

8.11.4 Treatment cycles

8.11.4.a Number of cycles

On the CEF arm, 2088 cycles were completed, compared to 2135 on CMF. The percentage of patients who completed 6 cycles of therapy was 96% on CEF and 97% on CMF.

8.11.4.b Duration of treatment cycles

The median duration of a treatment cycles was 28 days in both groups for all cycles. The mean values ranged from 29.16 to 31.27 days on CEF and from 29.10 to 30.64 days on CMF.

Cycle duration was also calculated as the ratio of actual days/expected days. The median was 1.00 in both groups, for treatment overall and by cycle. In the CEF group, 70% of cycles were delivered in the 0.9-1.15 relative time class, and 73% of the CMF cycles were delivered in this time class. Two percent of patients on each arm had a cycle duration ratio of 1.30.

8.11.4.c Treatment delays

Sixty-three percent of cycles in the CEF group and 67% of the cycles in the CMF group were delivered on schedule. The median delay for postponed cycles was 7 days in each group; mean delays were also similar (6.4 versus 6.3 days respectively).

The median D1-D8 treatment delay was 1 day for both groups with a mean delay of 2.5 days in each group. Day 8 treatment was delivered on time in 95% of the CEF cycles and 94% of the CMF cycles.

The comparison of the proportion of Day 1-to-Day 1 delayed administrations comparing CEF with CMF approached statistical significance: chi-square p-value=0.054 (a trend for more delays of CEF than CMF). No difference in the proportions of D1-D8 delays was observed (chi-square p-value=0.112).

Reviewer Comments:

1. A high percentage of patients on both arms completed the planned course of therapy.
2. There were no significant differences between treatment arms in the number of treatment delays or the length of the delay.

8.12 Efficacy results (intent-to-treat analyses)

8.12.1 Relapse-free survival

One hundred thirty-six of the 356 patients on CEF (38%) and 169 of the 360 randomized patients on CMF (47%) relapsed or died of tumor-related causes. The Kaplan-Meier (KM) estimates of RFS at 5 years were 62% (95% CI 57-67%) and 53% (95% CI 48-58%) respectively (stratified logrank p-value = 0.013). The KM estimates of the median RFS could not be determined, as the upper limit of the 95% CI is not yet

estimable (ne). The estimates of the 25th percentile (75% RFS) and the 95% CI are 2.6 years (95% CI=2.0-3.5) for CEF and 1.9 years (95% CI=1.7-2.2) for CMF.

Estimates of RFS at 5 years and at the 25th percentile were calculated for the stratification factors and selected prognostic factors and are summarized in the following table:

Table 13. RFS estimates at 5 years and 25th percentile by strata and prognostic factors (Sponsor's table 7, volume 2.19, page 64)

Variable	CEF			CMF		
	Randomized n (%)	% 5-year RFS	25 th percentile yrs (95% CI)	Randomized n (%)	% 5-year RFS	25 th percentile yrs (95% CI)
All patients	356 (100)	62	2.6 (2.0-3.5)	360 (100)	53	1.9 (1.7-2.2)
Positive nodes:						
1-3	218 (61)	68	3.6 (2.6-4.9)	218 (61)	62	2.2 (2.0-3.0)
≥ 4	138 (39)	52	1.8 (1.5-2.4)	142 (39)	39	1.4 (1.2-1.9)
4-10	115 (32)	60	2.0 (1.6-3.1)	118 (33)	42	1.7 (1.4-2.0)
> 10	23 (6)	16	1.5 (1.0-1.9)	24 (7)	25	0.9 (0.6-1.3)
Surgery:						
Partial mastectomy	175 (49)	66	3.0 (2.0-4.5)	176 (49)	56	2.1 (1.7-2.6)
Total mastectomy	181 (51)	58	2.0 (1.8-3.2)	184 (51)	50	1.9 (1.5-2.1)
Receptor status						
Negative	75 (21)	58	1.7 (1.2-2.6)	70 (19)	55	1.7 (1.3-2.2)
Positive	241 (68)	62	2.9 (2.0-3.7)	245 (68)	51	1.9 (1.6-2.2)
Unknown	40 (11)	70	4.0 (1.4-5.8)	45 (13)	62	3.5 (2.1-5.7)
Menopausal status						
Perimenopausal	80 (22)	61	2.0 (1.8-4.3)	75 (21)	60	2.3 (1.9-4.5)
Premenopausal	276 (78)	62	2.8 (2.0-3.5)	285 (79)	51	1.8 (1.6-2.1)
Tumor size						
T0-T2	311 (87)	63	2.8 (2.0-3.5)	315 (88)	53	1.9 (1.8-2.3)
T3-T4	14 (4)	17*	1.5 (1.2-3.9)	22 (6)	18*	0.8 (0.4-1.9)
Tx or missing	31 (9)	59	2.0 (1.5-5.3)	23 (6)	58	3.1 (1.6-ne)

*Estimate at 4.3 years for the CEF group and at 4.9 years for the CMF group respectively
n.e. Not estimable

The sponsor notes that the study was not designed with enough power to analyze the subgroups. However, RFS was superior with CEF treatment compared to CMF therapy in women with 1-3 positive nodes and in women with 4 or more involved nodes; the majority of the benefit was observed in women with 4 or more involved nodes. Women treated with a partial mastectomy had a better RFS than women treated with total mastectomy, but patients treated with CEF had a better RFS than women treated with

CMF in either strata. CEF was associated with an improved RFS compared to CMF regardless of receptor results.

In the CEF group, a similar proportion of perimenopausal and premenopausal women relapsed. In the CMF group, more premenopausal women relapsed compared to perimenopausal women. Among premenopausal women, treatment with CEF was associated with a better RFS compared to treatment with CMF.

Tumor size was predictive of relapse with a direct correlation. CEF was associated with a higher 5-year RFS than CMF for T₀₋₂ tumors. RFS rates were similar between both treatment arms for larger tumors.

The Cox model indicated that the number of positive nodes and tumor size are significant predictors of outcome in this patient population (p=0.0001). The conditional risk ratio for patients with 4 or more involved lymph nodes is 1.7 times that of patients with ≤ 3 involved nodes (95% CI 1.33-2.13). The conditional risk ratio for patients with T_{3,4} tumors compared to patients with T₀₋₂ tumors is 2.5 (95% CI 1.67-3.68). The estimate of the conditional risk ratio of CEF/CMF is 0.76 (95% CI 0.60-0.96) with p=0.021.

Reviewer Comments:

1. The primary analysis is the comparison of RFS rates for all patients. The absolute difference in RFS is 9%; the proportional reduction in recurrence is 24%. Treatment with CEF increased relapse-free survival (estimated at the 25th percentile) by 8 months compared to CMF. These reductions are consistent with reported benefits from other adjuvant breast cancer treatment interventions, and are clinically as well as statistically significant.

2. The trial stratification factors (number of positive nodes, type of surgery, and receptor status) were prospectively defined, although strata were not individually powered to detect differences. For this reason, these subset analyses should be considered as exploratory. Trends towards superior RFS with CEF compared to CMF were seen in all subsets except women with greater than 10 positive nodes. In this subset, CMF was associated with a better RFS than CEF (25% compared to 16%). This difference should be viewed with caution, as only 47 patients in this trial had greater than 10 positive nodes. The 95% CI of the 75% RFS do not meet criteria for statistical significance in either arm.

3. Menopausal status was not a prospectively defined stratification factor. CEF was associated with improved RFS compared to CMF in premenopausal women and was comparable to CMF in perimenopausal women. Twenty percent of women were considered perimenopausal. This comparison is of unclear clinical significance, since these two groups of women are usually treated in the same fashion. Finally, table 7.1.3, volume 2.19, page 142 indicates that the percent of women with amenorrhea increased with increasing number of cycles given. At cycle 6, 52% of women on CEF and 45% on women on CMF experienced some grade of amenorrhea. Thus, some women became menopausal as a result of therapy, further complicating the interpretation of this analysis. Overall, these results support the efficacy results observed in the intent-to-treat analysis.

4. Tumor size was not a prospective stratification factor. CEF produced a clinically meaningful improvement in RFS in women with T₀₋₂ lesions compared to

CMF. The two treatments appeared comparable for women with T₃₋₄ tumors. The results in larger tumors should be viewed with caution because few women had T₃₋₄ lesions.

5. Figure 6.1, volume 2.19, page 170 shows overall DFS. The curves separate at approximately 1 year and remain separate until 6 years, when they come together. At this timepoint, 30 patients on CEF and 27 on CMF remain at risk, and the curves represent point estimates.

6. The curves are separate for women with 1-3 positive lymph nodes and cross at 6.0 years, when few women remain at risk and the curves represent point estimates. They remain separated at all time points for women with 4 or more involved nodes.

7. The subset analyses support the primary analysis, which demonstrates the superiority of CEF to CMF both clinically and statistically.

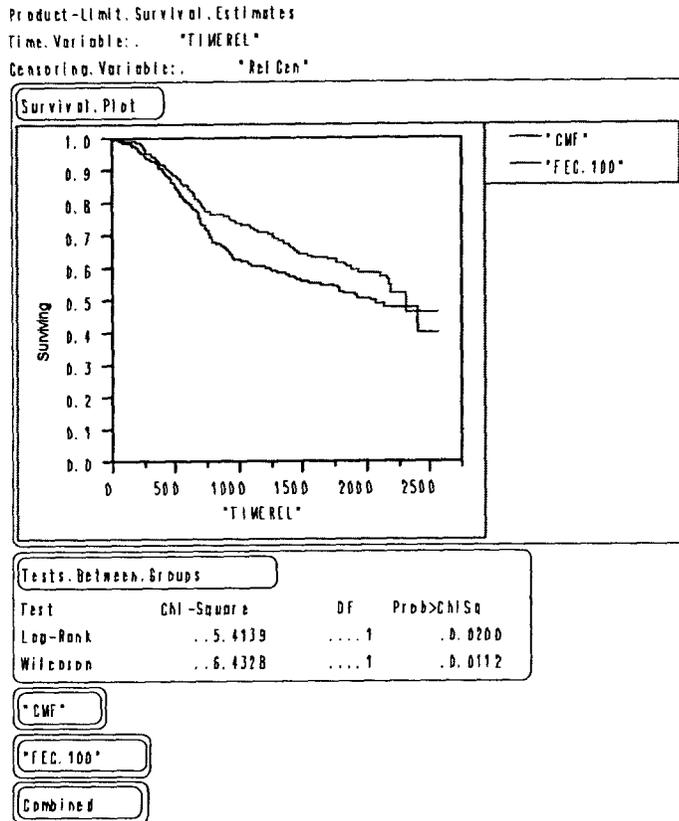
8. Disease-free survival results were verified in several ways. First, audits by DSI compared reported date of recurrence to the source documentation for this finding. Second, the sponsor submitted 124 case report forms (17% of the study population), selected for patients with leukemia, cardiac toxicity, deaths, and drop-out due to toxicity, which were reviewed for date of recurrence. The following comments pertain to the CRFs:

- As per protocol, second breast primaries were not considered to be recurrences.
- Patients were censored for recurrence at the last date seen.
- Randomized trials have shown no difference in survival between women treated with modified radical mastectomy and lumpectomy and radiation therapy, suggesting that an in-breast recurrence may be successfully salvaged with a mastectomy. Using in-breast recurrence as a criterion for relapse might bias the study results. For this reason, the submitted CRFs were reviewed in order to identify patients with the first recurrence of disease in the ipsilateral breast. Four patients in this CRF sample (3%) were considered to have recurrence on the basis of an in-breast recurrence (MP21, PN18, LM21, and NL37). Two were randomized to CMF and 2 were randomized to CEF. In all 4, in-breast recurrence was followed by distant recurrence within 1-8 months. An in-breast recurrence may not increase the risk of death, but it may be a predictive marker of a poor prognosis in an individual patient. As will be discussed later, the number of in-breast recurrences was similar on both arms. It is unlikely that this factor biased the reported outcome of the trial.
- The data lock date was 5/15/97. Because forms were not always forwarded promptly from the investigative centers to the sponsor, 20 patients (16% of the CRF sample) without recurrence were seen prior to the data lock date, but did not have these visits included in the analysis (patients KG1, LC15, LC26, LC37, LY5, MG6, MN25, MP4, MP15, MP16, MP24, MP26, MP29, NL82, PN9, PT4, VC1, LM31, LM61, and NL13). Follow-up was shortened by 3-15 months. Four were randomized to CMF and 16 to CEF, as might be expected from CRFs enriched for CEF-related problems. This discrepancy could influence the calculation of time to recurrence.
- Patient LM50 was listed with a recurrence on 5/11/95; however, the biopsy of the nodes of concern was negative. This patient was last seen on 10/10/96 with no evidence of disease.

