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Survival analyses from the ZEBRA study: goserelin (Zoladex^{TM}) 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^{TM}) 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 *Z*oladex Early Breast Cancer Research *A*ssociation (ZEBRA) trial was designed to directly compare the efficacy and tolerability of goserelin with

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cyclophosphamide, methotrexate and 5-fluorouracil (CMF) chemotherapy in pre-/perimenopausal women with lymph node-positive (LN+) breast cancer [1]. The trial compared the disease-free survival (DFS), overall survival (OS) and tolerability for goserelin versus CMF in 1640 patients recruited between 1990 and 1996. After a median follow-up of 6 years, goserelin was shown to be equivalent to CMF for DFS in oestrogen receptor (ER)-positive patients. Goserelin was not associated with the acute side-effects of chemotherapy, such as nausea, vomiting, alopecia and infection, leading to an improved quality of life during the early 6-month treatment period [7]. Permanent menostasis was induced in 65% of patients treated with CMF, so that 1 year after treatment with goserelin had ceased, fewer women were suffering hormonal side-effects than those that had been treated with CMF. Data on OS lacked maturity in the earlier report from the ZEBRA study and are reported here.

The results presented here are from an extended follow-up analysis of the ZEBRA patient population to determine whether the previously reported efficacy and adverse event profiles are continued into the longer term, after a median follow-up of 7.3 years.

2. Patients and methods

2.1. Patients

The ZEBRA study is an international, multicentre, open, randomised study in pre-/perimenopausal women with node-positive early breast cancer [1]. Patients were recruited over a 6-year period between 1 October 1990 and 30 December 1996 from 102 centres in 15 countries. Eligibility criteria included pre-/perimenopausal women 50 years of age with node-positive, histologically-proven invasive breast cancer and no evidence of metastatic disease.

At the time of recruitment, information on ER status was not mandatory for trial entry. Analysis of outcome by ER status was a protocolled intention, with centres being encouraged to perform ER testing. Centres could decide to enter only ER-positive patients if they so wished. During recruitment, tumour ER and progesterone receptor (PgR) status were prospectively analysed in the centres where this was routine practice. To standardise this information, independent external investigators, blinded to the study treatment, reviewed all the hormone-receptor data to ensure that consistent and reliable criteria were used in defining disease as being ER-/PgR-positive, -negative or unknown/unevaluable.

2.2. Randomisation and treatment

The randomisation process is described in the earlier report in Ref. [1]. Patients received either goserelin 3.6 mg depot subcutaneously (s.c.) every 28 days for 2 years or CMF chemotherapy (six cycles, with each cycle being 28 days, unless delayed). A CMF cycle consisted of cyclophosphamide (500 mg/m^2 given intravenously (i.v.) on days 1 and 8, or 100 mg/m^2 given orally (p.o.) on days 1 to 14), methotrexate (40 mg/m^2 given on days 1 and 8) and 5-fluorouracil (600 mg/m^2 given i.v. on days 1 and 8).

2.3. Efficacy

The primary efficacy parameters were DFS and OS. DFS was defined as the time from the initial randomisation to a confirmed tumour recurrence, a second primary cancer or death. Similarly, OS was defined as the period from the date of randomisation to the date of death from any cause. Distant disease-free survival (DDFS) was also examined as a secondary endpoint, the events considered included new primary tumours, disease in the opposite breast, distant metastases and deaths.

2.4. Tolerability

Safety was assessed by overall therapy tolerance and the occurrence of adverse events, as previously described in Ref. [1]. Briefly, patients were given a physical examination at baseline along with routine haematological and biochemical tests, a chest X-ray and bone scan or skeletal survey. Additional assessments were made every 12 weeks up to 96 weeks and then at 2 years, 2.5 years, 3 years and annually up to 10 years and at recurrence. Adverse events commonly associated with the trial therapies were elicited and recorded on specifically designed tolerance case report forms. Gradings of severity were according to World Health Organisation (WHO) criteria. All other possible adverse reactions were recorded on adverse event case report forms.

2.5. Statistics

The study was designed as an equivalence trial, with an 80% power to compare goserelin with CMF. As such, a minimum of 688 events was necessary to demonstrate equivalence in DFS. Clinical and statistical criteria for equivalence with respect to the primary efficacy endpoints were defined in advance as a hazard ratio (HR) for DFS and OS and 95% confidence intervals (CI) lying entirely within the range 0.80–1.25. If equivalence was not demonstrated, non-inferiority of goserelin relative to CMF was concluded if the upper CI was <1.25.

