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Tailoring endocrine treatment for early breast cancer

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CHAPTER

14

EFFICACY OF SIX MONTHS NEOADJUVANT HORMONAL THERAPY IN POSTMENOPAUSAL, HORMONE RECEPTOR-POSITIVE BREAST CANCER PATIENTS – A PHASE II TRIAL

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ABSTRACT

Introduction

Neoadjuvant hormonal therapy (NHT) is playing an increasing role in the clinical management of breast cancer and may improve surgical outcomes for postmenopausal, estrogen receptor (ER)-positive breast cancer patients. However, there is currently no consensus on the optimal duration of NHT before surgery. Here, we present the outcomes of the TEAM IIA trial, a multicentre, phase II trial investigating the efficacy of six months of neoadjuvant exemestane in postmenopausal, strong ER-positive (≥50%) breast cancer patients.

Methods

102 patients (stage T2-T4ac) were included in the study after exclusion of ineligible patients. Primary endpoint was clinical response at 3 and 6 months as measured by palpation. Secondary endpoint was radiological response as measured by MRI, mammography and/or ultrasound. Linear mixed models (95%confidence interval (CI)) were used to compare changes in mean tumor size (in mm) between baseline, 3 and 6 months after the start of hormonal therapy. Conversion rates from mastectomy to breast-conserving surgery (BCS) were evaluated.

Results

Median age of all patients was 72 years (range 53-88). Overall response rate by clinical palpation was 64.5% in all patients with a final palpation measurement. 4 patients had clinically progressive disease. 63 patients had both 3-month and >3-month palpation measurements. Overall response was 58.7% at 3 months and 68.3% at final palpation (>3 months). Mean tumor size by clinical palpation at T=0 was 39.1mm (95%CI 34.8-43.4mm), and decreased to 23.0mm (95%CI 18.7-27.2mm) and 16.7mm (95%CI 12.6-20.8) at T=3 and T>3 months respectively (p=0.001). Final radiological response rates at the end of treatment for MRI (n=37), ultrasound (n=77) and mammography (n=56) were 70.3%, 41.6% and 48.2% respectively. Feasibility of BCS improved from 61.8% to 70.6% (McNemar p=0.012).

Discussion

6 months of neoadjuvant exemestane therapy helps reduce mean tumor size further in strongly ER-positive breast cancer patients without significant side effects compared to 3 months. Nevertheless, some patients still experience disease progression under exemestane. Feasibility of breast conservation rates improve by almost 10%.

INTRODUCTION

Neoadjuvant hormonal therapy (NHT) with aromatase inhibitors has been gaining recognition due to its ability to improve surgical outcomes for hormone sensitive breast cancer patients with stage II or III breast cancer. In recent years, NHT has come to play a major role in the treatment of large breast tumors, attesting its ability to render inoperable tumors suitable for mastectomy and for breast conservation in patients who would otherwise undergo ablative surgery.[1] Moreover, NHT provides the prospect of investigating the effects of hormonal treatment, with or without new targeted antitumor agents, on biochemical, molecular and histological tumor response features, which can help guide subsequent treatment decisions.[2]

Although long-term survival benefit of adjuvant chemotherapy do not differ between ER-positive and ER-negative tumors based on an Early Breast Cancer Trialists' Collaborative Group (EBCTCG) meta-analysis[3], neoadjuvant studies have demonstrated that ER-positive tumors are less sensitive to chemotherapy than ER-negative tumors in terms of pathological Complete Response (pCR).[4-7]

In estrogen receptor-positive, postmenopausal breast cancer patients, NHT is an appropriate option for patients who are considered unfit for neoadjuvant chemotherapy. Not infrequently, NHT is also prescribed for long-term treatment in elderly patients who are too fragile to undergo surgical intervention. During the 13th St. Gallen International Breast Cancer Consensus Conference, the majority of the breast cancer experts' consensus panel voted in favour of the use of NHT for postmenopausal patients with highly endocrine-responsive disease.[8]

Currently, the most commonly applied treatment duration of NHT in early breast cancer patients with large inoperable tumors is three months. Arguably, however, this may be too short a period for aromatase inhibitors to work to their full potential, as tumor response may continue if treatment is extended.[9, 10] Importantly, the St. Gallen 2013 preliminary summary of the consensus discussion reported that 62.2% of panelists were in favour of continuing NHTtreatment until maximal response[8], with only 11% of panelists recommending a treatment duration of 3-4 months.[11] 26.7% of panelists were in favour of a treatment duration of 4-8 months.[11] Clinical studies investigating the optimal duration of NHT in order to optimize operability of large tumors otherwise unsuitable for breast conservation are still relatively lacking.[2, 12] We report the results of the TEAM IIA study, a nationwide, multi-institutional, phase II trial that investigated six months of neoadjuvant therapy with exemestane on tumor response in strongly endocrine-sensitive breast cancer patients, which was developed to address the optimal duration of NHT.

