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InforMatrix Aromatase Inhibitors in Breastcancer

Janknegt R*

Hospital pharmacist, clinical pharmacologist Sittard, Netherlands

Abstract

The InforMatrix method was applied to aromatase inhibitors. The following selection criteria were used: clinical efficacy, safety, tolerability, ease of use (from a patient's perspective), applicability (from a caregiver's perspective) and cost. All three available aromatase inhibitors were included: anastrozole, letrozole and exemestane. The InforMatrix method provides the user with all relevant clinical information concerning the medicines. By assigning a weight to both the selection criteria and judging the performance of the medicines on each criterion a personal selection of the most suitable medicines is made, which serves as the starting point for a concrete discussion in the formulary committee.

Introduction

InforMatrix is drug selection method in which pharmacotherapeutic strategies are supported in a rational manner by the use of a transparent selection methodology. This is achieved by the application of an independent report from interactive workshops in the field, in which participators are facilitated in the determination of their own preference [1].

The determination of the position of individual aromatase inhibitors in the treatment of breast cancer is being kept in constant motion due to the arrival of new compounds or new studies with available drugs. The purpose of this InforMatrix programme is to make a rational choice of first choice compounds possible. It is important that the selection process be described and made transparent. The InforMatrix methodology is an aid, with which selection criteria are described and tested against the available literature, and the clinical value of different therapeutic alternatives can be judged.

A short description of the InforMatrix methodology and the subject matter, and a description of the different selection criteria, are provided below.

InforMatrix Methodology

InforMatrix is a so-called decision matrix technique with which a group of technical experts who, guided by criteria, establish an order within different treatment options that strive for similar aims. These criteria are weighted against each other for this order determination because, after all, they do not always have the same weight. The different options per criterion are subsequently compared to each other. Data is required for this; data from the literature as well as from personal practical experience. An independent editorial staff tests the clinical value of the literature and assesses the literature per criterion.

The InforMatrix technique has six fixed criteria. They ar

1. Efficacy (the realisation of positive results and treatment aim
2. Safety (the avoidance of negative results, such as dangerous undesirable effects
3. Tolerance (the disturbance of the care process due to less dangerous, chiefly temporary, but bothersome undesirable effects
4. Ease of use (convenient for the patient; for example, dosing frequencies)
5. Applicability (how large is the treatment freedom (interactions and such) and the convenience for the care provider)
6. Costs (price per month)

These criteria have been specifically described per choice-subject ('operationalised').

The InforMatrix technique proceeds through the following steps

- Operationalising the six criteria
- Literature review
- Relative weighing of the six criteria
- Valuing the different treatment options based on the literature, as well as personal knowledge and experience
- Summary of the weights and values in the selection matrix: calculation of order

A group of technical experts are asked to test the relevancy of the operationalisation of the above-mentioned six selection criteria in the context of the use of aromatase inhibitors in the treatment of breast cancer. Digitalis conducts a literature review in association with these selection issues. This leads to a report with which a group of technical experts assess a number of different compounds on the basis of these selection criteria. The report is assessed for its utility for making possible a rational weighing of the determination of preferred compounds.

The following subcriteria are described for the main criteria

Effica

Clinical efficacy in comparative studies

Safety

***Corresponding author:** Dr. Robert Janknegt, clinical pharmacist/clinical pharmacologist, Maasland Ziekenhuis, P.O. Box 5500, 6130 MB Sittard, Netherlands, Tel: (+31) 464597709; Fax: (+31) 464597971; E-mail: r.janknegt@orbisconcern.nl

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Rare, hazardous undesirable effects

Documentation

Tolerance

Frequently occurring, but harmless undesirable effects

Ease of use

Dosage frequency

User friendly formulations

Intake in relation to meals

Applicability

Medicinal interactions

Registered indications

Contra-indications

Use by children and the elderly

Use with kidney and liver impairment

Use during pregnancy and lactation

Special precautions and warnings

Costs

Daily cost

Breast Cancer

Breast cancer is the most frequent form of cancer in women. It is estimated that about 1 million women develop breast cancer every year, half of which in the United States and Europe [2]. In the Netherlands 11,000 new cases of breast cancer occur per year. Almost 1 in 9 women in the Netherlands eventually develops breast cancer. About 2/3 of the cases of breast cancer is estrogen-dependent [2,3].

Tamoxifen was regarded as the golden standard for adjuvant treatment of hormone-dependent breast cancer for a long time. Relapse-free survival after 5 years of treatment with tamoxifen is longer than for placebo. The risk of a relapse or contralateral breast cancer decreases by about 50% [4,5]. Application of tamoxifen for longer than 5 yearsis not useful [6,7]. Tamoxifen has a favourable effect on mortality until at least 15 years after the beginning of treatment [8].

Disadvantages of tamoxifen are the higher incidence of endometrial carcinoma and thrombosis. Tamoxifen is a competitive antagonist of estrogen. The interactions of tamoxifen with the estrogen receptor are complex and tamoxifen also has a partially agonist activity [9].

Aromatase inhibitors have an important place in the treatment of breast cancer. By inhibition of the enzyme aromatase, the metabolism of androgens, especially androstenedion, in oestrogens is decreased [3,10]. Aromatase is found in high concentrations in tumor tissue [11]. The first generation aromatase inhibitors (aminoglutethimide) was not very effective and selective, resulting in a high incidence of side-effects, such as sedation and rash [3,9].

Application of aromatase inhibitors is not useful in premenopausal women, because the drugs have no effect on estrogen production in the ovaria [3,12]. Three selective aromatase inhibitors are available. Anastrozole and letrozole have a non-steroidal structure and show a competitive inhibition of aromatase. Exemestane has a steroid-structure and shows an irreversible inhibition of aromatase [8]. It has not been shown that differences in the extent of aromatase inhibition between the drugs affect clinical efficac [11]. Letrozole showed a more powerful inhibition of aromatase than anastrozole in a small scale double blind study [13].

Applications of aromatase inhibitors

- Application as primary adjuvant treatment
- Application as adjuvant treatment after 2-3 years treatment with tamoxifen
- Application as adjuvant treatment after 5 years treatment with tamoxifen
- First line treatment in postmenopausal women with hormone-dependent breast cancer in an advanced stage
- Second line treatment in postmenopausal women with hormone-dependent breast cancer in an advanced stage

The following drugs are included in the analysi

- Anastrozole
- Exemestane
- Letrozole

Efficac

Principally, the achievement of improved overall survival should be the aim of all cancer treatments. This is however difficul to prove, because this makes it necessary to design very large scale and long term studies. Both relapse-free survival as disease-free survival are used alternative endpoints in the judgement of clinical efficacy Probably relapse-free survival is a more relevant endpoint than disease-free survival, because death without relation to breast cancer or its complications is included in the latter endpoint. Disease free survival is a relevant criterion for safety [4]. Another relevant endpoint is distant relapses. Local relapses may adequately be treated and have a good prognosis, whereas distant metastases have a much poorer prognosis.

Anastrozole has also demonstrated efficac in the prevention of breast cancer in women at high risk of developing breast cancer [14]. This application is not an approved indication and is not discussed in detail.

Application as primary adjuvant treatment

Anastrozole: In the double blind international Arimidex, Tamoxifen Alone or in Combination (ATAC) study, postmenopausal patients were included with operable invasive breastcarcinoma. Patients were excluded in case of documented metastases. The study medication (anastrozole 1 mg (n=3125), tamoxifen 20 mg (n=3116) or the combination of both drugs (n=3125)) was started within 8 weeks after surgery. On the moment of inclusion of the study it was not yet known whether the patient had estrogen receptor negative tumor, in all groups 83-84% had an estrogen receptor positive receptor. The groups were well matched regarding age (64 years), positive glands (34-35%) and tumor size. The primary endpoint was disease free survival (defined as the time to the occurrence of a local or distant relapse, new primary breast cancer or death from any cause). Secondary endpoints were time to relapse and incidence of cases of contralateral primary breast tumors. Distant relapse and total mortality were also secondary endpoints [15].

The results of the study are described in a number of publications, with a median follow up of 33, 47 and 68 months respectively [15-17]. After a follow-up of 47 months the primary endpoint was significantly less often reached in anastrozole (relative risk reduction 14%, 95% confidence interval 1-24%) than in tamoxifen. In the (most relevant) subgroup of patients with hormone-receptor positive tumors, the relative risk reduction was 18% (95% confidence interval 4-30%). There were no significant differences between tamoxifen and the combination group. The absolute risk reduction in the anastrozole group was 1.5% in the whole group and 1.7% in the group with hormone receptor susceptible tumors [16].

The disease free survival was significantly better in the anastrozole group compared to tamoxifen. HR: 0.86 (95% confidence interval 0.87-0.99). In the group with hormone positive tumors the difference was larger: 18% lower risk of a relapse at the end of the treatment and an absolute difference of 2.9% after 4 years [16]. Especially the subgroup of patients with positive estrogen receptors and negative progesterone receptors showed a relatively low HR concerning betreft time to relapse: 0.43 (95% confidence interval 0.31-0.61) [18].

A significant reduction was observed of the number of cases of contralateral breast cancer, especially in the group with hormone susceptible tumors: 44%, but the absolute numbers were quite small: 20, respectively 35 resulting in a very wide confidence interval of the reduction: 2-68% [16].

The combination of anastrozole and tamoxifen did not show any advantages. The efficac was lower than that of anastrozole monotherapy and the incidence of side effects was higher [15-17].

