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Has been at the forefront of breast cancer treatment development for the past 50 years[1], starting with the discovery of NOLVADEX (tamoxifen).

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Zoladex® goserelin

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PI

AstraZeneca

has supported breast cancer research and facilitated advances in medical research since the 1970s.[1]

1991[2]

TAMOXIFEN
approved for treatment of breast cancer[3]

1993[4,5]

GOSERELIN
Approved for the treatment of advanced breast cancer in pre-menopausal women.[4,5]

1996[6,7]

ANASTROZOLE
Approved for the treatment of advanced breast cancer in postmenopausal women with progression following tamoxifen therapy.[6,7]

2000[6,7]

ANASTROZOLE
Treatment of hormone receptor positive (HR+) advanced breast cancer in postmenopausal women.[6,7]

2001[4,5]

GOSERELIN
Adjuvant therapy in early breast cancer in pre- and peri-menopausal women[4,5]

2003[6,7]

ANASTROZOLE
Adjuvant treatment of HR+ early breast cancer in postmenopausal women[6,7]

2006[8]

FULVESTRANT
Approved for the treatment of HR+ postmenopausal women with locally advanced or metastatic breast cancer with disease progression following tamoxifen therapy[9]

FURTHER RESEARCH & DEVELOPMENT 2016 »»

PI

Prescribing Information

Arimidex® anastrozole

PBS Information: Arimidex Restricted Benefit.
Breast cancer. The condition must be hormone receptor positive.

ARIMIDEX APPROVED PRODUCT INFORMATION

Zoladex® goserelin

PBS Information: Zoladex 3.6 mg Restricted Benefit.
Breast cancer. The condition must be hormone receptor positive.

ZOLADEX APPROVED PRODUCT INFORMATION

FASLODEX® fulvestrant

PBS Information: Faslodex. This product is not listed on the PBS.

FASLODEX APPROVED PRODUCT INFORMATION

Nolvadex-D® tamoxifen

PBS Information: Nolvadex Restricted Benefit.
Treatment of breast cancer. Reduction of breast cancer risk.
Refer to PBS Schedule for full restricted benefit information.

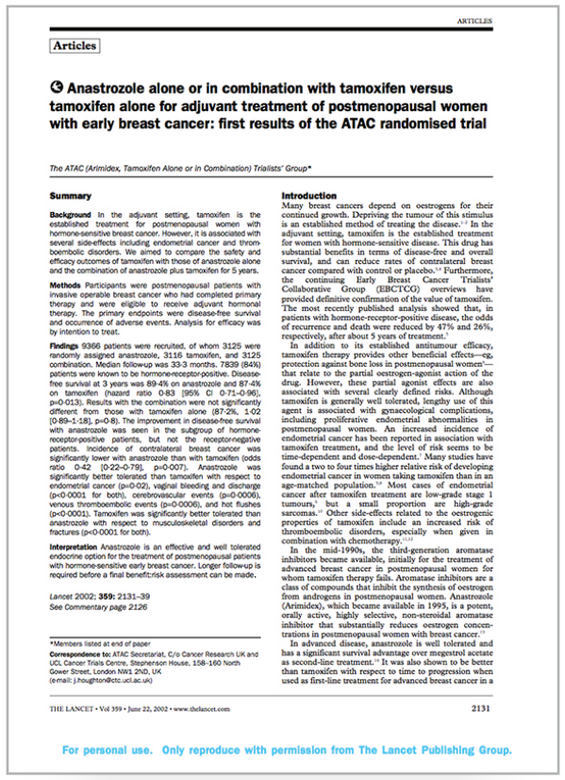
NOLVADEX APPROVED PRODUCT INFORMATION

Please review Product Information before Prescribing. Product Information is available via the link on this page or on request from AstraZeneca

AstraZeneca

Clinical Papers

ARIMIDEX



ARTICLES

Articles

Anastrozole 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

*The ATAC (Arimidex, Tamoxifen Alone or in Combination) Trialists' Group**

Summary

Background In the adjuvant setting, tamoxifen is the established treatment for postmenopausal women with hormone-sensitive breast cancer. However, it is associated with several side-effects including endometrial cancer and thromboembolic disorders. We aimed to compare the safety and efficacy outcomes of tamoxifen with those of anastrozole alone and the combination of anastrozole plus tamoxifen for 5 years.

Methods Participants were postmenopausal patients with invasive operable breast cancer who had completed primary therapy and were eligible to receive adjuvant hormonal therapy. The primary endpoints were disease-free survival and occurrence of adverse events. Analysis for efficacy was by intention to treat.

Findings 9366 patients were recruited, of whom 3125 were randomly assigned anastrozole, 3116 tamoxifen, and 3125 combination. Median follow-up was 33·3 months. 7839 (84%) patients were known to be hormone-receptor-positive. Disease-free survival at 3 years was 89·4% on anastrozole and 87·4% on tamoxifen (hazard ratio 0·83 [95% CI 0·71–0·96], p=0·013). Results with the combination were not significantly different from those with tamoxifen alone (87·2%, 1·02 [0·89–1·18], p=0·8). The improvement in disease-free survival with anastrozole was seen in the subgroup of hormone-receptor-positive patients, but not the receptor-negative patients. Incidence of contralateral breast cancer was significantly lower with anastrozole than with tamoxifen (odds ratio 0·42 [0·22–0·79], p=0·007). Anastrozole was significantly better tolerated than tamoxifen with respect to endometrial cancer (p=0·02), vaginal bleeding and discharge (p<0·0001 for both), cerebrovascular events (p=0·0006), venous thromboembolic events (p=0·0006), and hot flushes (p<0·0001). Tamoxifen was significantly better tolerated than anastrozole with respect to musculoskeletal disorders and fractures (p<0·0001 for both).

Interpretation Anastrozole is an effective and well tolerated endocrine option for the treatment of postmenopausal patients with hormone-sensitive early breast cancer. Longer follow-up is required before a final benefit:risk assessment can be made.

Lancet 2002; **359:** 2131–39
See Commentary page 2126

*Members listed at end of paper

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Introduction

Many breast cancers depend on oestrogens for their continued growth. Depriving the tumour of this stimulus is an established method of treating the disease.[1,2] In the adjuvant setting, tamoxifen is the established treatment for women with hormone-sensitive disease. This drug has substantial benefits in terms of disease-free and overall survival, and can reduce rates of contralateral breast cancer compared with control or placebo.[3,4] Furthermore, the continuing Early Breast Cancer Trialists' Collaborative Group (EBCTCG) overviews have provided definitive confirmation of the value of tamoxifen. The most recently published analysis showed that, in patients with hormone-receptor-positive disease, the odds of recurrence and death were reduced by 47% and 26%, respectively, after about 5 years of treatment.[5]

