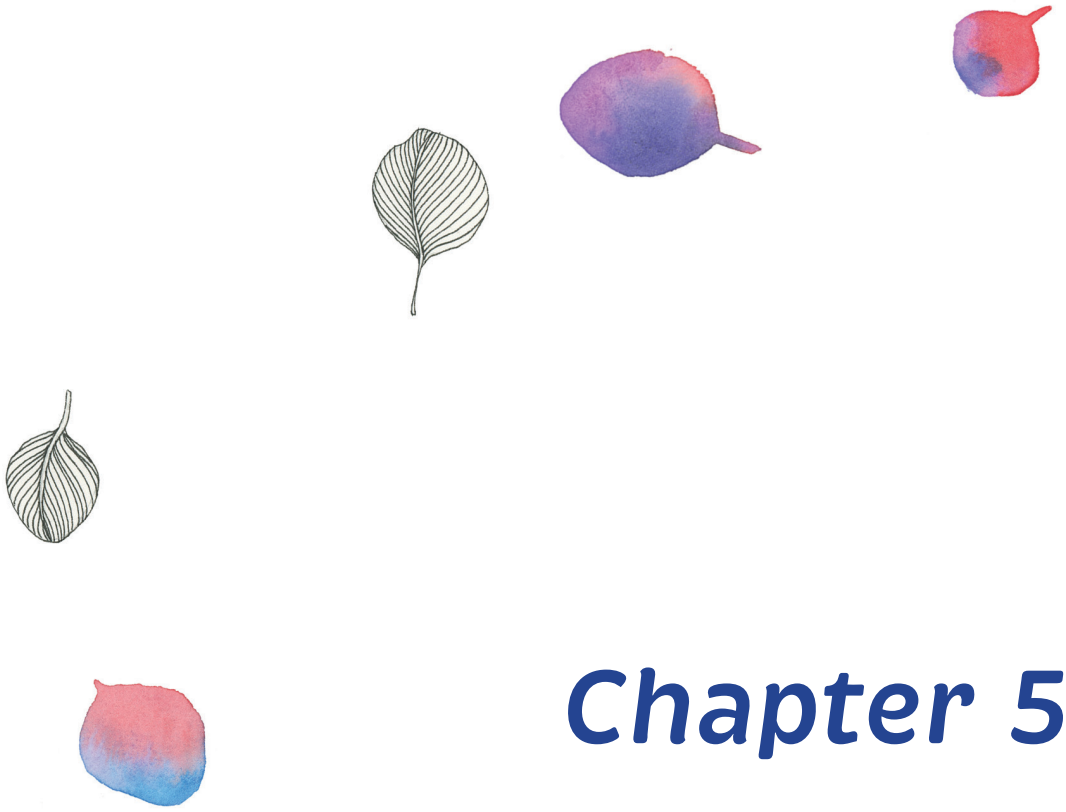

Chapter 5

Efficacy of Anastrozole after Tamoxifen in Early Breast Cancer Patients with Chemotherapy-Induced Ovarian Function Failure

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International Journal of Cancer 2019;145:274-83.

Abstract

The DATA study (NCT00301457) compared 6 and 3 years of anastrozole in postmenopausal women with hormone receptor-positive early breast cancer after 2–3 years of tamoxifen. Patients with chemotherapy-induced ovarian function failure (CIOFF) were also eligible, but could be at risk of ovarian function recovery (OFR). The current analysis compared the survival of women with CIOFF with definitely postmenopausal women and examined the influence of OFR on survival. Therefore, we selected patients from the DATA study aged 45–57 years at randomisation who had received (neo)adjuvant chemotherapy. They were classified by reversibility of postmenopausal status: possibly reversible in case of CIOFF (n = 395) *vs* definitely postmenopausal (n = 261). The former were monitored by E2 measurements for OFR. The occurrence of OFR was incorporated as a time-dependent covariate in a Cox-regression model for calculating the hazard ratio (HR). We used the landmark method to calculate residual 5-year survival rates. When comparing CIOFF women with definitely postmenopausal women, the survival was not different. Among CIOFF women with available E2 follow-up values (n = 329), experiencing OFR (n = 39) had an unfavourable impact on distant recurrence-free survival (HR 2.27 [95% confidence interval [CI] 0.98–5.25; p= 0.05] and overall survival (HR 2.61 [95% CI 1.11–6.13; p= 0.03]). After adjusting for tumour features, the HRs became 2.11 (95% CI 0.89–5.02; p= 0.09) and 2.24 (95% CI 0.92–5.45; p= 0.07), respectively. The residual 5-year rate for distant recurrence-free survival was 76.9% for women with OFR and 92.1% for women without OFR, and for 5-year overall survival 80.8% and 94.4%, respectively. Women with CIOFF receiving anastrozole may be at increased risk of disease recurrence if experiencing OFR.

Introduction

Aromatase inhibitors (AIs) are used as adjuvant therapy for postmenopausal breast cancer patients with hormone receptor-positive breast cancer.[1] By inhibiting the aromatase enzyme, they prevent the conversion from androgens to oestradiol (E2) leading to E2 deprivation in postmenopausal women and thereby possibly preventing tumour cell growth if still present. In premenopausal women, AIs stimulate the gonadotropin secretion by inducing feedback stimulation of the hypothalamus–pituitary–ovary axis, resulting in a strong rise of the E2 level.[2] Consequently, AI-monotherapy is contraindicated in premenopausal breast cancer patients.[3,4] However, in postmenopausal women, AIs have been shown to be more efficient than tamoxifen in preventing disease recurrence and improving survival.[5]

In common practice, the menopausal status is not always easy to determine, causing AIs to be used in patients with chemotherapy-induced ovarian function failure (CIOFF) while little is known about the efficacy of AIs in this subgroup of women who are at risk of ovarian function recovery (OFR).[4,6,7]

The phase III DATA study assesses the impact of different durations of adjuvant anastrozole on survival after prior tamoxifen in postmenopausal women with hormone receptor-positive early breast cancer.[8] Women with CIOFF were also eligible. A recent analysis of the DATA study showed biochemical OFR in 12.4% of women with CIOFF at 30 months after randomisation.[9] Furthermore, the E2 levels of these OFR patients were significantly higher during anastrozole treatment, even before developing OFR, in comparison to those who remained postmenopausal.[9] As a consequence, patients who experienced OFR may have received inefficient anticancer treatment and thereby a worse outcome. Therefore, in the current sub-study, we analysed the survival of women with CIOFF receiving adjuvant treatment with anastrozole for early breast cancer, and the impact of OFR on survival.

Methods

Study design and participants

This was an unplanned sub-study from the open-label multicentre phase III randomised DATA trial, investigating the efficacy and safety of 6 *vs* 3 years of adjuvant anastrozole after 2–3 years of tamoxifen in postmenopausal, hormone receptor-positive early breast cancer patients.[8] The randomisation procedure took place after 2–3 years of tamoxifen and before the initiation of adjuvant anastrozole. The study was conducted in the Netherlands by the Dutch Breast Cancer Research Group (BOOG) and included 1,860 eligible patients from 2006 until 2009. The protocol is available online (NCT00301457).

For the current sub-study, we identified patients aged 45–57 years at randomisation who had received (neo)adjuvant chemotherapy. The patient selection was described into more detail in an earlier publication.[9] Women who used gonadotropin releasing hormone (GnRH) agonists before randomisation or had no postmenopausal E2 or FSH levels at randomisation were excluded. We classified the patients in two main groups regardless of anastrozole assignment: (*i*) patients who had their last menstrual bleeding more than 1 year before chemotherapy administration or underwent a bilateral ovariectomy before randomisation (definitely postmenopausal), and (*ii*) patients with CIOFF. Patients were considered having CIOFF if they had their last menstrual bleeding less than 1 year before administration of chemotherapy and had postmenopausal E2 and FSH levels at randomisation according to local reference values in the participating hospitals. CIOFF women of whom follow-up information on E2 levels was available were followed for the occurrence of OFR. OFR was considered if any of the following events occurred: (*i*) return of menstrual bleeding and/or (*ii*) E2 levels not corresponding with postmenopausal levels according to local reference values. These E2 levels were monitored at 6-monthly intervals for 30 months after randomisation. The physicians in the local hospitals decided on any treatment adjustments in case OFR was observed, either by adding ovarian function suppression (GnRH agonist, ovariectomy) or switching to tamoxifen. OFR and menstrual bleeding were reported as adverse events.

Objectives

The primary objective of our study was to compare disease-free survival, distant recurrence-free survival and overall survival between patients with CIOFF and those definitely postmenopausal. Second, we aimed to analyse the impact of OFR on survival in CIOFF patients with available follow-up E2 measurements. Events ending a period of disease-free survival included (non) invasive breast cancer recurrences (local, regional and distant), second primary (non)invasive (breast) cancer other than basal-cell or squamous-cell carcinoma of the skin or carcinoma *in situ* of the cervix and death of any cause.[10] Events ending a period of distant recurrence-free survival were distant recurrence and death due to any cause.[10] Overall survival was defined as the interval between randomisation and death from any cause.[10]

Statistical analysis

Survival curves were estimated with the Kaplan-Meier method in which time was censored at the date of last follow-up. We compared the survival of CIOFF patients with definitely postmenopausal women by using the log-rank test. The 5-year survival rates were calculated starting at randomisation. About 42% of the women included in the DATA study were aged 60 years and above.[8] Of note, to overcome the influence of age (and its associated comorbidities) on survival in the analyses, we selected only those definitely postmenopausal patients who were within the same range of age (45–57 years) as the women with CIOFF. For the second research objective, we examined the influence of OFR, occurring at any time during the 30 months at which the E2 level was monitored, on survival in CIOFF women with a Cox proportional hazards model for calculating the hazard ratio (HR), with OFR as a time-dependent covariate. In addition, for graphical representation, the landmark method was used to assess the survival after a particular point in time, the so-called residual survival.[11] As we were interested to learn about the impact of OFR on survival, we chose 12 months after randomisation as a landmark because the risk on OFR is highest in the first year after the start of anastrozole. The survival of patients who experienced OFR in the first year was plotted together with the survival of those not experiencing OFR in the first year. Consequently, patients who already had a survival event at that point in time were excluded for the residual survival curves. Those still at risk for an event after 12 months were included in the Kaplan-Meier survival curves and the 5-year residual survival rates. Cox proportional hazards regression analysis was used to estimate HRs and 95% confidence intervals (CIs). Because of the inherently strong biological association between age and OFR, we decided not to correct our survival analyses for age to avoid multicollinearity. The worse prognosis of tumours at a younger age will be reflected in more aggressive tumour features (tumour size, nodal status, tumour grade and hormone receptor status), for which we adjusted the HRs in a multivariable analysis. The reported *p*-values were calculated with Wald tests. All reported *p*-values are two-sided and a *p*-value ≤0.05 was considered statistically significant. All analyses were performed using SAS version 9.2.

Results

Patient characteristics

Of the 1860 randomised DATA patients, 790 were 45–57 years at randomisation and had received (neo)adjuvant chemotherapy. Of these, 261 women were considered definitely postmenopausal and 395 were considered to have CIOFF, of whom 39 experienced OFR and 290 did not. Of 66 patients, it remained unknown whether they experienced OFR as no follow-up E2 levels were available. Another 134 patients were not eligible for this sub-study because they used GnRH agonists before randomisation or had no postmenopausal E2 or FSH levels available at randomisation. Figure 1 presents the flow chart on the patient selection.

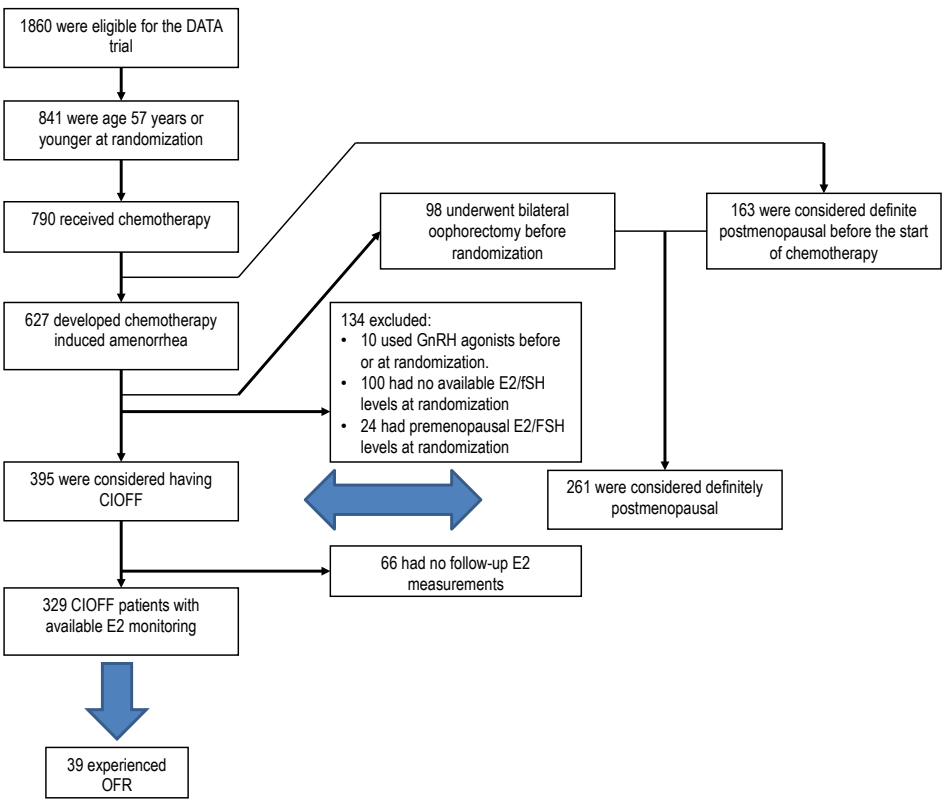


Figure 1. Flowchart of the patient selection out of the DATA study. CIOFF, chemotherapy-induced ovarian function failure.

Table 1 presents the baseline characteristics of the groups. Between the CIOFF and definitely postmenopausal groups there were clinically small but statistically significant differences regarding nodal involvement (p= 0.02), histological grade (p= 0.01), oestrogen/progesterone receptor status (p= 0.04) and body mass index (p= 0.01). The median age of both groups was 51.0 years (range, 45.0–57.0).

Among the patients with CIOFF, the 30-month rate of OFR was 5.1% for patients age 50 and above (n = 209), *vs* 25.2% for patients younger than age 50 (n = 120), as reported previously.[9] Patients with OFR (n = 39) were younger than those without OFR (median age 48.0 years [range, 45.0–54.0] *vs* 51.0 years [range, 45.0–57.0]) ($p \leq 0.0001$). Other than age, there were no differences between the OFR and no-OFR groups. Of the 39 OFR patients, 19 (48.7%) reported menstrual bleeding.[9] In 27 (69.2%) patients experiencing OFR, adjuvant endocrine treatment was adjusted by adding a GnRH agonist (with or without an AI) (n = 14), switching to tamoxifen (n = 6) or performing a bilateral ovariectomy (n = 7), as previously reported.[9] In all OFR patients with a breast cancer recurrence, the endocrine treatment had been adjusted.

CIOFF vs definitely postmenopausal patients

After a median follow-up of 7.3 years after randomisation (P_5 = 5.9, P_{95} = 9.0), the 5-year rate for disease-free survival was not statistically significantly different between women with CIOFF and definitely postmenopausal women (86.8% and 85.4%, respectively; HR 0.79, 95% CI 0.55–1.12; p= 0.18). The 5-year rates of distant recurrence-free survival (90.6% *vs* 88.8%, HR 0.77, 95% CI 0.50–1.18; p= 0.22) and overall survival (93.4% *vs* 90.7%, HR 0.87, 95% CI 0.54–1.41; p= 0.58) were also not statistically significantly different. Table 2 presents the incidence of the efficacy endpoint events. The survival curves are presented in Figure 2. After adjustment for tumour size, nodal status, tumour grade and hormone receptor status, the HRs changed only marginally (Table 3).

Table 1. Baseline characteristics of the patients included in this study.

	CIOFF total group
	***N* = 395**
Age at randomisation (median, range)	51.0 (45.0 – 57.0)
45-50 years – no. (%)	134 (33.9)
³ 50 years – no. (%)	261 (66.1)
Tumour status – no. (%)	
pT1	165 (41.8)
pT2	181 (45.8)
pT3/4	49 (12.4)
Nodal status – no. (%)	
pN0 / pN0(i+)	102 (25.8)
pN1	230 (58.2)
pN2 / pN3	63 (16.0)
Histological grade – no. (%)	
Grade I	72 (18.2)
Grade II	213 (53.9)
Grade III	100 (25.3)
Unknown	10 (2.5)
Hormone receptor status – no. (%)	
ER-positive / PgR-positive	323 (81.8)
ER-positive / PgR-negative/unknown	63 (16.0)
ER-negative / PgR-positive	9 (2.3)
HER2 status – no. (%)	
Negative	382 (96.7)
Positive	10 (2.5)
Unknown	3 (0.8)
Type of breast surgery – no. (%)	
Breast-conserving surgery	188 (47.6)
Mastectomy	207 (52.4)
Type of axillary surgery – no. (%)	
Sentinel node only	129 (32.7)
Sentinel node plus axillary lymph node dissection	187 (47.3)
Axillary lymph node dissection	78 (19.7)
None	1 (0.3)

Definitely postmenopausal	*CIOFF SUBGROUPS*	
	CIOFF with OFR	**CIOFF without OFR**
***N* = 261**	***N* = 39**	***N* = 290**
51.0 (45.0 – 57.0)	48.0 (45.0 – 54.0)	51.0 (45.0 – 57.0)
89 (34.1)	28 (71.8)	92 (31.7)
172 (65.9)	11 (28.2)	198 (68.3)
106 (40.6)	15 (38.5)	122 (42.1)
129 (49.4)	20 (51.3)	136 (46.9)
26 (10.0)	4 (10.3)	32 (11.0)
94 (36.0)	13 (33.3)	76 (26.2)
136 (52.1)	21 (53.9)	171 (59.0)
31 (11.9)	5 (12.8)	43 (14.8)
33 (12.6)	4 (10.3)	55 (19.0)
124 (47.5)	19 (48.7)	157 (54.1)
96 (36.8)	15 (38.5)	72 (24.8)
8 (3.1)	1 (2.6)	6 (2.1)
192 (73.6)	32 (82.1)	241 (83.1)
59 (22.6)	5 (12.8)	43 (14.8)
10 (3.8)	2 (5.1)	6 (2.1)
257 (98.5)	39 (100)	279 (96.2)
4 (1.5)	0 (0.0)	8 (2.8)
0 (0.0)	0 (0.0)	3 (1.0)
131 (50.2)	19 (48.7)	140 (48.3)
130 (49.8)	20 (51.3)	150 (51.7)
80 (30.7)	9 (23.1)	89 (30.7)
115 (44.1)	21 (53.6)	141 (48.6)
63 (24.1)	9 (23.1)	59 (20.3)
3 (1.1)	0 (0.0)	1 (0.3)

Table 1. Continued.

	CIOFF total group
	***N* = 395**
Radiotherapy – no. (%)	
Local and regional lymph nodes	167 (42.3)
Local	103 (26.1)
Regional	6 (1.5)
None/unknown	119 (30.1)
Prior (neo)adjuvant chemotherapy – no. (%)	
Anthracycline- and taxane-containing regimen	47 (11.9)
Anthracycline-containing regimen without taxane	332 (84.1)
Taxane without antracycline	2 (0.5)
Regimen without anthracycline or taxane	2 (0.5)
Prior HER2-targeted therapy – no. (%)	
Yes	14 (3.5)
Previous duration of tamoxifen – no. (%)	
≤ 2.5 years	276 (69.9)
>2.5 years	119 (30.1)
Body Mass Index (kg/m^2) (median, range)	24.9 (14.5–52.0)
<25.0	194 (49.1)
25.0-29.9	127 (32.2)
>30.0	60 (15.2)
Missing	14 (3.5)

Definitely postmenopausal	*CIOFF SUBGROUPS*	
	CIOFF with OFR	**CIOFF without OFR**
***N* = 261**	***N* = 39**	***N* = 290**
103 (39.5)	19 (48.7)	113 (39.0)
76 (29.1)	7 (17.9)	79 (27.2)
4 (1.5)	0 (0.0)	5 (1.7)
78 (29.9)	13 (33.3)	93 (32.1)
27 (10.4)	4 (10.3)	38 (13.1)
230 (88.1)	34 (87.2)	239 (82.4)
1 (0.4)	0 (0.0)	1 (0.3)
3 (1.2)	1 (2.6)	12 (4.1)
2 (0.7)	0 (0.0)	2 (0.7)
183 (70.1)	28 (71.8)	201 (69.3)
78 (30.0)	11 (28.2)	89 (30.7)
26.1 (19.1 – 60.2)	24.0 (19.1 – 36.1)	25.1 (1.45 – 52.0)
101 (38.7)	23 (59.0)	137 (47.2)
104 (39.8)	14 (35.9)	95 (32.8)
49 (18.8)	2 (5.1)	46 (15.9)
7 (2.7)	0 (0.0)	12 (4.1)

Table 2. Incidence of the efficacy end-point events.

	CIOFF
	***N* = 395**
Primary end point n (%)	
Disease-free survival event *	85
Local recurrence	3 (3.5)
Regional recurrence	9 (10.6)
Distant recurrence **	38 (44.7)
Visceral	20 (23.5)
Bone	24 (28.2)
Soft tissue	3 (3.5)
Other	5 (5.9)
Second (non-invasive) breast cancer	11 (12.9)
Ipsilateral invasive breast cancer	1 (1.2)
Ipsilateral DCIS	0 (0.0)
Contralateral invasive breast cancer	7 (8.2)
Contralateral DCIS	3 (3.5)
Second, non-breast cancer	17 (20.0)
Death without prior breast cancer event	7 (8.2)
Secondary end points n	
Distant recurrence-free survival event§	47
Death from any cause	40

Definitely Postmenopausal	*CIOFF SUBGROUPS*	
	CIOFF with OFR	CIOFF without OFR
***N* = 261**	***N* = 39**	***N* = 290**
71	11	51
9 (12.7)	1 (9.1)	2 (3.9)
9 (12.7)	2 (18.2)	5 (9.8)
25 (35.2)	6 (54.5)	23 (45.1)
11 (15.5)	4 (36.4)	12 (23.5)
15 (21.1)	4 (36.4)	14 (27.5)
1 (1.4)	1 (9.1)	2 (3.9)
2 (2.8)	0 (0.0)	3 (5.9)
9 (12.7)	1 (9.1)	8 (15.7)
1 (1.4)	0 (0.0)	1 (2.0)
2 (2.8)	0 (0.0)	0 (0.0)
4 (5.6)	0 (0.0)	5 (9.8)
2 (2.8)	1 (9.1)	2 (3.9)
11 (15.5)	0 (0.0)	11 (21.6)
8 (11.3)	1 (9.1)	2 (3.9)
39	7	26
29	7	21

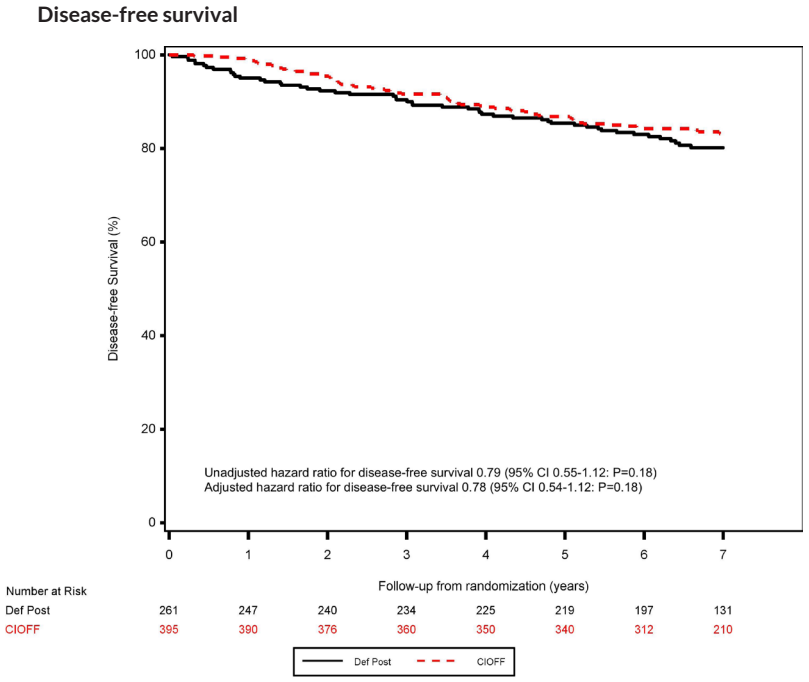
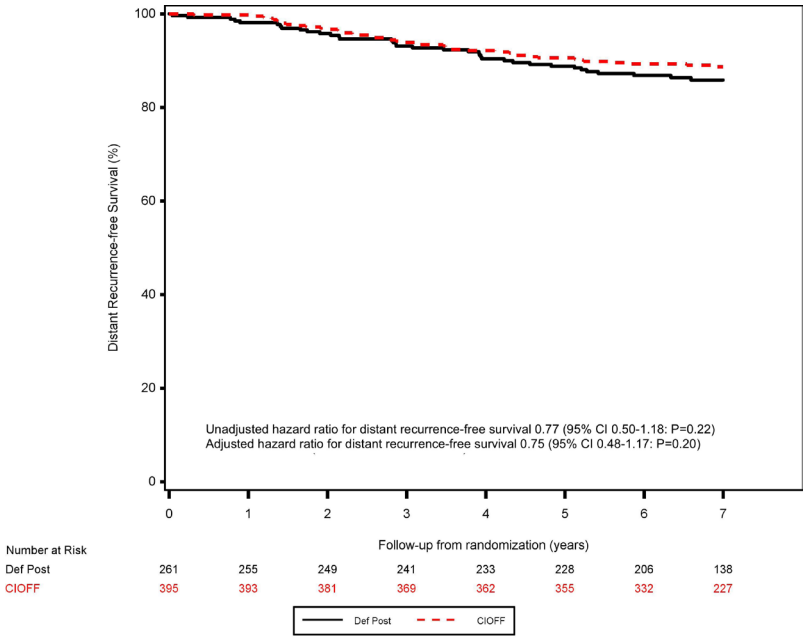


Figure 2. Survival curves for patients with chemotherapy-induced ovarian function failure (CIOFF) *vs* definitely postmenopausal women. (*a*) Disease-free survival, (*b*) distant recurrence-free survival and (*c*) overall survival. The adjusted hazard ratios were corrected for tumour size, nodal status, tumour grade, and hormone receptor status.

B. **Distant recurrence-free survival**



C. **Overall survival**

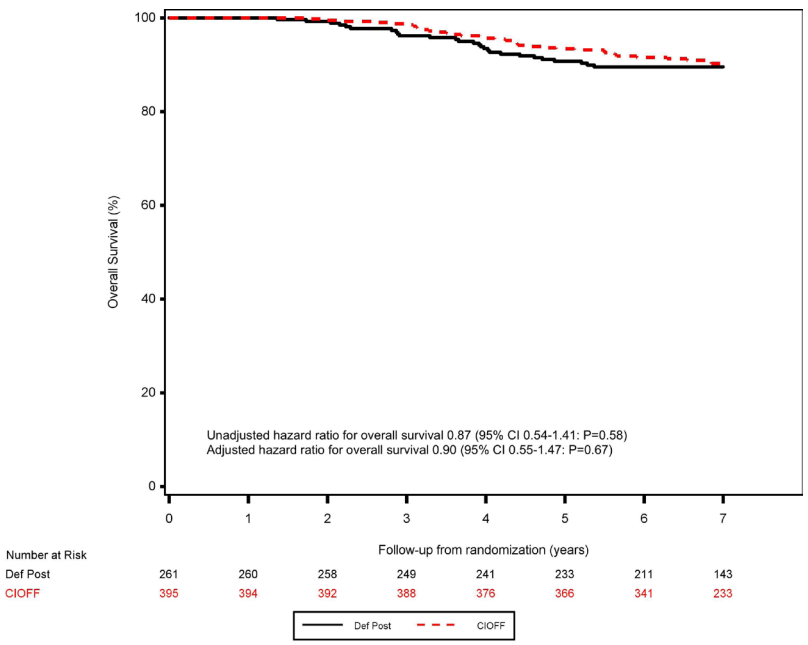


Figure 2. Continued.

Table 3. A. The Hazard ratio on an event when patients with CIOFF (n=395) were compared with definitely postmenopausal women (n=261). **B.** The hazard ratio on an event after OFR had been observed (n=39) amongst the women with CIOFF.

A	**CIOFF vs definitely postmenopausal**	
	Unadjusted hazard ratio	
	Hazard ratio after adjusting for tumour size, nodal status, tumour grade, and hormone receptor status	
B	**Impact of OFR on survival amongst women with CIOFF**	
	Unadjusted hazard ratio	
	Hazard ratio after adjusting for tumour size, nodal status, tumour grade, and hormone receptor status	

Abbreviations: CIOFF, chemotherapy-induced ovarian function failure; OFR, ovarian function recovery; 95% CI, 95% confidence interval.

Impact of OFR on survival

The disease-free survival for patients experiencing OFR (*n* = 39) was not different in comparison to patients without OFR (*n* = 290) (HR 1.45, 95% CI 0.68–3.11; *p*= 0.34). However, experiencing OFR was associated with an increased risk of distant recurrence (HR 2.27, 95% CI 0.98–5.25; *p*= 0.05) and a reduced overall survival (HR 2.61, 95% CI 1.11–6.13; *p*= 0.03). The HR and 95% CI after adjusting for tumour size, nodal status, tumour grade and hormone receptor status changed only slightly but became statistically nonsignificant (HR 2.11 [95% CI 0.89–5.02; *p*= 0.09] and 2.24 [95% CI 0.92–5.45; *p*= 0.07], respectively) (Table 3). The survival curves are presented in Figure 3.