In the meantime, the follow-up results after 100 months have been reported, 40 months after the end of treatment with anastrozole or tamoxifen. The difference between both drugs regarding the various endpoints was sustained during this period. The hazard ratios of anastrozole compared to tamoxifen regarding disease free survival was 10% more favourable in the whole group and 15% in the subgroup with hormone-receptor positive tumors (p=0.025. respectively p=0.003). The hazard ratio of anastrozole compared to tamoxifen regarding time to relapse was 0.81 in the whole group, respectively 0.76 in the subgroup with hormone-receptor positive tumors (p=0.0004 and p=0.0001). The risk of contralateral breast cancer was lowered by anastrozole by 32% compared to tamoxifen in the whole group and by 40% in the hormone-receptor positive group (p=0.02, respectively p=0.004). There were no significant differences regarding total mortality, mortality with relapse of mortality without relapse [19].

Letrozole: In the double blind Breast International Group (BIG 1-98) study, four different treatments of adjuvant treatment of breast cancer were compared during a total duration of 5 years: letrozole 2.5 mg during 5 years, letrozole during 2 years, followed by tamoxifen 20 mg during 3 years, tamoxifen during 5 years and tamoxifen during 2 years followed by letrozole during 3 years. A total of 8010 patients were randomised. An interim analysis was published in 2005, after a mean treatment duration of 25.8 months.

The primary endpoint was disease free survival (defined as the time to the occurrence of a local, regional of distant relapse, cases of invasive cancer in the contralateral breast, other forms of cancer not being breast cancer, or death without objectified cancer). Secondary endpoints were total survival, systemic disease free survival, the occurrence of another form of cancer or total mortality [20]. In the analysis, the "pooled" results were presented of the subgroups whose treatment was started with letrozole or tamoxifen.

After a mean follow-up of 25.8 months the primary endpoint was significantly less often reached in letrozole (relative risk reduction 19% compared to tamoxifen, 95% confidence interval 7-30%). In the subgroup of patients with positive glands the relative risk reduction was 29% for letrozole compared to tamoxfen (95% confidence interval 15-41%). The absolute risk reduction in the letrozole group was 1.9% in the whole group (10.7% vs. 8.8%). The difference in relapses was visible after 1 year of treatment and in the group treated during 5 years a relapse was observed in 10.3% in the letrozole treated group versus 13.6% in the tamoxifen treated patients. The difference in the primary endpoint was especially determined by a lower incidence of distant relapses: 5.8% vs. 4.4%, a relative risk reduction of 27% compared to tamoxifen [20].

In a subgroup analysis the advantage of letrozole versus tamoxifen was maintained independent of the ERBB2 status of the patient. The disease free survival was less favourable in the ERBB2 positive group [21].

After a follow-up of 51 months, an 18% risk reduction on the primary endpoint was observed in the group who were treated with letrozole during the whole study period versus the tamoxifen group [22].

The positive effect of letrozole was observed in all age groups, although the number of women of >75 years was too small to be able to draw conclusions [23].

After a follow-up of 71 months there was no significant difference in disease free survival between the 3 groups [24].

Application as adjuvant treatment after 2-3 years treatment with tamoxifen

Large scale studies were performed with respectively anastrozole and exemestane [25,26] and also an smaller scale open study with anastrozole [27].

Anastrozole: In a combined analysis of two open studies: Austrian Breast and Colorectal Cancer Study Group, (ABCSG trial 8)/ Arimidex-Nolvadex (ARNO 95) postmenopausal patients with operable invasive breastcarcinoma were included. Patients were excluded in case or proven metastases or during chemotherapy. The study medication (anastrozole 1 mg (n=1606) or tamoxifen 20-30 mg (n=1618) was started after 2 years of treatment with tamoxifen 20-30 mg in an open setting. In both groups 78-79% of patients had an estrogen and progesterone receptor positive tumor and 18% an estrogen receptor positive and a progesterone receptor negative tumor. Both groups were well matched concerning age (62 years), positive glands (26%) and tumor size. The primary endpoint was "event" free survival (defined as the time to the occurrence of a relapse or the occurrence of contralateral tumors). Secondary endpoints were relapse-free survival and tolerability [27].

After a mean follow-up of 28 months the primary endpoint was significantly less often reached in anastrozole: 9.7%, than in tamoxifen: 13.2% (relative risk reduction 40%, 95% confidence interval 19-56%). In the (large) subgroup of patients with estrogen- and progesterone receptor positive tumors the relative risk reduction was 34%. In the group with estrogen positive and progesterone-negative tumors a stronger reduction of the primary endpoint was observed for anastrozole: 58% (95% confidence interval 8-81%).

Metastases were significant more often observed in the tamoxifen group (5%) than in the anastrozole group (3%), p=0.007. There was

no significant difference in the survival between both groups: 97% vs. 96% [25].

In a more recent analysis of only the data of the ARNO studies (n=979), a (borderline) significant reduction was observed of the risk of a relapse (hazard ratio 0.66. p=0.049) and a better total survival (hazard ratio 0.53. p=0.045) was observed for anastrozole compared to tamoxifen [28].

A small scale open-label Italian study (Italian Tamoxifen Anastrozole, ITA trial) compared anastrozole 1 mg and tamoxifen. The study medication (anastrozole 1 mg (n=223) or tamoxifen 20 mg (n=225) was started after pretreatment with 20 mg tamoxifen during 28 months. In both groups almost all patients had an estrogen receptor positive tumor. In the anastrozole group the hormone status was unknown in 8% of the patients vs. 14% of the tamoxifen treated patients. No data were reported regarding the progesterone receptor status of the tumors. The groups were similar regarding age, surgical procedure, radiotherapy and adjuvant chemotherapy, number of positive glands and tumorsize. Primary endpoints were a relapse tumor and "event" free survival. "Events" was defined as locoregional relapse, distant metastases, cases of primary tumors including contralateral breast cancer and non- cancer related death [27].

The median follow-up was 36 months (with a very wide range of 1-70 months). In both groups 18, respectively 19 patients did not complete the study. In the anastrozole group a relapse tumor (5.4%) was less often observed than in the tamoxifen group (14,2%). No significance level was presented. There were 45 "events" in the tamoxifen group vs. 17 in the anastrozole group (p=0,0002). There was a significant difference in event free and relapse-free survival (Hazard ratio anastrozole/tamoxifen=0.35 for both parameters) favouring anastrozole. The absolute difference in relapse-free survival after 3 years of treatment was 5.8% [27].

Exemestane: The international (37 countries) double blind Intergroup Exemestane Study (IES) study also included patients with postmenopausaal operable invasive breastcarcinoma. The study medication (exemestane 25 mg (n=2380) or tamoxifen 20-30 mg (n=2362)) was started after pretreatment with tamoxifen during 2.4 years. In both groups 81% of patients had an estrogen receptor positive tumor and 56% a progesterone receptor positive tumor. In 17% of the patients the hormone status of the tumor was unknown. The groups were well matched regarding age, positive glands, tumorsize and pretreatment. The primary endpoint was disease free survival (defined as the time to the occurrence of a relapse tumor, diagnosis of a second primary breast tumor or death from any cause). Secondary endpoints were survival, the incidence of contralateral breast tumors and long term tolerability [26].

After a first follow-up of 31 months 4% of the patients were excluded because of the earlier occurrence of breast cancer, other tumors, breast saving surgery without radiotherapy, unclear menopausal status or estrogen receptor negative tumors. Fourteen percent of the patients stopped the treatment prematurely, mainly because of side effects (5%).

Metastases were significant more often observed in the tamoxifen group (5%) than in the exemestane group (3%), p=0.007. There was no significant difference in survival between both groups: 97% vs. 96%. The primary endpoint was reached in 183 patients in the exemestane group versus 266 in the tamoxifen group. The corrected hazard ratio was 0.68 with a 95% confidence interval of 0.56 to 0.82, p<0.001). The absolute risk reduction of exemestane compared to tamoxifen was 4.7% after 3 years. Disease free survival was 91.5% in the exemestane group vs. 86.8% in the tamoxifen group. Breast cancer free survival was significantly longer in the exemestane group: hazard ratio 0.63. as well as the time to the development of a contralateral breast cancer, hazard ratio 0.44. Total mortality in both groups was not significant different: 93 in the exemestane group vs. 106 in the tamoxifen group [26]. After a follow-up of 56 months an absolute advantage of 3.3% was observed regarding the primary endpoint. The mortality was nor significantly different in both groups. When patients with an estrogen-receptor negative tumor were excluded, the difference in mortality (17%) was marginally significant, p=0.05 [29].

The randomised, non-blinded, TEAM study compared tamoxifen (20 mg) during 2-3 years, followed by exemestane 25 mg for a total treatment duration of 5 years (n=4868) with exemestane treatment during 5 years (n=4898). The primary endpoint was disease free survival after 2 years and 9 months and after 5 years. Secondary endpoints were overall survival, relapse-free survival and safety. No significant differences were observed between both treatment strategies on any of the efficacy endpoints [30]

Application as adjuvant treatment after 5 years of treatment with tamoxifen

Anastrozole: In a follow-up of the ABCSG trial [31], patients with hormone-positive postmenopausal breast cancer were treated with tamoxifen during 5 years, partly combined with aminogluthetimide in the first two years, after which patients who had completed treatment were randomised in an open setting for 3 years treatment with anastrozole or no further treatment: ABCSG trial 6a [32]. 560 patients were randomised to anastrozole and 575 controls. More patients in the anastrozole group gave no consent for the study (170) than in the tamoxifen group (105). 389 patients were evaluable in the anastrol group vs. 469 in the control group. The demographic data of both groups, including pretreatment (tamoxifen or tamoxifen/aminogluthetimide) were comparable in both groups. The incidence of relapses after 3 years of treatment was lower in the anastrozole group (7.8%) compared to the control group (12.2%) (p=0.031), especially because of a lower incidence of distant metastases (4,1% vs. 7.5%). There were no differences in the incidence of locoregional relapses of contralateral breast cancer [32].

