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# CMF versus goserelin as adjuvant therapy for node-negative, hormone-receptor-positive breast cancer in premenopausal patients: A randomised trial (GABG trial IV-A-93)

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ABSTRACT

Gonadotrophin-releasing hormone analogues were investigated as adjuvant treatment for patients with node-negative, hormone-sensitive, premenopausal breast cancer. Patients were randomised to either three cycles of cyclophosphamide, methotrexate, and 5-fluorouracil (CMF) chemotherapy ($n = 378$) or goserelin every 28 d for 2 years ($n = 393$). During a median follow-up of 4.9 years, 123 events were observed. The first-failure event of CMF versus goserelin, respectively, was ipsilateral locoregional recurrence (18 versus 20), contralateral breast cancer (7 versus 6), distant failure (35 versus 24) and death without recurrence (2 versus 2). Forty-two (23 versus 19) deaths of any cause occurred. The estimated adjusted hazard ratio for goserelin versus CMF (intention-to-treat analysis) was 0.79 (95% CI = 0.54–1.14; $P = 0.19$). It is concluded that medical ovarian ablation with goserelin represents a valid option for premenopausal patients with node-negative breast cancer.



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## 1. Introduction

Hormone manipulation has been used for more than 100 years to treat women with advanced breast cancer, but how to translate this into adjuvant treatment remains in doubt.[1] Clearly, 5 years of tamoxifen is standard care in young women with steroid-hormone-receptor–positive disease.[2] Ovarian ablation or suppression (OA or OS) is accepted in some cases.[3,4] Methods of ovarian ablation include surgery and irradiation, whereas OS can be accomplished by gonadotrophin-releasing hormone (GnRH) agonists. A meta-analysis by the Early Breast Cancer Trialists' Collaborative Group (EBCTCG) demonstrated clear benefit from OA/OS as monotherapy in the adjuvant treatment of women younger than 50 years.[2]

Several randomised trials have suggested that OA/OS may have effects similar to those of cyclophosphamide, methotrexate, and 5-fluorouracil (CMF)-type adjuvant chemotherapy. Six cycles of CMF was the first standard chemotherapy for early breast cancer.[4] However, to improve the risk-benefit ratio, several studies[5–7] compared six with three CMF cycles as adjuvant treatment and found no significant survival difference. There was a trend towards greater survival of three cycles for patients with a more favourable risk profile, e.g. receptor-positive tumours.[8]

Given these results, in 1993 the German Adjuvant Breast Cancer Group (GABG, now GBG) initiated trial IV-A-93 to compare three cycles of CMF with 2 years of goserelin in premenopausal patients with hormone-receptor-positive breast cancer. The trial recruited node-negative patients only, in contrast to the international Zoladex Early Breast Cancer Research Association (ZEBRA) study,[9,10] which was conducted in node-positive breast cancer patients during an overlapping time period in Germany.[11,12]

The primary aim of the study was to compare the event-free survival (EFS); secondary objectives were the comparison of overall survival and clinically significant toxicities.

## 2. Patients and methods

### 2.1. Study design

Initiated in 1993, GABG IV-A was one trial of a package of five (A–E) launched throughout Germany that made it possible to enrol patients according to menopausal status and hormone-receptor and lymph-node status.

Premenopausal status was defined on the basis of regular menses in the last 6 months or on the basis of hormone levels (follicle stimulating hormone (FSH) <20 IU/l, luteinising hormone (LH) >50 pg/ml).

Oestrogen receptor (ER) and progesterone receptor (PgR) status were determined at local laboratories, either biochemically by a dextran-coated charcoal assay and/or by immunohistochemistry.[13] The tumour was defined as hormone responsive if the biochemical analysis detected $\geqslant$20 fmol/mg protein or the immunoreactive score (IRS) was 2 or higher.[13] To be eligible, the tumour had to be positive either for ER or PgR, or both. After an amendment in September 2000, only patients with positive ER status were enrolled (as a consequence of the results of the ZEBRA trial).[9]

Patients were centrally randomised and stratified based on participating sites. Within each centre, block randomisation with randomly varying block size and a 1:1 treatment ratio was performed. Starting in December 1997, retrospective and prospective 100% source data verification was performed by an external clinical research organisation.

The trial protocol was approved by all associated ethical committees.

### 2.2. Patient eligibility

Premenopausal women with histologically confirmed, node-negative, hormone-responsive breast cancer were eligible if they met the following criteria: no prior systemic, or radiation treatment for breast cancer and Karnofsky index $\geqslant$60.

