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A randomised trial of goserelin versus control after adjuvant, risk-adapted chemotherapy in premenopausal patients with primary breast cancer – GABG-IV B-93 ☆

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ABSTRACT

GABG-IV B-93 is a prospective, randomised study comparing goserelin ($n = 384$) with no further treatment ($n = 392$) in hormone receptor (HR)-negative breast cancer patients ($n = 465$) after 3 cycles cyclophosphamide, methotrexate, 5-fluorouracil (CMF) for patients with 0–3 positive lymph nodes (LN) or 4 cycles epirubicin, cyclophosphamide (EC) followed by 3 cycles CMF for patients with 4–9 positive LN. After completion of the ZEBRA trial the study was amended to enrol also HR-positive patients with 1–9 + LN ($n = 311$).

After a median follow-up of 4.7 years neither HR-negative nor HR-positive patients showed a benefit for goserelin. The adjusted estimated hazard ratio for event-free survival in HR-negative patients was 1.01 (goserelin versus control, 95% confidence interval [CI] 0.72–1.42, $P = 0.97$) and 0.77 in HR-positive patients (95% CI 0.47–1.24, $P = 0.27$).

These results do not support the general use of goserelin after adjuvant chemotherapy in this group of premenopausal patients.

☆ The results of this study have been presented in part at the meeting of the American Society of Clinical Oncology in New Orleans, 2004.

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1. Introduction

The role of ovarian ablation as therapeutic option for premenopausal patients with primary breast cancer has been investigated over many years.[1–3] It has also been suggested that ovarian suppression, as reflected by amenorrhea, and also caused by chemotherapy, improved relapse-free and overall survival.[4–6]

As an alternative to permanent ovarian ablation by surgical oophorectomy or radiotherapy, luteinising hormone-releasing hormone (LHRH) analogues such as goserelin have been suggested.[7–9] This led to the initiation of several clinical trials in the early 1990s exploring the potential of goserelin in the adjuvant breast cancer setting.[5,10,11]

At that time, the role of ovarian ablation after adjuvant chemotherapy was unclear as was the role of endocrine treatment in receptor negative breast tumours. The German Adjuvant Breast Cancer Study Group (GABG) therefore initiated a randomised clinical trial to investigate the role of goserelin after risk-adapted chemotherapy in premenopausal patients with HR negative breast cancer. The study was conducted – under the short title GABG-IV B-93 – as part of a comprehensive series of trials covering the whole adjuvant setting including the international ZEBRA study.[5] After the completion of the ZEBRA study in April 1997, the inclusion criteria of GABG-IV B-93 were amended to allow the additional inclusion of patients with lymph node positive, HR-positive breast cancer.

This analysis includes the whole study population focussing the hormone receptor negative patients.

2. Patients and methods

2.1. Study design

Initiated in 1993, GABG-IV B-93 was one trial of a package of five launched throughout Germany to enrol patients according to their menopausal, hormone-receptor and lymph-node status.

In GABG-IV B-93 premenopausal patients were randomised either to goserelin (Zoladex® 3.6 mg subcutaneously every four weeks for two years) or no further treatment after a risk-adapted adjuvant chemotherapy consisting of either three cycles of CMF (cyclophosphamide 500 mg/m^2, methotrexate 40 mg/m^2 and 5-fluorouracil 600 mg/m^2, intravenously day 1, 8, every 4 weeks) for patients with 0–3 positive lymph nodes or four cycles of EC (epirubicin 90 mg/m^2 and cyclophosphamide 600 mg/m^2, intravenously every 3 weeks) followed by three cycles CMF in patients with 4–9 positive lymph nodes.

Premenopausal status was defined on the basis of regular menses in the last six months or on the basis of hormone levels (follicle stimulating hormone (FSH) < 20 IU/l, luteinising hormone (LH) > 50 pg/ml). Oestrogen and progesterone hormone receptor (HR) status were determined at local laboratories either biochemically by a dextran-coated charcoal assay (positive: score $\geqslant$ 20 fmol/mg), and/or based on an immunohistochemistry assay (positive: score $\geqslant$ 2).[12] After chemotherapy no registration of amenorrhoea was done. Negative HR status was defined as negative oestrogen and progesterone receptor status. Positive HR status was defined as positive for either oestrogen or progesterone receptor, or both.