Letrozole: A double blind study included patients with postmenopausal operable invasive breastcarcinoma (MA17 study). The study medication (letrozole 2.5 mg (n=2575) of placebo (n=2582) was started after pretreatment with tamoxifen during 5 years (range 4.5 to 6 years). The primary endpoint was disease free survival (defined as the time to the occurrence of a relapse in the breast, chest, glands or metastases) or the occurrence of a contralateral tumor. Secondary endpoints were survival, quality of life and long term safety. The planned duration of treatment with letrozole or placebo was 5 years. Almost all (98%) patients had hormone positive tumors. After a median follow-up of 2.4 years, an interim analysis was performed, which showed a significant difference between the letrozole group and the placebo group regarding the primary endpoint. According to the protocol patients treated with placebo were given the option to shift to letrozole. In both groups 98% of patients had an estrogen receptor positive tumor. The hormonestatus of the tumor was unknown in of 2% of the patients. The groups were well matched regarding age, positive glands, tumorsize and pretreatment were the both groups [33].

The "hazard ratio" for a local relapse or metastasis in the letrozole group compared to the placebo group was 0.57 (95% confidence

interval 0.43-0.75. p<0.0001). The hazard ratio of death, relapse or contralateral breast cancer was 0.61 (95% confidence interval 0.47-0.79. p<0.0001. There was no significant difference in total mortality: hazard ratio 0.76 for letrozole compared to placebo (95% confidence interval 0.48-1.21) [33].

In an analysis of the final data the number of "events" was increased to a limited extent. Disease free survival was 94% in the letrozole group vs. 90% in the placebo group. The absolute risk reduction was 4.6% after 2.5 years of treatment. Letrozole showed a 42% reduction of the incidence of relapses or contralateral tumors compared to placebo. The incidence of contralateral tumors (3.0 vs. 4,8%) was non significantly different from the placebo group. There were no statistically significant differences in survival between both groups. A positive effect on mortality was observed in patients with positive glands and in patients who had used tamoxifen for longer than 5 years [34].

In a posthoc analysis a significant reduction of disease free survival was only observed in the women under 60 years of age [35].

Patients who were treated with placebo were offered the possibilty to change to open label letrozole. The median time from the cessation of tamoxifen was 2.8 years. The results in patients who were switched could not be compared to the group that did not change to letrozole, because more patients with a poor prognosis chose to be treated with letrozole. After a median follow-up of 5.3 years, disease free survival was significantly longer in the group that switched (HR 0.37. 95% confidence interval 0.23-0.61). Distant metastases were also more frequent in the placebo group: HR 0.39 and 95% confidence interval 0.20-0.74 [36].

Exemestane: An ongoing study with exemestane vs. placebo after 5 years of treatment with tamoxifen was stopped as soon the results of the MA17 study became available. Both groups were offered the possibility to continue with exemestane in an open setting: 560 patients who started with exemestane continued exemestane, whereas 344 patients who started on placebo were switched to exemestane. Disease free survival was not significantly different in both groups. A significant improvement of the 4-years relapse free survival was observed [37].

Discussion: The results of these studies are difficul to interpret. On the basis of the presently available information, no preference can be expressed for the application of aromatase inhibitors as primary treatment, after 2-3 years of tamoxifen treatment or after 5 years of tamoxifen treatment. The study populations of the three applications of aromatase inhibitors are different [7].

Aromatase inhibitors (anastrozole, letrozole) are more effective than tamoxifen as initial treatment or after 2-3 years of treatment with tamoxifen (anastrozole or exemestane). It is not clear whether long term results are also more favourable than initial treatment with tamoxifen (12). A number of studies in which strategies are directly compared are ongoing [4,6,12,38].

There are indications that aromatase inhibitors have a better clinical efficac than tamoxifen especially in postmenopausal women

Ref	15-17 ATAC	20 BIG 1-98	25 ABSCG/ARNO	27 ITA	26 IES	32 ABCSG6a	33 MA 17
Age	64	61	62	63	64	68	62
Glands+ (1-3)	24%		22%	64%	30%		
Glands+ (>4)	10%		4%		14%		
Glands neg	61%	57%	74%		51%		50%
Tumor <2 cm	64%	62%		47%		63%	
Tumor >5 cm	2%					2%	
ER +	84%	98%	96%	88%	81%	95%	98%
ER -	8%	2%	4%		1%	2%	
ER unknown	8%	0%		11%	17%	3%	2%
PR +		65%	80%		56%	80%	
Previous Mastectomy	48%	43%	24%	53%	52%	43%	50%
Breast saving surgery		57%	76%		47%	57%	
RTx	63%	72%		52%			60%
Chemotherapy	21%		0%	67%	32%	100% tamox	54%

Table 1: Patient characteristics of the most relevant studies regarding adjuvant treatment.

Ref	15-17 ATAC	20 BIG 1-98	25 ABSCG/ARNO	27 ITA	26 IES	32 ABCSG6a	33 MA 17
Number of patients	Ana 1 mg N= 3125 Tam 20 mg N=3116 Combi N=3125	Let 2.5 mg N=4003 Tam 20 mg N=4007	Ana 1 mg n=1618Tam 20-30 mg N=1606	Ana 1 mg N=223 Tam 20 mg N=225	Exe 25 mg N=2362 Tam 20-30 mg N=2380	Ana 1 mg N=387 Controls N=469	Let 2.5 mg N=2575 Pla N=2582
Follow up (months)	68 (100)	26 (51)	28	26	31 (56)	62	28
HR CT, LM, LR	0.79 ITT population 0.74 HR+ patients	---	0.60 p=0.0009	0.35 p=0.001	0.63 p=<0.001		0.57 p=0.00008
HR MA	0.86 p=0.04	0.73 p=0.001	0.54 p=0.0016 (first event)	0.49 NS	0.66 p=0.0004	0.53 P=0.034	
HR DFS	0.87 p=0.01 ITT 0.83 HR+ patients	0.81 p=0.003	---	0.35 p=0.0002	0.68 p=<0.001	0.62 P=0.031	0.61 p<0.001
HR OS	0.97 NS	0.86 NS	0.76 NS	---	0.88 NS		0.76 NS

CT contralateral tumor
DFS disease free survival (disease free survival)
LM local metastases
LR local relapse
MA Distant metastases
OS total survival (overall survival)

Table 2: Results of the most relevant studies regarding adjuvant treatment.

with a estrogen receptor positive and a progesterone receptor negative tumor, but there is no consensus yet [7,12].

Non-comparative studies, after failure of treatment with tamoxifen, are not included in the present analysis [39].

First line treatment in postmenopausal women with hormone-dependent breast cancer in an advanced stage

The most important methodological aspects and results of comparative studies are summarised in the Tables 1,2 below.

Anastrozole: Two studies (TARGET and North American Trial) [40,41], meant for combined evaluation, compared anastrozole with tamoxifen as first line treatment in postmenopausal women with breast cancer at an advanced stage. All patients had to have an estrogen- or progesterone-receptor susceptible tumor, or a tumor of unknown receptor susceptibility [40,43]. Use of tamoxifen in the 12 months prior to the studie was not allowed. The primary endpoint was time to disease progression, objective response and tolerability. Secondary endpoints were time to therapy failure, duration of the response, duration of clinical advantage and survival. All patients were followed to objective progression or death.

In the TARGET studies a significant proportion (55%) of patients had an unknown hormone sensitivity of the tumor [40]. An analysis of the subgroup with a hormone sensitive+ tumor is therefore relevant. Th combined analysis only reported the results of the influence of hormone sensitivity on time to progression. The total group did not show a significant difference between both treatments, whereas this was the case in the group with hormone dependent tumors Table 3,4.

Ref	40	41	45	46	48, 49	62	63
Age	67	67	67	64	65	60	64
Weight	68	70	69			55	
Advanced Breast cancer status at baseline (%)	50%	32%		82% (ECOG 0)	68%	5% (relapse 95%)	70% (ECOG 1 OF 2)
Pretreatment Hormonal	7%	12%		94%	18% (adjuvant)	82%	14%
Pretreatment oncolytics	19%	19%					20%
Hormonal + oncolytics	3%	8%		68% (“systemic therapy”)			
no pretreatment	69%	60%		4%	66%	66%	
Receptors:							
ER+/PR+	25%	65%	39%	>80%	67%	38%	
ER+/PR-	8%	19%	12%			24%	
ER+/PR?	10%	2%	7%				
ER?/PR?	55%	11%	40%		33%	27%	
Metastases							
Soft tissue	68%	50%		25%	38%		44%
Bone	46%	60%		27%	29%		25%
Internal organs	35%	51%		49%	46%		30%

Table 3: Patient characteristics of the most relevant double blind studies in advanced breast cancer as first line treatment.