The reviewer re-calculated relapse-free survival; these values agreed with those reported by the sponsor in the electronic database.

Relapse-free survival was analyzed by the Kaplan-Meier method using Jmp:

Figure 1. Time to relapse (sponsor's data)



These curves reproduce the sponsor's results. The median disease-free survivals calculated in this program (without evaluating 95% CI) were 6.3 years on CEF and 5.7 years on CMF, a difference of 7.2 months.

Treatment with CEF resulted in a statistically significant improvement in time to recurrence by both the log-rank and the Wilcoxon tests and in a clinically significant benefit with CEF.

8.12.2 Site of relapse

In both treatment groups, distant rather than local relapse was the first sign of recurrence in most patients who developed metastatic disease. Among the women in each group who recurred, 120/136 on CEF (88%) and 155/169 on CMF (92%) developed distant metastases. Similar percentages of patients in each group experienced local relapse in the breast or on the chest wall at any time (CEF 52/136 or 38%; CMF 65/169 or 38%). Regional recurrences occurred in 37% and 30% respectively. These results are summarized in the following table:

Table 14. Sites of relapse (Sponsor's table 6.2, volume 2.19, page 114)

Metastatic Site	CEF N=356		CMF N=360	
	Relapsed	Median time*	Relapsed	Median time*
Total	136 (38%)	22.8 months	169 (47%)	22.5
Local:	52 (38%)		65 (38%)	
Breast	23	21.8	26	24.5
Chest wall	39	20.5	44	22.6
Regional	50 (37%)	23.2	51 (30%)	24.0
Distant:	120 (88%)	23.3	155 (92%)	22.8
Lung	36 (30%)	27.5	52 (34%)	22.6
Liver	35 (29%)	23.5	46 (30%)	26.1
Bone	82 (68%)	29.1	108 (70%)	25.4
Brain	9 (8%)	23.3	29 (19%)	28.7
Bone marrow	2 (2%)	32.2	10 (6%)	21.8
Ascites	21 (18%)	28.7	37 (24%)	23.7
Other	20 (17%)	30.7	31 (20%)	26.8
Unknown	1 (0%)		0	

*As calculated among patients who relapsed

Reviewer Comments:

1. There was no significant difference in the pattern of distant relapse between treatment arms. The increased number of brain metastases in the CMF group compared to the CEF group, as a first event, is difficult to interpret. The percentages represent 9 CEF patients and 29 CMF patients. The difference is most likely due to small numbers of patients with this event. Similar statements can be made about the difference in bone marrow and ascites sites of relapse.

2. Thirteen percent of women on CEF (23/175) and 15% of women on CMF (26/176) who were treated with lumpectomy developed an in-breast recurrence. As mentioned previously, some of these women did not receive breast irradiation; these percentages may not accurately represent local recurrence rates in women with optimal local therapy. Recht and colleagues (N. Engl. J. Med. 334: 1356-61, 1996) performed a randomized trial of 12 weeks of chemotherapy followed by post-lumpectomy radiation therapy, or radiation therapy followed by chemotherapy. Local recurrence rates were 14% and 5% respectively. The results in this study are consistent with these rates, despite the 6 month course of chemotherapy used in this trial.

8.12.3 Overall survival

In the CEF group, 87 of 356 patients (24%) have died, compared to 107 of 360 (30%) patients randomized to CMF. The KM estimates of overall 5-year survival were 77% (95% CI 72-82%) for CEF and 70% (95% CI 65-75%) for CMF. A stratified analysis, using the protocol-defined stratification factors, indicated statistical superiority of CEF compared to CMF for survival (log-rank $p=0.043$).

An estimate of the median survival is not available, as an insufficient number of events have occurred. The estimates of the 25th percentile (75% survival) are 5.2 years (95% CI 4.3-6.2) for CEF and 3.9 years (95% CI 3.3-4.8) for CMF.

These results are summarized in the following table:

Table 15. Overall survival estimates at 5 years and 25th percentile by strata and prognostic factors (Sponsor's table 8, volume 2.19, page 68)

Variable	CEF			CMF		
	Randomized n (%)	% 5- year OS	25 th percentile (95% CI)	Randomized n (%)	% 5- year OS	25 th percentile (95% CI)
All patients	356 (100)	77	5.2 (4.3-6.2)	360 (100)	70	3.9 (3.3-4.8)
Positive nodes:						
1-3	218 (61)	82	5.8 (5.2-n.e.)	218 (61)	78	5.4 (4.0-n.e.)
≥ 4	138 (39)	69	3.8 (3.0-5.1)	142 (39)	58	2.9 (2.3-3.8)
4-10	115 (32)	72	3.8 (3.0-n.e.)	118 (33)	64	3.3 (2.6-4.8)
> 10	23 (6)	59	3.3 (1.7-5.1)	24 (7)	28	1.7 (1.2-2.8)
Surgery:						
Partial mastectomy	175 (49)	82	5.8 (5.2-n.e.)	176 (49)	76	5.0 (3.7-n.e.)
Total mastectomy	181 (51)	73	4.5 (3.6-5.7)	184 (51)	64	3.2 (2.7-4.0)
Receptor status						
Negative	75 (21)	61	2.8 (2.4-3.8)	70 (19)	59	2.9 (2.2-3.5)
Positive	241 (68)	83	5.9 (5.2-n.e.)	245 (68)	70	4.0 (3.4-5.8)
Unknown	40 (11)	74	4.3 (1.8-6.2)	45 (13)	85	n.e. (4.3-n.e.)
Menopausal status						
Perimenopausal	80 (22)	74	3.5 (2.7-n.e.)	75 (21)	74	4.8 (3.5-n.e.)
Premenopausal	276 (78)	78	5.2 (4.4-6.6)	285 (79)	69	3.6 (3.1-4.6)
Tumor size						
T0-T2	311 (87)	78	5.6 (4.4-6.6)	315 (88)	71	4.0 (3.5-5.8)
T3-T4	14 (4)	41	3.1 (2.4-5.2)	22 (6)	46*	1.5 (1.1-2.9)
Tx or missing	31 (9)	66	4.1 (3.2-n.e.)	23 (6)	68**	4.7 (3.6-n.e.)

*Estimate at 3.0 years

**Estimate at 4.8 years

n.e. Not estimable

The sponsor notes that the number of involved nodes at study entry was a significant prognostic factor. Survival was longer with CEF than with CMF in all nodal subgroups.

Survival was better in women who underwent a partial mastectomy rather than a lumpectomy; for both groups, survival was longer with CEF than with CMF.

Women with positive receptors survived longer than women with negative receptors. CEF therapy was associated with better survival than CMF in both negative and positive receptor subgroups.

Survival was longer with CEF compared to CMF in premenopausal women; survival in perimenopausal women was comparable between the two treatment arms.

Tumor size was predictive of survival. CEF treatment resulted in better survival in women with T₀₋₂ tumors compared to CMF. Survival rates were similar between treatments in women with T₃₋₄ tumors.

The Cox model indicated that the number of positive nodes, receptor status, and tumor size were significant predictors of treatment outcome ($p < 0.001$). The conditional risk ratio for the patients with 4 or more involved nodes compared to women with 1-3 nodes was 1.7 (95% CI 1.25-2.33). The conditional risk ratio in patients with negative receptors compared to positive receptors was 2.0 (95% CI 1.45-2.76). The conditional risk ratio in patients with T₃₋₄ lesions compared to T₀₋₂ lesions was 2.5 (95% CI 1.54-3.98). The estimate of the conditional risk ratio CEF/CMF was 0.71 (95% CI 0.52-0.98) with $p = 0.034$.

Reviewer Comments:

1. As for RFS, the primary analysis is the comparison of all patients. As reported by the sponsor, the absolute difference in survival is 6%; the proportion reduction in mortality is 25%. The data demonstrate a 16-month improvement in the estimates of the 25th percentile of survival with CEF compared to CMF. These values are clinically significant. Of note, no p-values were provided in the sponsor's analysis.

2. The significant p-value quoted by the sponsor for CEF therapy compared to CMF therapy is derived from a stratified analysis. Although the original statistical plan mentioned that a Cox model would be used, the primary analysis was a comparison of all patients. Thus, this comparison demonstrates an advantage for CEF therapy and lends support to the primary analysis, but does not supplant it.

3. The strata were not powered for subset analysis. The benefit for CEF therapy was seen in all prospectively stratified subgroups except for women with unknown receptor status. Few women were included in this category.

4. Menopausal status was not a prospective stratification factor. CEF showed a survival benefit for premenopausal women, the majority of the women entered on the trial. No clear difference between CEF and CMF was demonstrated in perimenopausal women. The same comments made for RFS in these subsets apply here.

5. CEF demonstrated a survival benefit for women with T₀₋₂ tumors. Few women had T₃₋₄ tumors; thus, no definite conclusions can be made about the apparent improvement in survival with CMF compared to CEF.

6. For survival, the curves separate between 2 and 2.5 years and remain separate until 6 years, when they cross. At this timepoint, there were 41 patients at risk on CEF and 35 on CMF, and the curve represents predicted outcomes. When examined by nodal status, the curves cross for patients with 1-3 positive nodes (again, the curve at this point represents estimates for few patients at risk), but remain separate for patients with 4 or more involved nodes.

7. Overall, the results of the subset analyses support the results of the intent-to-treat analysis.

8. Although RFS was the protocol-specified primary endpoint, the survival analysis provides additional evidence of clinical benefit.

9. Survival results were verified in several ways. DSI audits compared the reported date of death to the source documents for this finding. Second, the sponsor

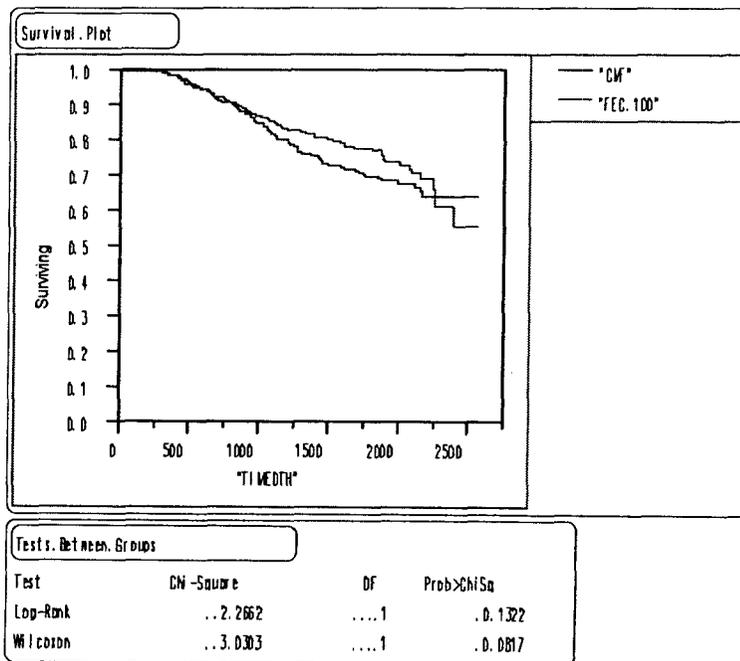
submitted 124 case report forms (17% of the study population) which were reviewed for date of death. The following discrepancies were found:

- Three patients were reported to be alive but had dates of death prior to the data lock date in the CRF.
- Three patients died after the data lock date.
- Two patients had errors in the date of death reporting in the database: one by 4 days and one by 2 months.

The sponsor did not include data reports received after the data lock date, even if the reports concerned an event that occurred prior to the data lock date. The sponsor corrected the date of death on the two patients listed above. Survival was recalculated with corrected values by the sponsor; the survivals were 77% for CEF and 70% for CMF. The differences detected in the database did not alter the reported outcome.