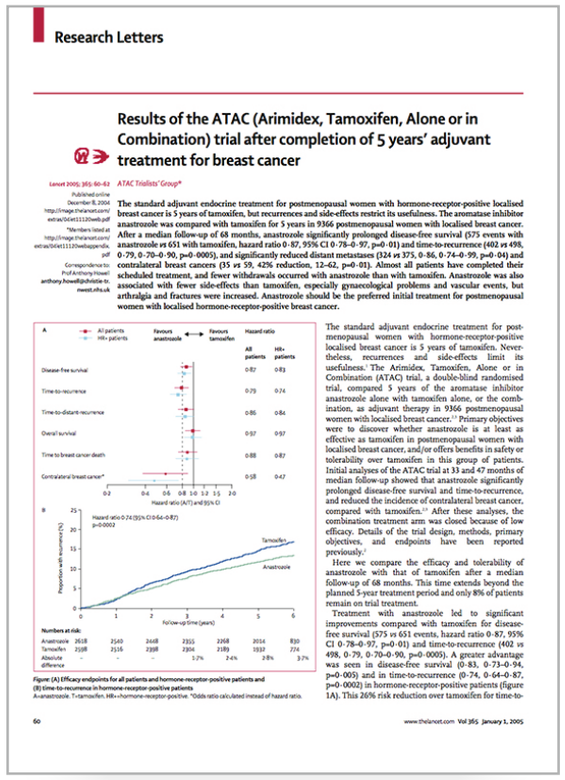
In addition to its established antitumour efficacy, tamoxifen therapy provides other beneficial effects—eg, protection against bone loss in postmenopausal women[6]—that relate to the partial oestrogen-agonist action of the drug. However, these partial agonist effects are also associated with several clearly defined risks. Although tamoxifen is generally well tolerated, lengthy use of this agent is associated with gynaecological complications, including proliferative endometrial abnormalities in postmenopausal women. An increased incidence of endometrial cancer has been reported in association with tamoxifen treatment, and the level of risk seems to be time-dependent and dose-dependent.[7] Many studies have found a two to four times higher relative risk of developing endometrial cancer in women taking tamoxifen than in an age-matched population.[8,9] Most cases of endometrial cancer after tamoxifen treatment are low-grade stage 1 tumours,[7] but a small proportion are high-grade sarcomas.[10] Other side-effects related to the oestrogenic properties of tamoxifen include an increased risk of thromboembolic disorders, especially when given in combination with chemotherapy.[11,12]

In the mid-1990s, the third-generation aromatase inhibitors became available, initially for the treatment of advanced breast cancer in postmenopausal women for whom tamoxifen therapy fails. Aromatase inhibitors are a class of compounds that inhibit the synthesis of oestrogen from androgens in postmenopausal women. Anastrozole (Arimidex), which became available in 1995, is a potent, orally active, highly selective, non-steroidal aromatase inhibitor that substantially reduces oestrogen concentrations in postmenopausal women with breast cancer.[13]

In advanced disease, anastrozole is well tolerated and has a significant survival advantage over megestrol acetate as second-line treatment.[14] It was also shown to be better than tamoxifen with respect to time to progression when used as first-line treatment for advanced breast cancer in a

The ATAC Trialists' Group. (2002) *Lancet.*

ARIMIDEX



Research Letters

Results of the ATAC (Arimidex, Tamoxifen, Alone or in Combination) trial after completion of 5 years' adjuvant treatment for breast cancer

Lancet 2005; 365: 60–62 — ATAC Trialists' Group*

Published online December 8, 2004 http://image.thelancet.com/extras/04let11120web.pdf

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The standard adjuvant endocrine treatment for postmenopausal women with hormone-receptor-positive localised breast cancer is 5 years of tamoxifen. Nevertheless, recurrences and side-effects limit its usefulness.[1] The Arimidex, Tamoxifen, Alone or in Combination (ATAC) trial, a double-blind randomised trial, compared 5 years of the aromatase inhibitor anastrozole alone with tamoxifen alone, or the combination, as adjuvant therapy in 9366 postmenopausal women with localised breast cancer.[2,3] Primary objectives were to discover whether anastrozole is at least as effective as tamoxifen in postmenopausal women with localised breast cancer, and/or offers benefits in safety or tolerability over tamoxifen in this group of patients. Initial analyses of the ATAC trial at 33 and 47 months of median follow-up showed that anastrozole significantly prolonged disease-free survival and time-to-recurrence, and reduced the incidence of contralateral breast cancer, compared with tamoxifen.[2,3] After these analyses, the combination treatment arm was closed because of low efficacy. Details of the trial design, methods, primary objectives, and endpoints have been reported previously.[2]

Here we compare the efficacy and tolerability of anastrozole with that of tamoxifen after a median follow-up of 68 months. This time extends beyond the planned 5-year treatment period and only 8% of patients remain on trial treatment.

Treatment with anastrozole led to significant improvements compared with tamoxifen for disease-free survival (575 *vs* 651 events, hazard ratio 0·87, 95% CI 0·78–0·97, p=0·01) and time-to-recurrence (402 *vs* 498, 0·79, 0·70–0·90, p=0·0005). A greater advantage was seen in disease-free survival (0·83, 0·73–0·94, p=0·005) and in time-to-recurrence (0·74, 0·64–0·87, p=0·0002) in hormone-receptor-positive patients (figure 1A). This 26% risk reduction over tamoxifen for time-to-

Figure: (A) Efficacy endpoints for all patients and hormone-receptor-positive patients and (B) time-to-recurrence in hormone-receptor-positive patients
A=anastrozole. T=tamoxifen. HR+=hormone-receptor-positive. *Odds ratio calculated instead of hazard ratio.

The ATAC Trialists' Group. (2005) *Lancet.*

ARIMIDEX

Articles

Effect of anastrozole and tamoxifen as adjuvant treatment for early-stage breast cancer: 100-month analysis of the ATAC trial

*The Arimidex, Tamoxifen, Alone or in Combination (ATAC) Trialists' Group**

Summary

Background Little data exist on whether efficacy benefits or side-effects persist after 5 years of adjuvant treatment with an aromatase inhibitor. We aimed to study long-term outcomes in the Arimidex, Tamoxifen, Alone or in Combination (ATAC) trial that compares anastrozole with tamoxifen after a median follow-up of 100 months.

Methods We analysed postmenopausal women with localised invasive breast cancer. The primary endpoint disease-free survival (DFS), and the secondary endpoints time to recurrence (TTR), incidence of new contralateral breast cancer (CLBC), time to distant recurrence (TTDR), overall survival (OS), and death after recurrence were assessed in the total population (intention to treat; ITT: anastrozole, n=3125; tamoxifen, n=3116; total 6241) and the hormone-receptor-positive subpopulation, the clinically important subgroup for which endocrine treatment is now known to be effective (84% of ITT: anastrozole, n=2618; tamoxifen, n=2598; total 5216). After treatment completion, fractures and serious adverse events continued to be collected blindly (safety population: anastrozole, n=3092; tamoxifen, n=3094; total 6186). This study is registered as an International Standard Randomised Controlled Trial, number ISRCTN18233230.

