

**CENTER FOR DRUG EVALUATION AND  
RESEARCH**

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**STATISTICAL REVIEW(S)**



**DEPARTMENT OF HEALTH AND HUMAN SERVICES  
PUBLIC HEALTH SERVICE  
FOOD AND DRUG ADMINISTRATION  
CENTER FOR DRUG EVALUATION AND RESEARCH**

**STATISTICAL REVIEW AND EVALUATION  
Clinical Studies**

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## 1. EXECUTIVE SUMMARY

### 1.1 CONCLUSIONS AND RECOMMENDATIONS

In this reviewer's opinion the results of the single study, TAX 316 appear to demonstrate efficacy of Taxotere<sup>®</sup> in combination with doxorubicin and cyclophosphamide (TAC) over 5-fluorouracil in combination with doxorubicin and cyclophosphamide (FAC) for the adjuvant treatment of patients with operable node-positive breast cancer. The results presented are based on a second planned interim analysis with 399 DFS events and a median follow-up of 55 months.

### 1.2 BRIEF OVERVIEW OF CLINICAL STUDIES

In this application, the sponsor submitted efficacy and safety results from a single study, TAX 316, which was designed as a multi-center, parallel, non-blinded, randomized, active-controlled multinational phase III trial. The primary objective of this study was to compare disease-free survival after treatment with Taxotere<sup>®</sup> 75 mg/m<sup>2</sup> in combination with doxorubicin 50 mg/m<sup>2</sup> and cyclophosphamide 500 mg/m<sup>2</sup> (TAC) to 5-fluorouracil 500 mg/m<sup>2</sup> in combination with doxorubicin 50 mg/m<sup>2</sup> and cyclophosphamide 500 mg/m<sup>2</sup> (FAC) as an IV infusion on day 1 every 3 weeks in operable breast cancer subjects with positive axillary lymph nodes. Patients in both treatment arms would receive 6 cycles of therapy.

The study was conducted in 112 centers among 20 countries, where 1491 patients were randomized. The submitted results were based upon the second interim data analysis, where 399 DFS events were recorded. In the sponsor's original protocol, only one (i.e., the first one) interim analysis was planned. Due to the borderline results of the first interim analysis results ( $p=0.0011$  vs. significance level of 0.001), the Independent Data Monitoring Committee (IDMC) recommended that the study protocol amend to include a second interim analysis to be performed at a 0.001 statistical significant level when 400 disease free survival (DFS) events had been recorded overall.

Based on the results from this second interim analysis, the sponsor concluded that the study showed both significantly longer disease free survival and overall survival for patients treated with Taxotere combined with AC (TAC) compared to those treated with 5-fluorouracil combined with AC (FAC).

### 1.3 STATISTICAL ISSUES AND FINDINGS

This NDA submission is to support administration of Taxotere in combination with doxorubicin and cyclophosphamide (TAC) as adjuvant treatment for operable breast cancer patients with positive axillary lymph nodes. Only one single study, Tax 316 which was conducted to establish efficacy and safety was submitted. The study

randomized a total of 1491 patients with 745 patients who received TAC treatment and 746 patients who received FAC treatment. The primary efficacy endpoint of this study was disease free survival (DFS) and the secondary efficacy endpoint was overall survival (OS). The sponsor submitted this application to claim the efficacy of TAC on both DFS and OS based on the second planned interim data analysis. The sponsor's p-values for DFS and OS were 0.001 and 0.008, respectively.

**Statistical Issues:**

1. The sponsor's analysis for the primary endpoint, DFS ignored patients who received any non-study anti-cancer therapy before their first relapse or discontinuation, which was different from what was planned in the protocol, and also different from the way that FDA has generally accepted.
2. The medical reviewer found 16 patients who had severe protocol violations, where 5 of whom as they had metastatic disease at entry were excluded from the intent to treat analysis. For the patients who had events due to second primary malignancy, (ex: endometrium, ovarian, leukemia and other cancers) could not be counted as events except that deaths occurred. In addition, the medical reviewer pointed out that 7 patients who had ovarian ablation before their first relapse, which were needed to be censored at the time of change of treatment.
3. The statistical analysis plan (SAP) of Study 316 specified the Peto's stopping rule for the interim analysis. However, when this SAP was submitted, the FDA statistician suggested the sponsor consider using the O'Brien-Fleming procedure instead. Although the sponsor insisted to use the Peto's stopping rule for the interim analysis, the O'Brien-Fleming procedure is what FDA usually considers as acceptable.

**Findings:**

- (1) Although this statistical reviewer confirmed the sponsor's analysis results for the primary and secondary endpoints, the issue about the censoring scheme that the sponsor used for patients who received non-study anti-cancer therapy before their relapse or discontinuation was raised and discussed since it was different from the method originally proposed in the statistical analysis plan. In addition, the medical reviewer found 16 patients who had severe protocol violations and 31 patients who were determined as events by the diagnosis of second primary malignancy but should have been censored. Some exploratory analyses by excluding patients and/or using different censoring schemes were performed and reported. Table 1.3.1 shows three different analysis results for the primary endpoint of disease free survival performed by this reviewer. Some other exploratory analyses for the DFS can be found in the section of 3.1.2.3.4, Statistical Reviewer's Findings and Comments.

