Table 33. Protocol deviations (ITT) (Sponsor's table 7, volume 2.28, page 43)

Deviation	FEC 50 (n=289)		FEC 100 (n=276)	
	No.	%	No.	%
None	143	49.5	145	52.5
At least one	146	50.5	131	47.5
Initial metastatic breast cancer	13	4.6	4	1.4
Inflammatory breast cancer	0	0	1	0.4
No breast cancer	0	0	2	0.7
Randomization error (randomized twice)	1	0.3	0	0
Neutrophils < 2000/mm^3	5	1.7	1	0.4
LVEF abnormal	8	2.8	4	1.4
LVEF not done	22	7.6	21	7.6
ECG abnormal	8	2.8	11	4.0
Age ≥ 65	5	1.7	4	1.4
Node < 3 and receptor +	7	2.4	7	2.5
Surgery to chemo > 42 d	9	3.1	10	3.6
Concomitant hormonal therapy (LHRH agonist)	7	2.4	3	1.1
Tamoxifen administration deviation	15	5.2	10	3.6
Menopausal patients without tamoxifen	8	2.8	11	4.0
Premenopausal pts receiving tamoxifen	17	5.9	8	2.9
Chemotherapy administration deviation	5	1.7	4	1.4
Wrong treatment arm allocation	2	0.7	4	1.4
Radiation therapy deviation	68	23.5	75	27.2

More women on FEC 50 had an initial diagnosis of metastatic breast cancer than on FEC 100. The number of women with 1-3 positive nodes who were receptor positive was the same in each group. A similar number of women on each arm had abnormal cardiac function at baseline, as measured by LVEF or ECG.

Reviewer Comments:

1. More women on FEC 50 had metastatic disease at presentation, which favored the FEC 100 arm. Patients with unrecognized M_1 disease represented less than 5% of the randomized population.

2. More women on FEC 100 received FEC 50 than the reverse situation, potentially favoring FEC 50.

3. More women on FEC 50 received tamoxifen than women on FEC 100, potentially favoring FEC 50.

4. Overall, these deviations are unlikely to significantly affect the outcome of the trial, because of the small number of women whose therapy deviated significantly from the protocol-specified treatment.

9.11 On-study treatment

9.11.1 Discontinuation of chemotherapy

Five percent (14/280) of patients on FEC 50 and 6% (16/266) on FEC 100 did not complete the planned 6 cycles of therapy. Reasons for stopping therapy are listed in the following table:

Table 34. Reasons for discontinuation of treatment (as-treated) (Sponsor's table 6, volume 2.28, page 42).

Reason for Withdrawal	FEC 50 (n=280)		FEC 100 (n=266)	
	No.	%	No.	%
Disease progression	1	0.4	0	0
Toxicity	5	1.8	11	4.1
Death	2	0.7	1	0.4
Pt refusal	3	1.1	2	0.8
Other	3*	1.1	2**	0.8
Total	14	5.0	16	6.0

* 2 for unknown reasons; 1 with technical problems at infusion site
** Unknown reasons

The most common reason for early withdrawal was toxicity. Three deaths occurred during treatment: 2 on FEC 50, due to a stroke and to metastatic disease progression; and 1 on FEC 100, due to disease progression.

Reviewer Comment:

1. The percent of patients with early discontinuation was comparable overall between the two treatment arms. A higher percentage of patients on FEC 100 withdrew because of toxicity; a slightly higher percentage of patients on FEC 50 withdrew because of disease progression and death.

2. A query of the electronic database yielded slightly different numbers than those in the above table:

Table 34a. Reviewer's assessment of discontinuation of treatment

Reason for Withdrawal	FEC 50 (n=280)		FEC 100 (n=266)	
	No.	%	No.	%
Disease progression	0	0	1	0.4
Toxicity	7	2.5	12	4.5
Death	2	0.7	1	0.4
Pt refusal	5	1.8	3	1.1
Other	3	1.1	3	1.1
Unknown	1	0.4	0	0
Total	18	6.4	20	7.5

The sponsor reported the "as-treated" population; the reviewer's table reports "as-randomized" patients. Table 34 does not include 5 patients who were never treated (3 on FEC 50 and 2 on FEC 100), and 3 patients who received cyclophosphamide and 5-FU but not epirubicin during cycle 6.

The "as-randomized" populations still shows an increased withdrawal rate on FEC 100 compared to FEC 50 for toxicity. Other reasons for withdrawal are comparable. Notably, the number of patients who refused further therapy was low and was similar on both arms.

9.11.2 Dose Intensity

9.11.2.a Actual dose-intensity

Dose-intensity was calculated as the total dose per square meter given over all cycles divided by the number of weeks between the first and last treatment cycles plus 21 days. The projected dose-intensities as per protocol were as follows:

FEC 50:
5-FU 166.7 mg/m^2/wk
Epirubicin 16.7 mg/m^2/wk
Cyclophosphamide 166.7 mg/m^2/wk

FEC 100:
5-FU 166.7 mg/m^2/wk
Epirubicin 33.3 mg/m^2/wk
Cyclophosphamide 166.7 mg/m^2/wk

The actual dose-intensities delivered are summarized in the following table:

Table 35. Actual dose-intensity (mg/m^2/wk) (As-treated) (Sponsor's table 10, volume 2.28, page 48)

Component	FEC 50			FEC 100		
	No. pts.	Median	Range	No.pts.	Median	Range
No radiotherapy during chemotherapy						
5-FU	258	156.8		245	153.4	
EPI	258	15.7		245	30.5	
CTX	258	156.8		245	153.4	
Radiotherapy during chemotherapy						
5-FU	11	111.4		15	107.6	
EPI	11	11.1		15	21.6	
CTX	11	111.4		15	107.6	

The delivered dose-intensity of each drug was lower than the targeted value, although the dose-intensities for 5-FU and cyclophosphamide were similar between FEC 50 and FEC 100 patients who did not receive radiation therapy with chemotherapy. Dose intensity was lower for all drugs in women in either treatment arm who received concomitant chemotherapy and radiation.

9.11.2.b Relative dose-intensity

The following table summarizes relative DI in both arms:

Table 36. Relative dose intensity (as-treated) (Sponsor's table 11, volume 2.28, page 49)

Component	FEC 50			FEC 100		
	No. pts.	Median	Range	No.pts.	Median	Range
No radiotherapy during chemotherapy						
5-FU	258	.94	[redacted]	245	.92	[redacted]
EPI	258	.94		245	.92	
CTX	258	.94		245	.92	
Radiotherapy during chemotherapy						
5-FU	11	.67	[redacted]	15	.65	[redacted]
EPI	11	.67		15	.65	
CTX	11	.67		15	.65	

For patients who did not receive concomitant chemotherapy and radiation therapy, the median DI of all 3 drugs was .94 for FEC 50 compared to .92 for FEC 100. Relative DI was lower in patients who received chemotherapy and radiation together.

Reviewer Comments:

1. Few patients received radiation therapy with chemotherapy. The reason for the decreased dose-intensity in this group is unclear. Review of the electronic database confirms that 12 patients on FEC 50 and 15 patients on FEC 100 received concomittant chemotherapy and radiation therapy. The sponsor lists 11 patients on FEC 50; one patient, whose radiotherapy overlapped with chemotherapy by 4 days, may have been excluded from their list. In these 27 patients, 3 on each arm were reported to have anemia, thrombocytopenia, or neutropenia/infection. It is possible that drugs were prophylactically reduced to avoid radiation recall.

2. The achieved dose-intensities were high in both arms. Although the DIs of 5-FU and cyclophosphamide on FEC 100 were somewhat lower than those on FEC 50, the DI of epirubicin remained approximately twice as high on FEC 100 compared to FEC 50. Any difference in outcome between the two arms may therefore be attributed to the effect of higher doses of epirubicin.

9.11.3 Cumulative dose

The planned cumulative dose of epirubicin was 300 mg/m^2 for FEC 50 and 600 mg/m^2 for FEC 100. Actual delivered cumulative doses are summarized as follows:

Table 37. Actual cumulative epirubicin dose (as-treated) (Sponsor's table 5.3, volume 2.28, page 96)

Cumulative Epirubicin Dose mg/m^2	**FEC 50 (n=280)**	**FEC 100 (n=266)**
≤100	1 (0.4%)	2 (0.8%)
>100-200	5 (1.8%)	1 (0.4%)
>200-300	177 (63.2%)	4 (1.5%)
>300-400	86 (30.7%)	7 (2.6%)
>400-500	0	9 (3.4%)
>500-600	0	176 (66.2%)
>600-700	0	61 (22.9%)
Unknown	11 (3.9%)	6 (2.3%)

Reviewer Comments:

1. A higher percentage of patients on FEC 50 received the planned cumulative epirubicin dose compared to those on FEC 100 (94% on FEC 50 and 89% on FEC 100).

9.11.4 Treatment cycles

9.11.4.a Number of cycles

A comparable number of patients on each arm completed 6 cycles of treatment; dropout was similar as well:

Table 38. Number of completed cycles (as-treated) (Sponsor's table 12, volume 2.28, page 50)

Cycle no. completed	FEC 50 (n=280)		FEC 100 (n=266)	
	No.	%	No.	%
1	280	100	266	100
2	280	100	264	99.2
3	277	98.9	263	98.9
4	276	98.6	259	97.4
5	275	98.2	255	95.9
6	266	95.0	250	94.0
Total	1654		1557	

9.11.4.b Duration of treatment cycles

The last cycle was excluded from this analysis. The median duration of all cycles was 21 days in each treatment group. The mean duration of cycles by treatment arm was 23.7 days for FEC 50 and 24.5 days for FEC 100. Mean and median durations of all cycles and for each cycle were comparable between arms.

The relative duration of cycles (actual days/expected days) was comparable between arms with a median ratio of 1 and a mean ratio of 1.1-1.2. Duration of cycles by time classes was similarly distributed between arms.

9.11.4.c Treatment delays

In the FEC 50 group, 59.9% (811/1354) of cycles were delivered on time. Cycles were delayed 40.1% (543/1354) of the time, with a mean delay of 6.9 days. In the FEC 100 group, 51.2% (658/1283) were given on time. Cycles were delayed 48.6% of the time (625/1283), with a mean delay of 7.3 days. The median delay for all delayed cycles was 7.0 days on both arms.

Reviewer Comment:

1. Withdrawal prior to completion of adjuvant therapy was uncommon on either arm.

2. Patients on FEC 100 had a higher drop-out rate during cycles 5 and 6 than patients on FEC 50.

3. Over half of the cycles on each arm were delivered on time. When delayed, the median delay was 1 week. Growth factors were not used in this trial.

4. The data on dose-intensity, cumulative dosing, and treatment cycle characteristics demonstrate that both treatment arms could be administered in the outpatient setting. Patterns of dropout and delay were similar for both regimens; any small differences favored the FEC 50 arm.

9.11.5 Tamoxifen therapy

The following table summarizes tamoxifen administration on the study.

Table 39. Concomitant tamoxifen (as-treated) (Sponsor's table 14, volume 2.28, page 52)

Menopausal status	FEC 50 (n=280)		FEC 100 (n=266)	
	No.	No. (%) treated with tamoxifen	No.	No. (%) treated with tamoxifen
Premenopausal	146	6 (4.1)	125	3 (2.4)
Perimenopausal	6	2 (33.3)	11	3 (27.3)
Postmenopausal	125	111 (88.8)	128	112 (87.5)
Unknown	3	0	2	0

Reviewer Comment:

1. A similar number of postmenopausal women on each arm received tamoxifen, as mandated per protocol.

2. On FEC 100, 147 women (regardless of menopausal status) were estrogen receptor positive. Sixty-five of them received tamoxifen (44%). On FEC 50, 139 women were ER(+); 66 of them received tamoxifen (47%). Although the protocol used menopausal status and not ER status to determine tamoxifen administration, use of tamoxifen was balanced by ER positivity between treatment arms.

