

12.8 Enrollment and patient disposition**12.8.1 Enrollment**

Four hundred fifty-six patients were randomized to receive FEC 100 (214 patients) or FEC 50 (242 patients). Treatment is summarized in the following table:

Table 82. Patient population (sponsor's table 1, volume 2.44, page 074)

Treatment	FEC 100	FEC 50	Total
Randomized patients	214	242	456
Not treated	4	5	9
Treated with FEC 100	206	3	209
Treated with FEC 50	4	234	238

Reviewer Comments:

1. The imbalance between treatment arms is probably due to the four strata and the need to balance by center. The sponsor answered an FDA request for information by noting that 38 centers participated in the study, and that accrual by center varied from 2 to 26. Consequently, not all blocks were used at many centers, accounting for the difference between treatment arms.

12.8.2 Patient disposition

Patient disposition on study is summarized in the following table:

Table 83. Patient disposition (modified from sponsor's table 5, volume 2.44, page 79)

Disposition	FEC 100	FEC 50	Total
Untreated patients:	4	5	9
Lost to follow-up	0	2	2
Death	1	1	2
Disease progression	1	0	1
Refusal	0	1	1
Other	2	1	3
Treated patients:	210	237	447
Completed treatment	104	143	247
Progressive disease	40	55	95
Patient refusal	21	9	30
Lost to follow-up	5	4	9
Death	7	3	10
Toxicity	12	6	18
Cardiac toxicity	10	8	18
Protocol violation	3	3	6
Other	8	6	14
Total randomized	214	242	456

Among untreated patients, "Other" reasons included one patient with brain metastases, one with surgical excision of a lesion, and one who did not return for treatment.

The disposition of treated patients reflects on-study assessments. Six patients were removed from study inappropriately and thus constitute protocol violations. "Other" reasons for withdrawal on FEC 100 include stable disease after 3-4 cycles (2 patients), deterioration of general condition, prolonged treatment delay, simple mastectomy for locally advanced breast cancer, one month of fever following MUGA scan, inappropriate number of cycles administered, and progressive brain metastases (one patient each). On FEC 50, the reasons included stable disease after 3 cycles (2 patients), delayed attendance (2 patients), pregnancy after the first cycle (1), and misdiagnosis of atrial myxoma (1 patient).

Reviewer Comments:

1. The number of patients who were randomized but did not receive treatment was comparable on the two arms.

2. More patients on FEC 50 than on FEC 100 completed the planned treatment (60% versus 50%). More patients on FEC 100 than on FEC 50 refused therapy (10% versus 4%).

3. A slightly higher percentage of patients on FEC 50 developed progressive disease during therapy, compared to FEC 100 (23% versus 19%).

4. More patients on FEC 100 were withdrawn for toxicity (10% versus 6%) or died on study than on FEC 50 (3% versus 1%).

5. The patient on FEC 50 who was removed because of pregnancy received one cycle. She subsequently had a spontaneous abortion.

12.9 Demographics

Demographic data were available for all but one patient on FEC 100 (21-30). These data are summarized in the following table:

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Table 84. Demographic and tumor characteristics (modified from sponsor's tables 6-17, volume 2.44, pages 80-91)

Characteristic	FEC 100 (n=214)	FEC 50 (n=242)
Age at study entry:		
< 50	91 (43%)	109 (45%)
50-59	67 (31%)	70 (29%)
≥ 60	55 (26%)	63 (26%)
Race:		
White	193 (90%)	214 (88%)
Black	11 (5%)	9 (4%)
Indian	4 (2%)	2 (1%)
Asian	0	2 (1%)
Other	5 (2%)	15 (6%)
Performance status:		
0	106 (50%)	113 (47%)
1	89 (42%)	98 (41%)
2	17 (8%)	30 (12%)
3	1 (0.5%)	0
Menopausal status:		
Premenopausal	68 (32%)	83 (34%)
Postmenopausal	145 (68%)	159 (66%)
Age at first diagnosis of breast cancer:		
< 50	111 (52%)	138 (57%)
50-59	67 (31%)	62 (26%)
≥60	35 (16%)	42 (17%)
Initial stage:		
T1S	1 (0.5%)	1 (0.4%)
Stage I	18 (8%)	19 (8%)
Stage IIA	29 (14%)	32 (13%)
Stage IIB	42 (20%)	64 (26%)
Stage IIIA	16 (8%)	31 (13%)
Stage IIIB	12 (6%)	4 (2%)
Stage IV	67 (31%)	65 (27%)
Any T Any N MX	7 (3%)	5 (2%)
Any T Any N M0	14 (7%)	11 (5%)
Unknown	8 (4%)	10 (4%)
ER status:		
Positive	59 (28%)	54 (22%)
Negative	33 (15%)	42 (17%)
Equivocal	2 (1%)	0
Unknown	3 (1%)	5 (2%)
Not assessed	117 (55%)	141 (58%)
PR status:		
Positive	53 (25%)	38 (16%)
Negative	29 (14%)	42 (17%)
Equivocal	2 (1%)	1 (0.4%)
Unknown	13 (6%)	20 (8%)
Not assessed	117 (55%)	141 (58%)
Disease-free interval:		
0-12	18 (15%)	21 (14%)
>12-24	34 (29%)	43 (29%)
>24	63 (53%)	82 (54%)
No surgery	3 (3%)	5 (3%)

Prior adjuvant therapy:		
None	137 (64%)	141 (58%)
Chemotherapy (CT)	36 (17%)	54 (22%)
Hormonal therapy (H)	29 (14%)	32 (13%)
H + CT +/- immunotherapy	11 (5%)	15 (6%)
H + immunotherapy	1 (0.5%)	0
Prior neoadjuvant therapy:		
None	211 (99%)	240 (99%)
Chemotherapy	3 (1%)	2 (1%)
Prior therapy for metastatic breast cancer:		
None	186 (87%)	204 (84%)
CT	0	1 (0.4%) [#]
H	27 (13%)*	35 (15%)*
H + CT	1 (0.5%)* [#]	1 (0.4%)* [#]
Prior anthracycline exposure, adj or met:	(n=51)	(n=73)
No	41	62
Yes	10	11
Organ involvement:		
Bone only	10 (5%)	17 (7%)
Soft tissue (ST) only	35 (15%)	41 (17%)
ST + bone	31 (15%)	27 (11%)
ST + viscera	35 (16%)	36 (15%)
ST + viscera + bone	31 (15%)	33 (14%)
Viscera only	40 (19%)	48 (20%)
Viscera + bone	31 (15%)	40 (17%)
No data	1 (0.5%)	0
Number of organs involved:		
1	54 (25%)	80 (33%)
2	73 (34%)	60 (25%)
3	53 (25%)	71 (29%)
4	24 (11%)	18 (7%)
5	8 (4%)	10 (4%)
6	1 (0.5%)	3 (1%)

* 7 patients on FEC 100 and 10 on FEC 50 had two lines of hormonal therapy for metastatic disease.

* One patient on FEC 50 had 2 lines of chemotherapy for metastatic disease; the other patients had 1 line.

Although not included in the above table, approximately 75% of patients on each arm had prior surgery for breast cancer; approximately 37% received prior radiation therapy.

Three patients on FEC 100 and 1 on FEC 50 received prior immunotherapy.

A higher percentage of patients on FEC 100 had PR(+) tumors (55% compared to 38% on FEC 50, p=0.028).

Prior anthracycline exposure was as follows:

Table 85. Prior anthracycline exposure

Prior anthracycline and median cumulative dose	FEC 100 (n=10)	FEC 50 (n=11)
Epirubicin 60 mg/m ²	0	5
Epirubicin 90 mg/m ²	6	0
Doxorubicin 30 mg/m ²	3	5
Mitoxantrone 8 mg/m ²	1	0
Mitoxantrone 57 mg/m ²	0	1

Reviewer Comment:

1. The treatment groups were well-balanced for factors that might affect response to chemotherapy and FEC in particular, such as disease-free interval, number of organs and sites of involvement, and prior anthracycline exposure.

2. Receptor status affects response to hormonal therapy but has not been clearly demonstrated to affect response to chemotherapy. The imbalance in PR status should not have affected study outcome.

12.10 Removal from study, protocol violations**12.10.1 Removal from study**

Patients were removed from study for the following reasons:

- Need for dose reduction below 80 mg/m² on Arm A
- Lack of recovery of counts to acceptable levels after 2 weeks
- Tumor progression
- Development of congestive heart failure, as defined by
 - Cardiomegaly on chest X-ray
 - Basilar rales
 - S₃ gallop
 - Paroxysmal nocturnal dyspnea and/or orthopnea and/or significant dyspnea on exertion
 - Apical pulsation > 3 cm diameter with patient in left lateral decubitus position
- Decline from baseline in LVEF by ≥ 10% (absolute) below the lower limit of normal for the institution
- Decline in LVEF by ≥ 15% (absolute) from baseline
- Development of other unacceptable toxicity which precludes further drug therapy
- Patient refusal

12.10.2 Protocol violations

Protocol violations occurred in 46 patients.