**Table 1.3.1 Statistical Analysis Results for Disease Free Survival**

Disease Free Survival	# of Events (%)	Hazard Ratio	95% CI for Hazard Ratio	Log-Rank p-value
<i>(1) By ITT population but ignoring patients who had any non-study anti-cancer therapy before their relapse or discontinuation (sponsor's analysis)</i>				
TAC (N=745)	172 (23.09)	0.719	(0.59, 0.877)	0.001
FAC (N=746)	227 (30.43)			
<i>(2) Censoring patients at the start of new chemo therapy before their first relapse or discontinuation</i>				
TAC (N=745)	167 (22.42)	0.737	(0.603, 0.901)	0.0026
FAC (N=746)	222 (29.76)			
<i>(3) Reanalysis per the medical reviewer's request. (See detailed explanation in Comment #1 of Section 3.1.2.3.4)(FDA Analysis)</i>				
TAC (N=744)	156 (20.97)	0.743	(0.603, 0.915)	0.0047
FAC (N=742)	206 (27.76)			

All the reanalysis results had p-values greater than 0.001, the interim significance level by the Peto's stopping rule. That implies the differences between the TAC and FAC were not statistically significant according to the Peto's stopping rule.

However, we notice that if the O'Brien-Fleming procedure was used for this sequential design instead, then the conclusions are completely different because the second interim boundary was calculated as  $\alpha=0.0057$  according to the number of events observed so far and the projected final number of events (700). This reviewer wants to emphasize that when the sponsor submitted the statistical analysis plan to the FDA, the agency's statistician indeed suggested the sponsor consider to use the O'Brien-Fleming procedure instead of the Peto's stopping rule. The O'Brien-Fleming procedure is generally accepted by FDA. Thus, with all the reanalysis results less than 0.0057, the differences between TAC and FAC are statistically significant based on the O'Brien-Fleming procedure. We also notice that with all different analysis methods, the hazard ratio is between 0.719 to 0.743.

- (3) For the second interim data, p-values of analysis results on both primary and secondary endpoints should be compared with the same interim significance level. Since the p-value for the analysis results of the secondary endpoint, i.e., overall survival, was 0.008 ( $>0.001$ ), what the sponsor concluded the significant finding in the overall survival analysis based on the Peto's stopping rule was not correct. For this secondary endpoint, overall survival, the data did not show TAC's efficacy based on either the Peto's stopping rule or the O'Brien's Fleming procedure. However, as we can observe from the following table, although the results were not statistically significant based on this second interim data, there is a strong trend of improved overall survival in the TAC treatment arm.

**Table 1.3.2 Analysis Results for Overall Survival**

Overall Survival	# of Events (%)	Hazard Ratio	95% CI for Hazard Ratio	Log-Rank p-value
<i>(1) By ITT population (sponsor's analysis)</i>				
TAC (N=745)	91 (12.21)	0.695	(0.532, 0.909)	0.008
FAC (N=746)	130 (17.43)			
<i>(2) Reanalysis per the medical reviewer's request (FDA Analysis)</i>				
TAC (N=744)	90 (12.10)	0.688	(0.526, 0.901)	0.0067
FAC (N=742)	129 (17.40)			

## 2. INTRODUCTION

### 2.1 OVERVIEW

At the time of surgery, women with early breast cancer and axillary lymph node are at high risk of relapse and subsequent death from metastatic disease. Without adjuvant therapy, the 10-year survival for women with nodal involvement historically ranged from 25% to 48%. The risk of death increases as the number of nodes increases. In the absence of adjuvant therapy, breast cancer treated patients with 1 to 3 positive nodes have 10-year survival of 40 to 60%, while for those with 4 or more involved nodes, the 10-year survival has decreased to approximately 25%. Adjuvant chemotherapy has been extensively studied over the past 30 years and is a major contributor to the improved survival rates among women diagnosed with axillary lymph node involvement.

The combination of cyclophosphamide, methotrexate and 5-fluorouracil (CMF) was the first chemotherapy regimen that proved the concept that adjuvant chemotherapy could improve outcomes of disease-free and overall survival. Later, the demonstration of the effectiveness of anthracyclines, particularly doxorubicin, for the treatment of metastatic breast cancer led to the experts' evaluation in the adjuvant treatment setting. The CMF was later modified by substituting doxorubicin for methotrexate in combination with cyclophosphamide and 5-fluorouracil (FAC). In 1984, the NSABP demonstrated that the combination of only doxorubicin and cyclophosphamide could be given over a shorter course and without 5-fluorouracil (AC). By mid 1990's, both 2 drug (AC) and 3 drug (FAC) regimens were used in both standard clinical practice and as reference regimens for further studies of adjuvant chemotherapy in women with early stage breast cancer at risk of recurrence.

Taxotere®, which was already approved for treating metastatic breast cancer, non-small cell lung cancer and prostate cancer, now in combination with doxorubicin and cyclophosphamide (TAC) is submitted as an adjuvant treatment for operable breast cancer subjects with positive axillary lymph nodes.