Ref	40	41	45	46	48, 49	62	63
Drugs	Ana 1 mg Tam 20 mg	Ana 1 mg Tam 20 mg	Ana 1 mg Tam 20 mg	Ana 1 mg Exe 25 mg	Let 2.5 mg Tam 20 mg	Let 1 mg Fad 1 mg	Let 2.5 mg ATA/ Tor
Number of patients	A 340 T 328	A 171 T 182	A 511 T 510	A 149 E 149	L 458 T 458	L 77 T 77	A/T 434 L 431
Follow-up mean	19 months	18 months	19 months	5 years	32 months	13 months	to 3 years
Clinical advantage whole group	A 55% T 56%	A 59% T 46% P=0.0098	A 57% T 52%	A 39% E 44% (CR/PR) NS	L 49% T 38% (p=0.001)	L 50% T 35% (p=0.013)	A/T 52% L 54%
Median time to progression whole group (months)	A 8.2 T 8.3	A 11 T 5.6 P=0.005	A 8.5 T 7.0	A 22,2 E 13,8 NS	L 41 weeks T 26 weeks P=0.0001	L 211 days T 113 days	A/T 11.2 L 11.2
Median time to progression ER+ group (months)	A 8.9 T 7.8		A 10.7 T 6.4 P=0.022				
Therapy failure whole group	A 78% T 81%	A 79% T 84%	A 79% T 82%		L 75% T 85%		
Median time to therapy failure whole group (months)		A 7.6 T 5.4			L 9.3 T 5.7 P=0.0001		A/T 9.2 L 10.4
Total mortality whole group	A: 56% T: 55% (43 months)	A: 56% T: 58% (43 months)	A: 56% T: 56% (43 months)		L: 34 months T: 30 months		

P only indicated in case of significance

Table 4: Results of the most relevant double blind studies in advanced breast cancer as first line treatment.

In general the results for anastrozole in the North American study were better than those in the TARGET study.

An interesting finding was that patients who had failed on anastrozole or tamoxifen in first instance responded to the other drug. The median time to progression on tamoxifen (after an original treatment with anastrozole) was 6.7 months and the median time to progression on anastrozole (after an original treatment with tamoxifen) was 5.7 months [44].

A Spanish monocentric open randomised comparative study between anastrozole 1 mg and tamoxifen 40 mg found differences between both drugs (45). A total of 121 patients were given anastrozole and 117 tamoxifen. All patients had a estrogen- susceptible tumor. Endpoints were clinical advantage, time to progression, total response and side effects. The median follow-up was 13 months. Clinical advantage (objective response + stable disease) was reached in 83% in the anastrozole group vs. 56% in the tamoxifen group, p<0.001). The median time to progression was significantly longer in the anastrozole group (18 months) than in the tamoxifen group (7 months), p<0.01 [45].

The median time to death was comparable in both groups: 17 months for anastrozole and 16 months for tamoxifen [44].

A Japanese study compared anastrozole and exemestane as fi st line treatment in patients with hormone-positive advanced breast cancer. The median overall survival was 60 months in the anastrozole group and was not reached in the exemestane group [46].

Exemestane: No phase III of IV studies have been performed with exemestane in this indication. In a randomised phase II study relatively favourable results were observed with exemestane 25 mg compared to tamoxifen 20 mg. The objective response was 41% in the exemestane group vs. 17% in the tamoxifen group. The clinical advantage was 57% in the exemestane group vs. 42% in the tamoxifen group [47].

Letrozole: A multinational (29 countries) double blind study compared letrozole 2.5 mg with tamoxifen 20 mg as first line treatment in postmenopausal women with breast cancer in an advanced stage until disease progression or another reason to stop treatment. Patients could then be crossed over to the other treatment. All patients had an estrogen- or progesterone-receptor susceptible tumor or an unknown sensitivity. Use of tamoxifen or other antioestrogenen in the 12 months preceeding the studie was not allowed. The primary endpoint was time to disease progression. Secondary endpoints were objective response, duration of the response, clinical advantage, duration of clinical advantage, time to therapy failure, time to response and total mortality [48,49]. After a median follow-up of 32 months letrozole had a significantly more favourable effect in objective response (32% vs. 21%, p=0.0002) and clinical advantage (50% vs. 38%, p=0.0004) [49].

Letrozole was significantly better than tamoxifen regarding time to progression and time to therapy failure. The presence of visceral metastases significantly shortened the time to tumor progression significantly (HR 1.52) as did bone metastases (HR 1.26) [48].

Second line treatment in postmenopausal women with hormone-dependent breast cancer at an advanced stage

The most important methodological aspects and results of comparative studies are summarised in Tables below.

Anastrozole: No double blind comparative studies have been performed between anastrozole and megestrol acetate. A number of studies compared dosages of 1 mg and 10 mg anastrozole in a double blind manner, whereas anastrozole was compared to megestrol 40 mg qid in an open setting [50-53].

No significant differences were seen between anastrozole 10 mg or megestrol acetate on the applied endpoints (clinical advantage, time to progression or time to death). A significantly lower mortality after 2 years was observed for anastrozole 1 mg compared to megestrol, hazard ratio 0.78 p<0.025 [51].

Anastrozole 1 mg once daily was as effective as fulvestrant 250 mg im once monthly in a double blind study [54,55].

Exemestane: An international (19 countries) double blind study compared exemestane 25 mg with megestrol acetate 40 mg qid as second line treatment in postmenopausal women with breast cancer at an advanced stage after failure of a treatment with tamoxifen. The treatment was continued until tumor progression or unacceptable toxicity [56,57].

The primary endpoint was an objective response. Secondary endpoints were clinical advantage, duration of clinical advantage, time to objective response, duration of stable disease, time to tumor progression, time to therapy failure, survival, subjective response and effects on estrogen concentrations.

An imbalance was seen in the patient inclusion, including more patients in the megestrol-arm than in the exemestane-arm, because most countries included less than 30 patients. The median duration of follow-up was 49 weeks. The median duration of treatment with exemestane and megestrol was 17 weeks. 75% of the women had taken 100 +/- 20% of the prescribed medication.

The objective response was better (3.4 x) in patients with only soft tissue metastases. The response was better in better in patients who received tamoxifen for advanced breast cancer than for patients who received tamoxifen as adjuvant treatment.

The quality of life improved significantly during treatment with exemestane and remained constant or deteriorated during treatment with megestrol [56]. Exemestane had a more favourable effect on survival compared to megestrol (p=0.039) [57]. In an open, non-randomised study in patients with metastatic breast cancer who no longer responded to non-steroidal aromatase inhibitors 46% of the exemestane treated patients showed clinical advantage after 24 weeks treatment. The median progression free survival was 18 weeks and the median survival was 61 weeks [58].

Letrozole: Two double blind studies were performed with letrozole. Both studies compared letrozole 0.5 mg and letrozole 2.5 mg with megestrol acetate 40 mg qid. The endpoints were comparable with those of the earlier described studies with anastrozole and exemestane [59,60].

In the first study a significantly better survival was observed for letrozole 2.5 mg compared to letrozole 0.5 mg, but there was no significant difference between letrozole 2.5 mg and megestrol. The objective response rate was significantly better for letrozole 2.5 mg than for megestrol and the duration of the response was longer (Odds ratio 1.82). The time to therapy failure was significantly longer for letrozole 2.5 mg than in megestrol. A better response was observed in patients with only soft tissue metastases [59].

The second study showed no significant differences between

Ref	54, 55	64	56	65	59	60
Age	63	54	65	63	64	65
Duration first disease free interval (months)			47		58% > 24 mnd	65% > 24 mnd
Response to tamoxifen						
Progression time adjuvant tamoxifen			38%			
Failure in advanced breast cancer			11%	100% (aromatase inhib)		
Failure after initial response			50%		21%	21%
Chemotherapy:						
no chemotherapy	37%	37%	56%		60%	60%
Adjuvant chemotherapy	63%		28%		22%	25%
Advanced breast cancer		100%	16%	45%	19%	10%
Metastases						
Soft tissue			24%		26%	22%
Bone	44%		27%	67%	30%	30%
Internal organs	21%		58%		40%	49%
ER or PR +	87%		78%	98%	59%	81%

Table 5: Patient characteristics of the most relevant double blind studies in advanced breast cancer as second line treatment.

Ref	54, 55	64	56	65	59	60
Drugs	Ana 1 mg Ful 250 mg (1 x per month sc)	Ana 1 mg Ful 250 mg (1 x per month sc)	Exe 25 mg Meg 160 mg	Exe 25 mg Fulv250 mg q 28	Let 0.5 mg Let 2.5 mg Meg 160 mg	Let 0.5 mg Let 2.5 mg Meg 160 mg
Number of patients	A 423 F 428	A 113 F 121	E 366 M 403	E 351 M 342	L 0.5 188 L 2.5 174 M 189	L 0.5 202 L 2.5 199 M 201
Follow-up mean	15 months	15 months	49 weeks		5.5 months (response) to 45 months (survival)	to 37 months
Clinical advantage whole group	A 40% F 43%	A 36% F 48%	E 36% M 33%		L 0.5 27% L 2.5 35% M 31%	L 0.5 33% L 2.5 27% M 24%
Median time to progression whole group (months)	A 4,1 F 5.5	A 5.3 F 3.7	E 4,5 M 3.9	E 3.7 F 3.7	L 0.5 5.5 L 2.5 6.5 M 5.1	L 0.5 6 L 2.5 3 M 3
Median time to therapy failure whole group (months)	A 3.6 F 4,6	A 4.9 F 3.7	E 3.7 M 3.7		L 0.5 3.2 L 2.5 5.1 M 3.9 (p=0.04)	L 0.5 5 L 2.5 3 M 3
Total mortality whole group	A 35% F 36% (15 months follow-up)	A 35% F 36% (15 months follow-up)				L 0.5 61% L 2.5 69% M 70%
Median time to death whole group (months)					L 0.5 21 L 2.5 25 M 21	

Table 6: Results of the most relevant double blind studies in advanced breast cancer as second line treatment.