The 5-year residual survival rates for patients experiencing OFR in the first year after randomisation (*n* = 26) in comparison to women without OFR were for disease-free survival 73.1% *vs* 87.4%, for distant recurrence-free survival 76.9% *vs* 92.1% and for overall survival 80.8% and 94.4%. The Kaplan-Meier curves for these outcome measures after a landmark of 1 year are presented in Figure 2.

	Disease-free survival			Distant recurrence-free survival			Overall survival		
	HR	**95% CI**	***P*-value**	**HR**	**95% CI**	***P*-value**	**HR**	**95% CI**	***P*-value**
	0.79	0.55-1.12	0.18	0.77	0.50-1.18	0.22	0.87	0.54-1.41	0.58
	0.78	0.54-1.12	0.18	0.75	0.48-1.17	0.20	0.90	0.55-1.47	0.67
	1.45	0.68-3.11	0.34	2.27	0.98-5.25	0.05	2.61	1.11-6.13	0.03
	1.33	0.61-2.90	0.48	2.11	0.89-5.02	0.09	2.24	0.92-5.45	0.07

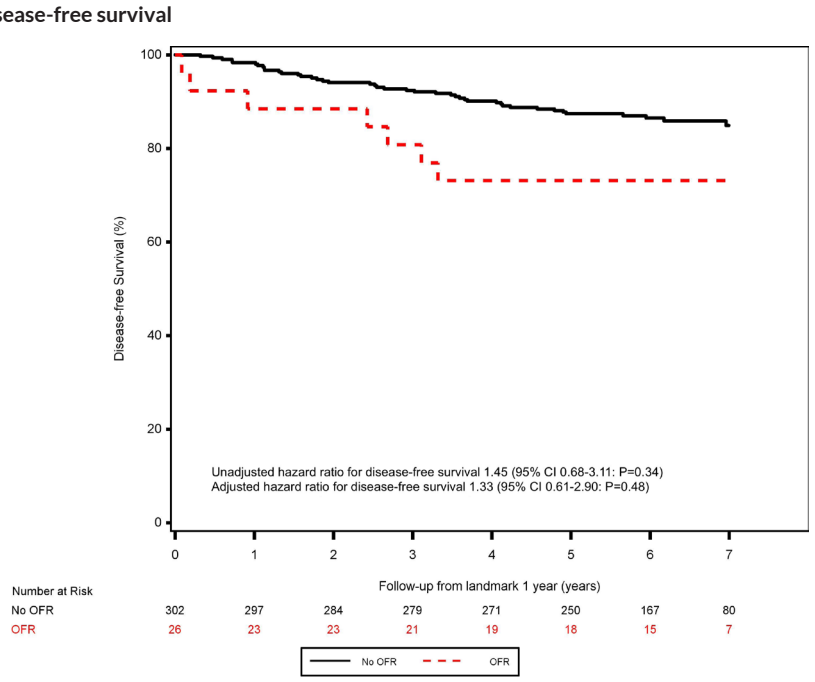
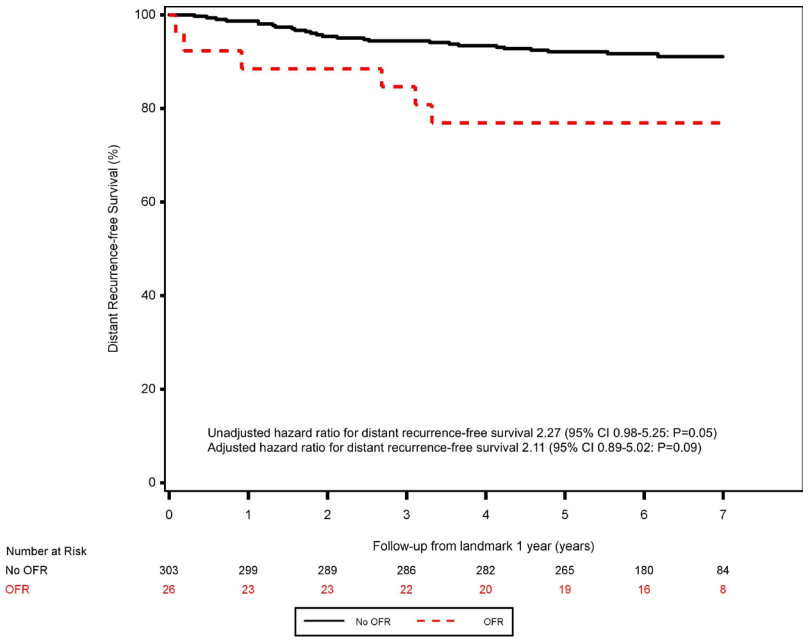


Figure 3. Residual survival curves for chemotherapy-induced ovarian function failure (CIOFF) patients experiencing ovarian function recovery (OFR) in the first year after randomisation *vs* CIOFF patients who did not experience OFR. (*a*) Disease-free survival, (*b*) distant recurrence-free survival, and (*c*) overall survival. These panels show the residual survival curves from the 12-month landmark analyses of the effect of OFR on survival. The adjusted hazard ratios were corrected for tumour size, nodal status, tumour grade, and hormone receptor status.

B. Distant recurrence-free survival



C. Overall survival

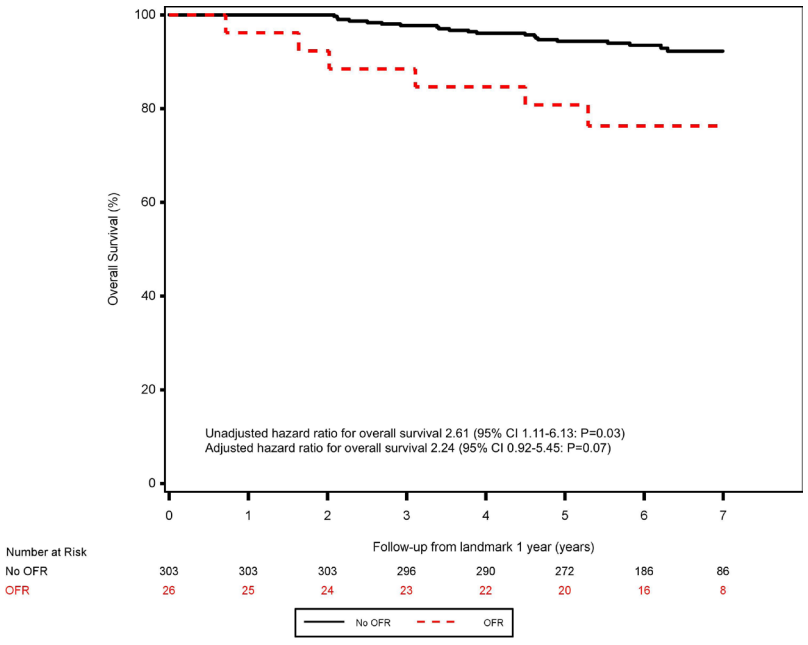


Figure 3. Continued.

Discussion

This is the first study in a large study population of 329 hormone receptor-positive early breast cancer patients with CIOFF showing that experiencing OFR during treatment with adjuvant anastrozole was associated with an increased risk of distant disease-recurrence and a reduced overall survival. The negative impact of OFR on breast cancer survival during adjuvant anastrozole treatment was observed despite regular E2 monitoring at 6-monthly intervals and adjusting endocrine treatment at OFR detection.

So far, only one other study reported on the impact of OFR in women using AIs.[4] In that study, 17 out of 53 (32%) patients with chemotherapy-induced amenorrhea developed OFR during exemestane therapy after prior tamoxifen. At detection of OFR, exemestane was replaced by tamoxifen. Despite treatment adjustment, OFR resulted in a worse disease-free survival (HR 9.3, 95% CI 3.3–48.0; p= 0.04) compared to the women without OFR. A possible explanation for these findings and those of our study is the existence of an increased E2 level before OFR detection and treatment adjustment. In our study this period was maximally 6 months. It is generally advised to monitor E2 levels during AI therapy every 3 months for at least 2 years.[12] Nevertheless, we believe our results show that strict monitoring is not safe either.

A meta-analysis of the Early Breast Cancer Trialists' Collaborative Group (EBCTCG) showed that the administration of an LHRH-agonist as adjuvant treatment in addition to chemotherapy, with or without tamoxifen, reduced the risk of breast cancer recurrence by 12.7% (95% CI 2.4–21.9; p= 0.02), death after recurrence by 15.1% (95% CI 1.8–26.7; p= 0.03) and overall survival by 13.6% (95% CI 0.6–24.9; p= 0.04).[13] In the NSABP-B30 study, concerning women with oestrogen receptor-positive breast cancer receiving tamoxifen as adjuvant endocrine treatment, those with chemotherapy-induced amenorrhea for at least 6 months had a better disease-free survival (HR 0.51, p < 0.001) and overall survival (HR 0.52, p= 0.002) in comparison to women who did not experience amenorrhea or regained their menstrual cycles within 6 months.[14,15] The Suppression of Ovarian Function Trial (SOFT) also showed an improved rate of disease-free survival and overall survival when adding ovarian function suppression to tamoxifen as compared to tamoxifen alone in premenopausal women who were at sufficient risk for recurrence to warrant adjuvant chemotherapy.[16] In our opinion, these results demonstrate that ovarian function suppression improves breast cancer outcome of women with hormone receptor-positive breast cancer treated with tamoxifen. Hence, a dual endocrine treatment is more effective than a single one.

However, a totally different situation exists for the use of AIs. Because of its working mechanism, absence of ovarian function, either naturally by postmenopausal status or by ovarian function suppression, is a pivotal condition for AIs to be effective. Therefore, if AIs are

used in premenopausal patients, these two treatment modalities should always be combined. The logical next question is whether in the presence of ovarian function suppression, AIs are more effective than tamoxifen in women with ER-positive early breast cancer who were initially premenopausal.

In a combined analysis of the SOFT and Tamoxifen and Exemestane Trial (TEXT),[16] administration of exemestane plus ovarian suppression resulted in a statistically significantly improved disease-free survival when compared to tamoxifen monotherapy (HR 0.65, 95% CI 0.35–0.81) or the combination tamoxifen/GnRH agonist (HR 0.77, 95% CI 0.67–0.90) after a median follow-up of 8 years. However, the combined treatment with exemestane/GnRH agonist did not result in an improved overall survival (HR 0.79, 95% CI 0.57–1.09) when compared to tamoxifen monotherapy, neither when compared to the combination tamoxifen/GnRH agonist (HR 0.98, 95% CI 0.79–1.22).[16] The ABCSG-12 trial, studying the efficacy of anastrozole/GnRH agonist *vs* tamoxifen/GnRH agonist (without chemotherapy) in premenopausal early breast cancer patients, even found a worse overall survival for the former after a median follow-up of 5.2 years.[17] Yet, in randomised trials of adjuvant endocrine therapy, maximal separation of Kaplan-Meier curves for overall survival has typically occurred more than 10 years after randomisation. Hence, these data regarding survival and late adverse events could be considered immature.[18,19]

The onset of menopause in Caucasian women is 51 years on average with a considerable variability; 5% of women above the age of 55 years and another 5% under the age of 45 years.[20] The supplementary figure S2A of the TEXT/SOFT trial manuscript shows an HR for disease-free survival approaching 1.0 with increasing age from less than 35 to above 50 years when comparing tamoxifen plus ovarian function suppression with tamoxifen alone, indicating no added value of GnRH agonists to tamoxifen as natural menopause steps in.[16] On the contrary, supplementary figure S6 of the TEXT/SOFT analyses regarding the combination of exemestane with a GnRH agonist and the additional analyses in women under 35 years of age show, as illustrated by the HRs, a gradually increasing favourable impact on the disease-free survival with rising age for the combination AI/GnRH agonist in comparison to tamoxifen/GnRH agonist, possibly due to incomplete ovarian function suppression by GnRH agonists in younger patients.[16,21] As this was not observed in patients treated with tamoxifen, this cannot point at an independent prognostic value of age.[22] The incomplete ovarian function suppression by a GnRH agonist was indeed observed in the SOFT-EST trial,[23] where during 12 months of follow-up, 34.2% of the patients had inadequately suppressed (increased) E2 levels, at least once.

Considering that the results of the TEXT/SOFT trials might lead to an increased prescription of the combination treatment of GnRH agonist/AI in premenopausal patients in real life, we believe that the data of the SOFT-EST trial,[23] the ABCSG-12 trial,[17] and our study show that the risk of incomplete ovarian function suppression—either by using GnRH agonists at a young

age or by OFR in case of CIOFF—in the presence of AIs is clinically important with respect to overall outcome. Until further follow-up results of the TEXT/SOFT and ABCSG-12 trials will be available, we suggest cautiousness.

As OFR is characterized by high E2 levels, the findings of the current study raise another essential question; if increased E2 levels cause worse survival outcomes, does a more pronounced decrease of E2 levels lead to improved breast cancer survival? And if so, what should the target value be? Currently, only few data are known about the clinical consequences of the extent of E2 reduction during AI treatment. Letrozole has been shown to decrease plasma E2 levels to a greater extent in postmenopausal women with ER-positive breast cancer, in comparison to anastrozole.[24] Yet, the efficacy of letrozole regarding survival outcomes has not shown to be superior over anastrozole or exemestane.[25,26,27] Future research on the optimization of AI treatment should focus hereon by linking periodically measured E2 levels during AI treatment to survival outcomes to identify a so-called target value at which maximum efficacy is expected. Also, the influence of BMI on the extent of E2 deprivation during AI treatment needs further investigation, as it has not been given by weight- or body-surface-area–related dosing: one standard dosage for all patients. This might explain the worse survival for obese women undergoing endocrine treatment found in several studies.[28,29,30,31]

As the performances of most E2 assays are modest and various tests are used in different laboratories, interpreting E2 levels can also be challenging.[32] Moreover, cross-reaction between E2 and metabolites of steroidal AIs can be problematic, even in specialized immunoassays.[33] Ultrasensitive assays incorporating tandem mass spectroscopy have been shown to be more sensitive at very low E2 concentrations in comparison to standard E2 assays.[34,35] However, agreement among mass spectrometry-based methods is also lacking.[36] Therefore, testing E2 levels during AI treatment with a mass spectrometry assay in a central laboratory might be valuable for a trial setting, but is not (yet) necessary/feasible for daily practice, the more since it was shown that both indirect and direct assays are accurate in determining the menopausal status.[4]

In our study the E2 levels were assessed at local laboratories, which may be considered a limitation. Furthermore, the current analysis was an unplanned sub-study whereby confounding by indication could not fully be ruled out. A significant number of patients were excluded from our sub-study due to the lack of E2 measurements. Nevertheless, our study concerns survival data on a large and quite homogeneous population with early breast cancer patients between 45 and 57 years, who all received prior chemotherapy and 2–3 years of tamoxifen before anastrozole initiation. However, as the number of patients with OFR after CIOFF was small, confirmation of our data in other patient sets would be very welcomed.

Conclusion

Hormone receptor-positive early breast cancer patients with CIOFF treated with anastrozole have comparable survival outcomes in comparison to women who are definitely postmenopausal. However, among the women with CIOFF, OFR had an unfavourable impact on the distant recurrence-free survival and overall survival. These data warrant further research for this group of patients.

Acknowledgements

The authors thank W. Lemmens and B. Schalk for their assistance with performing the statistical analyses.

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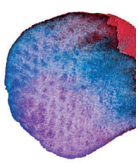
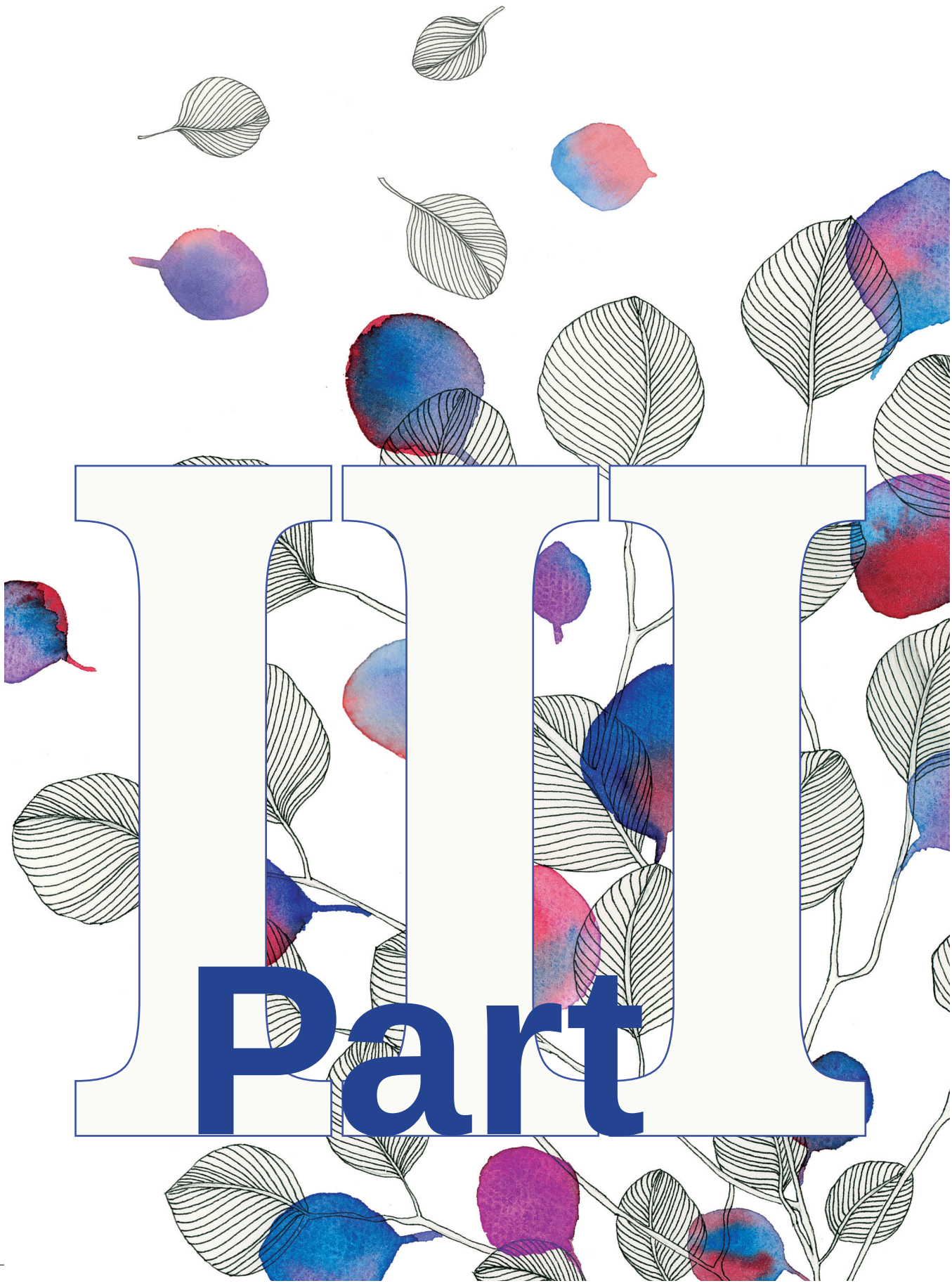
Bone health
during endocrine therapy

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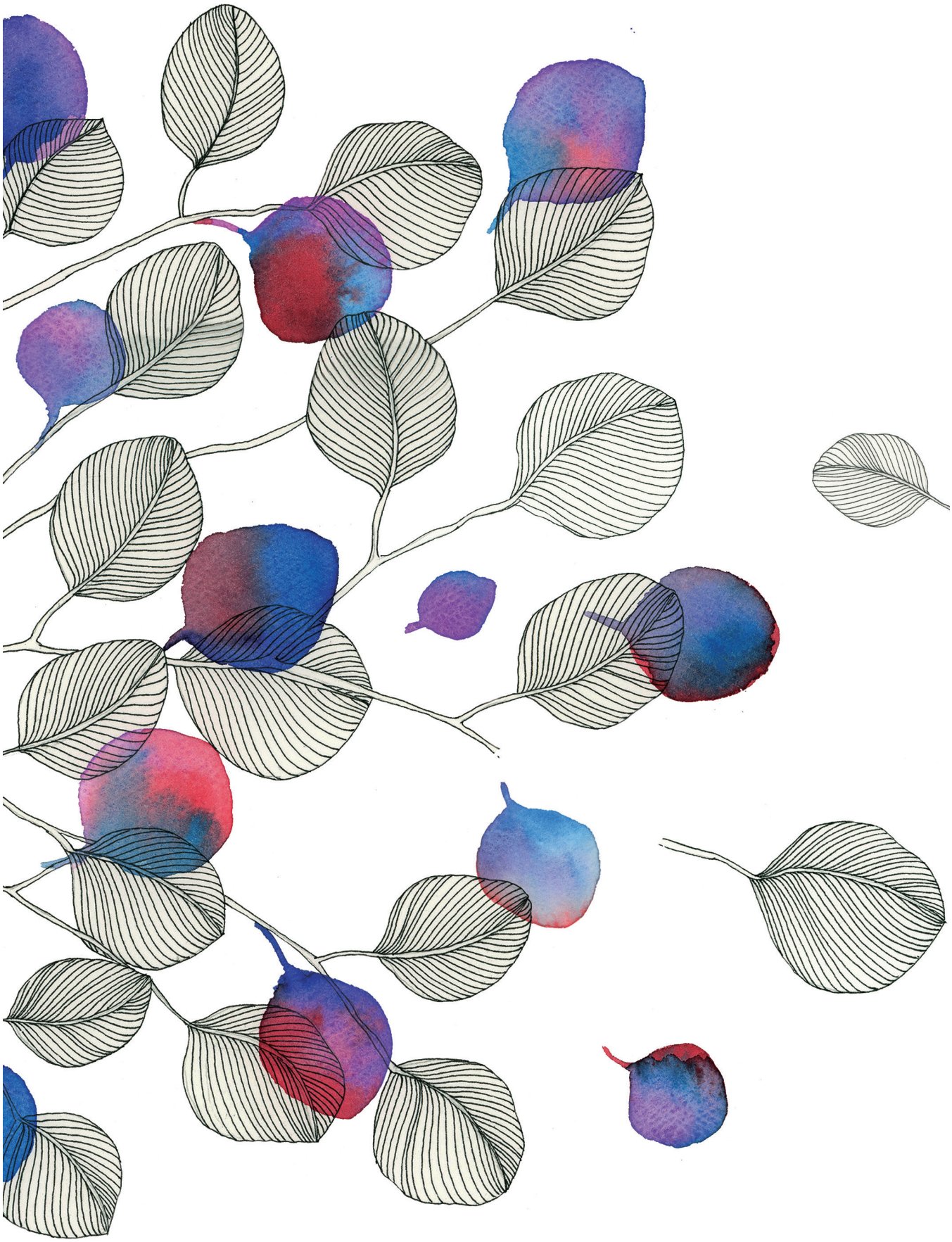

Chapter 6

Assessment and Management of Bone Health in Women with Early Breast Cancer Receiving Endocrine Treatment in the DATA Study

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International Journal of Cancer, Epub ahead 13.02.2019.

Abstract

The phase III DATA study investigates the efficacy of adjuvant anastrozole (6 *vs* 3 year) in postmenopausal women with breast cancer previously treated with 2–3 years of tamoxifen. This planned side-study assessed patterns of care regarding detection and treatment of osteopenia/osteoporosis, and trends in bone mineral density (BMD) during and after therapy. We registered all BMD measurements and bisphosphonate-use. Time to osteopenia/osteoporosis was analysed by Kaplan Meier methodology. For the trend in *T*-scores we used linear mixed models with random patients' effects. Of 1860 eligible DATA patients, 910 (48.9%) had a baseline BMD measurement. Among patients with a normal baseline BMD (n = 417), osteopenia was observed in 53.5% and 55.4% in the 6- and 3-year group respectively ($p = 0.18$), during follow-up. Only two patients (3-year group) developed osteoporosis. Of the patients with osteopenia at baseline (n = 408), 24.4% and 20.4% developed osteoporosis respectively ($p = 0.89$). Three years after randomisation 18.3% and 18.2% used bisphosphonates in the 6- and 3-year groups respectively and 6 years after randomisation this was 23.7% and 20.9% respectively ($p = 0.90$) of which the majority used oral bisphosphonates. The yearly mean BMD-change during anastrozole in the lumbar spine showed a *T*-score decline of 0.075. After bisphosphonate addition the decline became less prominent (0.047 ($p < 0.001$)) and after anastrozole cessation, while continuing bisphosphonates, the mean BMD yearly increased (0.047 ($p < 0.001$)). In conclusion, extended anastrozole therapy was not associated with a higher incidence of osteoporosis. Anastrozole-use was associated with a BMD decrease; however, the decline was modest and partially reversible after anastrozole cessation.

Introduction

Osteoporosis is estimated to affect 200 million women worldwide and the proportion of osteoporosis increases with advancing age - approximately in 3.3% for age 45–49, 6.4% for age 50–54, 13.5% for age 55–59, up to 50.3% in the highest age group of 85 years and above.[1] In both Europe and the United States, 30% of women have osteoporosis, and at the age of 50 roughly 40% of post-menopausal women will experience an osteoporotic fracture during their remaining life.[2,3]

A reduction of the bone mineral density (BMD) is a well-known side effect of aromatase inhibitors (AI), which is of substantial clinical concern in early breast cancer patients for whom endocrine therapy is indicated, because they survive for many years after treatment. As these women age, any early decrease in BMD puts them at a clear disadvantage with an increased fracture risk. In general, a 10–12% loss in BMD can be compared to a 1-point drop in *T*-score, and an increase of the fracture risk by 2.6 times.[4] Hence maintenance of BMD during endocrine therapy is important. Currently, very few data are available on how the BMD develops during and after cessation of (extended) endocrine therapy with aromatase inhibitors.[5,6] The DATA study investigated the efficacy of 6 *vs* 3 years of adjuvant anastrozole after a prior treatment with 2–3 years of tamoxifen in postmenopausal women with hormone receptor positive early breast cancer.[7] We pre-planned a side study to evaluate patterns of care considering bone health in these women, and the trend of BMD over time during and after cessation of anastrozole treatment. These research questions are addressed in the current report.

Methods

Study design

The DATA study (NCT00301457) is a prospective randomised phase III study in which postmenopausal women with early breast cancer were assigned to different durations of anastrozole therapy (6 *vs* 3 years) after 2 to 3 years of tamoxifen as adjuvant endocrine therapy.[7] The study included a total of 1860 eligible postmenopausal women from June 2006 till August 2009. The protocol of the bone-health side study was approved by the Medical Ethical Committee of the Radboud University Nijmegen at November 22, 2009.

Guidelines and definitions

In the DATA study it was advised to adhere to (inter)national guidelines on the management of bone health, including lifestyle recommendations. In 2008 the Dutch guidelines on osteoporosis were updated, with more stringent recommendations on BMD evaluations and (prophylactic) treatment with calcium, vitamin D, and lifestyle advices on smoking, alcohol, and exercise. In 2012 the guideline recommended evaluating BMD every 2 years and starting bisphosphonates from a *T*-score of −2.0 instead of −2.5. BMD measurements were done by dual-energy X-ray absorptiometry (DEXA) scans of the lumbar spine and/or total hip. The BMD was considered normal when the measurement was less than 1 standard deviation (SD) below the average value for young healthy women (*T*-score >−1), osteopenia when the BMD was between 1 and 2.5 SD below the average (*T*-score between −1 and −2.5), and osteoporosis when the BMD was more than 2.5 SD below the average (*T*-score <−2.5).[8] Only DEXA scans before appearance of a distant recurrence were analysed.

Data collection

Data on bone health issues were collected by local data managers in the 79 participating hospitals in the Netherlands, partly retrospectively and partly prospectively from 2 years before until 7 years after randomisation irrespective of treatment arm. We registered the absolute BMD measurements and the T score for both the total hip and lumbar spine. Patient records were checked for the presence of risk factors of reduced BMD at study entry. In addition, the use of calcium, vitamin D supplements, and bisphosphonates was collected. Finally, the date of bone fractures was registered.

Study objectives

The primary study objective was to assess patterns of care regarding prevention, detection and treatment of osteoporosis in postmenopausal breast cancer patients without distant recurrences who were treated with adjuvant anastrozole after prior tamoxifen. Therefore, we evaluated the frequency of BMD assessments, the follow-up assessments of BMD depending on the result of the baseline scan, and the prescription of bone protective medication, all related

to the duration of endocrine treatment (6 *vs* 3 years anastrozole). Moreover, we analysed the linear trend of the BMD measurements over time during and after anastrozole therapy and the effect of bone protective medication, and the number of fractures.

Statistical analyses

Figure S1 shows the patient selection for the performed analyses. The time from randomisation to first or second DEXA scan and the time period to the prescription of bisphosphonates were analysed by the Kaplan Meier method, considering distant recurrences or death a competing risk. The time periods were censored at the date of last follow-up. The baseline DEXA scan was defined as the last scan in the period between 2 years before, and 1 year after randomisation. If the event of interest (first DEXA scan, start bisphosphonates) occurred before randomisation, it was set at day 1 after randomisation. For the analysis on the time to first DEXA scan, the first scan reported could be a baseline scan or performed later on. The number of scans in the 6- and 3-year arm were compared to the Wilcoxon rank sum test.

Diagnosis of osteopenia and osteoporosis was based on the lowest *T*-score available in either the hip or the lumbar spine. Time to osteopenia or osteoporosis was censored at the last DEXA scan available for the patient when osteopenia or osteoporosis was not detected.

For assessing the effect of anastrozole on BMD we used a linear mixed model for the *T*-score, separately analysed for the hip and the lumbar spine. Dependency of measurements within the same patient was modelled by a random factor for patient. The time from anastrozole start to BMD measurement was included as a continuous covariate with a linear time effect that changed after stopping anastrozole. In addition, the linear effect of the time since start of bisphosphonate was incorporated in the model. Residual plots were used to verify the model assumptions of homogeneity and normally distributed errors.