In this application, the sponsor submitted efficacy and safety results from a single study, TAX 316, which was designed as a multi-center, parallel, non-blinded, randomized, active-controlled multinational phase III trial. The primary objective of this study was to compare disease-free survival after treatment with Taxotere® 75 mg/m<sup>2</sup> in combination with doxorubicin 50 mg/m<sup>2</sup> and cyclophosphamide 500 mg/m<sup>2</sup> (TAC) to 5-fluorouracil 500 mg/m<sup>2</sup> in combination with doxorubicin 50 mg/m<sup>2</sup> and cyclophosphamide 500 mg/m<sup>2</sup> (FAC) as an IV infusion on day 1 every 3 weeks in operable breast cancer subjects with positive axillary lymph nodes. Patients in both treatment arms would receive 6 cycles of therapy.

Based on the results from this second interim analysis, the sponsor concluded that the study showed both significantly longer disease free survival and overall survival for patients treated with Taxotere combined with AC (TAC) compared to those treated with 5-fluorouracil combined with AC (FAC).

## 2.2 DATA SOURCES

The sponsor's original submission and data are stored in the EDR with the following directory: \\CDSESUB1\N20449W\_029\2004-3-17.

## 3. STATISTICAL EVALUATION

### 3.1 EVALUATION OF EFFICACY

Taxotere®, which is approved for treating metastatic breast cancer, non-small cell lung cancer and prostate cancer, now in combination with doxorubicin and cyclophosphamide (TAC) is submitted as an adjuvant treatment for operable breast cancer subjects with positive axillary lymph nodes.

#### 3.1.1 Description of Study TAX 316

This section of description of the study is based on the sponsor's study report. Any difference between the sponsor's study report and the protocol will be discussed in Section 3.1.3 of the statistical reviewer's findings and comments.

##### 3.1.1.1 Study Objectives

The primary study objective was to compare disease-free survival after treatment with Taxotere® in combination with doxorubicin and cyclophosphamide (TAC) to 5-fluorouracil in combination with doxorubicin and cyclophosphamide (FAC) in operable breast cancer subjects with positive axillary lymph nodes.

The secondary objectives of this study included:

- To compare overall survival between the 2 above-mentioned arms.
- To compare toxicity and quality of life between the 2 above-mentioned arms.
- To evaluate pathologic and molecular markers for predicting efficacy.
- An independent socio-economic study was to be conducted in parallel with the clinical study.

##### 3.1.1.2 Study Design

This was a prospective, parallel, non-blinded, randomized, positive-controlled, multinational phase III trial comparing TAC with FAC as adjuvant chemotherapy following primary surgery for breast cancer.

Subjects in study TAX 316 were post-surgically stratified at inclusion, first according to the participating institution, then according to the number of axillary lymph nodes involved (1 to 3; 4 and more), and were randomly assigned to receive either:

- **TAC:** Taxotere® 75 mg/m<sup>2</sup> as 1-hour IV infusion on day 1 every 3 weeks in combination with doxorubicin 50 mg/m<sup>2</sup> as an IV infusion and cyclophosphamide 500 mg/m<sup>2</sup> as IV infusion on day 1 every 3 weeks; or
- **FAC:** 5-fluorouracil 500 mg/m<sup>2</sup> as an IV infusion on day 1 every 3 weeks in combination with doxorubicin 50 mg/m<sup>2</sup> as an IV infusion and cyclophosphamide 500 mg/m<sup>2</sup> as an IV infusion on day 1 every 3 weeks.

The first cycle of adjuvant chemotherapy was initiated within 8 days of the date of randomization. All randomized subjects were to receive a fixed number of six cycles (either TAC or FAC) of treatment.

### 3.1.1.3 Study Population

The intention-to-treat (ITT) population is defined as all randomized subjects in the treatment group who were assigned to, and according to the number of positive lymph nodes indicated in the randomization (1 to 3, 4 and more).

The eligible subject population is defined as all randomized subjects who did not experience some major protocol deviations listed in the Statistical Analysis Plan.

The safety population is defined as all treated subjects who started at least 1 infusion of study treatment, analyzed in the treatment group they actually received.

### 3.1.1.4 Efficacy Variables

#### Primary:

Disease-free survival (DFS) is the primary efficacy variable. DFS is defined as the time interval between the date of randomization and the date of local, regional or metastatic relapse, or the date of second primary cancer or death from any cause, whichever occurs first.

#### Secondary:

Overall survival (OS) is the main secondary variable and is defined as the time interval between the date of randomization and the date of death or last contact.

### 3.1.1.5 Statistical Analysis

#### Sample Size Determination

The study was originally designed to have 90% power to detect a 26% risk reduction of relapsing for TAC compared to FAC (hazard ratio=0.74) at the final analysis conducted after 450 DFS events with a two-sided 5% significance level. According to the sponsor, in response to the NCI Canada Clinical Trials Group's publication of a study of an intense adjuvant epirubicin-based regimen compared to CMF that failed to demonstrate a treatment advantage in nodal status subgroups for likely lack of power, TAX 316 was amended (3<sup>rd</sup> protocol amendment, January 1999).

