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CLINICAL TRIAL

Exemestane as primary systemic treatment for hormone receptor positive post-menopausal breast cancer patients: a phase II trial of the Austrian Breast and Colorectal Cancer Study Group (ABCSG-17)

Brigitte Mlineritsch · Christoph Tausch · Christian Singer · Gero Luschin-Ebengreuth · Raimund Jakesz · Ferdinand Ploner · Michael Stierer · Elisabeth Melbinger · Christian Menzel · Andrea Urbania · Michael Fridrik · Günther Steger · Peter Wohlmuth · Michael Gnant · Richard Greil · on behalf of the Austrian Breast, Colorectal Cancer Study Group (ABCSG)

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Abstract *Background* A multicenter phase II study was conducted to analyze the clinical activity of the steroidal aromatase inhibitor exemestane in the neoadjuvant treatment of post-menopausal women with strongly ER- and/or PgR- positive operable breast cancer. *Patients and methods* From September 2000 to December 2003, 80 women were recruited for treatment with exemestane 25 mg once daily for 4 months. The primary end-point was the clinical response rate according the WHO criteria; the secondary end-points included toxicity and the number of patients who qualified for breast conserving surgery at the end of treatment, comparability of evaluation methods for response, potential alterations of hormone receptor and Her2/neu status during treatment. *Results* On an intention to evaluate analysis, according to the prespecified criteria the overall clinical objective response rate was 34%, the pCR rate was 3% and the rate of breast conserving surgery was 76%. When sonographic and mammographic longitudinal measurements were included in patients with missing palpation data, response rates were 38% and 41%,

B. Mlineritsch · R. Greil (✉)
III[rd] Medical Department with Hematology, Medical Oncology, Hemostaseology, Rheumatology and Infectious Disease, Laboratory of Immunological and Molecular Cancer Research, Paracelsus Medical University Salzburg, Müllner Hauptstraße 48, 5020 Salzburg, Austria
e-mail: r.greil@salk.at

C. Tausch
Department of Surgery, BHS Hospital, Linz, Austria

C. Singer
Division of Special Gynaecology, General Hospital, Medical University of Vienna, Vienna, Austria

G. Luschin-Ebengreuth
Department of Gynaecology, Medical University of Graz, Graz, Austria

R. Jakesz · P. Wohlmuth · M. Gnant
Department of Surgery, Medical University of Vienna, Vienna, Austria

F. Ploner
Department of Internal Medicine, Division of Oncology, Medical University of Graz, Graz, Austria

M. Stierer
Department of Surgery, Hanusch Medical Center, Vienna, Austria

E. Melbinger
Department of Surgery, Wolfsberg Hospital, Wolfsberg, Austria

C. Menzel
Department of Special Gynaecology, Paracelsus Medical University Salzburg, Salzburg, Austria

A. Urbania
Department of Surgery, Klagenfurt Hospital, Klagenfurt, Austria

M. Fridrik
Department of Internal Medicine 3, Center for Hematology and Medical Oncology, General Hospital Linz, Linz, Austria

G. Steger
Department of Oncology, General Hospital, Medical University of Vienna, Vienna, Austria

on behalf of the Austrian Breast, Colorectal Cancer Study Group (ABCSG)
Vienna, Austria

respectively. The tumor response was independent of the Her2/neu status which remained unchanged during treatment. In contrast, while the ER expression remained unaltered, downregulation of the PgR was observed. The treatment was well tolerated with no grade 3 and 4 toxicities except gastrointestinal (one grade 3 case) and hot flushes (two grade 3 cases). *Conclusion* This study shows that exemestane is effective and safe as a preoperative therapy in post-menopausal patients with strongly hormone receptor-positive breast cancer.