Findings At a median follow-up of 100 months (range 0–126), DFS, TTR, TTDR, and CLBC were improved significantly in the ITT and hormone-receptor-positive populations. For hormone-receptor-positive patients: DFS hazard ratio (HR) 0·85 (95% CI 0·76–0·94), p=0·003; TTR HR 0·76 (0·67–0·87), p=0·0001; TTDR HR 0·84 (0·72–0·97), p=0·022; and CLBC HR 0·60 (0·42–0·85), p=0·004. Absolute differences in time to recurrence increased over time (TTR 2·8% [anastrozole 9·7% *vs* tamoxifen 12·5%] at 5 years and 4·8% [anastrozole 17·0% *vs* tamoxifen 21·8%] at 9 years) and recurrence rates remained significantly lower on anastrozole compared with tamoxifen after treatment completion (HR 0·75 [0·61–0·94], p=0·01). The fewer deaths after recurrence (anastrozole 245 *vs* tamoxifen 269) was not significant (HR 0·90 [0·75–1·07], p=0·2), and no effect was noted for OS (anastrozole 472 *vs* tamoxifen 477) HR 0·97 [0·86–1·11], p=0·7). Fracture rates were higher in patients receiving anastrozole than in those receiving tamoxifen during active treatment (number [annual rate]: 375 [2·93%] *vs* 234 [1·90%]; incidence rate ratio [IRR] 1·55 [1·31–1·83], p<0·0001), but were not different after treatment was completed (off treatment: 146 [1·56%] *vs* 143 [1·51%]; IRR 1·03 [0·83–1·31], p=0·79). We did not note any significant difference in risk of cardiovascular morbidity or mortality between anastrozole and tamoxifen treatment groups.

Interpretation These data show long-term safety findings and establish clearly the long-term efficacy of anastrozole compared with tamoxifen as initial adjuvant treatment for postmenopausal women with hormone-sensitive, early breast cancer, and provide statistically significant evidence of a larger carryover effect after 5 years of adjuvant treatment with anastrozole compared with tamoxifen.

Introduction

Breast cancer is the most common type of cancer in women and the most frequent cause of cancer-related death; the number of women diagnosed with breast cancer worldwide in 2002 was 1·15 million and about 410 000 women died as a result of breast cancer.[1] In developed countries, around 75% of all breast cancers occur in postmenopausal women, of which about 80% are hormone-receptor positive.[2] Until recently, tamoxifen has been the endocrine treatment of choice for postmenopausal women with hormone-receptor-positive early breast cancer. Tumour recurrence and mortality in women with hormone-receptor-positive breast cancer are significantly decreased by the use of 5 years of adjuvant tamoxifen, both in the presence and absence of chemotherapy.[3] Nonetheless, yearly recurrence rates remain above 2% long term and more than 30% of women develop recurrent disease within 15 years. Additionally, a small proportion of women have serious side-effects, including increased incidence of endometrial cancer, and thromboembolism and cerebrovascular events.[4,5]

Data from clinical trials comparing third-generation aromatase inhibitors with tamoxifen[6–8] have confirmed that aromatase inhibitors offer significant efficacy and tolerability advantages over tamoxifen during the treatment phase. Aromatase inhibitors are now recommended as adjuvant treatment for postmenopausal women with hormone-receptor-positive early breast cancer.[9,10] However, several questions

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See Reflection and Reaction page 8

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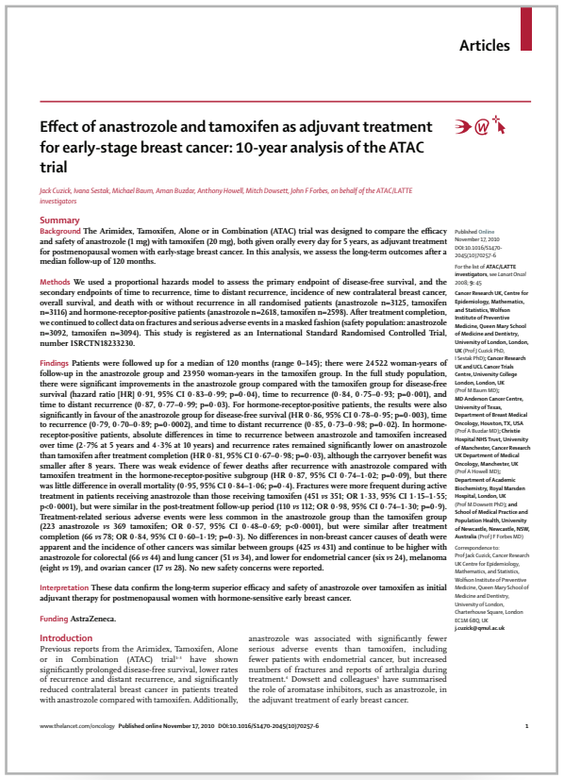
The ATAC Trialists' Group. (2008) *Lancet Oncol.*

ARIMIDEX



Articles

Effect of anastrozole and tamoxifen as adjuvant treatment for early-stage breast cancer: 10-year analysis of the ATAC trial

Jack Cuzick, Ivana Sestak, Michael Baum, Aman Buzdar, Anthony Howell, Mitch Dowsett, John F Forbes, on behalf of the ATAC/LATTE investigators

Summary

Background The Arimidex, Tamoxifen, Alone or in Combination (ATAC) trial was designed to compare the efficacy and safety of anastrozole (1 mg) with tamoxifen (20 mg), both given orally every day for 5 years, as adjuvant treatment for postmenopausal women with early-stage breast cancer. In this analysis, we assess the long-term outcomes after a median follow-up of 120 months.

Methods We used a proportional hazards model to assess the primary endpoint of disease-free survival, and the secondary endpoints of time to recurrence, time to distant recurrence, incidence of new contralateral breast cancer, overall survival, and death with or without recurrence in all randomised patients (anastrozole n=3125, tamoxifen n=3116) and hormone-receptor-positive patients (anastrozole n=2618, tamoxifen n=2598). After treatment completion, we continued to collect data on fractures and serious adverse events in a masked fashion (safety population: anastrozole n=3092, tamoxifen n=3094). This study is registered as an International Standard Randomised Controlled Trial, number ISRCTN18233230.