Patients were centrally randomised, stratified by participating site. Within each centre block randomisation with randomly varying block size and a 1:1 treatment ratio was performed. No blinding was attempted.

Approvals from ethics committees were obtained and the study was conducted according to Good Clinical Practice guidelines and according to the Declaration of Helsinki. Prior to study participation each patient gave written informed consent.

2.2. Patient eligibility

Premenopausal women with histological diagnosis of breast cancer and either hormone receptor (HR)-negative (node-negative and node-positive) patients were admitted throughout the entire recruitment phase. In addition, HR-positive, node-positive patients were also eligible from April 1997. Hence there was an overlap in the recruitment of HR-negative and HR-positive patients: stage pT1–3, N0–N3, M0; no prior surgical, systemic or radiation therapy for breast cancer; Karnofsky index $\geqslant$60. Major exclusion criteria were distant metastases; T4 tumours; incomplete surgical resection; 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 and randomisation not within 28 days of definitive primary surgery.

Patients were recruited from 66 centres all over Germany.

2.3. Evaluation criteria

Follow-up examinations were scheduled every three months for the first two years, every six months up to year five, and annually thereafter. The primary end-point was event free survival (EFS), defined as time from definitive primary surgery to the first event of failure (locoregional recurrence, metastases, second primaries including contralateral breast cancer, or death). The first event of failure was classified as isolated locoregional recurrence if locoregional recurrence occurred at least four weeks before an event at a distant site. The secondary end-point overall survival (OS) was defined as the interval from definitive primary surgery to death of any cause.

2.4. Statistical methods

Based on preliminary data of patients selected from previous studies[13] using the eligibility criteria, it was anticipated that EFS would be 60% at five years in the control group. Thus, 190 events would be required to detect a hazard ratio of 0.67 for goserelin versus control, i.e. an improvement to about 71% in the goserelin group, with a power of 80% using a two-sided log-rank test at the level $\alpha = 5\%$.[14] With four years of planned recruitment and two years additional follow-up, at least 700 patients would have to be included. No attempt was made to adapt these calculations after the amendment allowing inclusion of node-negative, HR-positive patients, since it was clear that recruitment of substantially more patients would not be feasible.

EFS and OS rates were estimated by Kaplan–Meier curves.[15] Event-free patients were censored at the last visit. 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 on EFS was estimated as the hazard ratio in a Cox model[18] with a two-sided 95% confidence interval. Two multiple Cox models were fitted in HR-negative and HR-positive patients, respectively, including treatment, tumour size, tumour grade and type of surgery. These models were stratified for the number of positive nodes (0, 1–3, 4–9) and were based on patients with complete data. P-values were based on two-tailed Wald tests.[19] During the study, two formal interim analyses of the treatment effect on EFS were conducted. To maintain the overall significance level of $\alpha = 5\%$, the present, final analysis with 215 events was carried out at the nominal significance level $\alpha' = 4.34\%$.[20] Accordingly, 95.66% confidence intervals are reported for the hazard ratios between treatment groups in the analyses of EFS.

Data were processed and evaluated with the Statistical Analysis System SAS.[21] Following the intention-to-treat principle, ineligible patients were not excluded, and treatment was analysed as randomised.

Analyses were carried out in accordance with a pre-specified analysis plan in which the joint evaluation of HR-negative and HR-positive patients was the primary analysis and subgroup evaluations were planned as secondary analyses. Given the meanwhile firmly established predictiveness of HR-status for response to goserelin, the focus in this presentation was shifted towards the separate analyses of HR-positive and HR-negative patients.

3. Results

3.1. *Recruitment and patient characteristics*

Between February 1993 and December 2000, a total of 776 patients (pts) were randomised, 465 pts were HR-negative (241 in the control arm, 224 in the goserelin arm), 311 pts were HR-positive, whose inclusion was allowed after April 1997 (151 in the control arm, 160 in goserelin arm). In the HR-negative subpopulation 32% of the pts were up to 40 years old and the majority (62%) were nodal negative. Tumours were greater than 2 cm in largest diameter in 52% and histological grade 3 was found in 59% of the tumours in this subgroup. Baseline characteristics were well balanced (Table 1).

The eligibility criteria turned out to be violated in 73 pts, mostly due to inadequate receptor or nodal status (receptor positive before amendment or receptor positive, node negative after amendment), and delayed start of chemotherapy or randomisation. Thirty-five were from the control group, 38 were in the arm allocated to goserelin. These patients were included in the analyses.