MATERIALS AND METHODS

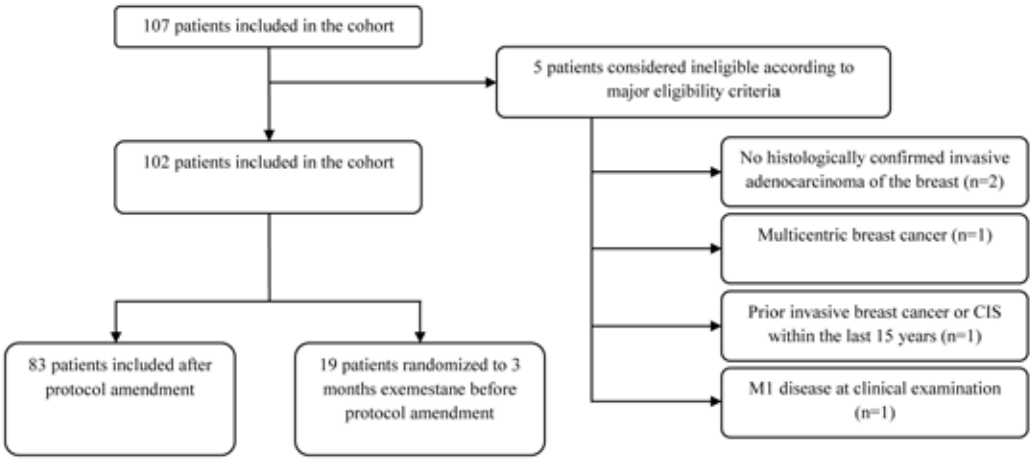
Trial design

The TEAM IIA trial was originally designed as a phase III, randomized clinical trial investigating three versus six months of neoadjuvant exemestane therapy on clinical response. Due to unexpectedly slow accrual, the TEAM IIA trial protocol was changed to a phase II single-arm study investigating six months of NHT on clinical response following an amendment in June 2009. The TEAM IIA trial was conducted in 11 hospitals throughout the Netherlands between March 2007 and May 2012. Database lock was on October 15th, 2013.

Patients

107 patients were enrolled in the study. 20 patients were randomized to 3 months of neoadjuvant treatment with exemestane before the amendment. 87 patients were included after the amendment and were allotted 6 months of NHT.(Figure 1) Patients randomized to 3 months and on-treatment were offered to continue until 6 months. Eligibility criteria included postmenopausal patients with histologically confirmed invasive adenocarcinoma (stage I-III) of the breast that was strongly ER-positive (≥50% based on core biopsies) and ≥2cm in diameter. Patients with metastatic disease (M1) were considered ineligible. In addition, patients with multicentric, bilateral, or inflammatory (cT4d) breast cancer were ineligible.

Figure 1. **CONSORT diagram showing patients included in the study.**



The protocol as well as the amendment were reviewed and approved by each participating institution and registered with the Netherlands Trial Register (NTR785) in compliance with the Declaration of Helsinki and Good Clinical Practice guidelines. All patients provided written informed consent.

Tumor response was assessed monthly by clinical palpation and at 3-month intervals for MRI, bidirectional mammography or ultrasound. Clinical palpation response was measured in terms of the largest diameter (in millimetres). For radiological response, perpendicular dimensions of the largest measurable primary tumor and lymph nodes were measured. Cut-off points for response categories included complete response (disappearance of all target lesions), partial response (≥30% decrease in tumor size), stable disease (<20% increase or ≤30% decrease in tumor size), and progressive disease (≥20% increase in tumor size, as well as an absolute increase of at least 5mm), and were based on the Response Evaluation Criteria in Solid Tumors (RECIST) version 1.1.13

Endpoints

The primary endpoint was overall clinical response at three and six months, as measured by clinical palpation. Only patients who enrolled in the study after the implementation of the amendment are included in these analyses.

Secondary endpoints consisted of objective radiological response; imaging modality was opted by the treating physician. Other secondary endpoints included pCR of the primary breast cancer and lymph nodes, and the feasibility of breast conserving surgery in all patients. pCR was defined as the absence of invasive tumor cells in the resection specimen and dissected lymph nodes (pT0/pN0) as reported by the pathology laboratories.