3. Analysis of perimenopausal women is not meaningful, because of the small number of women in this category.

4. More women on FEC 50 who were pre- or perimenopausal took tamoxifen compared to a similar group randomized to FEC 100. This small difference potentially favored the FEC 50 arm.

9.11.6 Radiation therapy

All patients were to receive radiation therapy within 30 days of finishing chemotherapy; radiation was not to be given concomitantly with chemotherapy. The following table shows the actual timing of radiation therapy:

Table 40. Radiation therapy (as-treated) (Sponsor' table 15, volume 2.28, page 52)

Radiotherapy	FEC 50 (n=280)		FEC 100 (n=266)	
	No.	%	No.	%
Administered	265	94.3	257	96.6
Per protocol	199	71.1	187	70.3
Delayed (>33 days after chemo)	53	18.9	55	20.7
Given with chemo	12	4.3	15	5.6
Unknown	16	5.7	9	3.4

Reviewer Comments:

1. Most patients received radiation therapy on this protocol. Post-mastectomy chest wall radiation was used as well as post-lumpectomy radiation therapy.

2. Because of the reported potential beneficial survival effect of post-mastectomy chest wall radiation in women with nodal involvement, the database was evaluated in

order to determine whether this procedure was used in similar numbers of women on each arm. Two hundred ninety-one patients in this trial were treated with a mastectomy, 136 on FEC 100 and 155 on FEC 50. Post-mastectomy chest wall irradiation was used in 123 and 142 of these patients respectively. It is unlikely to affect RFS or OS outcomes because of its extensive use in this study.

3. Most patients received therapy as per protocol.

4. Protocol violations for the timing of radiation were comparable between treatment arms. From a review of the electronic database, nearly all the violations occurred at one center (center L).

9.12 Efficacy results (intent-to-treat analyses)

9.12.1 Relapse-free survival

9.12.1.a Overall RFS

In the FEC 50 group, 137 of 289 (47.4%) patients relapsed, compared to 105 of 276 (38%) in the FEC 100 group. The KM estimate of RFS at 5 years was 52% (95% CI 46-58%) for FEC 50 and was 65% (95% CI 59-71%) in the FEC 100 group (p-value 0.007).

The KM estimate of median RFS is not available for either treatment group. The estimates of the 25th percentile (75% RFS) with 95% CI are 23.3 months (20.3-28.2) for FEC 50 and 35.2 months (25.1-51.1) for FEC 100.

9.12.1.b RFS by baseline prognostic factors

The following table summarizes RFS by baseline stratification and prognostic factors:

Table 41. RFS estimates at 5 years and 25th percentile: Overall and by baseline prognostic factors [Patients in "unknown" subgroups excluded] (Sponsor's table 16, volume 2.28, page 54)

Variable	FEC 50			FEC 100		
	No. (%) patients	% 5-year RFS	25th percentile (95% CI)	No. (%) patients	% 5-year RFS	25th percentile (95% CI)
All patients	289 (100)	52	23.3 (20.3-28.2)	276 (100)	65	35.2 (25.1-51.1)
Positive nodes:						
1-3	52 (18)	78	66.2 (22.4-ne)	46 (17)	71	45.0 (14.6-ne)
≥ 4	229 (79)	48	22.6 (17.4-27.1)	225 (82)	64	34.9 (26.4-47.9)
4-10	180 (62)	51	23.4 (19.1-29.6)	176 (64)	66	36.7 (28.7-54.3)
> 10	49 (17)	35	17.4 (6.5-29.2)	49 (18)	56	26.4 (16.9-36.8)
Receptor status						
Positive	174 (60)	52	23.8 (20.8-30.7)	169 (61)	66	36.8 (28.7-54.3)
Negative	81 (28)	52	20.5 (12.8-30.9)	85 (31)	62	26.9 (16.8-45.0)
Menopausal status						
Premeno-pausal	146 (51)	54	24.5 (21.2-32.0)	127 (46)	65	36.6 (26.4-54.0)
Peri-/postmeno-pausal	133 (46)	51	21.4 (14.2-29.2)	142 (51)	65	34.9 (22.7-54.3)
Surgery:						
Conservative	126 (44)	63	30.9 (24.5-47.4)	134 (49)	70	40.3 (26.4-63.1)
Radical	155 (54)	45	19.1 (14.1-23.8)	136 (49)	61	28.2 (21.4-47.9)
Tumor size						
T0-T2	210 (73)	57	29.1 (23.3-35.9)	210 (76)	66	36.7 (27.2-53.9)
T3-T4	66 (23)	40	13.5 (10.1-21.1)	51 (18)	59	26.9 (17.4-42.5)

The sponsor notes that RFS correlated with the number of involved nodes. The overall 5-year RFS was longer for patients who received FEC 100 than for patients who received FEC 50. FEC 100 was associated with an improved RFS compared to FEC 50 in women with ≥ 4 involved nodes; the converse was true for women with 1-3 positive nodes. The 25th percentile estimates of RFS reflect these trends.

The RFS was greater with FEC 100 treatment compared to FEC 50 in patients who were ER(+), in those who were ER(-), in premenopausal women, and in peri- and postmenopausal women. Women with breast-conserving surgery had a higher 5-year RFS than women treated with radical surgery; in both of these groups, women treated with FEC 100 had a longer DFS than women treated with FEC 50. RFS was longer in women with smaller tumors than in those with larger tumors; in both subsets, RFS was longer in women treated with FEC 100 than in women treated with FEC 50.

Application of the Cox model indicated that the number of positive nodes, the type of surgery, and the receptor status were significant predictors of RFS. With these prognostic factors in the model, there was a significant treatment effect (p=0.005) in favor of treatment with FEC 100. The estimate of the conditional risk ratio (FEC

100/FEC 50) was 0.68 (95% CI= 0.52, 0.89). The ratio for women with 4 or more involved lymph nodes compared to women with 1-3 involved nodes was 2.2 (95% CI = 1.43, 3.45). The conditional risk ratio for women with negative receptors compared to positive receptors was 1.6 (95% CI 1.17-2.20). The ratio for women with radical surgery compared to conservative surgery was 1.5 (95% CI 1.13-1.94).

9.12.2 Sites of relapse

Distant relapses were reported in 34.6% of patients on FEC 50 (100/289) and in 31.9% of women on FEC 100 (87/276). The most common sites of relapse are summarized in the following table:

Table 42. Site of relapse

Site of metastasis	FEC 50 (n=289)		FEC 100 (n=276)	
	Relapsed No. (%)	Median time (mo)	Relapsed No. (%)	Median time (mo)
Local relapse only	12 (4.2)	23.6	9 (3.3)	61.0
Regional relapse only	13 (4.5%)	30.7	5 (1.8)	9.3
Distant relapse:	100 (34.6)	24.4	88 (31.9)	27.1
Contralateral breast	16 (5.5)	22.8	14 (5.1)	22.0
Soft tissue	10 (3.5)	25.6	4 (1.4)	11.4
Lymph nodes	17 (5.9)	29.8	11 (4.0)	21.0
Bone	59 (20.4)	24.4	43 (15.6)	26.4
Lung	23 (8.0)	26.7	18 (6.5)	22.3
Liver	25 (8.7)	22.4	20 (7.2)	28.7
Other	22 (7.6)	25.2	25 (9.1)	28
Unknown	13 (4.5)		4 (1.4)	
Total	137 (47.4)	22.7	105 (38.0)	26.1

Reviewer Comments:

1. There was a statistically and clinically significant improvement in unadjusted RFS with FEC 100 treatment compared to FEC 50 therapy. The absolute difference in RFS was 9%; the proportion reduction in recurrence with the higher dose arm was 32%. The data show a 12-month improvement in RFS as calculated at the 25th percentile for FEC 100. These differences are clinically meaningful.

2. Benefit was observed in all subgroups except for women with 1-3 positive nodes. The strata were not powered to detect a significant difference at this level. Given the relatively small number of patients in this strata (18% of the patient population), the difference between treatment arms for RFS is likely to be due to few events (22% and 29% of women with 1-3 nodes in each arm have recurred) in a small number of patients, rather than an adverse effect of FEC 100 in this subgroup.

3. Few patients experienced local or regional relapse only, even though radiation therapy was delayed until the end of chemotherapy. Fewer locoregional relapses were observed in women treated with FEC 100 compared to FEC 50 (5.1% compared to 8.7%).

4. The reported results were verified in several ways. The sponsor submitted 66 case report forms from this study for deaths, drop-outs due to adverse events, secondary leukemias, and cardiotoxicity. The CRFs were reviewed and the date of recurrence was compared to the date entered in the electronic database. The reviewer disagreed with the sponsor's assessment in the following cases:

FEC 50:

- Patient A36: The sponsor indicated that this patient did not recur. The CRF shows relapse on 7/13/94 (site illegible)
- Patient B8: The sponsor gave 4/15/93 as the recurrence date; the reviewer noted 12/15/93 as the first evidence of recurrence
- Patient P2: The sponsor listed 6/14/94 as the recurrence date. The patient had an abnormal and changed bone scan on 4/15/94.

FEC 100:

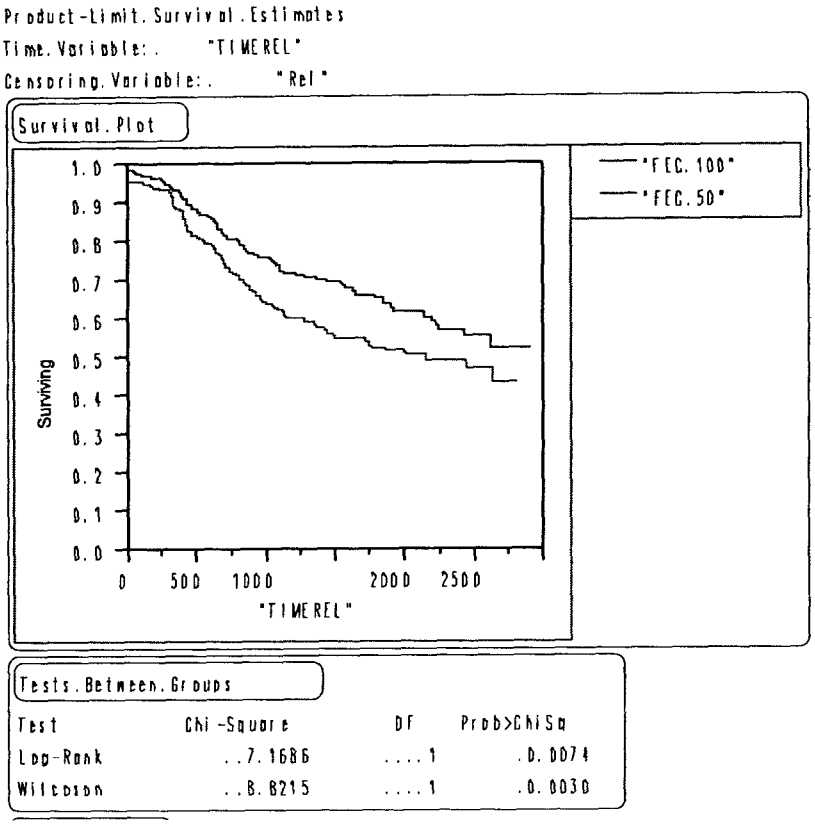
- Patient I5: The sponsor erroneously listed 3/10/97, the date of diagnosis of a contralateral breast cancer, as the recurrence date. Distant metastasis was first documented 4/6/98.

These differences represent 4/66, or 6% of the submitted CRFs. It is unlikely that revising the above dates (1 change in status, 2 with later recurrence than stated, and 1 with earlier recurrence than stated) will change the calculated values.

The reviewer re-calculated time to relapse; these values agreed with those entered in the database by the sponsor.