For each year of follow-up, the annual fracture rate was calculated for patients being distant recurrence free and plotted at the midpoint of the interval. Multiple fractures could be reported in a single patient. A univariate Cox regression analysis was used to identify risk factors for developing fractures. The 6- and 3-year treatment groups were compared for the incidence of fractures starting after 3 years of anastrozole treatment because until that time both groups received the same treatment by using the log-rank test. All reported *p*-values are two-sided and a *p*-value ≤ 0.05 was considered statistically significant. All analyses were performed using SAS version 9.2.

Results

Patients

In the DATA study, 1860 patients were considered eligible. At randomisation, the median age was 58.1 years (interquartile range (IQR) 51.9–64.8) in the 6-year arm and 57.8 years (IQR 51.5–64.6) in the 3-year arm. Of these patients, 67.7% had received (neo-) adjuvant chemotherapy, and 32.5% of patients had node-negative disease. All patients had hormone receptor positive disease and 2.6% HER2 positive disease. Table 1 shows the risk profile and prior history regarding BMD. The baseline characteristics were well balanced.

Table 1. Baseline characteristics of all eligible randomised patients in the DATA study comparing 3 and 6 years of anastrozole after 2 to 3 years of tamoxifen (n = 1860)

	Total group n = 1860	**6 years Anastrozole** n = 931	**3 years Anastrozole** n = 929
Age (years) (median (IQR))		58.1 (51.9; 64.8)	57.8 (51.5; 64.6)
< 60 n (%)	1063 (57.2)	531 (57.0)	532 (57.3)
≥ 60 n (%)	797 (42.8)	400 (43.0)	397 (42.7)
Duration of post menopause at randomisation (years) n (%)			
< 5	805 (43.3)	392 (42.1)	413 (44.5)
5-10	242 (13.0)	116 (12.5)	126 (13.6)
10-20	345 (18.5)	181 (19.4)	164 (17.7)
> 20	331 (17.8)	164 (17.6)	167 (18.0)
Unknown	137 (7.4)	78 (8.4)	59 (6.4)
BMI (kg/m^2) n (%)			
≤24.9	689 (37.0)	345 (37.1)	344 (37.0)
25.0 – 29.9	712 (38.3)	368 (39.5)	344 (37.0)
30.0 – 34.9	298 (16.0)	142 (15.3)	156 (16.8)
≥ 35.0	93 (5.0)	48 (5.2)	45 (4.8)
Unknown	68 (3.7)	28 (3.0)	40 (4.3)
Smoking n (%)			
Current/previous smoker	943 (50.7)	465 (50.0)	478 (51.5)
Prior (neo) adjuvant chemotherapy n (%)			
Yes	1259 (67.7)	628 (67.5)	631 (67.9)
Prior Tamoxifen duration (years) n (%)			
≤ 2.5	1344 (72.3)	677 (72.7)	667 (71.8)
> 2.5	516 (27.7)	254 (27.3)	262 (28.2)

Table 1. Continued.

	Total group n = 1860	**6 years Anastrozole** n = 931	**3 years Anastrozole** n = 929
History of bone fractures at baseline n (%) *			
Yes	106 (5.7)	65 (7.0)	41 (4.4)
Baseline BMD measurement n (%) *			
Not done	950 (51.1)	470 (50.5)	480 (51.7)
Done	910 (48.9)	461 (49.5)	449 (48.3)
Normal	417 (45.8)	201 (43.6)	216 (48.1)
Osteopenia	408 (44.8)	216 (46.9)	192 (42.8)
Osteoporosis	85 (9.3)	44 (9.5)	41 (9.1)
Actual treatment at baseline n (%)*			
Vitamin D and/or Calcium			
Yes	445 (23.9)	241 (25.9)	204 (22.0)
Bisphosphonates			
Yes	168 (9.0)	89 (9.6)	79 (8.5)

* Baseline was considered -2 years before randomisation until 1 year after randomisation
BMI: Body Mass Index, BMD: Bone Mineral Density

BMD assessments

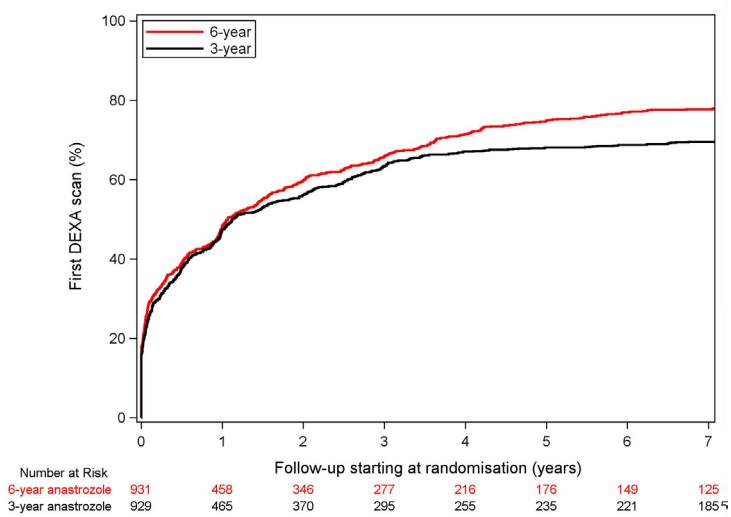
During 7 years of follow-up, the BMD was measured in 730 patients (78.0%) in the 6-year and in 650 (69.6%) in the 3-year arm (Figure 1 *a*). More measurements were performed in the 6-year treatment arm in comparison with the 3-year arm ($p < 0.001$). The baseline characteristics of the patients with a BMD measurement (n = 1,380) were comparable to the total study population (n = 1,860; Table S1).

Follow-up assessments BMD after baseline scan

Overall, 910 (48.9%) patients had a baseline BMD measurement, which indicated a normal BMD in 417 (45.8%) patients, osteopenia in 408 (44.8%), and osteoporosis in 85 (9.3%). At sixth year, after the baseline scan, a second DEXA scan was performed in 60.6% of the patients in the 6-year and 54.4% in the 3-year group if the baseline scan was normal (Figure 1b), and in 73.3% and 68.1% respectively if the baseline scan showed osteopenia (Figure 1c), and in respectively 76.4% and 62.6% if the baseline scan showed osteoporosis (Figure 1d).

If the baseline measurement showed a normal BMD, osteopenia was observed in the following 6 years in 53.5% of patients in the 6-year group and in 55.4% of the 3-year group (p = 0.18), while osteoporosis developed in only two patients in the 3-year arm (Figs. 2a-b). If the baseline measurements showed osteopenia, 24.4% developed osteoporosis in the 6-year group and 20.4% in the 3-year group (p = 0.89) within 6 years after baseline measurement (Figure 2c).

A. Time to first DEXA scan



B. Time to second DEXA scan, normal BMD

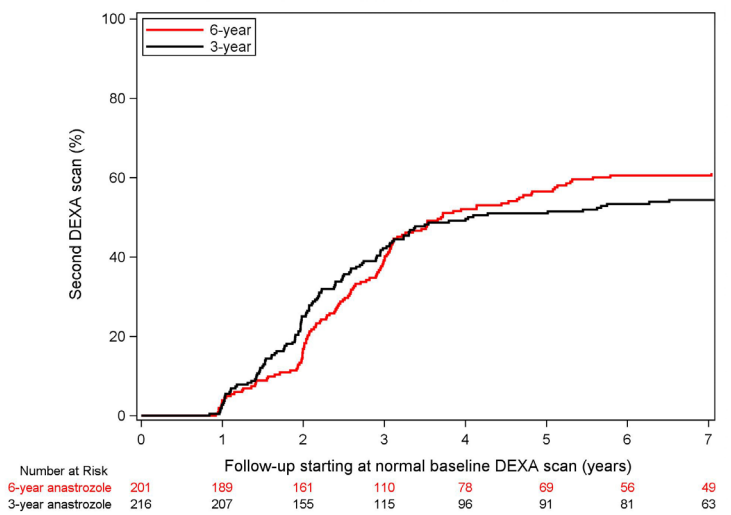
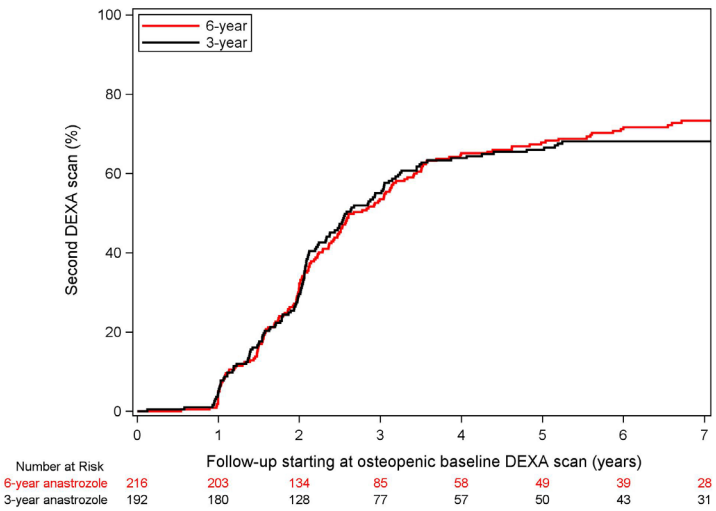


Figure 1. (A) Time to first DEXA scan, related to duration of anastrozole therapy (3 *vs* 6 years). Time to the second DEXA scan if the baseline scan showed a **(B)** normal BMD ***(C)*** osteopenia **(D)** osteoporosis. Overall, 30.2% of the patients had one BMD measurement, 20.3% had two measurements, 13.7% had three measurements, 10.0% had four or more measurements, and in 25.8% of the patients no BMD measurement was performed in the period from 2 years before randomisation until 7 years after randomisation.

C. Time to second DEXA scan, osteopenia



D. Time to second DEXA scan, osteoporosis

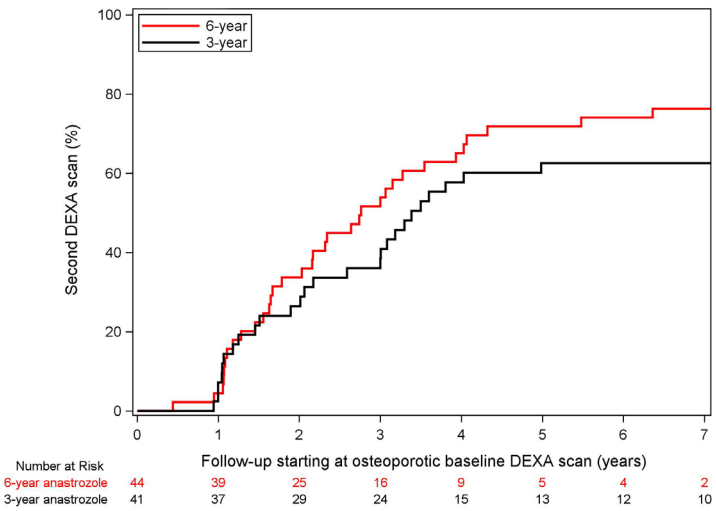
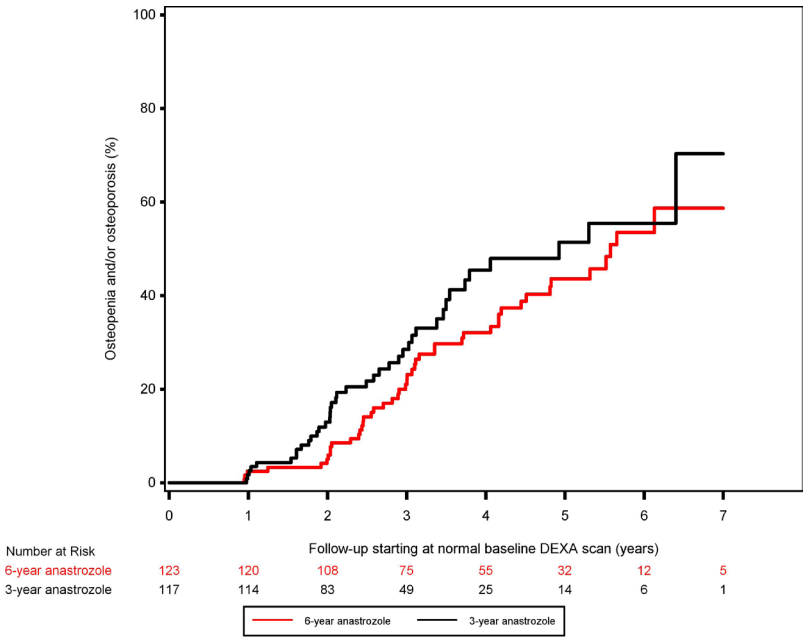


Figure 1. Continued.

A.


Osteopenia and/or osteoporosis (%)
100
80
60
40
20
0
0 1 2 3 4 5 6 7
Follow-up starting at normal baseline DEXA scan (years)
Number at Risk
6-year anastrozole 123 120 108 75 55 32 12 5
3-year anastrozole 117 114 83 49 25 14 6 1
6-year anastrozole
3-year anastrozole

B.

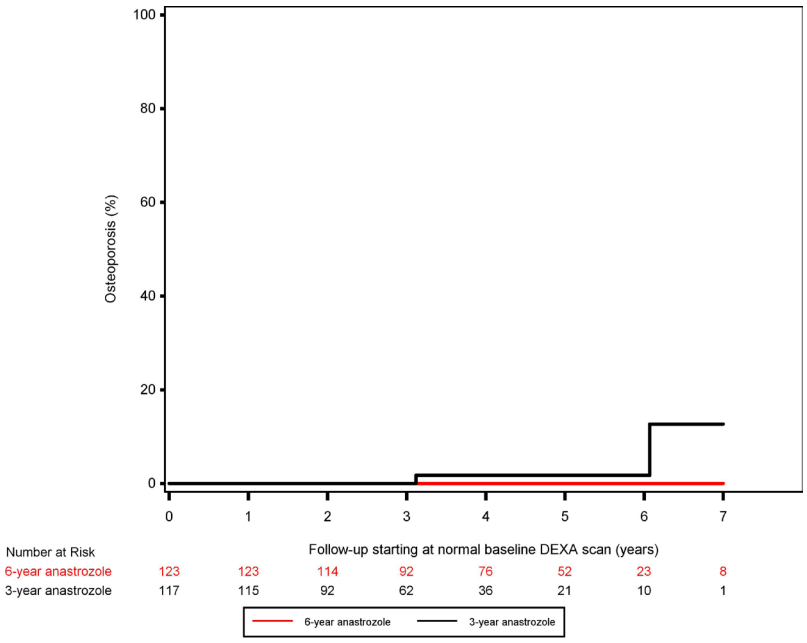

Osteoporosis (%)
100
80
60
40
20
0
0 1 2 3 4 5 6 7
Follow-up starting at normal baseline DEXA scan (years)
Number at Risk
6-year anastrozole 123 123 114 92 76 52 23 8
3-year anastrozole 117 115 92 62 36 21 10 1
6-year anastrozole
3-year anastrozole

Figure 2.

C.

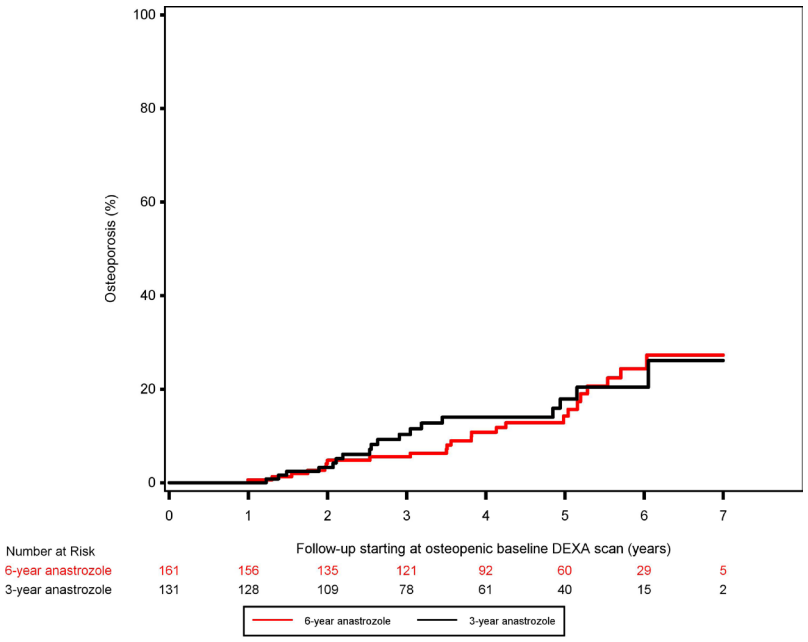
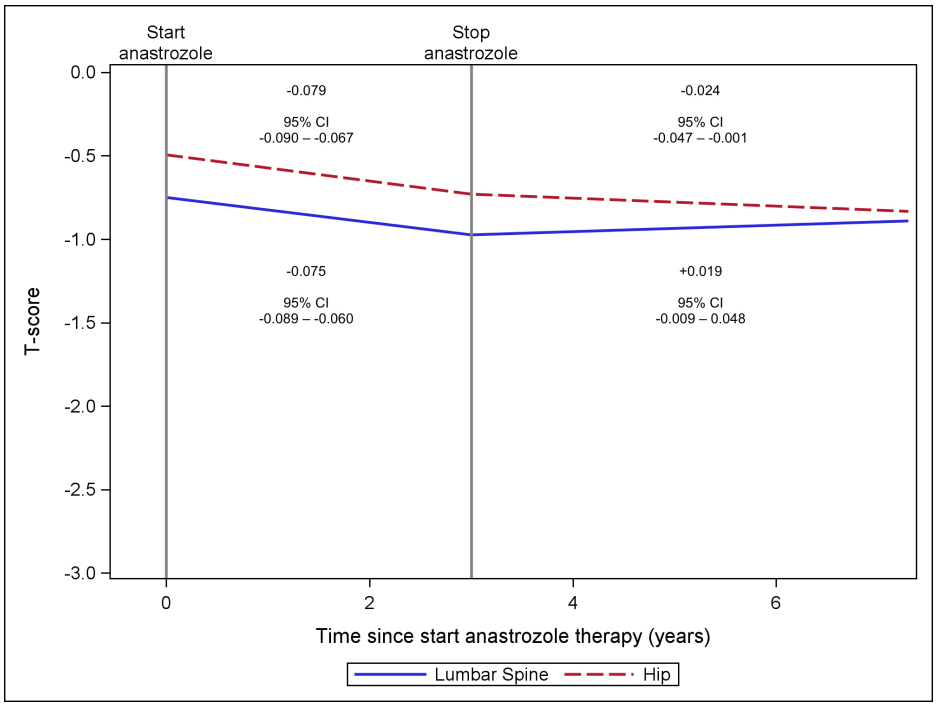
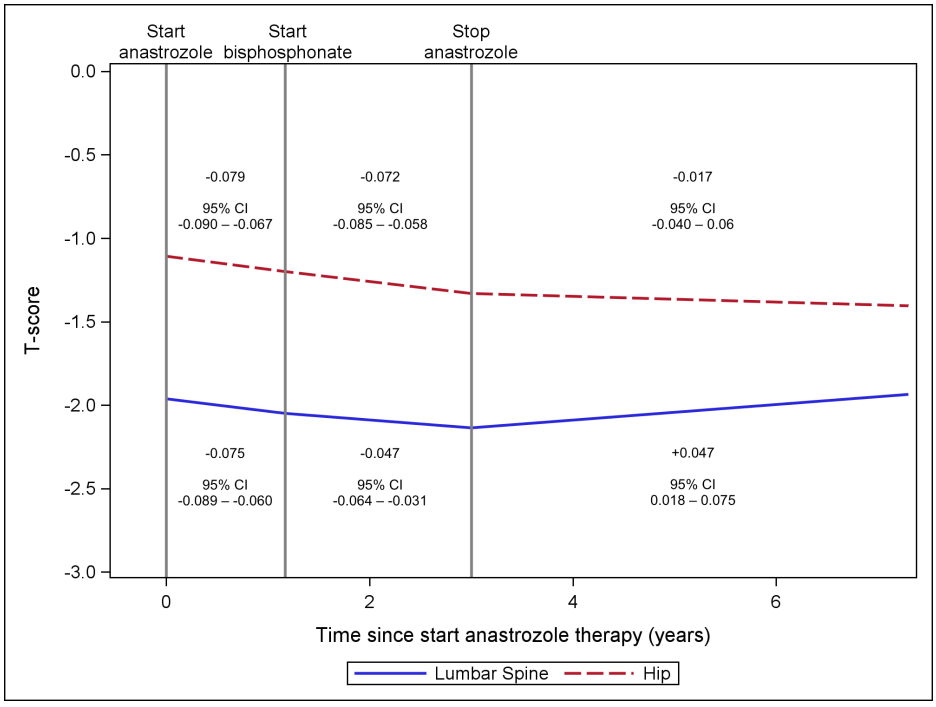


Figure 2. (A) Time to the development of osteopenia or osteoporosis if the DEXA scan at baseline showed a normal BMD. **(B)** Time to the development of osteoporosis if the DEXA scan at baseline showed a normal BMD. **(C)** Time to the development of osteoporosis if the DEXA scan at baseline showed osteopenia. At the beginning the lines remain horizontal because of the time interval between the baseline scan and the second scan. The scan performed within 1 year after randomisation was by definition the baseline scan.

A. No bisphonates



B. Bisphonates



◂ **Figure 3.** The annual change in mean *T*-score showing the effects of anastrozole and bisphosphonates on the hip and lumbar spine **(A)** in patients not receiving bisphosphonates, **(B)** in patients in whom bisphosphonates were started during the use of anastrozole. This figure shows the trend of the mean BMD in *T*-score for an average patient. In the linear mixed models with random effects, the development of the BMD in the hip during anastrozole use over time showed a decrease of the mean *T*-score of −0.079 (95% CI −0.090 to −0.067). When anastrozole was stopped the yearly decline was −0.024 (95% CI −0.47 to −0.001), which was a statistically significant change ($p < 0.001$) (A). During anastrozole-use, the prescription of bisphosphonates failed to stop the decrease of the mean *T*-score (yearly decrease of −0.072 (95% CI −0.085 to −0.058)) (*p*-value for change = 0.21). When anastrozole was stopped and bisphosphonates were continued the *T*-score stabilised (yearly decrease of −0.017 (95% CI −0.040 to 0.006)) which was a statistically significant change ($p < 0.001$) (B). The development of the BMD in the lumbar spine during AI use over time showed a yearly decrease of the mean *T*-score of −0.075 (95% CI −0.089 to −0.060). When anastrozole was stopped, the *T*-score stabilised to a yearly change of 0.019 (95% CI −0.009 to 0.048), which was a statistically significant change ($p < 0.001$) (A). During anastrozole-use, the prescription of bisphosphonates resulted in a less steep decline of −0.047 (95% CI −0.064 to −0.031) per year (*p*-value for change <0.001), and when the AI was stopped the *T*-score increased yearly with 0.047 (95% CI 0.018–0.075) (*p*-value for change <0.001) (B).

Of the 1,380 patients with at least one DEXA scan, 59.4% in the 6-year arm *vs* 67.4% in the 3-year arm had either osteopenia or osteoporosis at 3 years after randomisation. Six years after randomisation these percentages were 84.9% and 86.3% for the 6- and 3-year arm respectively ($p = 0.08$). Osteoporosis was diagnosed in 12.9% *vs* 15.5% at 3 years after randomisation and 25.1% *vs* 27.4% 6 years after randomisation in the 6- and 3-year groups respectively ($p = 0.24$).
Prescription of bone protective medication

Three years after randomisation 18.3% and 18.2% used bisphosphonates in the 6- and 3-year groups respectively and 6 years after randomisation this was 23.7% and 20.9% respectively ($p = 0.90$). Of the patients in whom bisphosphonates were prescribed, the majority used oral bisphosphonates (59.3% alendronate, 27.0% risedronate, 0.6% clodronate, 6.6% ibandronate) and few used intravenous bisphosphonates (3.2% pamidronate, 2.7% zoledronate). Only 0.6% received denosumab.

BMD outcome
The annual change of the mean T-score in the hip and the lumbar spine is shown for the average patient not treated with bisphosphonates (Figure 3 a) and the average patient treated with bisphosphonates (Figure 3 b).

Fractures

The annual incidence of fractures per treatment arm as of randomisation is shown in Figure 4. Fractures, as of 3 years after randomisation, occurred in 67 (7.9%) and 52 (6.1%) patients in the 6- and 3-year treatment arms, respectively ($p = 0.85$). We identified age above 60 years, a decreased BMD at baseline (osteopenia/osteoporosis), previous fractures, and a family history for osteoporosis as risk factors for experiencing fractures.

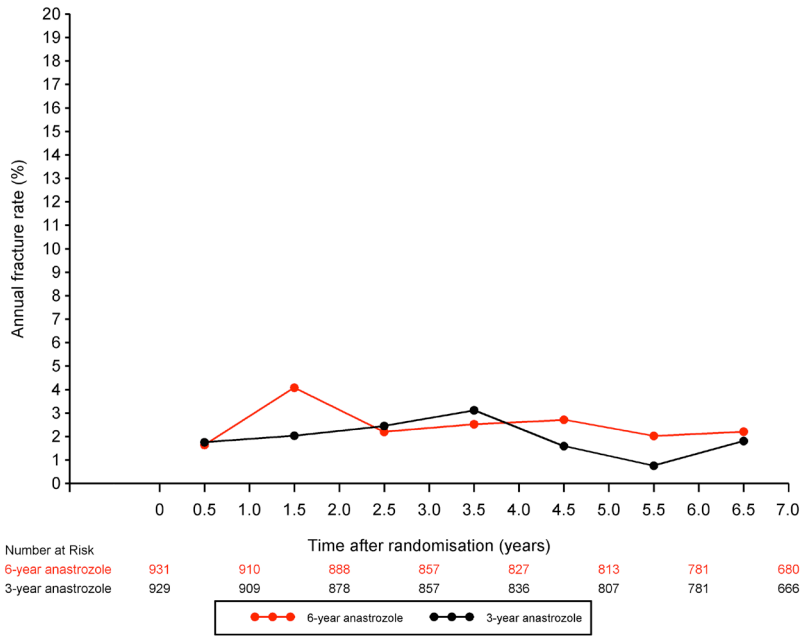


Figure 4. Annual fracture rate for the patients in the 6- *vs* 3-year anastrozole treatment group. The total number of fractures during the 7 years after randomisation was 217 (n = 118 in the 6-year group and n = 99 in the 3-year group). Patients could have multiple fractures.

Discussion

In this planned side-study of the phase III DATA study investigating the efficacy of 6 *vs* 3 years of adjuvant anastrozole after 2–3 year of tamoxifen in postmenopausal women with breast cancer we assessed patterns of care regarding detection and treatment of osteopenia/osteoporosis and linear trends over time in BMD both during and after anastrozole therapy. Only 48.9% of all eligible patients had a baseline BMD measurement. It showed osteopenia in 44.4% and osteoporosis in 9.3% of them which is comparable with the general population.[9] Although subsequent anastrozole use was associated with a BMD decrease, in patients with a normal baseline BMD only two patients in the 3-year arm developed osteoporosis, none in the 6-year arm. The BMD decline was seen regardless of assigned treatment arm. Of the patients with osteopenia at baseline, about a fifth developed subsequent osteoporosis. Interestingly, the average yearly absolute decrease in mean *T*-score during anastrozole therapy seemed rather limited (−0.075 in the lumbar spine, −0.079 in the hip; ~1%). Bisphosphonate use partially compensated this effect in the lumbar spine, but not in the hip. After cessation of anastrozole and continuation of bisphosphonates, the *T*-score stabilised in the hip, whereas it actually increased in the lumbar spine. The fracture rate was quite low and during the 6-year observation period not related to the assigned anastrozole treatment duration.

Healthy women experiencing natural menopause undergo an accelerated, transient phase of bone loss of ~3% per year during the first 1–2 years, slowing to ~1% annually thereafter.[10] AI-associated bone loss occurs at approximately twice the rate of physiologic postmenopausal bone loss at an average of ~2% per year which continues throughout the duration of therapy.[11,12] The extent of AI-associated bone loss was studied in several trials. The ATAC trial found significant BMD reductions in patients during 5 years of anastrozole treatment: −6.1% at lumbar spine and −7.2% at the hip.[12,13] Treatment with letrozole resulted in comparable bone loss in the MA.17 trial: at 24 months showing a significant additional decrease in total hip BMD (−3.6% *vs* −0.7%; $p = 0.044$) and lumbar spine BMD (−5.4% *vs* 0.7%; $p = 0.008$).[14] Also the ZO-FAST trial showed a median loss in lumbar spine BMD of −5.4% after 5 years of letrozole treatment without bisphosphonate use ($p < 0.0001$).[15] Decrease in BMD was apparently lower in patients treated with exemestane in the Intergroup Exemestane Study (IES), possibly related to its steroidal structure: −1.0% (lumbar spine) and −0.8% (total hip) at 24 months.[16] In our study, we also observed a decline of ~1% per year.