Tumor pathology data

Core biopsies were obtained before the start of treatment and resection specimens were acquired at final surgery. Biopsies were evaluated by immunohistochemistry with conventional light microscopy at pathology laboratories.

Assessment of safety

Patient-reported toxicities were assessed at 1-month intervals. The National Cancer Institute Common Terminology Criteria for Adverse Events, version 3.0, was used to classify adverse events following exemestane treatment.

Statistical analyses

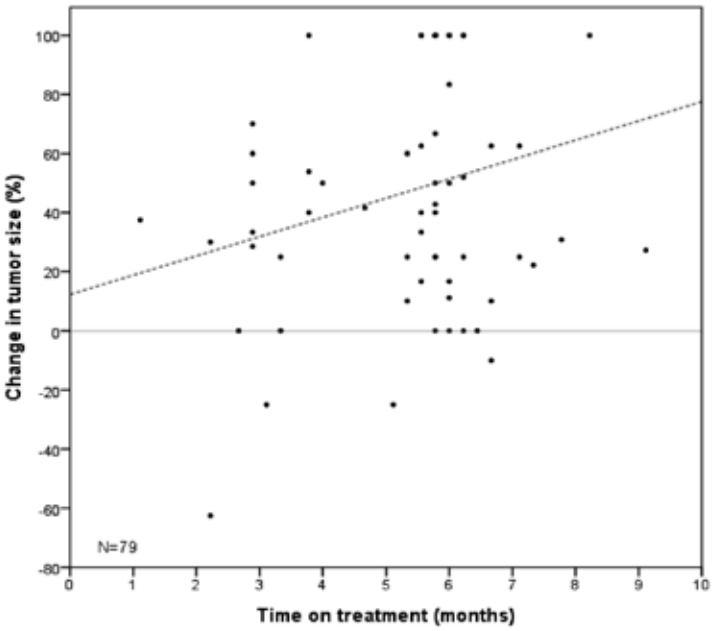
Cross tabs with McNemar tests for paired samples were used to assess palpability and clinical response at baseline, three and six months. If treatment was discontinued before six months due to progressive disease or due to patient or investigator request, response up to the last clinical examination was used. Mean changes in tumor size from baseline to 3 months and 6 months after the start of exemestane were assessed in linear mixed models with 95% confidence intervals (CI) for clinical palpation, MRI, bi-directional mammography, and/or ultrasound. All available radiological modalities were included in the analyses. If more than one modality was used for tumor size measurement, we used radiological modality in order of accuracy (MRI followed by mammography, followed by ultrasound).[13]

RESULTS

Study population

107 patients were included in the study, of which 20 patients were allocated 3 months of exemestane before implementation of the protocol amendment. After exclusion of ineligible patients (n=5), the final cohort comprised 102 (stage T2-T4a-c) patients.(Figure 1) Median treatment time for all patients was 5.78 months

Figure 2. **Scatter plot of the percentage change in tumor size as measured by palpation in relation to time on treatment (months) in patients treated with neoadjuvant exemestane in all included patients.**



(mean 5.32, range 0.89-9.11 months) and 3.33 months (mean 3.46, range 2.22-5.78 months) for patients randomized to 3 months of treatment before the amendment. The scatter plot that makes up Figure 2 reveals the percentage change in tumor size as measured by palpation in relation to time on exemestane treatment for all patients in the cohort. Mean age was 72 years (range 53-88). Baseline characteristics of patients at the start of treatment (T=0) are presented in Table 1, with primary tumor characteristics representing the results following core needle biopsy.

Tumor downstaging

Clinical response to exemestane was quantified and classified as complete response, partial response, stable disease and progressive disease. Overall response rates at the end of treatment for palpation, MRI, ultrasound and mammography are shown in Table 2. At the end of neoadjuvant exemestane treatment, overall clinical response (complete response + partial response) was 64.5% (51 out of 79 evaluable patients). There were 22 complete clinical responses, 29 partial responses, 24 stable diseases and 4 progressive diseases according to palpation assessments. Of the 4 patients with progressive disease based on clinical palpation, only 2 were also radiologically confirmed progressive diseases (2 stable disease). Mean percentage reduction in tumor size was 47.35% (range -63% - 100%). 63 patients had palpation measurements at 3 months and