Ref	15, 16		25	
	Anastrozole	Tamoxifen	Anastrozole	Tamoxifen
Fractures	7.1%	4.4%	2.1%	1.0%
Stroke	1.1%	2.3%		
Thrombotic events	2.2%	3.8%		
Deep venous thrombosis	1.1%	1.8%		
Endometriumca	0.1%	0.7%	0.1%	0.5%
Embolism			0.1%	0.6%

Table 7: Serious adverse events in studies comparing anastrozole to tamoxifen.

letrozole 2.5 mg (of letrozole 0.5 mg) and megestrol in investigated endpoints, Table 3.6 [60].

An open randomised study compared letrozole 0.5 mg, letrozole 2.5 mg and aminogluthetimide, with a median follow-up of 20 months [58]. The survival was significantly longer on letrozole 2.5 mg, than in both other groups. In the Cox-regression the time to tumor progression was significantly longer in the letrozole 2.5 mg group compared to aminoglutethimide: RR 0.72 (p=0.008). The median time to tumor progression was comparable in the three groups: slightly more than 3 months. A similar effect was observed in the time to therapy failure: a significant difference in the Cox-regression, no difference in the median time to therapy failure Tables 1-6 [61-65].

Safety

Rare, life threatening side effect

Anastrozole: Direct comparative studies [15,16,25] showed the following serious side effects for anastrozole compared to tamoxifen Table 7.

Cardiovascular side effects were observed significantly more often in tamoxifen than in anastrozole. This was also true for the development of endometrial carcinoma [16,25]. Bone fractures, however were observed significantly more for anastrozole: 7.1% versus 4.4% [16], also after a median follow-up of 68 months: 11.0% vs. 7.7%, p<0.0001) [17].

After a treatment during 5 years less patients from the anastrozole

arm had stopped treatment because of a side-effect: 11% for anastrozole and 14% on tamoxifen (p=0.0002). Drug related serious adverse events were seen less often with anastrozole than with tamoxifen: 4,7% versus 9.0% p<0.0001) [17].

There was no difference in the incidence of fractures in the 40 months after cessation of the treatment: 1.56 per years vs. 1.51 per years for anastrozole and tamoxifen, respectively [19].

In the BIG1-98 study with an increased incidence of bone fractures was observed for letrozole (9.3%) compared to tamoxifen (6.5%) [66].

All aromatase inhibitors may cause osteoporosis [67].

Advanced breast cancer

Anastrozole: The studies in advanced breast cancer also showed a comparable incidence of side effects for anastrozole and tamoxifen: 84% in both groups and 42% drug-related side effects. Cessation of the treatment because of side effects occurred in 5%. Serious side effects were seen in 3.4% of anastrozole patients and 3.9% for tamoxifen. Trombo-embolism was more often observed in tamoxifen (9.0%) than in anastrozole (5.3%) [43].

In direct comparative studies between anastrozole 1 mg or 10 mg and megestrol acetate a lower incidence of serious side effects was observed for anastrozole: 6.1% for 1 mg; 4.9% for 10 mg and 9.1% for megestrol. Two patients in the megestrol group died because of a serious side-effect (stroke en pulmonary embolism) [51].

One direct comparative study between anastrozole and exemestane showed a similar incidence of adverse events.

Serious adverse reactions were observed in 13% in both groups, these were considered to be treatment-related in 3.4% of patients with anastrozole and in 4% with exemestane. Witdrawal due to adverse events was seen in 2% of patients with anastrozole and in 3% with exemestane [46].

Exemestane: Exemestane showed a lower incidence of thrombo-embolism than tamoxifen in the IES study (1.0% vs. 1.9%) [26].

In one study exemestane 25 mg showed a slightly stronger reduction of bone mineral density compared to placebo: 2.17% vs. 1.84% in the lumbal spint (not significant). The difference in the femoral neck was significant: 2.72% vs. 1.48% per years [68]. This effect was also seen in the IES study. The BMD in the lumbal spine decreased by 2.7% and the BMD in the hip by 1.4% binnen 6 months after the switch of tamoxifen to exemestane. A significant difference in the incidence of fractures was observed: 5% for tamoxifen vs. 7% for exemestane, p=0.003 [69].

Anastrozole and letrozole have a neutral to slightly negative (increased LDL cholesterol) effect on the lipid spectrum [67]. Exemestane however, showed a favourable effect on total cholesterol (12% lower) and triglycerides (15% lower). HDL cholesterol was however also lowered (by 32%) [70,71]. In another placebo-controlled study no significant differences were observed in the effects on lipids [68]. Exemestane and tamoxifen showed no major differences in the effects on the lipid spectrum. Exemestane had a more favourable effect on triglycerides than tamoxifen [71,72]. The clinical relevance of these findings is unclear [73,74].

Letrozole: In a placebo-controlled study in which letrozole was used after 5 years of treatment with tamoxifen as adjuvant treatment no higher incidence of serious side effects observed than in placebo. A trend in the direction of a higher frequency of osteoporosis was observed (5.8% vs. 4,5%), but the difference was not statistically significant (p=0.07). The incidence of fractures (3.6% vs. 2.9%) was not different (p=0.24) (33). A comparative study with tamoxifen showed a significant toename of the incidence of fractures for letrozole: 5.7% vs. 4,0%, p<0.001) (20).

In the same study with tamoxifen, letrozole showed a significantly higher incidence of heart failure (0.8% vs. 0.4%). Thrombo-embolic events were more often observed in tamoxifen: 3.5% vs. 1.5%. The incidence of stroke was comparable in both groups (1.0%) [20].

In an analysis of the BIG 1-98 study, both letrozole and tamoxifen showed a low incidence of cardiovascular side effects. After a follow-up of 30 months the total incidence was almost identical: 4.8% for letrozole vs. 4.7% for tamoxifen. The incidence of grade 3-4 reacties was significantly higher in the letrozole group: 2.4% vs. 1.4%, especially because of a higher incidence of tromboembolic events: 2.3% vs. 0.9% [75].

In a comparative study with megestrol acetate a lower incidence of serious side effects was observed for letrozole than for megestrol. Cardiovascular events (trombo-embolism) were seen in more than

	Studies	Patients	Years	Patient days (million)
Anastrozole	1	3125	>10	>100
Exemestane	---	---	>10	>100
Letrozole	1	4003	>10	>100

Table 8: Application as primary adjuvant treatment.

	Studies	Patients	Years	Patient days (million)
Anastrozole	2	1618	>10	>100
Exemestane	1	2362	>10	>100
Letrozole	---	---	>10	>100

Table 9: Application as adjuvant treatment after 2-3 years treatment with tamoxifen.

	Studies	Patients	Years	Patient days (million)
Anastrozole	1	387	>10	>100
Exemestane	---	---	>10	>100
Letrozole	1	2575	>10	>100

Table 10: Application as adjuvant treatment after 5 years treatment with tamoxifen.

	Studies	Patients	Years	Patient days (million)
Anastrozole	2	660	>10	>100
Exemestane	1	149	9	>100
Letrozole	3	866	>10	>100

Table 11: First line treatment in postmenopausal women with hormone-dependent breast cancer at an advanced stage.

	Studies	Patients	Years	Patient days (million)
Anastrozole	2	423	10	>100
Exemestane	1	366	>10	>100
Letrozole	2	763	>10	>100

Table 12: Second line treatment in postmenopausal women with hormone-dependent breast cancer at an advanced stage.

	Anastrozole	Tamoxifen
Flushes	35%	41%
"Musculoskeletal side effects"	30%	24%
Vaginal bleeding	4.8%	8.7%
Vaginal discharge	3.0%	12%

Table 13: Mild to moderate adverse events in studies comparing anastrozole to tamoxifen.

10% of the patients treated with megestrol, whereas it was not observed in letrozole 2.5 mg [59].

Aromatase inhibitors have an unfavourable effect on BMD. There is insufficien direct comparative data to make any statements concerning the relative risk of fractures between the drugs [76].

Documentation: The documentation regarding large scale randomised studies is summarised below Tables 8-12.

Tolerability

Frequent, but harmless side effect

Anastrozole: In the ATAC studies [16] the following side effects were seen significantly more often or less often for anastrozole compared to tamoxifen Table 13.

Anastrozole was slightly better tolerated than tamoxifen. Significantly more patients (28%) with tamoxifen stopped treatment (for any reason) than with anastrozole (24%). Cessation because of side effects was also observed significantly more in tamoxifen: 8.1% vs. 5.6% [16].

After a follow-up of 68 months a significantly lower incidence of side effects was observed for anastrozole (61%) compared to tamoxifen (68%). Serious side effects were more often observed for tamoxifen: 9% vs. 5%. Cessation of the treatment because of side effects occurred significantly more often during tamoxifen: 14% vs. 11% [77]

In another study (ABCSG) no significant differences in the incidence of flushes, bone pain and vaginal complaints were observed between anastrozole and tamoxifen. Only nausea (0.9% vs. 2.0%) occurred significantly more often during anastrozole [25]

In the ITA study, no significant differences in the incidence of side effects were observed between anastrozole and tamoxifen. Significantly more patients showed more than one side-effect on anastrozole than on tamoxifen. The percentage of patients that stopped treatment because of side effects (4.0% in tamoxifen and 4.4% in anastrozole) was almost identical [27].