Moreover, it is important to realise that premenopausal women, who experience chemotherapy-induced ovarian function failure and receive ovarian suppression, pass through a much more distinct decrease in BMD within a short period of time (up to −7.7% in the first year).[17,18] The effect of ovarian suppression in combination with AIs is even worse, with reports of up to −17.3% BMD loss within 3 years compared to baseline ($p < 0.0001$).[5,17,19]

Hence, several prospective randomised studies observed negative consequences of AI-therapy on BMD in pre- and postmenopausal women. However, only few data are available on how BMD changes after adjuvant endocrine therapy is ended. In the ABCSG-12 trial, patients receiving endocrine therapy alone (i.e., goserelin plus tamoxifen or anastrozole) had a partial BMD recovery 2 years after completing therapy, but their BMD remained significantly lower than baseline BMD (mean for lumbar spine −6.3%, $p = 0.001$).[5] The ATAC trial also showed a recovery at 2 years after completion of anastrozole treatment (+4.0% at the lumbar spine and +0.5% at the hip).[6] Our study is the first trial to specifically investigate bone health during and after extended AI therapy after initial tamoxifen treatment. Even though approximately half of the women with a normal BMD developed osteopenia, we showed no clinically relevant differences in the occurrence of osteopenia, osteoporosis, or fractures between 6 and 3 years of anastrozole treatment. Therefore, for women with a normal BMD at the start of AI therapy being postmenopausal at breast cancer diagnosis, the time interval between DEXA scans can be longer than the 2 year currently advised in (inter)national guidelines.[20]

Moreover, we showed that after the start of anastrozole the yearly decrease in absolute *T*-score was −0.079 and −0.075 in the hip and lumbar spine respectively (absolute decrease of ~0.23 in *T*-score over a 3-year treatment and ~0.45 over a 6-year treatment), which was partially compensated if bisphosphonates were prescribed. Consequently, we consider a decreased BMD not as a major reason for disregarding extended endocrine therapy. Several trials demonstrated that treatment-induced bone loss could be successfully prevented if bisphosphonates were started immediately at the initiation of endocrine therapy not depending on actual BMD.[5,15,21,22] Yet, it remains unknown whether upfront use of bisphosphonates also reduces the incidence of fractures. More recently, denosumab was shown to increase BMD and reduce fractures into a great extent.[23] However, discontinuation of denosumab in patients with osteoporosis or vertebral fractures is associated with a strong decrease in BMD, exceeding the initial increase in BMD shown over a period of 7–10 years, and an increased risk of vertebral fractures.[24-26] Therefore, denosumab should not be stopped in these patients without considering alternative treatment.

When we compared the fracture rates of our study (6.1–7.9%) with those of the ABCSG-18 trial, the NSABP B42, and the IDEAL trial, all concerning postmenopausal breast cancer patients receiving aromatase inhibitor treatment, these were comparable.[23,27,28] Only the fracture rate in the placebo arm from the ABCSG-18 trial had a higher incidence of fractures (9.6%). We believe this is possibly due to the fact that these patients were not allowed to receive bisphosphonates which is in contrast with both treatment arms in the DATA trial.

In our study, we identified an age above 60 years, osteopenia or osteoporosis at baseline, a history of fractures, and a family history of osteoporosis as risk factors for experiencing fractures during and after adjuvant anastrozole therapy. These risk factors match with the factors implemented in the WHO fracture risk assessment tool (FRAX®; http://www.sheffield.ac.uk/FRAX/).[29] Therefore we suggest that the management of bone health during adjuvant endocrine therapy should be based on the baseline BMD measurement and the presence of risk factors for developing fractures according to FRAX®.

In our study anastrozole therapy was started after 2–3 years of tamoxifen, which is known to counteract BMD loss and decreases bone fracture rate in postmenopausal women.[30] Therefore it can be questioned into which extend our results are influenced by the positive effect of tamoxifen on bone health. A sub-study of the BIG 1–98 trial, comparing four 5-year regimens of endocrine therapy, looked at the effect of each regimen on BMD.[31] They found that the sequenced treatment of tamoxifen followed by letrozole had the worst effect on BMD and that letrozole followed by tamoxifen appeared to preserve BMD. They hypothesized that the interruption of tamoxifen combined with the rapid fall in oestrogen levels induced by letrozole promotes an accelerated bone turnover and loss of BMD following the switch as was confirmed by bone turnover biomarkers.[31]

Limitations

Our study has several limitations. The evaluation of BMD was not standardised but left at the discretion of the treating physician. The reason not to perform a DEXA scan at baseline in more than half of the women and no DEXA scan at all in a quarter of the patients is unknown. Moreover, the DEXA scans were not standardised since patients were treated in different hospitals. Selection based on patient characteristics (e.g. fractures, and familial osteoporosis) could not be ruled out. In our study, we report on the linear change of BMD over time during the use of anastrozole with or without bisphosphonates. In our model we could not evaluate if the BMD decrease over time was more profound in the early years of menopause and/or directly after the start of anastrozole because the minimum interval between DEXA scans was 1 year and scans were not performed at set times.

Conclusion

This is one of the first studies reporting on bone health during and after extended endocrine therapy. We conclude from our study, that although subsequent anastrozole use was associated with a BMD decrease, extended endocrine therapy was not associated with a higher incidence of osteoporosis or fractures. Nowadays, an increasing number of postmenopausal women are treated with bisphosphonates in the adjuvant setting, which also showed to compensate the negative effect of AIs on BMD. Therefore, with the availability of bisphosphonates, we believe bone health should not be a major reason for disregarding extended endocrine therapy.

Acknowledgements

We thank Wim Lemmens, Bianca Schalk, and Ton de Haan for their assistance with performing the statistical analyses. This study was funded by AstraZeneca NL, ClinicalTrials.gov number, NCT00301457.

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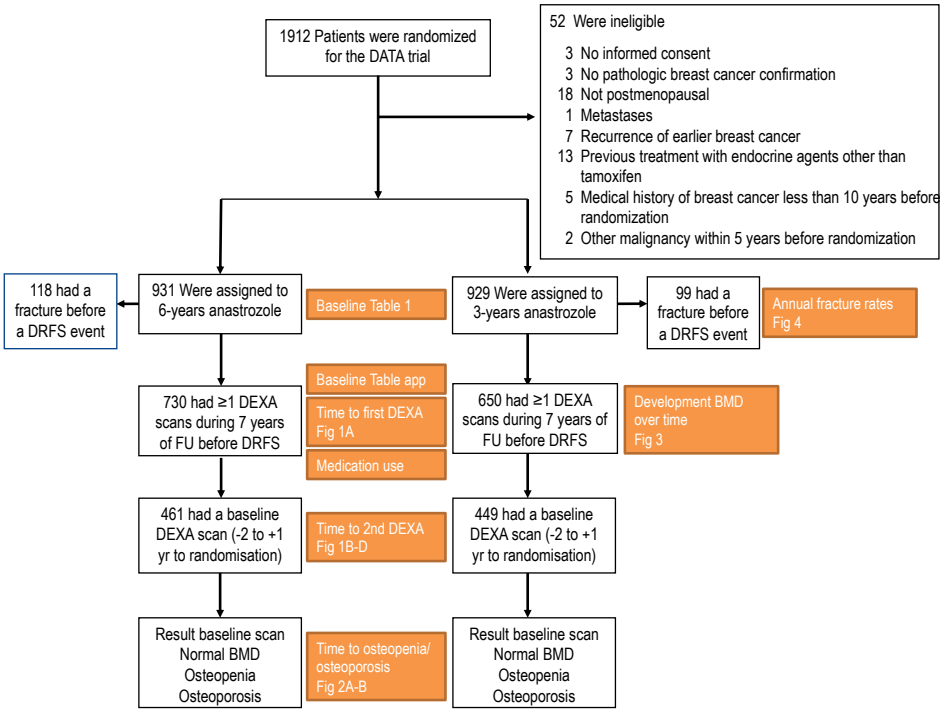
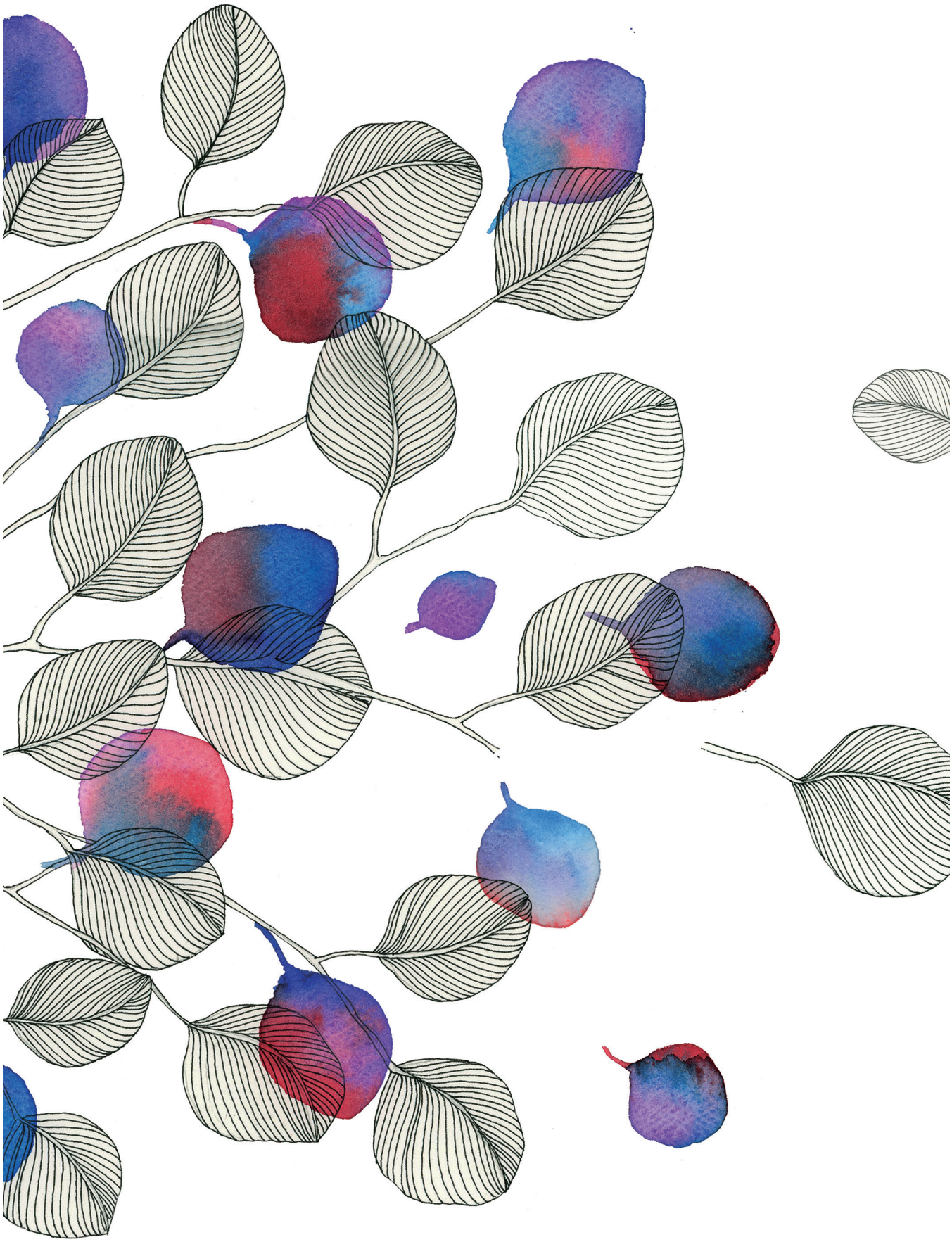
Supplementary appendix

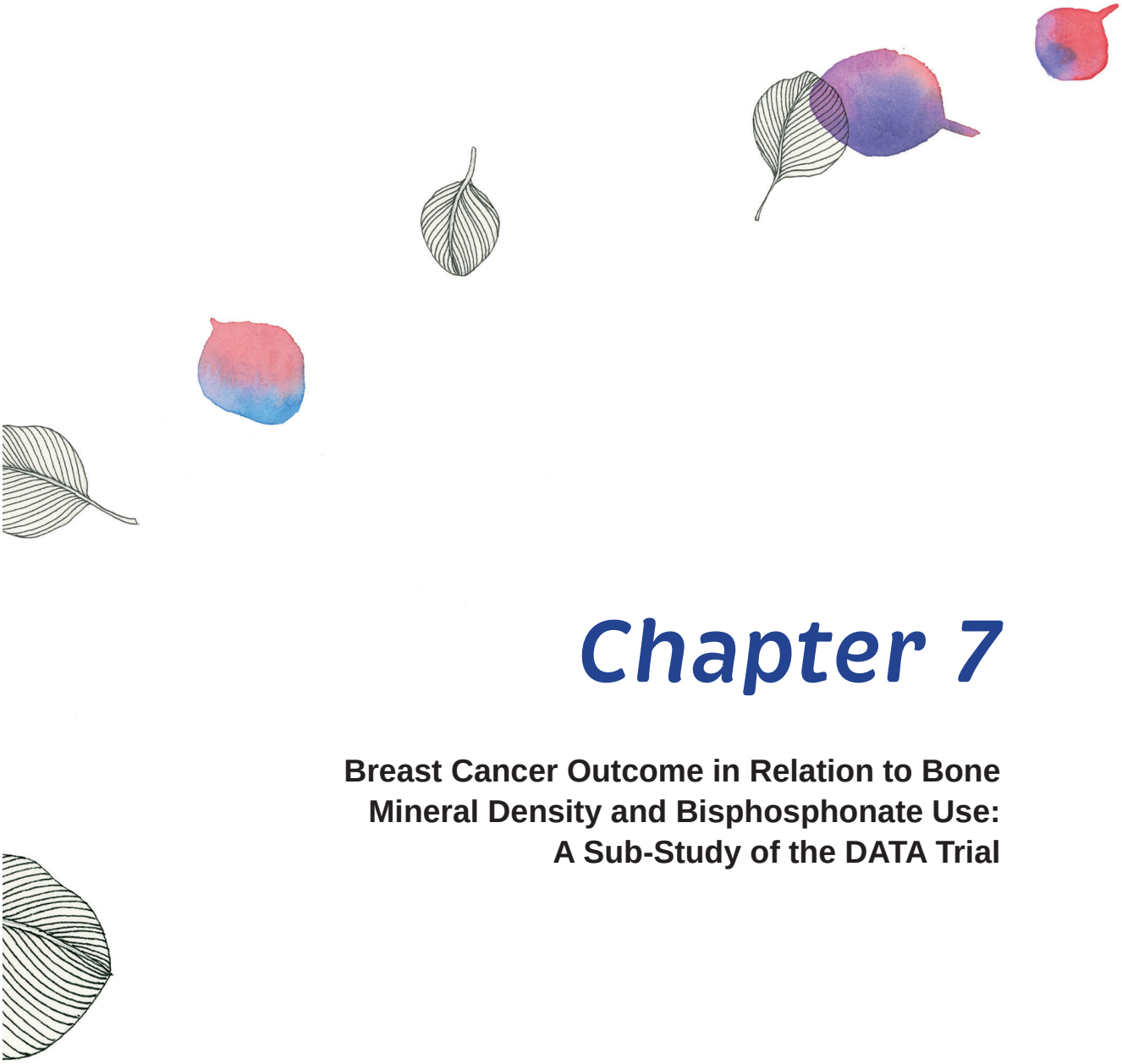


Appendix figure 1. Patient selection

Appendix Table 1. Baseline characteristics of the patients in the DATA study who had at least one BMD measurement (n=1380)

	Total group N = 1380	6 years Anastrozole n = 730	3 years Anastrozole n = 650
Risk factors for reduced BMD at randomisation			
Age (years) (median (IQR))		57.4 (51.5; 63.9)	56.9 (50.8; 63.2)
< 60 n (%)	832 (60.3)	434 (59.5)	398 (61.2)
≥ 60 n (%)	548 (39.7)	296 (40.6)	252 (38.8)
Duration of post menopause at randomisation (years) n (%)			
< 5	626 (45.4)	318 (43.6)	308 (47.4)
5-10	191 (13.8)	97 (13.3)	94 (14.5)
10-20	261 (18.9)	145 (19.9)	116 (17.8)
> 20	205 (14.9)	111 (15.2)	94 (14.5)
Unknown	97 (7.0)	59 (8.0)	38 (5.8)
BMI (kg/m^2) n (%)			
≤24.9	527 (38.2)	275 (37.7)	252 (38.8)
25.0 – 29.9	528 (38.3)	285 (39.0)	243 (37.4)
30.0 – 34.9	219 (15.9)	109 (14.9)	110 (16.9)
≥ 35.0	62 (4.5)	38 (5.2)	24 (3.7)
Unknown	44 (3.2)	23 (3.2)	21 (3.2)
Smoking n (%)			
Current/previous smoker	714 (51.7)	374 (51.2)	340 (52.3)
Prior (neo) adjuvant chemotherapy n (%)			
Yes	985 (71.4)	518 (71.0)	467 (71.9)
Prior Tamoxifen duration (years) n (%)			
≤ 2.5	1022 (74.1)	544 (74.5)	478 (73.5)
> 2.5	358 (25.9)	186 (25.5)	172 (26.5)
History of bone fractures at baseline* n (%)			
Yes	83 (6.0)	52 (7.1)	31 (4.8)
Baseline BMD measurement n (%)*			
Not done	470 (34.1)	269 (36.8%)	201 (30.9)
Done	910 (65.9)	461 (63.2%)	449 (69.1%)
Normal	417 (45.8)	201 (43.6)	216 (48.1)
Osteopenia	408 (44.8)	216 (46.9)	192 (42.8)
Osteoporosis	85 (9.3)	44 (9.5)	41 (9.1)
Actual treatment at baseline n (%)*			
Vitamin D and/or Calcium			
Yes	416 (30.1)	223 (30.6)	193 (29.7)
Bisphosphonates			
Yes	156 (11.3)	81 (11.1)	75 (11.5)





Chapter 7

Breast Cancer Outcome in Relation to Bone Mineral Density and Bisphosphonate Use: A Sub-Study of the DATA Trial

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Submitted for publication.

Abstract

Background

The phase III DATA study compared 6 and 3 years of adjuvant anastrozole after initial 2-3 years of tamoxifen in postmenopausal breast cancer patients. This pre-planned side-study assesses the relationship between a reduced bone mineral density (BMD) and distant recurrence-free survival (DRFS), and evaluated the effect of bisphosphonates on DRFS.

Methods

We selected all patients with a BMD measurement within 3 years after randomisation (landmark) and without any DRFS events. BMD was measured by dual-energy x-ray absorptiometry (DEXA) scan. Osteopenia/osteoporosis was treated according to guidelines. Kaplan Meier methods and Cox proportional hazards models were used for analyses. The hazard ratios (HR) were adjusted for tumour status, nodal status, tumour grade, and hormone receptor status.

Results

Of 1860 eligible patients, 1142 (65.5% 6-year arm, 62.9% 3-year arm) had a DEXA scan within three years after randomisation. The BMD was normal in 436 (38.2%), showed osteopenia in 565 (49.5%), and osteoporosis in 141 (12.3%) patients. After a median follow-up of 5.0 years from the 3-year landmark, neither osteopenia nor osteoporosis (compared with normal BMD) were associated with DRFS in both the 6-year (osteopenia HR 0.82 (95%CI 0.45–1.49), osteoporosis HR 1.10 (95%CI 0.26-4.67)) and the 3-year arm (osteopenia HR 0.75 (95%CI 0.40–1.42), osteoporosis HR 1.86 (95%CI 0.43–8.01)). Moreover, bisphosphonate-use did not impact DRFS.

Conclusion

In this DATA sub-study, we did not observe an association between a reduced BMD and DRFS after a median follow up of 5 years. Neither did we observe an impact of bisphosphonate use on DRFS.

Introduction

Bisphosphonates, and supplementation of vitamin D and calcium are pivotal in the medical treatment of osteoporosis. Aside from preventing bone loss and fractures, the role of bisphosphonates as an adjuvant agent for breast cancer recurrence was investigated in several clinical trials.[1-6] Hereby, a consistent trend for improved breast cancer outcomes by adjuvant bisphosphonate therapy was observed in postmenopausal breast cancer patients. Next, the Early Breast Cancer Trialists' Collaborative Group (EBCTCG) meta-analysis observed a significant improvement in the rate of distant recurrences (18.4% in the bisphosphonate group vs 21.9% in the group without bisphosphonate, $p < 0.001$), mainly driven by a reduction in bone recurrences (5.9% vs 8.8% respectively, $p < 0.001$), and a lower 10-year breast cancer mortality.[7] The effect was seen irrespective of bisphosphonate type. Additionally, in epidemiological studies bisphosphonate-use for osteoporosis in healthy postmenopausal women was associated with a 30% reduced risk of breast and colon cancer.[8] Also, earlier studies showed that a reduced bone mineral density (BMD) was associated with a lower risk of breast cancer.[9,10] On the other hand, neoadjuvant use of bisphosphonates in combination with chemotherapy in women with stage II/III breast cancer did not result in an improved clinical and pathological response rate.[11] Hence it remains insufficiently clear how to explain the effects of bisphosphonates on breast cancer prevention and recurrence, respectively. Is the effect directly caused by the bisphosphonates? Or are women with early breast cancer and osteoporosis simply at a lower risk of developing metastases due to lower oestrogen levels?

The phase III DATA trial investigated the efficacy of 6 vs 3 years of anastrozole after an initial 2-3 years of tamoxifen in postmenopausal women with early breast cancer. In this pre-planned side-study we assessed the relationship between a reduced BMD and distant recurrence free survival (DRFS), and evaluated the effect of bisphosphonates on DRFS.

Methods

Study design, participants and procedures

The DATA trial included 1860 eligible postmenopausal women with hormone receptor-positive early breast cancer who had already received 2-3 years of adjuvant tamoxifen after curative local treatment, and who were without signs of loco-regional and/or distant metastases. Patients used anastrozole for 6 or 3 years according to randomisation. Ethics approval was obtained at the central commission of research involving humans in Nijmegen in the Netherlands. The DATA trial (NCT00301457) is described in detail elsewhere.[12] Decisions on BMD measurements and bisphosphonate use were left to the treating physician. The DATA study protocol advised to follow the recommendations of (inter)national guidelines. During the conduct of the study adjuvant bisphosphonates were not recommended, therefore they were predominantly prescribed as treatment for osteopenia and osteoporosis. We registered all BMD measurements and start of bisphosphonate-use. BMD was measured by a dual-energy x-ray absorptiometry (DEXA) scan of the lumbar spine/hip. For the current analyses, DATA patients were selected who had a DEXA scan within 3 years after randomisation and did not have any distant recurrences or death (flow chart shown in appendix figure 1).

Statistical analysis

We registered all results of DEXA scans performed within three years after randomisation. The outcomes (T-scores) were categorized according to the world health organization classification for BMD; normal BMD T-score ≥ -1.0 standard deviation (SD), osteopenia T-score < -1.0 and > -2.5 SD, and osteoporosis T-score ≤ -2.5 SD.[13] Assessment of osteopenia and osteoporosis was based on the lowest available T-score in either the hip or the lumbar spine. Based on the result of the DEXA scan we classified the patients in three groups (normal BMD, osteopenia, and osteoporosis). The landmark method was used to assess the survival after a particular point in time. The DRFS time was measured from the landmark of 3 years after randomisation to distant recurrence or death, the so-called residual survival, and was censored at the date of last follow-up. DRFS rates were obtained with the Kaplan Meier method. We analysed the relationship between BMD and DRFS by comparing women having either osteopenia or osteoporosis with those having a normal BMD in a Cox proportional hazards model. Secondly, we performed the same analyses selecting only those patients who had not received bisphosphonates before the landmark of 3 years, thereby correcting for a potential effect of bisphosphonates on DRFS. The hazard ratios (HR) were adjusted for tumour status, nodal status, tumour grade, and hormone receptor status. Further, we evaluated the effect of bisphosphonates, started before the 3-year landmark for a reduced BMD, on DRFS by comparing the women with and without bisphosphonates. All reported *P*-values are two-sided and a *P*-value ≤ 0.05 was considered statistically significant. All analyses were performed using SAS version 9.2.

Results

Of the 1860 randomised eligible DATA patients, 1142 (65.5% in the 6-year arm and 62.9% in the 3-year arm) had a DEXA scan within the first 3 years after randomisation. The median age at randomisation was 57.5 years (interquartile range 51.0 – 63.0), 67.3% of the patients had node-positive disease and 71.3% underwent (neo-)adjuvant chemotherapy. Except for T-stage, the baseline characteristics were well balanced between the BMD groups (table 1). Women with a normal BMD more frequently had a larger tumour size at diagnosis, but the patient characteristics were similar to these of the total study population (appendix table 1).

At the 3-year landmark, the BMD was considered normal in 436 (38.2%), showed osteopenia in 565 (49.5%), and osteoporosis in 141 (12.3%) patients. Seventeen (3.4%) patients of the normal BMD group used bisphosphonates in comparison with 161 (28.5%) in the osteopenia group, and 112 (80.9%) in the osteoporosis group. The median follow-up from the landmark was 5.0 years (interquartile range 4.3 to 5.7). The number of DRFS events were 61 and 66 in the 6- and 3-year arm respectively. In the 6-year arm the 5-year residual DRFS rate was 89.7% in the osteopenia group, 86.7% in the osteoporosis group, and 88.9% in the normal BMD group (osteopenia vs normal BMD: adjusted HR 0.91 (95% CI 0.53–1.58); osteoporosis vs normal BMD: adjusted HR 1.40 (95% CI 0.62-3.17)). In the 3-year treatment arm the 5-year residual DRFS rate was 89.2% in the osteopenia group, 89.7% in the osteoporosis group and 85.8% in the normal BMD group (osteopenia vs normal BMD: adjusted HR 0.86 (95% CI 0.51–1.44); osteoporosis vs normal BMD: adjusted HR 0.85 (95% CI 0.37–1.94)) (figure 1A-B).

When we repeated the analyses selecting only those patients who did not use bisphosphonates (n=852) we neither observed an impact of BMD on DRFS (6-year arm osteopenia vs normal BMD: adjusted HR 0.82 (95% CI 0.45–1.49); osteoporosis vs normal BMD: adjusted HR 1.10 (95% CI 0.26-4.67); 3-year arm osteopenia vs normal BMD: adjusted HR 0.75 (95% CI 0.40–1.42); osteoporosis vs normal BMD: adjusted HR 1.86 (95% CI 0.43–8.01)) (Figure 2A-B). The number of 5-year DRFS events were 42 and 50 in the 6- and 3-year arm respectively.

Bisphosphonate treatment was started at a median T-score of -2.3 (IQR -2.7 to -1.7). After a median follow up of 5.0 years, the use of bisphosphonates before the landmark did not lead to a better DRFS in each of the BMD categories in comparison with women without bisphosphonates (normal BMD unadjusted HR -0.95 (95% CI 0.23–3.88), osteopenia unadjusted HR 1.42 (95% CI 0.84–2.41), and osteoporosis unadjusted HR 0.78 (95% CI 0.25–2.43) (figure 3A-C).

Table 1. Baseline characteristics of all eligible randomised patients in the DATA study who underwent a DEXA scan before the landmark of 3 years after randomisation.

Characteristic	Total group (N=1142)
Age at randomisation – no. (%)	
Median age at randomisation (IQR)	57.5 (51.0 – 63.0)
< 49 years	227 (19.9)
50-59 years	462 (40.5)
≥ 60 years	453 (39.7)
Tumour status – no. (%)	
pT1	519 (45.5)
pT2	540 (47.3)
pT3/4	82 (7.2)
Unknown	1
Nodal status – no. (%)	
pN0 / pN0(i+)	373 (32.7)
pN1	612 (53.6)
pN2 / pN3	157 (13.8)
Histological grade – no. (%)	
Grade I	202 (18.2)
Grade II	571 (51.4)
Grade III	338 (30.4)
Unknown	31
Hormone-receptor status – no. (%)	
ER and PR positive	877 (76.8)
ER or PR positive	265 (23.2)
HER2 status – no. (%)	
Positive	19 (1.8)
Negative	1063 (98.2)
Unknown	60
Histology – no. (%)	
Lobular	207 (18.1)
Other	935 (81.9)
Type of breast surgery – no. (%)	
Breast-conserving surgery	568 (49.7)
Mastectomy	574 (50.3)

	Normal BMD (N=436)	Osteopenia (N=565)	Osteoporosis (N=141)
	56.8 (51.0 – 62.0)	57.6 (51.0 – 64.0)	59.0 (51.0 – 64.0)
	94 (21.6)	113 (20.0)	20 (14.8)
	175 (40.1)	227 (40.2)	60 (42.6)
	167 (38.3)	225 (39.8)	61 (43.3)
	170 (39.0)	276 (48.9)	73 (51.8)
	237 (54.4)	244 (43.3)	59 (41.8)
	29 (6.7)	44 (7.8)	9 (6.4)
	0	1	0
	136 (31.2)	190 (33.6)	47 (33.3)
	235 (53.9)	300 (53.1)	77 (54.6)
	65 (14.9)	75 (13.3)	17 (12.1)
	72 (16.9)	103 (18.7)	27 (20.0)
	226 (53.1)	277 (50.4)	68 (50.4)
	128 (30.0)	170 (30.9)	40 (29.6)
	10	15	6
	346 (79.4)	428 (75.8)	103 (73.1)
	90 (20.6)	137 (24.2)	38 (26.9)
	7 (1.7)	11 (2.1)	1 (0.7)
	406 (98.3)	523 (97.9)	134 (99.3)
	23	31	6
	80 (18.4)	100 (17.7)	27 (19.2)
	356 (81.7)	465 (82.3)	114 (80.9)
	214 (49.1)	291 (51.5)	63 (44.7)
	222 (50.9)	274 (48.5)	78 (55.3)

Table 1. Continued.