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

Before surgery	**n**	**%**
Age		
Median (range)	*72*	*(53-88)*
Tumor size		
<3cm	43	42.2
3-5cm	41	40.2
>5cm	15	14.7
T4a-c	3	2.9
Nodal status		
cN-	77	75.5
cN+	25	24.5
Tumor type		
Ductal	66	64.7
Lobular	30	29.4
other/unknown	6	5.8
Histological grade (BR)		
G1 (well)	12	11.8
G2 (moderate)	27	26.5
G3, G4 (poor)	7	6.9
unknown	56	54.9
PR status		
Positive (≥10%)	70	68.6
Negative	32	31.4
HER2 status		
Positive	9	8.8
Negative	85	83.3
unknown	8	7.9
Feasibility of BCS before surgery		
Not feasible	34	32.5
Feasible	68	67.5

BR, Bloom&Richardson; BCS, breast-conserving surgery.

a final measurement at the end of neoadjuvant treatment (>3 months). At the end of treatment, overall clinical palpation response (compared to 3 months) increased from 58.7%to 68.3% at last palpation. (McNemar p=0.031).

Mean tumor size was 39mm at the start of treatment, and decreased significantly after 3 and >3 months of exemestane treatment (Table 3). Mean reductions in tumor size at 3 and >3 months were 16mm and 22mm respectively (p<0.001). After >3 months of neoadjuvant treatment, there was a statistically significant decrease in tumor size when compared with 3 months of treatment (p=0.003).

Table 2. **Overall response at final assessment in all patients, as determined by clinical palpation, MRI, mammography and ultrasound.**

Response modality‡	n	%
Clinical palpation	*(n=79)*	
Complete response	22	21.6
Partial response	29	28.4
Stable disease	24	23.5
Progressive disease	4	3.9
Not available	23	22.5
*Overall response**	*51*	*64.5*
MRI	*(n=37)*	
Complete response	9	8.8
Partial response	17	16.7
Stable disease	8	7.8
Progressive disease	3	2.9
Not available	65	63.7
*Overall response**	*28*	*70.2*
Mammography	*(n=56)*	
Complete response	2	2.0
Partial response	25	24.5
Stable disease	26	25.5
Progressive disease	3	2.9
Not available	46	45.1
*Overall response**	*27*	*48.2*
Ultrasound	*(n=77)*	
Complete response	3	2.9
Partial response	29	28.4
Stable disease	39	38.2
Progressive disease	6	5.9
Not available	25	24.5
*Overall response**	*32*	*41.6*

‡Final response assessment at any time since the start of neoadjuvant treatment; *Out of all evaluable patients.

Radiological assessment

93 patients had a radiological assessment (91.2%). Based on radiological assessment, overall clinical response rate was 54.8%. There were 11 complete responses (11.8%), 40 partial responses (43%), 35 stable diseases (37.6%) and 7 patients with progressive disease (7.5%). Patients who had MRI measurements (n=37) had larger tumors at palpation than patients without MRI measurements (n=65) (35mm versus 47mm, p=0.003). In the MRI group there was a greater proportion of invasive lobular carcinomas (45.7%) than in the group without MRI measurements (20.3%). Patients who had both MRI in addition to mammography or ultrasound measurements did not have larger tumors on MRI than on mammography or ultrasound (independent samples T-test p=0.694 and p=0.142). Figure 3 shows the mean tumor sizes (95% confidence interval, CI) for individual radiological modalities. In addition, Table 3 depicts mean reductions in tumor

Table 3. **Mean tumor size and mean change in tumor size at 3 months and at the end of neoadjuvant exemestane treatment in patients enrolled after protocol amendment**

	Time (months)	n	Mean size (mm)	SE	(95% CI)	Mean reduction in size (mm)	(95% CI)	p-value
Palpation	T=0	63	39.08	2.16	(34.82 – 43.35)	0 (ref)		
	T=3	64	22.98	2.15	(18.73 – 27.23)	16.11	(11.87 – 20.35)	<0.001
	T=last**	72	16.68†	2.07	(12.59 – 20.78)	22.4	(18.28 – 26.53)	<0.001
MRI	T=0	37	41.15	3.35	(35.65 – 46.65)	0 (ref)		
	T=3	24	24.66	3.42	(17.85 – 31.46)	16.5	(8.09 – 24.9)	<0.001
	T=last	25	19.77*	2.76	(13.11 – 26.44)	21.38	(13.05 – 29.7)	<0.001
Mammo-graphy	T=0	62	32.99	1.65	(29.71 – 36.26)	0 (ref)		
	T=3	37	21.85	1.93	(18.02 – 25.67)	11.38	(7.62 – 14.66)	<0.001
	T=last	38	22.22*	1.92	(18.43 – 26.01)	10.77	(7.31 – 14.22)	<0.001
Ultra-sound	T=0	69	27.81	1.37	(25.1 – 30.52)	0 (ref)		
	T=3	50	20.67	1.48	(17.73 – 23.6)	7.15	(4.65 – 9.64)	<0.001
	T=last	49	18.39*	1.49	(15.44 – 21.35)	9.42	(6.87 – 11.96)	<0.001

