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# An open randomised trial of second-line endocrine therapy in advanced breast cancer: comparison of the aromatase inhibitors letrozole and anastrozole

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**Abstract**

It was previously shown that letrozole (Femara®) was significantly more potent than anastrozole (Arimidex®) in inhibiting aromatase activity *in vitro* and in inhibiting total body aromatisation in patients with breast cancer. The objective of this study was to compare letrozole (2.5 mg per day) and anastrozole (1 mg per day) as endocrine therapy in postmenopausal women with advanced breast cancer previously treated with an anti-oestrogen. This randomised, multicentre and multinational open-label phase IIIb/IV study enrolled 713 patients. Treatment was for advanced breast cancer that had progressed either during anti-oestrogen therapy or within 12 months of completing that therapy. Patients had tumours that were either positive for oestrogen and/or progesterone receptors (48%) or of unknown receptor status (52%). The primary efficacy endpoint was time to progression (TTP). Secondary endpoints included objective response, duration of response, rate and duration of overall clinical benefit (responses and long-term stable disease), time to treatment failure, and overall survival, as well as general safety. There was no difference between the treatment arms in TTP; median times were the same for both treatments. Letrozole was significantly superior to anastrozole in the overall response rate (ORR) (19.1% versus 12.3%, $P=0.013$), including in predefined subgroups (receptor status-unknown, and soft-tissue- and viscera-dominant site of disease). There were no significant differences between the treatment arms in the rate of clinical benefit, median duration of response, duration of clinical benefit, time to treatment failure or overall survival. Both agents were well tolerated and there were no significant differences in safety. These results support previous data documenting the greater aromatase-inhibiting activity of letrozole and indicate that advanced breast cancer is more responsive to letrozole than to anastrozole as second-line endocrine therapy.


*Keywords:* Breast cancer; Endocrine therapy; Aromatase inhibitors; Letrozole; Anastrozole

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## 1. Introduction

Approximately 75% of breast cancers are hormone-responsive, and anti-oestrogen therapy with tamoxifen is effective in most of these patients. However, in patients with advanced, or metastatic breast cancer, progressing during or after tamoxifen treatment, the appearance of resistance to tamoxifen is common [1]. Further endocrine therapy in these cases must rely on either an alternate oestrogen receptor (ER) modulator, a progestin like megestrol acetate, or an aromatase inhibitor to prevent the terminal step (aromatisation) in oestrogen biosynthesis. Initial treatment in this setting was with either megestrol acetate or the first-generation aromatase inhibitor, aminoglutethimide, but the third-generation aromatase inhibitors, which include the non-steroidal agents, letrozole and anastrozole, and the steroidal inhibitor, exemestane, have proven superior and are now commonly used as second-line hormonal agents [2,3–8].

Preclinical comparison of letrozole and anastrozole indicate that letrozole is the more potent inhibitor of aromatisation in several models [9,10]. In addition, more pronounced shrinkage of chemically-induced rodent mammary tumours has been achieved with letrozole than with anastrozole, at 10-fold lower concentrations of letrozole. Letrozole was also at least 10 times more effective than anastrozole in reducing uterine weight in cycling rats [11,12]. In postmenopausal women with metastatic breast cancer, a crossover study of the two agents demonstrated significantly more potent suppression of total-body aromatisation and plasma oestrogen levels with letrozole than with anastrozole [13]. While these data suggest that letrozole might translate into more effective second-line therapy than anastrozole for postmenopausal women who have progressed while on tamoxifen, there has been no comparative evaluation in this clinical setting.

In trials of aromatase inhibitors in postmenopausal patients with tamoxifen-resistant advanced breast cancer, letrozole provided survival benefits and was better tolerated than either aminoglutethimide or megestrol acetate [4–6]. In two separate studies for which results were pooled for statistical analysis, anastrozole in the same setting also improved survival over megestrol acetate, and was better tolerated [14]. Both letrozole and anastrozole were superior to megestrol acetate with respect to serious adverse side-effects, including thromboembolic events. Exemestane has also been shown to be more efficacious, and better tolerated, than megestrol acetate in a comparative trial [8].

Since there have been no head-to-head comparisons of these new aromatase inhibitors, it is unclear whether any of these agents is superior in this tamoxifen-resistant advanced breast cancer group of patients. To determine whether there is an advantage to using either letrozole or anastrozole in this setting, we directly compared these two agents in an open randomised trial in postmenopausal women following failure of tamoxifen or other anti-oestrogen [15].