Exemestane: In the IES study the following side effects occurred significantly more or less in exemestane than in tamoxifen [26] Table 14.

A comparable incidence of flushes was observed In both groups: 42% vs. 40% [26].

Advanced breast cancer

In a comparative study between exemestane and megestrol acetate the following side effects were observed more often in exemestane than in megestrol: flushes (13% vs. 5.0%), nausea (9.2% vs. 5.0%) and vomiting (2.8% vs. 0.8%). Dyspnoe was observed in more often megestrol (0.3 vs. 3.0%). The total incidence of treatment-related side effects was slightly higher for megestrol (46%) than for exemestane (39%). Less patients stopped the study because of side effects in exemestane than in megestrol [56].

An American substudy of the TEAM study, investigated the incidence of menopausal symptoms. Vaginal discharge and flushes were seen more often in tamoxifen than in exemestane, whereas bone- and musclepain, vaginal dryness, decreased libido and sleeping disturbances were more frwquent in exemestane than in tamoxifen [78].

Letrozole: In the BIG 1-98 study the following differences in the incidence of side effects observed were between letrozole and tamoxifen [20] Table 15.

The total incidence of side effects of letrozole 2.5 mg was comparable with that of megestrol in two double blind comparative studies. Cardiovascular side effects were significantly more often observed in megestrol. The most frequent drug-related side effects of letrozole were nausea (11%), headache (6%), peripheral oedema (3%), flushes (5%), tiredness (4%) and weight increase (2%) [56]. In another study similar side-effects were observed [60].

The incidence of therapy-related side effects was lower for letrozole 2.5 mg (33%) than for aminoglutethimide (46%). The most frequent side-effect of letrozole was nausea [79]

Ease of Use

Dosage frequency

All drugs can be taken once daily.

User friendly dosage forms

No specific user friendly formulations are available.

Intake in relation to the meals

The rate of absorption of anastrozole and letrozole is slightly decreased during intake with food, but the extent of absorption is not influenced by food. Both drugs may be taken dependent of food.

The bioavailability of exemestane increases by 40% when the drug is taken with food. It is advised to take the drug after food.

Applicability

Drug interactions

Anastrozole and letrozole show little to no clinically relevant interactions. No interactions were observed with cimetidine or bisphosphonates. Anastrozole must not be combined with tamoxifen or oestrogens, because these lower the clinical efficac of the drug. Anastrozole inhibits (in decreasing order) CYP1A2, CYP2C8/9 and CYP3A4, but this does not lead to clinically relevant interactions [3].

Letrozole may decrease the activity of CYP2A6 and to lesser extent CYP2C19 and CYP3A4. Interactions with drugs that are metabolised through these isoenzymes cannot be excluded, but so far no clinically relevant interactions have been described [3].

Both anastrozole and letrozole interact with tamoxifen, but there is no reason to use this combination [3].

	Exemestane	Tamoxifen
Visual disturbances	7.4%	5.7%
Gynaecological complaints	5.8%	9.0%
Arthralgia	5.4%	3.6%
Diarrhea	4.3%	2.3%
Cramps	2.8%	4.4%

Table 14: Mild to moderate adverse events in studies comparing exemestane to tamoxifen.

	Letrozole	Tamoxifen
Flushes	34%	41%
Arthralgia	20%	12%
Myalgia	6.4%	6.1%
Vaginal bleeding	3.3%	6.6%

Table 15: Mild to moderate adverse events in studies comparing letrozole to tamoxifen.

Exemestane is metabolised by CYP3A4. Ketoconazole, a powerful inhibitor of CYP3A4, did not affect the pharmacokinetics of exemestane however. Rifampicin lowered the AUC of exemestane by 54%. Exemestane must not be combined with oestrogens, because these lower the clinical efficacy of the dru

Approved indications

The following indications are approved in the Netherlands

Anastrozole

- Adjuvant treatment of postmenopausal women with a non-metastatic hormone sensitive breastcarcinoma
- Treatment of inoperable or metastatic hormone sensitive breastcarcinoma in postmenopausal women.

Exemestane

- Adjuvant treatment of postmenopausal women at an early stage of estrogenreceptor positive invasive breast cancer, afte initial adjuvant treatment of 2-3 years with tamoxifen
- Treatment of advanced breast cancer in women with a natural or induced postmenopausal state in whom progression occurred after anti-estrogentherap
- The efficac has not been shown in patients with a negative estrogenreceptor status

Letrozole

- Adjuvant treatment of postmenopausal women with hormone-receptor positive breast cancer in an early stage
- Continued adjuvant treatment of hormone-dependent breast cancer at an early stage in postmenopausal women who previously received standard adjuvant tamoxifen therapy during 5 years
- First line treatment in postmenopausal women with hormone-dependent breast cancer at an advanced stage
- Breast cancer at an advanced stage in women with a natural or induced postmenopausal state, after a deterioration in patients previously treated with anti-oestrogenen

Contra-indications

Anastrozole

- Hypersensitivity for one of the components of the product
- Premenopausal women

Exemestane

- Hypersensitivity for one of the components of the product
- Premenopausal women

Letrozole

- Hypersensitivity for one of the components of the product
- Premenopausal endocrine state

Use in children and elderly

These drugs are not indicated for use in children.

No dose adjustment is necessary in elderly women, when there is no major decrease in renal or hepatic function.

Drug	Trade name	Dosage	Daily cost
Anastrozole	generic	1 mg qd	0.07
Exemestane	generic	25 mg qd	0.33
Letrozole	generic	2.5 mg qd	0.53

Table 16: Daily acquisition cost (Dutch situation).

Use in renal- and liver function impairment

Anastrozole

- No dose adjustment in mild to moderate renal- or lever function impairment
- The drug has not been investigated in serious renal- or liver function impairment. The pros and cons should be thoroughly balanced.

Exemestane: Exemestane should be used with caution in patients with renal- or lever function impairment.

Letrozole

- No dose adjustment in patients with a creatinine clearance of >30 ml/min
- Insufficien experience in patients with a creatinine clearance of <30 ml/min
- Insufficien experience in patients with serious liver function impairment. Its half-life is increased 2-3 fold in patients with livercirrhosis and Child-Pugh score C

Use in pregnancy and lactation

The drugs are not indicated in this population.

Special precautions and warnings

Anastrozole

- Anastrozole is not indicated for application in premenopausal women, because effectivity and safety have not been identifi
- Drugs that lower estrogen levels, like anastrozole, may cause a reduction of the BMD veroorzaken. BMD measurement is indicated.
- Patients with rare conditions like galactose-intolerance, lactasedeficiency or glucose-galactose malabsorption should not use the drug

Exemestane

- Exemestane tablets contain sucrose and should ot be used in patients with rare conditions like fructose intolerance, glucose-galactose malabsorption or sucrase-isomaltase insufficien
- Exemestane tablets contain methyl-parahydroxybenzoate which may cause allergic reactions
- Drugs that lower estrogen levels, like exemestane, may cause a reduction of the BMD veroorzaken. BMD measurement is indicated.

Letrozole: The median follow-up in clinical studies (28 months) was insufficientl long to be able to estimate the risk of osteroporosis or fractures. The BMD should be determined in women with existing osteroporosis or fractures at baseline and prophylactic or therapeutic treatment with bisphosphonates should be started.

Cost

Daily cost

The officia cost in Euro, based on the "Vergoedingsprijs" of the Z-index is shown below Table 16.