The increased sample size provides 90% power to detect a 27% risk reduction of relapsing for TAC compared to FAC (hazard ratio=0.73) in the subgroup of subjects with 1 to 3 positive axillary nodes at a one-sided 5% significance. The objective was also to detect a 29% risk reduction of relapsing (hazard ratio=0.71) in the subgroup of subjects with 4 or more positive axillary nodes at a one-sided 5% significance level. As a direct consequence the overall power of the study was 97% for detecting a 27% risk reduction of relapsing for TAC compared to FAC (hazard ratio=0.73) at a two-sided 5% significance level. The number of DFS events required for conducting the final DFS analysis was calculated equal to 590 overall providing 341 are observed in the stratum of 1-3 positive axillary nodes.

#### **Reviewer's Comments:**

Although the sponsor planned to have the final analysis performed after 590 overall DFS events, it was mentioned in the statistical analysis plan that to have at least 341 DFS events occurring in the 1-3 positive axillary nodes, current rate projections indicate that perhaps about 700 DFS events in total will have occurred for the final analysis.

#### Primary Efficacy Analysis

The primary efficacy analysis is the comparison of DFS distribution for the ITT population between treatment groups using the two-sided stratified log-rank test. The stratification variable is the nodal status (1 to 3 positive nodes versus 4 or more) as per information available at the time of the randomization. The hazard ratio of TAC versus FAC is obtained from a Cox model adjusted on the nodal status.

#### Secondary Efficacy Analyses

The analysis of DFS is repeated on different populations or using different models to assess the robustness of the results, as summarized by the p-value and the hazard ratio of TAC versus FAC with its 95% confidence interval.

#### Analysis of the Secondary Endpoint: Overall Survival (OS)

The OS distributions of the two treatment arms are compared using the two-sided log-rank test, stratified on the number of axillary nodes involved (1 to 3, 4 and more), as per randomization. The test is conducted at the 5% significance level.

The OS analysis is also repeated on different populations or using different models as described for the DFS in previous section.

## Interim Analysis

The results presented in this report are based on a second interim analysis (IA). In the original protocol, only one interim efficacy analysis was planned at 3 years after recruitment of 50% of the expected events and the Peto's method was proposed. The first IA, when the data were cut off on 31 August 2001, showed that TAC was associated with a 32% relapse risk reduction (HR 0.68, 95% CI 0.54 –0.86) but the corresponding p-value of 0.0011 which did not meet the Peto's stopping rule of 0.001. With this borderline results, the independent data monitoring committee (IDMC) concluded that the study protocol should be amended to include a second IA when 400 DFS events had been recorded overall.

### 3.1.2 Efficacy Analysis Results

#### 3.1.2.1 Data Sets and Disposition of Patients

According to the sponsor's study report, one thousand four hundred ninety-one subjects were randomized into the study. The first subject was randomized on 11 June 1997 and the last one on 3 June 1999. The cutoff date of the first interim analysis was 31 August 2001, at which time 289 protocol defined events had occurred and the median follow-up was 32.8 months.

The sponsor's current study report is based on the results of the 2<sup>nd</sup> interim analysis (IA) that was to be conducted, as recommended by the IDMC after 400 DFS events had been recorded. Based on the event rate observed in the study population subsequent to the first IA, a prediction model predicted 15 July 2003 as the best estimate for a cut-off date at which time 400 DFS events would have been recorded. At this date, 399 DFS had actually been recorded. Using actual data and the Kaplan-Meier method, the study median follow-up is equal to 55 months at the cut-off date.

Table 3.1.2.1 shows the different study data sets from the sponsor's study report. Of the 1491 randomized subjects, 11 did not receive any study treatment: 1 in the TAC group and 10 in the FAC group. Of these 11 patients, eight withdrew consent, one was lost to follow-up and two did not receive treatment for other reasons. In total, therefore, 1480 subjects were treated with study chemotherapy and are included in the safety analysis: 744 received TAC and 736 received FAC.

**Table 3.1.2.1 Study Data Sets**

	TAC arm n (%)	FAC arm n (%)	All n (%)
Randomized Subjects	745 (100.0)	746 (100.0)	1491 (100)
Eligible Subjects	709 (95.2)	712 (95.4)	1421 (95.3)
Treated Subjects	744 (99.9)	736 (98.7)	1480 (99.3)
Not Treated	1 (0.1)	10 (1.3)	11 (0.7)

Of the 1491 subjects enrolled, 1390 subjects completed all six cycles of treatment as defined in the protocol. Reason for discontinuation are presented in Table 3.1.2.2.

**Table 3.1.2.2 Reasons for Treatment Discontinuation**

Reasons	Randomized Subjects		
	TAC (N=745) n (%)	FAC (N=746) n (%)	All (N=1491) n (%)
Treatment completed as per protocol	679 (91.1)	711 (95.3)	1390 (93.2)
Adverse Event	45 (6.0)	8 (1.1)	53 (3.6)
Consent Withdrawn	17 (2.3)	17 (2.3)	34 (2.3)
Death	2 (0.3)	2 (0.3)	4 (0.3)
Mon-septic death related to study chemotherapy	1 (0.1)	1 (0.1)	2 (0.1)
Other	1 (0.1)	1 (0.1)	2 (0.1)
Breast Cancer Relapse	1 (0.1)	4 (0.5)	5 (0.3)
Lost to Follow-up	0 (0.0)	1 (0.1)	1 (0.1)
Other	1 (0.1)	3 (0.4)	4 (0.3)

**Reviewer's Comment:**

The above two tables were confirmed by this reviewer according to the sponsor's submitted data.