Keywords Exemestane · Neoadjuvant systemic therapy · Post-menopausal breast cancer · Surgery · Her2/neu status

Introduction

The rationale behind neoadjuvant systemic therapy for the management of breast cancer is to reduce tumor size in order to allow secondary operability in otherwise non-resectable cancers [1], and to avoid mastectomy that might otherwise be necessary in operable cancers, thus increasing the rate of breast conserving-surgery. Finally, a setting is provided for testing in vivo the sensitivity of breast cancer to novel drugs or clarify mechanisms of resistance development [2–4]. In most instances, and particularly in pre-menopausal women, primary chemotherapy is used as the treatment of choice due to rapid onset of response and often marked reduction in tumor volume. However, particularly in post-menopausal women, endocrine therapy, if sufficiently effective, might be an important option as primary systemic therapy due to its lower degree of side effects [5]. Nevertheless, neoadjuvant endocrine therapy has not yet received wide acceptance in clinical practice although balancing the pros and cons provides some strong arguments in favor of such an approach in selected women. Chemotherapy has been challenged as the treatment of choice in ER-positive patients in the postoperative adjuvant setting, with tamoxifen being at least equivalent to CMF [6] and complete hormonal ablation with Goserelin alone or combined with tamoxifen being equivalent even to anthracyclin-containing regimens in pre-menopausal women [7, 8]. In metastatic disease, such direct comparisons of chemo- or anti-hormonal therapy are historical and lacking with modern treatment regimens, but a reduced sensitivity to chemotherapy has been well described in ER-positive compared to ER-negative patients [9]. It has previously been demonstrated that in hormone receptor-positive post-menopausal women, primary endocrine therapy with tamoxifen can substantially reduce the tumor volume when applied over a 3–4 month period of treatment. [10].

In addition, the efficacy of anti-hormonal therapy has increased with the development of newer drugs. Initially, tamoxifen was used as primary treatment for elderly women with locally advanced breast cancer [11–14], but the third- generation non-steroidal aromatase inhibitors anastrozole and letrozole have proved to be superior over tamoxifen in the metastatic [15] as well as in the adjuvant setting of endocrine-responsive breast cancers [16, 17]. They are therefore now being tested as primary systemic treatment instead of tamoxifen, similar to the adjuvant setting [18, 19]. In these approaches, response rates of 40% and 60% have been reported in randomized clinical trials for letrozole and anastrazole, respectively [20–22]. However, the rate of pathologic complete remission (pCR) was only between 0% and 8%, and considering the role of pCR as a potential surrogate marker for an improved overall outcome of the disease [4, 23, 24] in trials of neoadjuvant chemotherapy, this has to be considered disappointingly low. It is therefore reasonable to search for more efficient anti-hormonal neoadjuvant treatment options.

Exemestane, a steroidal aromatase inhibitor, irreversibly inhibits the aromatase enzyme and suppresses aromatase activity in a dose-dependent fashion [25]. This in vitro finding is associated with a marked reduction in peripheral aromatization as well as aromatase activity in breast tumor tissue and adjacent non-malignant tissue after 3 months of treatment [10, 24]. Due to the stronger suppression of aromatase and the more pronounced reduction in estrogen levels, exemestane might be superior to non-steroidal agents like anastrazole and letrozole [24]. This finding served as the basis for usually very small trials to improve the efficacy of anti-hormonal therapy in the neoadjuvant setting by using exemestane [24, 26–28] and also for initiating this study. The objective response rate was the primary endpoint of this phase II prospective trial. Furthermore, information was collected regarding toxicity, rate of surgery, the impact of Her2/neu receptor expression on endocrine responsiveness and tumor regression, the changes of ER, PgR, and Her2/neu receptor status after 4 months of therapy with exemestane.

Comparing response rates of endocrine therapy is difficult between different trials due to the eccentric shrinkage of tumors under anti-hormonal therapy. This may result not only in substantial deficits in the comparability of different drugs tested in different trials and by different physicians or institutions, but also in a biased interpretation of breast-conserving therapy rates which are apparently based on size estimations [4]. The comparability of re-evaluation methods of tumor size therefore was within the scope of this study.

Patients and methods

Inclusion and exclusion criteria

This multicenter phase II trial was initiated by the ABCSG and involved 11 participating hospitals across Austria.

Post-menopausal patients with a histologically confirmed invasive component of breast cancer, ER- and/or PgR-positivity and in clinical stages T2 (>3 cm)-T4a-c N0-1, M0 were included after written informed consent had been obtained. The following conditions and co-morbidities were considered as exclusion criteria: inflammatory breast cancer, prior or concurrent therapy with anti-estrogens or aromatase inhibitors, concurrent use of hormonal replacement therapy, any invasive secondary malignancy other than basal cell carcinoma or cervical carcinoma in situ, investigational drug-treatment within 30 days and medical or psychiatric conditions making informed consent impossible. Patients with a performance status according to WHO-criteria of >2 or with coincident uncontrolled endocrine or cardiac disease were also excluded.