Characteristic	Total group (N=1142)
Type of axillary surgery – no. (%)	
Sentinel node only	310 (27.1)
Axillary lymph node dissection only	298 (26.1)
Sentinel node plus axillary lymph node dissection	517 (45.3)
None	17 (1.5)
Radiotherapy – no. (%)	
Local	320 (28.0)
Regional lymph nodes	24 (2.1)
Local and regional lymph nodes	414 (36.3)
None/unknown	384 (33.6)
Prior (neo)adjuvant chemotherapy – no. (%) *	
Anthracycline- and taxane-containing regimen	77 (6.7)
Anthracycline-containing regimen without taxane	712 (62.3)
Taxane-containing regimen without anthracycline	6 (0.5)
Regimen without anthracycline or taxane	19 (1.7)
No chemotherapy	328 (28.7)
Prior HER2-targeted therapy – no. (%)	
Yes	3 (0.4)
Previous duration of tamoxifen	
Median and IQR (years)	2.3 (2.1 – 2.5)
Treatment with bone protecting agents at inclusion – no. (%)	
Bisphosphonates	139 (12.2)
Vitamin D and/or Calcium	375 (32.8)

TX: size of tumour could not be assessed. ER: Oestrogen Receptor. PR: Progesterone Receptor. HER2: human epidermal growth factor receptor 2

* all patients received cyclophosphamide-based chemotherapy

	Normal BMD (N=436)	Osteopenia (N=565)	Osteoporosis (N=141)
	129 (29.6)	144 (25.5)	37 (26.2)
	106 (24.3)	158 (28.0)	34 (24.1)
	195 (44.7)	253 (44.8)	69 (48.9)
	6 (1.4)	10 (1.7)	1 (0.7)
	119 (27.3)	162 (28.6)	39 (27.7)
	12 (2.8)	9 (1.6)	3 (2.1)
	159 (36.5)	201 (37.2)	45 (31.9)
	146 (33.5)	184 (32.6)	54 (38.3)
	25 (5.7)	39 (6.9)	13 (9.2)
	281 (64.4)	350 (61.9)	81 (57.4)
	1 (0.2)	4 (0.7)	1 (0.7)
	6 (1.4)	13 (2.3)	0 (0.0)
	123 (28.2)	159 (10.4)	46 (32.6)
	3 (1.0)	0 (0.0)	0 (0.0)
	2.3 (2.1 – 2.5)	2.3 (2.1 – 2.5)	2.3 (2.1 – 2.8)
	5 (1.2)	73 (12.9)	61 (43.3)
	83 (19.0)	216 (38.2)	76 (53.9)

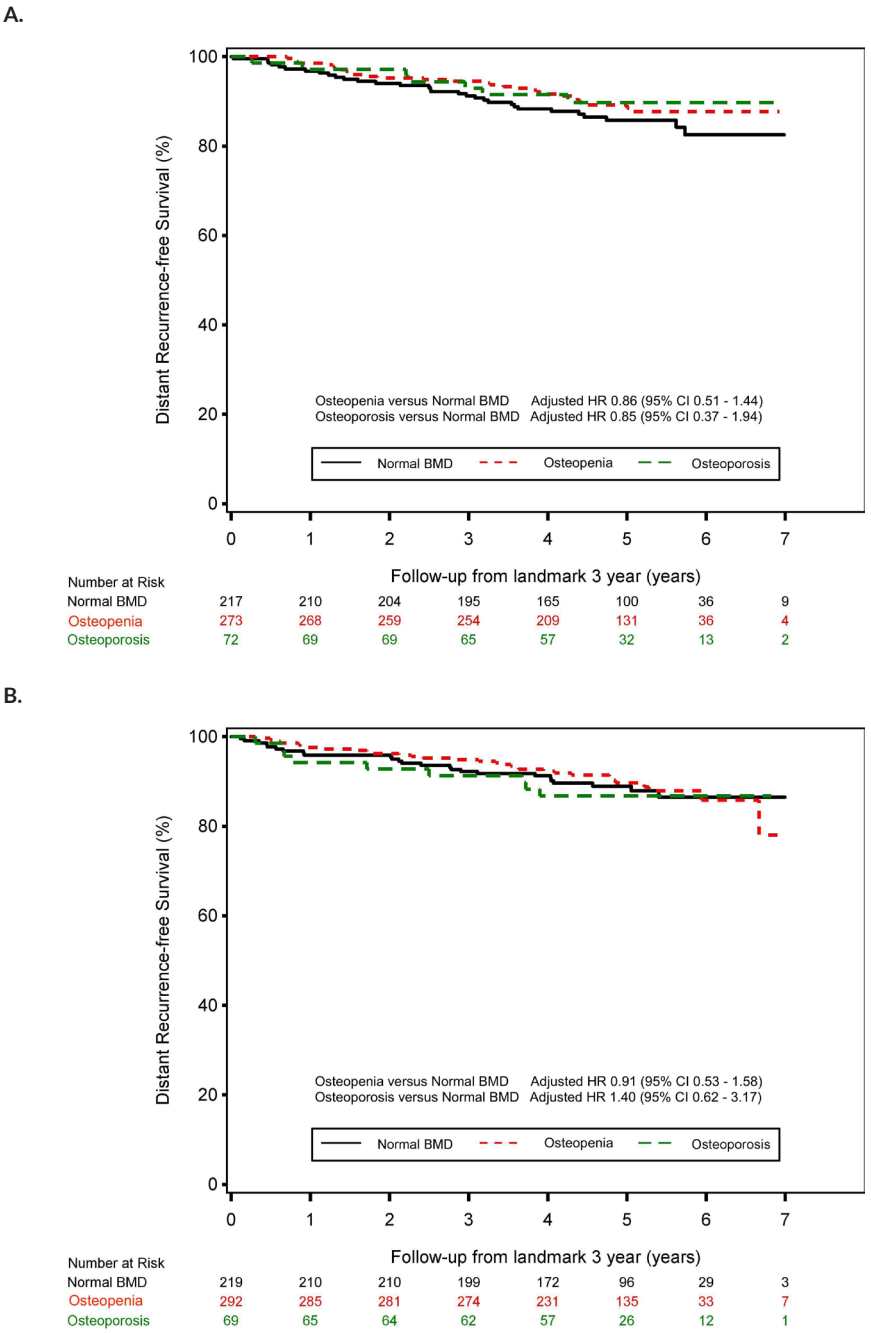
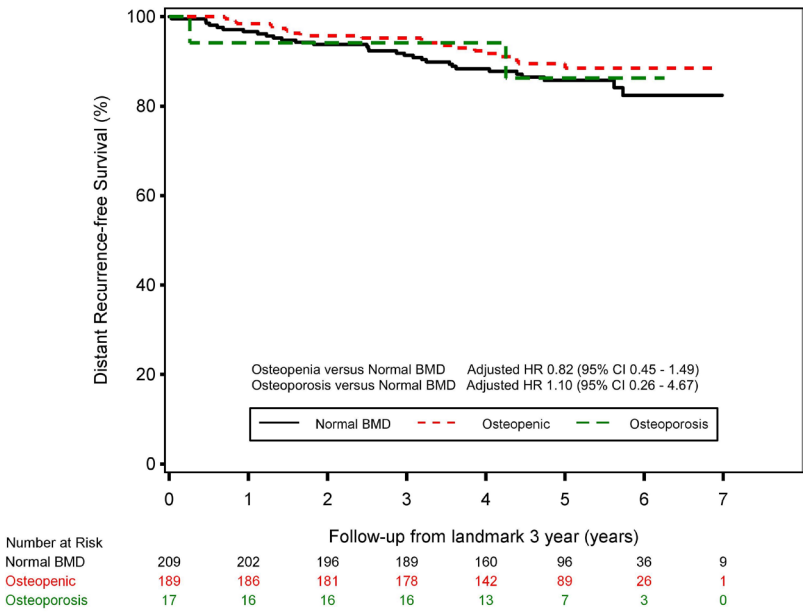


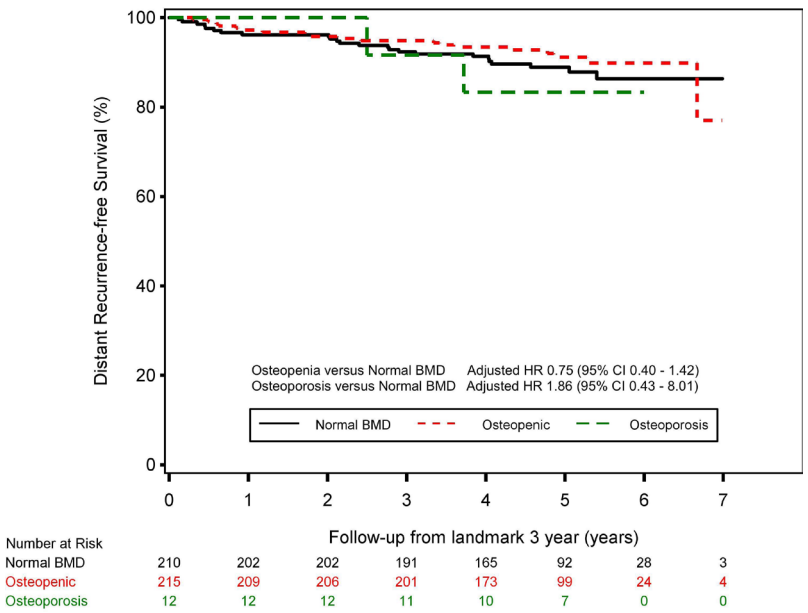
Figure 1. The impact of bone mineral density on distant recurrence free survival for the patients in **(A)** the 3-year anastrozole treatment arm, **(B)** the 6-year anastrozole treatment arm. Hazard ratios were adjusted for tumour size, nodal status, tumour grade and hormone receptor status.

A.



Number at Risk								
Normal BMD	209	202	196	189	160	96	36	9
Osteopenic	189	186	181	178	142	89	26	1
Osteoporosis	17	16	16	16	13	7	3	0

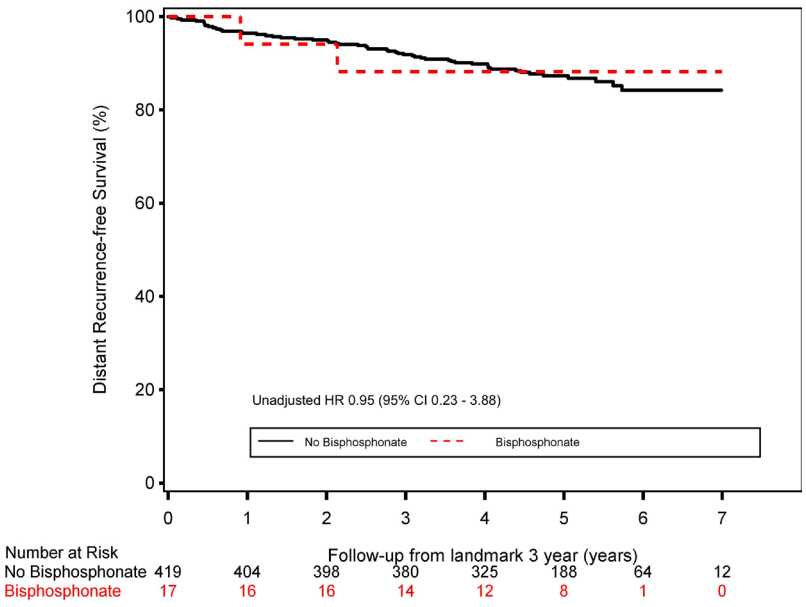
B.



Number at Risk								
Normal BMD	210	202	202	191	165	92	28	3
Osteopenic	215	209	206	201	173	99	24	4
Osteoporosis	12	12	12	11	10	7	0	0

Figure 2. The impact of bone mineral density on distant recurrence free survival selecting only the patients without bisphosphonates before the landmark in **(A)** the 6-year anastrozole treatment arm, **(B)** the 3-year anastrozole treatment arm. Hazard ratios were adjusted for tumour size, nodal status, tumour grade and hormone receptor status.

A.



B.

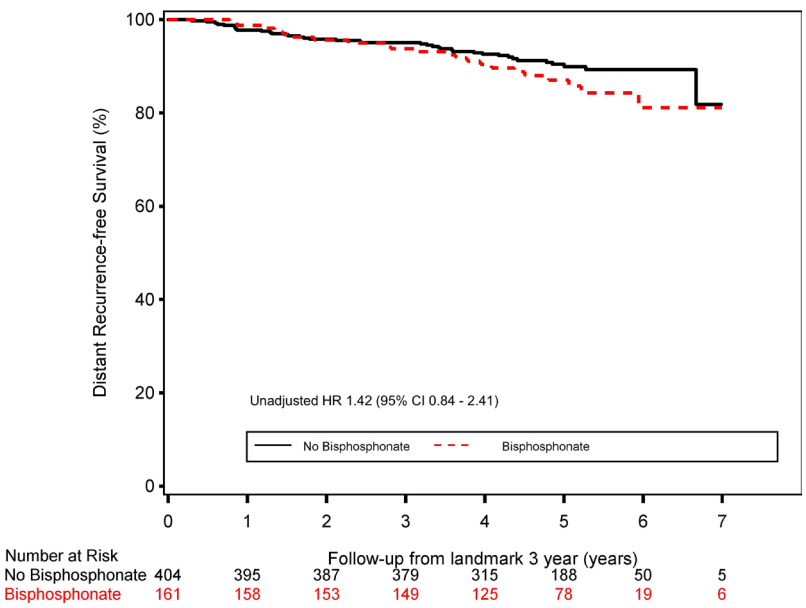


Figure 3: The impact of bisphosphonate-use before the landmark on distant recurrence free survival in the women with **(A)** a normal BMD, **(B)** osteopenia, and **(C)** osteoporosis at the 3-year landmark.

C.

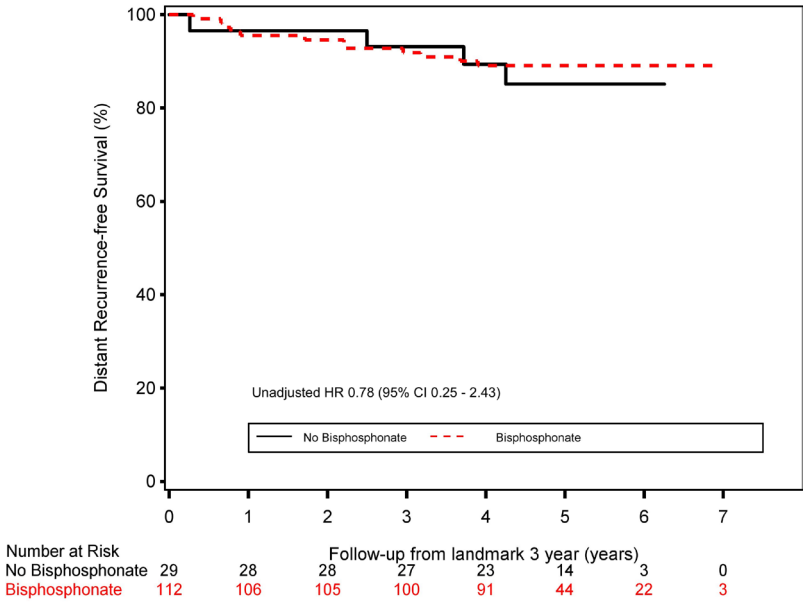


Figure 3: Continued.

Discussion

The phase III DATA study investigates the optimal duration of adjuvant anastrozole (6 vs 3 years) in postmenopausal women with hormone receptor-positive breast cancer, after previous 2-3 years of adjuvant tamoxifen. In this pre-planned side-study we found no relationship between BMD and DRFS. Moreover, we did not observe a relationship between bisphosphonate treatment and DRFS.

Multiple observational trials observed that a reduced BMD was associated with a lower risk of developing breast cancer,[9,10] but it is insufficiently clear whether a reduced BMD in early breast cancer patients is related to a lower risk of distant recurrences. We were not able to show such a relationship in DATA patients, neither after adjusting for bisphosphonate use, as this could be a potential confounder. To our knowledge, this has only been studied partly in two trials. First, in the MA.14 trial it was studied whether baseline beta C-telopeptide, a marker of bone resorption, predicted relapse in postmenopausal breast cancer patients.[14] They showed that a higher bone resorption was associated with a higher incidence of bone metastases (HR 2.80 (95% CI, 1.05-7.48; P 0.03)) during follow-up. Adjustment for bisphosphonate-use was not performed, patients were treated with tamoxifen instead of an aromatase inhibitor, and importantly, no information on BMD measurements was available.[14] The second study, the MA.27 trial, examined the effects of self-reported osteoporosis and

osteoporosis therapy on breast cancer outcomes. The study included 7576 postmenopausal patients during adjuvant aromatase inhibitor treatment (anastrozole/exemestane) for breast cancer.[15] Of patients who did not receive bisphosphonates, the event-free survival rate was 86% (95% CI, 78%-91%) in case of osteoporosis (n=193) and 87% (95% CI, 86%-89%) in patients without osteoporosis (n=4672) (no HR reported). While their findings are in line with the results of the current study, it should be recognised that in the MA.27 trial no detailed information was collected on BMD assessments and information on osteoporosis was self-reported.[15]

A possible explanation for not finding an association between a reduced BMD and a lower breast cancer recurrence risk might be that women with osteoporosis have less benefit of aromatase inhibitors because their oestrogen levels tend to be lower than in women with a normal BMD. Hence, in patients with lower intrinsic oestrogen levels – resulting in higher risk of osteoporosis – the breast recurrence risk is reduced in a similar way as in patients with intrinsic higher oestrogen levels treated with aromatase inhibitors.

Earlier studies found bisphosphonates to be valuable in both breast cancer prevention and improved breast cancer survival (when given as adjuvant therapy) irrespective of bisphosphonate type.[1-3,7,16] Further, another trial showed that cessation of bisphosphonate treatment after breast cancer diagnosis doubled the risk of developing bone metastases (HR = 2.03, 95% CI 1.26 to 3.26),

whereas taking bisphosphonates post-breast cancer diagnosis only, or continuing post-diagnosis reduced the risk of bone metastases (45% and 28% relative reduction respectively) after a median 5-year follow-up.[17] Also in the MA.27 trial a 5-year absolute 3% improvement of the event-free survival was observed for the patients receiving osteoporosis therapy in comparison with the patients who did not receive osteoporosis therapy (86% vs 89%, HR 0.63 (95% CI, 0.40-1.00)) during adjuvant aromatase inhibitor therapy for breast cancer.[15] The benefit was larger in patients without osteoporosis (87% vs 92%, HR 0.65 (95% CI, 0.61-0.68)). The bisphosphonate treatment in our study was also predominantly started for a reduced BMD, however, we did not observe an effect on DRFS. A possible explanation for the diverging observations is that in the MA.27 trial a standard Cox regression analysis was used, potentially overestimating the treatment effect of osteoporosis therapy by introducing 'immortal time bias'.[18] When the start of osteoporosis therapy was used as a time dependent covariate the effect on DRFS was not found.[15]

Bisphosphonates inhibit osteoclastic bone resorption by attaching to bony surfaces undergoing active resorption and prevent osteocyte and osteoblast apoptosis.[19,20] Through these mechanisms bisphosphonates increase the BMD, decrease the incidence of osteoporotic fractures, and were implemented as therapy for metastatic skeletal disease.[21] However, increasing evidence exists that bisphosphonates might not only target the osteoclast, but also have direct anti-tumour activity and work synergistic with cytotoxic therapies.[22-24] These might be the mechanisms responsible for the observed clinical benefits in trials investigating the efficacy of zoledronic acid in combination with standard anticancer therapy in early breast cancer patients.[2,4,5] Noticeably the indirect metastasis-preventing effect of bisphosphonates seems limited to postmenopausal patients,[7] which implies that the effect of oestrogen on the bone microenvironment might play an important role in the benefit from adjuvant bisphosphonate therapy.[25]

Even though this was a planned side-study of the DATA-trial, the execution of DEXA scans was not protocolized but was advised to adhere to (inter)national guidelines. This probably explains the absence of BMD measurements within 3 years after randomisation in about one third of the patients. Furthermore, 19.1% of the women with osteoporosis did not use any bisphosphonates which was not in accordance with the recommendations in the national guideline. Additionally, the use of bisphosphonates was not randomised but based on the outcome of the DEXA scans, therefore confounding by indication could not be ruled out. The occurrence of bone metastases was not registered as specific item anymore after the occurrence of distant metastases elsewhere, and therefore we could not use bone metastases free survival as an outcome. Also, with longer follow-up results may change. Nevertheless, this is the first prospective trial studying the relationship between BMD and DRFS with detailed information on BMD in 1142 patients.

In conclusion, we observed no association between BMD and DRFS in this pre-planned DATA sub-study. Neither did we observe a relationship between bisphosphonate use and DRFS.

Acknowledgements

We thank Wim A.J.G. Lemmens, Bianca Schalk, and Ton de Haan for their assistance with performing the statistical analyses.

Funding

Funded by AstraZeneca NL, ClinicalTrials.gov number, NCT00301457.

Disclosures

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 other from Novartis, other from Cergentis, other from Philips Health BV, grants, non-financial support and other from AstraZeneca, grants and non-financial support from Roche, grants and non-financial support from Genentech, other from IBM, grants from Tesaro, other from Bayer, other from Pfizer, outside the submitted work. 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. All other authors declare no competing interests.

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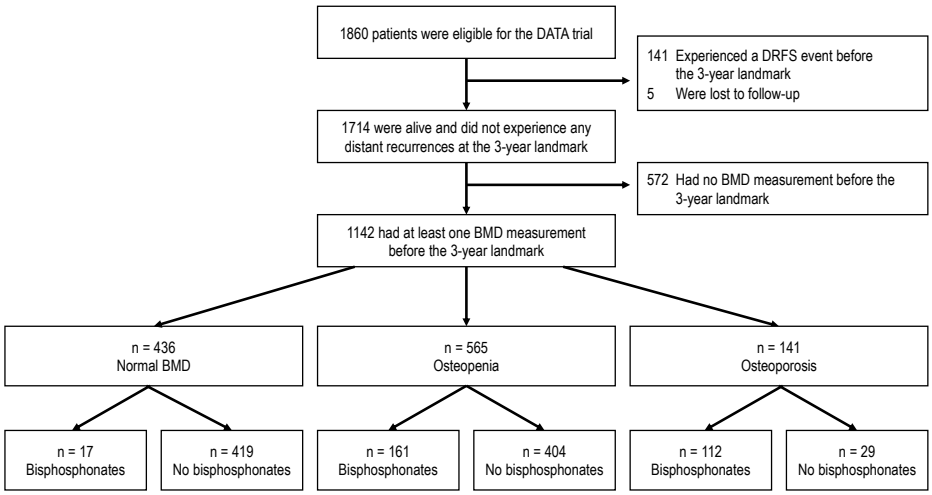
Supplementary appendix

Appendix Table 1. Baseline characteristics of all eligible randomised patients in the DATA study comparing 3 and 6 years of anastrozole after 2 to 3 years of tamoxifen (n=1860).

Characteristics	Total group n = 1860	6 years Anastrozole n = 931	3 years Anastrozole n = 929
Age at randomisation (years) – no. (%)			
Median age at randomisation (IQR)		58.1 (51.9; 64.8)	57.8 (51.5; 64.6)
< 49 years	328 (17.6)	159 (17.0)	169 (18.2)
50-59 years	735 (39.5)	372 (40.0)	363 (39.1)
≥ 60 years	797 (42.9)	400 (43.0)	397 (42.7)
Tumour status – no. (%)			
pT1	832 (44.8)	411 (44.2)	421 (45.4)
pT2	878 (47.3)	448 (48.2)	430 (46.3)
pT3/4	148 (8.0)	71 (7.6)	77 (8.3)
TX	2	1	1
Nodal status – no. (%)			
pN0 / pN0(i+)	605 (32.5)	295 (31.7)	310 (33.4)
pN1	991 (53.3)	490 (52.6)	501 (53.9)
pN2 / pN3	264 (14.2)	146 (15.7)	118 (12.7)
Histological grade – no. (%)			
Grade I	311 (17.2)	146 (16.2)	165 (18.3)
Grade II	940 (52.1)	475 (52.8)	465 (51.4)
Grade III	552 (30.6)	278 (30.9)	274 (30.3)
Unknown	57	32	25
Hormone-receptor status – no. (%)			
ER and PR positive	1396 (75.1)	698 (75.0)	698 (75.1)
ER or PR positive	464 (25.0)	233 (25.0)	231 (24.9)
HER2 status – no. (%)			
Positive	37 (2.1)	21 (2.4)	27 (3.1)
Negative	1675 (97.2)	841 (97.6)	834 (96.9)
Unknown	137	69	68
Histology – no. (%)			
Lobular	338 (18.2)	177 (19.0)	161 (17.3)
Other	1522 (81.8)	754 (81.0)	768 (82.7)
Type of breast surgery – no. (%)			
Breast-conserving surgery	919 (49.4)	474 (50.9)	445 (48.0)

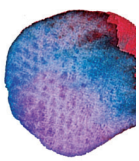
Appendix Table 1. Continued.

Characteristics	Total group n = 1860	6 years Anastrozole n = 931	3 years Anastrozole n = 929
Mastectomy	940 (50.6)	457 (49.1)	483 (52.0)
Unknown / Other	1	0	1
Type of axillary surgery – no. (%)			
Sentinel node only	505 (27.2)	263 (28.2)	242 (26.0)
Sentinel node plus axillary lymph node dissection	832 (44.7)	414 (44.5)	418 (45.0)
Axillary lymph node dissection	499 (26.8)	240 (25.8)	259 (27.9)
None	24 (1.3)	14 (1.5)	10 (1.1)
Radiotherapy – no. (%)			
Local	520 (28.0)	264 (28.4)	256 (27.6)
Local and regional lymph nodes	682 (36.7)	355 (38.1)	327 (35.2)
Regional lymph nodes	45 (2.4)	25 (2.7)	20 (2.1)
None/unknown	613 (33.0)	287 (30.8)	326 (35.1)
Prior (neo)adjuvant chemotherapy – no. (%)*			
Anthracycline- and taxane-containing regimen	112 (6.0)	49 (5.3)	63 (6.8)
Anthracycline-containing regimen without taxane	1115 (59.9)	566 (60.8)	549 (59.1)
Taxane-containing regimen without anthracycline	7 (0.4)	4 (0.4)	3 (0.3)
Regimen without anthracycline or taxane	25 (1.3)	9 (1.0)	16 (1.7)
No chemotherapy	601 (32.3)	303 (32.5)	298 (32.1)
Prior HER2-targeted therapy – no. (%)			
Yes	6 (0.3)	3 (0.3)	3 (0.3)
Previous duration of tamoxifen – no. (%)			
Median (IQR) (years)	2.3 (2.1 – 2.5)	2.3 (2.1 – 2.5)	2.3 (2.1 – 2.5)
Treatment with bone protective agents at inclusion – no. (%)			
Bisphosphonates	445 (23.9)	241 (25.9)	204 (22.0)
Vitamin D and/or Calcium	168 (9.0)	89 (9.6)	79 (8.5)



Appendix figure 1. Flow chart of the patient selection.

