# 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

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***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 58.6% 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.**

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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

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density have been measured. Data for the QoL and bone mineral density substudies will be published separately.

## PATIENTS AND METHODS

### *Study Design*

The ZEBRA study is an international, multicenter, open, randomized study initiated in 1990 in premenopausal patients with node-positive early breast cancer. Patients were recruited over a 6-year period between October 1, 1990, and December 30, 1996, from 102 centers in 15 countries. Randomization of patients onto the study took place by the investigator contacting the Institute of Medical Biometry and Informatics at Freiburg, Germany, where the randomization was performed centrally. If a patient was compliant with inclusion and exclusion criteria, a patient number and the appropriate treatment were assigned to the patient from a central randomization list. Patients were stratified for randomization by center, and within each center randomized blocks with a block length of six or eight chosen at random were used. After local therapy for breast cancer (mastectomy or breast-conserving therapy with or without radiotherapy, according to local practice), patients were randomized in a 1:1 ratio to receive goserelin or CMF chemotherapy.

Information on ER status was not mandatory for entry but was encouraged, because analysis by ER status was a protocoled intention and centers could decide to enter only ER-positive patients if they wished. Trial treatment continued for the protocoled period unless a treatment end point was reached. Treatment end points were as follows: disease recurrence (including second primary cancer), death, serious possible adverse drug reaction, patient unwilling or unable to continue, retrospective recognition of violation of inclusion or exclusion criteria, use of nontrial systemic treatment, and investigator decision (the local investigator was allowed to withdraw the patient if he thought it was in the patient's best interest). Treatment after recurrence was not specified in the protocol and was performed according to local management practice at each center. If first recurrence was in the breast or breast region, protocoled follow-up was continued to first distant metastases. All patients were followed up to death. The study was conducted in accordance with Good Clinical Practice guidelines and the Declaration of Helsinki and after approval by the local ethics committee at each center.

### *Patient Population*

Patients were eligible if they were pre- or perimenopausal and $\leq$ 50 years of age; had node-positive (International Union Against Cancer) stage II histologically proven operable invasive breast cancer with no evidence of metastatic disease, which was excluded by primary tumor, regional lymph node, and distant metastases criteria; and had not received previous systemic therapy. If there was doubt about menopausal status, pre- or perimenopausal status was confirmed by a follicle-stimulating hormone level less than 30 IU/mL. All patients gave their informed consent to participate in the trial. Patients were excluded if they had concurrent or previous invasive malignancy (except squamous- or basal-cell skin carcinoma or cervical carcinoma), had received bilateral oophorectomy or radiation of the ovaries, were pregnant or breast-feeding, had inadequate liver function (serum bilirubin $>$ 1.25 times upper limit of normal [ULN] and AST or ALT $>$ two times ULN) or renal function (serum creatinine $>$ 1.5 times ULN), or had evidence of blood disorders (WBC count $<$ 3,000/mm$^3$ or platelet count $<$ 100,000/mm$^3$).

### *Treatment*

Patients received goserelin 3.6 mg depot subcutaneously (every 28 days for 2 years, ie, 26 depots) or CMF chemotherapy (six cycles, each cycle being 28 days unless treatment was delayed).[13] The duration of goserelin treatment was derived from the recommended duration of adjuvant tamoxifen at the time at which the study was initiated. A cycle of CMF consisted of cyclophosphamide (500 mg/m$^2$ intravenously [IV] on days 1 and 8, or 100 mg/m$^2$ orally on days 1 through 14), methotrexate (40 mg/m$^2$ IV on days 1 and 8), and fluorouracil (600 mg/m$^2$ IV on days 1 and 8).

### *Efficacy Parameters*

The primary efficacy parameters were DFS and OS. DFS was defined as the interval from date of randomization to the date of confirmed tumor recurrence, secondary primary cancer, or death. OS was defined as the interval from the date of randomization to the date of death from any cause. Menstrual status was recorded at each visit as normal, menorrhagia, oligomenorrhea, or amenorrhea. These classifications were not formally defined in the protocol but were assessed by the investigator based on their assessment of the patients' menstrual status at the time.

### *Measurement of Tumor Receptor Status*

ER and/or progesterone receptor status of the tumor was analyzed prospectively at study entry at centers where it was standard practice at the time of recruitment onto the trial. Tumor receptor status was derived from a review procedure of the assays used by each trial center, by reassessment of some values, and by retrospective measurement of missing values. To standardize this information, the Tenovus Cancer Research Centre (Cardiff, United Kingdom) reviewed all the data in order to apply consistent cutoff levels for determining tumor receptor status that could be applied across the different assay procedures. After a literature review of contemporary receptor assay methodologies and consultation of experts, common receptor status cutoff levels were derived that reflected the most current views regarding definitions of receptor positivity/negativity.

Tumors were recorded as receptor-positive according to the following cutoff values from the various assays used: dextran-coated charcoal/radioligand assay ($\geq$ 10 fmol/mg), enzyme immunoassay ($\geq$ 20 fmol/mg), immunohistochemistry assay, immunoreactivity score ($\geq$ 2), percentage positive (stained) cells ($\geq$ 10%), or HScore ($\geq$ 20). Original laboratory parameters were applied to enzyme-multiplied immunosorbent, enzyme-linked immunosorbent radioimmunosorbent, and radioimmunosorbent assays. Where tumor receptor status was not recorded at the time of recruitment, stored tumor samples were sent to Nottingham City Hospital (Nottingham, United Kingdom) for analysis. Tumors were then categorized as receptor-positive, receptor-negative, or unknown/unassessable for estrogen and progesterone by independent experts at the Tenovus Cancer Research Centre who were blinded to treatment allocation and outcome.