The reviewer analyzed disease-free survival, using the Kaplan-Meier method in Jmp. The results are presented below:

Figure 3. Disease-free survival in GFEA-05



As stated by the sponsor, median RFS times have not yet been reached. The estimates of the 25th percentile (75% RFS) from Figure 3 match those reported by the sponsor.

These results are statistically significantly different and show a clinically significant difference between treatment arms.

9.12.3 Survival

9.12.3.a Overall survival

One hundred eight of 289 (37.4%) patients treated with FEC 50 died, compared to 75 of 276 patients (27.2%) on FEC 100. The KM estimate of survival at 5 years was 65% (95% CI 60-71%) and 76% (95% CI 71-81%) respectively (p=0.007). The KM estimate of median survival is not available, since there have not been enough events to calculate this value. The estimates of the 25th percentile (75% OS) are 47.7 months (95% CI 40.5-52.2) and 65.6 months (95% CI 46.0-76.3) respectively.

9.12.3.b Survival by prognostic factors

The following table summarizes survival by stratification and prognostic factors:

Table 43. Overall survival at 5 years and 25th percentile: Overall and by baseline prognostic factors (ITT) (Sponsor's table 17, volume 2.28, page 57)

Variable	FEC 50			FEC 100		
	No. (%) patients	% 5-year OS	25th percentile (95% CI)	No. (%) patients	% 5-year OS	25th percentile (95% CI)
All patients	289 (100)	65	47.7 (40.5-52.2)	276 (100)	76	65.6 (46.0-76.3)
Positive nodes:						
1-3	52 (18)	84	Ne (49.2-ne)	46 (17)	78	76.3 (30.7-ne)
≥ 4	229 (79)	60	44.5 (36.6-49.6)	225 (82)	76	64.7 (46.0-74.9)
4-10	180 (62)	62	47.2 (37.4-54.0)	176 (64)	79	72.7 (48.2-ne)
> 10	49 (17)	52	30.9 (21.8-49.6)	49 (18)	66	38.3 (28.2-65.8)
Receptor status						
Positive	174 (60)	64	47.7 (43.3-54.2)	169 (61)	80	68.8 (56.9-ne)
Negative	81 (28)	60	31.6 (24.9-49.2)	85 (31)	67	39.5 (30.3-76.3)
Menopausal status						
Premeno-pausal	146 (51)	68	50.2 (47.2-63.4)	127 (46)	80	68.8 (48.2-ne)
Peri-/postmeno-pausal	133 (46)	60	38.9 (26.8-49.6)	142 (51)	73	50.2 (37.2-76.3)
Surgery:						
Conservative	126 (44)	73	59.2 (49.6-ne)	134 (49)	79	74.9 (48.2-ne)
Radical	155 (54)	57	36.6 (27.2-47.2)	136 (49)	74	55.9 (35.1-72.7)
Tumor size						
T0-T2	210 (73)	69	52.2 (47.2-61.5)	210 (76)	77	67.0 (46.0-87.1)
T3-T4	66 (23)	48	24.8 (19.4-40.5)	51 (18)	70	47.2 (25.9-ne)

The sponsor notes that survival was lower in women with 4 or more involved nodes than in women with 1-3 involved nodes. Survival was longer in women treated with FEC 100 than in women treated with FEC 50 in the group with 4 or more involved nodes; survival was somewhat better with FEC 50 than FEC 100 in women with 1-3 involved nodes.

Positive hormonal status was associated with better survival. FEC 100 was associated with longer survival in both hormone receptor positive and hormone receptor negative patients. Premenopausal women lived longer than peri- or postmenopausal women; both groups of women benefited from FEC 100 compared to FEC 50.

Women treated with conservative surgery had longer survival times than women treated with radical surgery. Again, women in either group treated with FEC 100 lived longer than women treated with FEC 50. Similar findings were described for tumor size.

The Cox model identified type of local surgery and tumor size as significant predictors of OS. The treatment effect estimated by the model was of the same size as that estimated in the unstratified analysis. The conditional risk ratio FEC 100/FEC 50 for all patients was 0.69 (95% CI 0.51-0.92). The ratio in women with radical

surgery/conservative surgery was 1.39 (95% CI 1.00-1.91). The ratio in women with T3-4 lesions compared to T0-2 was 1.5 (95% CI 1.08-2.16).

Reviewer Comment:

1.Treatment with FEC 100 improved overall survival by an absolute difference of 10%. The proportional reduction in mortality was 31%. The data demonstrate an 18-month improvement in the estimates of survival at the 25th percentile with the higher-dose chemotherapy arm.

2. Benefit for the higher dose regimen was seen in all subsets except women with 1-3 involved nodes, where overall survival at 5 years is 84% on FEC 50 and 78% on FEC 100. However, few patients were randomized in this stratum (18% of the population), which was not powered to detect a significant difference. Few events have occurred to date.

3. Survival data were verified as follows. The sponsor submitted 66 CRFs, selected as described in the Reviewer's Comments following section 9.12.1. The CRFs were reviewed and the date of death was compared to the date entered in the electronic database. The reviewer found one discrepancy:

- Patient A3: listed as alive by the sponsor; date of death in the CRF is 4/28/92. Randomized to FEC 50.

Several patients who were still alive had discrepancies in the "last seen" date which might affect survival calculations:

FEC 50:

- A6: Sponsor lists date as 4/24/97; the reviewer could not find any records after 11/17/94

FEC 100:

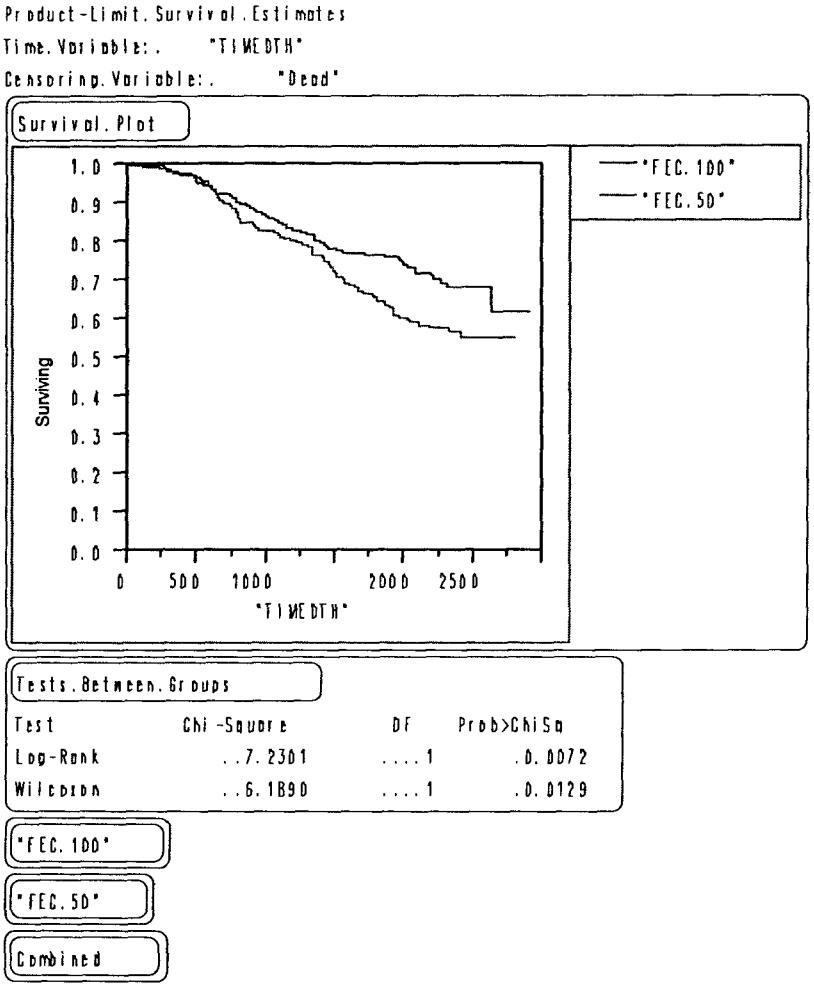
- A30: sponsor lists date as 6/4/97; the patient was seen 4/27/98
- A102: sponsor lists date as 10/21/97; the patient was seen 6/18/98
- G36: sponsor lists date as 7/8/96; the reviewer could not find any records after 12/13/95
- I5: sponsor lists date as 3/28/97; the patient was seen 4/6/98

Two patients were listed with longer survival times (1 on each arm), 3 with shorter ones (all on FEC 100). It is unlikely that these differences would substantially change the reported analysis.

The reviewer calculated survival times; these times matched those reported by the sponsor in the electronic database.

The reviewer analyzed survival using Jmp:

Figure 4. Overall survival in GFEA-05



The median survivals in each arm have not yet been reached. The estimates of the 25th percentile match those reported by the sponsor. The difference between treatment arms is statistically significant and clinically meaningful.

9.13 Safety

9.13.1 Mortality, other serious adverse events, and discontinuations due to serious adverse events

9.13.1.a Mortality

Two patients on FEC 50 and 1 patient on FEC 100 died during the planned course of adjuvant treatment. Patients on FEC 50 had a greater frequency of deaths than patients on FEC 100 at all time points, particularly at the 3-year follow-up visit.

Table 44. Frequency of deaths (as-treated) (Modified from sponsor's table 20, volume 2.28, page 65)

Time Interval	FEC 50		FEC 100	
	Patients on study	Deaths	Patients on study	Deaths
Cycle 1	280	0	266	0
Cycle 2	280	1 (0.4%)	266	0
Cycle 3	279	0	266	0
Cycle 4	279	0	266	1 (0.4%)
Cycle 5	279	1 (0.4%)	265	0
Cycle 6	278	0	265	0
1 year F/U	272	46 (16.4%)	264	36 (13.5%)
3 year F/U	223	46 (16.4%)	227	22 (8.3%)
5 years F/U	134	14 (5.0%)	155	13 (4.9%)
TOTAL	[redacted]	108 (38.6%)	[redacted]	72 (27.1%)

The causes of death are listed below:

Table 45. Summary of deaths (as-treated) (Sponsor's table 21, volume 2.28, page 66)

Cause	FEC 50 (n=280)			FEC 100 (n=266)		
	On treatment	Off treatment	Total	On treatment	Off treatment	Total
Disease progression	0	93 (33.2%)	93 (33.2%)	0	62 (23.3%)	62 (23.3%)
Intercurrent disease	0	3 (1.1%)	3 (1.1%)	1 (0.4%)**	0	1 (0.4%)
Other	2 (0.7%)*	8 (2.9%)	10 (3.6%)	0	8 (3.0%)	8 (3.0%)
Unknown/ missing	0	2 (0.7%)	2 (0.7%)	0	1 (0.4%)	1 (0.4%)
Total	**2 (0.7%)**	**106 (37.9%)**	**108 (38.6%)**	**1 (0.4%)**	**71 (26.7%)**	**72 (27.1%)**

* One of stroke, one of disease progression
** Disease progression and respiratory insufficiency

"Other reasons" includes adverse events, death from a second primary cancer, and suicide. The most common cause of death was disease progression, which accounted for more deaths on FEC 50 than on FEC 100.

Reviewer Comment:

1. The sponsor attributes the two deaths on FEC 50 and one death on FEC 100 during chemotherapy to "other causes" as listed in the footnote to the table; these deaths could also be attributed to progressive disease.

2. The line listings for "other deaths" (listing 7.1.5.1, volume 2.28, page 216 and listing 17 volume 2.32) show that the 8 deaths after FEC 50 therapy were due to septic shock, myocardial infarction, deaths from a second primary (nasal fossa cylindroma and ALL), 3 patients with metastatic disease at baseline with progression, and an unknown cause. "Other deaths" on the FEC 100 arm were due to cardiovascular collapse, unknown reason, death from AML (9 months after randomization), 2 suicides,

progressive disease in a patient with metastatic disease at baseline, death from pancreatic cancer, and stroke.