Table 86. Protocol violations (modified from sponsor's table 2, volume 2.44, page 75)

Violation	FEC 100	FEC 50	Total
Wrong or unconfirmed diagnosis	2	1	3
No metastatic disease	1	1	2
Prior chemotherapy for metastatic disease	2	1	3
Prior adjuvant chemotherapy with cum. anthracycline dose ≥ 60 mg/m ²	4	3	7
No measurable/evaluable disease	0	1	1
Randomized while on tamoxifen	1	0	1
Never treated	4	5	9
Treated with non-randomized regimen	4	3	7
Treated with fewer cycles than per protocol	3	2	
Treated with more cycles than per protocol	1*	2*	3
Removed from study despite normal counts	2	0	2
Delayed attendance	0	2	2
Lack of hepatic assessment	0	1	1

* FEC 100: received 11 cycles; FEC 50: received 9 and 10 cycles

According to the study report, 13 patients on each arm were treated with a new chemotherapy regimen prior to documented progression. On FEC 100, 9 patients received FEC or FAC, 3 received CMF, and 1 received another regimen. On FEC 50, 7 received FEC or FAC, 2 received CMF, and 4 received other regimens.

Reviewer Comments:

1. The narratives for ineligible patients were reviewed.

Wrong/unconfirmed diagnosis:

Solitary lung nodule without a biopsy; FEC 50. Excluded because of the possibility of a primary lung cancer

3-year history of hepatosplenomegaly with idiopathic thrombocytosis, followed by adenopathy and abnormal bone scan. No biopsy. Subsequently developed lung metastases. FEC 100. Excluded because of the possibility of myeloproliferative disorder.

Left T4 ulcerating breast mass with bilateral axillary adenopathy and a positive bone scan. FEC 100. Excluded because pathology report was read as "skin adnexal adenocarcinoma".

Wrong stage:

Classified as metastatic disease on the basis of persistent left axillary adenopathy after a left-sided lumpectomy and axillary nodal dissection; FEC 50

Patient with DCIS and subsequent inflammatory breast cancer; no evidence of metastatic disease; FEC 100

Prior chemotherapy for advanced disease:

Received 3 cycles of FEC with 90 mg/m² for liver metastases, then hormonal therapy. Two years after first FEC, enrolled in this study on FEC 100

Prior CMF for a local recurrence. Randomized to FEC 100

Prior CMF followed by CF with tamoxifen for chest wall recurrence. Entered on study when lung metastases developed; FEC 50

Prior anthracycline > 60 mg/m²:

Received FEC with cumulative dose of 600 mg/m² as adjuvant therapy. Randomized to FEC 50 2 years later.

Received FEC with cumulative dose of 269 mg/m² as adjuvant therapy. Randomized to FEC 100 2 years later.

Received FEC with cumulative dose of 300 mg/m² as adjuvant therapy. Randomized to FEC 100 5 months later.

Received epirubicin 90 mg/m² cumulative dose in combination with cyclophosphamide, followed by CMF as adjuvant therapy. Randomized to FEC 50 2 years later.

Received epirubicin 90 mg/m² cumulative dose in combination with cyclophosphamide as adjuvant therapy. Randomized to FEC 100 4 years later.

Received FAC with cumulative doxorubicin dose of 150 mg/m² and CMF as adjuvant therapy. Randomized to FEC 50 1 year later.

Received AC with cumulative doxorubicin dose of 150 mg/m². Randomized to FEC 100 3 years later.

Lack of measurable/evaluable disease:

Baseline bone scan and X-rays performed 4 weeks, not 2 weeks, prior to study entry

Concurrent tamoxifen therapy:

Received tamoxifen at the time of randomization and continued tamoxifen therapy.

2. Exclusion of patients on the basis of ineligible status, as listed above, can lead to bias. Intent to treat analyses are preferred.

3. Major protocol violations were well-balanced between treatment arms.

4. Approximately 5% of patients on each arm received other treatment prior to documentation of disease progression. This violation was balanced between arms, affected a small percentage of the randomized population, and should not have significantly influenced calculation of TTP or survival for the entire population.

12.11 On-study treatment

These analyses were conducted on patients who were treated as randomized.

12.11.1 Treatment cycles**12.11.1.a Number of cycles**

The median number of cycles administered to patients in each treatment group was 6. The maximum number of delivered cycles is summarized below:

Table 87. Maximum number of cycles administered per patient (sponsor's table 19, volume 2.44, page 93)

Number of cycles	FEC 100 (n=206)	FEC 50 (n=234)
1	19 (9%)	16 (7%)
2	15 (7%)	16 (7%)
3	28 (14%)	24 (10%)
4	12 (6%)	18 (8%)
5	22 (11%)	15 (6%)
6	90 (44%)	114 (49%)
7	5 (2%)	6 (3%)
8	14 (7%)	23 (10%)
9	0	1 (0.4%)
10	0	1 (0.4%)
11	1 (0.5%)	0

Reviewer Comments:

1. This table does not reflect long-term tolerability of treatment, as patients were to receive at least 3 cycles and to discontinue therapy after cycle 6 unless they had achieved a CR. If the patient had a complete response, the maximum number of cycles could be 8 cycles. The table may more accurately reflect compliance with the protocol.

2. A comparable number of patients on each arm received less than 3 cycles. A comparable number on each arm received 3-8 cycles of therapy.

12.11.1.b Duration of treatment cycles

The median cycle duration was 22 days for FEC 100 compared to 21 days for FEC 50 during cycle 1, and was 23 compared to 22 days respectively for subsequent cycles.

12.11.1.c Treatment delays

The primary reason for treatment delay was hematologic toxicity. The number of patients with delayed cycles is summarized below:

Table 88. Cycle duration in intervals—number of cycles (sponsor's table 22, volume 2.44, page 96)

Cycle duration	FEC 100 (n=785)	FEC 50 (n=962)
< 19 days	1 (<1%)	3 (<1%)
19-23 days	407 (52%)	605 (63%)
24-25 days	65 (8%)	67 (7%)
26-30 days	219 (28%)	219 (23%)
> 30 days	91 (12%)	68 (7%)

Reviewer Comments:

1. A higher percentage of cycles on FEC 50 were given on time. More cycles on FEC 100 were likely to be delayed greater than 30 days.

12.11.2 Dose Intensity

The actual and relative dose-intensity calculations are summarized below:

Table 89. Median dose-intensity, mg/m²/wk (modified from sponsor's table 24 and 25, volume 2.44, pages 98-99)

Drug	FEC 100	FEC 50
Received DI:		
5-FU	146.9	154.4
Epirubicin	29.5	15.5
Cyclophosphamide	146.9	154.4
Relative DI:		
5-FU	.88	.93
Epirubicin	.89	.93
Cyclophosphamide	.88	.93

Reviewer Comments:

1. A higher dose-intensity was delivered for 5-FU and cyclophosphamide on the FEC 50 arm than on the FEC 100 arm.
2. The delivered dose-intensity of epirubicin was approximately twice as high on FEC 100 as on FEC 50.
3. Overall, relative dose-intensity was higher on FEC 50, suggesting that cycles were more often able to be delivered on time with full doses (or fewer dose reductions).

12.11.3 Cumulative epirubicin dose

The projected dose (6 cycles of therapy) was 600 mg/m² on FEC 100 and 300 mg/m² on FEC 50. The median delivered cumulative doses were 522 and 288.5 mg/m² respectively.

The distribution of the doses is shown in the following table.

Table 90. Epirubicin total dose administered (sponsor's table 60, volume 2.44, page 134)

Epirubicin dose (mg/m ²)	FEC 100 (n=209)	FEC 50 (n=238)
1-100	17 (8%)	31 (13%)
>100-200	13 (6%)	38 (16%)
>200-300	29 (14%)	96 (40%)
>300-400	12 (6%)	69 (29%)
>400-500	22 (11%)	4 (2%)
>500-600	50 (24%)	
>600-700	50 (24%)	
>700-800	7 (3%)	
>800-900	7 (3%)	
>900-1000	2 (1%)	

12.12 Efficacy results

Analyses were performed on the following populations:

Table 91. Populations used for efficacy analyses (sponsor's table, volume 2.44, page 50)

Endpoint	Patient population		
	Fully eligible and evaluable	All with confirmed diagnosis of breast cancer	All
Response rate	X	X	
Time to response	X		
Duration of response	X		
TTP	X		
TTF		X	
Overall survival			X

The sponsor notes that 17 patients, as described earlier, were ineligible. Forty-nine patients, 22 on FEC 100 and 27 on FEC 50, were considered inevaluable. The reasons for inevaluable status are summarized in the following table:

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Table 92. Inevaluable status per the sponsor

Reason	FEC 100 (n=22)	FEC 50 (n=27)
Withdrawal prior to tumor evaluation	7	4
Loss to follow-up or delayed attendance	2	8
Toxicity other than myelotoxicity	3	3
Treatment delay due to prolonged myelosuppression	3	3
Protocol violation	1	1
Inappropriate tumor evaluation	1	1
Pregnancy	0	1
Second malignancy	0	1
Worsening of general condition	1	0
Not treated	4	5

Reviewer Comments:

1. Restricting analyses to eligible/evaluable patients introduces the possibility of bias. The Agency considers the primary analyses as the intent-to-treat analyses.
2. The narratives for inevaluable patients were reviewed. There were minor differences in the reviewer's and the sponsor's interpretations of the data.
3. It is reasonable to exclude untreated patients from the analysis. However, the other exclusion criteria remove patients who experienced toxicity of therapy.

