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Dose-intensified epirubicin versus standard-dose epirubicin/cyclophosphamide followed by CMF in breast cancer patients with 10 or more positive lymph nodes: Results of a randomised trial (GABG-IV E-93) – The German Adjuvant Breast Cancer Group ☆

Wolfgang Eiermann [a,], Erika Graf [b], Beyhan Ataseven [a], Bettina Conrad [c], Jörn Hilfrich [d], Heidi Massinger-Biebl [e], Sabine Vescia [f], Sibylle Loibl [g], Gunter von Minckwitz [g,h], Martin Schumacher [b], Manfred Kaufmann [h], for the German Adjuvant Breast Cancer Group*

[a] *Frauenklinik vom Roten Kreuz, Taxistraße 3, 80637 München, Germany*
[b] *Medizinische Biometrie und Statistik, Universitätsklinikum Freiburg, Stefan-Meier-Straße 26, 79104 Freiburg, Germany*
[c] *Brustzentrum, Elisabeth-Krankenhaus Kassel, Weinbergstraße 7, 34117 Kassel, Germany*
[d] *Henriettenstiftung, Schwemannstraße 17, 30559 Hannover, Germany*
[e] *Gemeinschaftspraxis, Marktplatz/Weißbräugasse 2a, 94065 Waldkirchen, Germany*
[f] *Stadtkrankenhaus Hanau, Leimenstr. 20, 63450 Hanau, Germany*
[g] *German Breast Group, GBG Forschungs GmbH, Schleussnerstraße 42, 63263 Neu-Isenburg, Germany*
[h] *Klinik für Gynäkologie und Geburtshilfe, J.W. Goethe Universität, Theodor-Stern-Kai 7, 60590 Frankfurt, Germany*

ARTICLE INFO

Article history:
Received 23 June 2009
Received in revised form 1 September 2009
Accepted 1 October 2009
Available online 30 October 2009

Keywords:
High-risk node-positive breast neoplasms
Adjuvant chemotherapy
Anthracyclines

ABSTRACT

To compare dose-intensified epirubicin monotherapy with a standard sequential regimen, patients with primary breast cancer and ⩾10 involved axillary nodes were randomised to either four 21-day cycles of epirubicin 120 mg/m^2 (E120; $n = 202$) or four 21-day cycles of epirubicin 90 mg/m^2 plus cyclophosphamide 600 mg/m^2 (EC) followed by three 28-day cycles of cyclophosphamide, methotrexate and 5-fluorouracil (CMF; $n = 209$). Simultaneous hormonal treatment was applied in both arms. At 5 years' median follow-up, the 5-year event-free survival (EFS) rates were 47.7% (95% confidence interval [CI], 40.2–55.2%) for E120 and 45.9% (38.5–53.3%) for EC-CMF. E120 was as effective as EC-CMF with regard to EFS (hazard ratio [HR] for E120 versus EC-CMF 1.04; 95% CI, 0.79–1.36; $p = 0.79$) and overall survival (HR 1.06; 95% CI 0.77–1.46; $p = 0.72$). The data demonstrate that 4 cycles of dose-intensified epirubicin monotherapy can be as effective as 7 cycles of standard sequential polychemotherapy in high-risk breast cancer patients with ⩾10 positive lymph nodes, despite treatment with a single agent and a shorter treatment duration.

☆ This report presents the final analysis of trial GABG-IV E-93. Preliminary results were reported at the ASCO Annual Meeting in 2001.

* *Corresponding author:* Tel.: +49 89 15706 620x621; fax: +49 89 15706 623.
E-mail address: w.eiermann@gmx.net (W. Eiermann).

0959-8049/$ - see front matter
doi:10.1016/j.ejca.2009.10.001

1. Introduction

Randomised trials in early breast cancer have assessed the long-term effects of various systemic adjuvant therapies on breast cancer recurrence and survival. The use of adjuvant polychemotherapy and the implementation of anthracycline for the treatment of breast cancer could improve event-free survival (EFS) and overall survival (OS). High-risk patients with ⩾10 positive lymph nodes also derive significant benefit from adjuvant chemotherapy, but these patients exhibit a high recurrence rate at 5 years, with an EFS of less than 50%.[1]

In 1993 the German Adjuvant Breast Cancer Group (GABG) started a series of trials which enrolled patients according to their menopausal, hormone-receptor and lymph-node status.[2–4] The GABG trial IV E-93 was designed for patients with ⩾10 positive lymph nodes. In the standard arm a sequential chemotherapy of four cycles of epirubicin and cyclophosphamide (EC) followed by three cycles of cyclophosphamide, methotrexate and fluorouracil (CMF) was applied; in the experimental treatment arm, four cycles of dose-intensified epirubicin (120 mg/m^2) were chosen. The study design was based on the earlier trials, which showed a benefit of sequential doxorubicin/CMF application in women with extensive nodal involvement,[1] equal efficacy but lower toxicity for epirubicin compared with doxorubicin,[5] comparable efficacy of three versus six cycles of CMF,[6] and evidence that 120 mg/m^2 epirubicin every 3 weeks was reasonably well tolerated, associated with promising activity and its simplicity.[7]

The study was conducted in parallel as an alternative to another trial comparing the same standard arm with a high-dose regimen requiring autologous stem-cell support.[8] Here we present the results of the GABG trial IV E-93 at 5 years' median follow-up; preliminary results have been reported previously.[9]

2. Patients and methods

2.1. Study design

Patients with ⩾10 positive axillary lymph nodes were randomised to either four 21-day cycles of epirubicin 120 mg/m^2 intravenously (E120) or four 21-day cycles of epirubicin 90 mg/m^2 and cyclophosphamide 600 mg/m^2 intravenously followed by three 28-day cycles of cyclophosphamide 500 mg/m^2, methotrexate 40 mg/m^2 and 5-fluorouracil 600 mg/m^2 intravenously on days 1 and 8 (EC-CMF).