## 2. Patients and methods

### 2.1. Patient population

A total of 713 patients were enrolled at 112 centres in 19 countries between December 1997 and November 1999 (see Appendix). Eligibility criteria included: (1) age $\geqslant 18$ years; (2) defined postmenopausal status; (3) histological or cytological evidence of locally advanced or metastatic breast cancer; (4) measurable and/or evaluable disease according to International Union Against Cancer (UICC) criteria, with objective evidence for progression on first-line anti-oestrogen therapy; (5) to a lesser extent, clinical resistance to adjuvant tamoxifen therapy given for at least 6 months, with or without adjuvant chemotherapy, and with relapse occurring during therapy or within 12 months of stopping therapy; (6) World Health Organization (WHO) performance status grades 0–2; and (7) tumours that are either ER-positive and/or progesterone receptor (PgR)-positive, or with both receptors unknown. Exclusion criteria were: (1) central nervous system metastases; (2) bilateral diffuse lymphangitis, carcinomatosa involving $>50\%$ of the lungs, or inflammatory breast cancer; (3) extensive liver metastases, or blastic bone lesions only; (4) $>1$ chemotherapy regimen either in the adjuvant setting or for advanced disease; and (5) uncontrolled cardiac disease.

### 2.2. Trial design

This was an open-label, multicentre, randomised phase IIIb/IV trial. Patients were randomly assigned, without stratification (other than by centre), either letrozole 2.5 mg or anastrozole 1 mg according to a predetermined randomisation list. Treatment was daily, by oral tablet. All trial endpoints and patient subsets were prospectively defined. The primary endpoint for the comparison of the treatment arms was time to progression (TTP). Secondary objectives were to compare objective response rate (ORR); duration of response (DOR); rate and duration of overall clinical benefit (complete responses (CR), partial responses (PR), and no change (NC) for $\geqslant 24$ weeks); time to treatment failure (TTF); overall survival; and tolerability and toxicity. This trial was designed in two stages: a core phase for the first 12 months, and if there was evidence of overall patient benefit at 12 months, a second phase extending an additional 18 months. The study was closed in late 2001 (Fig. 1).

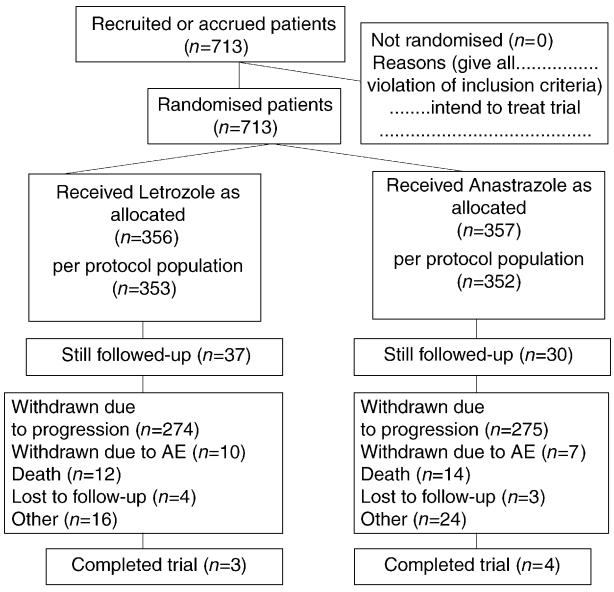


Fig. 1. Flow chart of the progress of patients through the trial (adapted from Ref. [27]). AE, adverse events.

### 2.3. Study evaluation

Baseline tumour staging was based on full skeletal surveys, bone scans and abdominal ultrasonograms. During treatment, efficacy and safety were assessed at 3-month intervals until either disease progression or the 30-month cut-off. A computer algorithm was applied to determine the earliest date of disease progression.

#### 2.3.1. Definition of events

Responses were based on UICC criteria. CR was defined as the disappearance of all known disease as determined by two observations $\geqslant$4 weeks apart (in practice, all assessments, including confirmation of responses, were conducted at 3-month intervals). PR was designated as $\geqslant$50% decrease in the sum of the two largest diameters of a bidimensional tumour, determined by two observations $\geqslant$4 weeks apart, in the absence of the appearance of new lesions or progression of any lesion. Bone disease was evaluable, but not measurable. Eighty-four of the 112 responders were reviewed by an external peer review committee (J. Huober and K. Siegmann, University of Tübingen, Germany; A. Makris and A. Padhani, Mount Vernon Hospital, London, UK) that had no treatment information available. Confirmatory assessment was only possible for those responses that were fully documented by tumour imaging and for which changes in the size or extent of lesions could be determined. Of the 75% of responding patients who were reviewed, there was 83% concordance with investigator-determined responses.