Major exclusion criteria were distant metastases; any T4 tumour; incomplete surgical resection or resection of <10 axillary lymph nodes; simultaneous contralateral breast cancer; previous malignancy except basal cell carcinoma of the skin or carcinoma *in situ* of the cervix uteri; pregnancy or lactation; insufficient organ function; and randomisation not within 28 d of definitive primary surgery.

### 2.3. Study treatments

Patients received either goserelin 3.6 mg subcutaneously (s.c.) every 28 d for 2 years or 3 cycles of CMF chemotherapy. A CMF cycle consisted of cyclophosphamide 500 mg/m$^2$, methotrexate 40 mg/m$^2$, 5-fluorouracil 600 mg/ m$^2$ given intravenously (i.v.) on days 1 and 8 of a 28-d cycle.

### 2.4. Evaluation criteria

Follow-up examinations were scheduled every 3 months for the first 2 years, every 6 months up to 5 years from surgery, and annually thereafter. Event-free survival (EFS) and overall survival (OAS) were defined as time from definitive primary surgery to the first event of failure (ipsilateral locoregional recurrence, contralateral breast cancer, distant metastases, or secondary non-breast primaries, including death) or death, respectively.

### 2.5. Statistical methods

Based on preliminary data of patients selected from previous studies,[14] an 80% EFS rate at 5 years was anticipated for the CMF group. To detect an improvement to 87% with goserelin (a hazard ratio (HR) of 0.625 for goserelin versus CMF), 140 events would be required to achieve an 80% power for a two-sided log-rank test at the level $\alpha = 5\%$.[15] With 4 years of planned recruitment and 2 years additional follow-up, it was anticipated that 1060 patients would have to be included. However, the study recruited more slowly than expected. Recalculations performed in 1999 showed that, because of the resulting prolongation of follow-up with the same assumptions for superiority, 140 events could also be achieved by including 770 patients in 7.5 years with 2 years of additional follow-up.

EFS and OAS rates were estimated by Kaplan–Meier curves, treating patients as censored at the time of the last reported visit if the event of failure had not yet occurred. Median follow-up was based on the estimated censoring distribution,[16] and the completeness of follow-up was quantified according to Clark and colleagues.[17] The treatment effect was estimated as the hazard ratio in a Cox model with a two-sided 95% confidence interval (CI). *P* values were based on two-tailed Wald tests.[18] An adjusted analysis of treatment and prognostic factors was performed in a multiple Cox model including treatment, tumour size, tumour grade, and type of surgery as pre-specified in the statistical analysis plan. In addition, differential treatment effects were investigated for tumour size and grade (pre-specified analyses) and for age and simultaneous expression of both steroid receptors (retrospective analyses).

The interaction of pre-specified prognostic factors was tested by a Wald test of equality of the treatment effects in the resulting groups. Because of multiple testing, a significance level of 1% was used for these tests with 99% CIs.

Data were processed and evaluated with the Statistical Analysis System (SAS) according to a pre-specified analysis plan. Following the intention-to-treat principle, ineligible patients were not excluded, and treatment was analysed as randomised. All tests, *P*-values and CIs were two-sided.

## 3. Results

### 3.1. *Recruitment and patient characteristics*

A total of 771 patients were randomised to CMF ($n = 378$) or to goserelin ($n = 393$) between March 1993 and February 2001 in 62 German centres. A quarter of all patients were 40 years of age or younger at randomisation. The size of most tumours (64%) was 20 mm or smaller. Histological grade 3 was identified in 21% of the tumours, and 85% of patients had positive ER and 93% positive PgR status, respectively. The eligibility criteria were not met in 4.3% of the patients.

Baseline characteristics were well balanced between treatment groups (Table 1).

### 3.2. *Compliance*

Information about the actual treatment is available for 753 patients, and 717 started their treatment according to randomisation. In the CMF group, almost all patients who started treatment received three cycles (97.7%); only 7 patients