Chemotherapy and endocrine therapies (goserelin 3.6 mg subcutaneously every 28 days for 2 years in premenopausal women, tamoxifen 30 mg once a day for 5 years in postmenopausal women) were initiated simultaneously within 28 days after surgery irrespective of hormone-receptor status. Optional radiotherapy was applied according to the local guidelines.

Patients with confirmed eligibility were centrally randomised by fax based on computer generated lists, stratified by participating site and menopausal status. Within each stratum, block randomisation with randomly varying block size and a 1:1 treatment ratio was performed. No blinding was attempted. All data were verified against patients' records.

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

2.2. Patient eligibility

Women aged ⩽70 years with histologically confirmed invasive breast cancer with ⩾10 positive axillary lymph nodes were eligible if they met the following criteria: stage pT1-3, ⩾pN10+, M0; complete surgical resection; no systemic or radiation therapy against breast cancer; Karnofsky index ⩾60 or a World Health Organisation performance status of ⩽2; using effective non-endocrine contraception/hormone replacement therapy (HRT) to be stopped, if applicable; suitability for follow-up; and written informed consent. Major exclusion criteria were distant metastases; any T4 tumour; incomplete surgical resection; simultaneous contralateral breast cancer; previous malignancy except basal carcinoma of the skin or *in situ* carcinoma of the uterine cervix; pregnancy or lactation; insufficient organ function or significant co-morbidities; and randomisation more than 28 days after definitive primary surgery.

2.3. Evaluation criteria

Follow-up examinations were scheduled every 3 months for the first 2 years, every 6 months up to year five and annually thereafter. The primary end-point was EFS, defined as time from definitive primary surgery to the first occurrence of disease relapse (local, regional or distant), second primary malignancy or death. The secondary end-point was OS, defined as the interval from definitive primary surgery to death of any cause.

2.4. Determination of prognostic factors

For patients without HRT before enrolment, premenopausal status was defined as menses occurring within the preceding 6 months, or as a follicle-stimulating hormone (FSH) level <20 IU/L and a luteinising hormone (LH) level <50 pg/mL. Serum FSH and LH levels were determined 7 days after discontinuation of HRT if applicable. Oestrogen receptor (ER) and progesterone receptor (PgR) status were determined at local centres using an immunohistochemical and/or an immunologic method (positive: score ⩾2) and/or, preferably, a biochemical assay (positive: ⩾20 fmol/mg protein following consensus practice in Germany).

For a combined description of baseline prognosis, the Nottingham Prognostic Index (NPI) was used (defined as 0.2 × tumour size [cm] + lymph-node stage [1 = node negative, 2 = 1–3 positive nodes, 3 = ⩾4 positive nodes] + tumour grade [1–3]).[10,11]

2.5. Statistical methods

Based upon the early analysis of the previous studies,[12] it was estimated that EFS after 5 years would be 25% following EC-CMF. To detect a hazard ratio (HR) of 0.67 for E120 versus EC-CMF, corresponding to an improvement to 40% EFS in

the E120 group, with a power of 80% using a two-sided log-rank test at the 5% level, 190 events were necessary. Assuming 4 years recruitment and 2 years additional follow-up, 320 patients had to be randomised.

EFS and OS rates were estimated using Kaplan–Meier curves, censoring event-free patients at the last reported visit. Median follow-up was based on the estimated censoring distribution, and the percentage of complete follow-up was calculated.[8,13] The treatment effect was estimated as HR in a Cox model with a 95% confidence interval (CI), and *p*-values were based on Wald tests. The unadjusted effects of a predefined set of prognostic factors were examined for EFS. An adjusted analysis of treatment and prognostic factors was performed in a multiple Cox model for EFS including treatment, number of positive lymph nodes, degree of lymph node involvement, tumour grade, hormone receptors and those prognostic factors which had shown a significant effect at the 5% level in the unadjusted models (candidate factors: age, menopausal status, type of surgery, number of lymph nodes examined and tumour size) to establish comparability with other study reports.[8] OS was analysed adjusting for the same factors as EFS.

As in another dose-intensified trial,[8] differential treatment effects on EFS were examined for menopausal status, tumour grade and ER status. A separate Cox regression model for each of these was fitted which included the three factors and those

Table 1 – Characteristics of treatment groups.