Findings Patients were followed up for a median of 120 months (range 0–145); there were 24 522 woman-years of follow-up in the anastrozole group and 23 950 woman-years in the tamoxifen group. In the full study population, there were significant improvements in the anastrozole group compared with the tamoxifen group for disease-free survival (hazard ratio [HR] 0·91, 95% CI 0·83–0·99; p=0·04), time to recurrence (0·84, 0·75–0·93; p=0·001), and time to distant recurrence (0·87, 0·77–0·99; p=0·03). For hormone-receptor-positive patients, the results were also significantly in favour of the anastrozole group for disease-free survival (HR 0·86, 95% CI 0·78–0·95; p=0·003), time to recurrence (0·79, 0·70–0·89; p=0·0002), and time to distant recurrence (0·85, 0·73–0·98; p=0·02). In hormone-receptor-positive patients, absolute differences in time to recurrence between anastrozole and tamoxifen increased over time (2·7% at 5 years and 4·3% at 10 years) and recurrence rates remained significantly lower on anastrozole than tamoxifen after treatment completion (HR 0·81, 95% CI 0·67–0·98; p=0·03), although the carryover benefit was smaller after 8 years. There was weak evidence of fewer deaths after recurrence with anastrozole compared with tamoxifen treatment in the hormone-receptor-positive subgroup (HR 0·87, 95% CI 0·74–1·02; p=0·09), but there was little difference in overall mortality (0·95, 95% CI 0·84–1·06; p=0·4). Fractures were more frequent during active treatment in patients receiving anastrozole than those receiving tamoxifen (451 *vs* 351; OR 1·33, 95% CI 1·15–1·55; p<0·0001), but were similar in the post-treatment follow-up period (110 *vs* 112; OR 0·98, 95% CI 0·74–1·30; p=0·9). Treatment-related serious adverse events were less common in the anastrozole group than the tamoxifen group (223 anastrozole *vs* 369 tamoxifen; OR 0·57, 95% CI 0·48–0·69; p<0·0001), but were similar after treatment completion (66 *vs* 78; OR 0·84, 95% CI 0·60–1·19; p=0·3). No differences in non-breast cancer causes of death were apparent and the incidence of other cancers was similar between groups (425 *vs* 431) and continue to be higher with anastrozole for colorectal (66 *vs* 44) and lung cancer (51 *vs* 34), and lower for endometrial cancer (six *vs* 24), melanoma (eight *vs* 19), and ovarian cancer (17 *vs* 28). No new safety concerns were reported.

Interpretation These data confirm the long-term superior efficacy and safety of anastrozole over tamoxifen as initial adjuvant therapy for postmenopausal women with hormone-sensitive early breast cancer.

Funding AstraZeneca.

Introduction

Previous reports from the Arimidex, Tamoxifen, Alone or in Combination (ATAC) trial[1–3] have shown significantly prolonged disease-free survival, lower rates of recurrence and distant recurrence, and significantly reduced contralateral breast cancer in patients treated with anastrozole compared with tamoxifen. Additionally, anastrozole was associated with significantly fewer serious adverse events than tamoxifen, including fewer patients with endometrial cancer, but increased numbers of fractures and reports of arthralgia during treatment.[1] Dowsett and colleagues[4] have summarised the role of aromatase inhibitors, such as anastrozole, in the adjuvant treatment of early breast cancer.

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For the list of ATAC/LATTE investigators, see *Lancet Oncol* 2010; 9: 45

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Cuzick J *et al.* (2010) *Lancet Oncol.*

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Clinical Papers

ZOLADEX

Goserelin Versus Cyclophosphamide, Methotrexate, and Fluorouracil as Adjuvant Therapy in Premenopausal Patients With Node-Positive Breast Cancer: The Zoladex Early Breast Cancer Research Association Study

By W. Jonat, M. Kaufmann, W. Sauerbrei, R. Blamey, J. Cuzick, M. Namer, I. Fogelman, J.C. de Haes, A. de Matteis, A. Stewart, W. Eiermann, I. Szakolczai, M. Palmer, M. Schumacher, M. Geberth, and B. Lisboa

Purpose: **Current adjuvant therapies have improved survival for premenopausal patients with breast cancer but may have short-term toxic effects and long-term effects associated with premature menopause.**

Patients and Methods: **The Zoladex Early Breast Cancer Research Association study assessed the efficacy and tolerability of goserelin (3.6 mg every 28 days for 2 years; n = 817) versus cyclophosphamide, methotrexate, and fluorouracil (CMF) chemotherapy (six 28-day cycles; n = 823) for adjuvant treatment in premenopausal patients with node-positive breast cancer.**

Results: **Analysis was performed when 684 events had been achieved, and the median follow-up was 6 years. A significant interaction between treatment and estrogen receptor (ER) status was found (*P* = .0016). In ER-positive patients (approximately 74%), goserelin was equivalent to CMF for disease-free survival (DFS) (hazard ratio [HR], 1.01; 95% confidence interval [CI], 0.84 to 1.20). In ER-negative patients, goserelin was inferior to CMF for DFS (HR, 1.76; 95% CI, 1.27 to 2.44). Amenorrhea occurred in more than 95% of goserelin patients by 6 months versus 28.6% of CMF patients. Menses returned in most goserelin patients after therapy stopped, whereas amenorrhea was generally permanent in CMF patients (22.6% v 76.9% amenorrheic at 3 years). Chemotherapy-related side effects such as nausea/vomiting, alopecia, and infection were higher with CMF than with goserelin during CMF treatment. Side effects related to estrogen suppression were initially higher with goserelin, but when goserelin treatment stopped, reduced to a level below that observed in the CMF group.**

Conclusion: **Goserelin offers an effective, well-tolerated alternative to CMF in premenopausal patients with ER-positive and node-positive early breast cancer.**

***J Clin Oncol* 20:4628-4635.** © **2002 by American Society of Clinical Oncology.**

ADJUVANT THERAPY is recommended for the majority of patients with breast cancer after local therapy (surgery with or without radiotherapy) with the aim of preventing recurrence of distant metastases and ultimately prolonging survival. The current choice of adjuvant therapy for premenopausal patients includes cytotoxic chemotherapy, ovarian ablation (by surgery or irradiation), and antiestrogen therapy (predominantly with tamoxifen).

The value of permanent ovarian ablation by surgical oophorectomy or radiotherapy as adjuvant therapy in premenopausal women younger than 50 years of age with node-positive or node-negative disease was clearly established in the Early Breast Cancer Trialists' Collaborative Group (EBCTCG) overview.[1] Ovarian ablation has been shown to have efficacy comparable to chemotherapy in both direct[2,3] and indirect[4] comparisons. The benefit of endocrine manipulation with tamoxifen in early breast cancer has also been demonstrated in patients younger than 50 years of age with estrogen receptor (ER)-positive disease.[5] Approximately 60% of premenopausal patients with primary breast cancer have ER-positive tumors.[6]

Luteinizing hormone-releasing hormone (LHRH) analogs offer an alternative form of ovarian estrogen suppression for premenopausal women. These agents have appeal in that the endocrine intervention produces reliable, targeted suppression of ovarian estrogen production, which is potentially reversible on cessation of therapy, thus avoiding the long-term morbidity associated with permanent ovarian suppression. Goserelin (Zoladex; AstraZeneca, Macclesfield, United Kingdom) is the most widely used LHRH treatment, with more than 8,500 patients involved in adjuvant trials in premenopausal women. A number of clinical trials have shown that goserelin is effective for the treatment of advanced breast cancer in premenopausal patients,[7-10] with a response rate similar to that of surgical oophorectomy or ovarian irradiation.[11,12]

The Zoladex Early Breast Cancer Research Association (ZEBRA) trial is a randomized trial directly comparing goserelin monotherapy with the cytotoxic combination regimen cyclophosphamide, methotrexate, and fluorouracil (CMF). The aims of this study were to compare the efficacy of goserelin and CMF in terms of disease-free survival (DFS) and overall survival (OS) and to compare therapy tolerability and quality of life (QoL). In addition, the effects of goserelin and CMF on bone mineral