References

1. Brenninkmeijer R, Mairs J, Timoney M, Scott M, McElnay J, et al. (2007) InforMatrix as an alternative tool in rational and transparent drug-decision making. Expert Opin Pharmacother Suppl 1: S31-6.
2. Jänicke F (2004) Are all aromatase inhibitors the same? A review of the current evidence. Breast 13 Suppl 1: S10-18.
3. Buzdar AU, Robertson JF, Eiermann W, Nabholtz JM (2002) An overview of the pharmacology and pharmacokinetics of the newer generation aromatase inhibitors anastrozole, letrozole, and exemestane. Cancer 95: 2006-2016.
4. Howell A (2005) Adjuvant aromatase inhibitors for breast cancer. Lancet 366: 431-433.
5. Smith IE (2004) Aromatase inhibitors--extending the benefits of adjuvant therapy beyond tamoxifen. Breast 13 Suppl 1: S3-9.
6. Pritchard KI (2005) Aromatase inhibitors in adjuvant therapy of breast cancer: before, instead of, or beyond tamoxifen. J Clin Oncol 23: 4850-4852.
7. Ingle JN (2005) Endocrine therapy trials of aromatase inhibitors for breast cancer in the adjuvant and prevention settings. Clin Cancer Res 11: 900s-5s.
8. Early Breast Cancer Trialists' Collaborative Group (EBCTCG) (2005) Effects of chemotherapy and hormonal therapy for early breast cancer on recurrence and 15-year survival: an overview of the randomised trials. Lancet 365: 1687-1717.
9. Smith IE, Dowsett M (2003) Aromatase inhibitors in breast cancer. N Engl J Med 348: 2431-2442.
10. Joensuu H, Ejlertsen B, Lønning PE, Rutqvist LE (2005) Aromatase inhibitors in the treatment of early and advanced breast cancer. Acta Oncol 44: 23-31.
11. Osborne C, Tripathy D (2005) Aromatase inhibitors: rationale and use in breast cancer. Annu Rev Med 56: 103-116.
12. Winer EP, Hudis C, Burstein HJ et al. (2005) American Society of Clinical Oncology technology assessment on the use of aromatase inhibitors as adjuvant therapy for postmenopausal women with hormone receptor-positive breast cancer: status report 2004. J Clin Oncol 23: 619-29.
13. Geisler J, Haynes B, Anker G et al. (2002) Influence of letrozole and anastrozolee on total body aromatization and plasma estrogen levels in postmenopausal breast cancer patients evaluated in a randomized cross-over study. J Clin Oncol 20: 751-757.
14. Cuzick J, Sestak I, Forbes JF, Dowsett M, Knox J, et al. (2014) Anastrozole for prevention of breast cancer in high-risk postmenopausal women (IBIS-II): an international, double-blind, randomised placebo-controlled trial. Lancet 383: 1041-1048.
15. Baum M, Budzar AU, Cuzick J, Forbes J, Houghton JH, et al. (2002) Anastrozolee alone or in combination with tamoxifen versus tamoxifen alone for adjuvant treatment of postmenopausal women with early breast cancer: first results of the ATAC randomised trial. Lancet 359: 2131-2139.
16. Baum M, Buzdar A, Cuzick J, Forbes J, Houghton J, et al. (2003) Anastrozolee alone or in combination with tamoxifen versus tamoxifen alone for adjuvant treatment of postmenopausal women with early-stage breast cancer. Cancer 98: 1802-1810.
17. Howell A, Cuzick J, Baum M, Buzdar A, Dowsett M, et al. (2005) Results of the ATAC (Arimidex, Tamoxifen, Alone or in Combination) trial after completion of 5 years' adjuvant treatment for breast cancer. Lancet 365: 60-62.
18. Dowsett M, Cuzick J, Wale C, Howell T, Houghton J, et al. (2005) Retrospective analysis of time to recurrence in the ATAC trial according to hormone receptor status: an hypothesis-generating study. J Clin Oncol 23: 7512-7517.
19. Arimidex, Tamoxifen (2008) Effect of anastrozolee and tamoxifen as adjuvant treatment for early-stage breast cancer: 100-months analysis of the ATAC trial. Lancet Oncol 9: 45-53.
20. Breast International Group (BIG) 1-98 Collaborative Group1, Thürlimann B, Keshaviah A, Coates AS, Mouridsen H, et al. (2005) A comparison of letrozole and tamoxifen in postmenopausal women with early breast cancer. N Engl J Med 353: 2747-2757.
21. Rasmusen BB, Regan MM, Lykkesfledt AE, et al. (2008) Adjuvant letrozole versus tamoxifen according to centrally-assessed ERBB2 status for postmenopausal women with endocrine-responseive early breast cancer; supplementary results from the BIG1-98 randomised trial. Lancet Oncol 9: 23-28.
22. Coates AS, Keshaviah A, Thürlimann B, Mouridsen H, Mauriac L, et al. (2007) Five years of letrozole compared with tamoxifen as initial adjuvant therapy for postmenopausal women with endocrine-responsive early breast cancer: update of study BIG 1-98. J Clin Oncol 25: 486-492.
23. Crivellari D, Sun Z, Coates AS, Price KN, Thürlimann B, et al. (2008) Letrozole compared with tamoxifen for elderly patients with endocrine-responsive early breast cancer: the BIG 1-98 trial. J Clin Oncol 26: 1972-1979.
24. Mouridsen H, Giobbie-Hurder A, Goldhirsch A, et al. (2009) Letrozole therapy alone or in sequence with tamoxifen in women with breast cancer. N Engl J M 361: 766-776.
25. Jakesz R, Jonat W, Gnant M, et al. (2005) Switching of postmenopausal women with endocrine-responseive early breast cancer to anastrozolee after 2 years' adjuvant tamoxifen: combined results of ABCSG trial 8 and ARNO 95 trial. Lancet 366: 455-462.
26. Coombes RC, Hall E, Gibson LJ, Paridaens R, Jassem J, et al. (2004) A randomized trial of exemestane after two to three years of tamoxifen therapy in postmenopausal women with primary breast cancer. N Engl J Med 350: 1081-1092.
27. Boccardo F, Rubagotti A, Puntoni M, Guglielmini P, Amoroso D, et al. (2005) Switching to anastrozole versus continued tamoxifen treatment of early breast cancer: preliminary results of the Italian Tamoxifen Anastrozole Trial. J Clin Oncol 23: 5138-5147.
28. Kaufmann M, Jonat W, Hilfrich J, Eidtmann H, Gademann G, et al. (2007) Improved overall survival in postmenopausal women with early breast cancer after anastrozole initiated after treatment with tamoxifen compared with continued tamoxifen: the ARNO 95 Study. J Clin Oncol 25: 2664-2670.
29. Coombes RC, Kilburn LS, Snowdon CF, Paridaens R, Coleman RE, et al. (2007) Survival and safety of exemestane versus tamoxifen after 2-3 years' tamoxifen treatment (Intergroup Exemestane Study): a randomised controlled trial. Lancet 369: 559-570.
30. van de Velde CJ, Rea D, Seynaeve C, Putter H, Hasenburg A, et al. (2011) Adjuvant tamoxifen and exemestane in early breast cancer (TEAM): a randomised phase 3 trial. Lancet 377: 321-331.
31. Schmid M, Jakesz R, Samonigg H, et al. (2003) Randomized trial of tamoxifen versus tamoxifen plus aminogluthetimide as adjuvant treatment in postmenopausal breast cancer patients with hormone receptor-positive disease: Austrian Breast and Colorectal Cancer Study Group trial 6. J Cin Oncol 21: 984-990.
32. Jakesz R, greil R, Gnant M, et al. (2007) Extended adjuvant therapy with anastrozole among postmenopausal btreast cancer patients: results from the randomized Austrian Breast and Colorectal Cancer Study Group trial 6a. J Natl Cancer Inst 99: 1845-53.
33. Goss PE, Ingle JN, Martino S, Robert NJ, Muss HB, et al. (2003) A randomized trial of letrozole in postmenopausal women after five years of tamoxifen therapy for early-stage breast cancer. N Engl J Med 349: 1793-1802.
34. Goss PE, Ingle JN, Martino S, Robert NJ, Muss HB, et al. (2005) Randomized trial of letrozole following tamoxifen as extended adjuvant therapy in receptor-positive breast cancer: updated findings from NCIC CTG MA.17. J Natl Cancer Inst 97: 1262-1271.
35. Muss HB, Tu D, Ingle JN, Martino S, Robert NJ, et al. (2008) Efficacy, toxicity, and quality of life in older women with early-stage breast cancer treated with letrozole or placebo after 5 years of tamoxifen: NCIC CTG intergroup trial MA.17. J Clin Oncol 26: 1956-1964.
36. Goss PE, Ingle JN, Pater JL, Martino S, Robert NJ, et al. (2008) Late extended adjuvant treatment with letrozole improves outcome in women with early-stage breast cancer who complete 5 years of tamoxifen. J Clin Oncol 26: 1948-1955.
37. Mamounas EP, Jeong JH, Wickerham DL (2008) Benefit from exemestane as extended adjuvant therapy after 5 years of adjuvant tamoxifen: intention-to-treat analysis of the National Surgical Adjuvant Breast And Bowel Project B-33 trial. J Clin Oncol 26:1965-1971.

38. Boccardo F, Rubagotti A (2007) Switching to aromatase inhibitors in early breast cancer. Lancet 369: 533-535.

39. Yadav BS, Sharma SC, Patel FD, Ghoshal S, Kapoor V (2007) Results of letrozole in postmenopausal women after tamoxifen treatment for advanced breast cancer. J Cancer Res Ther 3: 71-74.

40. Bonneterre J, Thürlimann B, Robertson JF, Krzakowski M, Mauriac L, et al. (2000) Anastrozole versus tamoxifen as first-line therapy for advanced breast cancer in 668 postmenopausal women: results of the Tamoxifen or Arimidex Randomized Group Efficacy and Tolerability study. J Clin Oncol 18: 3748-3757.

41. Nabholtz JM, Buzdar A, Pollak M, Harwin W, Burton G, et al. (2000) Anastrozole is superior to tamoxifen as first-line therapy for advanced breast cancer in postmenopausal women: results of a North American multicenter randomized trial. Arimidex Study Group. J Clin Oncol 18: 3758-3767.

42. Bonneterre J, Buzdar A, Nabholtz JM, Robertson JF, Thürlimann B, et al. (2001) Anastrozole is superior to tamoxifen as first-line therapy in hormone receptor positive advanced breast carcinoma. Cancer 92: 2247-2258.

43. Nabholtz JM, Bonneterre J, Buzdar A, Robertson JF, Thürlimann B (2003) Anastrozole (Arimidex) versus tamoxifen as first-line therapy for advanced breast cancer in postmenopausal women: survival analysis and updated safety results. Eur J Cancer 39: 1684-1689.

44. Thürlimann B, Hess D, Köberle D, Senn I, Ballabeni P, et al. (2004) Anastrozole ('Arimidex') versus tamoxifen as first-line therapy in postmenopausal women with advanced breast cancer: results of the double-blind cross-over SAKK trial 21/95--a sub-study of the TARGET (Tamoxifen or 'Arimidex' Randomized Group Efficacy and Tolerability) trial. Breast Cancer Res Treat 85: 247-254.

45. Milla-Santos A, Milla L, Portella J, Rallo L, Pons M, et al. (2003) Anastrozole versus tamoxifen as first-line therapy in postmenopausal patients with hormone-dependent advanced breast cancer: a prospective, randomized, phase III study. Am J Clin Oncol 26: 317-322.