SE, standard error; CI, confidence interval.
†p=0.003 (statistically significant) with respect to T=3 months; *p>0.05 (not statistically significant) with respect to T=3 months; **last measurement after >3 months of neoadjuvant hormonal therapy

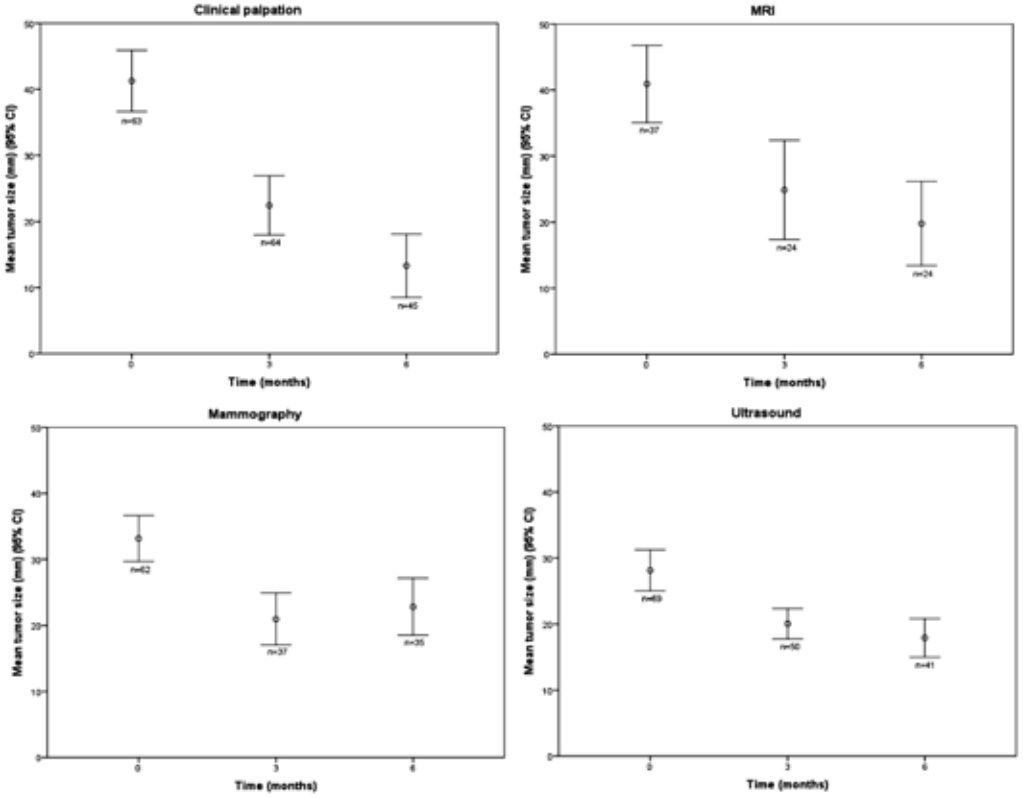
size for each radiological modality separately. For all modalities, there was a significant decrease in mean tumor size over time. Mean tumor size was not statistically significantly lower after 6 months of exemestane than after 3 months (p>0.05).

8 patients (8.8%) had confirmed HER2-positive disease after surgery, of whom 5 had clinical response assessments available (2 complete responses (25%), 1 partial response (12.5%), 2 stable diseases (25%)). All patients had radiological response data available, which showed 1 complete response (12.5%), 1 partial response (12.5%), 3 stable diseases (37.5%) and 3 progressive diseases (37.5%).

Feasibility of breast-conserving surgery

Median time to surgical intervention was 28 weeks (range 8 – 47 weeks). Tumor and nodal stage, grade, histology, and hormone receptor status were also determined after final surgery and are presented in Supplementary Table 1. The number of patients with feasible BCS increased from 63 before treatment to 72 at the end of treatment (McNemar p=0.012) (Table 4). A total of 98 patients (96.1%) underwent surgical resection of their tumor. Primary surgery consisted of BCS in 58 patients (56.9%) and mastectomy in 40 patients (39.2%). 9 patients (9.2%) deemed ineligible for BCS at the start of treatment had successful breast conservation. 9 patients (8.8%) required a re-excision (5 mastectomy, 4 BCS) following tumor-positive resection margins (invasive carcinoma and/or carcinoma in situ).