12.12.1 Survival

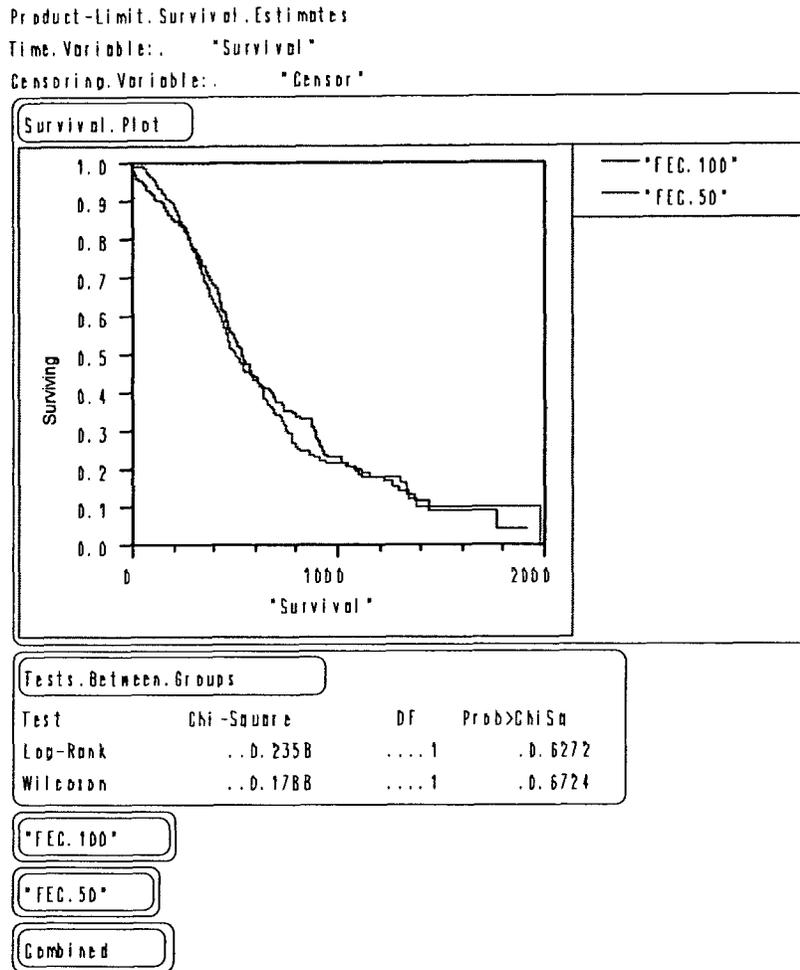
The median survival was 18 months for FEC 100 and 17 months for FEC 50. The hazard ratio for FEC 100/FEC 50 was 0.94 with 95% CI [0.75-1.15]. The difference was not significant.

Reviewer Comments:

1. The reviewer verified the survival analysis, using the dates of death reported in the database. Events were verified through case report form review. The following curves were obtained:

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Figure 10. FDA's analysis of overall survival



Median survivals for FEC 100 and FEC 50 were 18 and 17 months, respectively, matching the sponsor's analysis.

2. At the time of analysis, 154 patients on FEC 100 (72%) and 169 patients on FEC 50 (70%) had died.

3. There was no difference between FEC 100 and FEC 50 in the first-line treatment of metastatic breast cancer in this trial.

12.12.2 Response

12.12.2.a Response rate

The following table summarizes the sponsor's assessment of response.

Table 93. Best response in breast cancer patients (Modified from sponsor's tables 26 and 27, volume 2.44, pages 100-101)

Response	FEC 100 (n=212)	FEC 50 (n=241)	p-value
CR	22 (10%)	14 (6%)	0.07
PR	81 (38%)	73 (30%)	
CR + PR	103 (49%)	87 (36%)	0.007
NC	36 (17%)	57 (24%)	
PD	45 (21%)	68 (28%)	
NE	28 (13%)	29 (12%)	

Additional analyses were performed with eligible and evaluable patients, by number of metastatic sites, and by the presence or absence of visceral metastases. Overall response rates and CR rates demonstrated a trend to improvement with FEC 100. Significantly better responses with FEC 100 were seen in patients with more than 2 sites of disease and in patients with visceral metastases.

Reviewer Comments:

1. Response rate, in a regulatory sense, is a surrogate endpoint used for accelerated, but not full approval, in refractory malignancy. In a trial of first-line therapy for metastatic breast cancer, this endpoint is not considered relevant to the approval process. Time to progression and survival analyses take precedence.

2. Because response rate was the only positive result reported in this trial, the reviewer re-analyzed tumor data for response. There were 98 and 73 responders on FEC 100 and FEC 50 respectively. Calculation of response rates using the entire randomized population in an intent-to-treat analysis yields values of 46% and 30% respectively, $p=0.03$. The reviewer's analysis should be considered as a general verification of the sponsor's reported results rather than as a meticulously documented review and adjudication of individual patient results.

3. Response rates were better with FEC 100 than for FEC 50 in analyses conducted by the sponsor. These analyses included patients with measurable and evaluable disease and only those patients shown to have breast cancer. Because they do not represent intent-to-treat analyses and because evaluable disease is difficult to measure, they may not adequately address a dose-response question.

12.12.2.b Time to best response

The median time to response was 2.2 months for FEC 100 and 2.3 months for FEC 50. Per protocol, the first assessment time was after cycle 3 (9 weeks), which is similar to the times responses were first noted.

12.12.2.c Duration of response

Duration of response was 9.1 months for FEC 100 and 9.3 months for FEC 50, not significantly different.

12.12.3 Time to progression

The time to progression was 7.6 months in FEC 100 and 7 months in FEC 50. Additional analyses were performed by number and type of metastatic sites. No significant differences between treatment arms were identified.

Reviewer Comments:

1. Time to progression was the same in both arms, suggesting no advantage in the metastatic setting for high-dose therapy.

12.12.4 Time to treatment failure

The median TTF was 5.8 months for FEC 100 and 5.3 months for FEC 50, not significantly different.

An addendum report was included in the NDA, which analyzed TTF for all randomized patients, not only those with a confirmed diagnosis of breast cancer. The median TTF for all patients was 5.7 months for FEC 100 and 5.3 months for FEC 50, $p=0.60$.

Reviewer Comments:

1. TTF was not a prospectively identified endpoint.
2. There was no difference between treatment arms.

12.13 Safety

All patients who received at least one drug administration were included in the safety analysis and were analyzed by treatment received, not as randomized. Four hundred forty-seven patients were treated, 209 on FEC 100 and 238 on FEC 50.

12.13.1 Mortality, other serious adverse events, and discontinuations due to serious adverse events**12.13.1.a Mortality**

Ten patients died during therapy: 7 on FEC 100 and 3 on FEC 50. The following table summarizes the causes of death:

Table 94. Causes of death during therapy

Cause of death	FEC 100 (n=7)	FEC 50 (n=3)
Progressive disease	4	1
CVA	1	0
Complications of myelosuppression:		
Febrile neutropenia	2	0
Thrombocytopenia with cerebral hemorrhage	0	1
Severe leukopenia/anemia	0	1

Reviewer Comments:

1. More deaths occurred on FEC 100 than on FEC 50.
2. Overall, few deaths occurred during therapy; half were due to progressive disease.
3. Toxic deaths were distributed comparably between treatment arms.
4. The narratives for deaths on study were reviewed. Patient 29-5, listed as death from progressive disease, died shortly after admission for a presumed pulmonary embolus.

12.13.1.b Other serious adverse events

The following table summarizes patients taken off study for non-cardiac toxicity and patients with serious adverse event reports.

Table 95. Withdrawal for non-cardiac toxicity and serious AE reports

Event	FEC 100	FEC 50
Myelosuppression	8	6
Anemia/cardiac symptoms	1	0
Mucositis, n, v, phlebitis	1	0
Leukopenia, mucositis	1	0
Mucositis, febrile neutropenia, pneumonia	1	0
Vertigo, muscle weakness	1	0
Epistaxis, thrombocytopenia	1	0
Multiple brain infarcts	1	0
Febrile neutropenia, n, v, mucositis	1	0
CHF	0	1

Reviewer Comments:

1. Twelve patients on FEC 100 compared to 6 on FEC 50 were withdrawn for toxicity.
2. Nearly all the withdrawals and adverse events were related to myelosuppression.

12.13.1.c Cardiac toxicity

Serial cardiac evaluation was required throughout the study. The following table describes compliance with the evaluation schedule.

Table 96. Patients with LVEF evaluation

Timepoint	FEC 100 (n=209)	FEC 50 (n=237)
Baseline only:		
ECHO	24	49
MUGA	32	53
Baseline + at least 1 evaluation:		
ECHO	69	49
MUGA	80	84
MUGA-ECHO	4	1
No baseline:		
MUGA	0	1
Method not specified	0	1

Overall, 149 patients on FEC 100 (71%) and 133 on FEC 50 (56%) were considered evaluable for analysis.