		EC-CMF *n* = 209	E120 *n* = 202	All patients *n* = 411
Age (in years)	⩽40	13 (6%)	16 (8%)	29 (7%)
	41–60	127 (61%)	122 (60%)	249 (61%)
	>60	69 (33%)	64 (32%)	133 (32%)
Menopausal status*	Pre	60 (29%)	59 (29%)	119 (29%)
	Post	149 (71%)	143 (71%)	292 (71%)
Number of positive lymph nodes	10–11**	54 (26%)	45 (22%)	99 (24%)
	12–15	69 (33%)	59 (29%)	128 (31%)
	⩾16	86 (41%)	98 (49%)	184 (45%)
Number of lymph nodes examined	10–19	54 (26%)	50 (25%)	104 (26%)
	⩾20	152 (74%)	151 (75%)	303 (74%)
	Unknown	3	1	4
Degree of lymph node involvement	<100% positive	187 (91%)	178 (89%)	365 (90%)
	=100% positive	19 (9%)	23 (11%)	42 (10%)
	Unknown	3	1	4
Tumour size (in mm)	⩽20	38 (18%)	49 (24%)	87 (21%)
	21–30	72 (35%)	72 (36%)	144 (35%)
	>30	98 (47%)	80 (40%)	178 (44%)
	Unknown	1	1	2
Tumour grade	1	3 (1%)	5 (2%)	8 (2%)
	2	105 (51%)	80 (40%)	185 (46%)
	3	98 (48%)	116 (58%)	214 (53%)
	Unknown	3	1	4
Nottingham Prognostic Index	25% Quantile	5.6	5.6	5.6
	Median	6.3	6.4	6.3
	75% Quantile	6.6	6.6	6.6
	Unknown	4	2	6
Oestrogen receptor status	Positive	138 (67%)	116 (57%)	254 (62%)
	Negative	67 (33%)	86 (43%)	153 (38%)
	Unknown	4	0	4
Progesterone receptor status	Positive	129 (63%)	110 (54%)	239 (59%)
	Negative	76 (37%)	92 (46%)	168 (41%)
	Unknown	4	0	4
Type of surgery	Breast preservation	68 (33%)	74 (37%)	142 (35%)
	Mastectomy	141 (67%)	127 (63%)	268 (65%)
	Unknown	0	1	1
Adjuvant radiotherapy	Yes	117 (57%)	110 (56%)	227 (56%)
	No	89 (43%)	87 (44%)	176 (44%)
	Unknown	3	5	8

* Determines hormonal treatment.

** Includes two patients with <10 positive lymph nodes.

prognostic factors that showed an effect at the 15% level in the adjusted EFS analysis described above. Separate treatment effects were included for both values of the factor in question, and the interaction was tested with a Wald test. Because of multiple testing, a significance level of 1% was used in these tests. The corresponding multiplicative interactive effects and the HRs between the treatments within each subgroup were estimated with 99% CIs. Data were evaluated using SAS according to a pre-specified analysis plan. Following the intention-to-treat principle, treatment was analysed as randomised. For all tests, *p*-values and CIs were two-sided.

3. Results

3.1. Patients included

Four-hundred and eleven patients were randomised in 54 centres across Germany between March 1993 and December 2000, 209 patients to EC-CMF and 202 to E120. Overall, the patients in the two treatment groups were well matched for baseline clinical characteristics, with slightly more hormone receptor-positive patients allocated to the EC-CMF arm. The patients in the E120 group tended to have smaller tumours but higher tumour grade compared with those randomised to EC-CMF, therefore, the NPI was similar in the two arms (Table 1).

A small number of patients violated the eligibility criteria ($n = 13$); eight in the EC-CMF group (<10 positive lymph nodes, $n = 2$; pT4 breast cancer, $n = 4$; randomisation more than 28 days after surgery, $n = 2$), and five in the E120 group (simultaneous contralateral breast cancer, metastases at randomisation, pT4 breast cancer, inflammatory breast cancer and occult cancer with resection of only the axilla in one patient each). These patients were included in the analyses.

3.2. Compliance

The assigned chemotherapy was applied in 97.1% ($n = 203$) of the patients in the EC-CMF group and 94.6% ($n = 191$) in the E120 group; of whom 89.2% and 93.2%, respectively, completed the therapy (Fig. 1). Dose reductions of more than 10% in $\geqslant 1$ chemotherapy component occurred in 12.8% versus 3.1% of patients who commenced EC-CMF or E120 as randomised. The allocated chemotherapy was initiated more