A supplementary analysis was defined in advance in terms of the ER status. The effect of ER status on the HR was estimated by adding a binary variable for ER status and a variable for interaction with treatment in

Table 1
Defined patient populations within the ZEBRA study

	Number of patients ($n=1640$)	
	Goserelin	CMF
Randomised population	817	823
Major protocol violations	20	6
Primary efficacy population	797	817
Safety population	803	802
Follow-up population	562	603
Deaths during current follow-up	235	214

CMF, cyclophosphamide, methotrexate and 5-fluorouracil ZEBRA, Zoladex Early Breast Cancer Research Association.

the predefined final model, which included age and tumour size as binary variables, and the number of positive lymph nodes with three categories. Estimates for the HRs and corresponding 95% CIs were adjusted for these factors; in the first analysis a significant interaction between treatment and ER-status was shown and therefore most analyses will be presented by ER-status. DFS and OS in the two groups were assessed using Cox proportional hazards regression models. All randomised patients were included in the primary efficacy population, apart from those with major protocol violations, such as postmenopausal status or prior oophorectomy.

Cause-specific incidence rates of different first events were estimated in a competing risk model, with 95% CIs [8]. First events were classified into isolated locoregional recurrence, new primaries occurring as first events or distant metastases/death without previous recurrence. Further details concerning the methods are given in the earlier report in Ref. [1].

3. Results

3.1. Patients

A total of 1640 women entered the trial, with 26 of these having major protocol violations. Thus, the primary efficacy population consisted of 1614 patients, of whom 797 were randomised to goserelin and 817 were randomised to CMF (Table 1). The treatment groups were very similar in terms of patients' characteristics, including age, menstrual status and ER/PgR status [1].

3.2. Efficacy

A total of 758 events (disease recurrence, second primary cancer or death before recurrence) occurred during the follow-up period (median 7.3 years), of which 400 (52.8%) were in patients randomised to goserelin and 358 (47.2%) occurred in the CMF-treated patients. The distribution of events by treatment and ER status is shown in Table 2.

The ER-positive patient subgroup (approximately 74% of the patient population) continues to demonstrate equivalence between goserelin and CMF for DFS (HR = 1.05; 95% CI: 0.88–1.24; $P=0.597$) (Fig. 1a). Goserelin is still inferior to CMF in the ER-negative patients (HR = 1.83; 95% CI: 1.33–2.52; $P=0.0001$) (Fig. 1b) and in the primary efficacy population as a whole (HR = 1.22; 95% CI: 1.05-1.40; $P=0.007$).

Similar proportions of patients in the two treatment groups exhibited distant disease events, with 361 (45.3%) and 327 (40.0%) patients treated with goserelin and CMF, respectively, having an event (Table 2). Distant events accounted for approximately 90% of all events, and therefore DDFS would be expected to reflect DFS. For DDFS, as for DFS, there was a significant interaction between treatment and ER status ($P=0.008$), indicating that the treatment effect was not consistent across the ER subgroups. In the ER-positive patients, a similar number of distant disease events occurred in both treatment groups (42.8% versus 40.6% of goserelin and CMF-treated patients, respectively; Table 2). This was reflected in a HR of 1.03 (95% CI: 0.86-1.23; $P=0.749$), demonstrating that goserelin was equivalent to CMF for DDFS in patients with ER-positive tumours. As indicated by the treatment interaction, an increased number of DDFS events were noted in the ER-negative patients treated with goserelin, compared with those treated with CMF (56.3% versus 38.8%, respectively; Table 2). This difference in events indicates that goserelin is inferior to CMF for DDFS in ER-negative patients (HR = 1.65; 95% CI: 1.19–2.30; $P=0.0028$).

Table 2
The number of DFS and DDFS events by ER status at a median follow-up of 7.3 years

	Goserelin			CMF		
	No. of patients	DFS events *n* (%)	DDFS events *n* (%)	No. of patients	DFS events *n* (%)	DDFS events *n* (%)
ER + ve	591	281 (47.5)	253 (42.8)	598	269 (45.0)	243 (40.6)
ER-ve	144	89 (61.8)	81 (56.3)	160	66 (41.3)	62 (38.8)
ER-unknown	62	30 (48.4)	n/a	59	23 (39.0)	n/a
Total	797	400 (50.2)	361 (45.3)	817	358 (43.8)	327 (40.0)

DFS, disease-free survival; DDFS, distant disease-free survival; ER, oestrogen receptor; n/a, not available.