The following abnormalities were observed:

Table 97. Number of cardiac events based on LVEF evaluation (sponsor's table 63, volume 2.44, page 138)

Epi dose mg/m ²	FEC 100					FEC 50				
	Cumulative number of patients	Prior mediastinal RT	Prior anthra- cycline	≥ 10% below normal	>15%	Cumulative number of patients	Prior mediastinal RT	Prior anthra- cycline	≥ 10% below normal	>15%
1-100	149	13	5			133	7	4	2	1
>100-200	145	12	4	1	2	124	7	4	1	3
>200-300	139	11	3	1	3	110	7	2	2	3
>300-400	124	8			5	44	4		1	1
>400-500	109	6			4	2				1
>500-600	82	4		1	7					
>600-700	44	2	1	1	4					
>700-800	8									
>800-900	4									
>900-1000	1									

Among evaluable patients, there were 29 events of decreased LVEF and 15 events of decreased LVEF on FEC 100 and FEC 50 respectively. These events occurred in 23 patients on FEC 100 and 12 patients on FEC 50. The number of events at each dose level was similar between treatment arms. At a dose of 400 mg/m² or higher, few patients remained on the FEC 50 arm. The incidence of events was 2-4% (events/patients at risk) until a dose greater than 500 mg/m² was reached. At this dose level and higher, the incidence increased to 10-11%, although fewer patients remained on treatment.

The following table summarizes the number of cardiac events in all treated patients:

Table 98. Number of cardiac events in all patients (sponsor's table 64, volume 2.44, page 138)

Epi dose mg/m ²	FEC 100					FEC 50				
	Cumulative number of patients	Prior mediastinal RT	Prior anthra- cycline	LVEF drop	Other cardiac tox	Cumulative number of patients	Prior mediastinal RT	Prior anthra- cycline	LVEF drop	Other cardiac tox
1-100	209	12	11	2	2	238	17	10		1
>100-200	192	10	9	1	1	207	16	9	2	1
>200-300	179	9	7	1	1	169	15	9		
>300-400	150	5			1	73	12	5	2	1
>400-500	138					4	12	5		
>500-600	116						7	3	2	
>600-700	66						4	3	1	
>700-800	16							1		
>800-900	9									
>900-1000	2									

The above table reflects events, not patients. Ten patients on FEC 100 (5%) and 8 patients on FEC 50 (3%) were removed from study for cardiac toxicity. Other forms of cardiac toxicity observed in the study were:

FEC 100: Asymptomatic cardiomegaly
Sinus bradycardia
LVH on ECG
DOE with tachycardia, rales, and abnormal repolarization on ECG

FEC 50: Acute heart failure after C1
Coronary ischemia on ECG
Atrial fibrillation
AV block
CHF (reason for off-study: treatment completion)

Reviewer Comments:

1. A large percentage of patients did not comply with the protocol-mandated cardiac evaluations.
2. A significant drop in LVEF, whether defined by number of events or number of patients, occurred twice as often on FEC 100 as on FEC 50.
3. Review of the electronic database shows 2 patients, both on FEC 50, who were reported to have CHF (patients 20-5 and 36-2).
3. Because of the limitations in the number of cycles administered, thus capping the cumulative dose of epirubicin, it is difficult to determine a threshold dose for cardiotoxicity in this trial.

12.13.2 Laboratory abnormalities**12.13.2.a Hematology**

The majority of patients had normal baseline hematologic tests. Most of the abnormalities consisted of grade 1 anemia.

The worst nadir toxicity during therapy is summarized in the following table:

Table 99. Hematologic toxicity during therapy—all treated patients (modified from sponsor's tables 42 and 43, volume 2.44, pages 116-117)

Parameter	FEC 100	FEC 50
Neutrophils:		
Grade 0-2	37 (18%)	178 (75%)
Grade 3	57 (27%)	39 (16%)
Grade 4	110 (53%)	15 (6%)
No data	5 (2%)	6 (3%)
Platelets:		
Grade 0-2	195 (93%)	231 (97%)
Grade 3	5 (2%)	3 (1%)
Grade 4	6 (3%)	0
No data	3 (1%)	4 (2%)
Hemoglobin*:		
Grade 0-2	191 (93%)	231 (98%)
Grade 3	13 (6%)	2 (1%)
Grade 4	2 (1%)	1 (0.5%)

* Evaluable patients

The sponsor presented additional analyses by evaluable cycles with similar results.

Reviewer Comments:

1. The high-dose arm was designed to achieve neutrophil counts of 500-1000, consistent with grade 3 neutropenia. Almost half the patients experienced grade 4 neutropenia.
2. Neutropenia was less frequent and less severe on the FEC 50 arm.
3. The greater incidence of treatment delays on FEC 100 and the lower relative DI for this arm are probably due to the increased myelosuppression.
4. The clinical consequences of myelosuppression are shown in the following table:

Table 100. Clinical events associated with hematologic toxicity

Event	FEC 100	FEC 50
Infection:		
Grade 0	166 (79%)	211 (89%)
Grade 1	13 (6%)	12 (5%)
Grade 2	20 (10%)	9 (4%)
Grade 3	5 (2%)	1 (0.4%)
Grade 4	1 (0.5%)	0
Fever:		
Grade 0	157 (75%)	215 (90%)
Grade 1	15 (7%)	11 (5%)
Grade 2	33 (16%)	9 (4%)
Febrile neutropenia	16 (8%)*	1 (0.4%)
Hemorrhage:		
Grade 0	202 (97%)	232 (98%)
Grade 1	0	0
Grade 2	2 (1%)	1 (0.4%)
Grade 3	1 (0.5%)	0
Grade 4	0	0
Platelet transfusions	1 (0.5%)	1 (0.4%)
Blood transfusions	14 (7%)	9 (4%)

*18 episodes in 16 patients

Infection and febrile neutropenia were more common on FEC 100 than on FEC 50.

5. The use of colony stimulating factors and/or prophylactic antibiotics might decrease the infection rate and the febrile neutropenia rate.

6. Grade 3-4 thrombocytopenia occurred more frequently on FEC 100 than on FEC 50, but overall was a rare occurrence. A query of the database showed that one patient on each arm required a platelet transfusion during therapy.

7. Anemia was more common on FEC 100 than on FEC 50. Fourteen patients on the high-dose arm received blood transfusions, compared to 9 on FEC 50. Transfusions were given for hemoglobin levels ranging from 5.3 to 10.9 grams on each arm, consistent with current clinical practice.

12.13.2.b Liver function tests

Few patients had abnormal liver function tests at baseline (13). Most of the abnormalities were grade 1, with 1 grade 2 test in a patient with liver metastases.

During treatment, 8 patients on FEC 100 and 6 on FEC 50 developed some elevation (grade 2 or higher) of bilirubin or SGOT. Ten of these 14 patients had liver disease.

12.13.3 Clinical toxicity

The majority of patients (greater than 97%) were asymptomatic at baseline. Toxicity during therapy is summarized as follows:

Table 101. Worst WHO grade by patient (sponsor's table 56, volume 2.44, page 130)

Adverse Event	FEC 100 (n=209)*	FEC 50 (n=238)*
Nausea and vomiting:		
Grade 0	13 (6%)	21 (9%)
Grade 1	46 (22%)	55 (23%)
Grade 2	84 (40%)	96 (40%)
Grade 3	54 (26%)	59 (25%)
Grade 4	8 (4%)	2 (1%)
Diarrhea:		
Grade 0	170 (81%)	199 (84%)
Grade 1	26 (12%)	26 (11%)
Grade 2	9 (4%)	6 (3%)
Grade 3	0	2 (1%)
Grade 4	0	0
Mucositis:		
Grade 0	124 (59%)	205 (86%)
Grade 1	34 (16%)	23 (10%)
Grade 2	27 (13%)	4 (2%)
Grade 3	17 (8%)	1 (0.4%)
Grade 4	3 (1%)	0
Alopecia:		
Grade 0	11 (5%)	14 (6%)
Grade 1	18 (9%)	33 (14%)
Grade 2	28 (13%)	56 (24%)
Grade 3	147 (70%)	129 (54%)
Grade 4	1 (0.5%)	1 (0.4%)
Cutaneous:		
Grade 0	186 (89%)	231 (97%)
Grade 1	9 (4%)	1 (0.4%)
Grade 2	8 (4%)	1 (0.4%)
Grade 3	1 (0.5%)	0
Grade 4	1 (0.5%)	0

* 4 patients on FEC 100 (2%) and 5 on FEC 50 (2%) had no data available

Nausea and vomiting were common on both arms, with similar degrees of severity. Mucositis was seen more commonly on the FEC 100 arm compared to FEC 50, although few cases of grade 4 events were observed. Complete alopecia was somewhat less common with FEC 50 than with FEC 100. The infection rate was higher on FEC 100, as was fever. The patients with grade 3-4 cutaneous toxicity had these conditions present at baseline (abnormal pigmentation; cutaneous metastasis).

Reviewer Comments:

1. Fifty-nine patients on FEC 100 (28%) and 70 on FEC 50 (29%) received ondansetron at least once during therapy. In current clinical practice, all patients receive prophylactic treatment prior to therapy. The use of these agents might decrease the incidence and/or severity of nausea and vomiting.

2. Grade 3-4 mucositis occurred in 9% of patients on FEC 100, in contrast to 0.4% of patients on FEC 50.

12.14 Quality of life

Of the 453 patients randomized on study, 76 never completed a QOL questionnaire (17%), 27 completed only a baseline questionnaire (6%), and 63 completed at least one questionnaire during treatment but did not complete a baseline evaluation (14%). The overall noncompliance/inevaluable rate was 37%.

Among patients who completed a baseline and at least one follow-up questionnaire, compliance in completing the questionnaire was poor.

No statistical comparisons were performed because of the large amount of missing data.