Figure 3. **Mean change in tumor size after 3 and 6 months after the start of neoadjuvant treatment in patients enrolled after protocol amendment.**



Patient preference for either mastectomy or BCS was also assessed. 79 patients reported a surgical preference at baseline and at the end of treatment. Patient preference regarding the type of breast surgery shifted from 13.7% in favour of mastectomy (n=14) at the start of treatment to 23.5% (n=24) in favour of mastectomy at the end of treatment. Preference for BCS was 66.7% (n=68) at baseline and decreased to 63.7% (n=65) at the end of exemestane treatment.

Sentinel lymph node biopsy

25 out of 102 patients (24.5%) had clinically or cytologically confirmed node-positive disease at the start of exemestane treatment. In total, 71 patients underwent a sentinel lymph node biopsy (SLNB) (9 patients before neoadjuvant therapy and 62 patients after neoadjuvant therapy). Three out of the 25 patients (12%) who were clinically node-positive before the start of exemestane became pathologically node-negative after neoadjuvant treatment. Forty-two out of 62 patients (67.7%) who had a SLNB after neoadjuvant treatment were also node-negative (pN0 or pN0(i+)).

Table 4. **Feasibility of breast conserving surgery before and after neoadjuvant treatment in all patients**

	Before treatment		End of treatment		McNemar p-value
	n	%	n	%	
Feasibility of breast-conserving surgery					
not feasible	39	38.2	24	23.5	0.012
feasible	63	61.8	72	70.6	
unknown	0	0.0	3	2.9	
Conversion rate*	-	-	9	9.2%	
Performed surgery					
breast conserving surgery	-	-	58	56.9	
mastectomy	-	-	40	39.2	
no resection	-	-	4	3.9	
Re-excision required	-	-	*9*	*(8.8%)*	
Patient preference					
breast conserving surgery	68	66.7	65	63.7	
mastectomy	14	13.7	24	23.5	
no resection	2	2.0	1	1.0	
not reported	18	17.6	12	11.8	

*conversion from mastectomy before treatment to breast conserving surgery after treatment.

Safety and toxicities

Adverse events were graded according to the CTC-AE version 3.0. All toxicities that make up >1% of all reported adverse events (n=188) are included in Supplementary Table 2. Only 10 toxicities (4.1%) were reported to be grade 3-4 toxicities. Pain, fatigue, and sensory neuropathy make up the majority of grade III-IV toxicities reported in this study. Importantly, only three patients discontinued exemestane due to toxicities. There were no serious unexpected adverse events.

DISCUSSION

Six months of neoadjuvant exemestane resulted in improved clinical and radiological responses, without an increased risk of toxicity. Overall clinical response rate was 64.5% after 6 months of neoadjuvant exemestane. Radiologically confirmed progressive disease was limited to four patients. In addition, neoadjuvant treatment resulted in a greater feasibility of breast conservation, although the number of patients who required a re-excision for tumor-positive margins was 8.8%.

Two earlier studies have shown that in patients with ER-positive breast cancer, hormonal therapy may be at least as effective as chemotherapy for inducing tumor response.[14, 15] In the last decade, neoadjuvant therapy has gained popularity, owing to the prospect of downsizing tumors to facilitate breast conservation and to evaluate biological features associated with tumor response to treatment.[2] Neoadjuvant chemotherapy

(NCT) with several cycles comprising around 4 months (e.g. TAC chemotherapy for 6 x 3-week cycles), of which it is suggested that early clinical response to the first few cycles is predictive for survival after surgery.[16] Conversely, however, NHT demonstrates a more gradual tumor response rate and may thus require longer treatment durations in order to attain maximum effect.[9] Our investigation revealed that prolonged treatment with neoadjuvant exemestane therapy results in sustained tumor response, with a reduction in mean tumor size of more than 2cm at the end of treatment.

Previous prospective, randomized studies have investigated the feasibility of aromatase inhibitors in inducing tumor downsizing in endocrine-sensitive breast cancer patients. The P024 and PROACT studies investigated 4 months of aromatase inhibitor therapy compared with tamoxifen therapy and found response rates of 55% and 50% respectively in the aromatase inhibitor arm.[17, 18] Similarly, the IMPACT study by Smith and colleagues reported a response rate of 37% following 3 months of anastrozole.[19] Aromatase inhibitor therapy in these phase III studies showed lower response rates than those found in our study, possibly related to the longer treatment duration in our cohort.