**3.1.2.2 Demographic and Baseline Characteristics**

The sponsor's demographic data are summarized in Table 3.1.2.3 for all subjects. According to the table, age and performance status of subjects at baseline were comparable between treatment arms.

**Table 3.1.2.3 Demographic data**

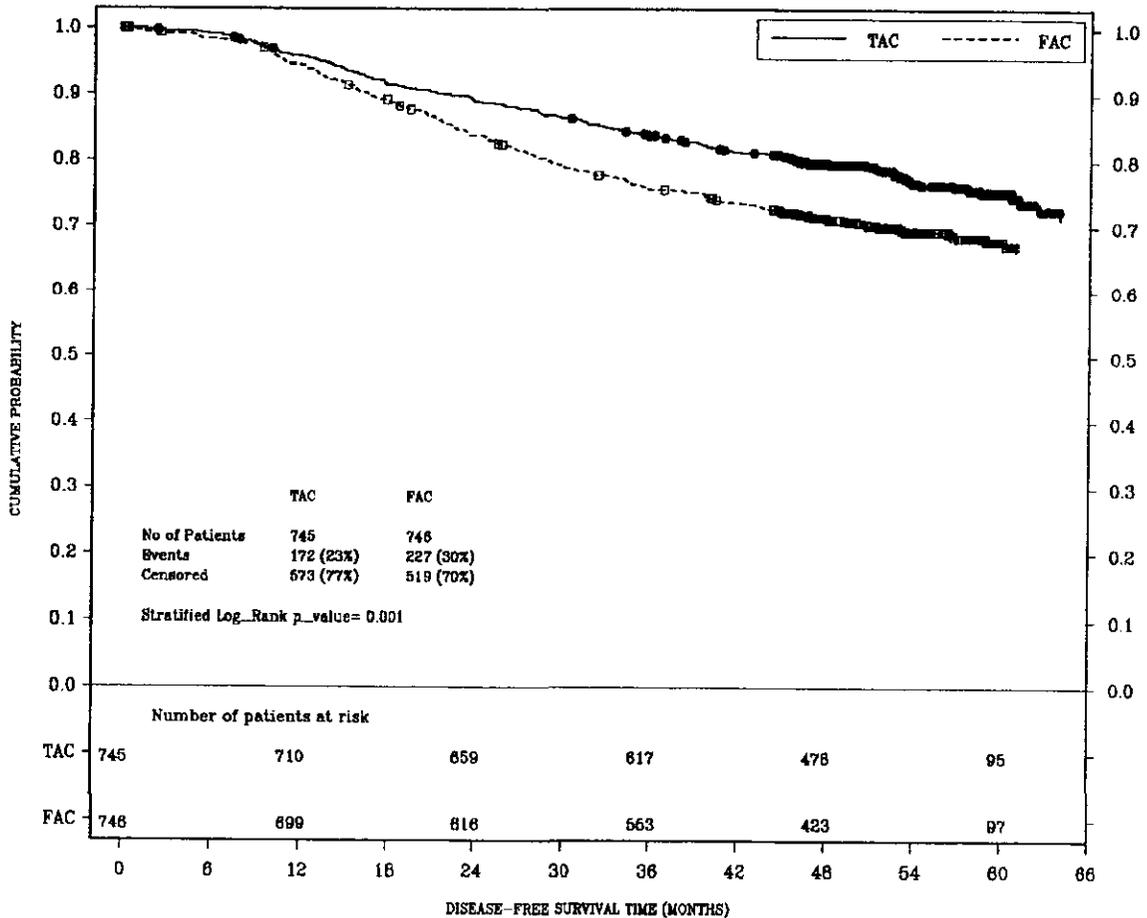
	Randomized Subjects		All Subjects
	TAC n (%)	FAC n (%)	n (%)
No of Subjects	745 (100.0)	746 (100.0)	1491 (100.0)
Age (years)			
Median	49	49	49
Range	26-70	23-70	23-70
< 35	52 (7.0)	36 (4.8)	88 (5.9)
35-49	349 (46.8)	358 (48.0)	707 (47.4)
50-64	296 (39.7)	311 (41.7)	607 (40.7)
≥ 65	48 (6.4)	41 (5.5)	89 (6.0)
Karnofsky Performance Status at Baseline			
Median	100	100	100
Range	80-100	80-100	80-100
80	24 (3.2)	20 (2.7)	44 (3.0)
90	141 (18.9)	153 (20.5)	294 (19.7)
100	580 (77.9)	573 (76.8)	1153 (77.3)

### 3.1.2.3 Sponsor's Efficacy Results

#### 3.1.2.3.1 Primary Analysis on Disease-Free Survival

Figure 3.1.2.1 shows the disease-free survival curves for both treatment groups by the sponsor. As defined in the sponsor's Protocol Amendment 4, the second interim analysis was to be conducted with the treatment comparison to be done at the 0.001 level for the primary endpoint of DFS. At the cut-off date of 15 July 2003, and with a median follow-up time of 55 months, there had been a total of 399 DFS events with 172 and 227 events in TAC and FAC arms, respectively. TAC was associated with a 28% relapse risk reduction compared to FAC (HR 0.72, 95% CI 0.59-0.88). The distribution of DFS was significantly different between the two treatment groups using the logrank test stratified on the number of axillary lymph nodes involved at randomization (logrank p-value = 0.001).