The reviewer performed survival analysis with the Kaplan-Meier method, using Jmp. The following curve summarizes the results:

Figure 2. Unadjusted survival time MA-5



This analysis reproduced the sponsor's results. The median survivals have not been reached in either arm. The 25th percentile estimates (75% OS) from these curves were 5.16 years for CEF and 3.92 years for CMF, identical to those quoted by the sponsor. However, although the curves diverge, they are not statistically significantly different by either the log-rank or Wilcoxon tests.

It is likely that the lack of statistical significance is due to the small number of events; only 27% and 37% of the patients in each arm have died. The trend observed in survival supports the observed significant difference in RFS.

8.13 Safety

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

8.13.1.a Mortality

Eighty-seven of 354 patients (25%) on CEF died compared to 107 of 360 (30%) on CMF during greater than 5 years of follow-up. One death occurred on treatment: a 46 year old woman on CEF died of a cerebral hemorrhage during cycle 3. She experienced sudden onset of headache and died the next day of a pontine and midbrain hemorrhage. According to the narrative, there was no correlation with abnormal laboratory tests. This death was judged to be unrelated to treatment by the investigator.

The timing of the deaths on study is shown in the following table:

Table 16. Frequency of deaths by time interval (Sponsor's table 10, volume 2.19, page 75)

Time Interval	CEF (N= 354)		CMF (N=360)	
	Patients on study	Deaths	Patients on study	Deaths
Cycle 1	354 (100%)	0	360 (100%)	0
Cycle 2	351 (99%)	0	359 (100%)	0
Cycle 3	350 (99%)	1 (0%)	359 (100%)	0
Cycle 4	347 (98%)	0	355 (99%)	0
Cycle 5	345 (97%)	0	352 (98%)	0
Cycle 6	341 (96%)	0	350 (97%)	0
1 year F/U	347 (98%)	3 (1%)	356 (99%)	4 (1%)
3 year F/U	298 (84%)	46 (13%)	290 (81%)	60 (17%)
5 years F/U	118 (33%)	26 (7%)	122 (34%)	37 (10%)
> 5 years F/U		11 (3%)		6 (2%)
TOTAL		87 (25%)		107 (30%)

The cause of death is shown in the following table:

APPEARS THIS WAY
ON ORIGINAL

Table 17. Cause of death (Modified from sponsor's table 11, volume 2.19, page 76 and RFRI 2/25/99)

Cause	CEF N= 354			CMF N=360		
	On therapy	Off therapy	Total	On therapy	Off therapy	Total
Any cause	1 (0%)	86 (24%)	87 (25%)	0	107 (30%)	107 (30%)
Disease	0	76 (21%)	76 (21%)	0	106 (29%)	106 (29%)
Disease and non-protocol therapy	0	2 (1%)	2 (1%)	0	0	0
Secondary leukemia	0	3 (1%)	3 (1%)	0	0*	0
Other	1 (0%)	4 (1%)	5 (1%)	0	1 (0%)	1 (0%)
Unknown	0	1 (0.3%)	1 (0.3%)			

* One CMF patient died of secondary leukemia after the database was locked, and is not included

Reviewer Comments:

1. Therapy was tolerated without fatal adverse events related to drug treatment.
2. The subsequent death rate increased with continued follow-up, consistent with the natural history of breast cancer, and was greater on the CMF arm than on the CEF arm beginning at 3 years of follow-up.
3. Most patients died of progressive disease, with more deaths on CMF than on CEF. The incidence of secondary malignancies, particularly leukemias, will be discussed below.
4. The death narratives were reviewed. Death from "disease and non-protocol treatment" included patient KO 003, who died two days after receiving paclitaxel for progression of disease in the liver and bone, and patient MJ 002. The latter patient died of cardiac arrest one month after high-dose chemotherapy and transplant for bony metastases.

Death from "other primary malignancies" included 3 patients who died of treatment-related leukemias.

"Other" causes of death on CEF included patient SA 011, who died on therapy of an intracerebral hemorrhage; EJ 007, who died of an intracerebral hemorrhage 11 months after completing chemotherapy; SS 018, who received high-dose chemotherapy with transplant for progressive disease and died of pulmonary problems (infectious or neoplastic); SS 038, who died of an intracerebral hemorrhage 21 months after randomization; and NL 108, who died of acute monoblastic leukemia.

The narrative for the one patient on CMF who died of "other" causes was provided: patient LM 046 died of a myocardial infarction 3.5 years after randomization.

One patient, KG 003, had disease progression and died 16 months later; no cause of death was assigned, as information on this patient was not reported by her local physician.

The categories used by the sponsor are somewhat arbitrary; patients could be reclassified. However, the primary efficacy analysis used all deaths. This information does not suggest that CEF was associated with a higher incidence of treatment-related mortality (except for secondary leukemia, discussed below).

8.13.1.b Second primary cancers

The incidence of secondary malignancies is summarized in the following table:

Table 18. Incidence of secondary malignancies

Cancer Site	CEF	CMF
Contralateral breast	8	9
Skin	3	1
Bladder	0	1
Colon	1	0
Lung	1	0
Ovary	1	0
Tongue	1	0
Leukemia	5	1*

*Occurred after the database lock date

Five patients on CEF developed leukemia. Two patients developed M5 leukemia and one developed M4 leukemia, which developed 13-18 months after randomization. A fourth patient developed AML 39 months after randomization; no cytogenetic testing was performed. All 4 patients died, 3 of leukemia and 1 of septic shock associated with treatment of the leukemia. The fifth patient had ALL diagnosed 24 months after randomization. No cytogenetic studies were performed. She received L-17 induction chemotherapy and remains in remission.

One patient on CMF developed a contralateral breast cancer 6 years after randomization, which was treated with radiation therapy and tamoxifen. One year later, she was diagnosed with AML (no cytogenetic studies available) and died despite induction therapy with Ara-C and idarubicin.

Reviewer Comments:

1. The number of second breast primaries was comparable between the two treatment arms. At 5 years of follow-up, the incidence of second breast cancers was 2-2.5%, consistent with published reports in the literature.
2. Review of the narratives for second cancers indicates that "contralateral breast cancers" includes both ductal carcinoma in situ and invasive lesions.
3. Review of the narratives indicates that one patient, AJ 004, was diagnosed with a contralateral breast cancer, then a well-differentiated follicular thyroid cancer. She was randomized to CMF.
4. There was no difference in the incidence of solid tumors between treatment arms.
5. The 5 leukemias on the CEF arm represent a 1.4% incidence, compared to 0.3% on CMF. These leukemias had features consistent with treatment-induced malignancy as shown in the following table:

Table 19. Features of leukemias diagnosed on MA-5

Feature	CEF: Patient ID					CMF
	NL-108	HO-05	LM-62	MG-04	NL-69	SA008
Age at randomization	42	46	46	47	51	55
Cumulative epirubicin dose	616 mg/m ²	712.5	495	676	593	--
Radiation therapy/field	None	5000 cGy L breast; no boost	5000 cGy R breast; no boost	5000 cGy L breast; no boost	None	L breast
Additional drug exposure before leukemia diagnosis	None	None	30 mg doxorubicin C6D1	None	None	Contra. Breast CA 6 yrs after randomization; RT/tamoxifen
Time from randomization to diagnosis	14 months	18 months	2 years	15 months	36 months	6.5 years
Type of leukemia	M5	M4	ALL; early pre-B	M5	"AML"	AML
Cytogenetics	Non-dx	Non-dx	Non-dx	t (9; 11) (p22; q 23)	Not done	Del 5q Trisomy 8 Abn. 11 Loss of 19
Time from leukemia to death	3 days	14 days	In CR 3 years post-leukemia dx	6 months	Alive 8 months after induction, then LTFU	About 2 months

ALL has not been associated with cytotoxic agents, making it likely that 1 leukemia on CEF occurred by chance. The 4 cases of AML on CEF are highly likely to be directly related to treatment. These patients did not receive other cytotoxic agents. Half received breast irradiation and half did not. Radiation for local breast cancer therapy has been associated with an increased risk of leukemia; there is an increased risk in women who receive both radiation therapy and alkylating agents, such as cyclophosphamide (Curtis RE et al, N. Eng. J. Med. 326: 1745-51, 1992). The short time of onset and the presence of a classic translocation in the one case in which adequate cytogenetic testing was performed are pathognomic of this entity (Albain KS et al, Genes Chromosomes Cancer 2: 53-8, 1990). These patients were refractory to therapy and died soon after the diagnosis of leukemia (NL-69 had undergone a bone marrow transplant prior to being lost to follow up).

The 1.1% rate of AML on the CEF arm is higher than that reported by the NSABP for protocol B-25. The NSABP Progress Report for August 1997 noted 17 cases of AML/MDS among the 2548 patients randomized to NSABP B-25, which evaluated standard AC compared to 2 schedules of dose-intensified AC (increased DI of cyclophosphamide but not doxorubicin). Overall, the rate of leukemia is 0.7%. On the two dose-intensified arms, the incidence is 13/1698, or 0.8%. While cyclophosphamide

has been implicated in the development of leukemia, more recent reports suggest that topoisomerase II inhibitors, such as anthracyclines or epipodophyllotoxins, may be more potent inducers of leukemia. Henderson and colleagues reported the results of the Intergroup trial of 3 dose levels of doxorubicin in the AC regimen, followed by randomization to 4 cycles of paclitaxel or observation (ASCO 1998, abstract 390a). The trial enrolled 3170 women; 8 cases of treatment-related AML/MDS were reported for an incidence of 0.3%. A Danish group (Pedersen-Bjergaard et al, J. Clin. Oncol. 10: 1444-1451, 1992) reported a 16% rate of AML among patients treated with epirubicin at doses of 120-140 mg/m² in combination with cisplatin (3/74). However, a total of 360 patients received epirubicin therapy. Five patients developed leukemia, a rate of 1.4%. Cremin and colleagues reported 3 cases of AML/MDS in 59 women who received adjuvant mitoxantrone, for a rate of 5% (Ann. Oncol 7: 745-6, 1996). Because of the rarity of actual cases despite a significantly elevated relative risk, an estimate of the true incidence of treatment-related leukemia requires a large sample size.

The rates of leukemia reported in this trial are increased for CEF compared to CMF. The rates are generally consistent with those reported by other groups for topoisomerase II inhibitors. Despite the significant increase in risk, the number of cases is low. It is likely that for most patients, the survival benefit conveyed by CEF for breast cancer treatment outweighs the risk of leukemia. However, it will be important to include this information in the label, if approved, to permit a risk-benefit discussion between the patient and the oncologist.

8.13.1.c Other serious adverse events

Three patients on CMF and 1 on CEF developed a pulmonary embolus. One patient on CMF developed a deep vein thrombosis; one on CEF had "severe thrombophlebitis". Two patients on CEF had allergic reactions to Septra. One patient on CMF developed radiation burns to the chest with subsequent infection.

A total of 44 patients on CEF and 15 on CMF were reported to have serious adverse events, which consisted mostly of febrile neutropenia, nausea, and vomiting. All other adverse events were rare and were comparable between the two treatment arms.

Reviewer Comments:

1. There were more serious adverse events on CEF than CMF; most involved episodes of nausea, vomiting, and febrile neutropenia. Some of these events might be addressed in current clinical practice by the use of serotonin antagonist anti-nausea medications and colony stimulating factors.
2. Other serious adverse events, exclusive of those discussed in point 1, were balanced between treatment arms.
3. The three year study report (volume 2.26, page 8/17/204) indicates that 19% of patients on CEF (66) were hospitalized during therapy, compared with 7.5% of patients on CMF (27 patients), a significant difference (p<0.0001). Thirty and 4 patients respectively (8.5% and 1.1%) were hospitalized for febrile neutropenia. The sponsor has been asked to provide the other reasons for hospitalization. Review of the narratives for serious adverse events suggests that some patients were hospitalized for prophylaxis or

treatment of severe nausea and vomiting, a side effect that may be obviated by newer anti-nausea medications.