Patients were considered post-menopausal if they were older than 60 years of age, had undergone bilateral oophorectomy, were younger than 60 years with a uterus and had been amenorrhoic for at least 12 months, or were younger than 60 years without a uterus and had follicle stimulating hormone levels greater than 20 U/L.

Baseline staging consisted of clinical breast examination, ultrasound and/or mammographic measurements, all of which were read at the primary institutions. In addition, blood sampling for liver and renal function tests, hematological assessment and determination of endocrine markers were carried out and thoracic x-ray, abdominal ultrasound and bone-scan performed. For histological assessment and for the determination of hormone receptors and Her2/neu receptor expression, diagnostic core needle biopsies were mandatory in all cases. ER or PgR had to be higher than 10 fmol/mg cytosolic protein or ER-immuncytochemical assay positive or PgR- immuncytochemical assay positive [29].

For inclusion of patients into this trial, tumors had to be strongly positive for hormone receptors. If the immune reactive score was low, in the range 1–3, for either of the two receptors, the other had to be positive too and only double-positive patients were enrolled. When one receptor was negative, the score of the other had to be in a range of 4–8.

Primary resectability was defined by the following criteria: (i) absence of distant metastases, (ii) no adherence of the tumor to the chest wall, (iii) lack of inflammatory breast cancer and (iv) tumor size below 5 cm.

Treatment and follow-up

Immediately after entry into the trial, patients started treatment with a daily dose of exemestane of 25 mg for 12 weeks followed by surgery. Clinical measurement of tumor size and nodal status was performed monthly, blood was drawn for the definition of side effect profiles and clinical grades of toxicities were denoted at the same time points. The final clinical, sonographic and/or mammographic measurements as well as blood chemistries were performed 4 months after the start of treatment prior to the planned surgical excision of the tumor.

Patients who had breast-conserving surgery and patients with involved axillary nodes after mastectomy were administered postoperative radiotherapy based on individual hospital protocols. The choice of the postoperative adjuvant therapy was at the discretion of the local centers.

Patients with progressive disease during regular assessment of response

In case of suspicion of early progression, restaging was performed immediately. Patients with radiologically confirmed progressive disease according to the WHO criteria were considered off study and treated as considered adequate by the local centre.

Study end-points and evaluation of response

The primary study end-point was overall objective response rate determined by clinical palpation and following the WHO criteria [30]. The secondary study endpoints were as follows: (i) Response rate (i.e. CR and PR) as assessed by ultrasound and mammographic measurements after 4 months of treatment with exemestane [30]. (ii) Safety of the treatment and side effects as measured by the WHO—toxicity—criteria Grade 1–4, (iii) Rate of breast-conserving surgery, (iv) Response in patients with overexpression of Her2/neu, change in hormone and Her2/neu receptor expression during treatment and the correlation of the various assessment systems of tumor size. These end-points were all prospectively defined in the protocol.

Analysis of estrogen receptor, progesterone receptor, and Her2-/neu receptor

All immunohistological investigations were performed on the core biopsy material obtained at diagnosis and at the local centers but according to pre-specified criteria [31, 32]. The hormone receptor status was determined by the pathologist prior to entry into the trial. Tumors were considered as overexpressing HER2/neu if they scored 3+ by immunhistochemistry using the Dako HerceptⓇ test [32].

Tolerability assessments

Adverse events, defined as the development of new medical conditions or the deterioration of a preexisting medical condition, were recorded every 4 weeks. Serious adverse events were recorded as they occurred within 24 h.

Statistical analysis

Data on tumor and patients characteristics were analyzed descriptively and depicted in frequency tables. For continuous variables the mean, median, standard deviation and variance were calculated.

Clinical response rates as determined by WHO [30] were estimated with exact binomial confidence intervals. Changes in tumor size as assessed by ultrasound or mammography as well as histologically defined tumor sizes of resected specimens were compared with each other using cross tables.

Ethical considerations

The trial was conducted in accordance with the principles of Good Clinical Practice as specified in the Declaration of Helsinki (1996 revision). The study protocol was approved first by a national lead ethics committee and subsequently by local ethics committees. All patients gave written informed consent before enrolment into the study.