From the Klinik fur Gynakologie und Geburtshilfe, Kiel, Universitatsklinik Frauenklinik, Frankfurt, Institute fur Medizinische Biometrie und Informatik and University Hospital, Freiburg, Frauenklinik vom Roten Kreuz, Munich, Universitätsklinikum Heidelberg, Heidelberg, and Universitätskrankenhaus Eppendorf, Hamburg, Germany; Nottingham City Hospital, Nottingham, Imperial Cancer Research Fund, Guy's and St Thomas' Hospital, London, Christie Hospital, Manchester, and AstraZeneca, Macclesfield, United Kingdom; Medicin Chef de Service du Centre-Antoine, Nice, France; University Hospital AMC, Amsterdam, the Netherlands; Istituto Nazionale Tumori, Naples, Italy; and National Institute of Oncology, Budapest, Hungary.

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0732-183X/02/2024-4628/$20.00

Jonat W *et al.*
(2002) *J Clin Oncol.*

ZOLADEX

Quality of Life in Goserelin-Treated Versus Cyclophosphamide + Methotrexate + Fluorouracil–Treated Premenopausal and Perimenopausal Patients With Node-Positive, Early Breast Cancer: The Zoladex Early Breast Cancer Research Association Trialists Group

By H. de Haes, M. Olschewski, M. Kaufmann, M. Schumacher, W. Jonat, and W. Sauerbrei

Purpose: **To compare quality of life (QoL) in premenopausal and perimenopausal patients with node-positive, early breast cancer treated with the endocrine agent goserelin (Zoladex; AstraZeneca Pharmaceuticals LP, Wilmington, DE) or cyclophosphamide + methotrexate + fluorouracil (CMF).**

Patients and Methods: **Patients from 86 centers worldwide were randomly assigned to receive either goserelin (3.6 mg every 28 days for 2 years; n = 514) or CMF (six 28-day cycles; n = 496), and were included in the QoL study. QoL was assessed using a self-administered patient questionnaire that consisted of 39 items from the Rotterdam Symptom Checklist, including dimensions evaluating physical and psychological symptom distress, activities of daily living, hormonal effects, and an assessment of overall QoL.**

Results: **Early benefits were noted during months 3 to 6 of treatment, for goserelin compared with CMF. Significant differences were found for changes in overall QoL (eg, 6.96 ± 0.88 v 0.69 ± 0.92 at 6 months; *P* < .0001) and for physical symptom distress, activity levels, and "effort to cope with illness" dimensions. At 1, 2, and 3 years, there were no significant differences in overall QoL or specific QoL dimensions. Scores for hormonal symptoms were worse with goserelin during the 2-year goserelin treatment period; however, this trend was reversed at 3 years.**

Conclusion: **Goserelin offers improved overall QoL during the first 6 months of therapy compared with CMF chemotherapy in premenopausal and perimenopausal patients with early breast cancer. Coupled with equivalent efficacy in estrogen receptor-positive patients, these data support the use of goserelin as an alternative to CMF in premenopausal and perimenopausal patients with estrogen receptor-positive, node-positive early breast cancer.**

***J Clin Oncol* 21:4510-4516.** © **2003 by American Society of Clinical Oncology.**

THE ZOLADEX Early Breast Cancer Research Association (ZEBRA) study was a large, international trial to compare goserelin (Zoladex; AstraZeneca Pharmaceuticals LP, Wilmington, DE) with the cytotoxic chemotherapy regimen cyclophosphamide + methotrexate + fluorouracil (CMF) in premenopausal and perimenopausal patients with node-positive early breast cancer. This study demonstrated that, in terms of disease-free survival, goserelin was equivalent to CMF in patients with estrogen receptor- (ER-) positive tumors, while in patients with ER-negative tumors, CMF was superior to goserelin.[1] Goserelin has a favorable adverse effect profile, and, therefore, factors such as quality of life (QoL) and patients' preferences become important in deciding which treatment to choose in the ER-positive patient population.

Studies to date have shown a range of acute and late adverse effects of adjuvant chemotherapy that have the potential to substantially affect patients' QoL. Adverse effects that may be particularly debilitating include nausea, vomiting, alopecia, and fatigue. In two large-scale clinical trials conducted by the International Breast Cancer Study Group (IBCSG VI and VII), adjuvant chemotherapy (CMF) was shown to have a measurable effect on health-related QoL during the 6-month treatment period.[2] QoL measurements have been shown to worsen during adjuvant chemotherapy, but to improve after cessation of treatment.[3]

Both CMF chemotherapy and goserelin treatment induce amenorrhea; however, while it is reversible in the majority of patients following cessation of goserelin, it is generally permanent with chemotherapy.[4] Patients in whom treatment results in permanent amenorrhea will have to endure the short- and long-term effects of an early menopause, including hot flashes, psychological and genitourinary effects, bone loss, earlier onset of osteoporosis, and an increased risk of heart disease.[5,6]

In general, goserelin has been well tolerated, with the most common adverse effects being hormonal. In the ZEBRA study, menopausal symptoms, such as vaginal dryness and hot flashes, were initially lower with CMF than with goserelin (13.9% v 23.8% and 42.4% v 72.4% at 6 months, respectively).[3] However, after the end of goserelin treatment, the incidence of these effects

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Authors' disclosures of potential conflicts of interest are found at the end of this article.

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(2013) *J Clin Oncol.*

ZOLADEX

Multicenter Randomized Clinical Trial of Goserelin Versus Surgical Ovariectomy in Premenopausal Patients With Receptor-Positive Metastatic Breast Cancer: An Intergroup Study

By Charles W. Taylor, Stephanie Green, William S. Dalton, Silvana Martino, Dorothy Rector, James N. Ingle, Nicholas J. Robert, G. Thomas Budd, Jorge C. Paradelo, Ronald B. Natale, James D. Bearden, James A. Mailliard, and C. Kent Osborne

Purpose: **To compare failure-free survival (FFS) and overall survival (OS) for patients with metastatic breast cancer treated with the gonadotropin-releasing hormone (GN-RH) agonist, goserelin versus surgical ovariectomy.**

Patients and Methods: **Between August 1, 1987 and July 15, 1995 138 (136 eligible) premenopausal patients with estrogen receptor (ER)- and/or progesterone receptor (PgR)-positive metastatic breast cancer were entered by the Southwest Oncology Group (SWOG), North Central Cancer Treatment Group (NCCTG), and Eastern Cooperative Oncology Group (ECOG). Prior chemotherapy or hormone therapy for metastatic disease was not allowed. Patients were randomly assigned to goserelin (3.6 mg subcutaneously every 4 weeks; (n = 69) versus surgical ovariectomy (n = 67). The study was initially designed as an equivalence trial with 80% power to rule out a 50% improvement in survival due to ovariectomy. However, accrual was slow and the study was terminated early, which resulted in a final power of 60% for the alternative hypothesis of equal survival distributions.**