8.13.1.d Cardiac toxicity

The following cardiovascular events were recorded during the study:

Table 20. Cardiovascular adverse events (as-treated) (Adapted from sponsor's table 9, volume 2.19, page 71)

Cardiovascular Event	CEF (N=354) No. pts (%)		CMF (N=360) No. pts (%)	
	Grades 1-2	Grades 3-4	Grades 1-2	Grades 3-4
Dysrhythmias	6 (1.7)	1 (0.3)	1 (0.3)	0
Edema	25 (7.1)	0	23 (6.4)	0
Function	274 (77.4)	4 (1.1)	220 (61.1)	1 (0.3)
Pain	18 (5.1)	0	10 (2.8)	2 (0.6)
Venous	14 (4.0)	5 (1.4)	7 (1.9)	5 (1.4)

MUGA scans or ECHOs were used to monitor LVEF, which are recorded in the following table:

Table 21. LVEF findings by time of recording (as-treated patients) (Sponsor's table 16, volume 2.19, page 83)

LVEF	CEF (N=354)		CMF (N=360)	
	Evaluated n (%)	Abnormal n (%)	Evaluated n (%)	Abnormal n (%)
Baseline	354 (100)	0	360 (100)	0
6 months	291 (82)	8 (2)	297 (83)	5 (1)
12 months	270 (76)	13 (4)	286 (79)	2 (1)
36 months	184 (52)	7 (2)	171 (48)	2 (1)
60 months	55 (16)	4 (1)	66 (18)	2 (1)

The sponsor stated that 4 patients on CEF and 1 on CMF developed congestive heart failure. The events occurred at 2-5 years of follow-up on CEF and at 15 months on CMF.

Reviewer Comments:

1. The specific cardiac problems included in "function", "pain", and "venous" are not defined; the investigator descriptions are not available in the database. According to the sponsor, the investigator terms were not collected.

2. Table 19 contains the number of patients with each reported cardiovascular events; patients may have had more than one event. A total of 229 patients on CMF and 286 on CEF had at least 1 cardiovascular adverse event.

3. The incidence of edema was similar on both arms (25 on CEF, 23 on CMF). Seven and 10 patients respectively were treated symptomatically.

4. Patients on CEF had a greater incidence of dysrhythmias, pain, and venous complaints. Most of these events were grade 1-2. No patient on either arm required treatment for dysrhythmia. Eighteen patients on CEF and 10 patients on CMF

experienced chest pain; 2 patients on each arm required treatment. Of the 14 CEF patients and the 7 CMF patients with venous complaints, 8 and 6 respectively required treatment.

5. More patients on CEF had “function” complaints (274) compared to patients on CMF (220). The incidence of grade 3-4 events was higher on CEF. Five patients on CEF and 2 on CMF required treatment for this problem; 4 and 1 respectively were patients with congestive heart failure, who are discussed below. Information about the two remaining patients (MM8 on CEF and KO9 on CMF) in this category was not provided. Review of the line listings (listing 8, volume 2.22, page 8/13/369) shows that patient KO9 had a LVEF of 58% at baseline, which decreased to 42% at the end of treatment. The value improved to 58% and 62% on subsequent evaluations. Patient MM8 had an ejection fraction of 53% at baseline; it decreased to 43% at the end of therapy. Repeat measurements at 1.2 and 1.5 years were 36% and 34%. In the reviewer’s opinion, the low ejection fraction and the need for symptomatic therapy indicate that this patient should also be considered as having congestive heart failure.

6. The narratives for the patients with CHF were reviewed. On the CEF arm:

- Patient KK004: A 46 year old woman had normal LVEF values (64%) through 3.5 years of follow-up. Five years after randomization, a MUGA scan demonstrated an LVEF of 19% with clinical manifestations of CHF. She improved with medical therapy.
- Patient LY005: A 50 year old woman had MUGA scans with slow declines in LVEF over 3 years from 58% at baseline to 34%. She became symptomatic 4 years after randomization with chest X-ray evidence of cardiomegaly and CHF. She did not improve on medical therapy. Five years after randomization, the LVEF was 14%.
- Patient MX016: A 38 year old woman had normal MUGA scans and recurred 16 months after randomization. She was treated with tamoxifen. At 34 months, the LVEF was 20% with CXR manifestations of failure and cardiomegaly.
- Patient MW002: A 43 year old woman had a baseline LVEF of 79%, with decreased to 43% at 6 months, then improved to 62% at 1.5 years. She recurred at this time, was treated with 1 cycle of doxorubicin and vincristine, then with 2 cycles of CMF, and finally with 2 cycles of 5-FU and leucovorin. A repeat MUGA (2.5 years after randomization) showed an LVEF of 28%.

On the CMF arm:

- Patient NL024: A 51 year old woman had a normal MUGA scan at 1 year of follow-up. At 15 months, she presented with CHF and a chest X-ray with signs of cardiomegaly and failure. She improved minimally with medical therapy. She subsequently developed recurrent breast cancer and did not have further cardiac evaluation.

These narratives suggest a causal relationship to epirubicin for 3 of the 4 patients on CEF. The 4th patient developed failure 5 years after randomization. This event is consistent with delayed anthracycline cardiotoxicity, although other causes/risks may have been contributory.

7. The database was queried in order to obtain the number of patients with LVEF values of 40% or less at any time during treatment or follow-up. Patients with a transient value of 40% and subsequent improvement were not included in this list. The cutoff of 40% or less was chosen by the reviewer as a value that most physicians would consider likely to be indicative of cardiac insufficiency and a value likely to be associated with clinical symptoms. The following table, including patients discussed above, summarizes patients with clinical CHF or LVEF values \leq 40%:

Table 21a. Patients with significant cardiac impairment, study MA-5*

Treatment	Patient ID	Age	LVEF	Time period
CEF:	KK4	46	19%	5 years
	LC21	49	36%	1 year
	LY5	50	34%	3 years
	MM3	48	38%	3 years
			53%	3.5 years
			55%	5 years
	MM8	45	36%	1.2 years
			34%	1.5 years
	MW2	43	28%	2.5 years
	MX16	38	20%	3 years
	NL54	45	55%	Baseline
			53%	0.5 years
			44%	1 year
			40%	5 years
NL84	31	38%	0.5 years	
NL90	49	37%	0.5 years	
		41%	1 year	
		36%	4 years	
PN1	48	58%	Baseline	
		48%	3 years	
		40%	5 years	
PS3	52	27%	4.8 years	
		36%	5 years	
CMF:	EJ4	40	34%	5 years
			36%	5.2 years
			41%	5.5 years
			48%	5.9 years
	NL24	51	64%	1 year**
RM16	38	36%	0.5 years	
		44%	1 year	
		43%	1.5 years	
		46%	3 years	
		49%	5 years	
SA5	33	39%	3 years	

*Includes first value \leq 40% and all subsequent measurements; all values given for patients with 40% as the lowest and last value

** Presented with CHF 3 months later

Patient MM3 on CEF either had a transient episode of cardiac dysfunction or a falsely low MUGA reading. Eleven patients on CEF, in the reviewer's opinion, had

significant cardiac findings. On the CMF arm, it is difficult to assess patients EJ4 and RM16. Both had significantly low LVEF values; both have had some improvement in LVEF values. It is unknown whether these patients were symptomatic. Either 2 or 4 patients on CMF can be considered to have had significant cardiac findings. These figures translate into a 3% incidence of cardiovascular problems with CEF and either a 0.6 or 1.1% incidence of cardiovascular problems on CMF.

8. The localization of the tumor (right or left breast) was not entered in the database. In response to an FDA question, the NCIC-CTG investigators noted that CT treatment planning was unlikely to have been used in this study. Only 50% of radiation centers in Canada currently use CT planning; in 1990, the percentage was far less.

8.13.2 Laboratory abnormalities

8.13.2.a Hematology

Blood counts were routinely monitored through the course of the study. Most patients experienced depressed counts during the course of the study, which are summarized in the following table:

Table 22. Hematologic abnormalities (as-treated analysis) (Sponsor's table 13, volume 2.19, page 80)

Test	CEF				CMF			
	All grades		Worst grade		All grades		Worst grade	
	No. pts	Grades 1-4 N (%)	Grades 1-2 N (%)	Grades 3-4 N (%)	No. pts	Grades 1-4 N (%)	Grades 1-2 N (%)	Grades 3-4 N (%)
Hb	331	324 (97.9)	292 (88.2)	32 (9.7)	330	234 (70.9)	231 (70.0)	3 (0.9)
WBC	354	353 (99.7)	19 (5.4)	334 (94.4)	360	353 (98.1)	136 (37.8)	217 (60.3)
Granulo- cytes	354	350 (98.9)	5 (1.4)	345 (97.5)	360	345 (95.8)	64 (17.8)	281 (78.1)
Platelets	354	297 (83.9)	264 (74.6)	33 (9.3)	360	185 (51.4)	172 (47.8)	13 (3.6)

A higher percentage of patients treated with CEF compared to CMF developed grade 3-4 anemia, grade 3-4 leukopenia, and grade 3-4 thrombocytopenia. The sponsor presented a table of the frequency of hematologic toxicity by cycle (volume 2.19, page 81, Table 14). At each timepoint, the frequency of grade 3-4 hematologic events was greater in the CEF arm than in the CMF arm, but there was no cumulative increase over time in either arm for any parameter.

The following table summarizes the incidence of adverse events resulting from hematologic abnormalities:

Table 23. Adverse events related to hematologic abnormalities (Adapted from part of sponsor's table 9, volume 2.19, page 71)

Event	CEF (N=354) No. pts (%)		CMF (N=360) No. pts (%)	
	Grades 1-2	Grades 3-4	Grades 1-2	Grades 3-4
Hemorrhage	6 (1.7)	2 (0.6)*	5 (1.4)	0 (0)
Fever	30 (8.5)	0 (0)	16 (4.4)	0 (0)
Rigors/chills	12 (3.4)	0 (0)	11 (3.1)	0 (0)
Infection	85 (24.0)	6 (1.7)	93 (25.8)	2 (0.6)
Febrile neutropenia	31 (8.8)	31 (8.8)	4 (1.1)	4 (1.1)
Lethargy	277 (78.2)	10 (2.8)	261 (72.5)	1 (0.3)

*One patient died of a brain hemorrhage unrelated to therapy (Reviewer note: this patient is in addition to the 2 reported in this column)

Reviewer Comment:

1. Grade 3-4 anemia and thrombocytopenia were more common on CEF than on CMF, but still occurred in less than 10% of patients. The number of non-serious hemorrhages was comparable on the two treatment arms. Two grade 3-4 hemorrhages occurred on CEF and none on CMF. An additional patient on CEF died of a brain hemorrhage unrelated to treatment. It appears from the database that there were no clinically significant sequelae of thrombocytopenia and anemia. The sponsor was asked to provide information about the number of patients who required a transfusion, which could be helpful in determining whether the abnormalities had clinical consequences. In a response dated 3/4/99, the applicant indicated that this information was not collected in the course of the study.

2. Review of the narratives for serious adverse events showed that one patient developed vaginal bleeding, thought by the treating physician to be unrelated to therapy, and required 3 units of packed red blood cells (PRBC). This patient was randomized to CEF (NL 98). One patient on CMF was reported to have grade 3 esophageal bleeding secondary to esophagitis; no transfusions were mentioned (PN019). One patient randomized to CMF (LC028) required 2 units of PRBC and 5 units of platelets for low counts. Review of the hospitalization list showed that patient LM 47, randomized to CEF, required a transfusion.

3. Neutropenia was more common on the CEF arm (97.5% compared to 78% on CMF), but occurred frequently on both arms. There were more infections on CEF than CMF (1.7% compared to 0.6%), but infection alone was uncommon.

4. There was a significantly greater incidence of febrile neutropenia with CEF than with CMF (8.8% compared to 1.1%). Listing 7.1.1, volume 2.19, page 189 lists the number of events of febrile neutropenia. Thirty-one patients on CEF experienced 37 episodes of febrile neutropenia, compared to 5 episodes in 4 patients on CMF. Of note, 8 of the 31 patients on CEF with febrile neutropenia did not have their dose reduced as per protocol. Only 1 of the 8 experienced a second episode of febrile neutropenia. An additional 3 patients on CEF had the regimen interrupted (i.e., treatment delayed) but did not have dose reductions. None of these patients had a second episode. Two of the 4 patients on CMF did not have a dose reduction for febrile neutropenia; one of the two had a subsequent episode of febrile neutropenia. In this study, prophylactic antibiotics were used on the CEF arm, but colony stimulating factors were not.

5. Lethargy may be an indicator of the clinical manifestations of anemia or neutropenia. The incidence of mild lethargy was high and was similar on both arms. Grade 3-4 lethargy was more common on CEF than CMF (2.8% compared to 0.3%), but its overall occurrence was infrequent.