#### 2.3.2. Statistical methodology

The sample size for this trial was chosen to provide 80% power to detect a hazard ratio between letrozole and anastrozole of 1.3 at a significance level of 5% (two-sided) for the primary endpoint, TTP (i.e. a 30% prolongation of TTP). This would correspond to a 23% reduction in the risk of progression for the more effective treatment. A loss of 10% of patients to follow-up was assumed. For a projected constant rate of enrollment over 18 months, a total of 602 patients were required, based on the Lachin–Foulkes method [16]. A blinded re-estimation of sample size was made around the end of the planned accrual period, as enrollment was slower than expected. In total, 713 patients were enrolled over a 2-year period.

Time to event data (TTP, TTF and overall survival) were analysed by Cox proportional hazards regression models, with the primary analysis adjusted for receptor status and dominant site of disease. The letrozole arm was compared with the anastrozole arm. The hazard ratio, 90% confidence intervals, and significance level for both the adjusted and unadjusted analyses were determined. Median time-to-event (and 90% confidence interval) was estimated by the Kaplan–Meier product-limit method with time to event calculated from the date of randomisation. The intent-to-treat approach was taken, defined as all patients enrolled.

ORR (confirmed CR + PR) and overall clinical benefit (confirmed CR + PR + NC $\geqslant$24 weeks) were analysed using logistic regression models, analogous to time-to-event analyses. DOR and duration of clinical benefit were estimated by the Kaplan–Meier product-limit method in the subsets of patients with response or benefit. Exploratory analyses were conducted for TTP and ORR examining the effects of various baseline covariates of interest. In addition to the key covariates of receptor status and dominant site of disease, geographical region, age, number of anatomical sites of disease, liver involvement, and bisphosphonate use were examined (all analyses were prespecified).

Baseline grade of performance status was cross-tabulated against the worst grade during the study, and the numbers of patients with a worse grade in each treatment arm were compared by a Chi-squared test. The reported incidence of 'target symptoms' (a predefined list of symptoms associated with either agent) in each treatment arm was compared by Chi-squared tests (including Fisher's exact test where appropriate). For safety analyses, patients who did not take any study treatment were excluded.

### 2.4. Ethics

This trial was performed in accordance with the Declaration of Helsinki recommendations on informed consent. The trial protocol and amendments, as well as

Table 1
Patient demographics and baseline data

| Baseline variable | Letrozole ($n=356$) | Anastrozole ($n=357$) | Total ($n=713$) |
|---|---|---|---|
| Age (years) | | | |
| Median (range) | 64 (32–92) | 63 (27–88) | 63 (27–92) |
| Age classification, no. (%) | | | |
| ⩽55 years | 88 (25) | 94 (26) | 182 (26) |
| 56–69 years | 164 (46) | 154 (43) | 318 (45) |
| ⩾70 years | 104 (29) | 109 (31) | 213 (30) |
| Race, no. (%) | | | |
| Caucasian | 336 (94) | 339 (95) | 675 (95) |
| Other | 20 (6) | 18 (5) | 38 (5) |
| Region, no. (%) | | | |
| Eastern Europe | 112 (31) | 111 (31) | 223 (31) |
| Western Europe | 173 (49) | 172 (48) | 345 (48) |
| Rest of world | 71 (20) | 74 (21) | 145 (20) |
| Body mass index (kg/m$^2$) | | | |
| Median (range) | 26.5 (17.8–52.7) | 26.6 (16.6–44.4) | 26.6 (16.6–52.7) |
| Hormone receptor status, no. (%) | | | |
| ER+ and PgR+ | 102 (29) | 104 (29) | 206 (29) |
| ER+ or PgR+ | 71 (20) | 63 (18) | 134 (19) |
| Unknown | 183 (51) | 190 (53) | 373 (52) |
| Dominant site of disease, no. (%)[a] | | | |
| Soft tissue | 85 (24) | 84 (24) | 169 (24) |
| Bone | 85 (24) | 87 (24) | 172 (24) |
| Viscera | 185 (52) | 186 (52) | 371 (52) |

ER, oestrogen receptor; PgR, progesterone receptor.
[a] One patient on letrozole had no active metastatic lesion at enrollment.

patient informed consent forms, were approved by each institution's Ethics Review Board or Institutional Review Board.