3.2. *Compliance*

All planned cycles of chemotherapy were completed in 97% in HR-negative pts in the control arm and in 96% in the goserelin

Table 1 – Characteristics of treatment groups according to receptor status

	Receptor negative		Receptor positive	
	Control, $n = 241$	Goserelin, $n = 224$	Control, $n = 151$	Goserelin, $n = 160$
Age (in years)				
⩽40	83 (34%)	65 (29%)	42 (28%)	40 (25%)
>40	158 (66%)	159 (71%)	109 (72%)	120 (75%)
Number of positive lymph nodes[a]				
0	146 (61%)	140 (63%)	10 (7%)	15 (9%)
1–3	56 (23%)	49 (22%)	87 (58%)	93 (58%)
4–9	39 (16%)	35 (16%)	54 (36%)	52 (33%)
Tumour size (in mm)				
⩽20	119 (49%)	106 (48%)	72 (48%)	82 (51%)
>20	122 (51%)	117 (52%)	79 (52%)	78 (49%)
Unknown	0	1	0	0
Tumour grade				
1	15 (6%)	11 (5%)	13 (9%)	13 (8%)
2	78 (33%)	87 (39%)	78 (53%)	92 (59%)
3	147 (61%)	124 (56%)	56 (38%)	52 (33%)
Unknown	1	2	4	3
Type of surgery				
Breast Conservation	148 (61%)	132 (59%)	89 (59%)	93 (58%)
Mastectomy	93 (39%)	92 (41%)	62 (41%)	67 (42%)
Adjuvant radiotherapy				
Yes	158 (66%)	137 (62%)	99 (66%)	105 (67%)
No	83 (34%)	85 (38%)	50 (34%)	52 (33%)
Unknown	0	2	2	3

a Linked to risk-adapted chemotherapy by study design.

arm, respectively. The whole population got all planned cycles in 96% in the control arm, and in 95% in the goserelin arm (Fig. 1).

Among at all patients who started and did not stop for recurrence or death ($n = 282$), 73% received all planned 24–26 depots (median duration 24 months, range 22–35 months). Forty six patients in the goserelin group did not start therapy, three due to recurrence. Thirty-one percent of those who started were delayed (>34 days after start of the third cycle of CMF chemotherapy). In the control group seven patients received adjuvant goserelin.

3.3. *Follow-up and observed events*

The data cut-off for this analysis was June 2003, leading to a median follow-up of 5.5 years (HR-negative) and 4 years (HR-positive), respectively. Completeness of follow-up was 88–90% (Fig. 1).

With regard to event-free survival, 215 events had been observed so far. 143 events occurred in HR-negative pts. Table 2 shows the distribution of the different events of failure. In HR-negative pts the first event of failure (goserelin versus control) was an isolated locoregional recurrence (25 versus 13), a distant failure (44 versus 59) and death without previous recurrence (0 versus 2). 104 deaths occurred so far in the whole study population. 85 deaths had been observed in HR-negative group, 44 pts died in the goserelin arm, and 41 in the control arm.

3.4. *Event-free and overall survival*

In all pts five-year EFS rates are estimated as 71% (95% confidence interval (CI), 66–76%) and 68% (95% CI, 62–73%) in the goserelin and in the control group, respectively. The unadjusted hazard ratio of goserelin versus control pooling HR-negative and HR-positive patients was 0.92 (95% CI, 0.70–1.21; calculated as 95.66% CI to account for two interim analyses; $P = 0.54$).

In HR-negative pts the adjusted hazard ratio goserelin versus control is 1.01 (95%-CI, 0.72–1.42; calculated as 95.66% CI