In the overall survival analysis, similar numbers of deaths (25.0% versus 25.8% of patients dying; Table 3) were observed in patients with ER-positive tumours treated with goserelin and CMF, respectively. Statistical analysis showed non-inferiority between goserelin and CMF for OS in ER-positive patients (HR = 0.94; 95% CI: 0.75-1.18; $P = 0.622$) (Fig. 2a). In the primary efficacy population, goserelin shows no significant difference with CMF for OS (HR = 1.15; 95% CI: 0.96–1.39; $P = 0.137$). For patients with ER-negative tumours, the number of deaths was significantly greater in the goserelin group than in the CMF group (45.8% versus 29.4% of patients dying, respectively; Table 3). As a result, goserelin continues to be inferior to CMF for OS in the ER-negative subgroup (HR = 1.64; 95% CI: 1.13-2.39; $P = 0.009$) at this follow-up time (Fig. 2b).

In the competing risk model, cause-specific 5-year event rates demonstrated a close similarity in the ER-positive patients. Event rates were 10.5% (95% CI: 8.0–13.0%) versus 10.3% (95% CI: 7.8–12.8%) (locoregional recurrence), 2.6% (95% CI: 1.3–3.9%) versus 1.9% (95% CI: 0.8–3.0%) (new primary) and 25.7%