## 3. Results

### 3.1. Disposition of patients and demographics

A total of 713 patients were enrolled, and treatment allocation was well balanced in that letrozole was assigned to 356 patients and anastrozole to 357 patients. Baseline characteristics of these patients were well balanced between treatment arms, in age, race, regional demographics, body mass, hormone receptor status, and extent of disease (Table 1). One patient assigned to the anastrozole arm was ineligible and no treatment was initiated; this patient was therefore excluded from the safety analysis. Approximately half of the total population had tumours positive for ER (ER+) and/or PgR (PgR+). For the remainder, both receptors were unknown, largely because in almost all of the patients enrolled in two countries, Russia (120) and the United Kingdom (110), receptor status was not determined. More than half (52%) of the patients had metastatic disease involving viscera.

### 3.2. Efficacy

There was no difference between the two treatment arms for the primary endpoint, TTP, with median TTP being 5.7 months for both treatments (Table 2). Letrozole was significantly better than anastrozole in ORR (19.1% versus 12.3%; adjusted odds ratio = 1.70, $P=0.013$). The overall clinical benefit rate was also greater for letrozole (27.0% versus 23.0%; odds ratio = 1.24), but the difference was not statistically significant. Median duration of treatment was similar for letrozole and anastrozole (5.9 months versus 5.6 months), as was median DOR, median TTF, and percentage of treatment failures (Table 2). Median overall survival (22.0 months for letrozole versus 20.3 months for anastrozole) was not significantly different between the two treatments (hazard ratio 0.95, $P=0.624$).

Letrozole was significantly superior to anastrozole in ORR when stratified by receptor status unknown versus positive ($P=0.014$) (Table 3). Similarly, when stratified by dominant site, soft tissue and viscera versus bone, letrozole had significantly higher response rates than anastrozole ($P=0.012$). Subgroup analysis of TTP yielded similar results for letrozole regardless of whether receptor status was positive (median 5.8 months) or

Table 2
Efficacy on an intent-to-treat basis

| Efficacy parameter | Letrozole ($n=356$) | Anastrozole ($n=357$) | Adjusted $P$ value |
|---|---|---|---|
| Median TTP, months (90% CI) | 5.7 (5.1–6.0) | 5.7 (4.6–6.1) | 0.92 |
| ORR, no. (%) | 68 (19.1)[a] | 44 (12.3)[b] | 0.013 |
| CR | 24 (6.7) | 13 (3.6) | |
| PR | 44 (12.4) | 31 (8.7) | |
| NC $\geqslant$ 6 months | 28 (7.9) | 38 (10.6) | |
| PD | 203 (57.0) | 222 (62.2) | |
| NE | 57 (16.0) | 53 (14.8) | |
| Median DOR, months | 22 | 25 | 0.645 |
| Clinical benefit (CR + PR + NC $\geqslant$ 6 months), no. (%) | 96 (27.0) | 82 (23.0) | 0.216 |
| Median TTF, months (90% CI) | 5.6 (4.4–5.8) | 5.6 (4.0–6.0) | 0.761 |
| Treatment failures, no. (%) | 315 (88.5) | 322 (90.2) | |
| Median OS, months (90% CI) | 22.0 (19.6–24.6) | 20.3 (18.0–23.1) | 0.624 |

TTP, time to progression; CI, confidence interval; ORR, objective response rate; CR, complete response; PR, partial response; NC, no change/stabilisation; PD, progressive disease; NE, not evaluable/not assessable; OS, overall survival; DOR, duration of response.
[a] 90% CI: 15.7–22.9%.
[b] 90% CI: 9.6–15.6%.

unknown (median 5.6 months), whereas for anastrozole median TTP was 6.5 months in patients with receptor-positive tumours, but only 4.0 months in those with receptor-unknown tumours.

### 3.3. Safety

There were no significant differences between treatment arms in the reported incidences of adverse events, including target events, serious events, or resulting discontinuations (adverse events leading to discontinuation were generally symptoms of progression) (Table 4). The most frequently reported adverse events were bone pain, dyspnoea and nausea. Potentially endocrine-related target adverse events were slightly lower in letrozole-treated patients (16%) than in anastrozole-treated patients (20%). The incidence of serious adverse events was very similar for both treatments. Deaths not attributed to cancer were reported for 7 (2%) patients on letrozole, and for 10 (3%) patients on anastrozole. In addition, death from unknown causes occurred in 1 patient on letrozole, and in 4 patients on anastrozole.