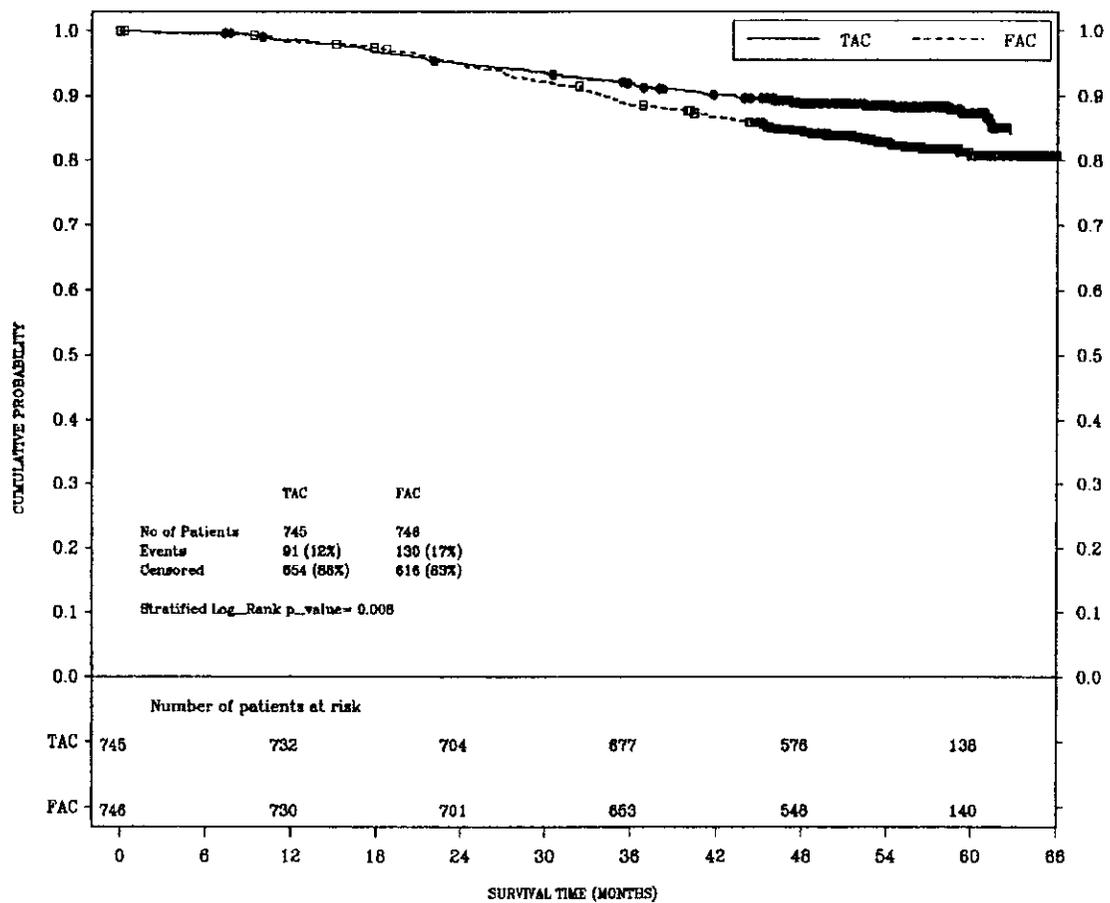
Figure 3.1.2.1 Disease-Free Survival Curves for ITT Population



### 3.1.2.3.2 Secondary Analysis on Overall Survival

Figure 3.1.2.2 shows the overall survival curves for both treatment groups by the sponsor. At the cut-off date of 15 July 2003, and with a median follow-up time of 55 months, there had been a total of 221 deaths with 91 and 130 in TAC and FAC arms, respectively. TAC is associated with a 30% risk reduction in mortality compared to FAC (HR 0.70, 95% CI 0.53-0.91). The distribution of OS was significantly different between the two treatment groups using the logrank test stratified on the number of axillary lymph nodes involved at randomization (logrank p-value = 0.008).

Figure 3.1.2.2 Overall Survival Curves for ITT Population



#### Reviewer's Comment:

What the sponsor mentioned about the statistically significant results on the overall survival analysis was not correct (See reviewer's Comment 5 in Section 3.1.2.3.4).

### 3.1.2.3.3 Sponsor's Efficacy Conclusions

The second interim analysis of TAX 316 is statistically significant in favor of TAC for the primary efficacy endpoint of disease-free survival (DFS) as well as the secondary endpoint of overall survival in the intention to treat population. (Notice that this statement was not correct. See Comment #5 of Section 3.1.2.3.4) The greater benefit of TAC over FAC applies irrespective of nodal and hormone receptor status. The magnitude of the benefit is clinically significant and remains so even when differences in toxicity are considered.