3. Deaths from "intercurrent disease" were due to 3 second primaries on FEC 50 (2 colorectal, 1 gastric) and to respiratory insufficiency on FEC 100.

4. The distinctions between the categories for cause of death are somewhat artificial. Overall, the most common cause of death was progressive disease, which occurred more frequently on FEC 50 than on FEC 100. There was no apparent difference in death rate from complications of therapy between the two arms.

9.13.1.b Second primary cancers

Eight patients on FEC 50 (2.9%) and 18 (6.8%) on FEC 100 were reported to develop a nonmalignant neoplasm.

Twenty-two patients (7.9%) and 15 (5.6%) respectively developed a second malignancy. These tumors are summarized in the following table:

Table 46. Second malignancy (as treated)

Neoplasm	FEC 50 (n=280)	FEC 100 (n=266)
Contralateral breast cancer	14 (5.0%)	7 (2.6%)
Colorectal cancer	2	1
Endometrial cancer	0	3
Basal cell cancer	0	2
Bladder cancer	1	1
Gastric cancer	1	0
Lung cancer	1	0
Nasal cancer	1	0
Pancreas	0	1
Skin	1	0
Leukemia	1 (0.4%)[1]	1 (0.4%)[2]
TOTAL	22 (8%)	16 (6%)[3]

[1] ALL

[2] AML

[3] 16 cancers in 15 patients

Reviewer Comment:

1. Twenty-one women developed a second breast cancer during the period of follow-up. Of interest, the incidence of second breast cancers was twice as high on the FEC 50 arm as on the FEC 100 arm (14 versus 7, or 5% versus 2.6%), despite the fact that women on FEC 50 had a higher incidence of recurrence and death.

2. All three women who developed endometrial cancer had taken tamoxifen 30 mg daily for 2 years (2 patients) or 3 years (1 patient).

3. Two patients, one on each arm developed leukemia. The characteristics of these patients are summarized in the following table:

Table 47. Features of leukemias diagnosed during GFEA-05

Feature	FEC 50: A 64	FEC 100 A 43
Age at randomization	46	63
Cumulative epirubicin dose	297 mg/m^2	602.9 mg/m^2
Radiation therapy/field	Yes/ thoracic, axillary, SC	Yes/ SC, parasternal, chest wall
Additional drug exposure before leukemia diagnosis	No	No
Time from randomization to diagnosis	56 months	9 months
Type of leukemia	ALL	AML-M4
Cytogenetics	t (9;22)	t (8;16) del (17q21)
Time from leukemia to death	11 months	1 month

The patient on FEC 50 developed ALL, which is not thought to be treatment-related. The AML diagnosed in the patient on FEC 100 did not have a translocation classic for treatment-related leukemia, but a treatment effect cannot be excluded, particularly in light of the short onset and rapid demise of the patient. The occurrence of 1 leukemia in 266 patients treated with FEC 100 represents an incidence of .4%, although the true incidence of leukemia cannot be estimated with accuracy from the small numbers in this single study.

9.13.1.c Cardiac toxicity

Most of the enrolled patients had normal cardiac function at baseline. The findings for LVEF and ECGs are noted in the following table:

Table 48. Baseline cardiac function

Cardiac Parameter	FEC 50 (n=289)	FEC 100 (n=276)
LVEF:		
Normal	219 (75.8%)	222 (80.4%)
Low (≤ 50%)	8 (2.8%)	4 (1.4%)
Unknown	62 (21.5%)	50 (18.1%)
ECG:		
Normal	250 (86.5%)	243 (88.0%)
Abnormal	8 (2.8%)	11 (4.0%)
Unknown	31 (10.7%)	22 (8.0%)

During the course of the study, some patients experienced cardiac adverse events:

Table 49. Cardiac events on study (as-treated)

Cardiac event	FEC 50 (n=280)	FEC 100 (n=266)
Decreased LVEF	3 (1.1%)	6 (2.3%)
ECG changes*	5 (1.8%)	6 (2.3%)
Delayed CHF	1 (0.4%)	3 (1.1%)

* LVH, RBBB, right fascicular hemiblock, repolarization disorders

Reviewer Comments:

1. Approximately 10% of patients did not have a baseline assessment of cardiac function.

2. The table of cardiac events on study represents events, not unique patients. Eight patients on FEC 50 and 12 on FEC 100 developed cardiotoxicity.

3. A summary of the characteristics of patients who developed cardiotoxicity is presented in the following table. The functional status of these patients is not known: some were reported to be asymptomatic, some were clearly symptomatic, and most did not have information submitted about the presence or absence of clinical symptoms. Note that cumulative anthracycline doses given for metastatic disease do not include the total cumulative anthracycline dose given as adjuvant therapy. Eight patients (5 on FEC 50 and 3 on FEC 100) received cumulative anthracycline doses that were higher than those administered during adjuvant therapy.

Table 50. Summary of cardiac toxicity on GFEA-05 (Modified from sponsor's listing 7.1.1.2, volume 2.28, page 178)

Treatment	Patient ID	Age	Event	Symptoms	Cum. epi—adjuvant (mg/m^2)	Cum. anthra.—metastatic (mg/m^2)	Radiation therapy	Time to event
FEC 50:	A26	63	LVH on ECG; LVEF 55% to 40%	No	136	--	Left chest, SC, paras	Cycle 2
	A 59	55	RBBB on ECG	No	292.9	--	R breast, SC	Cycle 6
	A 74	63	LVEF 58% to 50%; dec. septal contractility on ECG	Unknown	292.7	Epi 550	R breast, SC	67 mo
	D 15	43	LV impairment on ECG	No	296.4	Mitox-- unknown	L breast, axill, SC, paras	37
	L 16	42	"Cardiac funtion impairment"	No	318.4	Dox 675	L chest, axill, SC, paras	28
	L 56	50	L auricular hypertrophy on ECG	No	254.7	--	R chest, SC	Cycle 5
	P 27	30	Global cardiac deficiency (death)	Yes	298.1	Mitox 100	L breast, SC, axill, paras	39
	Z 10	66	LVEF 69% to 45% "Cardiac func.abn"	Unknown	294.3 294.3	Epi 300 Epi 300	L chest, SC, axill, paras	47 51
FEC 100:	A 5	57	CV collapse (death)	Yes	619.3	--	L breast, SC, paras	37
	A 11	56	Mitral collapsus on ECG	Yes	206.8	--	R chest, axill	Cycle 3
	A69*	47	LVEF 57% to 41%	No	493.3	--	R breast, SC	Cycle 5
	A 77	64	LVEF 70% to 56% Repolar.abn. on ECG	Unknown	588.7 588.7	--	L chest, SC, paras	41 53
	A 83	60	Incomplete RBBB Incomplete RBBB	Unknown	97.3 194.6	--	L chest, SC, paras	Cycle1 Cycle 2
	B 12	64	Cardiomyopathy	Yes	599.0	--	L chest, SC	75
	D 10	34	CHF	Yes	595.4	Mitox 90	R breast, SC, axill, paras	47
	D 26	35	CHF; LVEF 50% to 26%	Yes	578.1	Dox 240	R breast, SC	33
	G 36	63	LVEF unkn. at baseline with dec. to 45%; LVH on ECG	Treated w/ isopren-aline	383.1	--	R chest, SC	Cycle 4
	H 9	44	LVEF 62% to 48%	No	593.7	Dox 400	R chest, SC, axill	32
	Q 2	58	Repolar. abn on ECG	Unknown	587.9	--	R chest, SC, axill, paras	Cycle 3
	R 2	37	LVEF 44% to 20% CHF with abn. ECG CHF/abn. ECG/Waiting for cardiac transplant	Yes	590.7 590.7 590.7	-- -- --	R chest, SC, axill	27 68 95

Abbreviations: Epi = epirubicin; Mitox = mitoxantrone; Dox = doxorubicin; SC = supraclavicular; paras. = parasternal; axill = axillary

* Subsequent normalization of the LVEF to 54%; remains normal 5.5 yrs after randomization

It is difficult to evaluate the cardiac toxicity data from this study for several reasons. First, cardiac evaluations after the completion of chemotherapy were optional. Since most cardiac toxicity is expected to occur during follow-up, case ascertainment may be incomplete, particularly for patients with subtle manifestations of cardiac problems. Second, 8 of the 20 patients listed in this table received additional anthracycline therapy, which may have contributed to the observed toxicity. Third, CT treatment planning for left-sided lesions was not used in this study, which can slightly increase the risk for cardiac events. However, 9 patients in the above table had left-sided lesions and 11 had right-sided lesions, making radiation-related toxicity unlikely.

Despite these limitations, one patient on FEC 50 and 7 on FEC 100 had symptomatic cardiac disease. The symptomatic patient on FEC 50 received additional anthracyclines and eventually died of cardiac insufficiency. Of the 7 symptomatic patients on FEC 100, 5 of the 7 received only adjuvant epirubicin therapy. It is likely, as reported in other studies, that epirubicin is associated with an increased risk of cardiac toxicity, and that the risk increases with cumulative dose. It is not possible to conclude from these data whether risk is related to dose-rate or to estimate the true incidence of cardiac impairment.

9.13.1.d Other serious adverse events

One grade 1-2 coagulation event was reported on FEC 50 (none on FEC 100), which was described as aseptic thrombosis of a varicose vein (patient P6). Patient R31 on FEC 100 developed "infectious pneumopathy" after cycle 2, treated with antibiotics. She was removed from study because cycle 3 was delayed by greater than 4 weeks. She remains disease-free 5.5 years after randomization.

9.13.2 Laboratory abnormalities

9.13.2.a Hematology

The incidence of hematologic toxicities is summarized in the following table:

Table 51. Hematologic toxicities (as-treated) (Modified from sponsor's table 19, volume 2.28, page 61)

Test	FEC 50			FEC 100		
	No. pts	Grades 1-4 N (%)	Grades 3-4 N (%)	No. pts	Grades 1-4 N (%)	Grades 3-4 N (%)
Hb	280	36 (12.9%)	0	266	98 (36.8%)	2 (0.8%)
Granulocytes	280	148 (52.9%)	30 (10.7%)	266	145 (54.5%)	66 (24.8%)
Platelets	280	13 (4.6%)	0	266	13 (4.9%)	0

The following table describes clinical consequences of hematologic toxicity in the treatment arms:

Table 52. Clinical sequelae of myelosuppression

Event	FEC 50 (N=280) No. pts (%)		FEC 100 (N=266) No. pts (%)	
	Grades 1-4	Grades 3-4	Grades 1-4	Grades 3-4
Fever	4 (1.4%)	0	2 (0.8%)	0
Rigors/chills	0	0	1 (0.4%)	0
Infection	42 (15.0%)	0	48 (18.0%)	4 (1.5%)
Febrile neutropenia	0	0	7 (2.6%)	1 (0.4%)
Lethargy	3 (1.1%)	0	7 (2.6%)	2 (0.8%)
Sepsis	0	0	1 (0.4%)	0
Septic shock	2 (0.7%)*	0	1 (0.4%)	0

* One death; occurred at 52 months of follow-up

The frequency of granulocytopenia increased with increasing numbers of cycles in both groups, but occurred with greater frequency and severity on the FEC 100 arm. The incidence of any grade of anemia increased over time in both groups. Three cases of grade 3-4 anemia occurred during therapy, all on the FEC 100 arm (cycle 2, cycle 4, and cycle 6).

Reviewer Comments:

1. Grade 3-4 anemia and thrombocytopenia were rare in either arm. The predominant myelotoxicity observed in this trial was granulocytopenia.
2. Patients on FEC 100 had an increased incidence of infection, febrile neutropenia, and lethargy.
3. This trial did not use prophylactic antibiotics, as in MA-5, or colony stimulating factors.
4. The CTC coding used by the sponsor in the above table is inconsistent with the severity of the event. For example, in the old CTC criteria used in this study, all febrile neutropenia should be coded as grade 3.