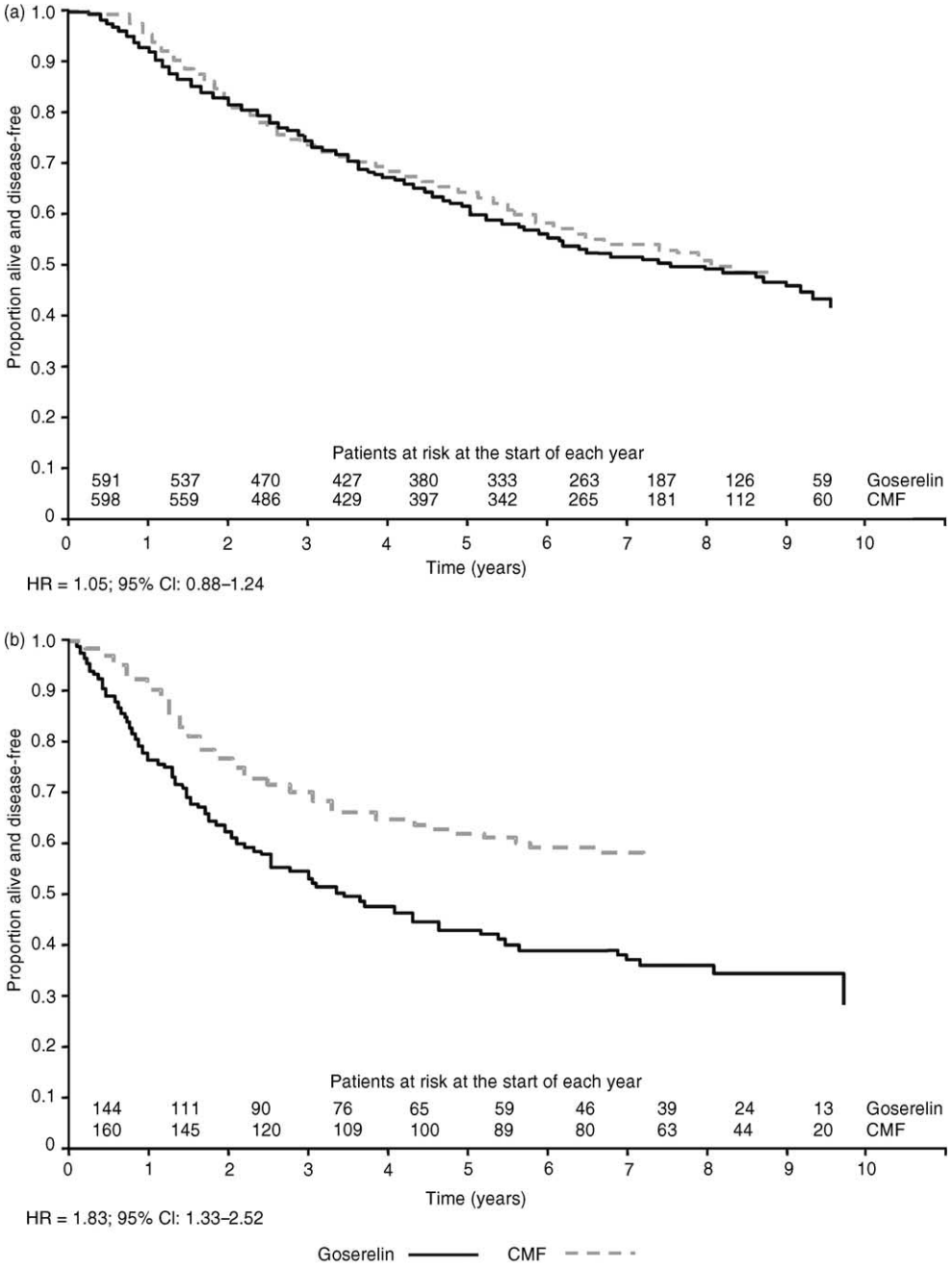

Fig. 1. (a) Kaplan–Meier curve of disease-free survival (DFS) in the oestrogen receptor (ER)-positive patient subgroup. (b) Kaplan-Meier curve of DFS in the ER-negative patient subgroup. HR, hazard ratio; CI, Confidence Interval; CMF, cyclophosphamide methotrexate and 5-fluorouracil.

Table 3
The number of deaths by ER status at a median follow-up of 7.3 years

	Goserelin		CMF	
	No. of patients	Deaths, *n* (%)	No. of patients	Deaths, *n* (%)
ER + ve	591	148 (25.0)	598	154 (25.8)
ER-ve	144	66 (45.8)	160	47 (29.4)
ER-unknown	62	21 (33.9)	59	13 (22.0)
Total	797	235 (29.5)	817	214 (26.2)

ER, oestrogen receptor.

(95% CI: 22.2–29.3%) versus 23.9% (95% CI: 20.4–27.3%) (distant metastases/death) for goserelin- and CMF-treated patients, respectively. The corresponding figures for patients with ER-negative or ER-unknown status indicated that goserelin-treated patients had higher rates of all three types of event, the largest difference being observed for locoregional recurrences.

3.3. Tolerability

The frequency of adverse events has remained broadly similar overall, with 45.8% and 49.9% of goserelin