Discussion and summary

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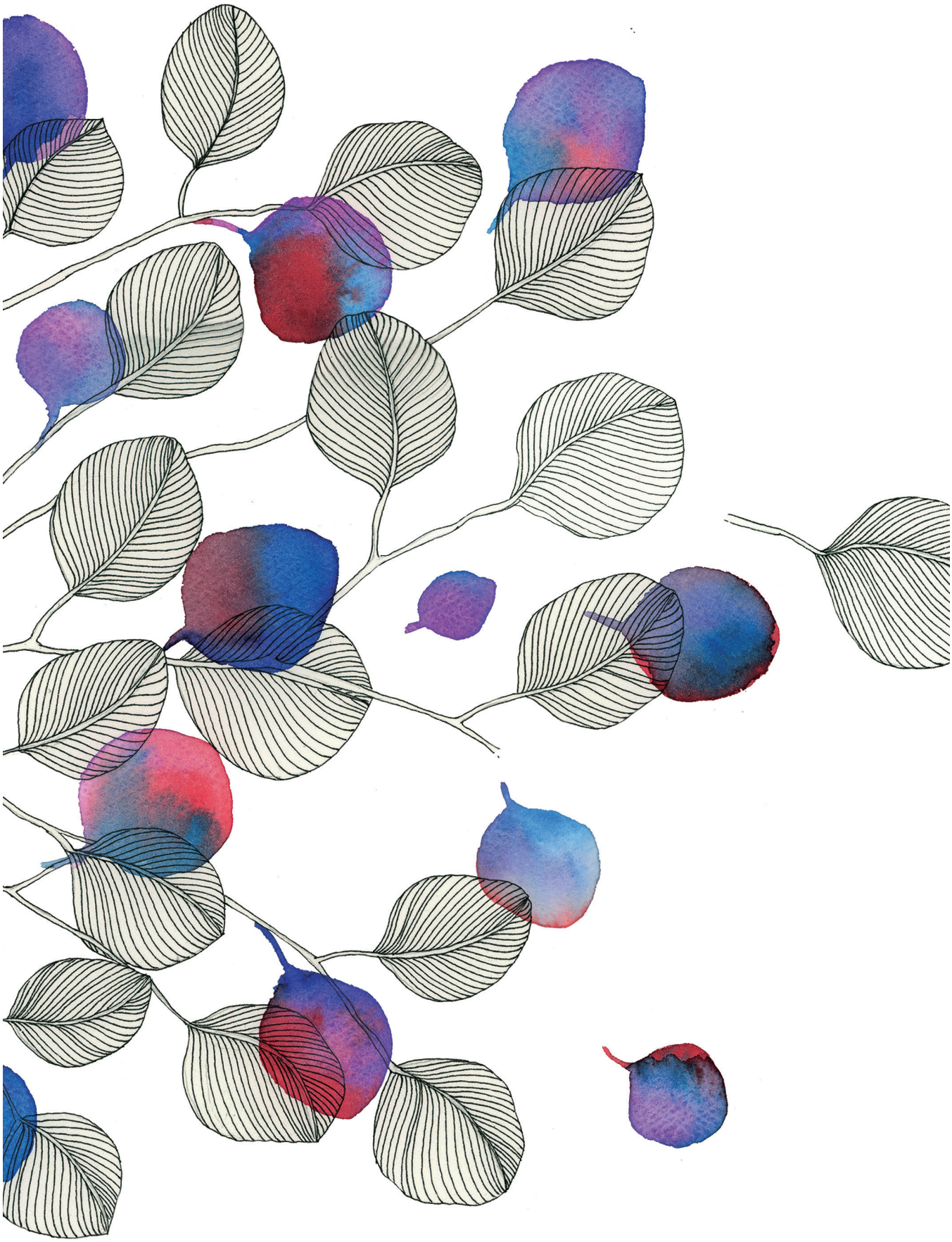

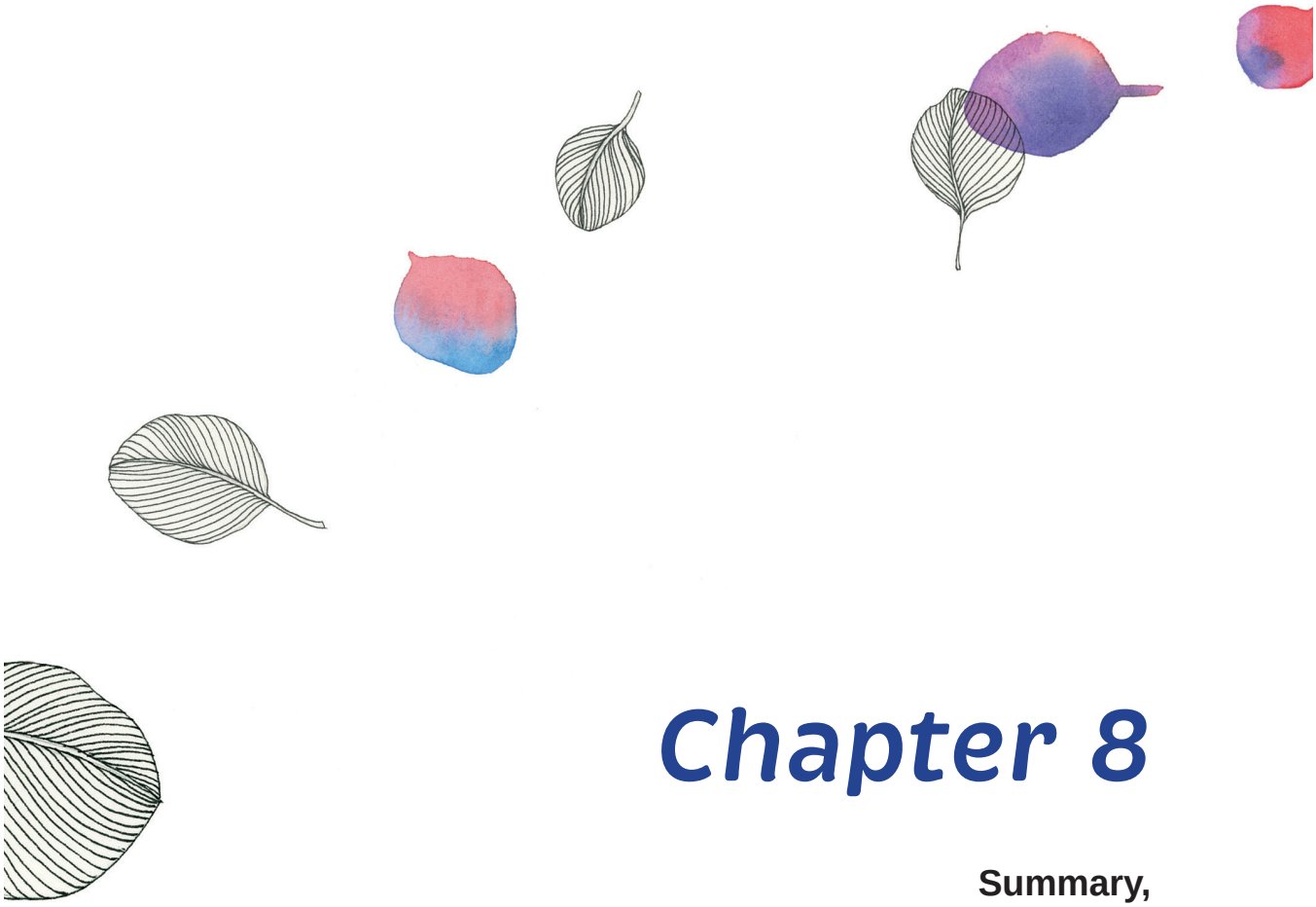

Chapter 8

Summary, general discussion, and future perspectives

Summary and general discussion

The central theme of this thesis is adjuvant endocrine therapy in postmenopausal early breast cancer patients, particularly focussing on prolonged duration and the potential drawbacks of endocrine therapy. This thesis includes several analyses from the phase III DATA trial, which was primarily designed to research the efficacy of extended adjuvant endocrine therapy with an aromatase inhibitor (AI). We aimed to give guidance for decision-making in common practice.

Part I

Chapter 1 is a general introduction, setting the stage at the moment the DATA trial was designed. The DATA trial included postmenopausal women with early breast cancer who completed 2-3 years of tamoxifen. Thereafter they were randomised to either 6 or 3 years of adjuvant anastrozole therapy. The results of the primary analysis are described in **chapter 2** showing no statistically significant benefit in adapted disease-free survival of 6 years of anastrozole in comparison with 3 years for the total group of patients. Adapted disease-free survival was defined as the disease-free survival beyond 3 years after randomisation, and was chosen as the primary end-point because all patients were on anastrozole therapy for 3 years. The median adapted follow-up was 4.2 years. The 5-year adapted disease-free survival was 83.1% in the 6-year and 79.4% in the 3-year group, yielding a hazard ratio of 0.79 (95% CI 0.62 to 1.02). Extended endocrine therapy did reduce the occurrence of secondary breast tumours, but had no or only a small impact on the distant metastasis-free survival. However, an exploratory analysis did show a possible benefit for women with high risk disease (e.g. node positive disease and a large tumour size). The five-year adapted overall survival did not differ between the treatment groups; 90.8% for the 6-year and 90.4% for the 3-year group (hazard ratio 0.91 (95% CI 0.65 to 1.29). There were no safety issues. **Chapter 3** puts the results of the DATA trial in perspective to other clinical trials on the duration and sequence of endocrine therapy. The efficacy results of the DATA trial were in line with the findings of the IDEAL and the NSABP B42 trial, both investigating the efficacy of extending AI therapy after 2.5 to 5 years of endocrine therapy with either tamoxifen or an AI. Moreover, all trials showed a similar pattern of gradually decreasing compliance rates due to the toxicity of adjuvant AIs. Therefore, we suggest considering extended adjuvant treatment only in motivated women with high-risk early breast cancer who tolerate treatment well.

Extended endocrine therapy

The benefit of extending adjuvant endocrine therapy with an AI in postmenopausal breast cancer patients has been reported on 9 randomised clinical trials over the last decade.[1-9] The design of these trials differed with respect to the type (tamoxifen, an AI, or both), and the duration (2.5 to 5 years) of the initial endocrine therapy, and the total duration of extended AI therapy (2.5 to 10 years). These differences complicate the interpretation of their findings. In general, extended AI treatment led to a modest 2-4% absolute reduction in recurrences, particularly in locoregional recurrences and second primary breast cancers. The absolute reduction in distant recurrences was 1-3%. Only one study showed a statistically significant improvement of the overall survival, but it was limited to patients with node positive disease.[4] The results of a meta-analysis of individual patient data on this topic by the early breast cancer trialists' collaborative group (EBCTCG) were presented at the San Antonio breast cancer conference in December 2018.[13] In this meta-analysis the effect of extended endocrine therapy with an AI was analysed for three different groups based on the treatment these patients had received in the preceding 5-10 years; 1) tamoxifen alone, 2) sequential treatment, 3) AI alone. The 5-year recurrence rates for extended treatment vs controls were 7.1% and 10.7% in the first group, 7.1% and 9.2% In the second group, and 6.6% and 7.9% in the third group, respectively, concluding that the benefit of extending endocrine therapy with AIs particularly exists for women who had received tamoxifen somewhere during the first 5 years. Also, the meta-analysis showed that mainly local and contralateral recurrences were prevented instead of distant recurrences. Moreover, they showed that the benefit mainly existed for the women with node-positive disease. The 5-year recurrence rates (from all included trails irrespective of initial treatment) for the extended treatment vs control groups were 5.1% vs 6.2% for women with node-negative disease, 8.7% vs 12.5% for 1-3 positive nodes, and 12.2% vs 19.9% for 4 or more positive nodes. Nevertheless, breast cancer mortality was not statistically significantly different.

Given the modest gain of extended treatment with AIs it can be debated on how these results should be interpreted for use in clinical practice. We should keep in mind that the survival curves of the included trials start to diverge from about 4-5 years after randomisation, which was also observed in the trials on extending treatment with tamoxifen.[11,12] In the ATLAS trial, the 5-year recurrence rates were 13.1% for extended tamoxifen vs 14.5% for controls, and at 10-year the rates were 21.4% vs 25.1% respectively (p=0.002).[11] The effect on distant recurrences was also limited but increasing over time (5-year distant recurrence rate of 10.4% for the extended group vs 11.4% in the control group, 10-years distant recurrence rate of 17.2% and 19.3% respectively (p=0.05)). The 5-year breast cancer mortality rates were 5.8% vs 6.0%, and after 10 years 12.2% vs 15.0% respectively (p=0.01). Thus, the effect of extending treatment with tamoxifen observed after 5 years was also marginally, but relevantly larger after 10 years. Therefore, since the median follow-up of the trials on extended AI therapy is

only 2.5-6.9 years, a longer follow-up is necessary to appreciate the full impact of extended treatment. Moreover, just as the patients with node positive disease, it is likely that other subsets of patients will have more clinically significant benefit. Therefore, it is important to understand the individual factors predicting safety, tolerance, and which individuals are at risk of late distant recurrences.

If extended AIs are not proven effective in patients who already received 5 years of an AI,[13] it could be questioned why we shouldn't just initially treat all women with this regimen. In this respect it is noteworthy to consider the long-term follow-up results of the TEAM trial[14] and the BIG 1-89 trial[15], showing that both 5 years of AI monotherapy and the 5-year sequential scheme are reasonable treatment strategies, given that no statistically significant differences were noted for disease-free survival and overall survival between the treatment groups.[14,15] As extended AI treatment results in a further survival improvement in patients with high-risk breast cancer treated with a 5-year sequential scheme, the overall outcome in the end may be superior in those who have received both types of drugs (tamoxifen and AIs) as compared with the patients treated with only one drug. To answer this question, the 5-year AI treatment needs to be compared with 2-3 years tamoxifen followed by 5-6 years of AI treatment. This has not been compared directly in a randomised clinical trial yet.

Although in the TEAM trial a small benefit was reported for exemestane monotherapy with regard to cumulative incidence of any breast cancer recurrence, this seemed to be counter-balanced by a higher number of other cause mortality.[14] Also the 10-year follow-up results from the ATAC trial suggested cardiovascular events to cause a higher non-breast cancer related mortality in the AI monotherapy treatment arm.[14] AIs do not have the cardioprotective effect of tamoxifen[16], which might be the preferred drug for patients with a relatively low-risk breast cancer and high-risk cardiovascular profile. But on the other hand, tamoxifen is associated with an increased risk of venous thrombosis and endometrial carcinoma.[17] A systematic review of clinical trials comparing AIs and tamoxifen as primary adjuvant endocrine therapy indeed showed that a longer duration of AI use was associated with higher risk of developing cardiovascular disease (odds ratio 1.26, $p<0.001$), and bone fractures (1.47, $p<0.001$), but a lower risk of venous thrombosis (0.55, $p<0.001$), and endometrial carcinoma (0.34, $p<0.001$).[17] Also the meta-analysis of the EBCTCG on extended endocrine therapy with AIs showed a statistically significant higher incidence of bone fractures in the 14026 women who received extended AIs (9.6% in the extended group vs 7.8% in the control group, $p=0.0003$).[10] Therefore, the type and duration of endocrine therapy should be carefully considered, weighing the pro's and con's for each individual patient based on the risk of recurrence, medical history, body mass index (BMI), and other cardiovascular risk factors, including family history. Hopefully long-term follow-up of the existing trials comparing tamoxifen monotherapy, sequential therapy, and AI monotherapy will provide further guidance for this decision.

If a 5-year sequential scheme is chosen, it is unclear if one should start with an AI or with tamoxifen. To our knowledge, the only clinical trial directly comparing the two 5-year sequential schemes with AI monotherapy is the BIG 1-89 trial, of which long-term follow-up results were published recently.[15] At 14 years from randomisation, 38.2% of the patients in the tamoxifen-letrozole group had experienced a disease-free survival event, 36.2% in the letrozole-tamoxifen group, and 35.5% in the letrozole monotherapy group. For the overall survival events these percentages were 26.8%, 25.8%, and 25.3% respectively, and for distant recurrence-free survival events 16.0%, 16.1%, and 14.6%. No hazard ratios for the direct comparisons were presented. Also, the EBCTCG-meta analysis indicated a preference for upfront treatment with an AI, either in sequence or as monotherapy.[10] Nevertheless, none of the patients included in the extended adjuvant endocrine therapy trials used the sequence AI-tamoxifen as upfront treatment. Therefore, the effect of extended AIs thereafter is unknown. Another important factor is the adherence to endocrine therapy. In common practice, tamoxifen is assumed to be associated with a higher compliance and lower numbers of early drop-out. Therefore, in most Dutch medical centres, adjuvant endocrine therapy in postmenopausal women is started with tamoxifen followed by an AI, depending on the presence of individual contra-indications.

Compliance

Despite a small benefit of extended endocrine therapy, we should not underestimate the fact that 5-10 years of endocrine therapy is a very long time. What about the compliance rates? In the reports on clinical trials investigating extended endocrine therapy in early breast cancer, treatment compliance emerged as a large concern. In the DATA trial, non-compliance rates were 16% at 3 years after randomisation and 34% at 6 years.[5] In a sub-analysis of the IDEAL trial, the majority of early AI treatment discontinuation was caused by adverse events (20.4% of all patients, 58.0% of all early discontinuations).[18] The most frequently reported adverse events associated with AI treatment discontinuation were arthralgia (9.9%), fatigue (6.7%), depression (6.5%), hot flashes (6.5%), and alopecia (5.4%), which were grade 1 or 2 in 86%.[18] Additionally, they suggested that after 5 years of tamoxifen, patients are more inclined to stop therapy when encountering new AI related adverse events compared with patients who were pre-treated with an AI.[18] A possible explanation for the high arthralgia rate could be both the loss of the protective effects of tamoxifen on cartilage and the simultaneously initiation of cartilage damage by AI initiated oestrogen depletion as observed in animal models,[19] causing the side effects to be experienced to be worse with the switch strategy. We believe that these results stipulate that treatment tolerance and patient motivation are important factors in considering extended adjuvant endocrine therapy.

Prediction tools

In an attempt to predict which women are at risk of distant recurrences a simple clinicopathologic tool (Clinical Treatment Score post–5 years (CTS5)) was developed and validated to estimate the residual risk of distant recurrences after 5 years of endocrine treatment.[20] The CTS5 was validated as highly prognostic for late distant recurrences and identified 42% of women with < 1% per-year risk of late distant recurrences in whom extended endocrine therapy is likely to be of limited value.[20] Recently, the prognostic value of four molecular signatures in addition to the Clinical Treatment Score (nodal status, tumour size, tumour grade, age, and endocrine treatment) were compared for distant recurrence for 0 to 10 years and 5 to 10 years after diagnosis.[21] For late distant recurrence, the Breast Cancer Index (BCI), the Risk of Recurrence (ROR), and the Endopredict (EPclin) scores provided independent prognostic information particularly for patients with node-negative disease. But, of note, patients who received chemotherapy, sequential endocrine therapy, or had 4 or more positive lymph nodes were excluded from this study.[21] As these excluded high-risk patients are expected to benefit the most from extended endocrine therapy, the results of these prior studies remain difficult to interpret.

While gene expression profiling may be used to complement pathologic assessment and gain additional information on the probability of disease relapse[21] and chemo-sensitivity,[22] available DNA microarray technologies are not yet part of routine practice in the majority of countries. The Ki-67 antigen is a nuclear protein expressed in all phases of the cell cycle except the G0 phase and is considered an independent prognostic factor in early breast cancer.[23] In hormone receptor positive breast cancer, high levels of Ki-67 are associated with higher recurrence rates.[24] In the St Gallen International Expert Consensus in 2015 it was decided that a Ki-67 level above 20% is seen as indicative of a high-risk group appropriate to receive adjuvant chemotherapy.[25,26] The Ki-67 expression is currently used in several clinical trials for selecting high risk patients in whom additional adjuvant therapy might be effective. One of those trials is the MonarchE trial (NCT03155997) investigating the efficacy of adding abemaciclib, a CDK4/6 inhibitor, to standard endocrine therapy in patients with node-positive, hormone receptor-positive, HER2-negative early breast cancer with a high Ki-67 expression. Also, the NEOLBC trial (NCT03283384) uses Ki-67 to guide treatment decisions. Ki-67 is measured after 2 weeks of letrozole treatment in the neoadjuvant setting of strongly hormone receptor-positive, HER2-negative breast cancer. The patients with a low Ki-67 after 2 weeks of letrozole will receive only endocrine therapy because it is likely these tumours are very sensitive to endocrine therapy. If the Ki-67 is higher, patients will be randomised between standard chemotherapy plus endocrine therapy or a CDK4/6 inhibitor (ribociclib) plus endocrine therapy. Other currently available options for predicting disease free survival by evaluating treatment effect are determining the pathological response after neoadjuvant treatment,[27,28] the use of multi-modal imaging such

as PET-MRI,[29,30] and the measurement of circulating tumour cells.[31,32] In a study with 1087 patients the prognostic value of circulating tumour cells was analysed.[33] At two years after the completion of chemotherapy, in 18.2% of the patients circulating tumour cells were detected, which had statistically significant and independent prognostic relevance for overall survival (HR = 3.91, 95% CI 2.04 - 7.52, P < .001) and distant recurrence-free survival (HR = 2.31, 95% CI 1.50 - 3.55, P < .001).[33] Yet, it remains unknown how these techniques should be implemented in clinical decision making.

Dormancy

The impact of endocrine therapy on breast cancer survival has been remarkable. Nevertheless, given the complexities of cell signalling pathways and heterogeneity of cancer cells, it is not surprising that targeting a single pathway does not always result in successful targeted cancer therapy. The high number of long-term recurrences in hormone receptor positive breast cancer remains of large concern.

The presence of tumour cells in the bone marrow at breast cancer diagnosis was found to be associated with a poor prognosis in several studies.[34-36] The 10-year relapse-free and overall survival were 43.9% and 44.9% in patients with bone marrow involvement, and 62.7% and 65.7%, respectively, in patients without involvement (p=0.001).[36] Nevertheless, these results could also be looked at differently; even if bone marrow tumour cells were present at diagnosis, 56.1% did not develop a breast cancer recurrence within the following 10 years. And in the same study after 30 years of follow-up, 43% of the patients with disseminated single tumour cells at breast cancer diagnosis was still alive or died without any sign of breast cancer recurrence.[34] How can this be explained?

The potentially long period that precedes distant recurrence is often referred to as a period of latency or tumour dormancy.[37] The term dormancy includes both concepts of reversible cellular quiescence and tumour mass dormancy which likely coexist.[37] In case of reversible cellular quiescence, individual cells with metastatic potential are conserved in a state of cell cycle arrest characterized by a major reduction or complete absence of proliferation. Tumour mass dormancy is considered a balance between a proliferating cellular population and another population with a higher cellular death rate.

Several mechanisms have been identified by which disseminated cancer cells or small tumours can remain dormant such as angiogenic insufficiency, immune-surveillance, exiting the cell cycle due to host-specific features at the metastatic site, or selection by chemotherapy.[38,39] Dormant cells are generally considered to be resistant to cytotoxic chemotherapy because

its efficacy is often dependent on malignant cells actively going through the cell cycle.[40] Most drugs approved for treating recurrent cancer are the same used to treat primary disease or disease that is already metastatic at diagnosis. Therefore, therapeutic agents targeting different elements in the multiple signalling pathways that enable cells to enter and maintain a dormant state became a focus of drug development strategies.[37,41,42] Future studies should be aimed at clarifying molecular triggers that bring about escape from dormancy, thereby, not focussing on extending existing therapies but on possibilities for intensifying therapy for a short duration.

Part II

The second part of this thesis focusses on the particular subgroup of breast cancer patients with chemotherapy-induced ovarian function failure (CIOFF). **Chapter 4** shows that the risk of ovarian function recovery (OFR) during the treatment with AIs in patients with CIOFF is relevant, even beyond the age of 45 years, since 12.4% of these women experienced OFR within 30 months after randomisation. Furthermore, women experiencing OFR had statistically significant higher oestradiol levels during AI treatment (before OFR) than those without. **Chapter 5** describes the effect of OFR on survival. We showed that experiencing OFR had an unfavourable impact on distant recurrence-free survival (HR 2.27 (95% CI 0.98-5.25; p=0.05) and overall survival (HR 2.61 (95% CI 1.11-6.13; p=0.03)) despite of adequate treatment adjustment at detection of OFR. With the landmark set at 1 year after randomisation, the residual 5-year rate for distant recurrence-free survival was 76.9% for women with OFR before the landmark and 92.1% for women without OFR. The 5-year rate for overall survival was 80.8% and 94.4%, respectively. Hence, women with CIOFF receiving an AI may be at increased risk of disease recurrence if experiencing OFR.

We believe that the risk of OFR during AI therapy in breast cancer patients with CIOFF above the age of 45 years has been underestimated by many clinicians. With AIs being the standard endocrine therapy in post-menopausal women, yet inappropriate as monotherapy in pre- and perimenopausal women, the accurate identification of a woman's menopausal status has never been so important. Determining the menopausal status in breast cancer patients may be challenging. The unpredictability of hormone levels and vaginal bleeding during the time leading up to menopause, and the variable endocrine effects of breast cancer therapy cause the identification of a specific hormonal trend or event to define menopause to be difficult.[43] Also the criteria for identifying women as postmenopausal vary between trials. Time limits for last menstrual bleeding only identify the menopause retrospectively, and levels of oestrogens and FSH in the postmenopausal range can also occur in the peri-menopausal stage. Moreover, factors as BMI, lifestyle, and menstrual irregularity all can cause amenorrhea which may lead to misdiagnosis of a postmenopausal status. Uncertainty regarding a patient's menopausal

state may complicate therapeutic decision making and disqualifies peri-menopausal breast cancer patients from switching from tamoxifen to an AI, unless combined with oophorectomy, which is irreversible, or ovarian suppression, which is potentially reversible but also potentially ineffective.[44] The acceptability of these approaches needs to be assessed on an individual basis.

Predicting OFR

Several trials tried to identify markers for predicting OFR in breast cancer patients with CIOFF. In a sub-study of the ASTRRA trial, the accuracy of post-chemotherapy biological markers for predicting OFR was investigated in premenopausal breast cancer patients receiving adjuvant tamoxifen.[45] They observed that age under 40 years (p=0.009), oestradiol levels ≥37 pg/mL (p=0.003), and an anti-Müllerian hormone (AMH) level ≥800 pg/mL at 2 months after completion of chemotherapy (p=0.026) were independent predictors for OFR. The positive - and negative predictive value of each independent factor were 94.1% and 16.2% for age under 40 years, 100% and 14.8% for oestradiol, and 92.3% and 50.0% for AMH, concluding that a post-chemotherapy high AMH level might be a relatively accurate predictor of OFR, but a low AMH level does not rule-out OFR.[45] Another study examined the serum AMH evolution during chemotherapy and 24-month follow-up in premenopausal breast cancer patients receiving chemotherapy.[46] The serum AMH level rapidly decreased in all patients after each chemotherapy cycle to undetectable levels in most of them, and slowly increased in 45% of the patients during the 24-month follow-up. Patients with chemotherapy-induced amenorrhea at 6 months after chemotherapy were significantly older and had significantly lower basal AMH levels than patients who had resumed menses. In a third study a lower AMH recovery after chemotherapy was associated with older age and 12 months of amenorrhoea.[47] A limitation of these trials was that high oestrogen and low FSH levels were not considered as OFR, only if women also regained their menses. This is of importance, because only 48.6% of the women with biochemical OFR also reported menstrual bleeding in a sub-study of the DATA trial.[48] Two smaller trials found no relationship between AMH levels and experiencing OFR.[49,50] Moreover, the relationship between AMH and the occurrence of spontaneous pregnancies was investigated.[51] Neither baseline nor post-chemotherapy AMH values were associated with the chance of spontaneous pregnancies. Therefore, AMH seems to be a predictor of OFR equally to age and oestradiol levels, but its value in determining if a woman is definitely postmenopausal seems to be limited since the levels can fluctuate over time.

Ovarian function suppression

The TEXT/SOFT trials investigated the efficacy and safety of the addition of ovarian function suppression (OFS) to tamoxifen and exemestane in premenopausal women with hormone receptor positive early breast cancer.[52] The authors concluded that the addition of OFS to tamoxifen resulted in significantly higher 8-year rates of both disease-free and overall survival than tamoxifen alone. The use of the AI-OFS combination resulted in even higher rates of freedom from recurrence but not (yet) in overall survival benefit. It is not known why an overall survival benefit was not observed. Long term toxicity may play a role. It is therefore possible that despite being more effective, the risk-benefit ratio of the AI-OFS combination is less favourable on the long term although this is considering the patient selection by young age not very likely. Another possible explanation for not finding an overall survival benefit for the use of exemestane plus ovarian suppression as compared to tamoxifen alone might be the heterogeneity of treatment effect according to HER2-status.[52] Appendix table S1 describes the 8-year survival rates within the SOFT trial for the treatment arms tamoxifen with OFS, and exemestane with OFS.[52] The disease-free survival rates for the HER2-negative group (n=860) were 82.8% and 88.0%, respectively (HR 0.70 (95% CI 0.60-0.83), and for the HER2 positive group (n=117), 85.4% and 75.2%, respectively (HR 1.18 (95% CI 0.80-1.73) (P-interaction = 0.014). The overall survival rates for the HER2-negative group were 93.4% and 93.4%, respectively (HR 0.86 (95% CI 0.68–1.10), and for the HER2-positive group 95.1% and 85.9%, respectively (HR 1.91 (95% CI 1.05-3.46) (P-interaction unknown). These rates suggest that tamoxifen with OFS is the preferred treatment with patients with HER2-positive disease. Still, these are subgroup analyses and therefore future studies should separate these groups.

A meta-analysis by the Translational Aromatase Inhibitor Overview Group, including three randomised trials (Arimidex, Tamoxifen, Alone or in Combination Trial (ATAC), Breast International Group (BIG) 1-98, and Tamoxifen Exemestane Adjuvant Multicentre Trial (TEAM)), also observed heterogeneous endocrine treatment effects in postmenopausal breast cancer patients depending on HER2-status.[53] The HER2-negative group gained greater benefit from AI vs tamoxifen (HR = 0.70, 95% CI 0.56-0.87) than the HER2-positive group (HR = 1.13, 95% CI 0.75-1.71).

Nevertheless, it remains important to keep in mind that in some breast cancer patients the OFS by gonadotropin-releasing hormone (GnRH) agonists is incomplete, as was observed in 34.2% of the patients in the SOFT-EST trial.[44] Recently, in another trial OFS with the use of degarelix, a GnRH antagonist, was compared with triptorelin, a GnRH agonist, in premenopausal breast cancer patients receiving neoadjuvant letrozole.[54] The authors observed that OFS was achieved more quickly and maintained more effectively with degarelix than with triptorelin. In the triptorelin group 15.4% of the women had inadequate OFS during 6 months of follow-

up, none in the degarelix group. Interestingly, these data imply that the treatment effects observed in the TEXT/SOFT trial are possibly underestimated, because 80.7% of the patients used triptorelin as OFS.[52]

Which adjuvant endocrine treatment regimen should we choose for women with CIOFF? The subgroup-analysis of the DATA trial observed it is not safe to treat women with CIOFF with AI monotherapy because of the risk of OFR, even if the hormone levels are checked regularly.[48] The TEXT/SOFT trials observed a DFS (but no OS) benefit for the combination of AIs and OFS in pre- and perimenopausal women over tamoxifen monotherapy and tamoxifen with OFS, however, the risk of incomplete OFS by GnRH agonists during AI treatment remains an issue.[44,52] We believe that until OFS by medication has proven to be a fully reliable treatment option, definitive OFS by surgery should be considered instead.

Part III

The third part of this thesis concentrates on bone health issues during endocrine therapy. A decrease in bone mineral density (BMD) is a well-known side effect of the use of AIs. **Chapter 6** describes the patterns of care regarding detection and treatment of osteopenia and osteoporosis, and the trends in BMD during and after AI therapy in the DATA study. Therefore, all BMD measurements and the use of bisphosphonates were registered. Firstly, we observed that only 48.9% of the women had a BMD measurement within 1 year after randomisation and 64.2 % within 3 years. Moreover, we showed that subsequent anastrozole use was associated with a decrease of the BMD although the decline was modest and partially reversible after anastrozole cessation when bisphosphonates were continued. Extended endocrine therapy was not associated with a higher incidence of osteoporosis. Consequently, we believe that a low BMD should not be a major motive for disregarding AI therapy. In **chapter 7** we addressed the question if BMD has an impact on distant recurrence-free survival. Beyond a landmark of 3 years after randomisation, at which patients were categorized by the observed BMD results before the landmark, the 5-year residual distant recurrence-free survival rate was 89.7% in the osteopenia group, 86.7% in the osteoporosis group, and 88.9% in the normal BMD group for the 6-year arm, and 89.2%, 89.7% and 85.8%, respectively, for the 3-year anastrozole treatment arm. The distant recurrence-free survival adjusted for tumour characteristics was not significantly different between BMD categories, neither when only selecting the patients who did not use bisphosphonates. Moreover, we did not observe a relationship between bisphosphonate use and distant recurrence-free survival.