8.13.2.b Liver function tests

Liver function tests were monitored through therapy and during follow-up. The incidence of grade 3-4 events was 1% or less during CEF therapy and was 3% or less during CMF therapy. In follow-up, grade 3-4 events occurred in 3% or less of patients on CEF and in 6% or less of patients on CMF.

Reviewer Comments:

1. The reviewer performed a series of MS Access queries to replicate these findings. After excluding patients who entered the trial with abnormal liver function tests at baseline, 17 patients on CEF (4.8%) and 33 patients on CMF (9.2%) were found to have grade 3-4 elevation of at least one LFT during the course of the study (treatment or follow-up). Definitions for grade 3-4 events were taken from the CTC criteria appended to the protocol. These values are similar to those cited by the sponsor.

8.13.3 Non-hematologic toxicity

The sponsor included a comprehensive listing of toxicities that occurred in 1% or fewer of patients on study. Toxicities that differed between the two arms are listed in the following table:

**APPEARS THIS WAY
ON ORIGINAL**

Table 24. Non-hematologic toxicities (Adapted from sponsor table 9, volume 2.19, pages 72-3)

Event	CEF (N=354) No. pts (%)		CMF (N=360) No. pts (%)	
	Grades 1-2	Grades 3-4	Grades 1-2	Grades 3-4
GI:				
Nausea	330 (93.2)	48 (13.6)	303 (84.2)	13 (3.6)
Vomiting	246 (69.5%)	41 (11.6)	156 (43.3)	19 (5.3)
Anorexia	15 (4.2)	0	21 (5.8)	1 (0.3)
Diarrhea	136 (38.4)	4 (1.1)	182 (50.6)	10 (2.8)
Dysphagia	20 (5.6)	3 (0.8)	8 (2.2)	1 (0.3)
Mouth dryness	18 (5.1)	0	8 (2.2)	1 (0.3)
Heartburn	61 (17.2)	1 (0.3)	49 (13.6)	1 (0.3)
Pain	14 (4.0)	2 (0.6)	22 (6.1)	2 (0.6)
Proctitis	8 (2.3)	2 (0.6)	1 (0.3)	0
Stomatitis	290 (81.9)	45 (12.7)	190 (52.8)	7 (1.9)
Altered taste	33 (9.3)	0	22 (6.1)	0
Gastritis/ulcer	9 (2.5)	0	3 (0.8)	0
GU:				
Cystitis	8 (2.3)	0	12 (3.3)	0
Dysuria	6 (1.7)	1 (0.3)	13 (3.6)	0
Frequency	9 (2.5)	0	13 (3.6)	1 (0.3)
Neurologic:				
Constipation	77 (21.8)	2 (0.6)	44 (12.2)	2 (0.6)
Dizziness	19 (5.4)	5 (1.4)	10 (2.8)	1 (0.3)
Extrapyramidal	9 (2.5)	2 (0.6)	13 (3.6)	0
Headache	49 (13.8)	7 (2.0)	51 (14.2)	1 (0.3)
Ocular:				
Conjunctivitis	79 (22.3)	0	138 (38.3)	0
Dry eye	24 (6.8)	1 (0.3)	48 (13.3)	0
Pulmonary:				
Shortness of breath	30 (8.5)	3 (0.8)	12 (3.3)	3 (0.8)
Skin:				
Alopecia	350 (98.9)	150 (42.4)	303 (84.2)	24 (6.7)
Local toxicity	117 (33.1)	2 (0.6)	29 (8.1)	0

The sponsor noted that patients on CEF had a higher incidence of acute toxicity, including nausea, vomiting, stomatitis, and alopecia. Diarrhea was more common with CMF therapy.

Hot flashes were present in 8% of both groups at baseline and increased to 49% and 43% in CEF and CMF groups during the course of 6 cycles of chemotherapy. Alopecia was progressive in both groups. Diarrhea, nausea, vomiting, and stomatitis decreased in frequency over the course of treatment.

Reviewer comment:

1. The frequency and grade of the above events was verified by the reviewer in the electronic database. The table appropriately counts unique patients and assigns the worst grade observed during therapy and follow-up.

2. The reviewer requested a list of hospitalizations from the sponsor. Twenty patients were hospitalized 31 times for nausea and vomiting or to prevent nausea and

vomiting (9 of these hospitalizations). Six patients were randomized to CMF and 14 to CEF. This rate might be expected to decrease with improved supportive care measures.

8.14 Quality of life

The quality of life analysis was presented in an addendum to the study report. The questionnaire consisted of 30 7-point items; the score was calculated as the mean of the scores on all 30 questions. Questionnaires, per protocol, were to be filled out at baseline, prior to each cycle of chemotherapy, at 6 months, and then every 3 months until the end of the second year. Three types of missing information were defined: intermittent missing data—failure to complete the questionnaire; non-monotone dropout—loss of data from 1 or more visits; and monotone dropout—definitive patient withdrawal. A three-step analysis was performed: one with complete cases only, one with complete cases plus patients with incomplete questionnaires, and one with all available data.

The pattern of correlation between repeated measures was explored using the empirical sample variogram and Diggle's autocorrelation model. General mixed linear models were used to fit longitudinal data. Treatment, visit, and treatment-by-visit interaction were used as fixed effects. The covariance structure for the sequence of measurements on each experimental unit was modeled by the general unstructured form allowing a robust approach to inference on parameters and by first-order autoregressive and Markovian antedependence forms where the covariance structure is specified by the values of a few unknown parameters (volume 2.27, page 8/18/318). Goodness of fit was checked with a likelihood ratio test and by Akaike's information and Schwartz's Bayesian criterion. Maximum likelihood estimates of the mixed model parameters were obtained using the iterative Newton-Raphson algorithm with the MIXED procedure.

Complete data were obtained in 15% (53 women) of women on CEF, in 18% (64) of women on CMF, and in 16% (117) of the overall population. Forty percent of patients had none or 1 missing observation. The pattern of dropouts was similar between the two treatment groups.

First analysis (complete cases only): Quality of life scores declined after beginning chemotherapy, more so in the CEF arm than on the CMF arm. During the 6 months of chemotherapy, the curves were parallel, although the CEF curve was lower than the CMF curve. After therapy was completed, there was a large increase in both groups, and the curves became close to each other.

Second analysis (211 patients: 117 with complete data plus 94 without lost visits but with incomplete questionnaires): The results were similar to those obtained in the first analysis. The treatment-by-time qualitative interaction is statistically significant ($p=0.0014$).

Third analysis (all available data from 715 patients): Both curves shift downwards, more so on CEF than on CMF. The profiles overlap only from month 15 on. There was a statistically significant interaction between time and treatment ($p=0.0001$) and a significant main effect of treatment ($p=0.0001$).

Reviewer Comments:

1. Volume 2.20 page 49 indicates that two questions were added to the BCQ.

These questions were:

- How often during the last four weeks have you been able to continue activities outside the home?
- How much during the past four weeks have you been able to continue activities inside the home?

These questions were added 9/11/91, when 346 patients had been randomized, with a median follow-up of 9.5 months. The analysis included in the NDA is based only on the original 30 questions on the questionnaire.

2. Table 8.1, volume 2.19, page 167 lists compliance with completing questionnaires. The number of patients with missing data was similar between treatment arms, but “missing data” is defined as both an entire questionnaire missing or any of the items missing. This definition encompasses a wide variety of missing information.

3. No prospective plan for handling missing data was provided in the original protocol.

4. The reviewer replicated the scores reported by the sponsor, based on the data provided. A review of the database indicates that 37 patients on CEF and 29 patients on CMF required assistance in completing at least one BCCQ.

5. Please see Reviewer Comments after section 8.7.1 for a discussion of a meaningful clinical difference in scores and some potential drawbacks in the questionnaire design.

6. The sponsor describes the results above. However, in reviewing the mean values (table 8.2, volume 2.19, page 168), it is difficult to determine whether there was a clinically meaningful difference. Baseline values were 5.4 on both arms. In the CEF group, the mean decreased to 4.7 at C1 (a drop of 0.7), improved to approximately 4.9 through cycle 5 (a difference of 0.5 from baseline), was 5.0 at C6, and then improved beyond baseline scores by 9 months (score 5.6). Scores continued to improve to 5.9 at 21 months. For CMF, the mean scores gradually declined to 4.9 (difference of 0.5) over the first 5 cycles, improved to 5.2 at cycle 6, increased above baseline scores to 5.7 at 9 months, and continued to increase to a high of 5.9 at 21 months.

7. The statistician will discuss the methodology used and the reliability of the results from a statistical standpoint in her review.

8. Overall, it appears that patients on CEF, despite an increased number of acute adverse events, scored themselves in the upper half of the quality of life scale throughout therapy and follow-up.

8.15 Differences between the published report and the study report of Trial MA-5

An analysis of trial MA-5 was performed by the NCIC-CTG in May 1997 and was published by Levine et al, *J. Clin. Oncol.* 1998; 16 (8): 2651-2658. Median follow-up in this analysis was 50 months; the median follow-up was 54 months in the study report.

The authors excluded 6 ineligible patients, 5 randomized to CEF and 1 randomized to CMF. Their analysis is based on 359 women on CMF and 351 women on CEF. In the study report, the sponsor included all randomized patients in an intent-to-treat analysis (356 on CEF, 360 on CMF).

Their results are similar to those submitted by the sponsor. Several women relapsed or died in the additional follow-up time in the current analysis, all on the CEF arm. The percentages for RFS and OS are not significantly different between the publication and the current study report.

The authors provided statistical analysis of some of the observed toxicities. There was a statistically significantly greater incidence of \geq grade 2 vomiting on CEF compared to CMF (42% v. 18%, $p=0.0001$). Thirty patients on CEF were hospitalized for febrile neutropenia compared to 4 patients on CMF (8.5% vs. 1.1%; $p=0.0001$). The 95% CI rate was calculated for the incidence of acute leukemia on the CEF arm: 0.0018-0.027.

The quality of life analysis in this paper was based on 270 patients who completely answered the monthly questionnaires on chemotherapy plus the questionnaires at 9, 12, and 15 months. Significant differences were found (but not described) between the two treatment arms.

Overall, the study report and the published results of the trial are similar, without significant or misleading differences between the two.

8.16 Sponsor's summary of safety and efficacy

CMF became the standard adjuvant regimen after initial reports demonstrated its beneficial effects on survival in early stage breast cancer patients. Overall, however, its effect has been modest. While most oncologists have come to consider doxorubicin-based regimens as the most active treatment in early stage breast cancer, prospective randomized trials have not shown a conclusive survival benefit for doxorubicin over CMF. Recently, meta-analyses demonstrated a trend supporting the superiority of doxorubicin-based regimens for RFS and OS in adjuvant breast cancer patients. At the time this trial was initiated, there was strong interest in exploring the dose-response relationship of anthracyclines, and epirubicin, with its potential for less cardiac and hematologic toxicity than doxorubicin, was considered a good candidate for investigation.

This trial demonstrates a statistically significant prolongation in RFS and OS with CEF compared to CMF. The benefit appears attributable predominantly to the inclusion of epirubicin. The CMF arm used the classic CMF schedule and had a higher dose-intensity than CEF. Despite this theoretical advantage, patients randomized to CEF had a better outcome.

CEF was associated with more acute toxicity, which might be managed in current clinical practice with better antiemetic prophylaxis and growth factor support. Serious toxicities included cardiac toxicity. Four patients on CEF developed CHF (1.1%), consistent with prior reports of the low frequency of this event. Treatment-related leukemias were observed in 4 patients on CEF in a pattern consistent with topoisomerase II-induced disease. The sponsor believes that the net benefit of CEF therapy outweighs the risks of cardiotoxicity and leukemia.

Quality of life differences during chemotherapy administration reflect the acute toxicity of the CEF regimen. After therapy, quality of life was similar in both arms.

The superior outcome in RFS and OS associated with CEF can be attributed predominantly to the inclusion of epirubicin in the regimen. These benefits outweigh the acute and chronic toxicities of CEF therapy. Epirubicin-based combination chemotherapy can be considered a preferred treatment option for adjuvant therapy of premenopausal node positive breast cancer patients.