**Table 1 – Patient characteristics according to treatment group**

| | | CMF $n = 378$ | | Goserelin $n = 393$ | |
|---|---|---|---|---|---|
| | | *n* | % of total | *n* | % of total |
| *Age (years)* | ⩽40 | 103 | (27) | 99 | (25) |
| | >40 | 275 | (73) | 294 | (75) |
| | Median | 45 | | 45 | |
| *Tumour size (mm)* | ⩽20 | 248 | (66) | 244 | (62) |
| | >20 | 130 | (34) | 148 | (38) |
| | Unknown | 0 | | 1 | |
| *Tumour grade* | 1 | 50 | (13) | 60 | (16) |
| | 2 | 244 | (66) | 248 | (64) |
| | 3 | 78 | (21) | 79 | (20) |
| | Unknown | 6 | | 6 | |
| *Oestrogen receptor status (ER)* | ER positive (+) | 315 | (84) | 336 | (86) |
| | ER negative (–) | 59 | (16) | 55 | (14) |
| | ER unknown (?) | 4 | | 2 | |
| *Progesterone receptor status (PgR)* | PgR (+) | 353 | (95) | 360 | (92) |
| | PgR (–) | 20 | (5) | 32 | (8) |
| | PgR (?) | 5 | | 1 | |
| *Steroid receptor content (ER and/or PgR)* | ER+, PgR+ | 294 | (78) | 306 | (78) |
| | ER+, PgR–/? | 21 | (6) | 30 | (8) |
| | ER–/?, PgR+ | 59 | (16) | 54 | (14) |
| | Overall + (ER?, PgR?) | 3 | (1) | 1 | (0) |
| | ER–, PgR– | 1 | (0) | 2 | (0) |
| *Type of surgery* | Breast conservation | 282 | (75) | 275 | (70) |
| | Mastectomy | 96 | (25) | 118 | (30) |
| *Adjuvant radiotherapy* | Yes | 280 | (76) | 273 | (72) |
| | No | 89 | (24) | 106 | (28) |
| | Unknown | 9 | | 14 | |

CMF, cyclophosphamide, methotrexate, and 5-fluorouracil; ER, oestrogen receptor; PgR, progesterone receptor.

stopped treatment early, and 1 received six cycles. In the goserelin group, of those who started treatment (omitting patients who stopped for recurrence or death, $n = 18$), 75.4% received all 24–26 planned injections (median duration 24 months, range 22–30 months) of goserelin; 3.4% stopped early after 1–6 injections; 16.3% received 7–23 injections; and 4.9% continued longer for a maximum of 28 injections. Twenty-one patients randomised to CMF did not start chemotherapy, and 12 of these chose goserelin, while in the goserelin group 15 patients did not start treatment and three received CMF (Fig. 1).

### 3.3. *Follow-up and observed events*

The data cut-off for this final analysis was the end of June 2003, leading to a median follow-up of 4.9 years. Completeness of follow-up, measured as the ratio of observed and potential follow-up information available at the data cut-off,[17] was 86%. Follow-up was similar in both treatment groups (Fig. 1). With regard to EFS, 123 events have been observed so far. The first event of failure (CMF versus goserelin) was an ipsilateral locoregional recurrence (18 versus 20), contralateral breast cancer (7 versus 6), distant relapse (35 versus 24), and death without recurrence (2 versus 2) (Table 2). In addition, the following secondary primaries were observed as first events in the CMF group: leukaemia (1), colorectal (1), bladder (1), unknown origin (1); in the goserelin group these were endometrium (3), renal (1), and bladder (1). With regard to OAS, 42 deaths (23 versus 19) of any cause have been observed to date (Table 2).

### 3.4. *Event-free survival*

Five-year EFS rates are estimated as 81.0% (95% CI = 76.3–85.7%) and 85.0% (95% CI = 81.0–88.9%) in the CMF and goserelin groups, respectively. The unadjusted HR for goserelin versus CMF is 0.81 (95% CI = 0.56–1.17, calculated as 95.70% CI to account for two interim analyses). This slight benefit for goserelin is not significant ($P = 0.25$) (Fig. 2).

In the analysis adjusted for tumour size, tumour grade, and type of surgery, all baseline factors exhibit a strong and statistically significant effect ($P < 0.05$) on EFS (Table 3). The adjusted HR of goserelin versus CMF is 0.79 (95% CI = 0.54–1.14, calculated as 95.70% CI to account for interim analyses). This result is similar to the unadjusted HR; thus, no significant effect can be demonstrated ($P = 0.19$).