Surprisingly, the number of women in the DATA trial who underwent a BMD measurement within the first year after randomisation was only 48.9%, and only 64.2% at three years, while at the time of inclusion, the national guideline on breast cancer treatment advised a BMD measurement at the start

of AI therapy and every year afterwards if the T score was below -1.[55] Moreover, the results of our analysis in the DATA trial show that the baseline BMD measurement is important for determining the intensity of further follow-up of bone health in these women. Therefore, we would strongly recommend to perform a BMD measurement within the first year after the start of an AI.

Endocrine therapies and bone mineral density

The impact of several endocrine therapy regimens on BMD has been studied in the BIG-98 trial.[56] Whereas tamoxifen is known to counteract BMD loss and to decrease the fracture rate in postmenopausal women,[4] in the BIG-98 trial the sequential treatment of tamoxifen followed by an AI for a total duration of 5 years was reported to have a worse effect on BMD than AI monotherapy.[56] At six years after randomisation, spine osteoporosis was even threefold higher in the tamoxifen-letrozole arm (14% *vs* 4 %) compared with the remaining treatment arms (tamoxifen monotherapy, letrozole monotherapy, and letrozole-tamoxifen for a total of 5 years). This was a rather unexpected finding. The authors hypothesized this was possibly caused by the interruption of tamoxifen combined with the rapid fall in oestrogen levels induced by the AI, thereby promoting accelerated bone loss. This was confirmed by rapidly increasing bone turnover biomarkers after the switch.[56]

These results are in contrast to the findings of the EBCTCG meta-analysis.[13] At 5 years after randomisation, the incidence of fractures in the AI monotherapy group was 6.8% vs 5.4% in the tamoxifen-AI group. When AI monotherapy and AI-tamoxifen were compared, the incidence of fractures was 6.6% and 4.6%, respectively. Also in the ATAC trial, more fractures occurred during treatment in the anastrozole group in comparison with the sequential treatment group, but were similar at 10 years of follow-up, suggesting no carryover effect after treatment completion.[14,57] Unfortunately, no long term data were collected on bone health issues in the TEAM trial.[14] Therefore, since both the EBCTCG meta-analysis and the ATAC trial showed more fractures in the 5-year AI monotherapy groups, it seems that sequential regimens are preferred in women with osteoporosis, but there is insufficient evidence to prefer either sequential regimen (tamoxifen-AI *vs* AI-tamoxifen).

Breast cancer and bone mineral density

The biological link between breast cancer and BMD is strongly suggested by observations such as breast cancer survivors being at increased risk for clinical fractures, a reduced BMD being associated with a lower risk of developing breast cancer, and the bone being the primary location for developing metastases. [58-61] The cumulative exposure to oestrogen may play a role, yet, other factors have also shown to have impact on both BMD and breast cancer risk. Serum levels of insulin are positively associated with BMD,[62] and hyper-insulinaemia is an independent risk

factor for developing breast cancer.[63] Insulin-like growth factors are important determinants of bone mass,[64] and their levels have been associated with increased breast cancer risk, particularly in hormone receptor positive tumours.[65] Vitamin D is essential for bone mineralization,[66] and accumulating results from preclinical and some clinical studies strongly suggest that vitamin D deficiency increases the risk of developing cancer and cancer progression because vitamin D is the potent precursor to the steroid hormone calcitriol (vitamin D_3), regulating multiple signalling pathways involved in proliferation, apoptosis, differentiation, inflammation, invasion, and angiogenesis.[67] Additionally, the immune system is important in both developing osteoporosis and cancer. High levels of interleukin-6, which is known to be an essential mediator of bone loss related to loss of gonadal function, is also associated with more advanced stages of breast cancer including the development of metastases.[68] Activated T-cells are key stimulators of osteoclast genesis and can increase the production of tumour necrosis factor (TNF)-alpha and RANKL, which is prominent in case of osteoporosis and bone metastases.[68] Hence, the relationship between bone mass and breast cancer (recurrence) risk, likely involves a complicated interaction of hormones, growth factors, and cytokines.

In the MA.14 trial it was studied whether baseline beta C-telopeptide, a marker of bone resorption, predicted relapse in postmenopausal breast cancer patients.[69] They showed that a higher bone resorption before the initiation of chemotherapy was associated with a higher incidence of bone metastases (HR 2.80 (95% CI, 1.05-7.48; P 0.03)) during follow-up. No data was available on BMD measurements. Hypothetically it could be possible that the women with a high beta C-telopeptide did not have osteoporosis, but that it represented an interaction between circulating tumour cells and bone, thereby predicting distant recurrences. A cohort study showed that pre- breast cancer osteoporosis was not associated with risk of developing bone metastasis.[70] Nevertheless, if patients with untreated precancer osteoporosis developed bone metastases, it occurred approximately 1 year earlier than those without precancer osteoporosis (median time, 1.78 years *vs* 2.87 years; P < .001).

Bisphosphonates

Bisphosphonates play a pivotal role in the treatment of osteoporosis. Aside from preventing further bone loss and reducing the risk of fractures in the presence of osteoporosis, several clinical trials investigated the role of bisphosphonates as an adjuvant agent for preventing breast cancer recurrence.[71-76] The EBCTCG performed a meta-analysis based on patient data showing significant improvements in distant recurrence rates (21.9% no bisphosphonate vs 18.4% bisphosphonate, p < 0.001) driven by a bisphosphonate-related reduction in bone recurrence.[74] Also the ten-year breast cancer mortality decreased (18.3% vs 15.2% respectively, p=0.004). The effect was seen irrespective of bisphosphonate type. Noticeably the metastasis-preventing

effect of bisphosphonates seemed limited to postmenopausal women,[74] which implies that the effect of oestrogen on the bone microenvironment might play an important role in the benefit from adjuvant bisphosphonate therapy.[77] However, in the absence of any prospective randomised trials in which oestrogen data has been systematically collected we cannot specifically answer this question. Moreover, in the MA.27 trial a larger benefit of bisphosphonates was found for the breast cancer patients without osteoporosis compared with those with osteoporosis (5-year event free survival 92% vs 87% (P<0.0003).[78]

Bisphosphonates inhibit osteoclastic bone resorption by attaching to bony surfaces undergoing active resorption.[79] When osteoclasts resorb bisphosphonate-impregnated bone, the bisphosphonate prevents the osteoclast from the formation of protons and the ruffled border, both necessary for adhesion to the bony surface and continued bone resorption. Bisphosphonates also decrease osteoclast progenitor development and recruitment and promote osteoclast apoptosis and prevent osteocyte and osteoblast apoptosis.[80] Through these mechanisms, bisphosphonates have shown to increase BMD and decrease the incidence of osteoporotic fractures. Since osteoclast-mediated bone resorption occurs at an accelerated rate in the presence of tumour cells, bisphosphonates became also important in the management of metastatic skeletal disease.[81] However, increasing evidence exists that bisphosphonates might not only target the osteoclast, but also have direct anti-tumour activity. In vivo studies suggest that bisphosphonates inhibit tumour cell proliferation, inhibit angiogenesis, stimulate γδ T-cell anti-tumour activity, inhibit tumour cell invasion, and effectively reduce tumour cell persistence in bone marrow.[82] Moreover, bisphosphonates have shown synergistic anti-tumour activity with cytotoxic therapies.[83,84] Another in vitro study showed that zoledronic acid exerts an anti-breast cancer effect via stromal cells, accompanied by decreased stromal TGF-β excretion and reduced TGF-β signalling in cancer cells.[85]

Denosumab

More recently, the anti–receptor activator of nuclear factor kappa-B ligand denosumab was shown to continuously increase BMD without plateau and reduce fractures into a great extent.[86] However, several other trials showed that cessation of denosumab in patients with osteoporosis and/or vertebral fractures was associated with a strong decrease in BMD, which exceeded the initial increase shown over a period of 7-10 years, and an increased risk of vertebral fractures.[87-89] Therefore, if denosumab is discontinued (no data are available on its use for more than 10 years), a treatment with bisphosphonates should be considered in order to avoid rapid BMD loss and a possible rebound in vertebral fracture risk.[89,90] Nevertheless, the optimal bisphosphonate regimen (oral *vs* intravenous) is still being studied (NCT03396315). Also, the optimal timing and duration are unknown. Small case-series suggest that a single infusion of zoledronic acid

may not be effective in preventing bone loss following denosumab when bone turnover is still suppressed.[91] Bone turnover markers could possibly be used to determine optimal timing.[89] Therefore, it could be questioned if denosumab should be used for osteoporosis until these questions are answered.

Also the effect of denosumab on breast cancer survival was investigated, showing contrasting results.[92,93] The ABCSG-18 trial observed a clear advantage of denosumab (60mg 6-monthly) on disease-free survival (HR 0.82, p=0.026) in a study population of postmenopausal women using AIs, who were generally at a low risk of recurrence (25% received prior chemotherapy).[93] In the denosumab group, disease-free survival was 80.6% at 8 years of follow-up, compared with 77.5% in the placebo group. The D-CARE trial, including both pre- and postmenopausal women of whom 96% received prior chemotherapy, observed no advantage of a more intense regimen of adjuvant denosumab (120mg monthly for 6 months followed by 120mg 3-monthly) on disease-free survival (HR 1.04, p=0.57).[92] A subgroup analysis neither showed an effect for the subgroup of postmenopausal women.[92] Because of these contrasting results denosumab has not been registered (yet) as adjuvant treatment in women with breast cancer.

In terms of adverse events, osteonecrosis in the jaw was reported significantly more often in the denosumab arm in the D-CARE trial as compared to placebo.[92] The ABCSG-18 trial, using a lower dose of denosumab, did not observe any differences in the occurrence of osteonecrosis between the use of adjuvant denosumab and placebo.[93] Further, the Medicines and Healthcare products Regulatory Agency recently cautioned that denosumab has been associated with an increased incidence of new primary malignancies (1-year cumulative incidence 1.1%).[94]

Future perspectives

Any large randomised controlled trial such as the DATA trial contains a wealth of information aside from the primary objective. As written in the protocol we additionally planned to evaluate the cost effectiveness of 6- vs 3-years of adjuvant anastrozole therapy, and to map differences in breast cancer management between different regions in the Netherlands. Furthermore, we are interested in the influence of BMI on the extent of oestradiol deprivation during AI treatment, since, in contrast to many other cytotoxic therapies, it has not been given by weight- or body-surface-area–related dosing. This might explain the worse survival for obese breast cancer patients undergoing endocrine treatment when compared with non-obese patients.[95-99] Additionally, the translational part of the DATA-trial (trans-DATA) focusses on the identification of DNA methylation markers associated with the distant recurrence-free interval. Lastly, as specified in the protocol, a second analysis on the primary objective with longer follow-up is planned in the year 2021, also further extracting the causes of death.

When looking at the future, after a long period without mind blowing changes in the initial adjuvant endocrine treatment, ongoing clinical trials have the potential to change the landscape, such as trials combining CDK4/6 inhibition and mTOR inhibitors with endocrine therapy. Currently, five ongoing randomised clinical trials evaluate the role of three different CDK 4/6 inhibitors in the adjuvant setting. The CDK 4/6 inhibitors are administered for two years and are combined with standard endocrine therapy, consisting of tamoxifen, an AI, or both (combined with OFS in case of premenopausal women). These trials focus on intermediate to high risk luminal breast cancer patients (Palbociclib: PALLAS (NCT02513394). Ribociclib: EarlLEE-1 (NCT03078751), and EarlLEE-2 (NCT03081234). Abemaciclib: MonarchE (NCT03155997)). Moreover, the PENELOPE-B trial (NCT01864746) investigates the addition of palbociclib for 1 year to standard endocrine therapy in patients with significant residual invasive disease after neoadjuvant chemotherapy. Two ongoing randomised clinical trials assess the impact of mTOR inhibitors in the adjuvant setting. The SWOG S1207 trial (NCT01674140) evaluates the use of everolimus for one year combined with standard endocrine therapy in patients with high-risk, hormone receptor positive, and HER2-negative breast cancer. A French trial (NCT01805271) researches the benefit of adding everolimus to adjuvant endocrine therapy in women with high risk breast cancer who show no sign of recurrence after 1 year of adjuvant endocrine therapy.

Sequencing of cell-free DNA circulating in the plasma of pregnant women to screen for the common fetal autosomal aneuploidies, the so-called NIP test, is the first widespread implementation of genomic medicine.[100] These techniques could also be used for detection circulating tumour DNA (ctDNA), which potentially could offer a precise and non-invasive tumour evaluation allowing a broad incorporation into clinical practice, ranging from cancer diagnosis to prognostic stratification, and treatment guidance. Some ctDNA assays have

demonstrated clinical validity and utility with certain types of advanced cancer; however, for the majority of assays there is still insufficient evidence. [101-103] Until now, there is no evidence of ctDNA assays used for cancer screening, use in early-stage cancer, treatment monitoring, or residual disease detection, outside of a clinical trial.[102] Hopefully future techniques will prove to be valuable in guiding treatment decisions with the possibility of intensifying treatment, only if necessary, based on the tumour biology.

To conclude, the use of increasingly effective systemic therapy strategies has significantly improved the outcome of early breast cancer patients over the last decades. Whereas the 10-year overall survival of women with breast cancer diagnosed in the Netherlands was only 61% in the period 1981 to 1990, it improved to 79% in the period from 2006 to 2010.[104] With the results from the DATA trial we were able to add relevant evidence for a better daily clinical practice, but there is still room for further improvement. To achieve this goal new targeted therapies are tested which hopefully prove valuable. Participation in randomised intervention trials remains very important in order to contribute to a better health care in the future.

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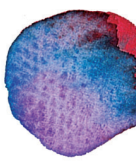
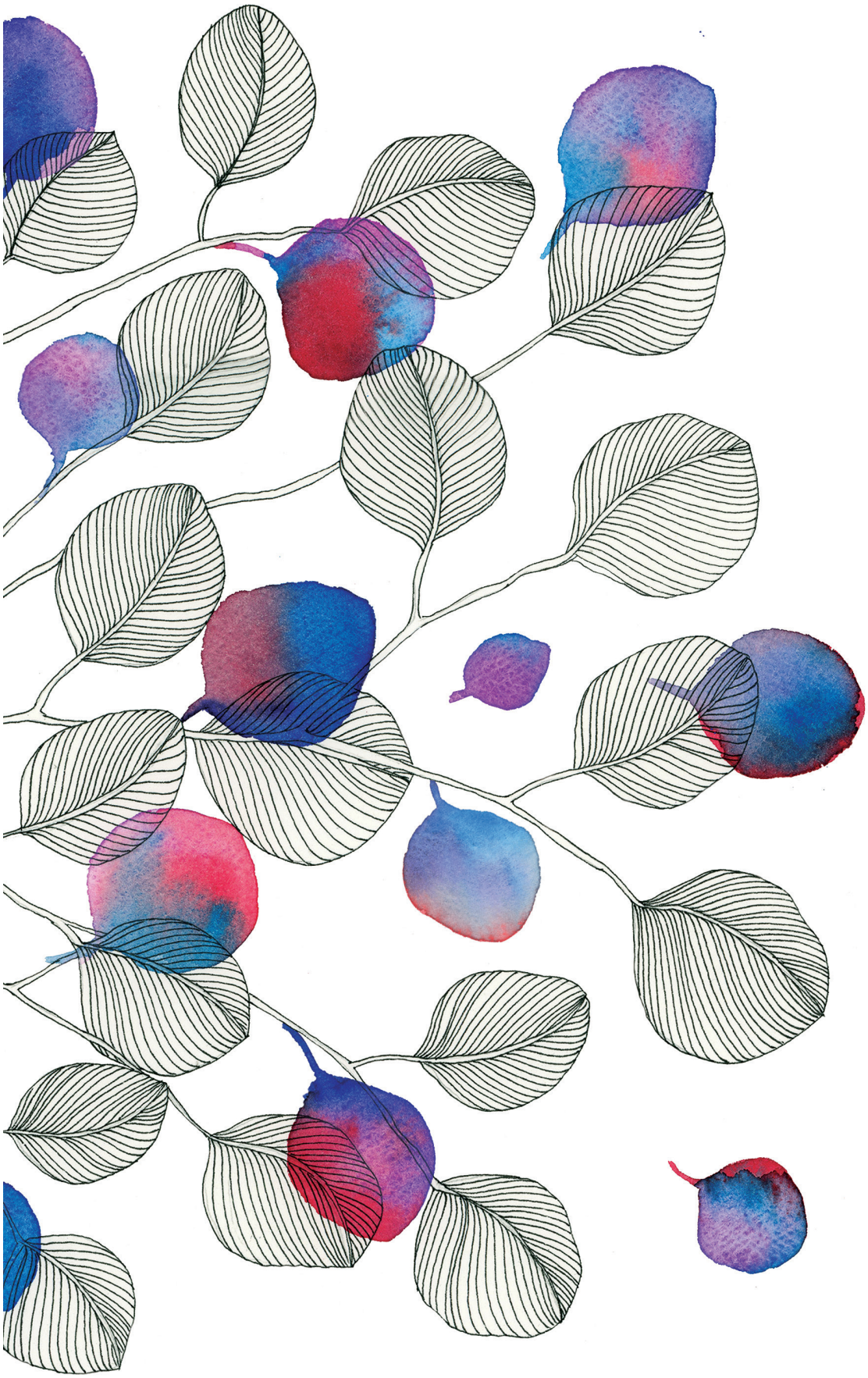
Addendum




Part V



Addendum

Nederlandse samenvatting

Nederlandse samenvatting

Met ruim 2 miljoen nieuwe diagnoses wereldwijd in 2018, is borstkanker de meest voorkomende vorm van kanker onder vrouwen. Wanneer borstkanker in een vroeg stadium wordt ontdekt, is de kans op loco-regionale genezing groot, maar enkele tumorcellen kunnen zich hebben verspreid voordat lokale behandeling middels chirurgie en radiotherapie worden geïnitieerd. Wanneer deze ontsnapte tumorcellen niet worden behandeld, kunnen zich levensbedreigende metastasen op afstand ontwikkelen. Het risico hierop is het grootst gedurende de eerste jaren na de diagnose borstkanker, maar nog steeds substantieel in de jaren daarna, met name bij patiënten met hormoonreceptor-positieve vormen van borstkanker.

Van alle gevallen van borstkanker is 60-70% hormoonreceptor-positief, wat betekent dat ze voor hun groei afhankelijk zijn van de hormonen oestrogeen en progesteron. De afgelopen decennia zijn verschillende medicamenten ontwikkeld die deze hormoonreceptoren als doelwit hebben, zoals tamoxifen, dat de effecten van oestrogenen op de tumorcel antagoneert, en aromataseremmers, die de circulerende concentratie van oestrogenen bij postmenopauzale vrouwen verlagen. Bij aanvang van de studies beschreven in dit proefschrift bedroeg de duur van de hormonale behandeling bij hormoonreceptor-positieve vormen van borstkanker meestal 5 jaar. Omdat bekend is dat het risico op terugkeer van borstkanker verhoogd blijft voor tientallen jaren na het stellen van de diagnose borstkanker, is het van belang te onderzoeken wat de effecten zijn van het verlengen van de duur van de hormonale therapie.

De mogelijkheden voor oncologische behandeling breiden zich in snel tempo uit, maar de enige juiste reden voor het starten van zo'n behandeling is wanneer het de prognose verbetert zonder al te veel bijwerkingen. Daarom is het belangrijk om de mogelijkheden en gevolgen van reeds bestaande behandelingen goed te onderzoeken. In dit proefschrift staat de hormonale behandeling van postmenopauzale vrouwen met een vroeg-stadium borstkanker centraal, waarbij de focus is gelegd op de vraag wat de optimale duur van hormonale behandeling is en wat de potentiële bijwerkingen zijn. Dit proefschrift bevat meerdere analyses van de DATA-studie, een fase III gerandomiseerde studie om het effect van verlengde hormonale therapie met aromataseremmers op overleving na de diagnose borstkanker te onderzoeken.

Deel I

Hoofdstuk 1 bevat een algemene introductie met de stand van zaken op het moment dat de DATA-studie in 2006 werd opgezet. Postmenopauzale vrouwen met een vroeg stadium borstkanker die een 2-3 jaar durende behandeling met tamoxifen hadden ondergaan werden in de DATA-studie geïncludeerd. Deze vrouwen werden verdeeld over twee behandelgroepen; de

ene groep werd over een periode van 6 jaar behandeld met anastrozol en de andere groep over een periode van 3 jaar. Anastrozol is een aromataseremmer die het oestrogeengehalte in het lichaam tot een minimum beperkt, met als doel eventuele achtergebleven hormoongevoelige borstkankercellen te vernietigen. De resultaten van de eerste analyse na een mediane follow-up van 4.4 jaar, gemeten vanaf 3 jaar na randomisatie, zijn beschreven in **hoofdstuk 2**. Hieruit komt naar voren dat de vrouwen in de 6-jaars behandelarm geen statistisch significant betere ziektevrije overleving hebben dan de vrouwen in de 3-jaars behandelarm. De 5-jaars ziektevrije overleving is namelijk 83.1% bij 6 jaar behandeling en 79.4% bij 3 jaar behandeling, met een hazard ratio (HR) van 0.79 (95% betrouwbaarheidsinterval 0.62 – 1.02). Wel is gebleken dat verlengde hormonale therapie het aantal gevallen van nieuwe primaire borstkanker reduceert, maar tegelijkertijd heeft dit geen of slechts een kleine impact op het ontwikkelen van metastasen op afstand. De algehele overleving na 5 jaar is niet verschillend tussen de behandelgroepen; namelijk 90.8% in de 6 jaar en 90.4% in de 3 jaar groep (hazard ratio 0.91 (95% betrouwbaarheidsinterval 0.65 - 1.29)). Een aanvullende analyse van de DATA-studie heeft aangetoond dat er wel een potentieel voordeel bestaat voor de vrouwen met borstkanker met slechte prognostische factoren zoals de aanwezigheid van kliermetastasen en/of een tumor groter dan 5 centimeter. Er zijn geen problemen met betrekking tot de veiligheid van verlengde hormonale behandeling geconstateerd. **Hoofdstuk 3** plaatst de resultaten van de DATA-studie in perspectief tot andere klinische studies over de duur en het type hormonale behandeling. De resultaten van de DATA-studie zijn in lijn met de bevindingen van de IDEAL en de NSABP B42 studies, welke het effect van aromataseremmers na 2.5 tot 5 jaar behandeling met tamoxifen hebben onderzocht. Interessant hierbij is, dat alle drie de studies een vergelijkbaar patroon van geleidelijke afname van de therapietrouw laten zien, voornamelijk vanwege de bijwerkingen die patiënten tijdens de behandeling ervaren. Dit is voor ons reden om alleen verlengde hormonale therapie met aromataseremmers te adviseren aan patiënten met een vroeg stadium borstkanker en een hoog risico op terugkeer van de ziekte, die de behandeling goed verdragen en zeer gemotiveerd zijn om deze therapie voort te zetten.

Deel II

Het tweede deel van dit proefschrift focust zich op de specifieke subgroep van vrouwen met borstkanker die door chemotherapie postmenopauzaal zijn geworden. Dit wordt chemotherapie-geïnduceerd ovarieel falen genoemd. **Hoofdstuk 4** behandelt het risico op herstel van de ovariële functie gedurende de behandeling met aromataseremmers, bij patiënten met chemotherapie-geïnduceerd ovarieel falen. Dit is een relevant probleem omdat herstel van de ovariële functie gepaard gaat met hoge oestrogeengehaltes in het bloed, hetgeen er potentieel toe kan leiden dat achtergebleven hormoongevoelige tumorcellen worden gestimuleerd tot groei. In de DATA-

studie hebben we gezien dat bij 12.4% van de vrouwen tussen de 45 en 52 jaar de ovariële functie binnen 30 maanden na het starten van de behandeling met aromataseremmers is hersteld, hetgeen gepaard gaat met evident hogere oestrogeengehaltes in het bloed. **Hoofdstuk 5** beschrijft het effect van herstel van de ovariële functie op de overleving. We hebben aangetoond, dat vrouwen waarbij de ovariële functie herstelde, vaker metastasen op afstand ontwikkelen (HR 2.27 (95% betrouwbaarheidsinterval 0.98-5.25; p=0.05)) en dat zij een slechtere algehele overleving hebben (HR 2.61 (95% betrouwbaarheidsinterval 1.11-6.13; p=0.03)). Van de vrouwen met herstel van de ovariële functie in het eerste jaar na randomisatie, ontwikkelde 76.9% geen metastasen op afstand binnen 5 jaar vs 92.1% van de vrouwen met persisterend ovarieel falen in het eerste jaar. Voor de algehele overleving is dit respectievelijk 80.8% en 94.4%.

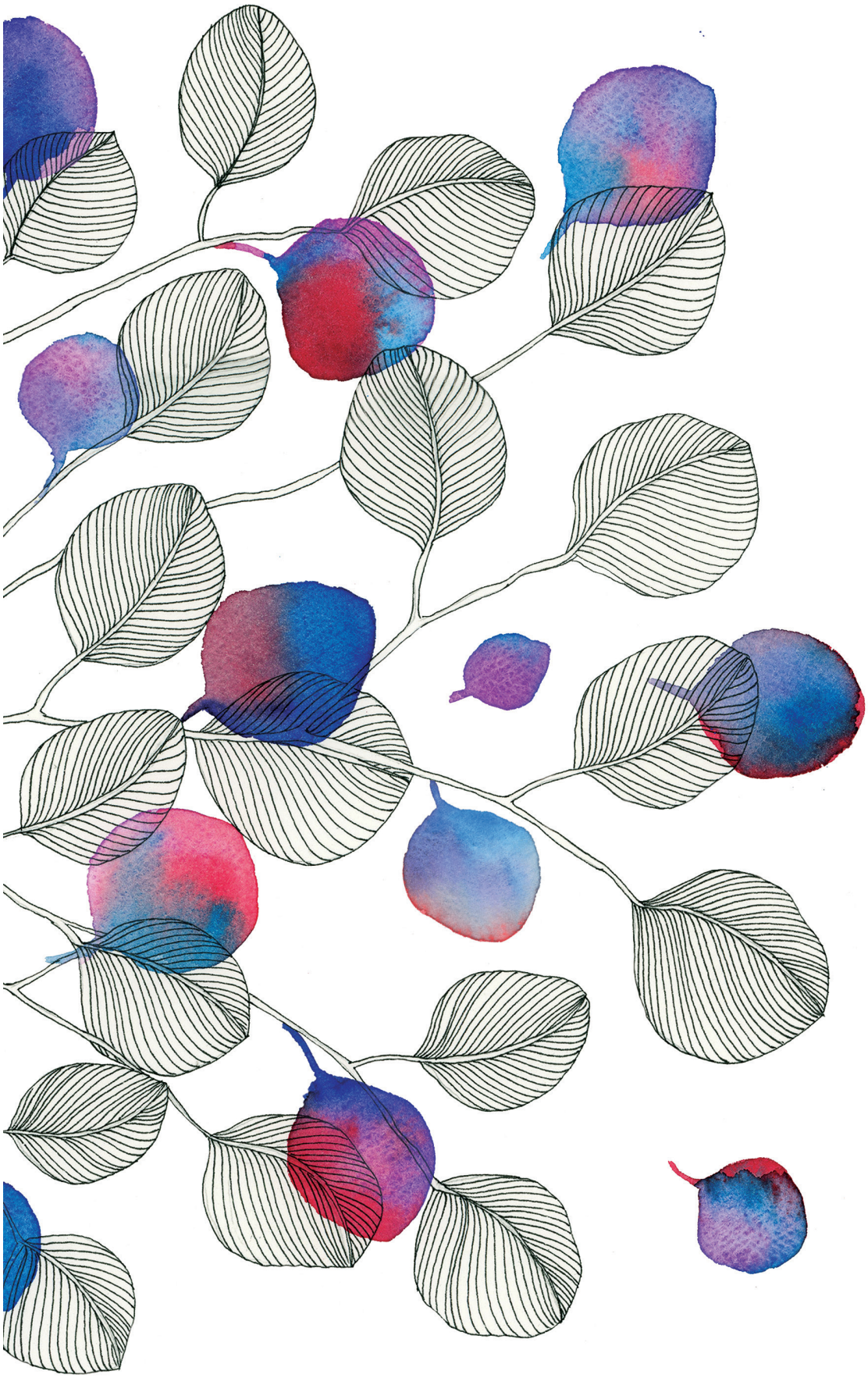
Deel III

Het derde deel van dit proefschrift concentreert zich op de botdichtheid tijdens hormonale therapie bij postmenopauzale vrouwen met hormoongevoelige borstkanker. Een afname van de botdichtheid is een bekende bijwerking van het gebruik van aromataseremmers. Voor de behandeling van een verlaagde botdichtheid worden naast calcium- en vitamine D preparaten ook bisfosfonaten gebruikt, welke een remmend effect hebben op de botresorptie door osteoclasten. **Hoofdstuk 6** beschrijft hoe vaak er in de DATA-studie diagnostiek werd verricht naar de botdichtheid en hoe vaak een behandeling werd gestart voor een verlaagde botdichtheid. Tevens wordt weergegeven hoe de botdichtheid zich ontwikkelt gedurende en na de behandeling met aromataseremmers. Hiervoor zijn alle botdichtheidsmetingen en het gebruik van bisfosfonaten geregistreerd. Allereerst hebben we geconstateerd, dat slechts 48.9% van de vrouwen een botdichtheidsmeting heeft ondergaan binnen het eerste jaar na het starten van de behandeling, hetgeen veel lager is dan destijds (2006-2009) in de Nederlandse richtlijn werd geadviseerd. Verder wordt bevestigd dat het gebruik van anastrozol inderdaad is geassocieerd met een afname van de botdichtheid. De afname van de botdichtheid is echter bescheiden en blijkt grotendeels reversibel na het stoppen van anastrozol, mits de bisfosfonaten werden gecontinueerd. Er is geen associatie gevonden tussen een verlengde hormonale behandeling en een hogere incidentie van osteoporose. Daarom zijn wij van mening, dat de aanwezigheid van osteopenie of osteoporose niet als een zwaarwegend motief moet gelden in de beslissing om wel of geen verlengde hormonale therapie te geven met aromataseremmers. In **hoofdstuk 7** bespreken we de relatie tussen de botdichtheid en het ontwikkelen van metastasen op afstand. Het idee voor deze studie kwam voort uit eerdere onderzoeken, waarin is gezien dat vrouwen met osteoporose een lagere kans hebben op het ontwikkelen van borstkanker, mogelijk als uiting van lagere oestrogeengehaltes in het bloed. Hiervoor werden de patiënten in 3 groepen verdeeld (osteopenie, osteoporose

en normale botdichtheid) op basis van de botdichtheidsmetingen die gedurende de eerste 3 jaar werden verricht. Vervolgens hebben we na de 3 daaropvolgende jaren gekeken, hoe vaak de vrouwen metastasen op afstand ontwikkelden. De 5-jaars overleving zonder metastasen op afstand was 89.7% in de groep met osteopenie (HR 0.82 (95% betrouwbaarheidsinterval 0.45–1.49) en 86.7% in de groep met osteoporose (HR 1.10 (95% betrouwbaarheidsinterval 0.26-4.67)) in vergelijking met 88.9% in de groep met een normale botdichtheid in de 6 jaars behandelarm. In de 3 jaars behandelarm werden vergelijkbare bevindingen gezien. De botdichtheid blijkt in deze studie dus niet voorspellend voor het ontwikkelen van metastasen op afstand. We hebben ook geen relatie gevonden tussen het gebruik van bisfosfonaten en het ontwikkelen van metastasen op afstand.