Results: **FFS and OS were similar for goserelin and ovariectomy. The goserelin/ovariectomy death hazards ratio was .80 and the associated 95% confidence interval (CI) was .53 to 1.20. The test of 50% improvement in survival due to ovariectomy was rejected at *P* = .006. Goserelin lowered serum estradiol to postmenopausal levels. Hot flashes (75% v 46%) and tumor flare (16% v 3%) were more common with goserelin.**

Conclusion: **Goserelin and ovariectomy resulted in similar FFS and OS. We can rule out a moderate advantage for ovariectomy. Goserelin was safe and well tolerated.**

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APPROXIMATELY 100 YEARS AGO, Beatson[1] reported that endocrine ablation via ovariectomy resulted in regression of skin metastases in breast cancer patients. A number of options for endocrine ablation are currently available, including surgical procedures such as adrenalectomy, ovariectomy, and hypophysectomy; radiation ablation of the ovaries; and, more recently, chemical ablation of ovarian function using gonadotropin-releasing hormone (GN-RH) analogs. Surgical ablation of ovarian function is invasive and irreversible. Response rates to surgical ovarian ablation in premenopausal metastatic breast cancer patients range from 30% to 75%, with higher response rates occurring in patients selected for positive estrogen receptor (ER) and/or progesterone receptor (PgR) status.[2] However, these results also indicate that approximately 50% of premenopausal patients with metastatic breast cancer do not respond to ovarian ablation, even though their tumors may be receptor-positive. Radiation can also effectively reduce ovarian function, and comparative studies with surgical ablation show similar clinical results.[3] However, exposure of patients to pelvic irradiation can make delivery of subsequent palliative chemotherapy more difficult.

The GN-RH analog, goserelin (Zoladex; Zeneca Pharmaceuticals, Wilmington, DE) has been studied in a number of phase II clinical trials in premenopausal patients with

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ZOLADEX

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Survival analyses from the ZEBRA study: goserelin (Zoladex™) versus CMF in premenopausal women with node-positive breast cancer

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Abstract

The Zoladex Early Breast Cancer Research Association (ZEBRA) trial compared the efficacy and tolerability of goserelin (Zoladex™) with cyclophosphamide, methotrexate and 5-fluorouracil (CMF) chemotherapy in pre-/perimenopausal women with node-positive early breast cancer. The results of disease-free survival (DFS) analyses have already been published. Here we present an update including data on overall survival (OS) from the ZEBRA trial at a median follow-up of 7.3 years. In patients with oestrogen receptor (ER)-positive tumours, non-inferiority of goserelin versus CMF for OS was shown; goserelin was again shown to be equivalent to CMF for DFS. This updated analysis has demonstrated that the two treatments are also equivalent for distant disease-free survival (DDFS). In patients with ER-negative disease, goserelin was inferior to CMF for DFS, DDFS and OS. This follow-up analysis confirms the previously reported outcomes from the ZEBRA trial and demonstrates that goserelin offers an effective alternative to CMF chemotherapy for adjuvant therapy of premenopausal patients with ER-positive, node-positive early breast cancer.

Keywords: Breast cancer; Premenopausal; Ovarian ablation; Chemotherapy; Goserelin; CMF

1. Introduction

Lowering of circulating female hormone levels may be achieved through surgical oophorectomy, radiotherapeutic ablation or pharmacological ovarian suppression. Oophorectomy and ablation result in a permanent, early menopause, with the associated side-effects. Similarly, chemotherapy induces a premature and permanent menopause in many women. Goserelin is a luteinising hormone-releasing hormone (LHRH) analogue that produces a reliable, specific suppression of ovarian oestrogen production that is reversible at the end of therapy in most women [1–3]. In advanced breast cancer, goserelin has been shown to be effective and well tolerated, resulting in a similar clinical benefit to surgical oophorectomy or ovarian irradiation [4,5].

Because of the marked efficacy and beneficial tolerability of goserelin in advanced breast cancer, a number of adjuvant studies have been initiated involving > 8000 patients [6]. The Zoladex Early Breast Cancer Research Association (ZEBRA) trial was designed to directly compare the efficacy and tolerability of goserelin with

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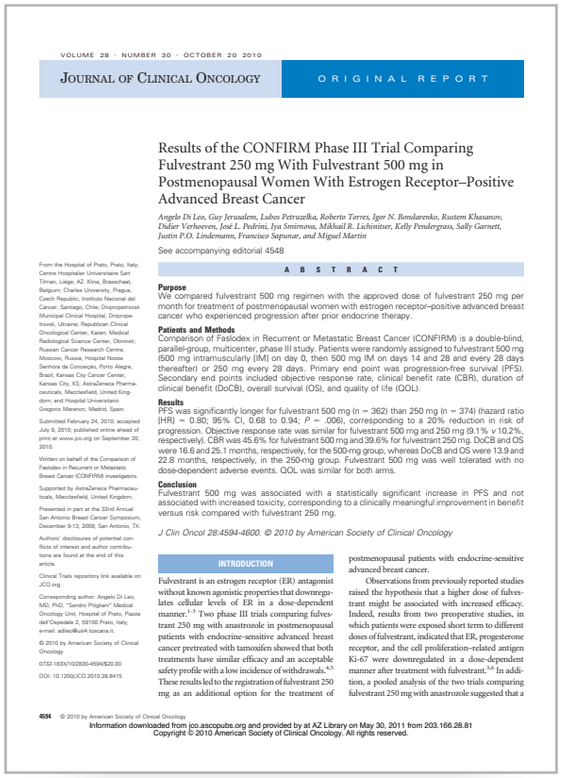

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JOURNAL OF CLINICAL ONCOLOGY | ORIGINAL REPORT

Results of the CONFIRM Phase III Trial Comparing Fulvestrant 250 mg With Fulvestrant 500 mg in Postmenopausal Women With Estrogen Receptor–Positive Advanced Breast Cancer

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See accompanying editorial 4548

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A B S T R A C T

Purpose

We compared fulvestrant 500 mg regimen with the approved dose of fulvestrant 250 mg per month for treatment of postmenopausal women with estrogen receptor–positive advanced breast cancer who experienced progression after prior endocrine therapy.

Patients and Methods

Comparison of Faslodex in Recurrent or Metastatic Breast Cancer (CONFIRM) is a double-blind, parallel-group, multicenter, phase III study. Patients were randomly assigned to fulvestrant 500 mg (500 mg intramuscularly [IM] on day 0, then 500 mg IM on days 14 and 28 and every 28 days thereafter) or 250 mg every 28 days. Primary end point was progression-free survival (PFS). Secondary end points included objective response rate, clinical benefit rate (CBR), duration of clinical benefit (DoCB), overall survival (OS), and quality of life (QOL).