### *Safety*

Safety was assessed by overall therapy tolerance and the occurrence of adverse events. At baseline, patients underwent a physical examination, routine hematology tests (hemoglobin, leukocytes, platelets, and granulocytes), biochemistry tests (bilirubin, liver transferases, alkaline phosphatase, blood urea, and creatinine), a chest x-ray, and a bone scan or skeletal survey. If liver function tests were abnormal, liver ultrasound or computed tomography was also performed. Further assessments were then made every 12 weeks until 96 weeks, at 2 years, at 2.5 years, at 3 years, and then annually up to 10 years and also at recurrence. Follow-up assessments included routine hematology and biochemistry studies (up to 3 years), a physical examination, and other safety tests at the discretion of the investigator and in patients demonstrating symptoms commonly associated with the trial therapies. Such symptoms were elicited and included hematologic, biochemical, and physical/psychologic symptoms (oral soreness/ulceration, nausea/vomiting, diarrhea, impairment of appetite, weight gain, epigastric pain, infection, cystitis, alopecia, depression, vaginal dryness/soreness, impairment of libido, and hot flashes). These were recorded on specifically designed tolerance case report forms. Grading of severity followed World Health Organization (WHO) criteria.[14] Possible adverse drug reactions that were fatal or life threatening, caused or prolonged hospitalization, caused disability or permanent incapacity, or led to withdrawal were, if considered to be related to trial therapy, detailed in adverse event reports. All other possible adverse reactions were recorded on adverse event case report forms.

### *Statistical Analysis*

The study was designed as an equivalence trial powered at 80% to compare goserelin with CMF and, as such, at least 688 events were required to demonstrate equivalence in DFS.[15] To achieve this number of events, as many as 1,700 patients in total were required (allowing for ineligibility). Clinical and statistical criteria for equivalence were defined in advance as a hazard ratio for DFS and OS and 95% confidence intervals (CIs) lying entirely within the range of 0.80 to 1.25. Subsidiary analyses were defined in advance in terms of ER status and age. Power calculations were determined on the basis of DFS. DFS and OS curves were calculated using the Kaplan-Meier method. Cox proportional hazards regression models were

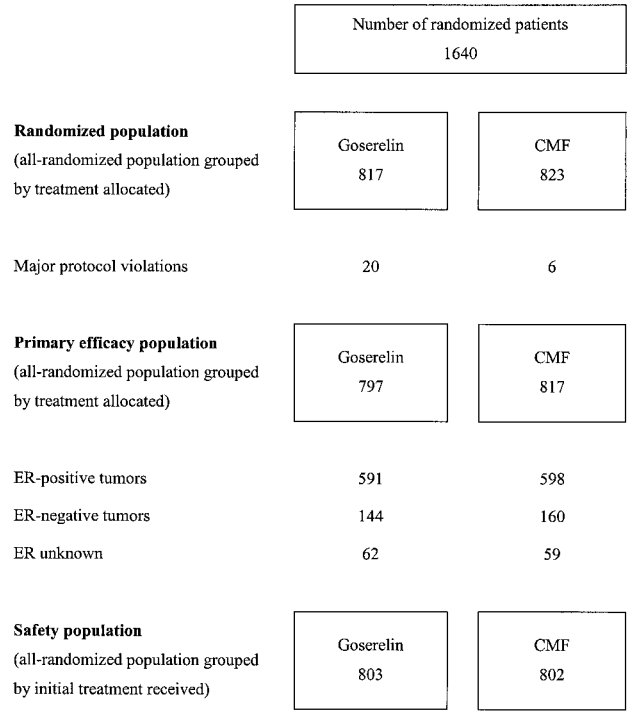



**Fig 1. Defined patient populations within the ZEBRA study.**

used to assess DFS and OS between the two randomized treatment groups and according to protocol for assessment of equivalence in DFS and OS according to ER status. As protocoled, treatment effect was adjusted for age (< 40 years, ≥ 40 years), tumor size (≤ 20 mm, > 20 mm), and the number of positive lymph nodes (one to three, four to nine, ≥ 10). The effect of ER status on the hazard ratio was estimated by adding a binary variable for ER status and a variable for interaction with treatment in the final model.

The primary efficacy population included all randomized patients except those with major protocol violations (postmenopausal, evidence of distant metastases at entry, other concurrent or previous malignancy, previous systemic breast cancer therapy, oophorectomy or radiotherapy of the ovaries, current pregnancy or breast-feeding, or lack of informed consent). Patients were analyzed in the group to which they were randomly allocated.

A retrospective analysis was performed to investigate the possible prognostic effect of chemotherapy-induced amenorrhea on DFS. Subgroups were defined on the basis of assessments at 36 weeks as amenorrhea versus normal menstrual status, oligomenorrhea, and menorrhagia (ie, excluding patients with hysterectomy and missing data) at 36 weeks (12 weeks after chemotherapy). The effect was estimated in a model adjusting for age, the number of positive lymph nodes, and tumor size.