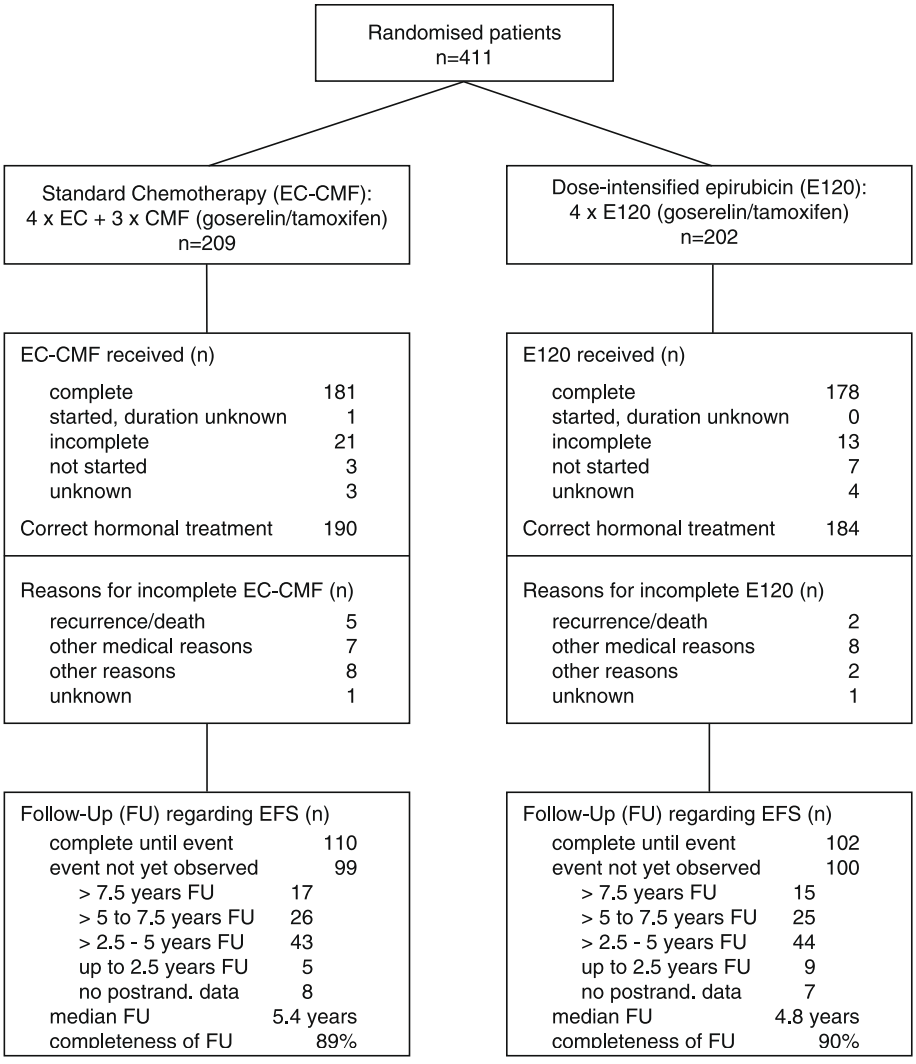


Fig. 1 – Flow diagram of study participants.

Table 2 – Distribution of events of failure.

	EC-CMF $n = 209$	E120 $n = 202$	All patients $n = 411$
Status			
Alive without recurrence	99	100	199
Alive with recurrence	34	27	61
Death without recurrence	5	2	7
Death after recurrence	71	73	144
Number of events for event-free survival (EFS)	110	102	212
Number of events for overall survival (OS)	76	75	151

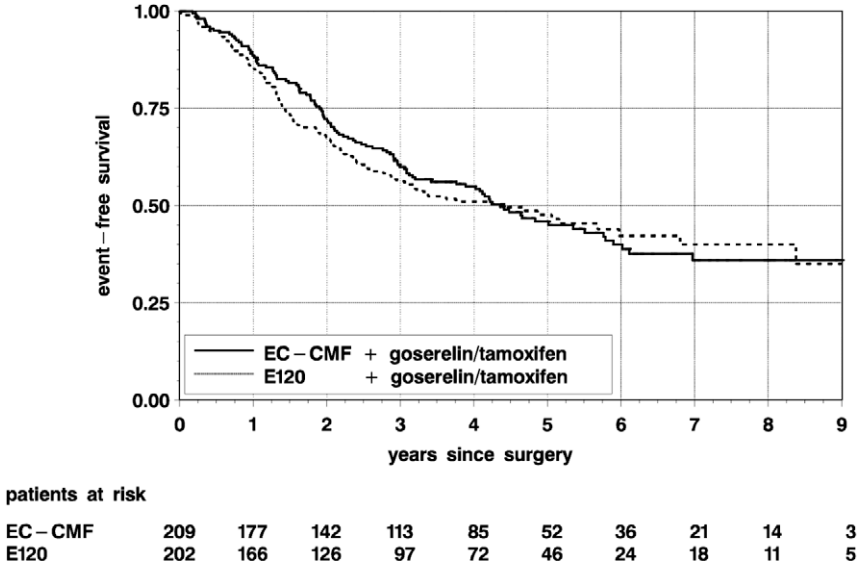


Fig. 2 – Event-free survival rate (EFS) by treatment arm.

than 28 days after surgery in 12 and 16 patients of the EC-CMF and E120 group, respectively. Three patients randomised to EC-CMF and 7 to E120 did not start therapy. Twelve and 9 patients randomised to EC-CMF and E120, respectively, did not receive the correct hormonal therapy (unknown in 7 and 9 patients, respectively). Among the patients who did receive the correct hormonal treatment, sequential therapy after chemotherapy occurred in 12.1% versus 11.4% of patients allocated to EC-CMF and E120, respectively.

3.3. *Follow-up and observed events*

The patients were followed up until June 2003 leading to a median follow-up of 5.1 years (E120: 4.8 years, EC-CMF: 5.4 years). No further follow-up was performed. Completeness of follow-up was similar in both groups (Fig. 1). For E120 versus EC-CMF, 102 versus 110 events with regard to EFS and 75 versus 76 events (deaths of any cause) with regard to OS were observed, respectively (Table 2).

3.4. *EFS*

EFS rates by treatment are displayed in Fig. 2. Five-year EFS rates were estimated as 47.7% (95% CI, 40.2–55.2%) and 45.9% (95% CI, 38.5–53.3%) in the E120 and the EC-CMF group, respectively. The unadjusted HR of E120 versus EC-CMF was 1.04 (95% CI, 0.79–1.36). This effect was not significant ($p = 0.79$).

Of the prognostic factors examined, age, type of surgery, number of positive lymph nodes, degree of lymph node involvement, tumour size, tumour grade and ER as well as PgR status were included into the adjusted regression model (Table 3). Age, number of positive lymph nodes, degree of lymph node involvement, tumour size and ER status exhibited significant effects ($p < 0.05$). The adjusted analysis confirmed the unadjusted results (HR 1.02 [95% CI, 0.77–1.34], $p = 0.91$).

3.5. *Treatment effects in prognostic subgroups*

The analysis of EFS in patient subgroups defined by menopausal status, tumour grade and ER status was prospectively planned with a significance level of 1% for the test of equal effects in the two groups of the corresponding factor. Although significant interactions could not be demonstrated (Table 4), there is an apparent trend indicating that patients with a poorer prognosis, such as premenopausal patients (Fig. 3) or women with ER-negative disease (Fig. 4), exhibit poorer EFS when treated with E120 compared with those patients receiving EC-CMF.