Results

PFS was significantly longer for fulvestrant 500 mg (n = 362) than 250 mg (n = 374) (hazard ratio [HR] = 0.80; 95% CI, 0.68 to 0.94; $P = .006$), corresponding to a 20% reduction in risk of progression. Objective response rate was similar for fulvestrant 500 mg and 250 mg (9.1% v 10.2%, respectively). CBR was 45.6% for fulvestrant 500 mg and 39.6% for fulvestrant 250 mg. DoCB and OS were 16.6 and 25.1 months, respectively, for the 500-mg group, whereas DoCB and OS were 13.9 and 22.8 months, respectively, in the 250-mg group. Fulvestrant 500 mg was well tolerated with no dose-dependent adverse events. QOL was similar for both arms.

Conclusion

Fulvestrant 500 mg was associated with a statistically significant increase in PFS and not associated with increased toxicity, corresponding to a clinically meaningful improvement in benefit versus risk compared with fulvestrant 250 mg.

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INTRODUCTION

Fulvestrant is an estrogen receptor (ER) antagonist without known agonistic properties that downregulates cellular levels of ER in a dose-dependent manner.[1-3] Two phase III trials comparing fulvestrant 250 mg with anastrozole in postmenopausal patients with endocrine-sensitive advanced breast cancer pretreated with tamoxifen showed that both treatments have similar efficacy and an acceptable safety profile with a low incidence of withdrawals.[4,5] These results led to the registration of fulvestrant 250 mg as an additional option for the treatment of postmenopausal patients with endocrine-sensitive advanced breast cancer.

Observations from previously reported studies raised the hypothesis that a higher dose of fulvestrant might be associated with increased efficacy. Indeed, results from two preoperative studies, in which patients were exposed short term to different doses of fulvestrant, indicated that ER, progesterone receptor, and the cell proliferation–related antigen Ki-67 were downregulated in a dose-dependent manner after treatment with fulvestrant.[6,7] In addition, a pooled analysis of the two trials comparing fulvestrant 250 mg with anastrozole suggested that a

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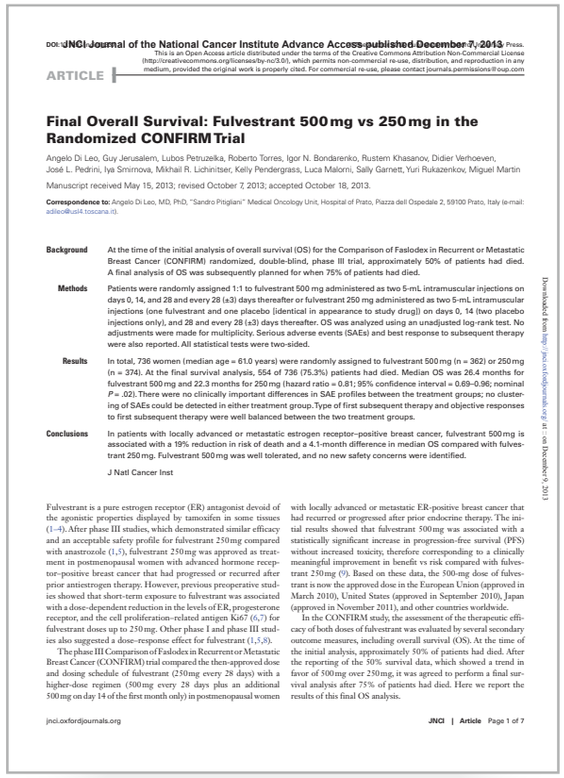

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ARTICLE

Final Overall Survival: Fulvestrant 500 mg vs 250 mg in the Randomized CONFIRM Trial

Angelo Di Leo, Guy Jerusalem, Lubos Petruzelka, Roberto Torres, Igor N. Bondarenko, Rustem Khasanov, Didier Verhoeven, José L. Pedrini, Iya Smirnova, Mikhail R. Lichinitser, Kelly Pendergrass, Luca Malorni, Sally Garnett, Yuri Rukazenkov, Miguel Martin

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Background At the time of the initial analysis of overall survival (OS) for the Comparison of Faslodex in Recurrent or Metastatic Breast Cancer (CONFIRM) randomized, double-blind, phase III trial, approximately 50% of patients had died. A final analysis of OS was subsequently planned for when 75% of patients had died.

Methods Patients were randomly assigned 1:1 to fulvestrant 500 mg administered as two 5-mL intramuscular injections on days 0, 14, and 28 and every 28 (±3) days thereafter or fulvestrant 250 mg administered as two 5-mL intramuscular injections (one fulvestrant and one placebo [identical in appearance to study drug]) on days 0, 14 (two placebo injections only), and 28 and every 28 (±3) days thereafter. OS was analyzed using an unadjusted log-rank test. No adjustments were made for multiplicity. Serious adverse events (SAEs) and best response to subsequent therapy were also reported. All statistical tests were two-sided.

Results In total, 736 women (median age = 61.0 years) were randomly assigned to fulvestrant 500 mg (n = 362) or 250 mg (n = 374). At the final survival analysis, 554 of 736 (75.3%) patients had died. Median OS was 26.4 months for fulvestrant 500 mg and 22.3 months for 250 mg (hazard ratio = 0.81; 95% confidence interval = 0.69–0.96; nominal $P = .02$). There were no clinically important differences in SAE profiles between the treatment groups; no clustering of SAEs could be detected in either treatment group. Type of first subsequent therapy and objective responses to first subsequent therapy were well balanced between the two treatment groups.

Conclusions In patients with locally advanced or metastatic estrogen receptor–positive breast cancer, fulvestrant 500 mg is associated with a 19% reduction in risk of death and a 4.1-month difference in median OS compared with fulvestrant 250 mg. Fulvestrant 500 mg was well tolerated, and no new safety concerns were identified.

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Fulvestrant is a pure estrogen receptor (ER) antagonist devoid of the agonistic properties displayed by tamoxifen in some tissues (1–4). After phase III studies, which demonstrated similar efficacy and an acceptable safety profile for fulvestrant 250 mg compared with anastrozole (1,5), fulvestrant 250 mg was approved as treatment in postmenopausal women with advanced hormone receptor-positive breast cancer that had progressed or recurred after prior antiestrogen therapy. However, previous preoperative studies showed that short-term exposure to fulvestrant was associated with a dose-dependent reduction in the levels of ER, progesterone receptor, and the cell proliferation–related antigen Ki67 (6,7) for fulvestrant doses up to 250 mg. Other phase I and phase III studies also suggested a dose–response effect for fulvestrant (1,3,8).

The phase III Comparison of Faslodex in Recurrent or Metastatic Breast Cancer (CONFIRM) trial compared the then-approved dose and dosing schedule of fulvestrant (250 mg every 28 days) with a higher-dose regimen (500 mg every 28 days plus an additional 500 mg on day 14 of the first month only) in postmenopausal women with locally advanced or metastatic ER-positive breast cancer that had recurred or progressed after prior endocrine therapy. The initial results showed that fulvestrant 500 mg was associated with a statistically significant increase in progression-free survival (PFS) without increased toxicity, therefore corresponding to a clinically meaningful improvement in benefit vs risk compared with fulvestrant 250 mg (9). Based on these data, the 500-mg dose of fulvestrant is now the approved dose in the European Union (approved in March 2010), United States (approved in September 2010), Japan (approved in November 2011), and other countries worldwide.