Results (Table 1)

Between September 2000 and December 2003, a total of 95 patients from 11 centers in Austria were enrolled in the study and assigned to receive treatment with exemestane. Fifteen patients were excluded from the final analysis by the independent data monitoring committee of the ABCSG: 2 patients did not properly sign the informed consent, 3 patients had no adequate staging, 1 patient turned out to be hormone receptor-negative, one had a prior pulmonary embolism which should have been considered an exclusion criterion, two had initial tumors smaller than 3 cm, four had secondary malignancies, two were found already metastasized within lung and bone upon completion of staging. For final evaluation, a total of 80 patients were available who received exemestane 25 mg daily for 4 months. Baseline characteristics of these patients are described in Table 1. All patients were post-menopausal with a median age of 71 years (range 54–59). All tumors were strongly hormone receptor-positive. Two thirds of the tumors measured between 3 and 5 cm by clinical palpation, one third had a locally advanced stage T4a-b. Forty three percent displayed a clinical involvement of axillary nodes. As expected, tumors were slightly smaller when measured by ultrasound or mammography than by clinical palpation (Table 2).

Table 1 Basic patient characteristics ($n = 80$)

Parameter	Frequency (%)
Age (years)	
Median	71 a
Range	54–92 a
WHO	
0	59 (74%)
1	21 (26%)
Grading	
1	4 (5%)
2	45 (56%)
3	22 (28%)
Not done	9 (11%)
Clinical stage	
T2 (>2 cm < 3 cm)	57 (71%)
T3	11 (14%)
T4a-c	12 (15%)
N0	45 (56%)
N1	35 (44%)
Hormone receptors	
ER + and PgR +	56 (70%)
ER + and PgR −	24 (30%)
ER − and PgR +	0
ER ++	15 (19%)
ER +++	65 (81%)
PgR −	24 (30%)
PgR +	11 (13%)
PgR ++	25 (31%)
PgR +++	20 (25%)
Her2neu status	
3+	10 (13%)
−, +, ++	62 (77%)
Not done	8 (10%)

Efficacy

An intention-to-treat analysis of all 80 patients that included clinical evaluation of the primary efficacy end-point revealed that the overall objective response rate was 34%. Six patients (8%) had a clinical CR, 21 patients (26%) obtained a clinical PR, 39 (49%) showed stable disease and no patient had documented progressive disease (Table 3a). Fourteen patients were not evaluable because of missing

Table 2 Tumor stages at screening

T stages	Clinical assessment $n = 80$	Mammographic assessment $n = 80$	Sonographic assessment $n = 80$
T1	0	21 (17%)	19 (15%)
T2	57 (71%)	42 (34%)	45 (36%)
T3	11 (14%)	5 (4%)	6 (5%)
T4a-c	12 (15%)	12 (10%)	10 (8%)

longitudinal palpatory assessments. However, data exist for longitudinal ultrasound, mammographic and comparison of clinical baseline with histologic size evaluation in these patients and demonstrated response in further 3, 6 and 10 cases, respectively (Table 3b). Including these patients into evaluation, the response rates increased to 38%, 41%, and 50%, respectively.

For 31 patients who were regarded evaluable for all three assessment means, response rates were found rather similar with 36% for palpation, 39% for ultrasound, and 39% for mammography (Table 3c).

The evolution of tumor stage during treatment as assessed by the different tumor evaluation systems is given in Table 4. The continuous reduction of the median tumor size was statistically significant and ranged from a reduction from 4.6 cm to 2.5 cm as measured by palpation ($P < 0.0001$), from 3.4 to 2.3 cm as assessed by ultrasound ($P < 0.0001$) and from 3.7 to 2.7 cm as determined by mammography ($P < 0.0002$) (Fig. 1). Despite the fact that the results obtained were rather comparable, it has to be mentioned that, depending on which tool was used for the longitudinal determination of the tumor response, progressive disease occurred in none, 4, and 5 patients, respectively.