## RESULTS

### *Patient Characteristics*

A total of 1,640 women entered the trial (goserelin, n = 817; CMF, n = 823) (Fig 1). Among these, a small number of patients (n = 26) had major protocol violations (goserelin, n = 20; CMF, n = 6) and were not included in the primary efficacy population. The greater number of protocol violators in the goserelin group was mainly because of differences in the number of patients who were postmenopausal at baseline (10 *v* three for goserelin and CMF, respectively). Each of the other major protocol violations occurred in four or fewer patients treated with either goserelin or CMF, and included evidence of distant metastases, previous systemic therapy for breast cancer, and concurrent or previous invasive malignancy. The primary efficacy population therefore included 1,614 patients: 797 patients randomized to goserelin and 817 patients randomized to CMF.

**Table 1. Patient and Disease Characteristics at Baseline**

| Characteristic | Goserelin (n = 797) No. | % | CMF (n = 817) No. | % |
|---|---|---|---|---|
| Age | | | | |
| < 40 years | 202 | 25.4 | 198 | 24.2 |
| 40-45 years | 326 | 40.9 | 345 | 42.2 |
| 46-50 years* | 269 | 33.8 | 274 | 33.5 |
| Menstrual and hysterectomy status | | | | |
| Normal | 666 | 83.6 | 710 | 87.0 |
| Menorrhagia | 9 | 1.1 | 20 | 2.4 |
| Oligomenorrhea | 37 | 4.6 | 36 | 4.4 |
| Amenorrhea | 12 | 1.5 | 7 | 0.9 |
| Hysterectomy | 68 | 8.5 | 40 | 4.9 |
| Unknown | 5 | 0.6 | 4 | 0.5 |
| No. of positive nodes | | | | |
| At least one (unspecified) | 2 | 0.3 | 2 | 0.2 |
| 1-3† | 556 | 69.8 | 580 | 71.0 |
| 4-9 | 205 | 25.7 | 202 | 24.7 |
| ≥ 10 | 28 | 3.5 | 26 | 3.2 |
| Unknown | 6 | 0.8 | 7 | 0.9 |
| Size of tumor | | | | |
| ≤ 10 mm | 52 | 6.5 | 83 | 10.2 |
| 11-20 mm | 309 | 38.7 | 308 | 37.7 |
| 21-30 mm | 269 | 33.8 | 264 | 32.3 |
| 31-40 mm | 113 | 14.3 | 91 | 11.1 |
| 41-50 mm‡ | 49 | 6.1 | 62 | 7.6 |
| Unknown | 5 | 0.6 | 9 | 1.1 |
| Grade of tumor | | | | |
| I G1 | 75 | 9.4 | 85 | 10.4 |
| II G2 | 382 | 47.9 | 403 | 49.3 |
| III G3 | 243 | 30.5 | 218 | 26.7 |
| Unknown | 97 | 12.2 | 111 | 13.6 |
| Estrogen receptor status | | | | |
| Positive | 591 | 74.2 | 598 | 73.2 |
| Negative | 144 | 18.1 | 160 | 19.6 |
| Unknown | 62 | 7.8 | 59 | 7.2 |
| Progesterone receptor status | | | | |
| Positive | 540 | 67.8 | 525 | 64.3 |
| Negative | 119 | 14.9 | 150 | 18.4 |
| Unknown | 138 | 17.3 | 142 | 17.4 |
| Local therapy | | | | |
| Breast-conserving therapy alone | 15 | 1.9 | 8 | 1.0 |
| Breast-conserving therapy plus radiotherapy | 365 | 45.8 | 369 | 45.2 |
| Mastectomy alone | 239 | 30.0 | 244 | 29.9 |
| Mastectomy plus radiotherapy | 178 | 22.3 | 196 | 24.0 |

*Five patients > 50 years of age included.
†Two node-negative patients included.
‡Nine patients with tumor size > 50 mm included.

The treatment groups were similar with respect to patient characteristics (age, menstrual status), primary tumor characteristics (tumor size, tumor grade, ER status, number of positive nodes), and local therapy or radiotherapy (Table 1). Overall, 70% of patients had one to three positive nodes and 25% had four to nine positive nodes. ER status was known for 92.5% of patients; 80% of these patients had ER-positive tumors.

### *Treatment Compliance*

In the primary efficacy population, 25 patients randomized to goserelin refused to start with this treatment, seven of whom chose CMF. In contrast, 29 of the patients randomized to CMF refused to start with this treatment, 16 of whom chose goserelin. Of the remaining 1,560 patients (other than stopping treatment for recurrence or death; n = 144), 86.8% of goserelin patients received the full course of 26 depots, 3.3% stopped treatment early (≤ six depots), 1.4% received seven to 12 depots, 5.1% received 13 to 25 depots, and 3.3% continued with goserelin

**Table 2. Effect of CMF and Goserelin Treatment on DFS and OS Estimated in a Protocoled Model Adjusted for Age, Tumor Size, and Number of Positive Lymph Nodes**

| Subgroup | DFS | | | OS | | |
|---|---|---|---|---|---|---|
| | HR* | 95% CI | *P* | HR | 95% CI | *P* |
| Primary efficacy population (n = 1,614) | 1.18 | 1.02-1.37 | .029 | 1.21 | 0.99-1.49 | .067 |
| ER-positive patients (n = 1,189) | 1.01 | 0.84-1.20 | .94 | 0.99 | 0.76-1.28 | .92 |
| ER-negative patients (n = 304) | 1.76 | 1.27-2.44 | .0006 | 1.77 | 1.19-2.63 | .0043 |
| ER-unknown patients (n = 121) | 2.00 | 1.07-3.75 | .026 | 1.81 | 0.81-4.05 | .14 |

NOTE. Number of events for DFS, number of events for OS: ER-positive (487,225), ER-negative (147,104), ER-unknown (50, 30).
*The HR compares goserelin with CMF; a ratio < 1.0 favors goserelin.

after the full course up to a maximum of 35 depots. Patients without recurrence in the first 6 months usually completed all six cycles of CMF (93.1%), 4.4% stopped treatment between cycles 1 and 3, and 2.6% stopped treatment between cycles 4 and 5. Cycles of CMF were delayed in 20.1% of cases for longer than 1 week. Of those patients who received CMF, 83.3% had intravenous and 16.6% had oral cyclophosphamide.