9.13.2.b Liver function tests

Three patients (1.1%) on FEC 50 and none on FEC 100 were reported to develop grade 1-2 hepatic toxicity due to an elevated bilirubin. No grade 3-4 events were reported.

9.13.3 Non-hematologic toxicity

Most of the patients on the study experienced at least 1 adverse event (98.6% of FEC 50 patients, 99.2% of FEC 100 patients). Adverse events that differed in incidence between the two arms are reported in the following table:

Table 53. Adverse events reported in ≥ 5% of patients that differed in incidence between arms (as-treated) (modified from sponsor's table 19, volume 2.28, page 61)

Adverse Event	FEC 50 (n=280)		FEC 100 (n=266)	
	Grades 1-4	Grades 3-4	Grades 1-4	Grades 3-4
Alopecia	195 (69.6%)	54 (19.3%)	242 (91.0%)	201 (75.6%)
Nausea/vomiting	233 (83.2%)	62 (22.1%)	240 (90.2%)	91 (34.2%)
Stomatitis	26 (9.3%)	0	73 (27.4%)	10 (3.8%)
Diarrhea	20 (7.1%)	0	18 (6.8%)	1 (0.4%)
Heartburn	8 (2.9%)	0	13 (4.9%)	0
Amenorrhea	194 (69.3%)	0	201 (75.6%)	0
Hot flashes	15 (5.4%)	0	8 (3.0%)	0
Motor	46 (16.4%)	0	52 (19.5%)	3 (1.1%)
Mood	13 (4.6%)	0	5 (1.9%)	0
Conjunctivitis	3 (1.1%)	0	13 (4.9%)	0
Cystitis	18 (6.4%)	0	13 (4.9%)	1 (0.4%)
Metabolic	1 (0.4%)	0	7 (2.6%)	0
Pulmonary	7 (2.5%)	0	12 (4.5%)	0

Complete alopecia was dose-related. Nausea and vomiting occurred commonly in both groups, but was more frequent and more severe in the FEC 100 arm. Stomatitis occurred more often and with greater severity on FEC 100.

Reviewer Comments:

1. Alopecia, nausea/vomiting, stomatitis, heartburn, amenorrhea, motor problems, conjunctivitis, metabolic, and pulmonary problems were more common on FEC 100 than on FEC 50.

2. Hot flashes, mood disorders, and cystitis were more common on FEC 50.

3. The database was searched for "motor" problems. All of these events except one were described as "asthenia" by the investigators. The exception was a patient on FEC 100 who developed paraplegia as a result of multiple sclerosis.

4. "Mood" disturbances on FEC 100 included 3 patients with depression, 1 with anxiety, and 1 with "anguish." On FEC 50, 5 patients had anxiety, 4 had depression, and 1 patient each was described with anxiety-depressive illness, "nervous breakdown", "unstable", and "psychiatric problems." There does not appear to be any significant difference in the distribution of these problems between treatment arms.

5. "Metabolic" problems included 1 patient on FEC 50 with sarcoidosis. On FEC 100, this category included 3 patients with diabetes, 3 with arthritis, and 1 with "tetany attack" (patient with normal calcium values).

6. An Access query of the database revealed 7 pulmonary adverse events on FEC 50 and 12 on FEC 100. These events were described as:

FEC 50:

4 cases of dyspnea on exertion
1 case of pulmonary fibrosis
1 case of pulmonary embolism during tamoxifen administration
1 cases of X-ray pneumopathy

FEC 100:

8 cases of dyspnea on exertion
1 case of pneumothorax after central venous access device insertion
1 case of pulmonary embolism
1 case of non-febrile pneumopathy
1 case of cough without fever

The difference between treatment arms seems due primarily to an increased number of cases of dyspnea on the FEC 100 arm. The patients with dyspnea were not the same patients who experienced cardiac problems. Dyspnea may be related to the increased incidence of lethargy and neutropenia observed on the FEC 100 arm.

7. FEC 100 was associated with more non-hematologic toxicity than FEC 50. Despite the increase in hematologic and non-hematologic toxicity with FEC 100, 12 patients on FEC 100 compared to 7 on FEC 50 withdrew, a small number. Patient refusal rates were similar between the two arms. This information suggests that the toxicity is tolerable from a patient's perspective.

9.14 Differences between the published report and the study report of Trial GFEA 05

The reviewer did not find a published account of this study.

9.15 Sponsor's summary of safety and efficacy

This clinical trial compared FEC 50 to FEC 100 in a population of patients that was well-balanced for baseline characteristics. There were comparable numbers of pre- and postmenopausal women in the trial; most had 4 or more lymph nodes involved. Compliance with the protocol was high. Although there were dose reductions in both arms, the dose-intensity remained approximately twice as high on the FEC 100 arm as on the FEC 50 arm. The higher dose regimen resulted in an improved RFS (65% versus 52%) and improved overall survival (76% versus 65%) compared to FEC 50. This benefit persisted even after adjustment for prognostic factors for breast cancer outcome.

The most frequent adverse events were neutropenia, nausea, vomiting, stomatitis, alopecia, and amenorrhea. Adverse event rates were increased on FEC 100 compared to FEC 50. More patients on FEC 100 than on FEC 50 discontinued treatment because of adverse events (4.1% vs. 1.8%), but the number of dropouts was low overall. Colony stimulating factors were not used in this trial.

Cardiotoxicity was reported in 4.5% of women on FEC 100 compared to 2.9% of women on FEC 50. The second primary cancer rates were 7.9% and 5.6% respectively. One leukemia was diagnosed on each arm.

Despite these adverse events, most patients tolerated and completed therapy. The risks of treatment are offset by the significant improvement in RFS and OS associated with FEC 100 therapy.

9.16 Reviewer's summary of safety and efficacy

This trial examined the effect of dose-intensification of epirubicin in a group of high-risk node positive patients. These women were selected for either a large number of positive lymph nodes or, in women with fewer positive nodes, the poor prognostic features of high histologic grade and negative receptors. The trial demonstrated a statistically and clinically significant improvement in both DFS and OS for women treated with FEC 100 compared to FEC 50. Adjuvant studies of dose-intensification of doxorubicin and cyclophosphamide have failed to show a comparable improvement. It is possible that the observed effect in this study results from a more accurate determination of an appropriate "threshold" dose of epirubicin.

The strengths of the study included:

- Randomized design with the same schedule in both arms, differing only in the dose of epirubicin
- Maintenance of 2:1 dose-intensity throughout the trial
- Demonstration of a clinically and statistically meaningful difference in DFS and OS for women on FEC 100 compared to FEC 50
- Median follow-up of 61 months

Weaknesses of the study included:

- Lack of serial cardiac monitoring
- High incidence of acute adverse events

Neutral findings of the study:

- Incidence of local recurrence of 4% in both arms with radiation delayed after chemotherapy

Toxicity in this study was greater with FEC 100 than with FEC 50. The toxicity consisted predominantly of nausea, vomiting, stomatitis, and neutropenia. The toxicity, while significant, did not cause a large number of patients to withdraw from treatment. Withdrawal rates were comparable on both arms. Some of the toxicity might be prospectively managed with colony stimulating factors. Information on serotonin-selective antiemetic therapy would have been helpful.

Long-term serious toxicity included leukemia and cardiac toxicity. Only two cases of leukemia were diagnosed during this study, one on each arm; the small numbers do not permit an accurate assessment of the risk of therapy. This issue will be discussed later in the review. The incidence of overall cardiac toxicity is as described by the sponsor. The incidence of symptomatic cardiac toxicity was 0.4% for women on FEC 50 and 2.6% for women on FEC 100. Cardiac toxicity appears to be due to epirubicin and seems to be related to cumulative dose.

Overall, FEC 100 conveyed a absolute improvement in RFS and OS of 9% and 10% respectively, compared to FEC 50. Estimates of the 25th percentiles showed a 12 month median improvement in RFS and a 18 month median improvement in OS for FEC 100. The benefit of therapy appears to outweigh the risks in a well-informed patient.

10.0 Adjuvant Breast Cancer: Reviewer summary and recommendations

The following table summarizes the results of the submitted pivotal adjuvant trials. Study MA-5 was conducted in node positive pre- or perimenopausal women. Study GFEA-05 was performed in node positive women of any age [if 1-3 positive nodes, must be ER(-) with tumor grade 2-3]. Study GFEA-05, because of its design, contained more women with greater than 4 involved lymph nodes.

Table 54. Efficacy, MA-5 and GFEA-05

Endpoint	MA-5			GFEA-05		
	CEF (n=356)	CMF (n=360)	p-value	FEC 100 (n=276)	FEC 50 (n=289)	P-value
RFS	62%	53%	0.013	65%	52%	0.007
OS	77%	70%	0.13	76%	65%	0.007

Trials MA-5 and GFEA-05 both demonstrate a statistically significant improvement in RFS relative to the comparator (CMF and FEC 50 respectively) for epirubicin at doses of 100 mg/m^2 or greater in combination. Trial MA-5 showed a trend towards improved survival with CEF and GFEA-05 showed a statistically significant improvement in survival for FEC 100. The survival analysis for MA-5 is statistically significantly different if a stratified logrank test is used. GFEA-05 is the only adjuvant trial to clearly show a survival benefit for anthracycline-based therapy compared to a non-anthracycline-containing chemotherapy regimen. The absolute and proportion reductions in risk are comparable to those reported by the Early Breast Cancer Trialists' Collaborative Group (Lancet 339: 71-85, 1992). The meta-analysis showed an absolute difference in RFS of 8.7% and an absolute difference in OS of 6.8% for node positive women treated with polychemotherapy compared to control. Proportional reductions in the chances of recurrence and death were reported to be 28% and 16% respectively in the meta-analysis. Together trials MA-5 and GFEA-05 provide evidence of efficacy and patient benefit for epirubicin-based combination adjuvant therapy compared to CMF.

Because study MA-5 enrolled only pre- and perimenopausal women, it is important to evaluate the effect of treatment in the postmenopausal subset of study GFEA-05. Logrank comparisons of FEC 50 and FEC 100 gave a p-value of 0.07 for DFS and p=0.09 for OS in the postmenopausal subset. The trend favored FEC 100. The study was not powered for subset analysis. The trends among subgroups are consistent with those observed for the overall population and indicate a similar effect in pre- and postmenopausal women.

Trial MA-5 used dose reductions to manage toxicity. Trial GFEA-05 used treatment delays to manage toxicity, although dose reductions were made on study. The actual delivered dose-intensities for epirubicin are summarized below:

Table 55. Comparison of epirubicin dose-intensity in the pivotal trials

Parameter	MA-5	GFEA-05	
	CEF	FEC 50	FEC 100
Epirubicin dose/schedule	60 mg/m^2 IV D1, 8 q 28 days	50 mg/m^2 q 21 days	100 mg/m^2 IV q 21 days
Projected DI	30 mg/m^2/wk	16.7 mg/m^2/wk	33.3 mg/m^2/wk
Delivered DI	23.8 mg/m^2/wk	15.7 mg/m^2/wk	30.5 mg/m^2

Despite the higher planned dose of epirubicin on MA-5, the delivered dose-intensity was greater with FEC 100. At this dose, RFS and OS were improved compared to the dose-intensity that was delivered with FEC 50. An epirubicin dose of 100 mg/m^2 delivered every 21 days was superior to a dose of 50 mg/m^2; the data do not allow a direct comparison of FEC 100 and CEF. The data do not permit a direct comparison of the best management of toxicity, dose reduction or treatment delay. Finally, the data do not address the potential achievable dose-intensities if colony stimulating factors were used. It appears that a dose-intensity of at least 24 mg/m^2/week results in the best outcomes reported to date.