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	E120 versus EC-CMF	1.02	[0.77, 1.34]	0.91
Age (in years)	41–60 versus ⩽40	0.47	[0.29, 0.77]	0.003
	>60 versus ⩽40	0.40	[0.23, 0.68]	
Type of surgery	Mastectomy versus breast preservation	1.37	[0.99, 1.88]	0.058
Number of positive lymph nodes	⩾16 versus 10–15*	1.37	[1.04, 1.82]	0.027
Degree of lymph node involvement	=100% Positive versus <100% positive	2.22	[1.51, 3.25]	<0.001
Tumour size (in mm)	>30 versus ⩽30	1.34	[1.01, 1.79]	0.046
Tumour grade	3 versus 1 or 2	1.12	[0.84, 1.48]	0.44
Oestrogen receptor status	Negative versus positive	1.43	[1.04, 1.96]	0.026
Progesterone receptor status	Negative versus positive	1.05	[0.77, 1.43]	0.75

Note: Patients with complete data for all prognostic factors ($n = 404$, 204 EC-CMF, 200 E120, 194 events). A hazard ratio <1 (>1) indicates an effect in favour of the first (second) treatment group or prognostic factor group.

* Includes two patients with <10 positive lymph nodes.

Table 4 – Interactions between treatment and the prognostic factors menopausal status*, tumour grade and oestrogen receptor (ER) status with regard to event-free survival.

Prognostic factor	Patient population	Hazard ratio** E120 versus EC-CMF with 99% CI	Interactive effect with 99% CI	*p*-Value for test of interaction***
Menopausal status*	Post	0.85 [0.54, 1.32]	1.76 [0.81, 3.86]	0.063
	Pre	1.49 [0.78, 2.83]		
Tumour grade	1/2	0.95 [0.54, 1.66]	1.13 [0.54, 2.37]	0.66
	3	1.07 [0.66, 1.74]		
ER status	Positive	0.79 [0.49, 1.30]	1.78 [0.84, 3.76]	0.048
	Negative	1.41 [0.80, 2.48]		

Note: Patients with complete data for all prognostic factors ($n = 404$, 204 EC-CMF, 200 E120, 194 events). A hazard ratio <1 (>1) indicates a subgroup effect in favour of E120 (EC-CMF). The interactive effect describes the factor by which the hazard ratio in the second subgroup is greater than that in the first subgroup.

* Determines hormonal treatment.

** Three separate Cox models including the factors menopausal status, tumour grade, ER status, age, type of surgery, number of positive lymph nodes, degree of lymph node involvement, tumour size and factor-specific treatment effects.

*** Significance level at 1% due to multiple testing.

3.6. OS

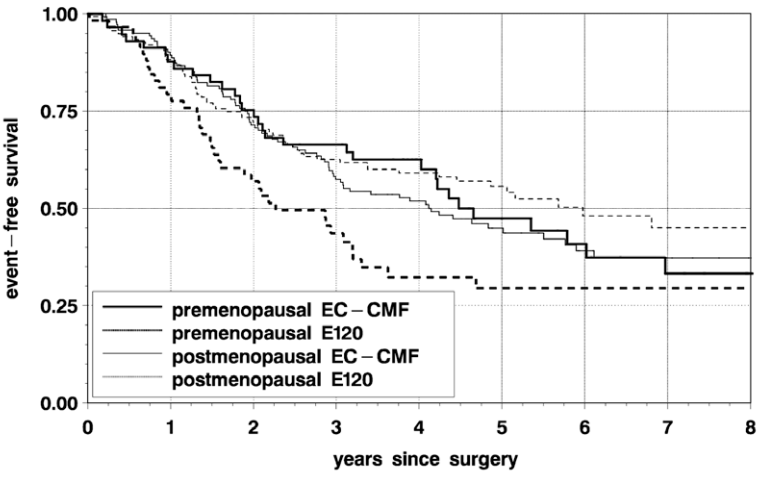
Five-year OS rates were similar under the two treatments, 64.1% (95% CI, 56.7–71.4%) in the E120 group versus 63.5% (95% CI, 56.2–70.8%) in the EC-CMF group (Fig. 5). The unadjusted HR of E120 versus EC-CMF was 1.06 (95% CI, 0.77–1.46; $p = 0.72$) confirming that E120 was not significantly different from EC-CMF for OS. A similar result was produced for the adjusted analysis of OS (HR 0.94; 95% CI 0.68–1.31; $p = 0.72$). Age, number of positive nodes, degree of node involvement and ER status exhibited significant effects on OS (Table 5).

3.7. Tolerability and adverse events

The protocolled chemotherapy was discontinued for medical reasons other than recurrence or death in 8 and 7 patients of the E120 and EC-CMF group, respectively. Toxicity data are based on the reports of serious adverse events before recurrence. Life-threatening adverse events were reported in 6 patients of the E120 group, 3 during or after chemotherapy (cardiotoxicity $n = 2$, sepsis with embolic pneumonia $n = 1$) and 3 during tamoxifen (deep vein thrombosis with pulmonary embolism $n = 2$, sepsis $n = 1$). In addition, 2 deaths occurred during treatment with E120. In the group randomised to EC-CMF a treatment-related life-threatening pancytopaenia with fever occurred in one patient, another patient suffered urosepsis 9 months after the end of chemoendocrine treatment. Three patients died on treatment, 2 during chemotherapy and one on tamoxifen.