*Efficacy Evaluation*

*DFS.* Analysis was performed after 684 events had occurred. In total, 357 patients (44.8%) randomized to goserelin and 327 patients (40.0%) randomized to CMF had an event (ie, disease recurrence, secondary primary cancer, or death) during a median follow-up of 6 years. Local (13.8% *v* 11.0%) and distant recurrences including contralateral breast cancer (28.3% *v* 26.2%), second primary cancers (2.4% *v* 2.1%), or deaths (0.3% *v* 0.7%) were comparable between treatment groups (goserelin *v* CMF). In the protocoled model, all three factors—age, tumor size, and number of positive lymph nodes—had a significant prognostic impact on DFS. In the primary efficacy population, goserelin was inferior to CMF for DFS (hazard ratio [HR], 1.18; 95% CI, 1.02 to 1.37; $P = .029$). However, in the protocoled DFS analysis, a highly significant interaction between treatment and ER status was observed ($P = .0016$). Thus, the results for the protocoled ER subgroups have been considered separately in order to draw meaningful conclusions (Table 2). In ER-positive patients, goserelin was equivalent to CMF for DFS (HR, 1.01; 95% CI, 0.84 to 1.20; $P = .94$) (Fig 2). In ER-negative patients, goserelin was inferior to CMF for DFS (HR, 1.76; 95% CI, 1.27 to 2.44; $P = .0006$) (Fig 3).

In the subgroup of ER-unknown patients, CMF was superior to goserelin (HR, 2.00; 95% CI, 1.07 to 3.75; $P = .026$). However, as only a small number of patients in the study population had unknown ER status (n = 121), the number of DFS events in this subgroup was low: 29 of 62 (45.6%) in the goserelin group and 21 of 59 (35.6%) in the CMF group (Table 2).

The statistical analysis also looked for a significant treatment by nodal status interaction. The analysis indicated no evidence of a relative goserelin/CMF difference on the basis of nodal status, thus indicating consistent results across the nodal subgroups. Subgroup analysis on the nodal subgroups was not protocoled and was not performed.

The relative effects of goserelin and CMF were similar across the different age subgroups; however, these were too small for definitive conclusions. In the group of patients randomized to CMF, a retrospective, nonrandomized comparison showed there was a significant improvement in DFS in patients who were amenorrheic at 36 weeks compared with those who were not (HR, 0.65; 95% CI, 0.48 to 0.87; $P = .005$) (Fig 4). Patients who had an event before 36 weeks were excluded from this analysis.

*OS.* In the primary efficacy population, deaths were recorded in 194 patients (24.3%) randomized to goserelin and 165 patients (20.2%) randomized to CMF during a median follow-up of 6 years. Among these deaths, 183 and 151 were attributable to breast cancer in the goserelin and CMF groups, respectively. The treatment by ER status interaction was highly significant for overall survival ($P = .0131$). This indicated that the treatment effects were different in the different ER subgroups and therefore should be reported separately. The results for OS reflect the results for DFS but with less maturity (Table 2): ER-positive

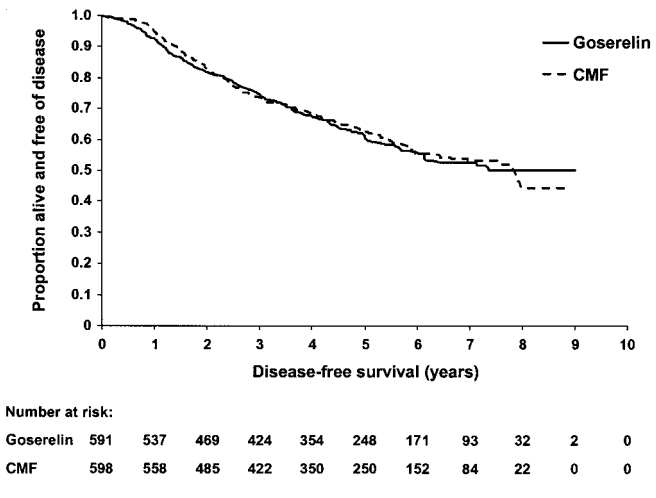



Fig 2. Kaplan-Meier analysis of DFS in ER-positive patients.