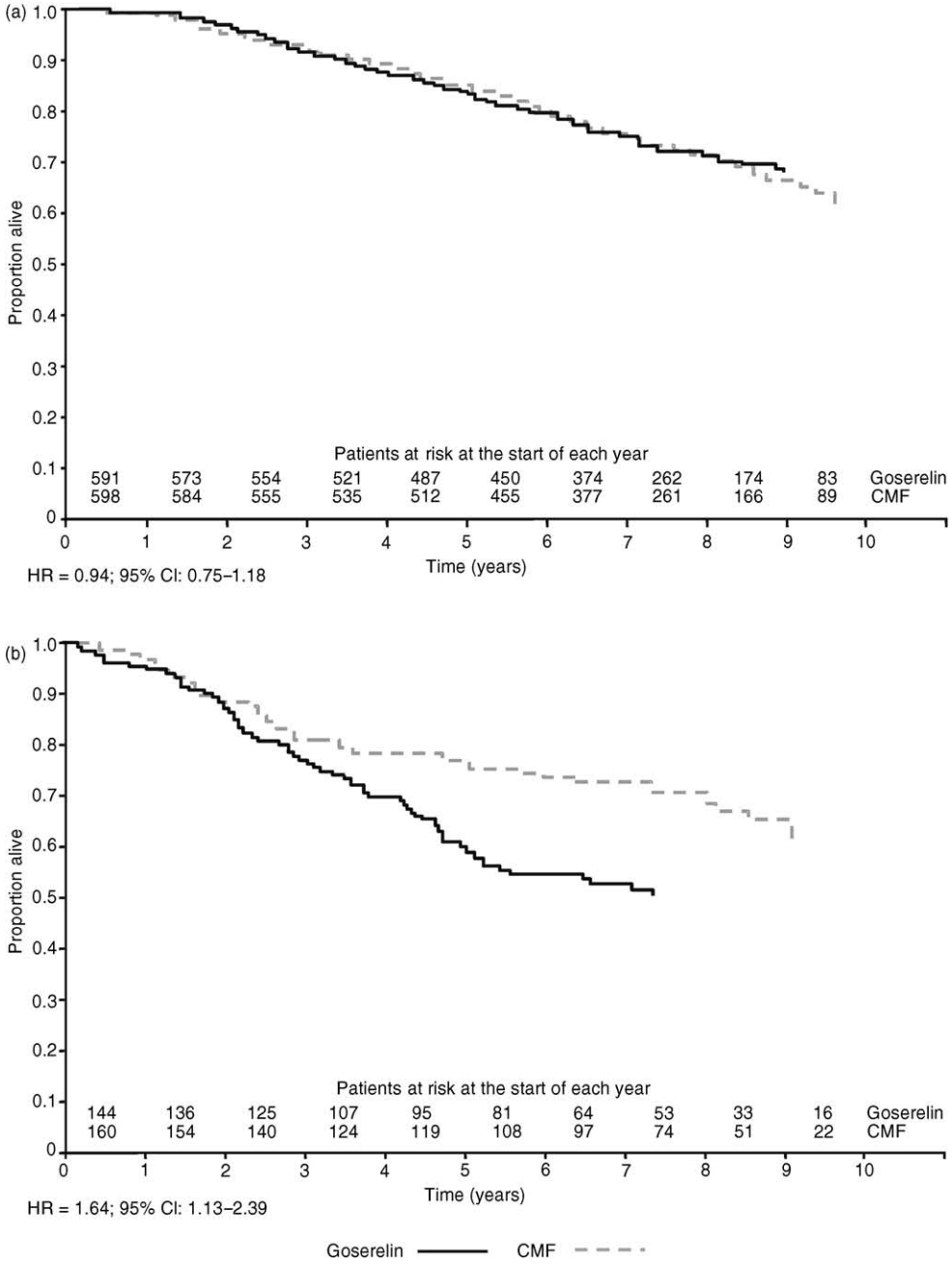

Fig. 2. (a) Kaplan–Meier curve of OS in the ER-positive patient subgroup. (b) Kaplan–Meier curve of OS in the ER-negative patient subgroup.

Table 4
Frequency of possible adverse drug reactions

	Number of patients (%)[a]	
	Goserelin ($n=803$)	CMF ($n=802$)
All adverse reactions, *n* (%)	368 (45.8)	400 (49.9)
Serious non-fatal adverse reactions, *n* (%)	123 (15.3)	120 (15.0)
Fatal adverse reactions, *n* (%)	13 (1.6)	13 (1.6)

[a] Patients may be counted in more than one category.

($n=803$) and CMF ($n=802$) patients, respectively, having experienced an adverse event during the follow-up period (Table 4). In addition, the numbers of patients with serious or fatal adverse events remained similar between the two treatment groups. The updated adverse event data demonstrate that the tolerability profile has not markedly altered since the previous analysis.

4. Discussion

This report supersedes the previous analysis from the ZEBRA trial that reported evidence of the efficacy of goserelin treatment up to 6.0 years [1], and establishes that with a median follow-up of 7.3 years, goserelin demonstrates non-inferiority versus CMF for OS, and shows equivalence to CMF for DFS in ER-positive, pre-/perimenopausal patients with node-positive, early breast cancer. These results support the findings of other trials that have demonstrated similar long-term benefits for adjuvant therapy with ovarian ablation in hormone-responsive, pre-/perimenopausal patients [9].

There are no substantial differences in the results obtained at this extended follow-up compared with those reported for the previous analysis at a median follow-up of 6 years [1]. The HR for DFS in ER-positive patients was 1.01 (95% CI: 0.84–1.20) in the previous analysis and 1.05 (95% CI: 0.88–1.24) in the current report. The HR for OS in ER-positive patients was 0.99 (95% CI: 0.76–1.28) in the initial report and 0.94 (95% CI: 0.75–1.18) in this update. The updated results continue to illustrate the equivalence between goserelin and CMF for DFS in patients with ER-positive disease, and clearly show that goserelin is not inferior to CMF for OS in patients with ER-positive disease.

For ER-negative patients, CMF continues to be superior to goserelin for both OS and DFS, confirming the result of the Early Breast Cancer Trialists' Collaborative Group (EBCTCG) overview that showed no significant effect for adjuvant endocrine treatment in patients with ER-negative disease [10]. When the ZEBRA trial was initiated in 1990, the importance of ER status was less well understood, and the available scientific evidence did not preclude the inclusion of women with ER-negative disease in trials of endocrine therapies. Two trials in patients with ER-positive tumours [5,11] have compared adjuvant hormonal therapy using goserelin and tamoxifen with CMF. The larger of these trials ($n=1099$) [11] showed that the combination of goserelin plus tamoxifen was significantly more effective than CMF, while the smaller trial ($n=244$) [5] reported no significant differences in efficacy between the two treatments.