Type of surgery was included in the model for EFS to adjust the treatment effect for otherwise unmeasured factors. The corresponding estimated, highly significant HR of 1.82 for

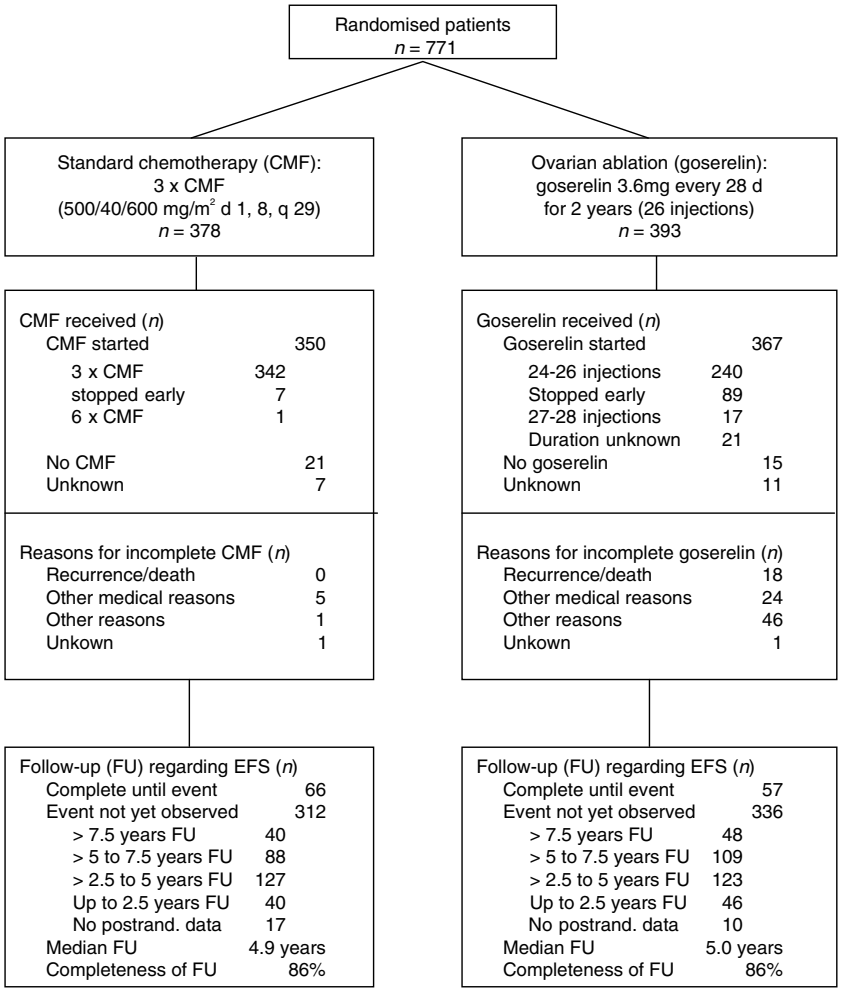


**Fig. 1 – Study participants.**

**Table 2 – Number and distribution of events**

| | CMF $n = 378$ $n$ | Goserelin $n = 393$ $n$ | Total $n = 771$ $n$ |
|---|---|---|---|
| *First event* | | | |
| Ipsilateral locoregional recurrence | 18 | 20 | 38 |
| Contralateral breast cancer | 7 | 6 | 13 |
| Distant site | 35 | 24 | 59 |
| Second non-breast-cancer malignancy | 4 | 5 | 9 |
| Death without recurrence | 2 | 2 | 4 |
| *Status* | | | |
| Alive without recurrence | 295 | 326 | 621 |
| Alive with recurrence | 43 | 38 | 81 |
| Death without recurrence | 2 | 2 | 4 |
| Death after recurrence | 21 | 17 | 38 |
| Number of events for event-free survival | 66 | 57 | 123 |
| Number of events for overall survival | 23 | 19 | 42 |

CMF, cyclophosphamide, methotrexate, and 5-fluorouracil.

mastectomy versus BCT should be interpreted as a prognostic factor rather than as a proven protective effect of BCT. Indeed, its size is partly to the result of the fact that patients with large tumours are more likely to have mastectomy (the BCT rate in patients with tumours ⩽20 mm and >20 mm was 78% and 62%, respectively). This association was confirmed