The toxicities of epirubicin can be divided into acute and long-term events. The acute events include side effects common to many cytotoxic agents: nausea, vomiting, myelosuppression, and infection. The incidence of these events was high and could be potentially reduced by the use of better supportive care. Other acute events observed with CEF or FEC with greater frequency than for CMF included mucositis, esophagitis, and diarrhea. These events can be troublesome for patients. Neutropenia may contribute to these problems, but mucositis is related to an independent effect of chemotherapy on the GI mucosa and is unlikely to be affected by the use of growth factors. Approximately 50% of patients scored the question on the quality of life questionnaire about mouth sores as 1-3 (a great deal, a lot, or a fair bit of trouble). This toxicity contributed to the observed short-term decrease in QOL, but discontinuation of study medication was uncommon. This information suggests that therapy was tolerable although not event-free.

More serious toxicities include the risks of cardiac failure and leukemia. The incidence of CHF/drop in LVEF to $\leq$ 40% on MA-5 was 3%, compared to 1% on CMF. In study GFEA-05, the incidence of symptomatic cardiac events was 2.5% on FEC 100 and 0.3% on FEC 50. The incidence of clinical cardiac problems on high-dose epirubicin (FEC 100 + CEF) was 2.9%. The cumulative dose on the high-dose arms in each study was approximately 600 mg/m^2. In comparison, the literature reports an incidence of CHF of <1% for cumulative doxorubicin doses of $\leq$ 300 mg/m^2 and an incidence of 4% at cumulative doxorubicin doses of 450 mg/m^2 (Buzdar et al, Cancer 55: 2761-65, 1985; Buzdar et al, Am. J. Clin. Oncol. 12: 123-8, 1989). Ganz and colleagues reported a 7% incidence of CHF with cumulative doxorubicin doses of 550 mg/m^2, 15% incidence at cumulative doses of 600 mg/m^2, and 35% at cumulative doses of 700 mg/m^2 (Oncology Basel 53: 461-70, 1996). The data in the application do not include a randomized comparison of the cardiac toxicity of doxorubicin and epirubicin. The cardiac toxicity of epirubicin appears to be comparable or somewhat less than that reported with doxorubicin.

The incidence of leukemia is difficult to estimate accurately unless a large database is available. In trials MA-5 and GFEA-05, 5 patients and 1 patient on CEF and FEC 100 developed leukemia. One patient on MA-5 had ALL, unlikely to be associated with therapy. The incidences of AML were 1.1% (4/354) and 0.4% (1/266) respectively, compared to 0.3% (1/360; AML) on CMF and 0.4% (1/280; ALL) on FEC 50. If the high-dose arms are combined, the incidence is 0.8% (5/620). Pooling the leukemia data from the two trials is unlikely to provide an accurate incidence of leukemia. As discussed below in the ISS, the sponsor indicates that the estimated 3-year risk of treatment-related leukemia is 0.24%, and the 5-year risk is 0.8%.

The following table summarizes the observed toxicity.

Table 56. Acute and chronic toxicities, adjuvant pivotal trials

Toxicity	MA-5		GFEA-05	
	CEF (n=354)	CMF (n=360)	FEC 100 (n=266)	FEC 50 (n=280)
Deaths on study	1 (0.3%)	0	1 (0.4%)	2 (0.7%)
Leukemia	5[1] (1.4%)	1 (0.3%)	1 (0.4%)	1[1] (0.4%)
Cardiac toxicity[2]	12 (3%)	4 (1%)	12 (5%)	8 (3%)
Febrile neutropenia	31 (9%)	4 (1%)	7 (2.6%)	0
Vomiting (grade 3-4)	41 (12%)	19 (5%)	91[3] (34%)	62[3] (22%)
Diarrhea	4 (1%)	10 (3%)	1 (0.4%)	0
Stomatitis	45 (13%)	7 (2%)	10 (4%)	0

[1] 1 case of ALL
[2] Drop in LVEF or CHF, reviewer's assessment
[3] Nausea or vomiting, grade 3-4

Overall, in the reviewer's opinion, the submitted trials demonstrate efficacy and clinical benefit for high-dose epirubicin in combination as adjuvant therapy for node positive breast cancer. While there is increased toxicity with the high-dose combination (acute adverse events, cardiotoxicity, and risk of leukemia), the benefit conveyed by the therapy (decreased recurrence and improved survival) is greater than the incidence of these serious adverse events. Women and their physicians should have the option to choose epirubicin-based therapy, the first regimen to document a statistically significant survival advantage compared to CMF. The data support approval for this indication.

Note:

The sponsor submitted the study report from trial C/4/87 as supportive evidence. In this trial, 604 postmenopausal node positive breast cancer patients were randomized to receive tamoxifen 20 mg daily for 4 years or tamoxifen plus epirubicin 50 mg/m^2 IV D1 and 8 every 4 weeks for 6 cycles. At a median follow-up of 5.7 years, DFS was 73% versus 65% in favor of tamoxifen plus epirubicin. The reduction in the odds of recurrence was 28% (p=0.023). Survival was not significantly different (79% versus 76%).

No primary data was provided for this trial. While it cannot be considered as a pivotal study for an indication for adjuvant therapy of early stage breast cancer, it provides additional safety information in postmenopausal women.

11.0 Advanced Breast Cancer: Study HEPI013

Title: Multinational randomized phase III open study comparing an intensive epirubicin-containing regimen including cyclophosphamide and 5-fluorouracil with a conventional non-anthracycline combination in patients with metastatic breast cancer

Trial Accrual Dates: September 1990 to November 1992
Data Lock Date: July 15, 1996
Additional intent-to-treat analysis with updated database as of December 30, 1997
Sites: 48 sites in 20 countries (73 centers recruited; not all accrued)

11.1 Rationale and objectives

11.1.1 Rationale

Phase I trials of epirubicin, conducted in 1979, defined dose-limiting toxicity at 90 mg/m^2, with a white blood cell count of 3.9. In 1987, a second group of Phase I trials identified the maximum tolerated dose as 165-180 mg/m^2 in previously untreated patients and 150 mg/m^2 in previously treated patients. Doses of 120-150 mg/m^2 were tolerated in combination chemotherapy. Use of higher doses of epirubicin, in these trials, was associated with an unexpected high response rate (approximately 50%) in previously treated patients.

Anthracyclines have been considered as the most effective agents in breast cancer therapy, and published studies suggest a dose-response relationship. Phase I and II trials with epirubicin demonstrated a dose-response effect. Study GFEA-05, a randomized Phase III trial in node positive patients, demonstrated a RFS and OS benefit with FEC 100 compared to FEC 50. The pilot study performed in preparation for study MA-5 demonstrated that a dose-intense epirubicin regimen could be given safely in the outpatient setting. Preclinical data suggested a more favorable safety profile for epirubicin than for doxorubicin.

For these reasons, the present study was designed to evaluate whether a dose-intensive epirubicin-based combination chemotherapy regimen was superior to CMF, the most commonly used non-anthracycline-containing regimen at the time.

11.1.2 Objectives

- To determine whether an intensive epirubicin combination produces a significant prolongation of time to progression in comparison with CMF in patients with metastatic breast cancer who have not received chemotherapy for this stage of disease
- To assess response rate
- To assess duration of response
- To assess toxicity
- To assess quality of life
- To assess survival

Reviewer Comments:

1. Time to progression was the primary endpoint as defined by the protocol. Determination of time to progression in this study may be complicated by the period of observation incorporated into the trial design. It is possible that patients progressed because of the lack of any therapy rather than because of lack of efficacy of one treatment compared to the other.

2. Response rate was a secondary endpoint. Because patients with evaluable but not measurable disease were eligible, this endpoint will look at a subset of patients on study (despite the use of response criteria for inevaluable lesions).

3. The interpretation of quality of life questionnaires may be potentially confounded by the observation period. Quality of life assessments on therapy evaluate the toxicity of therapy and may capture decreased tumor-related symptoms related to effective therapy. QOL assessments during the period of observation evaluate disease-related symptoms, an indirect measure of the long-term benefits of therapy. Because other reports have indicated that continuous chemotherapy is associated with improved quality of life compared to intermittent chemotherapy, data from the observation period must be interpreted cautiously. Significant differences between treatment arms will be needed to conclude that there is a meaningful difference in quality of life between treatments.

11.2 Design

11.2.1 Dose and schedule

The trial was a randomized, multicenter, open-label Phase III study of CEF compared to CMF as first-line therapy of women with metastatic measurable or evaluable breast cancer. Patients were randomized to receive:

CEF:	Cyclophosphamide	400 mg/m^2	IV D1, 8 every 21 days
	Epirubicin	50 mg/m^2	
	5-Fluorouracil	500 mg/m^2	

or

CMF:	Cyclophosphamide	500 mg/m^2	IV D1, 8 every 21 days
	Methotrexate	40 mg/m^2	
	5-Fluorouracil	600 mg/m^2	

The chemotherapy regimens were chosen to maximize their dose-intensity. The classic Bonadonna CMF regimen, with 14 days of oral cyclophosphamide, has been reported in the literature (one randomized trial, a number of retrospective comparisons) to have the highest activity. However, classic CMF was not considered feasible for use in this trial because of excessive gastrointestinal and hematologic toxicity, potential problems with evaluating compliance, and inconvenience for the patient. The CMF

regimen in which all drugs are given intravenously on day 1, repeated every 21 days, was reported in the literature to have a delivered dose-intensity of 0.62 relative to classic CMF and less efficacy, making it a less desirable comparator. The CMF regimen used in this trial was chosen because its dose-intensity, compared to classic CMF, was reported to be 0.91. It was expected to provide efficacy comparable to that observed with classic CMF, but have less toxicity.

The epirubicin regimen was chosen to mirror the administration schedule of CMF. The dose of epirubicin, considered to be the most active drug in the regimen, was maximized; the doses of cyclophosphamide and 5-FU were decreased in order to offset toxicity.

Patients received 6 cycles of the randomized therapy. Patients who had a complete or partial response after 6 cycles received an additional 3 cycles of chemotherapy followed by observation. For patients who had no change after 6 cycles, therapy was stopped and they were observed. Patients with progressive disease during therapy were taken off study. In both groups, at the time of progression, further treatment was given at the physician's discretion. These patients were then followed every 3 months for survival only.

A cycle was defined as the period of drug treatment plus the time required to recover from the acute effects of treatment (3-4 weeks). Patients were treated according to actual, not ideal, body surface area.

Reviewer Comments:

1. The choice of the comparator is acceptable, although from a regulatory perspective the most desirable study would have been a direct comparison of epirubicin and doxorubicin.

2. The CMF regimen chosen is acceptable. The classic CMF regimen has the highest reported activity in the literature, but because of its inconvenience and use of oral cyclophosphamide, it is not commonly used in clinical practice. CMF given IV days 1 and 8 is not used as commonly as CMF IV D1. The activity of the D1, 8 regimen makes it the best CMF comparator given the limitations of this regimen.

3. Maximizing the dose of epirubicin at the expense of cyclophosphamide and 5-FU is acceptable. Any benefit seen with CEF will be likely to result from the use of epirubicin rather than from the effect of cyclophosphamide and 5-FU in combination.

4. The use of an observation period is acceptable, although not consistent with clinical practice in the United States. It will be important to assess the comparability of follow-up during the observation period. Progression due to the lack of any therapy, rather than to the lack of a specific therapy, should be similar on both arms. Use of subsequent therapies should not affect time to progression. Survival may be affected by subsequent therapies, although second and third-line treatment for metastatic breast cancer has not been shown to convey a statistically significant survival advantage.

5. The use of actual BSA is acceptable. Some patients with high BSA measurements might have excess toxicity based on this approach. The reviewer queried the database and did not find excess toxicity (all adverse events, hematologic toxicity) in patients with BSA of 1.8 or higher compared to those with BSA < 1.8.