3.8. Chemotherapy-induced menopause

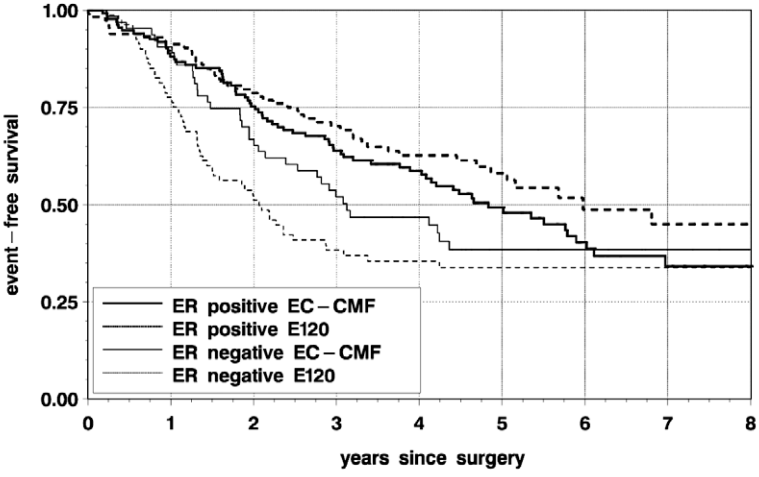
In spring 2005 additional data on chemotherapy-induced menopause were collected retrospectively to explore the potential of synchronous goserelin for ovarian protection. Of 84 premenopausal patients who received ⩾2 cycles of chemotherapy and started goserelin before the second cycle, menses



patients at risk

PRE ECCMF	58	50	42	36	26	16	12	8	5
PRE E120	59	46	32	21	13	8	4	3	3
POST ECCMF	146	126	99	76	58	35	24	13	9
POST E120	141	119	94	76	59	38	20	15	8

Fig. 3 – Event-free survival rate (EFS) by treatment arm and menopausal status (menopausal status also determines hormonal treatment).



patients at risk

ER+ ECCMF	138	118	99	82	61	38	24	13	9
ER+ E120	116	103	86	69	51	34	15	12	7
ER– ECCMF	66	58	42	30	23	13	12	8	5
ER– E120	84	62	40	28	21	12	9	6	4

Fig. 4 – Event-free survival rate (EFS) by treatment arm and oestrogen receptor status.

had stopped before therapy in 7 patients, menses stopped and did not return in 21 (E120 + EC-CMF: 5 + 16), menses returned in 7 (3 + 4) and continued despite goserelin in 3 (1 + 2; data unavailable in 46 patients).

4. Discussion

GABG trial IV E-93 demonstrated the efficacy and feasibility of dose-intensified epirubicin monotherapy application without severe toxicity issues. It showed that breast cancer patients with $\geqslant$10 positive lymph nodes can benefit equally from the monotherapy (4 cycles) and the standard-dose chemotherapy regimen consisting of four cycles of epirubicin and cyclophosphamide followed by three cycles of CMF. With 5 years' median follow-up, the HR of E120 versus EC-CMF was approximately 1 for both EFS and OS. A large benefit in favour of the monotherapy regimen can be ruled out, because the lower limits of the corresponding 95% CIs for the HR are both above 0.7. Prespecified subgroup analyses, which excluded any uncontrolled searching for statistical significance, showed no significant effect of menopausal status, tumour grade or ER status, applying a stringent significance level of 1%. In general patients with poor prognostic factors might benefit more from EC-CMF. HER2 amplifications predicting

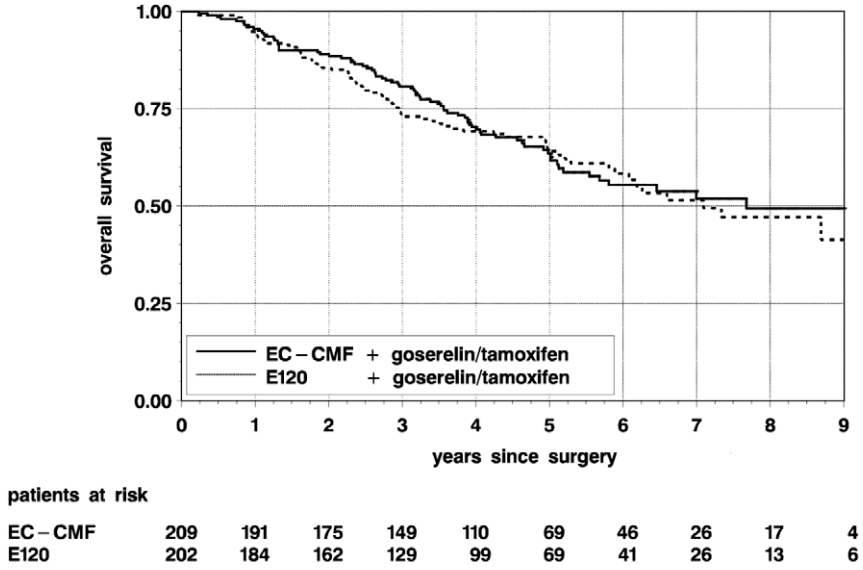


Fig. 5 – Overall survival rate (OS) by treatment arm.

Table 5 – Adjustment for prognostic factors: simultaneous effect of treatment and prognostic factors on overall survival.