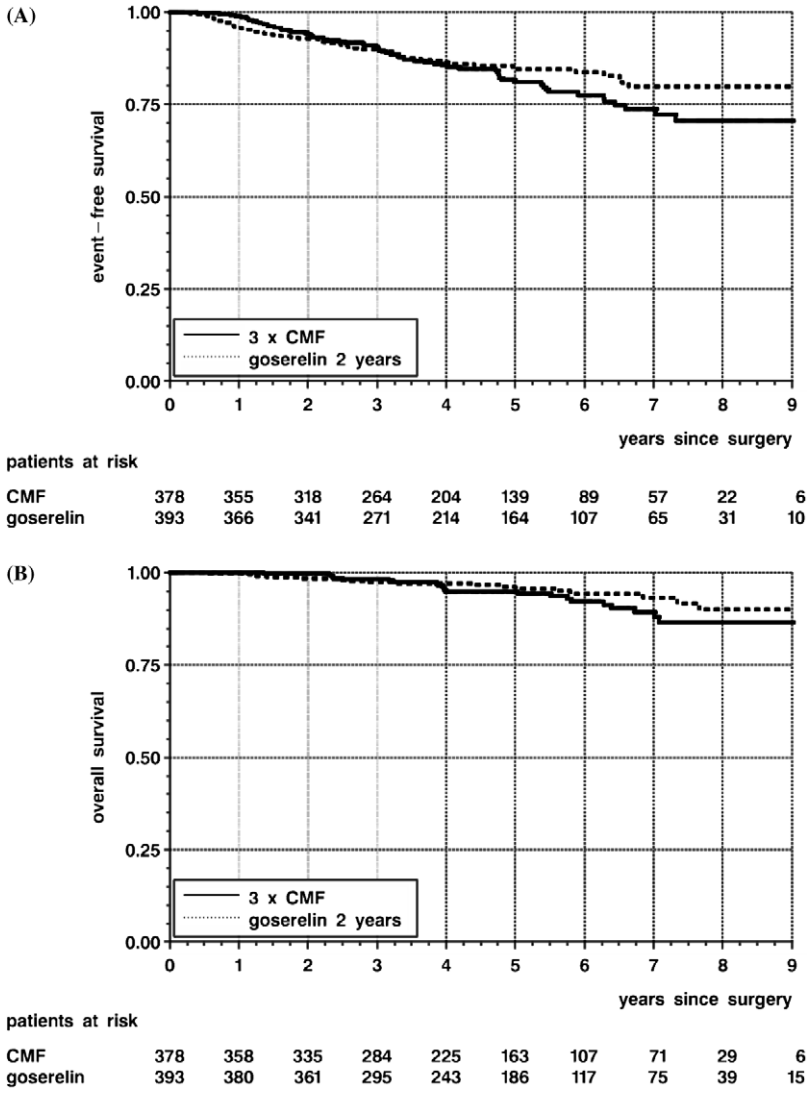


**Fig. 2 – Event-free (A) and overall (B) survival rate by treatment arm.**

**Table 3 – Adjustment for prognostic factors: simultaneous effect of treatment and prognostic factors on event-free survival**

| | | Hazard ratio | 95% confidence interval (CI) | P-value |
|---|---|---|---|---|
| Treatment | Goserelin versus CMF | 0.79 | (0.54–1.14)[a] | 0.19 |
| Tumour size (in mm) | >20 versus ⩽20 | 1.73 | (1.21–2.47) | 0.003 |
| Tumour grade | 3 versus 1/2 | 1.52 | (1.02–2.26) | 0.038 |
| Type of surgery | Mastectomy versus breast conservation | 1.82 | (1.27–2.63) | 0.001 |

CMF, cyclophosphamide, methotrexate, and 5-fluorouracil.
Patients with complete data for tumour size, grade, and type of surgery ($n = 758$, 372 CMF, 386 goserelin, 122 events). A hazard ratio <1 (>1) indicates an effect in favour of the first (second) treatment group or prognostic factor group.
a Confidence interval for treatment effect calculated with nominal level 95.7% to account for sequential test procedure in two interim analyses.

in a supplementary analysis not adjusted for type of surgery, in which the HR for large versus small tumours rose from 1.73 (Table 3) to 1.85 (data not shown).

### 3.5. *Analysis of differential treatment effects in prognostic subgroups*

No significant interaction was demonstrated for any of the examined prognostic factors at the pre-specified significance level of 1%. There is a trend to a benefit of goserelin for patients with good prognostic factors (small or grade 1–2 tumours, displaying positivity for both ER and PgR) (Table 4) and of younger age (⩽40) (Table 4, Fig. 3).

### 3.6. *Overall survival*

Five-year OAS rates are estimated as 95.0% and 96.2% in the CMF and goserelin groups, respectively. With only 42 deaths observed in total to date, it is too early for any definite analysis of overall survival (Fig. 2).

### 3.7. *Tolerability and serious adverse events*

The study medication was discontinued for medical reasons (other than recurrence or death) in 5 and 24 patients in the CMF and goserelin groups, respectively. Dose reductions to <90% of the planned dose of at least one component of CMF occurred in 3.4% of those who started. Overall, 5 patients treated in the CMF group versus 6 patients in the goserelin group experienced a treatment-related serious adverse event. One patient in the CMF group experienced a life-threatening febrile leukopaenia. No death occurred during treatment with CMF, and no life-threatening adverse events were reported in the goserelin group except two non-treatment related deaths (alcoholic liver damage (1), suicide (1)).