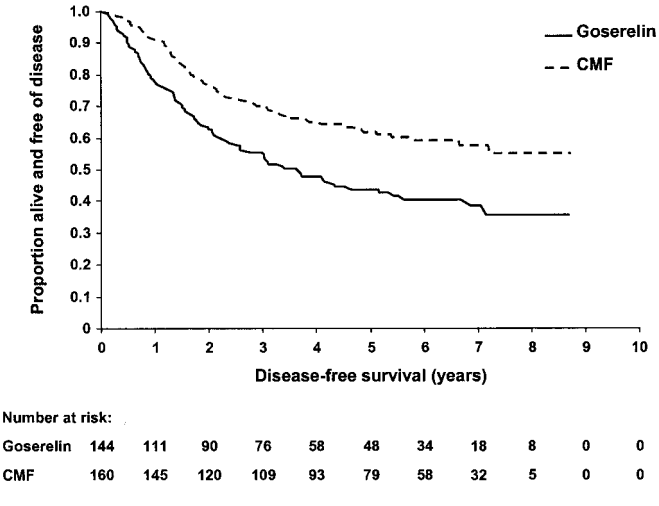
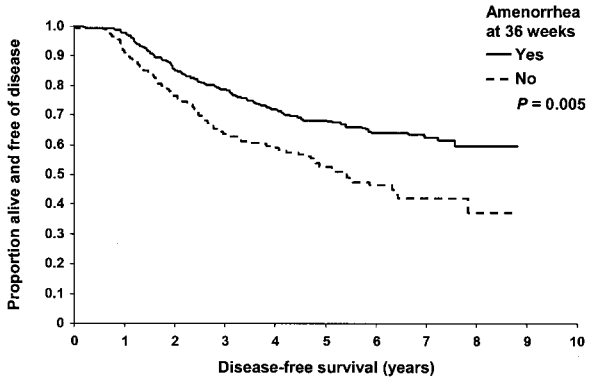


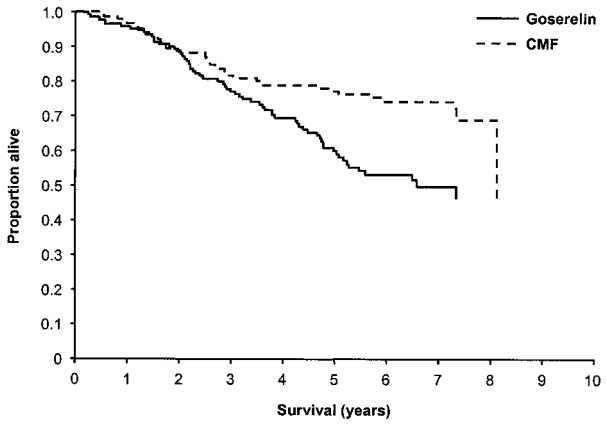

Fig 3. Kaplan-Meier analysis of DFS in ER-negative patients.




Number at risk:

| | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|
| Amenorrhea | 408 | 398 | 347 | 313 | 257 | 201 | 134 | 78 | 17 | 0 | 0 |
| No amenorrhea | 204 | 187 | 156 | 126 | 107 | 69 | 40 | 20 | 6 | 0 | 0 |

**Fig 4. Kaplan-Meier analysis of DFS in CMF-treated patients according to menstrual status at 36 weeks.**




Number at risk:

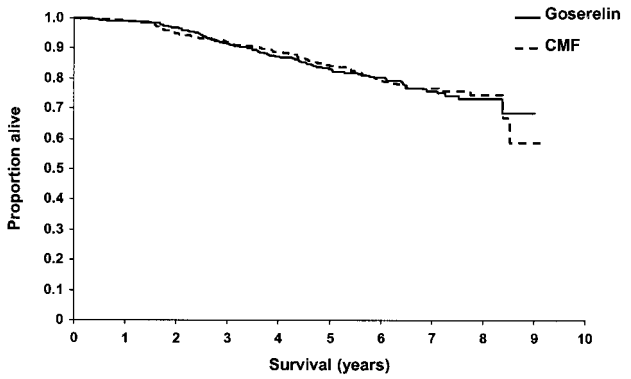
| | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|
| Goserelin | 142 | 135 | 124 | 106 | 85 | 66 | 44 | 21 | 6 |
| CMF | 155 | 148 | 135 | 121 | 108 | 92 | 68 | 36 | 7 |

**Fig 6. Kaplan-Meier analysis of OS in ER-negative patients.**

patients randomized to goserelin fared comparably to those randomized to CMF (HR, 0.99; 95% CI, 0.76 to 1.28; $P = .92$) (Fig 5) and ER-negative patients fared better with CMF (HR, 1.77; 95% CI, 1.19 to 2.63; $P = .0043$) (Fig 6). In the primary efficacy population, there was a trend for superiority with CMF with respect to OS (HR, 1.21; 95% CI, 0.99 to 1.49; $P = .067$). Further follow-up for OS is required as the data mature.

*Amenorrhea.* The onset of amenorrhea occurred more rapidly with goserelin than with CMF. Of the patients in the primary efficacy population with normal menstruation at entry, amenorrhea was achieved in more than 95% of goserelin patients by 6 months until the end of the 2-year treatment period compared with 58.6% of CMF patients at the end of the 6-month chemotherapy treatment period (Fig 6).

Results (excluding posthysterectomy and postrecurrence data) indicate that after 3 years (ie, 1 year after cessation of goserelin treatment), amenorrhea was reversible in the majority of patients randomized to goserelin; only 22.6% of patients remained amenorrheic at 3 years compared with 76.9% of CMF patients. As previously mentioned, 3.3% of patients receiving goserelin continued with treatment after 2 years up to a maximum of 35 months. Further analysis of goserelin patients by age showed that more than 90% of patients younger than 40 years of age at trial entry had a return of menstruation 1 year after the completion of therapy, compared with approximately 70% of patients older than 40 years of age. In the CMF group, 26% of patients younger than 40 years old at trial entry were amenorrheic after 3 years compared with approximately 90% of those older than 40 years of age.