For practical purposes, tumor size assessed by clinical palpation defined the primary endpoint of this study. There was a steady decrease in the number of patients with palpable tumors between baseline and 6 months of NHT. Although the greatest decrease in tumor size was observed between baseline and 3 months of treatment, tumor size continued to fall after more than 3 months of NHT, suggesting that prolonged treatment duration may be required to achieve maximum response to optimize surgery. In an earlier report by Dixon and colleagues, more than a third of the patients included in the study continued NHT beyond 3-4 months for various reasons, causing a rise in overall response rates to more than 80% and facilitating more BCS.[9] Furthermore, maximum response in other studies was achieved approximately 4-6 months after the start of NHT.[20, 21] Similar results were recently reported in a study by Carpenter et al, who showed that the median duration of neoadjuvant letrozole to allow for BCS in patients otherwise ineligible for breast conservation was 7.5 months.[22] These findings demonstrate that extended duration of NHT achievable optimal tumor response and is well-accepted by patients.

Radiological response as measured by MRI is considered the best available response assessment modality followed by mammography.[13, 23] Although our study is limited by the inconsistent use of MRI to assess tumor response, the highest overall response rate was observed with MRI (70.2%), suggesting that the lower response rates measured by mammography and ultrasound may underestimate the true response to NHT. Although recommended, the use of MRI was not required and was up to the local investigator. The RECIST criteria (1.1) were used to evaluate MRI data in this study.[13] It must be noted that those tumors which were reduced to scattered fragments should be regarded as responders to NHT, although accurate response assessment based on RECIST is not possible. In 2012, the ACRIN 6657/I-SPY study concluded that volumetric assessment of breast tumors is a better predictor of response than measuring the longest tumor diameter in patients treated with neoadjuvant chemotherapy.[24] Since the patients in this study were included between 2010 and 2012, routine volumetric assessments were not yet standard of care, but should be considered for use in clinical practice.

Our study comprised strongly ER-positive breast cancer patients, as studies have shown that the degree of quantitative ER expression might be a valuable discriminating factor to predict hormonal therapy efficacy. In this study, we utilized percentage of positively staining tumor cells (according to the Dutch National Breast Cancer guidelines)[25] to select our patients. The ACOSOG Z1031 study selected ER-positive patients based on the Allred score (Allred score 6-8), which may be of added value in predicting response to hormonal therapy.[26] When considering staining intensity in addition to percentage of positively staining cells when selecting eligible patients, response rates may be even higher than those reported in the current study and deserves further investigation. In the adjuvant setting, efficacy of hormonal therapy was superior with incremental increases in ER expression.[27-30] NHT may be a valid alternative to neoadjuvant chemotherapy in strong ER-positive patients, and quantitative ER expression may aid the decision to opt for NHT as opposed to NCT. Petit et al. found an inverse relation between ER expression and pCR in hormone receptor-positive breast cancer patients treated with neoadjuvant chemotherapy.[31] NHT provides the prospect of improving operability of large tumors, thereby opening up new domains for further improvements in breast cancer care.

pCR is a frequently used endpoint in patients treated with NCT. In our study, however, only one patient had a pCR in both tumor and regional lymph nodes. Accordingly, it is questionable whether pCR should be the aim in breast cancer patients undergoing NHT. Apart from much longer time to maximal response when compared with NCT, one must bear in mind that the primary objective of preoperative treatment is to allow for adequate tumor downsizing to enable breast conservation in patients who would alternatively require mastectomy, and breast surgery in otherwise inoperable patients.[1] As patients may differ in the time to maximum response, monitoring tumor downsizing up to response stagnation may be more important in anticipation of surgical resection as opposed to determining a set treatment duration.

Feasibility of BCS improved from 61.8% (n=63) to 70.6% (n=72) after completion of NHT, although breast conservation was performed in 58 patients. Of note, BCS can be considered a challenging endpoint for determining NHT efficacy and must be interpreted with caution, as type of surgery can also be driven by several other factors than post-treatment tumor size alone (i.e. patient preference, surgeon preference and/or experience).

A major advantage of NHT is its application in translational research, especially with regard to predicting efficacy of hormonal therapy.[32] Measurements of the proliferation marker Ki-67 can be used to tailor neoadjuvant treatment soon after the initiation of treatment.[33] In patients treated with letrozole, the change in Ki-67 level after two weeks of treatment was of prognostic value for RFS, as was demonstrated in an earlier study.[33] Ellis et al. concluded that a single tumor Ki-67 assessment after 2 to 4 weeks after initiating aromatase inhibitor treatment might identify ER-positive breast cancer patients with poor outcomes.[34] Although this is not always feasible in daily clinical practice, results from biomarker studies like these will help pave the way to a more personalized treatment approach pertaining to hormonal therapy.