8.17 Reviewer's summary of safety and efficacy

This trial was a prospective randomized study of CEF versus CMF in node positive pre- and perimenopausal breast cancer patients. *Its strengths include:*

- Use of the CMF schedule in the control arm with the highest reported activity
- Demonstration of a statistically and clinically significant improvement in RFS (median improvement of 8 months; absolute difference of 9%; proportional reduction of 24%) and OS (median improvement of 16 months; absolute difference of 7%; proportion reduction of 29%) with consistent findings in exploratory adjusted and subset analyses
- Median length of follow-up (54 months)
- Serial evaluation of cardiac status

Its drawbacks include:

- High incidence of acute toxicity (nausea, vomiting, febrile neutropenia)
- Cardiac toxicity
- Leukemia
- Exclusion of postmenopausal women

"Neutral" findings include:

- A rate of local recurrence after breast conserving surgery that is comparable to that reported by the Joint Center for Radiation for delayed radiation therapy

The low drop-out rate during therapy and the similar quality of life scores between the two arms suggest that patients were able to tolerate the acute toxicity of CEF. Some of the acute toxicities might be expected to diminish with additional supportive measures, such as serotonin receptor antagonist antiemetic therapy and the use of growth factor support.

This study does not provide a direct comparison to doxorubicin-based therapy. However, the reported rate of congestive heart failure is comparable to that reported in the literature for doxorubicin and other anthracyclines.

The incidence of leukemia, as reported, is higher for epirubicin than for dose-intense regimens of cyclophosphamide or doxorubicin. However, these compounds have not been compared directly, and the epirubicin trials contain significantly fewer patients than

the large adjuvant trials on which the estimates for cyclophosphamide- and doxorubicin-related leukemia are based.

The benefits of therapy appear to outweigh the risks of therapy for most patients. There is a meaningful difference in outcome between treatment arms in favor of CEF. The proportional reductions in recurrence and mortality observed in this trial are consistent with those observed in the original CMF trials, the Early Breast Cancer Trialists' Overview Analysis, and the report of the Intergroup study (3 dose levels of doxorubicin in AC +/- paclitaxel). Overall, this study supports approval of epirubicin as a component of adjuvant therapy for node positive breast cancer indication. It should be noted that this study enrolled only premenopausal women. The second study, GFEA-05, included postmenopausal women and will be used to determine the wording of the indication if approved.

**APPEARS THIS WAY
ON ORIGINAL**

**APPEARS THIS WAY
ON ORIGINAL**

- 9.0 Early Breast Cancer: Study GFEA 05 (No protocol title)**
[Protocol in French; translation provided]
Trial Accrual Dates: April 10, 1990 to July 13, 1993
Data Lock Date: June 19, 1998
Sites: Multicenter 20-site study in France

9.1 Rationale and objectives

9.1.1 Rationale

Adjuvant chemotherapy provides a survival advantage over observation alone. Most oncologists believe that anthracycline-based regimens are more effective than the Cooper regimen, yet despite the use of anthracycline-containing regimens, many women recur. Use of an optimal anthracycline dose and schedule might improve disease-free and overall survival, particularly in women with more aggressive tumors or with more extensive axillary lymph node involvement. Hryniuk and colleagues published extensively on the value of dose-intensity in adjuvant breast cancer regimens, based on retrospective analyses of planned and delivered doses of chemotherapy. Other investigators have noted a dose-response relationship for doxorubicin. The sponsor conducted two sets of Phase I trials with epirubicin that suggested that the original recommended Phase II dose might be too low to provide maximum efficacy. Based on these results, the investigators decided to prospectively evaluate the effects of a high-dose epirubicin-based combination chemotherapy regimen in women with 4 or more involved lymph nodes, or with 1-3 involved nodes and high histologic grade and negative estrogen and progesterone receptor assays.

9.1.2 Objectives

- To compare disease-free survival and overall survival between two therapeutic regimens in the postoperative adjuvant setting
 - 6 cycles of FEC 50 OR
 - 6 cycles of FEC 100

9.2 Design

9.2.1 Dose and schedule

This trial was designed as a prospective randomized open-label Phase III trial of FEC 50 versus FEC 100 in women with either 4 or more involved lymph nodes, or with 1-3 involved lymph nodes and tumor grade 2-3 and ER/PR negative. The dose and schedule of each treatment arm were as follows:

FEC 50:

Epirubicin	50 mg/m ²
5-Fluorouracil	500 mg/m ²
Cyclophosphamide	500 mg/m ²

FEC 100:

Epirubicin	100 mg/m ²
5-Fluorouracil	500 mg/m ²
Cyclophosphamide	500 mg/m ²

All drugs were given IV on D1 and were repeated every 21 days for 6 cycles. Treatment must have been started within 6 weeks of surgery.

Postmenopausal women (last menses > 1 year ago) received 30 mg/day of tamoxifen beginning on D1 of the first cycle of chemotherapy for 3 years.

Post-lumpectomy radiation therapy was to begin within 30 days after the last chemotherapy cycle. The use of a boost to the tumor bed and the use of nodal irradiation were at the discretion of the investigators.

No other antitumor treatments were permitted, unless there was evidence of recurrence.

Reviewer Comments:

1. This protocol targeted a high-risk group of women, who would be expected to have a higher rate of relapse than the women in study MA-5.

2. The schedule used in GFEA-05 involves all drugs given intravenously every 21 days. This regimen requires fewer trips to the clinic and is analogous to commonly used treatment schedules in the United States.

3. The dose of epirubicin in this study is lower than that in MA-5 (100 mg/m² in GFEA-05; 120 mg/m² in MA-5). However, patients in MA-5 required frequent dose-reductions because of neutropenia; most received at least 100 mg/m²/cycle.

4. There are several potential confounding factors introduced by concomitant tamoxifen therapy in this study. Tamoxifen induces cell cycle arrest and might theoretically interfere with the effectiveness of chemotherapy, which works best in rapidly dividing cells. A competing theory is that tamoxifen induces apoptosis and might increase cytotoxicity. It is unlikely that tamoxifen significantly altered the outcome of this study for the following reasons:

- Tamoxifen has not been shown clinically to increase or decrease the cytotoxicity of chemotherapy
- A suboptimal duration of tamoxifen therapy was used
- Patients in this study were predominantly ER/PR negative, a group in which tamoxifen has little or no activity, as per the 1995 EBCTG meta-analysis (published 1998).

The use of a higher than usual dose of tamoxifen (although consistent with European prescribing practices) might increase the adverse event rate in the subset of patients who took it. Evaluation of the electronic database showed that 3 cases of endometrial cancer were diagnosed, all in women on tamoxifen. One of the 3 stroke patients took tamoxifen. One of the two patients with pulmonary embolism had her event while taking tamoxifen. No cases of deep vein thrombosis occurred in the trial. No information on cataracts was collected.

Despite the increased dose, tamoxifen-related adverse events were rare.

5. Radiation therapy for conservative surgery was delayed until after chemotherapy was completed (18 weeks). In-breast recurrence rates will be evaluated (see section 9.12.2).

6. Post-mastectomy chest wall irradiation was permitted. The reviewer will assess how many women with mastectomies received local radiation therapy, as some recent reports have suggested a survival advantage for this modality (see section 9.11.6).

9.2.2 Dose modifications

9.2.2.a Hematologic toxicity

Day 1 counts must have improved to a neutrophil count of $\geq 2000/\text{mm}^3$ and a platelet count of $\geq 100,000/\text{mm}^3$ in order to give full doses. If counts did not recover, treatment was delayed 1 week. If after 3 weeks, the counts still had not recovered, treatment was to be discontinued.

9.2.2.b Non-hematologic toxicity

Epirubicin was to be dose-modified for changes in bilirubin:

Table 25. Epirubicin dose modifications for bilirubin elevations

Bilirubin		% dose administered
mg/dl	$\mu\text{mol/l}$	
>30	>50	0 (no administration)
20-30	35-50	50
<20	<35	100

Reviewer Comments:

1. The protocol did not use dose modifications to manage toxicity. It did not, for example, specify dose reductions after a treatment delay or for febrile neutropenia and did not use nadir counts to modify drug doses.

2. Treatment delays were used instead of dose reductions. Dose-intensity is affected by changes in both dose and schedule, and will be evaluated in this application.

3. Dose reductions for elevated bilirubin levels are appropriate given the hepatic metabolism of epirubicin.

9.2.3 Baseline and follow-up evaluations

Please see the schedule of evaluations in Appendix I. Patients were evaluated at baseline and prior to each cycle. All patients were followed for survival: they were seen every 6 months for the first 5 years, then yearly.

Cardiac monitoring was performed with measurement of LVEF prior to study entry and then 3-4 weeks after the last cycle of chemotherapy. Subsequent testing was optional. An ECG was obtained at baseline, before each cycle, at the end of treatment, and was then optional during follow up.

A chest X-ray, liver ultrasound or CT scan, and bone scan or skeletal X-rays were performed at baseline to rule out metastases, were repeated at the end of chemotherapy, and were repeated yearly for 5 years. After 5 years, these tests were required at least once every 2 years.

Reviewer Comments:

1. The CRF did not include space to record the medical history, PS evaluation, serial bilirubin values during chemotherapy, or results of radiologic studies during follow-up.

2. The lack of cardiac monitoring after the conclusion of therapy makes it difficult to accurately determine the risk of cardiac toxicity from epirubicin therapy, as cardiac toxicity is usually delayed, not immediate. Comparison of cardiac toxicity in the two arms relies on the completeness of ascertainment of CHF or other serious cardiac problems. The frequency of visits for the first 5 years increases the likelihood of obtaining meaningful data, provided that compliance was comparable on the two arms.

9.3 Randomization and stratification

Randomization was “done by Center” and was stratified by the number of involved lymph nodes (1-3, 4-10, and >10).

The study report states “the protocol-specified randomization procedure was not reflected in the randomization list.”

Reviewer Comment:

1. The translation of the protocol appears to have been performed by someone not familiar with medical terminology. After review of the original protocol (in French), the reviewer believes that randomization was intended to be performed centrally (study report, volume 2.28, page 8/19/024) and was to be stratified by center and number of nodes.

2. The randomization lists do not contain the date of randomization. The sponsor was asked about this point; Pharmacia & Upjohn responded that the date was not included on the logs. The database includes the randomization dates. The sponsor noted in this same response on 3/5/99 that randomization was not stratified. Further clarification was received from the applicant on 4/28/99. Stratification by center and nodal groupings was performed. Several problems were identified in the applicant’s retrospective review of the randomization for this trial:

- The computer randomization list assigned numbers according to strata, while the patient number was assigned by center. There is no direct correspondence between the two systems
- Some centers recruited more patients than anticipated, requiring the generation of additional randomization lists. Each new list started over from number 1.
- In other centers, unused sequences or portions belonging to centers which never opened were used.
- In 2 centers, accrual was so fast that an earlier part of the randomization list was used to randomize new patients.
- The computer-generated sequences do not contain the randomization dates.
- In a few cases the numbering system did not respect the temporal sequence; in 2 cases this mistake generated a treatment change.
- Occasionally, the number of dissected lymph nodes rather than the number of positive lymph nodes was considered in the stratification.
- In a few centers, the first position in the list was skipped.

The sponsor believes that because randomization was handled by an independent randomization officer, there was no selection bias in the treatment assignments.

3. The reviewer, with Grant Williams, prepared a query of the enrollment of this trial, sorted in order by center, nodal stratum, randomization date, and treatment assignment. It was unclear what the block size was for each center. In a number of centers, it appeared that the same pattern of treatment assignment was used (ABBA, ABBA, ABBA), which might permit investigators to anticipate the next treatment assignment. The sponsor was asked to provide the block size. The sponsor answered that the block size was planned to be 4, but because of the errors listed above, the actual assignment in some cases does not allow the appreciation of the size of the blocks. This observation is consistent with that of the reviewers.

While this situation is far from ideal, there is no apparent evidence of bias, intentional or otherwise. The patient population was balanced by demographic and tumor characteristics.

4. Randomization was not stratified for tumor size or ER/PR status, the other major prognostic factors for breast cancer. However, nodal status is the primary predictor of outcome in this patient population; thus, randomization was stratified for the most important prognostic factor.

9.4 Protocol amendments

The protocol was amended 11/16/90 to include women with 1-3 positive nodes and a tumor grade of 2 or 3.