Number at risk:

| | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|
| Goserelin | 591 | 573 | 553 | 516 | 449 | 330 | 233 | 126 | 44 | 3 | 0 |
| CMF | 598 | 584 | 554 | 525 | 455 | 338 | 223 | 121 | 37 | 2 | 0 |

**Fig 5. Kaplan-Meier analysis of OS in ER-positive patients.**

*Tolerability*

Of 1,640 patients at study entry, 1,605 patients received at least one dose of the study medication and were assessable for safety: 803 patients received goserelin and 802 patients received CMF. During therapy, hematologic side effects were reported in more patients receiving CMF than in those receiving goserelin (Table 3). Most importantly, 57 patients (7.2% of patients available for assessment) randomized to CMF had recorded a WHO grade 3 or 4 leukopenia and 55 (8.4%) had recorded a WHO grade 3 or 4 granulocytopenia, compared with two (0.3%) and three (0.4%) patients, respectively, for goserelin. Grade 3 or 4 increases in liver transferases were recorded in less than 2% of women randomized to either treatment.

Full details of the adverse event profiles (WHO grades $\geq 1$) are listed in Table 4. The incidence of elicited side effects of cytotoxic chemotherapy was substantially higher with CMF than with goserelin during the 6-month CMF treatment period (eg, at 6 months, nausea/vomiting [57.9% *v* 5.4%, respectively], despite the use of antiemetics in more than 97% of CMF patients at each cycle, alopecia [44.9% *v* 3.6%] and infection [13.4% *v* 4.9%]). Menopausal symptoms, such as vaginal dryness and hot flashes, were initially lower with CMF than with goserelin. For CMF patients, the endocrine-related side effects remained virtually unchanged for the subsequent 2.5 years under assessment. In contrast, the incidence of these effects decreased in the goserelin group to a level where they were lower than with chemotherapy (Table 4) at 1 year after cessation of goserelin therapy.

A similar number of patients randomized to goserelin for 2 years (342 patients [42.6%]) or CMF for 6 months (385 patients [48.0%]) experienced adverse reactions considered possibly related to the study medication. Serious possible adverse drug reactions occurred in 117 patients (14.6%) in the goserelin group and 111 patients (13.8%) in the CMF group and led to treatment

**Table 3. Side Effects According to Worst WHO Grade Recorded in the 3 Years After the Start of the Trial**

| | WHO Grade | | | | | | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | CMF (n = 802)* | | | | | | | | | Goserelin (n = 803)* | | | | | | | |
| | 0 | | 1-2 | | 3 | | 4 | | | 0 | | 1-2 | | 3 | | 4 | | |
| | No. | % | No. | % | No. | % | No. | % | Unknown | No. | % | No. | % | No. | % | No. | % | Unknown |
| Hemoglobin | 600 | 75.7 | 186 | 23.5 | 7 | 0.9 | 0 | 0 | 9 | 722 | 91.7 | 63 | 8.0 | 1 | 0.1 | 1 | 0.1 | 16 |
| Leukocytes | 317 | 39.9 | 417 | 52.5 | 51 | 6.4 | 9 | 1.1 | 8 | 576 | 73.2 | 208 | 26.4 | 3 | 0.4 | 0 | 0 | 16 |
| Granulocytes | 399 | 60.5 | 204 | 31.0 | 43 | 6.5 | 13 | 2.0 | 143 | 601 | 88.8 | 72 | 10.6 | 3 | 0.4 | 1 | 0.1 | 126 |
| Platelets | 739 | 93.2 | 44 | 5.9 | 3 | 0.4 | 4 | 0.5 | 9 | 780 | 99.1 | 6 | 0.8 | 1 | 0.1 | 0 | 0 | 16 |
| Oral soreness/ulceration | 573 | 72.3 | 206 | 26.0 | 12 | 1.5 | 2 | 0.3 | 9 | 649 | 82.2 | 138 | 17.5 | 3 | 0.4 | 0 | 0 | 13 |
| Nausea/vomiting | 169 | 21.3 | 517 | 65.0 | 103 | 13.0 | 6 | 0.8 | 7 | 593 | 75.1 | 187 | 23.7 | 9 | 1.1 | 1 | 0.1 | 13 |
| Alopecia | 340 | 42.9 | 452 | 57.1 | — | | — | | 10 | 656 | 83.0 | 134 | 17.0 | — | | — | | 13 |
| Diarrhea | 635 | 80.1 | 155 | 19.5 | 3 | 0.4 | 0 | 0 | 9 | 713 | 90.3 | 75 | 9.5 | 1 | 0.1 | 1 | 0.1 | 13 |
| Hot flashes | 245 | 31.0 | 546 | 69.0 | — | | — | | 11 | 85 | 10.8 | 703 | 89.2 | — | | — | | 15 |

*Percentage calculated as a proportion of patients available for assessment.

withdrawal in 12 patients (1.5%) randomized to goserelin and 11 patients (1.4%) randomized to CMF. A similar number of patients died in both groups (11 [1.4%] and 10 [1.2%] patients for goserelin and CMF, respectively). However, of these 21 cases, only one was considered by the investigator to be "probably" related to study therapy (leukopenia in one patient randomized to CMF), and seven cases were considered "unlikely" to be related to study therapy—five in the goserelin group (carcinoma in three patients, thrombosis in one patient, esophageal hemorrhage in one patient) and two in the CMF group (pulmonary embolus in one patient and suicide in one patient). The remaining 13 fatal possible adverse drug reactions were considered to be "definitely not" related to study therapy.