The conversion of our study from a double-arm phase III study investigating 3 versus 6 months of NHT to a single-arm phase II study of the efficacy and safety of 6 months of NHT is in part related to slow accrual and

Supplementary Table 1. **Patient and tumor characteristics after final surgery in all patients**

All patients	N	%
Feasibility of BCS (after surgery)		
not feasible	24	23.5
feasible	72	70.6
unknown	6	5.9
Final surgery performed		
breast conserving surgery	58	56.9
mastectomy	40	39.2
no resection	4	3.9
Axillary lymph node dissection		
yes	43	42.2
no	56	54.9
unknown	3	2.9
Pathological complete response (pCR)*		
pCR (pT0)	2	2.0
pCR (pTmicro)	3	2.9
No pCR	93	91.2
No surgery	4	3.9
Pathological tumor status		
pT0	2	2.0
pT1 (≤2cm)	42	41.2
pT2 (>2 - ≤5cm)	46	45.1
pT3 (>5cm)	5	4.9
pTx/unknown	7	6.9
Pathological nodal status		
pN-	55	53.9
pN+	41	40.2
unknown	6	5.9
Tumor type		
ductal	57	55.9
lobular	26	25.5
other/unknown	19	18.6
Tumor grade (BR)		
Well (G1)	32	31.4
Moderate (G2)	45	44.1
Poor (G2, G3)	9	8.8
Unknown (Gx)	16	15.7
PR status		
positive (≥10%)	54	52.9
negative	44	43.1
unknown	4	3.9
HER2 status		
positive	8	7.8
negative	83	81.4
unknown	11	10.8

BCS, breast-conserving surgery; pCR, pathological complete response.
*pCR in tumor only; BR, Bloom&Richardson

limits the assertion of our findings. During the early phases of this study, the reluctance to treating patients with NHT resulted in much resistance in the inclusion of patients in our trial. More than half of the patients allocated to 3 months of NHT continued for more than 3 months, suggesting that longer treatment duration has already gained acceptance by patients in clinical practice. Of crucial importance is the late St. Gallen consensus meeting, which confirmed that neoadjuvant hormonal treatment should be continued until maximum treatment response.[8]

CONCLUSION

A sustained response to neoadjuvant treatment with the aromatase inhibitor, exemestane, was observed up to 6 months, exceeding the generally accepted neoadjuvant treatment period of three months. Feasibility of BCS improved, consequently facilitating better cosmetic outcomes. Based on the results of this study and in line with current consensus, it is advised that the duration of NHT durations should be at least 6 months, in the absence of progressive disease. The potential to predict efficacy of adjuvant hormonal treatment based on initial response in the preoperative setting requires further exploration.

Supplementary Table 2. **Adverse events reported by all patients in this study**

	Overall		Grade 3 or 4 toxicities	
Adverse event	**N**	**%**	**N**	**%**
All adverse events*	236	100	11	100
Pain	35	14.8	3	1.3
Hot flashes	26	11.0	1	0.4
Fatigue	24	10.2	2	0.8
Insomnia	10	4.2	0	0
Mood alteration	11	4.7	0	0
Sensory neuropathy	10	4.2	2	0.8
Joint-function	9	3.8	0	0
Dizziness	8	3.4	0	0
Nausea	7	3.0	1	0.4
Hair loss/alopecia (scalp or body)	6	2.5	0	0
Rash/desquamation	6	2.5	0	0
Diarrhea	6	2.5	0	0
Dry mouth/salivary gland (xerostomia)	6	2.5	0	0
Dermal change lymphedema, phlebolymphedema	6	2.5	0	0
Musculoskeletal/Soft Tissue	6	2.5	0	0
Sweating (diaphoresis)	5	2.1	0	0
Gastrointestinal	4	1.7	0	0
Constipation	4	1.7	0	0
Weight gain	3	1.3	0	0
Infection	3	1.3	0	0
Dyspnea (shortness of breath)	3	1.3	0	0
Weight loss	1	0.4	1	0.4
Mucositis	1	0.4	1	0.4
Other (<1%)	36	14.2	-	-

*Only adverse events that make up >1% of all reported AEs or grade ¾ toxicities are specified in this table.

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