Table 3a Response rates following 4 months of treatment with exemstane and as determined with different evaluation systems[a]

Response	Clinical assessment $n = 80$	Mammographic assessment $n = 80$	Sonographic assessment $n = 80$
CR	6 (8%)	2 (3%)	2 (3%)
PR	21 (26%)	11 (14%)	11 (14%)
RR	27 (34%)	13 (17%)	13 (17%)
SD	39 (49%)	37 (46%)	43 (54%)
PD	0	5 (6%)	4 (5%)
Not done	14 (17%)	25 (31%)	20 (25%)

[a] All examinations were performed at the individual local institution. Mammograms and sonograms were usually carried out by independent radiologists whereas the clinical size determination was performed by the responsible clinician (medical oncologist and/or surgeon and/or gynaecologist)

Table 3b Patients clinically not evaluable by palpation and assessed by other methods ($n = 14$)

	Comparison of clinical tumor size before and histological tumor size in resection specimens	Mammographic assessment	Sonograpic assessment
CR	0	0	0
PR	10 (71%)	6 (42%)	3 (21%)
SD	4 (29%)	4 (29%)	6 (43%)
Not done	0	4 (29%)	5 (36%)

Table 3c Patients with response as defined by any type of measurement (intention to analyse)

Evaluable for palpation, ultrasound and mammography, $n = 31$			
	Palpation	Mammographic assessment	Sonographc assessment
CR	4 (13%)	2 (7%)	2 (7%)
PR	7 (23%)	10 (32%)	10 (32%)
RR	11 (36%)	12 (39%)	12 (39%)
SD	19 (61%)	18 (58%)	18 (58%)
PD	1 (3%)	1 (3%)	1 (3%)

Response according to the initial HR expression and change of receptor expression over time

The Her2/neu status was determined in 72 patients: 10 patients (14%) were Her2/neu-positive by immunohistochemistry (i.e. 3+ according to the Dako Hercept test) and 62 patients were negative. The response rate did not differ between these two groups, irrespective of the evaluation technique used for the determination of the tumor size (Table 5). The response rate was independent of the ER and PgR expression levels.

When the results of hormone receptor and Her2/neu expression were compared between core biopsy materials

Table 4 Downstaging of tumors after 4 months of exemestane treatment according to clinical evaluation

pT Stage at surgery	Clinical T stage at diagnosis ($n = 75$)		
Ptis	T2 (2–5 cm)	T3 (5–10 cm)	T4 a-c
Ptis	1	0	1
PT1a (<0.5 cm)	1	0	0
pT1b (0.5–1 cm)	2	1	0
pT1c (>1–2 cm)	15	2	0
pT2 (<2–5 cm)	30	6	5
pT3 (<5 cm)	4	2	0
pT4	2	0	3
Downstaged patients	19	9	6

Table 5 Response rates in tumors with or without Her2/neu overexpression

	HER2/neu^{+++} $n = 10$	HER2/neu$^{0,\ +,\ ++}$ $n = 62$
CR	0 (0%)	2 (3%)
PR	5 (50%)	32 (52%)
SD	3 (30%)	22 (36%)
PD	0 (0%)	4 (6%)
Not done	2 (20%)	2 (3%)

and postoperative surgical specimens, significant changes in ER and Her2/neu expression or grading could not be observed. In contrast, the treatment with exemestane led to a significant reduction in PgR expression from 76% to 40% of all cases (Table 6, $P < .001$).

Locoregional treatment

After 4 months of neoadjuvant hormone therapy with 25 mg exemestane daily, locoregional treatment was carried out in 75 of 80 patients (94%). Four patients refused surgery and one patient had systemic progressive disease with cerebral metastasis. Only 18 patients (24%) required mastectomy and 57 patients (76%) had breast-conserving-surgery plus irradiation. Five patients did not receive any locoregional treatment.

Tolerability assessments

The treatment was generally well tolerated. When toxicities were graded according to the WHO criteria as specified in the protocol, the most common adverse event was hot flushes (grade 1 in 27 patients (33.8%), grade 2 in 13 patients (16.3%), grade 3 in 3 patients (3.8%)). Bone pain grade 1 was reported by 6 patients (8%) and grade 2 by 4 patients (5%). Only one case of grade 3 nausea occurred. A complete toxicity profile is provided in Table 7.