## DISCUSSION

When the ZEBRA trial was initiated in the early 1990s, ER assessment was not routinely used for treatment decisions; consequently, patients with ER-positive and ER-negative tumors were included. Given these differences in patient populations, the protocoled analyses were performed on the whole data set of eligible patients and on the data set divided by ER status. In this trial, it was acknowledged that there would, inevitably, be differences between centers and over time with regard to the methodologies, reference ranges, and data interpretations used to measure tumor hormone receptors, and thus an independent laboratory has carefully verified ER status. In the primary efficacy population, CMF was superior to goserelin for DFS. A strong interaction was demonstrated between treatment outcome and ER status. Because of this, and because decisions on therapy should now be made on the basis of knowledge of ER status, the overall analysis is comparatively meaningless in clinical terms, and results for ER-positive and ER-negative subgroups should be considered separately.

In the subgroup of patients with ER-positive tumors, equivalence of the two treatments was demonstrated for DFS. This is consistent with the results of other clinical trials in which hormone therapy by ovarian suppression with goserelin and the addition of tamoxifen has been directly compared with CMF.[16,17] Recent data with the LHRH analog (LHRHa) leuprorelin have also demonstrated that in ER-positive patients ovarian suppression with an LHRHa produced progression-free survival rates comparable to those in patients treated with an intravenous CMF regimen.[18] Furthermore, a randomized study comparing triptorelin plus tamoxifen with an anthracycline-containing regimen (fluorouracil, epirubicin, and cyclophosphamide) has demonstrated good DFS and OS rates for both treatment groups.[19] Equivalence of ovarian ablation with cytotoxic therapy in premenopausal patients with ER-positive tumors is in line with comparisons that may be made from the EBCTCG overviews, which show comparable risk reductions from these two approaches.[1,20] This finding with respect to hormone receptor status is important, as approximately 60% of premenopausal women developing breast cancer have ER-positive tumors.[6]

Assuming 50% of the ER unknowns were ER-positive would only increase point and interval estimates for the HR by less than 0.03 to 1.034 (95% CI, 0.869 to 1.230). Even with 80% of the ER unknowns being ER-positive, the upper limit remains below the equivalence boundary. Therefore, the result of goserelin

**Table 4. Incidence of Elicited Side Effects**

| | Elicited Side Effect (%)* (WHO grades ≥ 1) | | | | | | | |
|---|---|---|---|---|---|---|---|---|
| | 3 Months | | 6 Months (end of CMF) | | 2 Years (end of goserelin) | | 3 Years (no treatment) | |
| | Goserelin | CMF | Goserelin | CMF | Goserelin | CMF | Goserelin | CMF |
| Cytotoxic side effects | | | | | | | | |
| Nausea/vomiting† | 8.4 | 66.3 | 5.4 | 57.9 | 3.8 | 2.3 | 3.7 | 2.4 |
| Alopecia | 5.4 | 45.4 | 3.6 | 44.9 | 3.4 | 2.8 | 2.4 | 1.6 |
| Infection | 4.3 | 11.3 | 4.9 | 13.4 | 1.5 | 3.0 | 3.5 | 3.0 |
| Diarrhea | 3.4 | 10.3 | 2.1 | 10.3 | 0.9 | 1.2 | 0.8 | 1.2 |
| Menopausal symptoms | | | | | | | | |
| Vaginal dryness | 23.0 | 10.1 | 25.6 | 15.2 | 25.9 | 13.5 | 9.5 | 14.1 |
| Hot flashes | 74.1 | 24.0 | 74.6 | 44.6 | 60.4 | 42.4 | 18.6 | 39.6 |

*Percentage calculated as a proportion of patients available for assessment at each time point.
†More than 97% of CMF patients received antiemetics at each cycle.

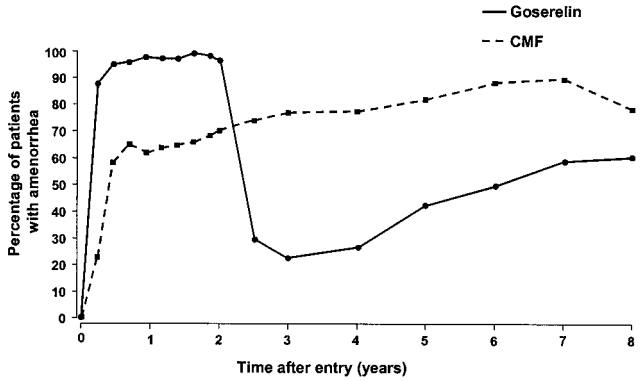
being equivalent to CMF in terms of DFS for ER-positive patients can be considered robust. In ER-negative tumors, CMF produced a highly significant advantage over goserelin. This result is consistent with the EBCTCG overview, which showed no significant effect from adjuvant hormone therapy in ER-negative tumors.[5]

The ZEBRA trial used CMF for chemotherapy, the standard at the time of starting the trial. Most of the patients were treated with intravenous cyclophosphamide, although the "classical" Bonadonna CMF regimen uses oral cyclophosphamide. However, there have been no randomized trials that directly compare CMF regimens where all three drugs are given IV on days 1 and 8 with classical CMF.[21] In addition, the International Breast Cancer Study Group Trial VIII, which recently reported similar efficacy for goserelin and CMF in ER-positive patients, used the classical CMF regimen.[22] Anthracycline-containing regimens are now widely used for cytotoxic chemotherapy. The EBCTCG overview demonstrated a small but statistically significant improvement in survival for anthracycline-containing adjuvant chemotherapy regimens compared with CMF regimens (2.7%, 5-year survival).[20] However, there are no data available that show that anthracycline-containing regimens are more effective than CMF in the specific population of patients who are premenopausal with ER-positive tumors.