6. Concomitant hormonal therapy (such as tamoxifen) was not permitted.

11.2.2 Dose modifications

11.2.2.a Hematologic toxicity

The following table summarizes dose-modifications for hematologic toxicity:

Table 57. Dose modifications according to hematologic toxicity (Sponsor's table 9.1.2, volume 2.33, page 154)

Blood count	Nadir count	Dose Adjustment
Day 21:		
ANC ≥ 1500 *and* platelets ≥ 100,000	ANC ≥ 200 *and* platelets ≥ 50,000	100% of D1 of prior cycle
ANC ≥ 1500 *and* platelets ≥ 100,000	ANC ≤ 200 *and/or* platelets ≤ 50,000	Reduce CTX, 5-FU to 75% of D1 of prior cycle; if same nadir occurs in the next cycle, reduce epi or MTX to 75%
ANC ≥ 1500 *and* platelets ≥ 100,000	Febrile neutropenia	Reduce all drugs to 75% of D1 of prior cycle
ANC < 1500 *or* platelets < 100,000	Any	Hold therapy. Repeat CBC weekly until ANC ≥ 1500 and platelets ≥ 100,000; then adjust based on nadir. Off study if no recovery after 2 weeks
Day 8:		
ANC ≥ 1500 *and* platelets ≥ 100,000		Same dose as D1
ANC 1000-1499 *and* platelets ≥ 100,000		Reduce CTX, 5-FU to 75% of D1 of this cycle
ANC < 1000 *or* platelets < 100,000		No treatment. Repeat CBC weekly. Next cycle may start on D21 if counts permit

Abbreviations: CTX=cyclophosphamide, 5-FU=5-fluorouracil, epi=epirubicin, MTX=methotrexate, ANC=absolute neutrophil count

An algorithm for the recommended management of febrile neutropenia was included in the protocol.

Reviewer Comments:

1. Low nadir counts were acceptable in this study.
2. Dose modifications were used in preference to treatment delays.
3. Cyclophosphamide and 5-FU were dose-reduced first in order to maintain dose-intensity of epirubicin (considered to be the most active drug).
4. Prophylactic antibiotics and growth factors were not used routinely in this study.

11.2.2.b Non-hematologic toxicity

Doses were modified for specified non-hematologic toxicities:

- Liver function tests
  - For total bilirubin 2-3 mg/dl or 34-51 umol/L and SGOT 3-5 x upper limit normal (ULN): give 50% of epi/5-FU or MTX/5-FU
  - For total bilirubin >3 mg/dl or > 51 umol/L: hold all drugs
- Serum creatinine
  - For creatinine 1.5-2.5 mg/dl or 130-220 umol/L: give 50% of CTX and 75% of epi/MTX and 5-FU
  - For creatinine >2.5 mg/dl or >220 umol/L: hold all drugs
- Mucositis
  - Grade 3-4: give 75% of 5-FU given in prior cycle and maintain future dosing at this level
  - If grade 3-4 recurs, reduce epi/MTX to 75% of prior cycle and maintain future dosing at this level
- Nausea/vomiting
  - Grade 3-4: treat with aggressive antiemetic therapy
  - If grade 3-4 recurs: reduce drugs to 75% of prior cycle and maintain future dosing at this level
- Hemorrhagic cystitis
  - Consider prophylaxis with mesna
  - If problem recurs with mesna, discontinue cyclophosphamide
- Cardiac toxicity
  - See section 11.2.3 for a description of discontinuation for cardiac toxicity
- Other toxicities
  - If other grade 3-4 toxicity occurs except alopecia, reduce drugs to 75% for one cycle.
  - May attempt re-escalation

Reviewer Comment:

1. According to a MS Access query, 75 patients (34%) on FEC and 62 patients (26%) on CMF used ondansetron during the trial.

11.2.3 Baseline and follow-up evaluations

See Appendix I for the Schedule of Evaluations. Patients were required to have a history and physical examination with routine bloodwork and staging of disease at baseline. Tumor staging was repeated every 2 cycles during therapy. Patients were examined and restaged every 3 months during the observation period.

Cardiac evaluations consisted of clinical exams, ECGs, and MUGA/ECHOs. ECGs were performed at baseline, before every cycle, and at the end of treatment. MUGA or ECHO scans were performed at baseline. Patients randomized to CEF had the scan repeated at a cumulative dose of epirubicin of 400-500 mg/m^2, at 700-800 mg/m^2, and before each subsequent treatment course. The same imaging modality was to be used for each evaluation. Patients with a drop in LVEF by $\geq$ 20% absolute units from

baseline to a value above the lower limit of normal for the institution or a fall of ≥ 10% to a value below the lower limit of normal for the institution were to be discontinued from study.

Quality of life assessments were performed at baseline, at each cycle prior to the administration of antiemetic therapy and chemotherapy, when the patient went off-treatment, and every 3 months up to 2 years post-randomization date. The FLIC (Functional Living Index Cancer) was used. The FLIC contains 22 statements. The patient is asked to place a vertical slash on a horizontal line divided into sections numbered 1-7 that reflected her feelings for the past week.

Reviewer Comments:

1. Patients on CMF did not undergo regular cardiac evaluations.
2. Data from quality of life scales can be difficult to interpret. Pen marks through a horizontal scale are subject to interpretation (for example, if the pen mark is not perpendicular to the scale, one could obtain a high or a low value, depending on which end is measured). The forms should be completed prior to the office visit and should be completed by the patient, unassisted if possible. Missing data poses a challenge to the statistician in determining the appropriate analysis techniques.

11.3 Randomization and stratification

Randomization was performed centrally in Milan by Farmitalia. Randomization was stratified by center and by:

- Number of sites of metastases
  - Referred to the number of organs involved, not the number of lesions within each organ
  - 1-2 sites versus >2
- Presence of visceral lesions (liver, lung, pleura, peritoneum, adrenals)
  - Patients with at least 1 visceral site were classified as "yes"
- Prior adjuvant chemotherapy

There were 8 randomization strata. All sites randomized patients at the central site except the Australian sites. The time difference made it impractical for the Australian sites to communicate with Milan for randomization. A separate randomization list was sent to Australia for centralized randomization of the 5 Australian sites.

Reviewer Comments:

1. The randomization strata were appropriate.

- Tumor burden and presence of visceral metastases are recognized predictive and prognostic factors for metastatic breast cancer.
- Most literature indicates that prior adjuvant chemotherapy does not affect response to subsequent chemotherapy for metastatic disease, although some publications have reported different results.

- Disease-free interval is another factor that affects response and prognosis and could have been considered as a stratum. However, the protocol excluded patients who relapsed within 12 months of adjuvant chemotherapy.

2. There will be insufficient power to analyze by strata.

11.4 Protocol amendments

The protocol was amended once, on December 18, 1991. Patients were permitted to have had adjuvant hormonal therapy and no more than 2 hormonal therapies for metastatic disease, provided that the second metastatic therapy was given for $\leq$ 8 weeks. At the time of the amendment, 90 patients on the FEC arm (40%) and 101 on the CMF arm (43%) had been randomized.

Reviewer Comment:

1. Use of prior hormonal therapy has not been reported to affect subsequent response to cytotoxic chemotherapy.

2. A query of the MS Access database showed that 4 patients on CMF and 3 on FEC had received 2 hormonal treatments for metastatic disease. This amendment is unlikely to significantly affect the conduct of the study.

11.5 Eligibility and enrollment

11.5.1 Inclusion criteria

- Female patients with histologic proof of breast cancer with metastatic disease, either at diagnosis or recurrent disease; may have locoregional or distant recurrence
- Measurable and/or evaluable lesions located outside prior radiation fields
- > age 18 and $\leq$ age 70
- ECOG PS $\leq$ 2
- Palliative radiotherapy to no more than 25% of red bone marrow
- May have received adjuvant hormonal therapy. May have received no more than 1 hormonal therapy for metastatic disease [AMENDED 12/18/91; see section 11.4]
- Must have recovered from prior toxicities of radiation and hormonal therapy
- Adequate bone marrow, liver, and renal function (defined in the protocol)
- Resting LVEF measured by MUGA or ultrasound within the normal limits set by the local institution

Reviewer Comments:

1. Patients with measurable or evaluable disease were eligible. Response criteria for evaluable disease were specified in the protocol, but are by their nature more difficult to verify than objective responses in patients with measurable disease. Time to progression, the primary endpoint, will be more reliable than response rate.

2. The protocol included a table that described the distribution of active bone marrow in adults.

11.5.2 Exclusion criteria

- Local recurrence within a partially resected breast
- Locally advanced inoperable breast cancer or inflammatory breast cancer
- Prior chemotherapy other than adjuvant chemotherapy
- Prior adjuvant chemotherapy with anthracyclines
- Failure of adjuvant CMF or variant within 12 months of completion
- Patients with pleural effusion involving more than the costophrenic space and/or ascites
- Patients with osteoblastic bone metastases and/or pleural or ascitic effusion and/or lymphangitic carcinomatosis as the only manifestation of disease
- Clinical or "instrumental" evidence of brain metastases
- Cardiovascular history of myocardial infarction within the last year or heart failure (including cardiac insufficiency controlled by digitalis and diuretics) or irreversible arrhythmias requiring permanent medication or uncontrolled arterial hypertension ($\geq$ 200/110 mm Hg)
- ECG evidence of left ventricular hypertrophy, complete LBBB, complete RBBB plus left anterior hemiblock or left posterior hemiblock, coronary insufficiency (ST depression at rest), high risk uncontrolled arrhythmia (multifocal ventricular extrasystoles)
- History of malignancy other than localized basal or SCCA skin cancer or non-invasive cervical malignancy within 5 years of entering the study
- Active infection
- Pregnancy; patients must agree to practice birth control

Reviewer Comments:

1. Patients with in-breast recurrence only were appropriately excluded.

2. Patients who failed within 12 months of adjuvant chemotherapy were excluded; this exclusion makes it unlikely that an imbalance in disease-free interval occurred.

11.6 Endpoints

Time to progression was the primary endpoint of the study. Progressive disease was defined as a greater than 25% increase in the sum of the products of the two largest perpendicular diamters of one or more measurable tumors or the appearance of new lesions. TTP was defined as the time period from the date of randomization to the date of first observation of progressive disease. The date progressive disease was first suspected was used as the progression date, provided that this date was documented in the CRF and that progression was subsequently confirmed objectively. For patients with bone disease, bone scans were performed, but plain X-rays were required and were the predominant modality used to evaluate disease in bone.

Certain circumstances were prospectively defined in the protocol as failing to meet criteria for progression:

- The presence of brain metastases in the absence of systemic progression was not considered to be progressive disease in a patient with a prior documented CR or PR.

Patients who had no change in their systemic disease and who developed brain metastases were considered to have progressed.

- Patients who required radiation therapy for painful bony metastases could remain on study if the irradiated sites were not followed for response, if the radiation field did not contain large marrow-containing bones, and if counts were adequate for chemotherapy. Otherwise, she was discontinued from treatment and followed for survival.
- Patients with a pathologic fracture were to undergo systemic restaging. If the fracture occurred in an area with no tumor and there was no evidence of progression on restaging, she remained on study.
- Hypercalcemia was considered to represent progression.

Response rate was defined as the ratio of the number of patients classified as CR and PR and the number of randomized patients. A series of response criteria were defined in the protocol: a set for patients with measurable disease, a set for patients with evaluable disease, a set for evaluation of liver lesions, a set for evaluation of bone metastases, and an overall scoring system for these responses.

Duration of response was defined as the time interval from the date a CR or PR was first recorded to the date progressive disease was first noted.

Survival was measured from the date of randomization until death.

Reviewer Comments:

1. Traditionally, the Agency has considered survival data as the "gold standard" in assessing the efficacy of first-line treatment of metastatic breast cancer, where doxorubicin is considered to convey a modest 6-month survival benefit. Given the widespread use of doxorubicin in the adjuvant rather than the metastatic setting and the development of new active drugs for advanced disease that may influence survival after first-line therapy, the DODP will discuss the value of TTP with the ODAC in June.

2.The definitions of progression were established prospectively.