		Hazard ratio	95% Confidence interval (CI)	*p*-Value
Treatment	E120 versus EC-CMF	0.94	[0.68, 1.31]	0.72
Age (in years)	41–60 versus ⩽40	0.37	[0.22, 0.63]	<0.001
	>60 versus ⩽40	0.36	[0.20, 0.63]	
Type of surgery	Mastectomy versus breast preservation	1.45	[0.98, 2.08]	0.063
Number of positive lymph nodes	⩾16 versus 10–15*	1.48	[1.05, 2.01]	0.025
Degree of lymph node involvement	=100% positive versus <100% positive	1.99	[1.26, 3.13]	0.003
Tumour size (in mm)	>30 versus ⩽30	1.14	[0.81, 1.60]	0.45
Tumour grade	3 versus 1/2	1.30	[0.92, 1.83]	0.14
Oestrogen receptor status	Negative versus positive	1.62	[1.11, 2.35]	0.012
Progesterone receptor status	Negative versus positive	1.20	[0.84, 1.71]	0.32

Note: Patients with complete data for all prognostic factors (n = 404, 204 EC-CMF, 200 E120, 149 deaths). A hazard ratio <1 (>1) indicates an effect in favour of the first (second) treatment group or prognostic factor group.

* Includes two patients with <10 positive lymph nodes.

sensitivity to dose intense anthracyclines or p53 mutations prediciting the opposite could not be investigated due to the lack of tumour material.[14]

Two circumstances deserve some comment. First, despite imbalances regarding the number of positive lymph nodes, tumour size and grade, the inclusion criteria (⩾10 positive nodes) helped to achieve overall comparable prognosis in both treatment groups, reflected by the similar distribution of the NPI (Table 1). Constructed in 1982, the NPI was validated by further studies and is used till today to describe breast cancer prognosis.[11] An imbalance with regard to ER and PgR status did not have any influence on the estimated treatment effect since adjustment for these factors led to almost identical results. Second, there is a slight difference in median follow-up between the two treatment groups (4.8 years for E120 and 5.4 years for EC-CMF). In an additional investigation (data not shown), we found that slightly more patients were randomised earlier to EC-CMF than to E120. However, completeness of follow-up, measured as the ratio of observed and potential follow-up information available at the data cut-off,[13] was comparable between the two groups (Fig. 1). We conclude that the differential follow-up is due to randomly occurred differential accrual into the treatment groups. Therefore it will not bias treatment comparisons. Given the high risk of the study population we believe 5 years of follow-up are sufficient, but may not tell the whole story for endocrine responsive patients.[15]

The observed EFS rates were comparable with standard arms of other studies in high-risk patients,[8,16,17] but higher than anticipated. However, this did not impair the power of our study to detect the presumed HR of 0.67 in favour of E120, since the planned number of observed events was exceeded. The follow-up period is 5 years only, which is consistent with the preplanned analysis.

Three other international trials of the pre-taxane era investigated a dose-intensified chemotherapy in a similar high-risk population, compared with an EC-CMF control arm which was the same as used in our trial. Zander and collegues

studied the effect of a mitoxantrone-containing high-dose chemotherapy with autologous haematopoietic stem-cell support.[8] The trial was designed as an alternative and was run in parallel with GABG-IV E-93, which accounts partly for the long recruitment period of over 7 years in our trial. In IBCSG trial 15-95[18] and the trial by Untch and collegues[19] the experimental arms were dose-intensified EC regimens applied with stem-cell support and in a dose-dense fashion with G-CSF support, respectively. The three studies showed a clear trend in favour of the more intensive regimen for EFS, although it was not statistically significant.

Available evidence on the benefit of high-dose chemotherapies is still controversial. Some studies showed that high-dose regimens benefit patients with high-risk early breast cancer.[20–24] EFS could be improved by increasing dose intensity[23] or by adding dose-intensified chemotherapy to standard anthracycline-based regimen in high-risk breast cancer patients with extensive lymph involvement, particularly for patients with HER-2/neu-negative tumours.[24] But in other trials, the high-dose approach was less successful.[16,17,25] Different conclusions from different clinical trials could be partially due to study design variation. In the studies that reported significantly improved EFS and OS with dose-intensified chemotherapies, the high-dose regimens usually have the same treatment duration and agents as the standard regimens, but with higher dose intensity.[20,23,24] In GABG-IV E-93, the patients in the high-dose arm received only four cycles of monotherapy (12 weeks in total), whereas the patients in the standard chemotherapy arm received 24 weeks of treatment with multiple agents (four cycles EC and three cycles CMF). A longer treatment duration may benefit patients.[26,27]

In addition, adjuvant CMF has been demonstrated to reduce the relative risk of relapse and death significantly.[28] A recent publication concludes that high-dose epirubicin is significantly superior to standard-dose epirubicin (both in combination with cyclophosphamide) for long-term EFS, but lacks superiority over CMF, all three regimens having the same treatment duration.[23] Given the substantially higher than expected 5-year EFS rate in the reference group of the present study (45.9% obtained versus 25% planned), the standard regimen EC-CMF was demonstrated to be very effective. Therefore, although the high-dose monotherapy E120 was slightly more effective than EC-CMF and had a better than expected EFS (47.7% versus 40%), the difference between the two treatment arms was not significant. Similarly, other studies failed to show superiority of high-dose chemotherapies, possibly partly due to the far better than expected outcomes in the conventionally dosed group.[16,17,25,26] In these studies, the very effective combination adjuvant chemotherapy FAC (FEC) was mostly used as a reference therapy, and the 5-year EFS rate in high-risk breast cancer patients with extensive lymph node involvement could reach approximately 60% with standard treatment.