12.15 Differences between the published report and the study report of Trial HEPI 010

This trial was published in 1997:

Brufman G, Colajori E, Ghilezan N, Lassus M, Martoni A, Perevodchikova N, Tosello C, Viaro D, Zielinski C. Doubling epirubicin dose intensity (100 mg/m² versus 50 mg/m²) in the FEC regimen significantly increases response rates. An international randomised phase III study in metastatic breast cancer. The Epirubicin High Dose (HEPI 010) Study Group. *Ann. Oncol.* 1997 Feb; 8 (2): 155-62.

The authors reported response rates in evaluable patients (n=390); the sponsor reported response rates in patients with documented breast cancer. The response rates in the publication were 57% versus 41%, p=0.003. The sponsor reported rates of 49% and 36% respectively, p=0.007.

The authors stated that cardiac toxicity occurred in 5% of patients on FEC 100 and 3% of patients on FEC 50, and that 2 patients on FEC 100 and 1 on FEC 50 experienced CHF.

The published articles report higher response rates and minimize the cardiac toxicity, compared to the sponsor's study report and the reviewer's analysis.

12.16 Sponsor's summary of safety and efficacy

The sponsor states that doubling the dose of epirubicin in the FEC combination results in a significant improvement in response rate, particularly in patients with large tumor volume or visceral metastases. No difference was observed in time to progression or survival. It is more difficult to achieve meaningful differences in time to event endpoints in the face of advanced disease. Also, continued therapy beyond the protocol-specified 6 cycle maximum might result in a better outcome.

The safety profile was favorable, as toxic deaths and serious adverse events were rare. The high-dose regimen can be given without colony stimulating factors. Cardiac toxicity was consistent with that reported in the literature for anthracyclines.

Overall, FEC 100 was well-tolerated with a high response rate, and provides a

“valuable therapeutic option in advanced breast cancer, especially for patients with visceral and/or extensive disease.”

12.17 Reviewer’s summary of safety and efficacy

Study HEPI/010 compared FEC 100 to FEC 50 in the first-line treatment of metastatic breast cancer patients.

The strengths of the study include:

- Well-designed dose-intensity study: doubling the dose of epirubicin, intensification of the most significant drug in the combination, escalation to individual tolerance, off study for significant dose reductions
- Use of a “patient-friendly” schedule (all drugs given intravenously on day 1)

The weaknesses of the study include:

- No difference between arms in OS or TTP
- Limitation of therapy to 6-8 cycles
- Limited evaluation of cardiac toxicity and poor compliance with the schedule
- Increased cardiac toxicity, myelosuppression, febrile neutropenia, mucositis with FEC 100

Neutral findings include:

- Significantly increased response rate with FEC 100 compared to FEC 50

This study shows only a difference in response rate in favor of the high-dose arm and provides indirect support only to the proposed indication. Traditional endpoints in this setting include survival; a discussion regarding the value of TTP will be held on the first day of the June ODAC meeting.

Toxicity in this trial, while manageable, was greater on the FEC 100 arm compared to the FEC 50 arm. While some of the toxicity might be ameliorated with current supportive measures, such as serotonin-specific antiemetic agents, prophylactic antibiotics, or colony stimulating factors, there was a greater incidence of cardiac toxicity with FEC 100 without evidence of increased benefit.

Overall, this study does not support the proposed indication in metastatic disease.

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13.0 Literature comparison of epirubicin to doxorubicin in first-line metastatic breast cancer

The Division has, to this point, required that the modest survival benefit that results from first-line therapy of metastatic breast cancer with doxorubicin be conserved when considering approval of a new drug. In order to demonstrate comparable survival to doxorubicin, sponsors have either directly compared their product to doxorubicin with an endpoint of overall survival, or have been asked to provide a review and analysis of all relevant literature that supports comparability. The sponsor prepared a comparison of epirubicin and doxorubicin from randomized trials in first-line treatment of metastatic breast cancer (MBC), and estimated the probability that epirubicin, even at lower doses, is not worse than doxorubicin. A second comparison of single agent doxorubicin to other active controls in randomized phase III trials of first-line therapy of breast cancer was performed, to estimate the true effect of doxorubicin in this setting.

13.1 Comparison of epirubicin and doxorubicin, first-line therapy of MBC

Statistical methods of Fleming were used to calculate the response odds ratio (OR). The OR was defined as the odds of failing to respond in the doxorubicin (D) group, divided by the odds of failing to respond in the epirubicin (E) group within each trial and within each group of trials. An odds ratio less than 1 indicates a benefit for D; an OR greater than 1 indicates a benefit for E. The survival hazard ratio (HR) was defined as the hazard ratio in D divided by the hazard ratio in E, within each trial and group of trials. Published survival curves were used to estimate the number of patients who would have died at 18 months in the absence of censoring. Eighteen months was arbitrarily chosen as the median survival of MBC, based on reported results in the published trials. Censoring was ignored because the number of censored observations prior to 18 months was likely to be small, and this approach overestimates the number of patients at risk at 18 months and therefore increases the power to detect a true difference between randomized groups. It may result in underestimating the CI of the hazard ratio. A separate HR was estimated as the weighted average of the HR of individual studies, calculated as the inverse of the ratio of median survivals.

Six trials were identified, containing 1257 randomized patients (635 on E and 622 on D) either on single agent or combination therapy. The dose of epirubicin ranged from 40 to 90 mg/m²/cycle; most were conducted with a dose of 50 mg/m². The sponsor provided a summary of baseline characteristics. Most were balanced; those that were not favored doxorubicin. Dose or schedule of the two agents differed in 2 studies but were the same in 4 studies.

The results are summarized in the following table.

Table 102. Sponsor's calculated comparisons of D versus E as first-line treatment of MBC, Efficacy

Efficacy Endpoint	Doxorubicin	Epirubicin	Ratio
Response rate	49%	46%	0.87 (95% CI 0.72, 1.06)
TTP (reported for 3 trials)			No significant differences between arms
FESG	9 mo	7 mo	
IMBSE	10 mo	9 mo	
Heidemann	8 mo	6 mo	
Survival			0.98 (95% CI 0.80, 1.20)
FESG	18.2 mo	15 mo	
IMBSE	20 mo	19 mo	
Heidemann	17 mo	16 mo	
Perez	12 mo	10 mo	
Gundersen	14 mo	14 mo	
Lawton	8 mo	10 mo	

Toxicities could not be summarized across studies, because of different evaluation points and grading criteria. Overall, epirubicin was associated with less neutropenia and less anemia than doxorubicin. Both drugs had little effect on platelets. Nausea and vomiting were reported to be less or comparable to that observed with doxorubicin. Differences in favor of doxorubicin were reported in trials where epirubicin was given at a higher dose per cycle. CHF was reported in 5 patients treated with epirubicin and in 8 patients treated with doxorubicin. Drops in LVEF were observed in 13 patients on epirubicin and in 16 treated with doxorubicin.

The sponsor concludes that these results demonstrate that epirubicin, at lower doses than those used in the pivotal trials, has efficacy that is comparable to that of doxorubicin. It is unlikely that epirubicin results in survival that is inferior to that of doxorubicin. Analysis indicates a more favorable safety profile. The sponsor acknowledges that the analysis is limited by publication of positive studies and by published analyses that frequently include only eligible or evaluable patients.

Reviewer Comments:

1. The analysis appears to support the sponsor's assertion about preservation of efficacy.
2. Statements that claim less toxicity must be viewed cautiously, as they refer to a dose of epirubicin that is lower than that sought in the indication.
3. The statistical reviewer has been asked to review this analysis. Her comments may be paraphrased as follows: there are limitations to this type of meta-analysis, including publication bias (negative studies are not published) and lack of details within a publication. Given all of these factors, the analysis as presented by the sponsor is the best that can be expected. It supports the hypothesis that epirubicin preserves the effect of doxorubicin in the first-line setting.

13.2 Comparison of doxorubicin versus other non-epirubicin controls in first-line treatment of MBC

Five studies were identified in the literature, where doxorubicin was compared to single-agent mitoxantrone (2 studies), doxorubicin plus vincristine, vincristine plus doxorubicin plus cyclophosphamide, and doxorubicin plus medroxyprogesterone acetate. No significant differences were identified in response rate, TTP, and survival, but doxorubicin was also included in the comparator arm in 3 of 5 studies.

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14.0 Advanced Breast Cancer: Reviewer summary and recommendations

Two pivotal trials for first-line therapy of metastatic breast cancer were submitted. Study HEPI/013 randomized patients previously untreated with chemotherapy to receive FEC 100 or CMF; study HEPI/010 randomized a similar patient population to receive FEC 100 or FEC 50. The following table summarizes the results of these studies.

Table 103. Summary of efficacy, pivotal trials in metastatic breast cancer

Endpoint	HEPI/013			HEPI/010		
	FEC 100	CMF	p-value	FEC 100	FEC 50	p-value
Survival	20.1 mo	18.2 mo	0.21	18 mo	17 mo	0.63
TTP	8.75 mo	6.25 mo	0.0002	7.6 mo	7.0 mo	NS
Response rate	57%	46%	0.01	49%	36%	0.007
TTF*	6.2 mo	4.8 mo	.008	5.7 mo	5.3 mo	0.60

* Not prospectively defined as an endpoint in either trial

Trial HEPI/013 demonstrated a significant improvement in TTP and response rate for FEC 100 compared to CMF. Although the reported survival was 2 months longer on FEC 100, this difference was not statistically significant. The hazard ratio of FEC:CMF was 0.87 (95% CI 0.7, 1.1). The difference in OS is, however, consistent clinically with the reported difference in TTP. It also should be noted that 44% of patients on CMF received a subsequent anthracycline-containing regimen, which may have contributed to a survival advantage as second-line therapy.