3. Most investigators consider the need for radiation of a painful lesion to represent progressive disease, unless it occurs within a prospectively defined timeframe (e.g., the first 4 weeks of therapy).

4. The protocol was not stratified for measurable versus evaluable disease. Review of the database indicates that 182 patients on CMF and 172 on FEC had at least 1 measurable lesion.

5. In a regulatory evaluation, response rate is considered to be a surrogate endpoint. This trial collected information on time to progression and survival, which preclude the need to rely on response rate for proof of patient benefit. As defined in the protocol, evaluation of response includes a variety of criteria for measurable and non-measurable disease. Some methods that were acceptable per protocol have not been validated in practice, such as relying on palpable liver size during the clinical examination as evidence of response. While a uniform evaluation system was used for both arms, reports of response rates are not likely to add meaningful information to the efficacy assessment.

11.7 Statistical plan

11.7.1 Prospectively defined

The following assumptions were made in order to calculate the sample size:

- Median time to progression on CMF is 8 months
- Median time to progression with CEF will improve by 35% to 11 months
- Accrual time will be 15 months
- Time to progression will be analyzed 12 months after the last patient is randomized

Four hundred patients were required to test these assumptions with α=0.05, power = 0.80, and a two-sided test of significance. Thirty centers were anticipated to provide 15 patients each in order to complete recruitment in the specified time.

Inevaluable patients were prospectively defined in section 9.1.8 of the protocol as those without sufficient data to evaluate toxicity or efficacy; patients who received concomitant hormonal therapy in addition to the randomized therapy; and patients who did not meet the eligibility criteria but who were randomized and treated. In section 10.3 of the protocol, evaluable patients were defined as those who received a minimum of 2 cycles of chemotherapy unless rapid disease progression or death occur earlier (then called treatment failures), patients who received therapy according to the dose/schedule and dose adjustment schedule required in the protocol, patients who did not receive any other specific therapy (chemotherapy, hormonal therapy, radiotherapy) until progression, and patients who fulfilled the eligibility criteria.

The primary analysis was defined as the intent-to-treat analysis. Secondary analyses using the evaluable population were specified in the protocol.

The primary endpoint of the trial was time to progression. TTP was analyzed by the Kaplan-Meier method; the two treatment groups were to be compared by the Wilcoxon test and the logrank test, with a one-sided 5% level of significance.

The response rate was calculated for each treatment as the ratio between the number of patients with CR and PR and all randomized patients, compared with the chi-square test.

The safety analysis was performed according to the worst toxicity grade observed during the study. All patients who received one cycle of treatment with appropriate evaluations per protocol were evaluable for safety.

The protocol indicated that quality of life would be analyzed for change from baseline for the first 6 cycles, maximum improvement from baseline, and the endpoint QOL, defined as the last QOL measured for each patient. Analysis of individual QOL questions was planned. Means, medians, and standard errors were listed for each variable as a summary of its distribution. QOL was to be analyzed in the intent-to-treat and the evaluable populations.

Reviewer Comment:

1. The FDA considers the intent-to-treat analysis as the primary analysis.

2. The sponsor's set of inevaluable and evaluable patient definitions are similar but not completely congruent. The definition of evaluable is restrictive; for example, it is

common to see minor protocol violations in terms of dosing. This definition excludes all patients not treated exactly per protocol.

3. All patients who received therapy should be evaluable for safety, not only those who were treated and evaluated according to the protocol schedule.

4. The analysis plan for quality of life was incomplete. A meaningful difference from baseline was not prospectively specified. No plans for handling missing data (either missing items or missing questionnaires) were outlined. Data obtained at the endpoint may not offer meaningful information, because patients may have been taken off-study for toxicity, for progressive disease, or by patient choice. The last measurement usually does not offer the best assessment of overall quality of life.

11.7.2 As defined in the study report

11.7.2.a Sample size calculation

The sponsor notes that because 461 patients were enrolled in the study instead of 400 and because they were followed for over 60 months, the power in the trial is greater than the 80% anticipated in the original design.

All patients entered on the study were included in the analysis except for patient Poland 55/40, who was treated prior to randomization.

11.7.2.b Patient characteristics

Baseline characteristics were summarized in frequency tables or with descriptive statistics. Chi-square tests were performed to evaluate potential imbalances. All randomized patients were evaluated on an intent-to-treat basis.

11.7.2.c Treatment

Treatment was described in terms of maximum number of cycles administered, cycle duration, and dose-intensity.

- The maximum number of cycles was defined as the total number of cycles that a patient received during the study.
- The duration of each cycle was calculated as the difference between the starting dates of two consecutive cycles. The last cycle was excluded from analysis.
- Dose intensity was calculated by summing each cycle dose in mg/m^2 divided by the number of weeks from the first day of cycle 1 to the date of the last cycle plus a fixed interval of 3 weeks. Relative DI was calculated as the ratio between the DI for each drug as received and the planned DI (a decimal fraction). The relative DI was calculated as the ratio between the DI for each drug as received and the planned DI. The average relative DI was calculated as the mean of the relative DIs of the single components.

All randomized patients were included in the analysis for the description of the maximum number of cycles given. All other calculations used only randomized and treated patients, analyzed by treatment actually received. Descriptive statistics were used to summarize these findings.

11.7.2.d Efficacy

Several endpoints were defined:

Best response: Assigned by an independent reviewer based on WHO criteria. A stabilization of 4 months was required for an assessment of stable disease.

Duration of response: Date of first documented response to the first date of documented tumor progression

Time to progression: Time in days between the date of randomization and the first date of documented progression or death due to any cause, whichever occurred first. Patients taken off study due to refusal, toxicity, and loss to follow-up in the absence of disease progression were censored at the last known date.

Time to failure: The interval in days between the date of randomization and the date of failure (defined as disease progression, death, treatment discontinuation due to patient refusal, toxicity, or loss to follow-up). Date of failure was the first date of documented tumor progression or death or the last known date in the other cases

Overall survival: Time in days from the date of randomization to the date of death or the last known date

A patient was considered evaluable if she received a minimum of 2 cycles unless rapid disease progression or death occurred earlier; in these cases, she was considered a treatment failure. Survival was assessed in the intent-to-treat population according to randomized treatment. Response and TTF were analyzed in all randomized patients with histologically proven breast cancer. Response, duration of response, and TTP were evaluated in randomized patients who were eligible and evaluable for response, analyzed by randomized treatment.

Response rate was calculated as the ratio of responders to the total number of patients analyzed and was compared between treatment arms with a chi square test. The odds ratio and its 95% CI were calculated.

OS, TTP, TTF, and duration of response were calculated using Kaplan-Meier curves, compared by the logrank and Wilcoxon tests. The hazard ratio with 95% CI was calculated.

For TTP, a Cox proportional hazard regression analysis was performed to investigate the effect of prognostic factors (the stratification factors used in the study).

11.7.2.e Safety

Hematologic toxicity was evaluated for evaluable cycles (at least one count available between day 8 and day 15 inclusive; for hemoglobin, one count at any time during the cycle was acceptable). A patient was evaluable if she received at least 1 evaluable cycle. Nadir counts were also assessed. Analyses by cycle and by patient were performed. Analyses were performed on evaluable patients and cycles per treatment actually received. A separate analysis was performed on all treated patients and all cycles to ensure that severe hematologic toxicity was not missed. Results were expressed by toxicity grades in frequency tables; the chi-square test was used for comparison.

Non-hematologic toxicity was summarized with WHO criteria by frequency and percentage at baseline and for all delivered cycles. All treated patients were analyzed by treatment received. Maximum grade experienced during treatment was computed. The two arms were compared in the following categories: absent (grade 0), mild (grade 1-2), and severe (grade 3-4). For statistically significantly different results, a further analysis was performed: grade 0 versus any grade (incidence) and grade 1-2 versus grade 3-4 (severity).

Cardiac toxicity was evaluated by LVEF as previously stated. The analysis was performed on the evaluable patients (patients with both a baseline value and at least one assessment during treatment performed with the same method). The frequency of cardiac events was shown for the evaluable patient population. Patients were analyzed by treatment received. Results were described in tables with known risk factors.

11.7.2.f Quality of life

The FLIC was analyzed according to groupings of questions as defined in the literature:

Physical well-being and ability (items 7, 15, 13, 4, 20, 11, 22, 10, 6)
Psychological well-being (items 18, 9, 3, 2, 1, 21)
Hardship due to cancer (items 12, 8, 14)
Social well-being (items 16, 19)
Nausea (item 5, 17)

For the first two areas, a prorated score was computed for missing values, provided that the number of missing values was less than 50%. The mean score for all answered questions was assigned to the missing values.

For the other areas, all questions had to be answered to calculate the area scores.

An overall score was computed by summing together all the subscale scores, provided that a value was obtained for each. All randomized patients per received treatment were analyzed.

The Quality of Life analysis was not included.

Reviewer Comments:

1. The statistical plan used in the study report was more detailed than the one-paragraph description in the original protocol.

2. The FDA considers the primary analysis to consist of an unadjusted analysis of all randomized patients. Analyses of eligible or evaluable patients or patients with histologically documented breast cancer are secondary.

2. The sponsor has been asked to submit the quality of life analysis.

11.8 Enrollment and demographics

11.8.1 Enrollment

Four hundred sixty-one patients were enrolled in the study; 460 were randomized and analyzed. One patient was treated prior to randomization and was not included in the analysis.

Table 58. Patient enrollment (sponsor's table 1, volume 2.33, page 069)

Treatment disposition	FEC	CMF	Total
Randomized patients	223	237	460
Not treated	5	1	6
Treated with FEC	218	2	220
Treated with CMF	N/A	234	234

11.8.2 Demographics

Patient characteristics are summarized in the following table:

Table 59. Baseline patient characteristics (modified from sponsor's table 7-16, volume 2.33, pages 77-86)

Characteristic	FEC (n=223)	CMF (n=237)
Age at study entry:		
< 50	69 (31%)	83 (35%)
50-59	66 (30%)	77 (33%)
≥ 60	88 (40%)	77 (33%)
Age at first diagnosis:		
< 50	87 (39%)	110 (46%)
50-59	70 (31%)	87 (37%)
≥ 60	64 (29%)	40 (17%)
Unknown	2 (1%)	0
Race:		
White	214 (96%)	228 (96%)
Black	4 (2%)	2 (1%)
Other	3 (1%)	7 (3%)
Unknown	2 (1%)	0
Performance status:		
0	76 (34%)	85 (36%)
1	124 (56%)	128 (54%)
2	22 (10%)	24 (10%)
Unknown data	1 (0.5%)	0
Menopausal status:		
Premenopausal	54 (24%)	74 (31%)
Postmenopausal	167 (75%)	162 (69%)
Unknown	2 (1%)	0
Histology:		
Infiltrating ductal	168 (75%)	182 (77%)
Infiltrating lobular	12 (5%)	15 (6%)
Other invasive	33 (15%)	31 (13%)
DCIS	5 (2%)	4 (2%)
Paget's disease	0	1 (0.4%)
Unknown/no data	5 (2%)	4 (2%)
Stage at diagnosis:		
I	15 (7%)	18 (8%)
IIA	59 (27%)	69 (29%)
IIB	55 (25%)	53 (22%)
IIIA	18 (8%)	20 (8%)
IIIB	8 (4%)	6 (3%)
IV	52 (23%)	54 (23%)
Unknown	16 (7%)	17 (7%)
ER status:		
Positive	37 (17%)	33 (14%)
Negative	32 (14%)	39 (17%)
"Equivocal"	3 (1%)	0
Unknown	2 (1%)	0
Not assessed	149 (67%)	165 (70%)
PR status:		
Positive	23 (10%)	26 (11%)
Negative	37 (17%)	34 (14%)
"Equivocal"	2 (1%)	0
Unknown	3 (1%)	0
Not assessed	158 (71%)	177 (75%)