Table 3
Objective response rate by baseline covariates

| Baseline covariate | No. of responders/total no. of patients (%) | | $P$ value |
|---|---|---|---|
| | Letrozole | Anastrozole | |
| Receptor status | | | 0.014 |
| ER+ and/or PgR+ | 30/173 (17.3) | 28/167 (16.8) | |
| Unknown | 38/183 (20.8) | 16/190 (8.4) | |
| Dominant site[a] | | | 0.012 |
| Soft tissue | 31/85 (36.5) | 16/84 (19.0) | |
| Bone | 11/85 (12.9) | 10/87 (11.5) | |
| Viscera | 26/185 (14.1) | 18/186 (9.7) | |

ER, oestrogen receptor; PgR, progesterone receptor.
[a] Dominant site was not determinable in 1 patient allocated letrozole (no active metastatic lesion).

## 4. Discussion

In this study, there were no significant differences between letrozole and anastrozole in the primary endpoint of TTP. For the secondary endpoint of ORR, letrozole was significantly superior to anastrozole overall (19.1% versus 12.3%, $P=0.013$), as well as for two predefined covariates, hormone receptor status and soft-tissue- and viscera-dominant disease. For patients with ER/PgR receptor status, which constituted 52% of the total study population, letrozole was more active than anastrozole, achieving a higher response rate (20.8% versus 8.4%) and longer median TTP (5.6 months versus 4.0 months). Given the observed differences in TTP in this study, the power of the test was extremely low ($<10\%$) for detecting small differences between treatments. The ORR was also much higher in the letrozole arm for patients with soft tissue-dominant disease, and to a lesser extent, viscera-dominant disease. Otherwise, there were no significant differences between the two treatment arms in other efficacy measures, including TTF and overall survival. Both treatments were well tolerated, with no significant differences in adverse events or their consequences.

Comparison with previous trial results in this treatment setting suggests that the observed response rate differences are valid. In this trial, a retrospective, blinded, independent peer review committee evaluated most of the investigator-determined patient responses. The

Table 4
Safety

| | Statistic | No. of patients (%) | |
|---|---|---|---|
| | | Letrozole ($n=356$) | Anastrozole ($n=356$) |
| Adverse events in $\geqslant 10\%$ of patients | Total | 289 (81) | 274 (77) |
| | Bone pain | 53 (15) | 47 (13) |
| | Dyspnoea | 37 (10) | 40 (11) |
| | Nausea | 28 (8) | 39 (11) |
| Patients reporting target adverse events[a] | Total | 58 (16) | 71 (20) |
| Target adverse events | Nausea | 28 (8) | 39 (11) |
| | Vomiting | 23 (6) | 19 (5) |
| | Abdominal pain | 15 (4) | 20 (6) |
| | Vaginal bleeding | 3 (1) | 3 (1) |
| | Myocardial infarction | 3 (1) | 1 (<1) |
| | Dermatitis | 1 (<1) | 3 (1) |
| | CVA | 2 (1) | 1 (<1) |
| | DVT or PE | 2 (1) | 1 (<1) |
| | Eczema | 0 | 1 (<1) |
| Serious adverse events | Total | 68 (19) | 63 (18) |
| Discontinuations due to adverse events[b] | Total | 28 (8) | 28 (8) |

CVA, cerebrovascular accident; DVT, deep venous thromboembolism; PE, pulmonary embolism.
[a] Target adverse events are potentially endocrine-related adverse events.
[b] Including symptoms of disease progression.

concordance between investigators' and reviewers' assessments was 83%. Treatment comparison based on the peer-reviewed responses indicated that letrozole remained superior to anastrozole (i.e. the initial statistical significance persisted). This rate of concordance was similar to the prospective, independent, blinded peer reviews carried out on all patients (not only in responders) for the second-line studies AR/BC2 (double-blind study of letrozole versus megestrol acetate) (79–81% concordance) and AR/BC3 (open-label study of letrozole versus aminoglutethimide) (84% concordance) [5,6]. For a population in which a high proportion (52%) of patients had visceral-dominant advanced breast cancer, the overall response rate for letrozole (2.5 mg daily) in our study (19.1%) was consistent with previously reported response rates for the same dose of letrozole, comparable visceral involvement, and similar treatment settings (16–24%) (Table 5) [4–6]. In other second-line trials, response rates for the same dose of anastrozole (1 mg daily), 10, were also very similar to the 12.3% response rate in this trial [3,7].