### 3.1.2.3.4 Statistical Reviewer's Findings and Comments

1. The sponsor's analysis results for the primary endpoint, disease free survival and the secondary endpoint, overall survival were confirmed by the statistical reviewer. However, it was found that the sponsor mentioned in the statistical analysis plan that according to the intent-to-treat principle, any delayed further anti-cancer therapy given before the first relapse will be ignored in the primary analysis, which was recommended by the Independent Data Monitoring Committee, but this action deviates from what was stated in the original protocol. The protocol specified that patient receiving prohibited anti-cancer therapy after completion of the study chemotherapy and before relapse would be considered as relapsing (i.e., DFS events) at the date of initiation of the prohibited anti-tumor therapy in the analysis of disease free survival. After identifying such patients, the data was reanalyzed. There were four patients (Patients# 22502, 25501, 23904 and 27601) identified and the reanalysis results are shown in Table 3.1.2.4.

Table 3.1.2.4 Statistical Reviewer's Re-Analysis Results after Treating 4 Patients as Events per the Study Protocol

ITT Population (N=1491)	# of Events (%)	Hazard Ratio	95% CI for Hazard Ratio	Log-Rank p-value
TAC (N=745)	173 (23.22)	0.723	(0.593, 0.881)	0.0011
FAC (N=746)	227 (30.43)			

As we can see from the table, the results are no longer significant since the p-value of 0.0011 is greater than 0.001, the interim significance level that the sponsor chose to use by the Peto's stopping rule.

2. Although the sponsor's final analysis for the primary endpoint of disease free survival was based on the analysis of ignoring all patients, who had delayed further anti-cancer therapy given before the first relapse as recommended by the IDMC, after discussions with the medical reviewer, this reviewer performed the reanalysis by censoring patients who took additional chemotherapy before their relapse or discontinuation. There were 44 patients in this category and the reanalysis results are shown in Table 3.1.2.5.

**Table 3.1.2.5 Statistical Reviewer's Re-Analysis Results after Censoring 44 Patients Who Took Additional Chemotherapy Before Their First Relapse or Discontinuation**

ITT Population (N=1491)	# of Events (%)	Hazard Ratio	95% CI for Hazard Ratio	Log-Rank p-value
TAC (N=745)	167 (22.42)	0.737	(0.603, 0.901)	0.0026
FAC (N=746)	222 (29.76)			

As we can see from the table, the results are again no longer significant since the p-value of 0.0026 is greater than 0.001. when the data was analyzed by censoring patients who took any additional chemotherapy prior to their relapse or discontinuation by their starting date of chemotherapy. Notice that this analysis is still using the so called Intent-to-Treat population but only by different censoring scheme.

- In addition to the sponsor's list of patients who used non protocol therapy, the medical reviewer also found 16 patients who had severe protocol violations. Among the above mentioned 16 patients, the medical reviewer believes 5 (who had metastatic disease at entry) of them should definitely be excluded from the intent-to-treat population. Moreover, 31 patients who had events due to second primary malignancy of the endometrium, ovarian, leukemia or other cancers can not be considered as events (per sponsor's definition) and should be censored except when deaths occurred. Seven more patients who had ovarian ablation before their first relapse or discontinuation should also be censored at the time of treatment as this can influence the outcome of interest. The statistical reviewer performed the re-analysis by redefining the data set (events, censoring and exclusions) as described above. Some exploratory analyses by separating each definition were also performed. The detailed analysis results by different scenarios are presented in Tables 3.1.2.6 and 3.1.2.7.

**Table 3.1.2.6 FDA's Analysis**

FDA Analysis*	# of Events (%)	Hazard Ratio	95% CI for Hazard Ratio	Log-Rank p-value
TAC (N=744)	156 (20.97)	0.743	(0.603, 0.915)	0.0047
FAC (N=742)	206 (27.76)			

\* Censoring 44 patients who had additional chemo at their start date, censoring 31 patients who had events but with reason as secondary primary malignancy of endometrium, ovarian, leukemia and others, however, if there were deaths, then were considered them as events but replace the original event dates by their dates of death. In addition, censoring 7 patients who had ovarian ablation by their start dates of ablation, and also excluding 5 patients who had distant metastases present at entry to study among those 16 severe protocol violators.

**Table 3.1.2.7 Some Exploratory Analyses**

Exploratory Analyses	# of Events (%)	Hazard Ratio	95% CI for Hazard Ratio	Log-Rank p-value
<i>(1) Deleting 16 severe protocol violation patients</i>				
TAC (N=740)	171 (23.11)	0.726	(0.595, 0.887)	0.0015
FAC (N=735)	222 (30.20)			
<i>(2) Excluding 16 severe protocol violation patients, excluding patients who took additional chemo and had 6 cycles (Patients# 22502, 12214, 25501, 23904, and 27601) and also excluding patients who had ovarian ablation prior to progressive disease</i>				
TAC (N=719)	168 (23.37)	0.733	(0.599, 0.896)	0.0022
FAC (N=722)	219 (30.33)			
<i>(3) Excluding 16 severe protocol violation patients and also excluding patients who took prohibited medication prior to progressive disease (all 45 patients)</i>				
TAC (N=684)	162 (23.68)	0.742	(0.605, 0.909)	0.0036
FAC (N=713)	217 (30.43)			
<i>(4) Excluding 16 severe protocol violation patients, but censoring patients who took prohibited medication prior to progressive disease</i>				
TAC (N=740)	162 (21.89)	0.737	(0.601, 0.903)	0.0029
FAC (N=735)	217 (29.52)			
<i>(5) Excluding 16 severe protocol violation patients and also excluding 5 patients who received additional radiotherapy and 30 patients who had ovarian ablation, and treating 4 patients who took additional chemo and had 6 cycles before relapse as events (Patients# 22502, 25501, 23904 and 27601).</i>				
TAC (N=719)	168 (23.37)	0.729	(0.596, 0.891)	0.0018
FAC (N=722)	221 (30.47)			