The division has generally considered a new therapy to be comparable in efficacy to a standard therapy when the lower limit of the 95% CI of the hazard ratio (standard regimen:innovator regimen) excludes 0.8. If one recalculates the hazard ratio as CMF:FEC, the ratio is 1.15 with 95% CI (0.91, 1.43). It is unlikely that CMF is superior to FEC therapy.

Trial HEPI/010, in contrast, showed a higher response rate for dose-intensified FEC (FEC 100) compared to lower dose FEC (FEC 50), but no significant differences in survival or TTP were observed.

The toxicities in these trials included acute and long-term events. Acute toxicities included myelosuppression, febrile neutropenia, nausea, and vomiting. Long-term toxicities included cardiac toxicity. The following table summarizes the toxicities seen in the pivotal trials.

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Table 104. Acute and chronic toxicities, pivotal metastatic trials (no. patients, not no. events)

Event	HEPI/013		HEPI/010	
	FEC 100 (n=220)	CMF (n=234)	FEC 100 (n=209)	FEC 50 (n=238)
Deaths on study	11 ¹ (5%)	8 (3%)	7 (3%)	3 (1%)
Cardiac toxicity ²	29 (13%)	9 (4%)	23 (11%)	12 (5%)
Febrile neutropenia	23 (10%)	18 (8%)	16 (8%)	1 (0.4%)
Nausea/vomiting grade 3-4	46 (21%)	32 (14%)	62 (30%)	61 (26%)
Anemia grade 3-4	26 (12%)	21 (9%)	15 (7%)	3 (1%)
Blood transfusions	13 (6%)	13 (6%)	14 (7%)	9 (4%)
Platelet transfusions	0	4 (2%)	1 (0.4%)	1 (0.4%)
Mucositis grade 3-4	27 (12%)	36 (15%)	20 (10%)	1 (0.4%)

¹ One died prior to any treatment

² Drop in LVEF or CHF, reviewer's assessment

The incidence of toxic events for FEC 100 was comparable between the two studies. FEC 50 was associated with less toxicity than FEC 100. It should be noted that CMF, as given in HEPI/013, was associated with more mucositis than FEC 100. Myelosuppression and the clinical sequelae of myelosuppression were greater on FEC 100 than on CMF, but by only a few percentage points. As mentioned earlier in the review, the use of colony stimulating factors, prophylactic antibiotics, and/or prophylactic serotonin-specific antiemetic agents might be expected to decrease the incidence of some of the acute toxicities.

The Agency has not approved a drug for the first-line treatment of metastatic breast cancer in many years. The division has recommended that sponsors designing pivotal studies for this indication demonstrate that the new drug does not lose the modest survival benefit thought to be associated with established front-line therapies such as doxorubicin. The sponsor's comparison of doxorubicin versus epirubicin as first-line therapy seems to indicate that the benefit of doxorubicin is preserved during epirubicin therapy. Doxorubicin's 6-month survival benefit was identified in trials that compared it to CMF-like regimens. Why was a 6-month survival benefit not observed for FEC compared to CMF? The reviewer looked at Henderson's review of this topic at the June 8, 1989 ODAC meeting and at the primary articles used in his analysis. The 6-month survival benefit was identified in a number of studies. However, comparable survival times were seen in later trials where crossover from CMF to doxorubicin was more common. It is possible that the 44% crossover rate in study HEPI/013 resulted in a survival benefit on the comparator arm, making it difficult to detect a difference.

The ODAC during the June meeting will discuss the value of TTP as an efficacy endpoint for approval in this setting, as there has been increasing discussion with other sponsors and clinical experts that this endpoint may demonstrate clinical benefit. If this criterion is used, HEPI/013 demonstrates efficacy relative to the best comparator at the time the study was initiated.

Can study HEPI/010 be considered supportive? Unlike study GFEA-05, there is a dose-response relationship demonstrated in this trial, but no dose-survival advantage. There are several possible interpretations of this finding. It is possible that this finding is accurate (that no meaningful dose-efficacy relationship exists in the metastatic setting), that this finding occurred by chance (see description of other supportive studies below), or that a dose-efficacy relationship exists but that it is dependent on the schedule of FEC used.

The sponsor submitted study reports (but no primary data) from other trials in metastatic breast cancer. Study BE-85008 randomized 164 women with no prior chemotherapy for metastatic disease to receive FEC 100 versus FEC 50. Patients with locally advanced breast cancer were eligible. Response rates were significantly higher on FEC 100 (69% versus 41%; $p < 0.001$), as was time to treatment failure (19 months versus 8 months; $p < 0.02$). There was a trend to improved survival on the high-dose arm (27.1 months versus 20.8 months). Of interest, the FEC 100 regimen was given on a D1, 8 schedule, and the FEC 50 regimen was given IV D1. The response rate, TTF, and OS for the FEC 50 regimen in this study are similar to those observed in HEPI/010; these rates for FEC 100 are higher than those observed in HEPI/010. This small study may have given different results by chance. It is also possible that the scheduling of epirubicin plays an important role in its effect.

In study —, 151 women who relapsed within 12 months after completion of CMF adjuvant therapy or who progressed after first-line treatment with CMF for metastatic disease were randomized to single agent epirubicin at either 135 or 75 mg/m² IV every 3 weeks. Treatment continued until a cumulative dose of 900 mg/m² was reached, or progressive disease/toxicity occurred. High-dose epirubicin was found to produce significantly higher response rates (27% versus 8%; $p = 0.002$), longer TTP (133 days versus 75 days, or 4 versus 2 months; $p = 0.003$), and longer survival (330 days versus 240 days, or 11 versus 8 months; $p = 0.042$). The incidence of drops in LVEF was approximately twice as high on the high-dose arm as the low-dose arm. Two cases of CHF occurred, both on high-dose epirubicin. This trial looked at single-agent epirubicin, which removes the potentially confounding effects of other drugs. While this trial was small and has not been reviewed by FDA, its results support those reported in the pivotal trials for metastatic disease.

Overall, the weight of evidence from both the adjuvant setting and the submitted pivotal trials for metastatic disease support approval for the metastatic indication, provided that TTP is considered as an appropriate measure of clinical benefit.

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15.0 Integrated Summary of Safety

The sponsor submitted a Periodic Safety Update to IND for epirubicin on February 22, 1999 (N 238 IM); this information was also submitted to the NDA. This report summarized adverse events reported to the sponsor between July 1, 1993 and June 30, 1998. One limitation of analyzing spontaneous reports is the absence of the size of the denominator: i.e., how many patients received the drug during the reporting period. The sponsor listed total drug sales for this period, normalized to 10 mg units. Using database information about the average BSA, the average number of cycles per patient, and the relative proportion of patients who received conventional versus intensified epirubicin dose, the sponsor estimated that approximately 1,085,880 patients received the drug during the reporting time period.

This report listed adverse events that were described in the randomized controlled trials submitted in the NDA as well as events specific to uses not approved in the United States or rare events.

As part of the required 4-month safety update, the sponsor submitted a periodic report for the period October 21, 1998 through March 15, 1999.

A formal ISS was also submitted as part of the NDA.

Several events warrant additional discussion. This section will not re-state the common acute toxicities of epirubicin therapy. Most of the material is taken from the 1993-1998 update; additional information was added from the four-month safety update and the ISS as needed.

15.1 Events observed in the submitted pivotal trials

15.1.1 Congestive heart failure

Forty-seven reports of CHF or cardiomyopathy and 3 reports of pulmonary edema have been submitted. There have been 11 cases of arrhythmia and 11 cases of ischemic disorders. Thirty to forty percent of the reports occurred in the setting of high-dose therapy, the rest with conventional dosing. Reports are partially confounded by concomitant administration of cardiotoxic chemotherapy agents, risk factors for cardiac disease in some of the patients, and a past medical history of cardiovascular disease in some patients.

The four-month safety update included 2 cases of CHF/cardiomyopathy, one case of atrial fibrillation, and one case of pulmonary edema.

In the overall database, there are 90 reports of CHF/cardiomyopathy; one-third were fatal. In the phase III trials, CHF occurred in 1.1% of patients. The risk increases after reaching a cumulative epirubicin dose of 900 mg/m².

Two recent publications have addressed epirubicin-related cardiotoxicity. Praga and colleagues (in Nimmo WS et al. Clinical measurement in drug evaluation, Wolfe Publishing Ltd, London, 1991, pages 131-142) described toxicity in 9144 patients treated with the drug for any indication, based on the sponsor's database. High-dose was defined as ≥ 90 mg/m²/cycle based on approvals at the time the article was written. The median cumulative dose in the group studied was 300 mg/m²; 1700 patients (18%) received greater than 550 mg/m²; 127 patients received a dose greater than 1000 mg/m².