Discussion

The concept of neoadjuvant systemic therapy was initially introduced by Fisher's experiments in human xenograft models which demonstrated that surgery of the primary tumor was associated with an increased compensatory outgrowth of micrometastatic disease [33]. Neoadjuvant treatment with cyclophosphamide and tamoxifen was shown to successfully counteract micrometastatic spread of disease [34]. Despite the demonstrated efficacy of anti-hormonal therapy in these pivotal and seminal experiments, the vast majority of neoadjuvant clinical trials have focused on the use of even more aggressive chemotherapy regimens. Such an approach is based on the expectation of higher response rates, on the one hand, and the fear that a slower and probably lower degree of tumor regression under endocrine treatment might be associated with an early progression of the primary and/or the micrometastatic spread, on the other [4]. However, the equivalent efficacy of endocrine treatment and some types of chemotherapy as well as the low response rate of cytotoxic therapy in ER +ve cases still render improvements in endocrine treatment an attractive option for the further development of neoadjuvant treatment strategies [35].

Table 6 The influence of neoadjuvant endocrine therapy with exemestane on hormone receptor and Her2/neu expression

Pretherapeutic (core biopsy) $n = 80$			Posttherapeutic (resection specimen) $n = 75$	
ER		PgR	ER	PgR
Negative	0 (0%)	24 (30%)	1 (1%)	45 (60%)
+	0 (0%)	11 (14%)	4 (5.%)	12 (16%)
++	15 (19%)	25 (31%)	22 (30%)	8 (11%)
+++	65 (81%)	20 (25%)	42 (56%)	3 (4%)
Nd	–	–	6(6%)	7 (9%)
ER^{-ve}/PgR^{-ve}: 0			ER^{-ve}/PgR^{-ve}: 1 (1%)	
ER^{+ve}/PgR^{-ve}: 30 (38%)			ER^{+ve}/PgR^{-ve}: −45(60%)	
1		4 (5%)	6 (8%)	
2		45 (56%)	48 (64%)	
3		22 (28%)	18 (24%)	
x		9 (11%)	3 (4%)	
HER2/neu status				
+++		$n = 10$ (12%)	$n = 10$ (13%)	
−ve, +, ++		$n = 62$ (78%)	$n = 60$ (80%)	
Not done		$n = 8$ (10%)	$n = 5$ (7%)	

Table 7 Toxicity according to the WHO criteria ($n = 80$)

WHO-Grade	1	2	3	4
Gastro-intestinal	11 (14%)	3 (4%)	1 (2%)	0
Depression	4 (5%)	4 (5%)	0	0
Headache	7 (9%)	0	0	0
Hot flushes	23 (18%)	13 (10%)	3 (4%)	0
Vag. fluor	0	0	0	0
Hair thinning	1 (1%)	0	0	0
Bone pain	6 (5%)	4 (3%)	0	0
Abdominal Pain	3 (4%)	1 (1%)	1 (1%)	0
Constipation	3 (4%)	1 (1%)	0	0
Diarrhea	1 (1%)	2 (3%)	0	0
Dyspnea	3 (4%)	0	0	0
Cough	1 (1%)	0	0	0
Hypertrichosis	0	1 (1%)	0	0
Acneiform Rash	2 (3%)	0	0	0
Hypertension	3 (4%)	2 (3%)	0	0
Cardiac Dysfunction	2 (3%)	1 (1%)	0	0
Alopezia	0	1 (1%)	0	0
Anxiety	1 (1%)	3 (4%)	0	0
Insomnia	3 (4%)	3 (4%)	0	0
Dizziness	3 (4%)	2 (3%)	0	0
Edema	2 (3%)	1 (1%)	0	0

We treated 80 eligible post-menopausal patients with invasive breast cancer strongly positive for HR with the steroidal aromatase inhibitor exemestane. To the best of our knowledge, this is the highest number of patients in a multicenter-phase II study who have ever received exemestane as neoadjuvant therapy in breast cancer. We observed an ORR of 34% on an intention to treat basis, 41% on an overall response analysis of any method, a downstaging rate of 45%, and a pCR rate of 3%. A survey of the relevant literature shows that to date one randomized trial of exemestane versus tamoxifen has been published but only in abstract [28]. In this Russian trial, 151 women with hormone receptor-positive breast cancer were randomized to receive either tamoxifen or exemestane for 3 months in an neoadjuvant setting. The clinical response rate was greater for exemestane (76%) than for tamoxifen (40%) and the rate of breast-conserving therapy after exemestane was 36.8% vs. 20% after treatment with tamoxifen. Furthermore, five very small phase II trials have been reported evaluating the response rate of exemestane in the neoadjuvant setting. The detailed results of these trials are shown in Table 8. In general, response rates between 37% and 85% were reported, and breast- conserving surgery could be achieved in 36–52% of cases. However, patient characteristics, the description of response, and re-evaluation methods of tumor size were rather heterogeneous, thus raising questions about the direct comparability of these data. These facts, together with the multicenter design of our trial may account for response rates in the lower range of those reported by others.