Table 5
Overall response rates for letrozole and anastrozole in second-line endocrine therapy studies in advanced breast cancer

| Study [Ref.] | Objective response rate (%) | |
|---|---|---|
| | Letrozole (2.5 mg daily) | Anastrozole (1 mg daily) |
| Dombernowsky and colleagues [5] | 24.1 | – |
| Gershanovich and colleagues [6] | 19.5 | – |
| Buzdar and colleagues [4] | 16.1 | – |
| Jonat and colleagues [7] | – | 10.4 |
| Buzdar and colleagues [3] | – | 10.3 |
| This study | 19.1 | 12.3 |

Overall clinical benefit rates in this trial only slightly favoured letrozole over anastrozole (27.0% versus 23.0%), because of a higher rate of long-term stable disease in the anastrozole arm. Letrozole and anastrozole in previous trials also achieved similar clinical benefit rates, as a consequence of higher response rates for letrozole and higher stable disease rates for anastrozole [4–6,14,17].

The superior responsiveness of advanced breast cancer to letrozole compared with anastrozole may be related to more complete suppression of total body oestrogen production by letrozole. Indirect evidence had suggested that there may be a dose–response relationship between the degree of oestrogen suppression and clinical efficacy in breast cancer [18]. For example, in the trial comparing letrozole (2.5 mg) with aminoglutethimide (500 mg) in second-line therapy of advanced breast cancer, the greater efficacy of letrozole may be due to the greater aromatase inhibition by letrozole (>99% versus approximately 85%) [6,13].

Early studies indicated that modest suppression of plasma oestrogen levels during endocrine therapy resulted in low response rates in breast cancer patients [18].

In addition, stepwise improvements in oestrogen suppression after failure of a less suppressive agent, translated into better treatment outcome [20]. More recently, several large trials comparing specific aromatase inhibitors with earlier agents suggest a direct relationship between the degree of oestrogen suppression and clinical effects in postmenopausal women with advanced breast cancer. Letrozole, anastrozole and exemestane, all of which are much more potent suppressors of oestrogen than megestrol acetate and aminoglutethimide [17], have achieved greater clinical efficacy than those agents [4–6,8].

Total body aromatisation is an index of aromatase inhibition which can be accurately determined. Phase II studies in which quantitation of total body aromatisation during treatment of patients indicates that letrozole inhibits 99% of that activity, compared with 93–97% inhibition by anastrozole [17,19]. Furthermore, letrozole has also been shown to be 10–30 times more potent than anastrozole in inhibiting intracellular aromatase *in vitro* in a variety of cells, both of animal and human origins as well as a human breast cancer cell line (MCF-7Ca) [9].

A recent randomised, double-blind crossover study compared the influence of letrozole versus anastrozole on total body aromatisation and plasma oestrogen levels in postmenopausal women with metastatic breast cancer [13]. 6 patients initially received letrozole 2.5 mg daily, and 6 patients received anastrozole 1 mg daily, for 6 weeks; treatment crossover was then to the other agent for 6 weeks. Inhibition of aromatisation by letrozole was consistently $>99\%$ regardless of sequence, whereas anastrozole averaged 97% (range: 93 to $>99\%$), significantly less. Correspondingly, plasma levels of oestrogens were also significantly lower following letrozole treatment. Secondary anastrozole treatment failed to maintain the low aromatisation or oestrogen levels achieved by letrozole, while secondary letrozole consistently lowered levels resulting from prior anastrozole treatment [13].