In the ZEBRA study, permanent amenorrhea was induced in approximately 70% of patients receiving CMF. Because all treatment options producing temporary or permanent menopause have been shown to lower the relative risk of recurrence,[1,20] it follows that some of the effect of CMF in ER-positive tumors must lie in its indirect action on the ovaries rather than direct cytotoxic action on the cancer cells. As permanent amenorrhea was induced in approximately 70% of patients treated with CMF, and as the overall effects of goserelin and CMF were the same in ER-positive tumors, it seems that a considerable part of the risk reduction achieved by CMF over no treatment is brought about by the side effect on the ovaries. In both the Austrian trial[23] and this trial, in patients treated with CMF, exploratory analyses indicated that DFS was significantly better in patients who became amenorrheic compared with those remaining premenopausal. However, it should be noted that the incidence of amenorrhea as a result of CMF chemotherapy is strongly related to age, and age itself is a significant prognostic factor for outcome in early breast cancer.

In contrast to CMF, amenorrhea induced by goserelin was reversible in the majority of patients. Most of the goserelin-treated patients not returning to menses were likely to have reached the natural menopause. The slow increase in amenorrhea rates observed in both treatment groups after cessation of treatment represents patients reaching the natural menopause (Fig 7).

With a median follow-up of 6 years, the Kaplan-Meier curves indicate that the event rate remains proportional across time and between goserelin and chemotherapy regimens. This indicates that within the time frame of the study, return of menses, which occurs in the majority of goserelin patients, does not impact on recurrence rate or overall survival. Only 80 ER-positive patients did not have return of menses at 3 years, with 13 events. Any further analyses regarding the impact of the return of menses on outcome will only be exploratory, as the groups being compared are selected and are not the result of randomization. The only




Number at risk:

| | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|
| Goserelin | 663 | 613 | 559 | 467 | 390 | 306 | 220 | 149 | 85 | 38 |
| CMF | 694 | 596 | 547 | 474 | 428 | 362 | 275 | 180 | 107 | 28 |

**Fig 7. Effect of goserelin and CMF on amenorrhea rates (includes only patients with normal menstruation at trial entry; excludes any postrecurrence or posthysterectomy data).**

accurate way of assessing this aspect is to directly compare longer versus shorter durations of goserelin treatment.

The results from this study also highlight the contrast in tolerability of goserelin and CMF. Patients receiving CMF experienced a much higher incidence of adverse events that are typically associated with cytotoxic chemotherapy than those receiving goserelin. Menopausal symptoms were initially lower with CMF than with goserelin but remained virtually unchanged after treatment, whereas on cessation of goserelin, the incidence of these effects fell to below that seen in the CMF group.

It is clear that all premenopausal patients with ER-positive tumors who are to receive adjuvant systemic therapy should undergo ovarian suppression, and for those who wish to recover their hormonal status, this is most reliably achieved with an LHRH agonist. In patients accepting the risk of permanent amenorrhea, cytotoxic therapy remains an option, and there is the potential to initiate goserelin treatment in those who remain premenopausal after cytotoxic administration. This represents a marked change of emphasis because, until now, cytotoxic therapy has been the choice for women younger than 50 years of age.

The combination of chemotherapy and tamoxifen is now routinely used as adjuvant treatment of premenopausal women with ER-positive tumors. However, there are still limited data available comparing the relative efficacy of chemotherapy versus chemotherapy plus tamoxifen for 5 years. In fact, the 1995 Oxford overview included only 177 such women. In this subgroup, there was a marginally significant improvement in DFS with combination therapy.[24] The addition of tamoxifen to goserelin therapy has been shown to be beneficial in advanced disease.[11,25,26] Similarly, for adjuvant therapy in receptor-positive tumors, the use of goserelin plus tamoxifen was superior to CMF for DFS,[17] whereas in the ZEBRA trial, as previously stated, there was equivalence between goserelin alone and CMF. Furthermore, the addition of goserelin plus tamoxifen to cytotoxic therapy provided a greater risk reduction than the addition of goserelin alone.[27] Thus, it seems that administration of goserelin plus tamoxifen should be considered. Furthermore, the side effects using the combination of goserelin plus tamoxifen are reported to be lower than with goserelin alone.[28]

In conclusion, in premenopausal patients with early breast cancer, treatment decisions must be made on the basis of ER

status. Cytotoxic therapy should remain the adjuvant treatment of choice in ER-negative tumors. However, approximately 60% of premenopausal women with breast cancer have ER-positive tumors.[6] Goserelin offers an effective, well-tolerated alternative to CMF chemotherapy in the management of premenopausal patients with ER-positive and node-positive early breast cancer.

## ACKNOWLEDGMENT AND APPENDIX

The acknowledgment and the appendix listing the ZEBRA investigators are available online at www.jco.org.

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