## 4. Discussion

Here we report results on the primary endpoint of the GABG-IV-A trial evaluating the effect of ovarian suppression for 2 years with goserelin or chemotherapy in premenopausal, hormone-responsive, node-negative breast cancer patients.

The strength of this trial is based on the strict eligibility criteria regarding endocrine responsiveness of the tumour. Because the ZEBRA study analysis showed that goserelin is effective in ER-positive patients, the inclusion criteria were changed towards the end of the recruitment phase to require positive ER status.[9]

The majority of the patients had tumours of 20 mm or less, and only 21% of patients had poorly differentiated or

**Table 4 – Interactions between treatment and prognostic factors with regard to event-free survival**

| Prognostic factor | Patient population | Hazard ratio[a] goserelin versus CMF with 99% CI | Interactive effect with 99% CI | P value for test of interaction |
|---|---|---|---|---|
| Tumour size[b] | ⩽20 mm | 0.54 (0.27–1.09) | 2.06 (0.79–5.38) | 0.053 |
| | >20 mm | 1.11 (0.58–2.14) | | |
| Tumour grade[b] | 1/2 | 0.62 (0.35–1.08) | 2.32 (0.82–6.60) | 0.038 |
| | 3 | 1.43 (0.59–3.46) | | |
| Age[c] | ⩽40 years | 0.51 (0.23–1.15) | 1.95 (0.72–5.29) | 0.086 |
| | >40 years | 1.00 (0.55–1.80) | | |
| Combined receptors (ER, PgR)[c,d] | ++ | 0.71 (0.40–1.26) | 1.64 (0.58–4.62) | 0.22 |
| | +– or –+ or – – | 1.16 (0.49–2.75) | | |

CMF, cyclophosphamide, methotrexate, and 5-fluorouracil; CI, confidence interval; ER, oestrogen receptor; PgR, progesterone receptor.
Patients with complete data for tumour size, grade and type of surgery ($n = 758$, 372 CMF, 386 goserelin, 122 events). A hazard ratio <1 (>1) indicates a subgroup effect in favour of goserelin (CMF). The interactive effect describes the factor by which the hazard ratio in the second subgroup is greater than in the first subgroup.
a Two separate Cox models including the factors tumour size, tumour grade, type of surgery, and factor-specific treatment effects.
b Prespecified analysis.
c Retrospective analysis.
d Patients with complete data and two known receptors ($n = 752$, 368 CMF, 384 goserelin, 119 events).

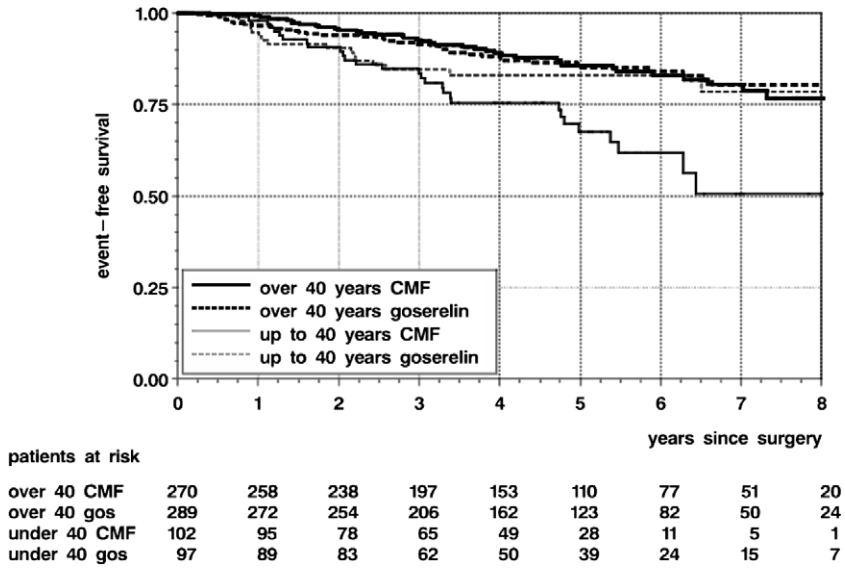


**Fig. 3 – Event-free survival rate by treatment arm and age.**

undifferentiated tumours. BCT in this young age group did not expose patients to an unacceptable risk of recurrence[19] because the rate of ipsilateral locoregional recurrence was only 4.9% (Table 2).