46. Iwata H, Masuda N, Ohno S, Rai Y, Sato Y, et al. (2013) A randomized, double-blind, controlled study of exemestane versus anastrozole for the first-line treatment of postmenopausal Japanese women with hormone-receptor-positive advanced breast cancer. Breast Cancer Res Treat 139: 441-451.

47. Paridaens R, Dirix L, Lohrisch C, Beex L, Nooij M, et al. (2003) Mature results of a randomized phase II multicenter study of exemestane versus tamoxifen as first-line hormone therapy for postmenopausal women with metastatic breast cancer. Ann Oncol 14: 1391-1398.

48. Mouridsen H, Gershanovich M, Sun Y, Pérez-Carrión R, Boni C, et al. (2001) Superior efficacy of letrozole versus tamoxifen as first-line therapy for postmenopausal women with advanced breast cancer: results of a phase III study of the International Letrozole Breast Cancer Group. J Clin Oncol 19: 2596-2606.

49. Mouridsen H, Gershanovich M, Sun Y, et al. (2003) Phase III study of letrozole versus tamoxifen as first-line therapy of advanced breast cancer in postmenopausal women: analysis of survival and update of efficacy from the International Letrozole Breast Cancer Group. J Clin Oncol 21: 2101-2109.

50. Buzdar A, Jonat W, Howell A, et al. (1996) Anastrozolee, a potent and selective aromatase inhibitor, versus megestrol acetate in postmenopausal women with advanced breast cancer: results of overview analysis of two phase III trials. Arimidex Study Group. J Clin Oncol 14: 2000-2011.

51. Buzdar AU, Jonat W, Howell A, et al. (1998) Anastrozolee versus megestrol acetate in the treatment of postmenopausal women with advanced breast carcinoma: results of a survival update based on a combined analysis of data from two mature phase III trials. Arimidex Study Group. Cancer 83: 1142-1152.

52. Buzdar AU, Jones SE, Vogel CL, et al. (1997) A phase III trial comparing anastrozolee (1 and 10 milligrams), a potent and selective aromatase inhibitor, with megestrol acetate in postmenopausal women with advanced breast carcinoma. Arimidex Study Group. Cancer 79: 730-739.

53. Jonat W, Howell A, Blomqvist C, Eiermann W, Winblad G, et al. (1996) A randomised trial comparing two doses of the new selective aromatase inhibitor anastrozole (Arimidex) with megestrol acetate in postmenopausal patients with advanced breast cancer. Eur J Cancer 32A: 404-412.

54. Osborne CK, Pippen J, Jones SE, et al. (2002) Double-blind, randomized trial comparing the efficacy and tolerability of fulvestrant versus anastrozolee in postmenopausal women with advanced breast cancer progressing on prior endocrine therapy: results of a North American trial. J Clin Oncol 20: 3386-3395.

55. Robertson JF, Osborne CK, Howell A, Jones SE, Mauriac L, et al. (2003) Fulvestrant versus anastrozole for the treatment of advanced breast carcinoma in postmenopausal women: a prospective combined analysis of two multicenter trials. Cancer 98: 229-238.

56. Kaufmann M, Bajetta E, Dirix LY, et al. (2000) Exemestane is superior to megestrol acetate after tamoxifen failure in postmenopausal women with advanced breast cancer: results of a phase III randomized double-blind trial. The Exemestane Study Group. J Clin Oncol 18: 1399-1411.

57. Kaufmann M, Bajetta E, Dirix LY, et al. (2000) Exemestane improves survival compared with megestrol acetate in postmenopausal patients with advanced breast cancer who have failed on tamoxifen: results of a double-blind randomised phase III trial. Eur J Cancer 36 Suppl 4: S86-87.

58. Steele N, Zekri J, Coleman R, Leonard R, Dunn K, et al. (2006) Exemestane in metastatic breast cancer: effective therapy after third-generation non-steroidal aromatase inhibitor failure. Breast 15: 430-436.

59. Dombernowsky P, Smith I, Falkson G, Leonard R, Panasci L, et al. (1998) Letrozole, a new oral aromatase inhibitor for advanced breast cancer: double-blind randomized trial showing a dose effect and improved efficacy and tolerability compared with megestrol acetate. J Clin Oncol 16: 453-461.

60. Buzdar A, Douma J, Davidson N, Elledge R, Morgan M, et al. (2001) Phase III, multicenter, double-blind, randomized study of letrozole, an aromatase inhibitor, for advanced breast cancer versus megestrol acetate. J Clin Oncol 19: 3357-3366.

61. Simpson D, Curran MP, Perry CM (2004) Letrozole: a review of its use in postmenopausal women with breast cancer. Drugs 64: 1213-1230.

62. Tominaga T, Adachi I, Sasaki Y, Tabei T, Ikeda T, et al. (2003) Double-blind randomised trial comparing the non-steroidal aromatase inhibitors letrozole and fadrozole in postmenopausal women with advanced breast cancer. Ann Oncol 14: 62-70.

63. Goss P, Bondarenko IN, Manikhas GN, Pendergrass KB, Miller WH Jr, et al. (2007) Phase III, double-blind, controlled trial of atamestane plus toremifene compared with letrozole in postmenopausal women with advanced receptor-positive breast cancer. J Clin Oncol 25: 4961-4966.

64. Xu B, Jiang Z, Shao Z, et al. (2011) Fulvestrant 250 mg versus anastrozole for Chinese patients with advanced breast cancer: results of a multicentre, double-blind, randomised Phase II trial. Cancer Chemother Pharmacol 67: 223-230.

65. Chia S, Gradishar W, Mauriac L, et al. (2008) Double-blind, randomized placebo controlled trial of fulvestrant compared with exemestane after prior nonsteroidal aromatase inhibitor therapy in postmenopausal women with hormone receptor-positive, advanced breast cancer: results from EFECT. J Clin Oncol 10:1964-1970.

66. Rabaglio M, Sun Z, Price KN, Castiglione-Gertsch M, Hawle H, et al. (2009) Bone fractures among postmenopausal patients with endocrine-responsive early breast cancer treated with 5 years of letrozole or tamoxifen in the BIG 1-98 trial. Ann Oncol 20: 1489-1498.

67. Anonymous (2009) Treatment with aromatase inhibitors for breast cancer is associated with bone loss in postmenopausal women. Drug Ther Perspect 25: no9.

68. Lonning PE, Geisler J, Krag LE, et al. (2005) Effects of exemestane administered for 2 years versus placebo on bone mineral density, bone biomarkers, and plasma lipids in patients with surgically resected early breast cancer. J Clin Oncol 23: 5126-5137.

69. Coleman RE, Banks LM, Girgis SI, et al. (2007) Skeletal effects of exemestane on bone-mineral density, bone biomarkers, and fracture incidence in postmenopausal women with early breast cancer participating in the Intergroup Exemestane Study (IES): a randomised controlled study. Lancet Oncol 8: 119-127.

70. Wasan KM, Goss PE, Pritchard PH, Shepherd L, Palmer MJ, et al. (2005) The influence of letrozole on serum lipid concentrations in postmenopausal women with primary breast cancer who have completed 5 years of adjuvant tamoxifen (NCIC CTG MA.17L). Ann Oncol 16: 707-715.

71. Atalay G, Dirix L, Biganzoli L, et al. (2004) The effect of exemestane on serum lipid profile in postmenopausal women with metastatic breast cancer: a companion study to EORTC trial 10951. "Randomized phase II study in first line hormonal treatment for metastatic breast cancer with exemestane or tamoxifen in postmenopausal patients". Ann Oncol 15: 211-217.

72. Markopoulos C, Chrissochou M, Michailidou A, et al. (2005) Effect of

exemestane on the lipidemic profile of post-menopausal operable breast cancer patients following 5-7 years of adjuvant tamoxifen: preliminary results of the ATENA substudy. Anticancer Drugs 16: 879-883.

73. Campos SM (2004) Aromatase inhibitors for breast cancer in postmenopausal women. Oncologist 9: 126-136.

74. Bundred NJ (2005) The effects of aromatase inhibitors on lipids and thrombosis. Br J Cancer 93 Suppl 1: S23-27.

75. Mouridsen H, Keshaviah A, Coates AS, et al. (2007) Cardiovascular adverse events during adjuvant endocrine therapy for early breast cancer using letrozole or tamoxifen : safety analysis of BIG1-98 trial. J Clin Oncol 25: 5715-5722.

76. Chien AJ, Goss PE (2006) Aromatase inhibitors and bone health in women with breast cancer. J Clin Oncol 24: 5305-5312.

77. Arimidex, Tamoxifen, Alone or in Combination Trialists' Group1, Buzdar A, Howell A, et al. (2006) Comprehensive side-effect profile of anastrozole and tamoxifen as adjuvant treatment for early-stage breast cancer: long-term safety analysis of the ATAC trial. Lancet Oncol 7: 633-643.

78. Jones SE, Cantrell J, Vukelja S, et al. (2007) Comparison of menopausal symptoms during the first yearsof adjuvant therapy with either exemestane or tamoxifen in early breast cancer: report of a Tamoxifen Exemestane Adjuvant Multicenter trial substudy. J Clin Oncol 30: 4765-4771.

79. Gershanovich M, Chaudri HA, Campos D, Lurie H, Bonaventura A, et al. (1998) Letrozole, a new oral aromatase inhibitor: randomised trial comparing 2.5 mg daily, 0.5 mg daily and aminoglutethimide in postmenopausal women with advanced breast cancer. Letrozole International Trial Group (AR/BC3). Ann Oncol 9: 639-645.