The response and downstaging rates with exemestane in ABCSG-17 are within the range of previously reported randomized trials on non steroidal 3rd generation aromatase inhibitors tested in comparison with tamoxifen. In the IMPACT trial, Smith et.al. reported a response rate of 38% in the anastrozole alone arm [20]. Eierman et al. observed an overall response rate of 55% for neoadjuvant letrozole [21]. The rate of pathological complete remissions in our trial was 3%, comparable to the results of the above-mentioned trials on non-steroidal aromatase inhibitors (IMPACT: 3% pCR rate; letrozole-trial: 0%).

Another important result of our trial was a high rate of breast-conserving surgery of 76% of the 75 patients who finally underwent surgery. In the studies with non steroidal aromatase inhibitors reported by Smith et al. and Eiermann et al., the rate of breast-conserving surgery was 46% and 45%, respectively [20, 21]. In fact, the degree of downstaging to resectability by breast-conserving surgery may be considered the most important clinical endpoint of such trials on neoadjuvant systemic therapy. Unfortunately, however, no uniform criteria on the applicability of breast conserving-surgery have been defined or analyzed for reproducibility [37].

Of even greater concern is the fact that substantial differences between radiologic preoperative and histological postoperative size determinations have been reported [38]. In fact, the marked differences between exemestane and tamoxifen response rates observed by clinical staging in the trial of Semiglazov et al. completely disappeared when the tumor sizes as measured by ultrasound or mammography were compared (60% vs. 64%). While small differences were observed in our trial between the tumor size evaluations with the different methods (Fig. 1), the longitudinal trends and the downstaging rates as indicated by the different methods were closely similar (Tables 3a–c, 4). This underlines the careful and robust evaluation system applied in our trial and to the clinical experience of the participating physicians.

The rapid and longitudinal assessment of predictive factors of response, such as ER, PgR and Her2/neu receptor status, represents a major advantage of neoadjuvant treatment allowing a more dynamic insight into the influence of endocrine treatment on the regulatory network of hormones and their receptors and the development of resistance to drugs [22].

In our trial, the PgR was downregulated in a significant proportion of patients. Neoadjuvant treatment with letrozole and anastrozole was also associated with a reduction of PgR staining in two randomised trials, pointing to a class effect of aromatase inhibitors. The PgR is under the tight control of signaling along the ER, and its co-expression on

Table 8 Results with exemstane in neoadjuvant trials on hormone receptor-positive breast cancer patients

References	*n*	Included stages	Included HR status	% Her2/neu pos	Response rate	Evaluation method	pCR	Downstaging	BCT-rate
Miller [24]	12	Locally advanced	ER rich	nr[a]	85% reduction of tumor voume	Palpation mammography ultrasound	nr[a]	nr[a]	BCS 80%
Krainick [26]	27	T″ < 2 cm	HR positive	nr[a]	37%	Palpation	0	14/27 (51%)	52%
Tubiana-Hulin [27]	41	Operable T2-4	ER positive 73% PR pos.	3%	76%	Palpation ultrasound	6 (18%)	45%	45%
Semiglazov [28]	76/151	nr[a]	ER+	nr[a]	76% 64% 60%	Palpation mammography ultrasound	2 (3%)	nr[a]	36%
Gil-Gil [36]	55	T2-4a-b >3 cm non BCS[c]	HR+	nr[a]	45%	Palpation	1 (2%)	nr[a]	38%
Mustacchi [11]	50	<70a	HR rich	nr[a]	60%	Palpation, mammography	0	nr[a]	BCS 76%
This trial	80	T2-4a-b	HR rich	12%	34%	Palpation (ultrasound, mammography)[b]	3%	45%	76%