After approximately 5 years of follow-up, adjuvant treatment with goserelin was not found to be significantly superior to CMF; however, there was a trend in favour of goserelin. An increase in the number of events with further follow-up might lead to statistically significant results, especially as the differences between the two arms became apparent only after the fourth year of follow-up. However, further follow-up is precluded because the analysis of the trial is linked to the analysis of a series of clinical trials undertaken by the GABG.[20–22]

In two other trials, a direct comparison of CMF with goserelin in premenopausal patients was performed. In the ZEBRA study[9,23] node-positive, premenopausal patients were randomised to either six cycles of CMF or 2 years of goserelin. When only patients with ER-positive tumours (74%) were considered, ovarian suppression by goserelin showed an outcome equivalent to CMF with respect to disease-free survival. Similar results have been observed in the International Breast Cancer Study Group (IBCSG) trial VIII,[24] where only node-negative, premenopausal patients were treated with either 'classical' CMF for six courses, goserelin for 2 years, or CMF followed by goserelin for 18 months. A fourth arm with no adjuvant treatment was stopped during the early conduct of the trial, following an interim analysis and also based on results from the EBCTCG overview.[2] Again, 30% of the registered patients had ER-negative disease. In the 475 patients with ER-positive tumours, no difference between CMF and goserelin with regard to 5-year EFS was found (81% in both treatment arms).

Two explanations are possible for the divergent results of these three trials. At first, it may be debatable that three cycles of intravenous CMF are as effective as six cycles and/or 'classical' CMF with oral application of cyclophosphamide. No data are so far available that compare the adjuvant use of these schedules.[25] In a combined analysis[8] of two studies of the IBCSG and the German Breast Cancer Study Group (GBSG), no significant difference between three and six cycles of CMF was found in 1024 patients. These results are supported by the GABG III trial.[5]

Another explanation might be drawn from the results of the performed prospective subgroup analysis. We found that the benefit of goserelin is more pronounced in patients with good prognostic features (grade 1 or 2, size $\leqslant$ 20 mm), while there is a slightly elevated risk compared with CMF in patients with unfavourable prognostic characteristics.

The distribution of these prognostic factors varies between this trial and the ZEBRA study, where more patients with poorly differentiated tumours and tumours larger than 20 mm have been included. This difference might explain the tendency towards greater EFS in the goserelin treatment arm in this trial.

In contrast to the ABCSG-5 trial, distant relapses were more frequent in the CMF group, whereas local relapses were equally distributed; however, 50% of the patients in the ABCSG 5-trial had involved lymph nodes.[26]

As mentioned, we are aware of the slow recruitment of the trial, which forced us to perform a recalculation of sample size in 1999. We recognise that CMF may not be the standard of care today, but must emphasise that the trial was planned in the early 1990s. Even nowadays chemotherapy for node-negative patients is not considered to be a must.

This trial reconfirms the efficacy of the GnRH agonists as an adjuvant treatment in hormone-sensitive early-stage breast cancer. Because of the higher percentage of low-risk patients in node-negative disease, subgroups could be discriminated in which goserelin might provide more benefit to the patients compared with CMF chemotherapy.

## Conflict of interest statement

Jörg Wollert is an employee of AstraZeneca. The other authors state no conflict of interest.