Reviewer Comment:

1. The amendment took place after 121 patients were randomized (21% of the sample size), 54 to FEC 100 and 67 to FEC 50. The number of involved nodes per patient is not reported in the database. The amendment lowered the pathologic criteria for entry from tumor grade 3 to tumor grade 2 or 3. Patients entered after the amendment might have a slightly better prognosis than those entered before the amendment was made, but

nodal involvement is a stronger prognostic factor than grade. It is unlikely that this amendment significantly affected the study outcome.

9.5 Eligibility

9.5.1 Inclusion criteria

- Invasive breast adenocarcinoma, treated with definitive local therapy
 - Must have ≥ 4 positive lymph nodes
 - OR
 - 1-3 positive lymph nodes AND Tumor grade 2-3 AND ER/PR negative
- Must have had at least 5 nodes dissected
- Age < 65 years
- No distant metastases
- No prior therapy except for cancer therapy
- No contraindication to one of the treatment arms
- Adequate hematologic counts
- PS ≤ 2

Reviewer Comments:

1. The protocol initially specified grade 3 tumors, but was amended 11/90 to include grade 2-3 tumors in women with 1-3 positive nodes. No central review of tumor grade was performed.

2. The protocol did not provide definitions for “ER and PR negative” status. The study report indicates that 80% of patients had biochemical determinations of receptors. In most of these cases, a negative test was defined as < 10 fmol/mg protein; some centers used < 15 fmol/mg protein as the cut-off. Twenty percent of the determinations were performed with immunohistochemistry and were scored as +, ++, or +++. The local pathologist’s interpretation was accepted. The technique used and the definitions of a negative assay are consistent with clinical practice

9.5.2 Exclusion criteria

- Men
- Patients aged 65 years or older
- Prior history of breast cancer
- Pregnant patients
- One to three axillary nodes, but with tumor grade < 2 and/or with ER/PR (+) tumor
- Inflammatory breast cancer
- Patients with locoregional skin involvement, contralateral breast cancer, presence of one or more axillary contralateral palpable nodes or upper or infraclavicular node, or edema in the homolateral upper limb that was present preoperatively
- Clear-cut clinical cardiac disease (one of the following):
 - Heart or coronary insufficiency
 - ECG

- ❖ LVH (Sokolow-Lyon degree ≥ 40)
- ❖ Complete LBBB
- ❖ Double block (complete RBBB and left fore- or back hemiblock)
- ❖ ECG signs of coronary insufficiency
- Ultrasonographic or radioisotopic LVEF at rest
 - ❖ Ultrasound: SF (sound field) $\leq 40\%$
 - ❖ Radioisotopic: LVEF $\leq 50\%$
- Hepatic or renal insufficiency
- Patients with prior malignancy other than cervical or cutaneous cancer
- Serious intercurrent non-malignant disease
- Patients inaccessible for follow-up

Reviewer Comment:

1. Although the protocol was designed to include the group of node positive women at highest risk of recurrence, it appropriately excluded patients with inflammatory or other T₄ lesions, whose clinical course differs from the target population.

9.6 Endpoints

The primary endpoint was disease-free survival, defined as the time from initial surgical treatment to the day a locoregional and/or distant metastasis was observed. The secondary endpoint was overall survival, defined as the period from surgery to death.

Relapse was defined as follows:

- Local: Tumor involvement at the level of the remaining breast and/or the soft tissues of the homolateral thoracic wall, confirmed by cytology or histology
- Regional: Nodal tumor involvement (internal breast, supra- or infraclavicular, homolateral axillary) and at the level of the soft parts of the homolateral axilla
- Distant: Tumor at areas different from above

The following definitions were applied to survival:

- Early death: death within 3 weeks following the first treatment, not explained by severe toxicity
- Toxic death: Death for which toxicity played a main role; advise post-mortem exam

Reviewer Comments:

1. The protocol defined DFS and OS as the interval beginning on the date of surgery until relapse or death respectively. The study report defined DFS and OS from the date of randomization, the more commonly used starting point.

2. Relapse included patients who developed ipsilateral breast disease, distant metastatic disease, or local/nodal/regional relapse. Patients with contralateral breast cancers, second primaries, or who died of a non-breast cancer-related cause were censored at the time of their last record. All patients who were alive without relapse at the time of analysis were censored at the time of their last contact.

3. Supraclavicular disease is considered as M₁ disease by AJCC criteria, rather than regional disease as listed in the protocol.

4. An in-breast recurrence can be treated with a subsequent mastectomy and does not, in itself, increase the risk of death. It may be appropriate to analyze patients with in-breast recurrences separately from those who fail in other sites.

5. The study report added a list of appropriate radiographic studies for determining relapse based on the site of relapse.

9.7 Statistical plan

9.7.1 Prospectively specified

The following assumptions were used to calculate the sample size: the use of a two-sided test with alpha of 0.05 and beta of 0.20, a 3-year accrual period, 5 years of follow-up, and an improvement in survival of 10% after 5 years assuming a 5-year survival of 70%. Based on these statements, 375 patients were required to demonstrate a difference between the two treatment arms.

Reviewer Comments:

1. The protocol did not identify which treatment group was assumed to have a 5-year survival of 70%. This figure is higher than anticipated for a poor prognostic group of node positive breast cancer patients.

9.7.2 Specified in the study report

9.7.2.a Recalculation of the sample size

The study report indicates that the actual calculated sample size was 592 assessable patients, 296 per arm, instead of the 375 patient sample listed in the protocol. The investigators were informed of the change in the target accrual, but the protocol was not amended to reflect the correct sample size. One hundred forty-eight events were needed to detect the difference described in the original protocol.

Reviewer Comment:

1. The protocol was not amended to reflect the correct sample size.
2. Accrual was stopped before the target goal was met.

9.7.2.b Patient population

The primary analysis was performed on the intent-to-treat population, including all randomized patients even if they were ineligible, did not receive protocol therapy, or inadvertently received a non-randomized therapy.

All patients who received at least one dose of study medication were included in the safety analyses. Patients who inadvertently received a treatment other than the one assigned were included in the actual treatment group for safety (as-treated analysis). The following table outlines these populations:

Table 26. Analysis populations (Sponsor's table 3.1, volume 2.28, page 87)

Population	FEC 50	FEC 100	Total
Efficacy analysis: Total randomized	289	276	565
Safety analysis: Total as treated	280	266	546

9.7.2.c Patient disposition

The patients at risk for death were summarized by the following intervals: baseline, 6 months, 1, 3, and 5 years. All patients were followed for survival, regardless of whether or not they received treatment, experienced toxicity, discontinued treatment, violated the protocol, progressed, or had any other outcome. Censored patients were not included in the withdrawn group, as they remained at risk for death.

Reviewer Comment:

1. The primary analysis should be conducted for OS and RFS and should treat time as a continuum, rather than breaking it into intervals.

9.7.2.d Patient characteristics

Demographic factors and age, menopausal status, histology of the primary tumor, type of surgery, number of evaluated and positive nodes, ER/PR status, tumor grade, and clinical TNM staging were summarized in frequency tables or using descriptive statistics. The distribution of patients with normal or abnormal LVEF results and ECG results was summarized in frequency tables.

9.7.2.e Treatment

Dose intensity was summarized as the actual weekly dose delivered in mg/m²/week and as the ratio between the weekly delivered dose and the per-protocol weekly dose. A fixed interval of 3 weeks was added to compute the length of the last cycle. Descriptive statistics and the upper and lower quartiles of distribution were used to display the data. Results were presented for the entire group and for patients who did and did not receive radiation therapy during chemotherapy. The cumulative dose of epirubicin was presented in a frequency table. These analyses were performed on the as-treated population.

A frequency table and summary statistics were used to describe the extent of exposure: maximum number of completed cycles, duration of each cycle and all cycles, and the relative duration of the cycles (ratio of the absolute duration of the cycle to the expected duration of the cycle). The duration of each cycle was computed as the difference between the starting dates of two consecutive cycles; the last cycle was excluded from this analysis. The frequency of delayed cycles and the extent of the delay were calculated, and the chi-square test was used to compare the two treatment groups.

Concomitant tamoxifen therapy was summarized by menopausal status (premenopausal, perimenopausal, postmenopausal) for the as-treated population.

Patients who received radiotherapy were described according to the time the radiation was delivered (per protocol, > 30 days after the last cycle, or during chemotherapy).

Reviewer Comment:

1. No definitions of menopausal status were prospectively stated.
2. Tamoxifen use should be summarized by receptor status.

9.7.2.f Relapse-free survival

The frequency of relapse was summarized for the entire ITT population for subgroups defined by the number of positive nodes, receptor status, menopausal status, type of surgery, and tumor size. As mentioned in the Endpoints section, RFS was re-defined from time of randomization until time of event and was calculated for these groups.

An unstratified log-rank test was used to compare RFS between the two groups. Kaplan-Meier curves (KM) were prepared for the overall treatment arm and for the factors listed above. RFS at 5 years and the 25th percentiles of the probability distribution of relapse (75% RFS) were calculated.

The Cox proportional hazards model was used to adjust for the influence of the listed prognostic factors. A forward stepwise procedure was used to select the model, with a significance level of 0.05 to enter or remove variables. An extended model which included first-degree interactions between the prognostic factor and the treatment was also used. The negative of twice the difference between the log likelihood for this model and the model without the interaction was compared against a chi-squared distribution with degrees of freedom equal to the number of possible interactions. Cases with missing data in any of the covariates were removed from the data set when the model was fit.

Sites of relapse were summarized.

Reviewer Comment:

1. The unadjusted analysis for the ITT population is considered the primary analysis by the FDA.
2. Randomization was prospectively stratified by the number of involved lymph nodes, but the strata were not powered to detect differences between treatment arms. Receptor status, menopausal status, type of surgery, and tumor size were not stratification factors. Tumor size is a recognized prognostic factor for outcome in breast cancer patients. Tumor size might be more likely to affect prognosis in women with 1-3 positive nodes. Receptor status is a recognized prognostic factor, but the only patients per protocol who could have been entered with positive results had 4 or more positive nodes. The prognostic value of positive receptors in this situation is diminished, as the number of involved nodes is more likely to determine the outcome of these patients. Menopausal status may be a prognostic factor when pre- or perimenopausal patients are compared to postmenopausal patients. The sponsor used 3 categories: pre-, peri-, and postmenopausal. No prospective definitions of menopausal status were used, and distinguishing pre- from perimenopausal patients is of uncertain clinical significance. The type of surgery is unlikely to affect outcome, since local surgical treatment has not been shown to result in a survival difference in long-term studies. For these reasons, these adjusted analyses should be considered exploratory.
3. The original protocol did not contain a detailed statistical plan. Variables to be used in the Cox model were not prospectively specified.

9.7.2.g Survival

The frequency of death and the overall survival were calculated for the entire ITT population and for subgroups of patients by number of involved nodes, receptor status, menopausal status, type of surgery, and tumor size. Survival was analyzed using methods similar to those described for RFS. KM curves were calculated for the ITT population and for the subgroups. OS at 5 years and the 25th percentiles of the probability distribution of death (75% OS) were calculated.

Reviewer Comments:

1. See comments for RFS.

9.7.2.h Safety

Adverse events were summarized by patient and worst WHO toxicity grade. Grade 3-4 toxicities were summarized by body system. Toxicities were presented by cycle.

The number and percentage of patients who died, who withdrew because of adverse events, or who withdrew due to nonfatal serious adverse events were summarized by cycle and by follow-up period. The frequency of death was summarized by cause and by timing (on treatment or on follow-up). Frequency of withdrawals due to adverse events was presented by event.

Descriptive statistics were used to describe hematology findings. The worst grade per cycle and the shift in grade from baseline to the most severe finding were presented.

There were insufficient data to analyze LVEF and ECG findings because these measurements were optional during follow-up. The actual events were coded and reviewed.

Reviewer Comment:

1. Because of the lack of periodic cardiac evaluation, the long-term risks of congestive heart failure and anthracycline-induced cardiomyopathy associated with the two dose levels of epirubicin are unknown.

9.7.2.i Interim analysis

An unplanned interim analysis was performed after 3 years of follow-up in order to present the results at the 1996 ASCO meeting.

Reviewer Comments:

1. The statistical plan was not clearly formulated in the protocol; most of the procedures were specified sometime after the study was begun. It is not clear whether the current methodology reflects what was performed during the 3-year analysis.
2. Despite these limitations, the survival analysis should not be subject to bias provided that follow-up was relatively complete and that the extent of follow-up was similar on the two treatment arms. The unadjusted analysis will be subject to the least amount of bias.