In the CONFIRM study, the assessment of the therapeutic efficacy of both doses of fulvestrant was evaluated by several secondary outcome measures, including overall survival (OS). At the time of the initial analysis, approximately 50% of patients had died. After the reporting of the 50% survival data, which showed a trend in favor of 500 mg over 250 mg, it was agreed to perform a final survival analysis after 75% of patients had died. Here we report the results of this final OS analysis.

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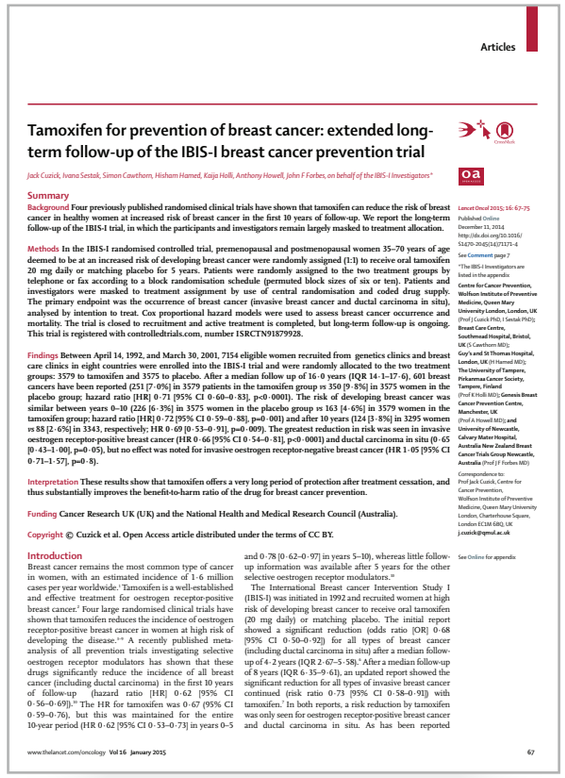

Tamoxifen for prevention of breast cancer: extended long-term follow-up of the IBIS-I breast cancer prevention trial

*Jack Cuzick, Ivana Sestak, Simon Cawthorn, Hisham Hamed, Kaija Holli, Anthony Howell, John F Forbes, on behalf of the IBIS-I Investigators**

Summary

Background **Four previously published randomised clinical trials have shown that tamoxifen can reduce the risk of breast cancer in healthy women at increased risk of breast cancer in the first 10 years of follow-up. We report the long-term follow-up of the IBIS-I trial, in which the participants and investigators remain largely masked to treatment allocation.**

Methods **In the IBIS-I randomised controlled trial, premenopausal and postmenopausal women 35–70 years of age deemed to be at an increased risk of developing breast cancer were randomly assigned (1:1) to receive oral tamoxifen 20 mg daily or matching placebo for 5 years. Patients were randomly assigned to the two treatment groups by telephone or fax according to a block randomisation schedule (permuted block sizes of six or ten). Patients and investigators were masked to treatment assignment by use of central randomisation and coded drug supply. The primary endpoint was the occurrence of breast cancer (invasive breast cancer and ductal carcinoma in situ), analysed by intention to treat. Cox proportional hazard models were used to assess breast cancer occurrence and mortality. The trial is closed to recruitment and active treatment is completed, but long-term follow-up is ongoing. This trial is registered with controlledtrials.com, number ISRCTN91879928.**

Findings **Between April 14, 1992, and March 30, 2001, 7154 eligible women recruited from genetics clinics and breast care clinics in eight countries were enrolled into the IBIS-I trial and were randomly allocated to the two treatment groups: 3579 to tamoxifen and 3575 to placebo. After a median follow-up of 16·0 years (IQR 14·1–17·6), 601 breast cancers have been reported (251 [7·0%] in 3579 patients in the tamoxifen group vs 350 [9·8%] in 3575 women in the placebo group; hazard ratio [HR] 0·72 [95% CI 0·60–0·83], p<0·0001). The risk of developing breast cancer was similar between years 0–10 (226 [6·3%] in 3575 women in the placebo group vs 163 [4·6%] in 3579 women in the tamoxifen group; hazard ratio [HR] 0·72 [95% CI 0·59–0·88], p=0·001) and after 10 years (124 [3·8%] in 3295 women vs 88 [2·6%] in 3343, respectively; HR 0·69 [0·53–0·91], p=0·009). The greatest reduction in risk was seen in invasive oestrogen receptor-positive breast cancer (HR 0·66 [95% CI 0·54–0·81], p<0·0001) and ductal carcinoma in situ (0·65 [0·43–1·00], p=0·05), but no effect was noted for invasive oestrogen receptor-negative breast cancer (HR 1·05 [95% CI 0·71–1·57], p=0·8).**

Interpretation **These results show that tamoxifen offers a very long period of protection after treatment cessation, and thus substantially improves the benefit-to-harm ratio of the drug for breast cancer prevention.**

Funding **Cancer Research UK (UK) and the National Health and Medical Research Council (Australia).**

Introduction

Breast cancer remains the most common type of cancer in women, with an estimated incidence of 1·6 million cases per year worldwide.[1] Tamoxifen is a well-established and effective treatment for oestrogen receptor-positive breast cancer.[2] Four large randomised clinical trials have shown that tamoxifen reduces the incidence of oestrogen receptor-positive breast cancer in women at high risk of developing the disease.[3–6] A recently published meta-analysis of all prevention trials investigating selective oestrogen receptor modulators has shown that these drugs significantly reduce the incidence of all breast cancer (including ductal carcinoma) in the first 10 years of follow-up (hazard ratio [HR] 0·62 [95% CI 0·56–0·69]).[6] The HR for tamoxifen was 0·67 (95% CI 0·59–0·76), but this was maintained for the entire 10-year period (HR 0·62 [95% CI 0·53–0·73] in years 0–5 and 0·78 [0·62–0·97] in years 5–10), whereas little follow-up information was available after 5 years for the other selective oestrogen receptor modulators.[6]

The International Breast cancer Intervention Study I (IBIS-I) was initiated in 1992 and recruited women at high risk of developing breast cancer to receive oral tamoxifen (20 mg daily) or matching placebo. The initial report showed a significant reduction (odds ratio [OR] 0·68 [95% CI 0·50–0·92]) for all types of breast cancer (including ductal carcinoma in situ) after a median follow-up of 4·2 years (IQR 2·67–5·58).[4] After a median follow-up of 8 years (IQR 6·35–9·61), an updated report showed the significant reduction for all types of invasive breast cancer continued (risk ratio 0·73 [95% CI 0·58–0·91]) with tamoxifen.[7] In both reports, a risk reduction by tamoxifen was only seen for oestrogen receptor-positive breast cancer and ductal carcinoma in situ. As has been reported

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See Online for appendix

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