The greater tumour responsiveness to letrozole overall may also relate to the potency of that agent in suppressing total body oestrogen levels, compared with anastrozole. In the data presented here, one remarkable finding has been that the response rate to letrozole was similar irrespective of whether the tumour was hormone receptor- positive or -unknown. However, for anastrozole, the response rate in patients whose tumour was hormone receptor-unknown was much lower than in patients whose tumour was hormone receptor-positive. This finding is difficult to reconcile with the speculation of a skewed distribution of hormone-receptor negative tumours in the anastrozole arm as all the other demographic parameters were well distributed in both arms. However, this observation with anastrozole is not new and has been reported previously in the two phase III studies comparing anastrozole with tamoxifen in the first-line setting [21]. In an attempt to explain this finding, one could speculate that in the study presented here, the hormone receptor-unknown group was characterised by a larger proportion of hormone receptor-poor tumours which were equally distributed over both arms. In hormone receptor-poor tumours, it is possible that a higher degree of oestrogen deprivation, as is the case with letrozole, could lead to a better response in these tumours. That letrozole elicits responses in hormone receptor-poor tumours has been reported previously in the phase III study comparing letrozole with tamoxifen in the neo-adjuvant setting [25]. In this study, responses to letrozole were seen in hormone receptor-poor tumours (assessed by the Allred score with readings of 3–5), whereas no responses at all were seen to tamoxifen in this group. Thus, the documented fact that letrozole is a more effective inducer of oestrogen deprivation than anastrozole, may explain why letrozole is effective in patients whose tumours are either hormone receptor-positive or -unknown, whereas anastrozole antitumour efficacy in hormone receptor-positive patients is not reflected to the same degree in the hormone receptor-unknown group.

Our trial represents the first direct comparison of letrozole and anastrozole in a clinical breast cancer treatment setting. Both agents have previously shown superiority over tamoxifen in first-line therapy of advanced breast cancer in separate trials. However, anastrozole superiority is based on retrospective analysis of combined results [14]. In a European trial in 668 patients, the ORR for anastrozole was 32.9%, and 32.6% for tamoxifen, with clinical benefit (ORR plus long-term stable disease) also similar (56.2% for anastrozole and 55.5% for tamoxifen) [21]. In a North American trial in 353 patients, ORR was similar for anastrozole and tamoxifen (21 and 17%, respectively), but clinical benefit was significantly higher for anastrozole than for tamoxifen (59% versus 46%) [22]. However, in a combined analysis of those two trials, anastrozole was not significantly better than tamoxifen in ORR (29.0% versus 27.1%) or clinical benefit (57.1% versus 52.0%). Anastrozole superiority over tamoxifen, based on that retrospective pooling, was limited to patients with ER+ tumours [21]. In a first-line trial in 907 patients, ORR was significantly higher for letrozole than for tamoxifen (32% versus 21%; $P=0.0002$) as was the clinical benefit (50% versus 38%; $P=0.0004$) [23].

In the neoadjuvant treatment setting, a recent randomised trial found that 4 months of preoperative letrozole provided a significantly higher clinical response rate than comparable treatment with tamoxifen. That improvement in tumour downstaging enabled significantly more of the letrozole-treated patients to successfully undergo breast-conserving surgery [24,25]. In a small study, letrozole and anastrozole were both

effective in tumour downstaging [26]. There has been no direct comparison of letrozole and anastrozole in this treatment setting.

In summary, this study was the first to directly compare the clinical activity of letrozole and anastrozole, as second-line therapy in postmenopausal women with advanced breast cancer after failure on tamoxifen. There was a significantly higher ORR for letrozole than for anastrozole, consistent with preclinical and *in vivo* data demonstrating a higher activity for letrozole.

## Appendix

The following investigators and their institutions participated in the study: Dr S. Maca, City Hospital, Vienna, Austria; Prof. E. Kubista, University Hospital for Women's Diseases, Vienna, Austria; Prof. G. Steger, University Hospital for Internal Medicine, Vienna, Austria; Dr L. Schiller, Voeklabruck County Hospital, Voeklabruck, Austria; Dr A. Murad, Federal University Hospital, Belo Horizonte, Brazil; Dr R. Hegg, Federal University Hospital of Sao Paulo, Sao Paulo, Brazil; Dr G. Delgado, University Hospital, Sorocaba, Brazil; Dr C. Tosello de Oliveira, Brazilian Cancer Institute, Sao Paulo, Brazil; Dr S. Juacaba, Cancer Hospital, Ceara, Brazil; Dr J. Vinholes, Misericórdia Clinic of Porte Alegre, Porto Alegre, Brazil; Dr A. del Giglio, Bairro Pricipale de Gales,Santo Andre, Brazil; Dr B. Melosky, B.C. Cancer Agency, Vancouver, Canada; Dr S.C. Tang, Dr H. Bliss Murphy Cancer Clinic, St. John, Canada; Dr M. Trudeau, Women's College Hospital, Toronto, Canada; Dr S. 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