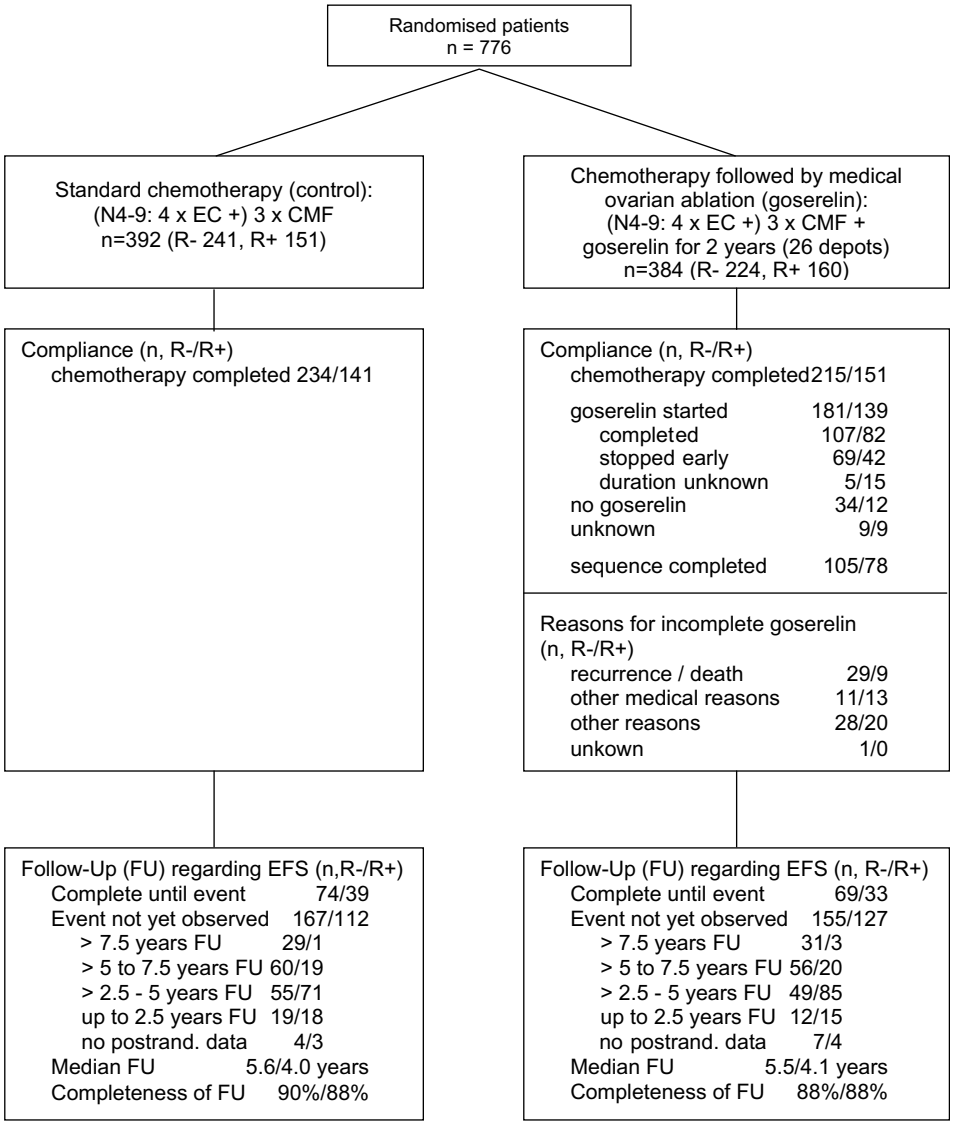

Fig. 1 – Flow diagram of study participants.

Table 2 – Distribution of events of failure

	Receptor negative		Receptor positive	
	Control, $n = 241$	Goserelin, $n = 224$	Control, $n = 151$	Goserelin, $n = 160$
First event of failure 1				
Isolated locoregional recurrence (ipsilateral)	13	25	16	18
Distant failure	59	44	23	15
Contralateral breast	7	0	5	0
Distant metastases (non-breast)	45	41	18	13
Second non-breast cancer malignancy	7	3	0	2
Death without recurrence	2	0	0	0
Status				
Alive without recurrence	163	148	109	123
Alive with recurrence	33	25	28	25
Death without recurrence	2	0	0	0
Death after recurrence	39	44	11	8
Number of events for event free survival (EFS)	74	69	39	33
Number of events for overall survival (OS)	41	44	11	8