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## REFERENCES

1. Beatson GT. On the treatment of inoperable carcinoma of the mamma: suggestions for a new method of treatment, with illustrative cases. *Lancet* 1898;**2**:104–62.
2. Early Breast Cancer Trialist's Collaborative Group. Effects of chemotherapy and hormonal therapy for early breast cancer on recurrence and 15-year survival: an overview of the randomised trials. *Lancet* 2005;**365**:1687–717.
3. Dees EC, Davidson NE. Ovarian ablation as adjuvant therapy for breast cancer. *Semin Oncol* 2001;**28**:322–31.
4. Goldhirsch A, Wood WC, Gelber RD, et al. Meeting highlights: updated international expert consensus on the primary therapy of early breast cancer. *J Clin Oncol* 2003;**21**:3357–65.
5. Maass HH. 3 versus 6 cycles of CMF in breast cancer patients with 1 to 9 positive nodes: results of the German Adjuvant Breast Cancer Group (GABG) III Trial. *Proc ASCO* 2000;**19**:283.
6. Schumacher M, Bastert G, Bojar H, et al. Randomized 2 x 2 trial evaluating hormonal treatment and the duration of chemotherapy in node-positive breast cancer patients. German Breast Cancer Study Group. *J Clin Oncol* 1994;**12**:2086–93.
7. International Breast Cancer Study Group. Duration and reintroduction of adjuvant chemotherapy for node-positive premenopausal breast cancer patients. *J Clin Oncol* 1996;**14**:1885–1894.
8. Colleoni M, Litman HJ, Castiglione-Gertsch M, et al. Duration of adjuvant chemotherapy for breast cancer: a joint analysis of two randomised trials investigating three versus six courses of CMF. *Br J Cancer* 2002;**86**:1705–14.
9. 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**:4628–35.
10. Kaufmann M, Jonat W, Blamey R, et al. Survival analyses from the ZEBRA study. goserelin (Zoladex) versus CMF in premenopausal women with node-positive breast cancer. *Eur J Cancer* 2003;**39**:1711–7.
11. von Minckwitz G, von der Assen A, Blohmer JU, et al. Medical ovarian ablation (Goserelin 2 yrs.) versus polychemotherapy (CMF x 3) in premenopausal patients with node-negative, receptor positive breast cancer – GABG trial 'IV-A-93'. *The Breast* 2001;**10**(suppl 1):S28.. abstr.
12. von Minckwitz G, Graf E, Geberth M, et al. Goserelin versus CMF as adjuvant therapy for node-negative, hormone receptor-positive breast cancer in premenopausal patients. The GABG IV-A-93 Trial. *Proc ASCO* 2004;**23**:534.. abstr.
13. Remmele W, Stegner HE. Recommendation for uniform definition of an immunoreactive score (IRS) for immunohistochemical estrogen receptor detection (ER-ICA) in breast cancer tissue. *Pathologe* 1987;**8**:138–40.
14. Schmoor C, Olschewski M, Sauerbrei W, et al. Long-term follow-up of patients in four prospective studies of the German Breast Cancer Study Group (GBSG): a summary of key results. *Onkologie* 2002;**25**:143–50.
15. Schoenfeld DA. Sample-size formula for the proportional-hazards regression model. *Biometrics* 1983;**39**:499–503.
16. Schemper M, Smith TL. A note on quantifying follow-up in studies of failure time. *Cont Clin Trials* 1996;**17**:343–6.
17. Clark TG, Altman DG, De Stavola BL. Quantification of the completeness of follow-up. *Lancet* 2002;**359**:1309–10.
18. Kalbfleisch JD, Prentice RL. *The statistical analysis of failure time data*. New York: Wiley; 1980.
19. Rutgers EJ. EUSOMA Consensus Group. Quality control in the locoregional treatment of breast cancer. *Eur J Cancer* 2001;**37**:447–53.
20. Kaufmann M, Graf E, Jonat W, et al. Tamoxifen versus control after adjuvant, risk-adapted chemotherapy in postmenopausal, receptor-negative patients with breast cancer: a randomized trial (GABG-IV D-93). *J Clin Oncol* 2005;**23**:7842–8.
21. Kaufmann M, Graf E, Jonat W, et al. Goserelin versus control after adjuvant, riskadapted chemotherapy in premenopausal patients with breast cancer: GABG-IV B-93. *J Clin Oncol* 2004;**22**(14S):588.. abstr.
22. Eiermann W, Graf E, Raab G, et al. Highdose epirubicin vs. standard-dose epirubicin cyclophosphamide followed by CMF in breast cancer patients with 10 or more positive lymph nodes: First results of a randomised trial of the German Adjuvant Breast Cancer Group (GABG). *Proc Am Soc Clin Oncol* 2001;**20**:A–127. abstr 127.

23. Kaufmann M, Jonat W, Blamey R, et al. Survival analyses from the ZEBRA study. goserelin (Zoladex) versus CMF in premenopausal women with node-positive breast cancer. *Eur J Cancer* 2003;**39**:1711–7.
24. Castiglione-Gertsch M, O'Neill A, Price KN, et al. Adjuvant chemotherapy followed by goserelin versus either modality alone for premenopausal lymph node-negative breast cancer: a randomised trial. *J Natl Cancer Inst* 2003;**95**:1833–46.
25. Engelsman E, Klijn JC, Rubens RD, et al. 'Classical' CMF versus a 3-weekly intravenous CMF schedule in postmenopausal patients with advanced breast cancer. An EORTC Breast Cancer Co-operative Group Phase III Trial (10808). *Eur J Cancer* 1991;**27**:966–70.
26. Jakesz R, Hausmanninger, Kubista E, et al. Randomized adjuvant trial of tamoxifen and goserelin versus cyclophosphamide, methotrexate, and fluorouracil: evidence for the superiority of 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**:4621–7.