Symptomatic CHF was identified in 65 patients (0.7%), at a median cumulative dose of 660 mg/m². Not all studies required sequential LVEF monitoring. In those that did, a total of 58 patients were reported to have significant drops, at a median cumulative epirubicin dose of 560 mg/m². The authors noted that these patients were usually identified prior to the onset of symptoms, and thus were withdrawn from study after a lower cumulative dose than those who developed CHF. Logistic regression analysis of CHF and dose was performed and found a significant positive correlation (p<0.0001). The risk of CHF was 1% at a cumulative dose of 550 mg/m² and increased to 5% at a dose of 1000 mg/m². At a dose of 1000 mg/m², the risk rose sharply. This curve appears similar in shape to a similar curve generated by Von Hoff and colleagues in an analysis of doxorubicin toxicity, except that the sharp increase for doxorubicin was observed at a dose of 500-550 mg/m². Analyses adjusted for risk factors showed that the risk of CHF was higher in conventional dose regimens than in high-dose regimens until a dose of 900-1000 mg/m² was reached. At that point, risk was higher in high-dose regimens.

Ryberg and colleagues performed a retrospective analysis of 469 patients enrolled in 2 randomized trials of epirubicin in metastatic breast cancer patients (J. Clin. Oncol. 16: 3502-8, 1998). The doses of epirubicin that were compared were 120 mg/m² (60 mg/m² IV D1, 8) with 90 mg/m² (45 mg/m² IV D1, 8) in the first trial, and 140 mg/m² (70 mg/m² IV D1, 8) with 120 mg/m² (60 mg/m² IV D1, 8) in the second trial. The higher dose of epirubicin in each trial was given as a single agent; the lower dose was given in combination with either vindesine or cisplatin. Approximately 100 patients did not participate in the clinical trials; they were treated with epirubicin 130 mg/m² IV D1. Initially, patients in both trials were to continue therapy until disease progression. After 4 cases of fatal CHF occurred at dose above 1000 mg/m², the trials were amended to cap the cumulative epirubicin dose at 1000 mg/m². Overall, 34 patients (7.2%) developed CHF at a median cumulative dose of 976 mg/m². No cases of CHF occurred at cumulative doses less than 300 mg/m². In patients without CHF, the median cumulative dose was 871 mg/m². The risk of CHF at various dose levels is summarized in the following table:

Table 105. Risk of CHF by cumulative epirubicin dose (data from Ryberg et al)

Cumulative epirubicin dose mg/m ²	Risk of CHF
800	2%
850	3%
900	4%
1000	15%

Risks were similar in patients treated with D1 and 8 schedules compared to those treated on D1 only. Risk did not vary by dose-intensity nor by the single-dose level of epirubicin. Only the cumulative epirubicin dose was associated with risk of CHF in this study. Age at the time of treatment was not associated with the risk of CHF, although a narrow age range of patients were included in this cohort. A history of mediastinal irradiation increased the risk.

The risk of CHF of 4% at a cumulative dose of 900 mg/m² is comparable to the 5% risk of CHF reported at a cumulative dose of 550 mg/m² of doxorubicin.

Reviewer Comments:

1. These published analyses of cardiac toxicity probably provide the best overall estimates of the risk of CHF.

2. They provide less data regarding the incidence of decrease in LVEF. However, drops in LVEF are used to remove patients from study or treatment before clinical sequelae of CHF develop. The risks cited in these studies may be considered as “worst case” scenarios, where patients are symptomatic. Serial monitoring may decrease the incidence of symptomatic events.

15.1.2 Secondary leukemias

The sponsor reported 4 leukemias associated with intra-arterial administration. The following table summarizes spontaneous reports of leukemia:

Table 106. Leukemias reported to the sponsor via spontaneous AE reporting (sponsor’s table 9, volume 2.55, page 45)

Leukemia	Dose			Treatment		Outcome	
	Total	HD	CD/Unk	Comb	SA/Unk	Fatal	Non-fatal/Unk
AML/MDS	28	19	8/1	24	2/2	10	15/3
ALL	3	1	2/0	1	0/2	2	1/0
Erythroleukemia	1	0/1	--	1	--	1	--

HD: high-dose

CD: conventional dose

Unk: unknown

Comb: epirubicin in combination with other cytotoxic agents

SA: epirubicin as a single agent

After this report was completed, 5 additional cases of AML/MDS were received. The sponsor states that 33 cases were identified; most occurred in the adjuvant setting.

The sponsor wrote a protocol and detailed analysis plan for monitoring the leukemogenic effects of epirubicin; these documents were submitted in the NDA. Leukemias have to date been identified only in breast cancer patients. The analyses included 9544 patients, 6187 treated adjuvantly and 3357 treated for advanced disease. Only two cases were observed in metastatic patients, precluding a meaningful analysis. In adjuvant patients, cumulative probabilities, hazard function calculations, and rates translate into a 3-year risk of AML of 0.24% and a 5-year AML risk of 0.77%. In comparison, the NSABP analysis of B-25 indicated a 4-year risk of 0.87%.

There was a statistically significant difference between patients treated with dose-intense epirubicin regimens (dose-intensity >25 mg/m²/week or > 90 mg/m²/cycle) compared to conventional-dose epirubicin.

Reviewer Comment:

1. The sponsor was asked to clarify the number of unique cases of leukemia reported with epirubicin administration. A total of 41 cases were identified: 36 cases of

AML/MDS, 1 with erythroleukemia, and 4 with ALL. The cases of AML/MDS were characterized by short latencies.

2. The four-month safety update contained two additional cases of leukemia. One occurred in a breast cancer patient treated with epirubicin 200 mg/m² in combination with cyclophosphamide every 4 weeks for 3 cycles, supported by stem cell transplant. The second patient had ovarian cancer treated with epirubicin, cyclophosphamide, and cisplatin.

15.2 Events associated with uses not approved in the United States

15.2.1 Intra-arterial Use

Intrahepatic administration of epirubicin in hepatocellular cancer patients is often used as the route of administration in Japan. All reports of adverse events after intra-arterial drug administration came from Japan (66 total). Events unique to this method of administration include the following, primarily due to locoregional effects:

- Gastroduodenal ulcers from reflux into the gastric artery (9 reports)
- Narrowing of bile ducts from drug-induced sclerosing cholangitis (8 reports)
- Hepatocellular damage/abnormal liver function tests/cholestasis
- Hepatic infarction
- Injection site abscess
- Extravasation

15.2.2 Intravesical Use

Intravesical use is common in Europe and Japan for the treatment of superficial bladder cancer and for prophylaxis against recurrence. These effects, also due to local toxicity, include:

- Chemical cystitis
- Bladder constriction
- Dysuria, polyuria, hematuria

15.3 Rare events

15.3.1 Pregnancy

One case of *in utero* exposure to epirubicin has been reported. A 34 year old woman, 28 weeks pregnant at the time of diagnosis of breast cancer, was treated with cyclophosphamide 800 mg and epirubicin 80 mg IV every 3 weeks for 3 cycles. She received the last dose at 34 weeks and gave birth to a healthy baby at 35 weeks.

A second pregnancy was identified in study HEPI/010. A 34 year old woman with breast cancer metastatic to the liver was randomized to FEC 50. After 1 cycle, she was removed from study because of pregnancy. She experienced a spontaneous abortion.

15.3.2 Overdose

Two unintended overdoses were reported to the sponsor. A 36 year old man with non-Hodgkin's lymphoma received 180 mg of epirubicin daily for 5 days. Observed toxicities included bone marrow aplasia, grade 4 mucositis, and GI bleeding. He required treatment with antibiotics, growth factors, and antifungal agents and recovered.

A 63 year old woman with metastatic breast cancer was given 600 mg of epirubicin. She experienced hyperthermia, respiratory failure, renal failure, lactic acidosis, anemia, and anuria. She died 24 hours after drug administration.

Additional information on overdose can be derived from high-dose epirubicin trials, where the observed toxicity is likely to predict the effects of an overdose. Severe neutropenia, thrombocytopenia, stomatitis, and acute and chronic cardiotoxicity were observed in these studies.

Doses of up to 180 mg/m² have been successfully managed without mortality. There is no known antidote for epirubicin. Management includes hospitalization, transfusions, antibiotics, symptomatic treatment of mucositis, and consideration of isolation/reverse barrier techniques.

15.4 Conclusions

No new findings are reported in the ISS and safety updates. Better estimates of the risk of secondary leukemia and cardiotoxicity are included in this section. Overall, treatment is generally well-tolerated, and the benefit conveyed by epirubicin in combination therapy appears to outweigh the risks of treatment.

16.0 Integrated Summary of Efficacy

The sponsor summarized and integrated the findings in early and metastatic breast cancer. No new information was included in these sections. The sponsor noted that the results for early stage breast cancer are consistent with those reported in the EBCTCG meta-analysis, which showed a trend in favor of anthracycline-containing regimens compared to CMF-like regimens.

17.0 Recommendations

The reviewer recommends approval for the indication for adjuvant treatment of breast cancer. The exact wording of the indication will describe the studied population if the ODAC agrees.

The reviewer recommends approval for the indication for first-line treatment of metastatic breast cancer if the ODAC session determines that TTP is acceptable proof of clinical benefit. If TTP is not considered to constitute clinical benefit, the data do not support approval based on other accepted endpoints, such as survival or improvements in quality of life.