Deel IV

Hoofdstuk 8 bevat een samenvatting en een algehele discussie over de bevindingen van het onderzoek beschreven in dit proefschrift. Daarnaast worden ideeën uiteengezet voor toekomstig onderzoek op het gebied van hormoonreceptor-positieve vormen van borstkanker.



Addendum

Valorisation

Valorisation

Breast cancer is the leading cause of death among women worldwide.[1] During the last three decades the prognosis of women with breast cancer has improved significantly, but since the risk of recurrence remains high for at least 20 years after diagnosis, especially in case of hormone receptor positive breast cancer, it seemed logical to explore the possibilities for extending endocrine therapy beyond the standard of 5 years. Therefore, the DATA trial was designed, a phase III randomised controlled trial, investigating the efficacy and safety of 6 vs 3 years of adjuvant anastrozole in the setting of postmenopausal women with hormone receptor positive breast cancer, who received prior treatment with tamoxifen for 2-3 years. This thesis includes several analyses of the DATA trial. We aimed to guide treatment decisions in adjuvant endocrine therapy for patients with hormone receptor positive breast cancer, focussing on the optimal duration and its potential drawbacks.

The first part concentrates on the optimal duration of endocrine therapy in postmenopausal women including aromatase inhibitors. The results of the DATA trial did not show a benefit of extended endocrine therapy with aromatase inhibitors on disease free survival for postmenopausal breast cancer patients.[2] Nevertheless, we found a possible benefit in the group at high-risk of recurrence (positive lymph nodes, tumour size > 5cm). These results were in line with those of the NSABP B42 trial, and the MA.17 trial which had a similar design.[3,4] The IDEAL and ABCSG-16 trials had a different design, comparing two extended regimens (10 vs 7 years) showing no statistically significant difference on disease-free survival.[5,6]

After the publication of these trials in 2018, the guideline of the American Society of Clinical Oncology (ASCO) was updated, recommending that extended endocrine therapy with an aromatase inhibitor should be considered in postmenopausal breast cancer patients with node positive disease for a maximum of 10 years.[7] The 2018 Dutch national guideline on breast cancer recommends that extended endocrine therapy with aromatase inhibitors should be considered in the node positive subgroup, but only if patients tolerate treatment well.[8] We hope that the long-term follow-up results of these trials will provide more information on the optimal duration and answer the question if extended adjuvant endocrine therapy will result in an overall survival benefit. Currently, health care costs are a hot topic of debate. The financial consequences of extending adjuvant endocrine therapy are small. In the Netherlands, the generic anastrozole tablets cost 15,12 euro per year[9] thereby, creating higher chances of breast cancer curation.

The second part of this thesis focusses on the subgroup op women with chemotherapy induced ovarian function failure (CIOFF). This is of interest because for a long time it was unknown if these women should be treated as premenopausal breast cancer patients, with only tamoxifen, or as postmenopausal breast cancer patients with a treatment regimen including an aromatase

inhibitor. We showed that women with CIOFF, who were between the age of 45 and 52 and who had not undergone ovariectomy / used LHRH agonists, had a 12.4% chance of ovarian function recovery (OFR) during the treatment with aromatase inhibitors.[10] Moreover, the women who experienced OFR had significantly higher oestradiol levels during the treatment before OFR was established, which probably led to a worse distant recurrence-free survival and overall survival.[11] We can conclude from these results that treatment with aromatase inhibitors without ovarian function suppression or ovariectomy in women with CIOFF is not safe, even if the oestradiol and FSH levels are checked regularly and treatment is adjusted if OFR is noted. The results of these trials were also referred to in the 2018 Dutch national guideline on breast cancer, thereby warning medical professionals about the risk of OFR.[8]

The third part considers bone-health during endocrine therapy in breast cancer patients. A decrease of the bone mineral density (BMD) is a well-known side effect of aromatase inhibitors, but it was unknown into which extent. We observed that the BMD decreased during the use of anastrozole, but that the decrease was modest and partially reversible if bisphosphonates were prescribed. Moreover, the BMD recovered after the aromatase inhibitors were discontinued. At 7 years after randomization, the incidence of osteoporosis was not higher in the patients who received extended aromatase inhibitor treatment. Therefore, we believe osteoporosis should not be a major reason for disregarding extended endocrine therapy with aromatase inhibitors. Moreover, we showed that of the women with a normal BMD at the start of endocrine therapy none developed osteoporosis. This might implicate that BMD measurements could be performed less often in this subgroup of women than the currently advised in the (inter)national guidelines, with consequently lower health care costs and a lower radiation load.

We believe this research has contributed to a better care for breast cancer patients because it examines the possibilities of endocrine therapy and the precautions needed during its use, which is essential for treatment optimization and the identification of the patients who benefit most. Since millions of women worldwide are on endocrine therapy, this is also important as is research on new cancer drugs.

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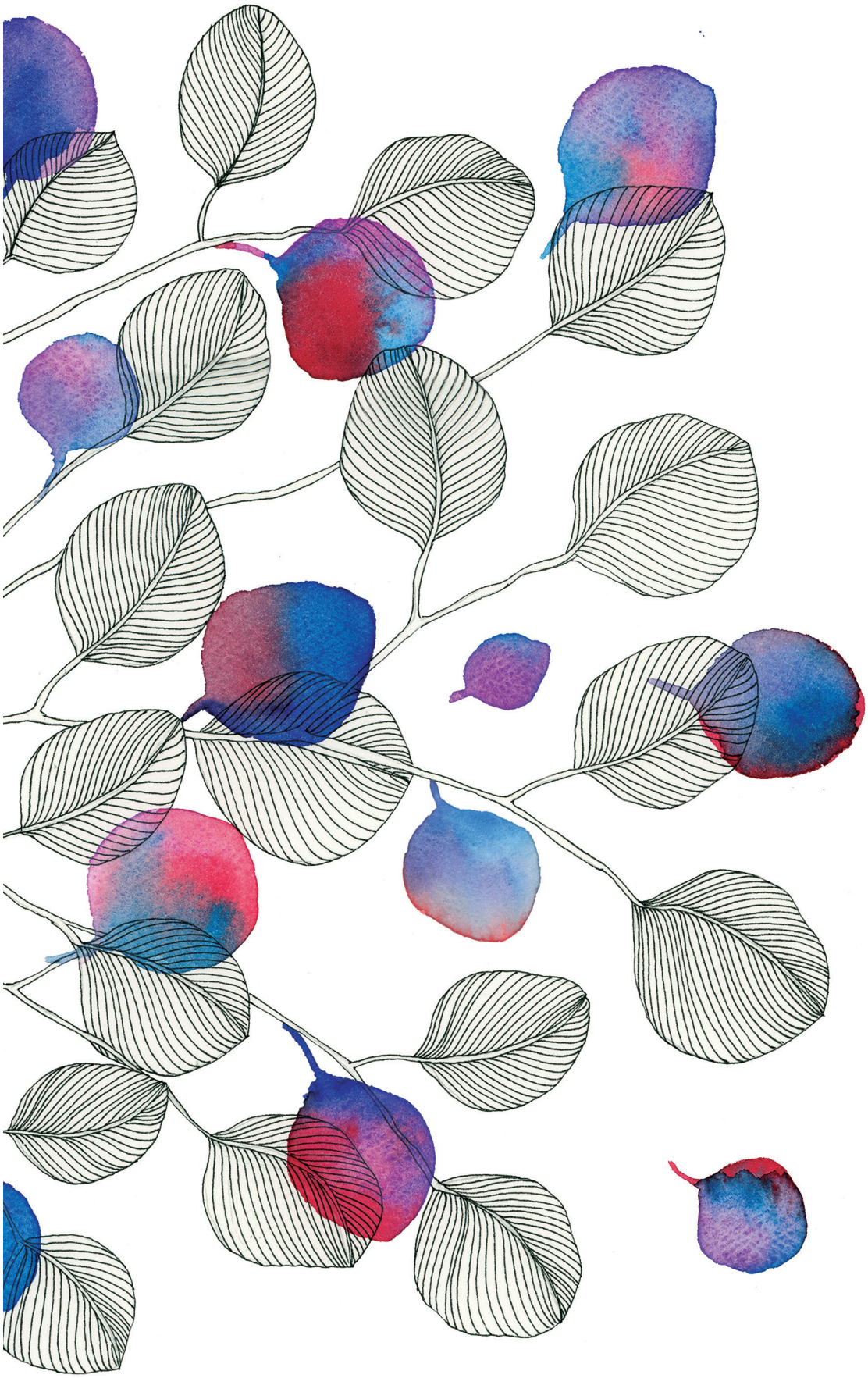

Addendum

List of Publications

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1. **van Hellemond IE**, Smorenburg CG, Peer PGM, et al. No impact of osteoporosis or bisphosphonate use for osteoporosis on breast cancer outcome: a sub-study of the DATA trial. *Submitted for publication.*

2. Vriens IJ, ter Welle-Butalid EM, de Boer M, van Golde RJ, Derhaag JG, Geurts SM, **van Hellemond IE**, et al. Preserving Fertility in Young Women Undergoing Chemotherapy for Early Breast Cancer; the Maastricht Experience. *Submitted for publication.*

3. **van Hellemond IE**, Smorenburg CG, Peer PGM, et al. Assessment and Management of Bone Health in Women with Early Breast Cancer Receiving Endocrine Treatment in the DATA Study. International Journal of Cancer 2019; e-pub ahead 13.02.2019.

4. **van Hellemond IE**, Vriens IH, Smorenburg CH, et al. Efficacy of anastrozole in patients with chemotherapy-induced ovarian failure; a DATA sub-study. International Journal of Cancer 2019;145:274-83.

5. **van Hellemond IE**, Thijs AM, Creemers GJ. Capecitabine Associated Terminal Ileitis. Case reports in oncology 2018;11:654-659.

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Presentations

Posterpresentation SABCS 2018

van Hellemond IE, Smorenburg CH, Peer PGM, et al. No impact of osteoporosis or bisphosphonate use for osteoporosis on breast cancer outcome: a sub-study of the DATA trial.

Posterpresentation ASCO 2018

van Hellemond IE, Smorenburg CH, Peer PGM, et al. Assessment and management of bone health in women treated with adjuvant anastrozole in the DATA study. Journal of Clinical Oncology, 2018

Nomination Pélerin Science Prize 2017, Maastricht UMC+

Abstract "Efficacy of anastrozole after tamoxifen in early breast cancer patients with chemotherapy-induced ovarian function failure." was nominated for the Pélerin Science Prize.

Posterpresentation ASCO 2017

Tjan-Heijnen VC, **van Hellemond IE**, Vriens I, Peer P, Swinkels A, Smorenburg CH, et al. Anastrozole after tamoxifen in early breast cancer patients with chemotherapy-induced ovarian function failure. Journal of Clinical Oncology. 2017;35(15_suppl):523-.

Posterpresentation ASCO 2013

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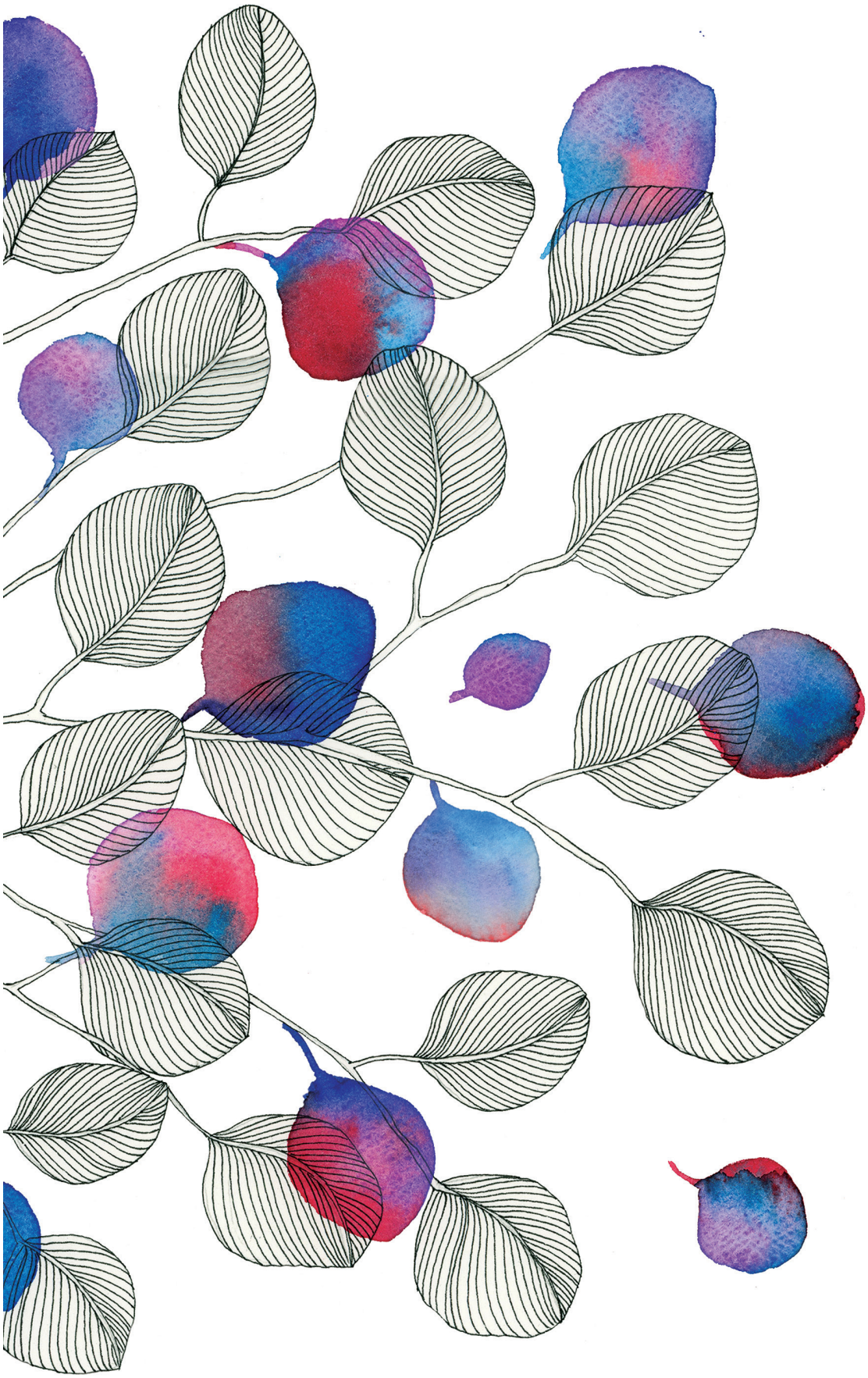
Nomination Professor Chris Gips Students Prize 2011

Thesis entitled "Estimation of the risk region during acute myocardial infarction." Was nominated for the Professor Chris Gips Students Prize on behalf of Maastricht University.



Addendum

Dankwoord

Dankwoord

Volgens sommigen bent u nu aangekomen bij het meest belangrijke hoofdstuk van het proefschrift. Ik denk dat dit te betwisten valt, maar het is waarschijnlijk wel het eerste, en mogelijk ook het enige hoofdstuk dat door velen écht gelezen wordt. Voordat jullie verder lezen, wil ik jullie attenderen op de hoofdstukken 1 tot en met 8, waar de laatste wetenschappelijke inzichten omtrent de hormonale behandeling van borstkanker te vinden zijn. De succesvolle afronding van dit proefschrift is te danken aan vele mensen.

Allereerst, beste **patiënten**, bedankt voor de participatie in de DATA-studie, zonder jullie deelname was dit werk in beginsel niet mogelijk geweest.

Prof. dr. Tjan-Heijnen. Beste **Vivianne**, heel erg bedankt voor de fantastische begeleiding de afgelopen jaren. Aanvankelijk alleen tijdens het onderzoek, maar nu ook als opleider in de vervolgopleiding medische oncologie. Jouw kritische interpretatie van de wetenschappelijke literatuur, snelle reacties op mijn vragen, creativiteit en positivisme maken het ontzettend fijn om met je samen te werken. Ik heb er bewondering voor hoe je alles zo efficiënt naast elkaar weet te managen en hoop nog veel van je te mogen leren de komende jaren.

Dr. Peer, beste **Nelly**, ik kan jou als mijn co-promotor niet genoeg bedanken voor de nieuwe inzichten die jij mij hebt gegeven. Mijn ideeën over statistiek zijn na onze maandelijkse vrijdagmiddag-besprekingen niet meer hetzelfde. Ik ging hier steeds weer vol goede moed vandaan. Wat bijzonder dat jij ook na je pensioen bereid was om mij te blijven begeleiden bij het afronden van mijn promotieonderzoek.

De beoordelingscommissie, bestaande uit **prof. dr. C.E.M. de Die-Smulders**, **dr. R.J.T. van Golde**, **prof. dr. J.J.M. van der Hoeven**, **prof. dr. H. Wildiers** en **dr. A.C. Voogd**, wil ik bedanken voor het beoordelen van mijn proefschrift.

Alle **lokale datamanagers** in de 79 ziekenhuizen in Nederland die hebben deelgenomen aan de DATA-studie, bedankt voor het verwerken van de gegevens en het beantwoorden van alle query's.

Evy, **Nanna** en **Floor**, mijn oud kamergenootjes, heel erg bedankt voor de fijne en oprechte gesprekken welke een welkome afwisseling waren tussen het analyseren en schrijven door. Nooit gedacht trouwens, dat het geluid van een kolfapparaat zo'n rustgevende werking op een omgeving zou kunnen hebben.

Natuurlijk niet te vergeten de andere leden van team Nijmegen, **Astrid Swinkels**, **Wim Lemmens**, **Bianca Schalk** en **Ton de Haan**. Astrid, bedankt voor jouw eindeloze geduld en nauwkeurigheid om keer op keer zaken opnieuw uit te zoeken. Wim, Bianca en Ton, hartelijk dank voor jullie hulp bij de statistische analyses en jullie snelle reacties wanneer er weer een deadline gehaald moest worden. Jullie onmisbare bijdrage aan de maandelijkse Nijmeegse bijeenkomsten maakte het erg leerzaam en bovenal ook erg gezellig!

Alle co-auteurs van de artikelen in dit proefschrift, **Ingeborg Vriens**, **Sandra Geurts**, **Carolien Smorenburg**, **Caroline Seynaeve**, **Maurice van der Sangen**, **Judith Kroep**, **Hiltje de Graaf**, **Aafke Honkoop**, **Frans Erdkamp**, **Franchette van den Berkmortel**, **Maaike de Boer**, **Wilfred de Roos**, **Sabine Linn** en **Alexander Imholz**, hartelijk dank voor jullie input en commentaar op de abstracts, (poster)presentaties en artikelen tijdens het gehele traject. Jullie zorgden ervoor dat het werk naar een hoger niveau werd getild.

Lilian Wishaupt, beste Lilian, heel erg bedankt voor de organisatie rondom dit proefschrift. Heel fijn dat ik nog steeds met al mijn vragen en een gezellig praatje bij je terecht kan.

Collega's bij de interne geneeskunde in het MUMC+, prof. dr. Koopmans en **prof. dr. Stehouwer**, bedankt voor jullie enthousiasme en inzet voor onze opleiding interne geneeskunde. Collega arts-assistenten heel erg bedankt voor de fijne samenwerking.

Ook de **medisch oncologen** en in het bijzonder mijn mede **fellows bij de medische oncologie in het MUMC+,** wil ik heel erg bedanken voor de prettige samenwerking en daarnaast de gezelligheid, belangstelling en steun die ik de afgelopen tijd van jullie heb mogen ontvangen.

Arts-assistenten en internisten in het **Catharina ziekenhuis** in Eindhoven, ontzettend bedankt voor de leerzame en gezellige tijd die ik in het Catharina ziekenhuis heb mogen meemaken. Beste **Stijn**, bedankt voor je altijd goede humeur, vrolijke deuntjes en steun. Beste **Geert-Jan**, je bent een heel bijzonder mens en een inspiratie voor velen.

Lieve **vrienden en familie**, het zal voor jullie vaak een raadsel zijn geweest waar ik mij nu toch al die jaren mee bezig hield. Zie hier het resultaat. Bedankt voor jullie belangstelling, maar bovenal voor de uitbundige feestjes, het samen sporten en de gezellig etentjes, welke een gewenste afwisseling vormden na een lange dag werken.

Lieve meiden van de **SSA**, ik vind het erg bijzonder dat we al die jaren na ons afstuderen nog steeds contact hebben. Tijdens onze studententijd zijn hechte vriendschappen gesmeed. Ik kijk steeds weer uit naar onze weekendjes. Ik hoop dat deze nog lang zullen blijven bestaan.

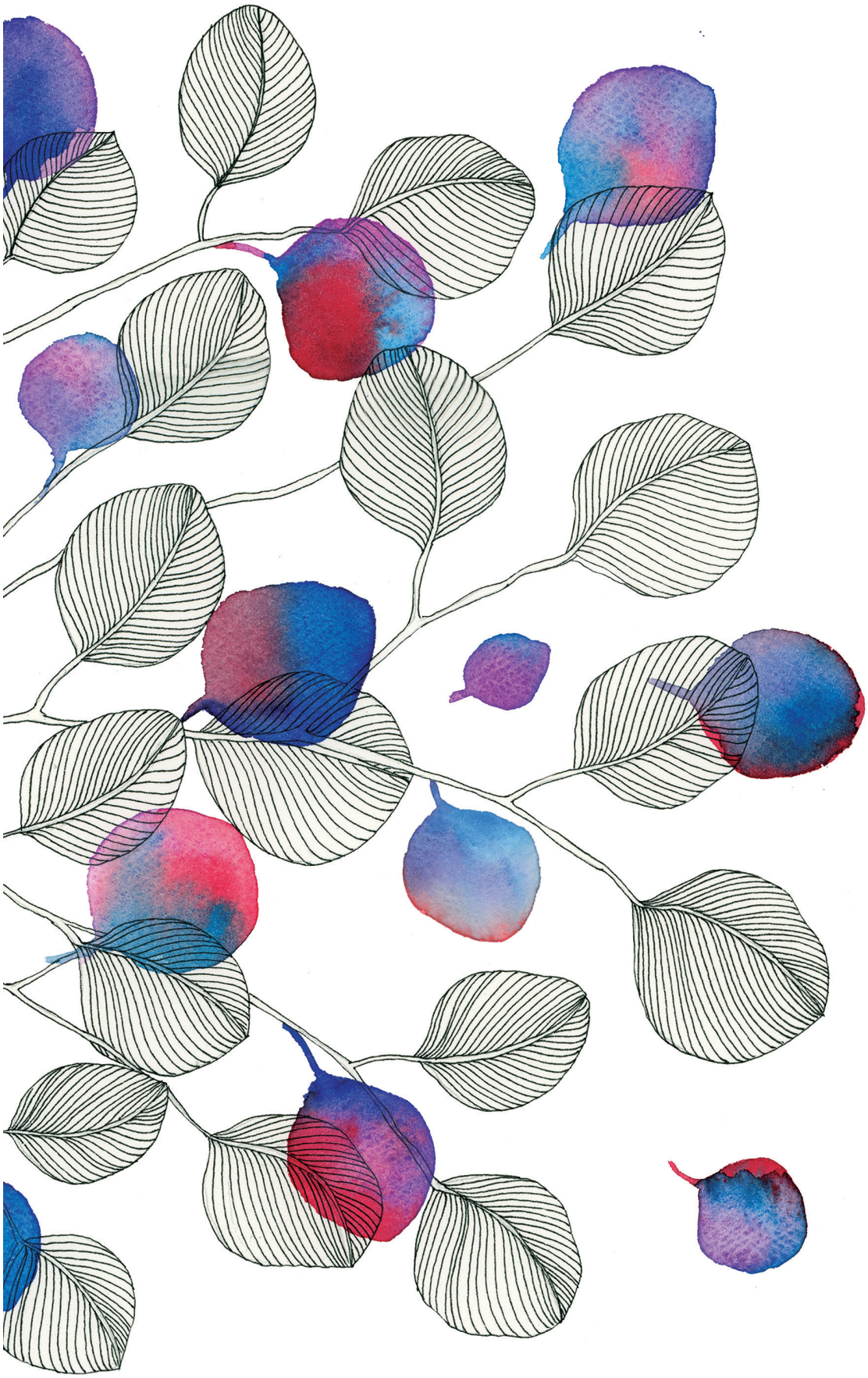
Lieve **Myrte**, we kennen elkaar door en door, van spelen bij de peuterspeelzaal, op hol geslagen paarden vangen, slidings maken in de modder op het voetbalveld en party vakanties in Spanje tot samen het moederschap ontdekken. Onze vriendschap is heel waardevol voor mij.

Paranimfen, **Linda en Veerle**, ik denk dat wij gebundeld zo'n beetje de gehele breedte van de geneeskundige kennis bezitten. Jullie weten van elke dag iets bijzonders te maken. Ik weet zeker dat we nog veel mooie en grappige avonturen gaan beleven met onze mannen en de kids. Ik waardeer het enorm dat ik altijd bij jullie terecht kan. Met jullie aan mijn zijde wordt deze dag zeker een succes!

Familie Bouwmeester, **Hans**, heel erg bedankt voor je interesse in het werk waar ik mee bezig ben. Ik vermoed dat jij na al die jaren inmiddels een volleerd cardio-oncoloog bent geworden. Ik kan mij geen fijnere schoonvader wensen op wie we altijd kunnen rekenen. **Noortje en Paul**, wat fantastisch om onze kinderen zo samen te zien opgroeien, vaak onder het genot van jullie geweldige kookkunsten.

Papa en Mama, dank jullie wel voor de onvoorwaardelijke steun en liefde. Ongeacht de keuzes die ik maak, jullie staan altijd achter me en dat is heel fijn om te weten. Mama, ik ken niemand met meer veerkracht dan jij! **Stefan**, wat ben ik blij met zo een lieve en sportieve broer, ook al is het soms een zoektocht naar wat nu het best bij jou past, ben ik ervan overtuigd dat je een hele mooie toekomst tegemoet zal gaan. Ik hou van jullie.

Lieve **Jurre en Céline**, ik voel mij zielsgelukkig dat jullie gedurende mijn promotietraject in ons leven zijn gekomen. Wat kan ik ervan genieten om jullie samen te zien spelen. Jullie knuffels en kusjes laten mij smelten van geluk. Lieve **Sjoerd**, wat hebben wij in de afgelopen 14 jaar veel bijzondere maar ook heftige dingen meegemaakt. Ik ben zo gelukkig met jou en ontzettend trots op ons mooie gezinnetje. Samen zijn we sterk. Ik hou van jullie. Jullie betekenen alles voor mij.



Addendum

Curriculum Vitae

Curriculum Vitae

Irene Elisabeth Gerarda van Hellemond werd geboren op 31 mei 1986 te Breda en groeide op in het dorp Ulicoten in Noord-Brabant. Na het behalen van het vwo-diploma in 2004 aan het Onze Lieve Vrouwelyceum te Breda studeerde zij geneeskunde aan de Universiteit van Maastricht. In 2010 volgde zij haar wetenschapsstage aan Duke University in North Carolina, USA, alwaar zij onder begeleiding van prof. dr. G. Wagner en prof. dr. A.P. Gorgels de passie voor wetenschappelijk onderzoek ontwikkelde. Aansluitend werd haar scriptie genomineerd voor de Professor Chris Gips studentenprijs namens de Universiteit van Maastricht. Na het behalen van haar basisarts examen in 2011 begon zij met de opleiding tot internist in het Catharina Ziekenhuis in Eindhoven (opleider dr. C.J.A.M Konings). In 2014 onderbrak zij haar opleiding gedurende 2 jaar ten behoeve van het onderzoek gebundeld in dit proefschrift. In 2017 werd haar onderzoek genomineerd voor de Pélerin wetenschapsprijs. In 2018 startte zij haar differentiatie medische oncologie in het Maastricht Universitair Medisch Centrum (opleider prof. dr. V.C.G. Tjan-Heijnen). Zij woont samen met Sjoerd Bouwmeester en samen hebben zij twee kinderen; Jurre (2015) en Céline (2017).