The earlier reports [1,7] showed that 65% of women treated with CMF suffered permanent amenorrhoea. The menopausal side-effects suffered by the goserelin population reduced markedly as menses returned at the end of the treatment period, while these side-effects became considerably higher in the CMF group after 2 years of follow-up. Those women treated with CMF who achieved permanent amenorrhoea fared significantly better in terms of DFS than those retaining their premenopausal status, as also shown in the Austrian study [11]. It has to be concluded that a part of the effect of CMF is achieved by the indirect ovarian ablative side-effect rather than through direct cytotoxic action on the tumour. This is closely balanced by the cytotoxic effect of CMF in patients with tumours that are ER-positive, but non-responsive to hormonal therapy.

Goserelin does not cause significant changes in the long-term adverse event profile. The continuing lack of any significant differences between goserelin and CMF, with respect to outcome in ER-positive patients, suggests further evidence to support the previous observation that return of menses seen with goserelin [1] does not impact upon the recurrence rate or OS.

5. Conclusions

These updated analyses provide confirmation that 2 years of goserelin treatment is equivalent to CMF in pre-/perimenopausal women with ER-positive, node-positive early breast cancer. Goserelin therefore represents a well-tolerated and effective alternative to adjuvant CMF chemotherapy for these patients.

References

1. Jonat W, Kaufmann M, Sauerbrei W, *et al*. 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. *J Clin Oncol* 2002, **20**, 4628–4635.
2. Matsumoto M, Miyauchi M, Yamamoto N, Shishikura T, Imanaka N. Investigation of menstrual recovery after LH-RH agonist therapy for premenopausal patients with breast cancer. *Breast Cancer* 2000, **7**, 237–240.
3. Nicholson RI, Walker KJ, Turkes A, *et al*. Therapeutic significance and the mechanism of action of the LH-RH agonist ICI 118,630 in breast and prostate cancer. *J Steroid Biochem* 1984, **20**, 129–135.
4. Taylor CW, Green S, Dalton WS, *et al*. Multicenter randomized clinical trial of goserelin versus surgical ovariectomy in premenopausal patients with receptor-positive metastatic breast cancer: an intergroup study. *J Clin Oncol* 1998, **16**, 994–999.
5. Boccardo F, Rubagotti A, Amoroso D, *et al*. Cyclophosphamide, methotrexate and fluorouracil plus ovarian suppression as adjuvant treatment of estrogen receptor-positive pre-/perimenopausal breast cancer patients: results of the Italian Breast Cancer Adjuvant Study Group 02 randomized trial. *J Clin Oncol* 2000, **18**, 2718–2727.
6. Kaufmann M, von Minckwitz G. The emerging role of hormonal ablation as adjuvant therapy in node+ and node- pre-/perimenopausal patients. *Breast* 2001, **10**(Suppl. 3), 123–129.
7. De Haes JC, Olschewski M, Kaufmann M, Schumacher M, Jonat W, Sauerbrei W on behalf of the ZEBRA Trialists' Group. Quality of life in goserelin-treated versus CMF treated pre/-perimenopausal patients with node-positive early breast cancer. 2002, submitted.
8. Anderson PK, Borgan O, Gill RD, Keiding N. *Statistical models based on counting processes*. New York, Springer-Verlag, 1993.
9. Early Breast Cancer Trialists' Collaborative Group. Ovarian ablation for early breast cancer: overview of the randomized trials. *Lancet* 1996, **348**, 1189–1196.
10. Early Breast Cancer Trialists' Collaborative Group. Tamoxifen for early breast cancer: an overview of the randomized trials. *Lancet* 1998, **351**, 1451–1467.
11. Jakesz R, Hausmaninger H, Kubista E, *et al*. Randomized adjuvant trial of tamoxifen and goserelin versus cyclophosphamide, methotrexate, and fluorouracil: evidence for the superiority treatment with endocrine blockade in premenopausal patients with hormone-responsive breast cancer. Austrian Breast and Colorectal Cancer Study Group Trial 5. *J Clin Oncol* 2002, **20**, 4621–4627.