1 **Signatures**

2
3
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5 /S/
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8
9 Susan Flamm Honig, M.D.
10 Medical Reviewer

11 /S/
12
13

14
15
16 Grant Williams, M.D.
17 Team Leader

18
19
20 cc: NDA 21-010
21 HFD-150/Division files
22 HFD-150/Susan Honig
23 HFD-150/Patrick Guinn

24
25

1 **Appendix A. Required on-study evaluations**

2

3

4 See attached documents from the 4 pivotal studies.

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6

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1 **Appendix B. ODAC questions and votes**

2
3 **NDA 21-010**

4 **Drug: Epirubicin**

5 **Sponsor: Pharmacia & Upjohn**

6
7
8 **Adjuvant therapy of early stage breast cancer**

9
10 Two randomized controlled trials were submitted for the indication, “epirubicin is indicated
11 as a component of adjuvant therapy in patients with evidence of axillary node tumor
12 involvement following resection of primary breast cancer (Stage II and III).” Study MA-5
13 randomized pre- and perimenopausal women with lymph node positive breast cancer to
14 receive FEC 120 versus CMF. Study GFEA-05 enrolled women with high-risk node positive
15 breast cancer (≥ 4 positive nodes, or 1-3 positive nodes with ER negative and grade 2-3
16 tumors) and randomized them to receive FEC 100 or FEC 50.

17
18 The following table summarizes the reported efficacy results for these studies.

19
20 **Table 1. Adjuvant Trials - Efficacy**

21

Endpoint (K-M 5-yr estimate)	MA-5 (n=716)			GFEA-05 (n=565)		
	CEF (n=356)	CMF (n=360)	p-value	FEC 100 (n=276)	FEC 50 (n=289)	p-value
RFS	62%	53%	0.013	65%	52%	0.007
OS	77%	70%	0.13	76%	65%	0.007

22
23 The planned epirubicin dose per cycle was 120 mg/m² for MA-5 and 100 mg/m² for GFEA-
24 05. The actual delivered dose-intensity in both trials was about 100 mg/m²/cycle.

25
26 **1. Do these randomized trials demonstrate that epirubicin at the planned doses of 100**
27 **and 120 mg/m², in combination with 5-FU and cyclophosphamide, is effective for the**
28 **proposed indication?**

29
30 YES 9

31 NO 0

1
2 The following table summarizes the reported safety results of these studies.

3
4 Table 2. Adjuvant Trials - Acute and Chronic Toxicities

5

Toxicity	MA-5 (n=714)		GFEA-05 (n=546)	
	CEF (n=354)	CMF (n=360)	FEC 100 (n=266)	FEC 50 (n=280)
Deaths on study	1 (0.3%)	0	1 (0.4%)	2 (0.7%)
Leukemia	5 ¹ (1.4%)	1 (0.3%)	1 (0.4%)	1 ¹ (0.4%)
Cardiac toxicity ²	12 (3%)	4 (1%)	12 (5%)	8 (3%)
Febrile neutropenia	31 (9%)	4 (1%)	7 (2.6%)	0
Vomiting (grade 3-4)	41 (12%)	19 (5%)	91 ³ (34%)	62 ³ (22%)
Diarrhea	4 (1%)	10 (3%)	1 (0.4%)	0
Stomatitis	45 (13%)	7 (2%)	10 (4%)	0

6 ¹ 1 case of ALL

7 ² Drop in LVEF or CHF, reviewer's assessment

8 ³ Nausea or vomiting, grade 3-4

9
10 Serotonin-specific antiemetic therapy and colony stimulating factors were not used in these
11 studies.

12
13 The applicant provided calculations of the incidence of CHF and AML based on all toxicity
14 information in their database and an estimate of the number of treated patients based on sales.
15 These calculations suggest a 4% incidence of CHF at cumulative epirubicin doses of 900
16 mg/m² or higher. The incidence of asymptomatic decreases in LVEF is probably higher.
17 The calculations also suggest a 0.24% risk of AML at 3 years and a 0.77% risk at 5 years.

18
19 **2. Do these trials demonstrate acceptable safety for epirubicin in combination with**
20 **cyclophosphamide and 5-FU at planned doses of 100 and 120 mg/m² for the**
21 **proposed indication?**

22
23 YES 8

24 NO 1

25
26 **3. Is epirubicin at planned doses of 100 and 120 mg/m² in combination with**
27 **cyclophosphamide and 5-FU approvable for adjuvant treatment of patients with**
28 **node-positive breast cancer?**

29
30 YES 9

31 NO 0

1 **First-line therapy of metastatic breast cancer**

2
3 Two randomized controlled trials were submitted for the indication “Epirubicin is indicated
4 for the therapy of patients with locally advanced or metastatic breast cancer.” Study
5 HEPI/013 randomized women with metastatic breast cancer and no prior chemotherapy to
6 receive FEC 100 or CMF. Study HEPI/010 randomized a similar patient population to
7 receive FEC 100 or FEC 50. Patients with the initial presentation of locally advanced breast
8 cancer without metastases were not included in these trials and cannot be considered in this
9 indication.

10
11 The following table summarizes the reported efficacy for these studies.

12
13 **Table 3. Metastatic Breast Cancer - Efficacy**

14

Endpoint	HEPI/013 (n=461)			HEPI/010 (n=456)		
	FEC 100 (n=233)	CMF (n=237)	p-value	FEC 100 (n=214)	FEC 50 (n=242)	p-value
Survival ¹ (median)	20.1 mo	18.2 mo	0.21	18 mo	17 mo	0.63
TTP ² (median)	8.8 mo	6.3 mo	0.0002	7.6 mo	7.0 mo	NS
Response rate ³	57%	46%	0.01	49%	36%	0.007
TTF ⁴ (median)	6.2 mo	4.8 mo	.008	5.7 mo	5.3 mo	0.60

15 ¹ Verified by the FDA reviewer in both trials

16 ² Verified by the FDA reviewer for HEPI/013

17 ³ Verified by the FDA reviewer for HEPI/010

18 ⁴ Not prospectively defined as an endpoint in either trial

19
20 Neither trial demonstrated a survival advantage for FEC 100 over the comparator. Forty-four
21 percent of patients on the CMF arm subsequently received an anthracycline-based regimen.
22 Significant differences were limited to a TTP advantage over CMF, and an improved
23 response rate with FEC 100 compared to FEC 50.

24
25
26 **4. In general, is an effect on TTP alone sufficient for demonstrating clinical benefit in**
27 **first-line treatment of metastatic breast cancer? In your answer please consider**
28 **both the activity of the control and the influence of crossover.**

29
30 NO (answered at the morning session)

1
2 **5. If not, does the evidence of epirubicin activity and survival benefit in the adjuvant**
3 **setting permit greater reliance on TTP in this setting?**

4
5 YES 2

6 NO 7

7
8 **6. Does the 2.5-month difference in TTP for FEC 100 compared to a dose-intense**
9 **CMF regimen represent a clinically meaningful effect of epirubicin in first-line**
10 **treatment of metastatic breast cancer?**

11
12 Not answered; questions 4 and 5 answered “no”

13
14 **7. Approval requires independent substantiation of the results from HEPI/013. Can**
15 **the reported response rate advantage for FEC 100 in study HEPI/010 provide**
16 **sufficient support? Can the RFS and survival results observed in the adjuvant**
17 **breast cancer trials provide sufficient support?**

18
19 Not answered; questions 4 and 5 answered “no”

20
21
22 The following table summarizes the toxicity of FEC 100.

23
24 Table 4. Metastatic Trials - Acute and Chronic Toxicities

1

Event	HEPI/013 (n=454)		HEPI/010 (n=447)	
	FEC 100 (n=220)	CMF (n=234)	FEC 100 (n=209)	FEC 50 (n=238)
Deaths on study	11 ¹ (5%)	8 (3%)	7 (3%)	3 (1%)
Cardiac toxicity ²	29 (13%)	9 (4%)	23 (11%)	12 (5%)
Febrile neutropenia	23 (10%)	18 (8%)	16 (8%)	1 (0.4%)
Nausea/vomiting grade 3-4	46 (21%)	32 (14%)	62 (30%)	61 (26%)
Anemia grade 3-4	26 (12%)	21 (9%)	15 (7%)	3 (1%)
Blood transfusions	13 (6%)	13 (6%)	14 (7%)	9 (4%)
Platelet transfusions	0	4 (2%)	1 (0.4%)	1 (0.4%)
Mucositis grade 3-4	27 (12%)	36 (15%)	20 (10%)	1 (0.4%)

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¹ One died prior to any treatment

² Drop in LVEF or CHF, reviewer's assessment

Most patients did not receive serotonin-specific antiemetic therapy and colony stimulating factors or prophylactic antibiotics were not used.

8. Do studies HEPI/013 and HEPI/010 demonstrate acceptable safety for FEC 100 for the proposed indication?

Not answered

9. Is epirubicin as administered in the FEC 100 regimen approvable for first-line treatment of metastatic breast cancer?

YES 3
NO 6

36 pages redacted from this section of
the approval package consisted of draft labeling

Appendix D. Recommended action

Based on the medical and statistical reviewers' analyses and the discussion by the ODAC members, we recommend approval of epirubicin in combination as adjuvant therapy of node positive breast cancer. We do not recommend approval of epirubicin as first-line therapy of metastatic breast cancer. The exact wording of the indication may be found in the package insert. Both adjuvant regimens used in studies MA-5 and GFEA-05 will be included in the PI.

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