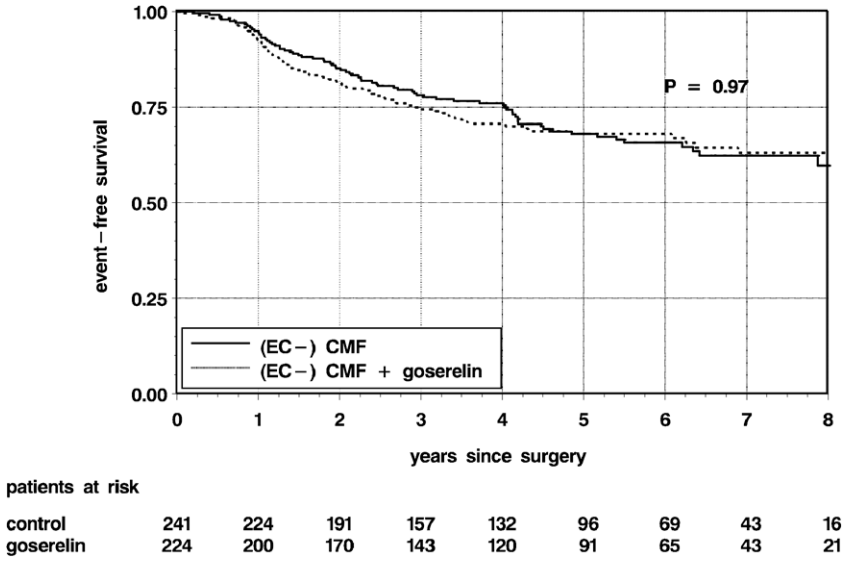

Fig. 2a – Event-free survival rate (EFS) by treatment arm, receptor negative patients.

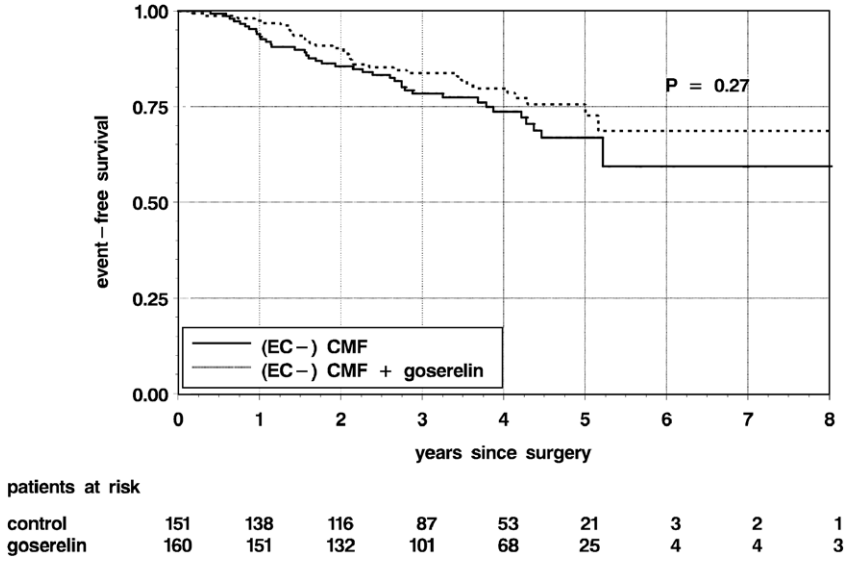

Fig. 2b – Event-free survival rate (EFS) by treatment arm, receptor positive patients.

to account for interim analyses; $P = 0.97$). In HR-positive pts the adjusted hazard ratio goserelin versus control is 0.77 (95%-CI, 0.47–1.24; calculated as 95.66% CI to account for interim analyses; $P = 0.27$).

EFS rates by treatment in HR-negative and positive pts are displayed in Figs. 2a and 2b.

Five-year OS rates of all pts are estimated as 86% and 85% in the goserelin and in the control group, respectively. With 104 (13%) deaths observed up to now, it is too early for any definite analysis of OS.

3.5. *Tolerability and adverse events*

Goserelin was discontinued for medical reasons other than recurrence or death in 24 pts. In the control group serious adverse events related to chemotherapy were reported in 17 pts (leucopenia/thrombopenia 5, emesis/nausea 2, seroma 2, abscess 2, and thrombophlebitis, hyponatriamia, stomatitis, virtiligo, infection, fever 1, respectively). In the goserelin group serious adverse events related to therapy were reported in 14 pts, six during chemotherapy (wound healing disorders 2, and emesis/nausea, paravasation, leucopenia, infection 1, respectively), eight during or after goserelin treatment (psychiatric disorders 3, erysipelas 2, wound pain, endometrial hyperproliferation, mastopathy 1, respectively). No patient died during study medication.