In the last years dose-dense chemotherapies have also been widely investigated, which appear to be superior to dose-intensified therapy regimen and less toxic. Several study groups proved good feasibility and advantages in EFS using dose-dense chemotherapy regimen. [29,30] GABG-IV E-93 confirmed the efficacy and feasibility of dose-intensified monoanthracycline application, without an advantage in EFS, compared with a standard anthracycline-based combination therapy. Nevertheless, today new and better therapy strategies are established or under investigation, including dose-dense, dose-intensified chemotherapies, taxanes, target therapies and aromatase inhibitors.

List of collaborators and their affiliations

Prof. Dr. G. Geier (Kreiskrankenhaus Albstadt); Dr. K.-J. Winzer (Universitätsklinikum Charité, Chirurgie, Berlin); Prof. Dr. J.R. Strecker (Krankenhaus Reinickendorf, Berlin); Dr. C. Kempter (Waldfriede Krankenhaus, Berlin); Dr. I. Schulz-Im Busch (St. Josefshospital Cloppenburg); Dr. D. Kress (Klinikum Deggendorf); Dr. O. Aga (Kreiskrankenhaus Eggenfelden); Prof. Dr. M. Kaufmann (J.W. Goethe Universität Frankfurt); Frau Dr. Kissel (Universitätsklinikum Freiburg); PD Dr. de Gregorio (Städtische Krankenhaus Friedrichshafen); Prof. Dr. A. Hettenbach (Klinik am Eichert, Göppingen); Prof. Dr. M.H. Carstensen (Albertinen-Krankenhaus, Hamburg); Prof. Dr. E. Goepel (Gynäkologische Gemeinschaftspraxis, Hamburg); Prof. Dr. F. Jänicke (Universitätsklinikum, Hamburg); Prof. Dr. H.H. Zippel (Klinikum Stadt Hanau); Prof. Dr. J. Hilfrich (Henriettenstiftung Hannover); Prof. Dr. P. Hohlweg-Majert (Krankenhaus Nordstadt, Hannover); Prof. Dr. G. Bastert (Universitätsklinikum Heidelberg); Dr. R. Gros (Stadtkrankenhaus Idar-Oberstein); Prof. Dr. K. Höffken (Universitätsklinikum Jena); Prof. Dr. A. Schneider (Universitätsklinikum Jena); Prof. Dr. Rossmanith (Diakonissenkrankenhaus Karlsruhe); Prof Dr. Ulmer (Städtisches Klinikum Karlsruhe); Prof. Dr. H.G. Meerpohl (St. Vincentius Krankenhaus, Karlsruhe); Prof. Dr. Dimpfl (Städtisches Klinikum Kassel); Prof Dr. W. Jonat (Universitätsklinikum Kiel); Dr. C. Beyerle (Frankenwaldklinik Kronach); Prof. Dr. R. Strigl (Klinikum Landshut); PD Dr. H. Wolf (Kreiskrankenhaus Leonberg); Prof. Dr. W. Ardelt (St. Bonifatius Hospital Lingen); Prof. Dr. K. Diedrich (Universitätsklinikum Lübeck); Prof. Dr. G. Gademann (Otto-v.-Guericke-Universität Magdeburg); Prof. Dr. P. Knapstein (Universitätsklinikum Mainz); Prof. Dr. W. Wiest (St. Vinzenz u. St. Elisabeth-Hospital Mainz); Prof. Dr. F. Melchert (Klinikum der Stadt Mannheim); Prof. Dr. K.-D. Schulz (Universitätsklinikum Marburg); Prof. Dr. W. Eiermann (Frauenklinik vom Roten Kreuz München); Prof. Dr. Kiesel (Universitätsklinikum Münster); Prof. Dr. H.-J. Kitschke (Frauenklinik der Städtischen Kliniken Offenbach a.M.); PD Dr. M. Butterwegge (Marienhospital Osnabrück); Prof. Dr. H. Hartlapp (Klinikum Osnabrück); Dr. W. Meinerz (St. Vincenz-Krankenhaus Paderborn); Prof. Dr. P. Faber (Prosper Hospital Recklinghausen); Prof. Dr. S. Kunz (Kreiskrankenhaus Reutlingen); Prof. Dr. T. Beck (Klinikum Rosenheim); Prof. Dr. B. Gerber (Universität Rostock); Prof. Dr. L. Heilmann (Stadtkrankenhaus Rüsselsheim); Prof. Dr. Anger (Martin-Luther-Krankenhaus Schleswig); Pr Hagen; Prof. Dr. R. Kreienberg (Universitätsklinikum Ulm); Prof. Dr. K.-W. Schweppe (Ammerland Klinik GmbH Westerstede); PD Dr. Hitschold (Stadtkrankenhaus Worms) of. Dr. R.C. Briel (Margaritenhospital Schwäbisch-Gmünd); Prof. Dr. H.J. Künzig (Evangelisches Jung-Stilling Krankenshaus Siegen); Dr. J. Feltz-Süßenbach (Klinikum Schaumburg Stadt).

Conflict of interest statement

The following potential conflicts of interest were declared: W. Eiermann (consultant, honoraria from Astra Zeneca), G. von Minckwitz (honoraria and research funding from Astra Zeneca) and M. Kaufmann (honoraria from Pfizer). The other authors declared no conflict of interest.

Acknowledgements

This study was supported by the Deutsche Krebshilfe; Pharmacia, Germany and Astra Zeneca, Germany.

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