[a] nr: not reported

[b] The primary evaluation parameter, which is given in this table was the tumor size as determined by clinical palpation. Ultrasound and mammography were carried out in parallel and results are presented in Tables 2 and 3a–c

[c] BCS: Breast conserving surgery

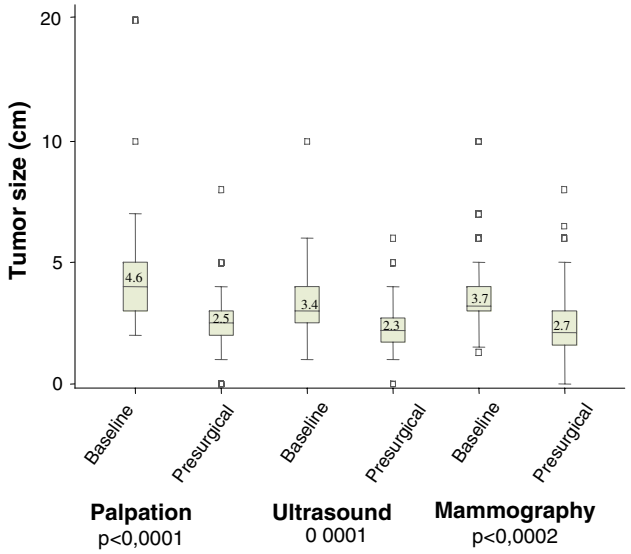

Fig. 1 Downsizing of tumors as determined by different methods of measurement. Data are presented in a box-plot and whiskers model with median, interquartile ranges and outliers. Levels of significance are given

ER-positive tumor cells has long been considered evidence for an intact ER signaling pathway (for review) [39]. Downregulation of the PgR might thus be the result of an efficient reduction in estrogen levels under exemestane treatment and the persistence of an intact signaling cascade and thus might be considered a favourable sign. Long-term follow up of our patients will clarify if downregulation of PgR under exemestane treatment was predictive of the further course of the disease. Our study cohort is too small to allow for further sub-classification of tumors, but it is worth mentioning that response was similar in Her2/neu-positive and Her2/neu-negative patients respectively.

In conclusion, the results of this trial show a substantial response rate, a valuable downsizing and breast-conserving surgery rate in post-menopausal women with HR-positive tumors. The efficacy results from this largest trial on neo-adjuvant exemstane are at least closely similar to those of non-steroidal aromatase inhibitors and also of taxane/anthracycline combinations in HR-positive patients [40, 41], but without the high toxicity rate and the observed fatalities (0.1%) in chemotherapy trials [2].

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Appendix

Apart from the authors of this article, members of the Austrian Breast and Colorectal Cancer Study Group participating in Trial 17 included the following:

H. Hausmaninger, M. Moik, C. Rass, R. Reitsamer, G. Russ (Paracelsus Medical University Salzburg, III[rd] Medical Department with Hematology, Medical Oncology, Hemostaseology, Rheumatology and Infectious Disease and Laboratory of Immunological and Molecular Cancer Research and Department of Special Gynaecology, Paracelsus Medical University Salzburg);

T. Bachleitner-Hoffmann, R. Bartsch, P. Blaha, P. Dubsky, F. Fitzal, T. D. Kandioler, P. Panhofer, U. Pluschnig, S. Schoppmann, S. Taucher, C. Wenzel (Departments of Surgery and Internal Medicine I, Division of Oncology, Medical University of Vienna, Vienna);

H. Samonigg, H. Stöger, M. Schmid (Departments of Internal Medicine and Surgery, Medical University of Graz, and Second Department of Surgery, Graz Hospital, Graz);

A. Galid, M. Seifert (Department of Gynecology, Medical University of Vienna, Vienna);

F. Kugler, G. Michlmayer, S. Pöstlberger (Departments of Surgery and Internal Medicine, BHS Hospital, Linz);

H. Matzinger, H. Spoula (Department of Surgery, Breast-Center-Hanusch Medical Center, Vienna);

I. Thiel, G. Zehtleitner (Department of Gynecology, Medical University of Graz, Graz);

R. Greul, G. Hochreiner, G. Wahl (First Medical Department, Linz Hospital, Linz).

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