4. Discussion

In GABG-IV B-93, we investigated whether premenopausal breast cancer patients may benefit from an additional treatment with goserelin after risk-adapted chemotherapy. The study was originally intended to enrol only HR-negative patients, independent of the lymph node status. At the beginning of the 1990s hormone receptor status was not yet a predictive marker for the effectiveness of ovarian ablation in premenopausal patients. Due to slow recruitment patients with lymph node positive, HR-positive breast cancer were also included after the completion of the ZEBRA study in April 1997, so that the trial could continue. We observed 215 events overall, 143 in HR-negative patients for whom 190 had been planned, and 72 in HR-positive patients. Thus although underpowered for both the HR-negative and HR-positive population, the study does contribute substantial further evidence to the evolving knowledge on the effectiveness of hormonal ovarian ablation.

The results of the study do not indicate an advantage of additional goserelin after a risk-adapted chemotherapy with respect to EFS in HR-negative patients. Although the role of endocrine treatment in HR-negative breast tumours was unclear in the beginning of the 1990s, no other trials investigated the effectiveness of goserelin in premenopausal HR-negative women. In a three-arm study, the International Breast Cancer Study Group (IBCSG) compared goserelin, CMF and the combination of CMF and goserelin in patients with node-negative breast cancer.[11] With the latter two treatment arms, this study is similar to ours which, however, was not restricted to node-negative breast cancer. Also, similar to our trial, more than 30% of all patients were HR-negative. In the IBCSG trial, the combination of CMF and goserelin provided a statistically non-significant improvement compared with CMF alone. The Zoladex in Premenopausal Patients (ZIPP) study compared HR-positive and negative (>30%), premenopausal patients with operable breast cancer treated with tamoxifen, goserelin, a combination of both or no further endocrine treatment after adjuvant therapy (radiation and/or chemotherapy).[22] After a median follow-up of 5.5 years there was a statistically significant benefit with respect to first events in women treated with goserelin ($p = 0.002$). Neither the IBCSG nor the ZIPP trial showed any benefit in HR-negative patients. Also our findings agree with the general evidence of endocrine therapy in postmenopausal, HR-negative patients, which has been accumulating since 1985.[23]

In contrast to most other trials we are also not able to demonstrate a significant improvement by adding goserelin to chemotherapy in the group of node-positive, HR-positive patients.[24] Superiority could theoretically be expected but there is only limited information from studies that cover such a direct comparison in a high risk subgroup. One of those is the three-arm trial of the Eastern Cooperative Oncology Group[25] that compared adding goserelin or tamoxifen to chemotherapy (cyclophosphamide, doxorubicin and fluorouracil) to chemotherapy alone in premenopausal, node-positive and oestrogen-receptor-positive patients. This study failed also to demonstrate a statistically significant advantage of adding goserelin, with an estimated hazard ratio of 0.93 based on a considerably larger number of patients and observed events than in the corresponding subgroup of patients in our study. Arriagada and colleagues, showed in a randomised trial with 926 premenopausal patients (90% node positive, 63% HR positive), treated with an adjuvant antracycline chemotherapy alone or a chemotherapy combined with ovarian suppression, no benefit of using ovarian suppression after a follow-up period of 9.5 years.[26] Thus, the results for the overall population were very similar to those obtained in our study in high risk, HR-positive patients.

It has been reported in the review of the Early Breast Cancer Trialists' Collaborative Group as well as in the ECOG and the IBCSG trial that a benefit of the combination therapy is most apparent in the subgroup of HR-positive patients <40 years of age.[3,11,25] We cannot investigate this issue in the group of node-negative patients since these have been included in another clinical trial conducted in parallel to this study.[27] In an additional subgroup analysis performed in our study, we did not find any indication for a differential treatment effect in patient $\leqslant$40 versus >40 years of age (data not shown). All these findings, however, suffer from the well-known limitations of retrospective subgroup analyses.[28]

In summary, goserelin is an attractive option for premenopausal, hormone receptor positive patients, when used alone.[27,29] Still there is no definitive conclusion on the value of goserelin after chemotherapy in a node positive and HR-positive population older than 40 years so far. In HR-negative patients no benefit of goserelin was evaluated.

Nevertheless the use of chemo-endocrine therapy in premenopausal patients needs further and more detailed evaluation, preferably in studies exploring a strategy of confining the use of ovarian suppression to women who do not become postmenopausal after chemotherapy.[30] An appealing possi-

bility to answer this question will be explored in the Suppression of Ovarian Function Trial (SOFT trial) promoted by the IBCSG.

Conflict of interest statement

None declared.

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