9.8 Enrollment and demographics

9.8.1 Enrollment

Five hundred sixty-five patients were enrolled on the study, 289 on FEC 50 and 276 on FEC 100. Eleven patients on FEC 50 (3.8%) and 8 on FEC 100 (2.9%) never received treatment. One of the 11 patients never treated on FEC 50 was randomized twice and was treated as R037. Two patients on FEC 50 (0.7%) and 4 (1.4%) on FEC 100 received treatment with the opposite regimen to which they were randomized. The as-treated group consists of 546 patients, 280 treated with FEC 50 and 266 treated with FEC 100.

These findings are summarized in the following table:

Table 27. Disposition of registered patients (sponsor's table 4, volume 2.28, page 40)

Population	FEC 50	FEC 100
Intent-to-treat	289 (100%)	276 (100%)
Never treated	11 (3.5%)	8 (2.9%)
Treated but received different arm than randomized	2 (0.7%)	4 (1.4%)
Treated according to randomized treatment	276 (95.5%)	264 (95.7%)
As-treated population	280	266

Reviewer Comments:

1. The target sample size was 592 evaluable patients; only 565 were enrolled. The study group did not document the reason for stopping accrual early.
2. There are unequal numbers of patients on the two arms of the study. The randomization logs do not include the date of randomization. The small disparity in numbers probably reflects the requirement to balance by center.
3. More patients on FEC 100 were treated with FEC 50 than vice versa, but the number of patients who refused higher dose therapy was small. The results should not affect the study outcome.
4. The number of patients who were never treated is similar on both arms of the study. The 19 patients who were never treated were entered at 10 different sites, which indicates that institutional bias is unlikely to account for treatment refusal.

9.8.2 Demographics

The treatment arms were well-balanced in terms of demographic characteristics, as shown in the following table:

Table 28. Patient characteristics at baseline (ITT) (Modified from sponsor's table 8, volume 2.28, page 45)

Characteristic	Parameters	FEC 50 (n= 289)	FEC 100 (n=276)
Age at study entry	Median [Range]	50 [25-66]	51 [23-67]
	Mean \pm SD	50.3 \pm 9.0	50.8 \pm 9.4
Age distribution	< 29	4 (1.4%)	3 (1.1%)
	30-39	30 (10.4%)	37 (13.4%)
	40-49	105 (36.3%)	84 (30.4%)
	50-59	96 (33.2%)	90 (32.6%)
	60-69	47 (16.3%)	57 (20.6%)
	Unknown	7 (2.4%)	5 (1.8%)
Menopausal status	Premenopausal	146 (50.5%)	127 (46.0%)
	Perimenopausal	6 (2.1%)	11 (4.0%)
	Postmenopausal	127 (43.9%)	131 (47.5%)
	Unknown	10 (3.5%)	7 (2.5%)
Primary tumor histology	Ductal	237 (82.0%)	228 (82.6%)
	Lobular	36 (12.5%)	28 (10.1%)
	Other	7 (2.4%)	12 (4.3%)
	Unknown	9 (3.1%)	8 (2.9%)
Surgery	Radical	155 (53.6%)	136 (49.3%)
	Conservative	126 (43.6%)	134 (48.5%)
	Unknown	8 (2.8%)	6 (2.2%)
	Surgery date missing	14	9
Median time (days) from surgery to Tx [range]		26 [1-114]	25 [1-60]

The distribution of women on the trial according to prognostic factors is shown in the following table:

APPEARS THIS WAY
ON ORIGINAL

Table 29. Pretreatment prognostic and stratification characteristics (ITT) (Sponsor's table 9, volume 2.28, page 46)

Variable	Parameter	FEC 50 (n=289)	FEC 100 (n=276)
No. nodes examined	1-5	4 (1.4%)	3 (1.1%)
	6-10	72 (24.6%)	50 (18.1%)
	>10	206 (71.3%)	217 (78.6%)
	Unknown	8 (2.8%)	6 (2.2%)
No. positive nodes	1-3	52 (18.0%)	46 (16.7%)
	4-10	180 (62.3%)	176 (63.8%)
	>10	49 (17.0%)	49 (17.8%)
	Unknown	8 (2.8%)	5 (1.8%)
Estrogen receptor	ER (+)	139 (48.1%)	147 (53.3%)
	ER (-)	115 (39.8%)	107 (38.8%)
	ER unknown	35 (12.1%)	22 (8.0%)
Progesterone receptor	PR (+)	146 (50.5%)	150 (54.3%)
	PR (-)	109 (37.7%)	104 (37.7%)
	PR unknown	34 (11.8%)	22 (8.0%)
Tumor size (mm ²)	Median [range]	625 [1 - 2051]	625 [1 - 1135]
	Mean ± SD	1122.5 ± 2051	972.6 ± 1135
	Unknown	16	14
Grade	1	13 (4.5%)	18 (6.5%)
	2	113 (39.1%)	108 (39.1%)
	3	125 (43.2%)	119 (43.1%)
	Unknown	38 (13.1%)	31 (11.2%)
Clinical stage	0	4 (1.4%)	6 (2.2%)
	I	33 (11.4%)	30 (10.9%)
	II	193 (66.8%)	183 (66.3%)
	III	36 (12.5%)	34 (12.3%)
	IV	6 (2.1%)	4 (1.4%)
	Unknown	17 (5.7%)	19 (6.2%)
T-clinical	T0	7 (2.4%)	7 (2.5%)
	T1	51 (17.6%)	51 (18.5%)
	T2	152 (52.6%)	152 (55.1%)
	T3	56 (19.4%)	37 (13.4%)
	T4	10 (3.5%)	14 (5.1%)
	Tx	5 (1.7%)	9 (3.3%)
	Unknown	8 (2.8%)	6 (2.2%)
N-clinical	N0	158 (54.7%)	143 (51.8%)
	N1	112 (38.7%)	116 (42.0%)
	N2	3 (1.0%)	3 (1.1%)
	N3	1 (0.3%)	0
	Nx	7 (2.4%)	8 (2.9%)
	Unknown	8 (2.8%)	6 (2.2%)

Reviewer Comments:

1. Less than 5% of randomized patients were designated "perimenopausal" on this trial.
2. "Radical" surgery referred to removal of the entire breast.
3. Approximately half the patients had ER or PR positive tumors.

4. Mean tumor size was greater on the FEC 50 arm, although the median tumor sizes were similar on both arms. There was a somewhat higher percentage of women with T₄ tumors on FEC 100. However, overall the two arms were balanced for tumor grade and clinical stage and TN status.

5. The characteristics were generally balanced between arms.

9.9 On-study follow-up

The median follow-up on this trial was 59.1 months on FEC 50 and 64.4 months on FEC 100. After 5 years of follow-up, 136/289 patients on FEC 50 (47.1%) and 159/276 patients on FEC 100 (57.6%) remained in the study. The following table summarizes follow-up over time:

Table 30. Disposition of patients by time interval (ITT) (Sponsor's table 5, volume 2.28, page 41)

Time interval	FEC 50				FEC 100			
	Pts. Completing each phase		Pts. withdrawn during the interval		Pts. Completing each phase		Pts. withdrawn during the interval	
	No.	%	No.	%	No.	%	No.	%
Registration	289	100			276	100		
Treatment start	282	97.6	7	2.4	271	98.2	5	1.8
6-mo F/U	278	96.2	4	1.4	269	97.5	2	0.7
1-year F/U	273	94.5	5	1.7	264	95.7	5	1.8
3-year F/U	223	77.2	50	17.3	228	82.6	36	13.0
5-year F/U	136	47.1	54	18.7	159	57.6	40	14.5
>5-year at data lock date	112	38.8	23	8.0	138	50.0	20	7.2
Median (range) F/U time (mo)	59.1 (0-92.5)				64.4 (0-95.8)			

A KM plot demonstrated that patients on FEC 50 were more likely to withdraw from the study earlier than those on FEC 100.

Reviewer Comment:

1. As discussed in section 9.9.1, more patients on FEC 100 withdrew because of adverse events compared to patients on FEC 50 (4.1% versus 1.8%), yet more patients on FEC 50 withdrew over time (a 10% difference between treatment arms). It is likely that patients on FEC 50 had a higher incidence of progressive disease.

9.10 Removal from study, protocol violations

9.10.1 Removal from study

Patients could be removed from study for the following reasons:

- Locoregional or distant progression of disease
- Toxicity which caused treatment discontinuation or which required treatment to be delayed by more than 3 weeks
- Severe postoperative hepatitis with biochemical evidence of hepatic dysfunction or injury
- Intercurrent medical or surgical disease requiring treatment discontinuation for at least 2 months

Patients who were removed from study were still followed.

The withdrawal rate was higher on the FEC 100 arm than on the FEC 50 arm, as shown in the following table:

Table 31. Frequency of withdrawals due to adverse events (as-treated) (Modified from sponsor's table 20, volume 2.28, page 65)

Time interval	FEC 50			FEC 100		
	Patients on study	Due to any AE	Due to nonfatal serious AE	Patients on study	Due to any AE	Due to nonfatal serious AE
Cycle 1	280	0	0	266	2 (0.8%)	0
Cycle 2	280	1 (0.4%)	1 (0.4%)	266	1 (0.4%)	1 (0.4%)
Cycle 3	279	0	0	266	2 (0.8%)	0
Cycle 4	279	0	0	266	2 (0.8%)	1 (0.4%)
Cycle 5	279	4 (1.4%)	1 (0.4%)	265	4 (1.5%)	2 (0.8%)
Cycle 6	278	0	0	265	0	0
1 year F/U	272	0	0	264	0	0
3 year F/U	223	0	0	227	0	0
5 years F/U	134	0	0	155	0	0
TOTAL		5 (1.8%)	2 (0.7%)		11 (4.1%)	4 (1.5%)

There were more withdrawals because of toxicity on the FEC 100 arm compared to the FEC 50 arm. Withdrawals on FEC 100 tended to occur earlier: most occurred within the first 4 cycles. In contrast, most of the withdrawals on FEC 50 occurred at cycle 5.

The reasons for the withdrawals are summarized as follows:

APPEARS THIS WAY
ON ORIGINAL

Table 32. Withdrawal from treatment due to adverse events (as-treated) (Sponsor's table 23, volume 2.28, page 68)

Adverse Event	FEC 50 (n=280)	FEC 100 (n=266)
Vomiting	1 (0.4%)	4 (1.5%)
Cardiotoxicity	1 (0.4%)*	4 (1.5%)**
Asthenia	0	2 (0.8%)
Malaise	0	1 (0.4%)
Infection	0	1 (0.4%)
Neutropenia	0	1 (0.4%)
Local toxicity (injection site)	3 (1.1%)	0
Total	5 (1.8%)	11 (4.1%)

* LVH

**Angina, Bouveret's disease, decreased LVEF, and decreased LVEF with LVH

Reviewer Comments:

1. All patients were followed, allowing for comparable assessments of DFS and OS between the two treatment arms.

2. There were more withdrawals for adverse events on FEC 100 than on FEC 50. Four of the withdrawals on the higher dose arm were due to nausea, 1 due to infection, and 1 due to neutropenia. Use of colony stimulating factors or prophylactic antibiotics (not permitted on the study) might decrease the incidence of these adverse events. Serotonin-selective antiemetics were available during this study, but the sponsor did not collect information on antiemetic use.

3. Table 35 shows that patients on FEC 100 had an increased withdrawal rate during cycles 5 and 6. While it is true that most of the withdrawals occurred in the first 4 cycles, the largest number of patients who withdrew for toxicity during any one cycle occurred during cycle 5. It appears that cumulative toxicity is important on both arms.

4. Bouveret's disease is a benign form of paroxysmal junctional tachycardia that occurs in a structurally normal heart. Five articles were found in the literature, 4 published in French and 1 in German. Bouveret's disease can also refer to a rare syndrome of pyloroduodenal obstruction by a large gallstone. The CRF for this patient was reviewed. While there is little information included, the investigator assessed this problem as related to the GI tract, not to the cardiovascular system.

9.10.2 Protocol violations

At least 1 protocol violation was reported in 50.5% (146/289) of patients on FEC 50 and in 47.5% (131/276) of patients on FEC 100. The violations are summarized in the following table.