As we can see from the table, none of the p-values was smaller than 0.001 and hence no statistically significant difference based on Peto's stopping rule.

4. Although the sponsor insisted in using the Peto's stopping rule of 0.001 for their interim analyses, when the original protocol was submitted to the FDA, the agency's statistical reviewer indeed suggested the sponsor to consider using the O'Brien-Fleming's procedure to perform the interim analysis and adjust the final alpha level accordingly. By using the number of events that the sponsor planned for this second interim analysis, the number of events had occurred in the first interim analysis and the projected number of events in the final analysis, this reviewer obtained the nominal critical point by p-value scale, 0.0057 for this second interim analysis. Although the p-values shown in above tables are greater than 0.001 (Peto's method) but they are all also smaller than 0.0057 (OBF method). So, if the sponsor had proposed using the O'Brien-Fleming procedure for their group sequential design, in this second interim analysis, the TAC's efficacy over the FAC could have been concluded.
5. The alpha allocated for the interim analysis of OS was also 0.001 and the p-value for the secondary endpoint of overall survival showed 0.008 ( $\geq 0.001$ ), which is not significant. The sponsor's final conclusion that the statistical significance is demonstrated on this secondary endpoint is NOT correct per the specified alpha for the interim look. However, as we can observe from the following table, although the results were not statistically significant based on this second interim data, there is a strong trend of improved overall survival in the TAC treatment arm.

**Table 3.1.2.8 Analysis Results for Overall Survival**

Overall Survival	# of Events (%)	Hazard Ratio	95% CI for Hazard Ratio	Log-Rank p-value
<i>(1) By ITT population (sponsor's analysis)</i>				
TAC (N=745)	91 (12.21)	0.695	(0.532, 0.909)	0.008
FAC (N=746)	130 (17.43)			
<i>(2) Reanalysis per the medical reviewer's request (FDA Analysis)</i>				
TAC (N=744)	90 (12.10)	0.688	(0.526, 0.901)	0.0067
FAC (N=742)	129 (17.40)			

### 3.2 EVALUATION OF SAFETY

The evaluation of safety was not performed in this review. Please refer the clinical review of this application for safety evaluation.

## 4. FINDINGS IN SPECIAL/SUBGROUP POPULATIONS

### 4.1 GENDER, RACE AND AGE

Since all patients are female and the majority of patients are white in the study, no subgroup analysis for gender and race are performed and reported in this review. Although the sponsor's results were confirmed, in this section, only this statistical reviewer's subgroup analysis by age group based on FDA defined endpoints are reported in Table 4.1. The differences between the sponsor's and FDA analyses are minimal.

**Table 4.1 Subgroup Analysis for Age**

Age Subgroup	TAC Event # / n	FAC Event # / n	Hazard Ratio TAC/FAC	95% Confidence Interval
<b>Disease Free Survival</b>				
< 50 years	87 / 400	119 / 391	0.71	(0.54 – 0.94)
≥ 50 years	69 / 344	87 / 351	0.77	(0.56 – 1.06)
<b>Overall Survival</b>				
< 50 years	51 / 400	69 / 391	0.72	(0.50 – 1.03)
≥ 50 years	39 / 344	60 / 351	0.64	(0.43 – 0.95)

### 4.2 OTHER SPECIAL/SUBGROUP POPULATIONS

According to the sponsor's statistical analysis plan, in addition to the subgroup analysis for age, the subgroup analysis for patients' nodal status and hormonal receptor status were also performed. The sponsor's results were confirmed by this statistical reviewer, however, Table 4.2, lists this statistical reviewer's results based on FDA defined endpoints. The differences between the sponsor's and FDA analyses were minimal.

**Table 4.2 Subgroup Analyses for Patients' Nodal Status and Hormonal Receptor Status**

	TAC Event # / n	FAC Event # / n	Hazard Ratio TAC/FAC	95% Confidence Interval
<b>Disease Free Survival</b>				
<b>Nodal Status</b>				
1 to 3 positive nodes	69 / 467	103 / 458	0.64	(0.47 – 0.87)
≥ 4 positive nodes	87 / 277	103 / 284	0.84	(0.63 – 1.12)
<b>Hormonal Receptor Status</b>				
Negative	54 / 178	72 / 181	0.68	(0.48 – 0.97)
Positive	102 / 566	134 / 561	0.76	(0.59 – 0.98)
<b>Overall Survival</b>				
<b>Nodal Status</b>				
1 to 3 positive nodes	30 / 467	63 / 458	0.45	(0.29 – 0.70)
≥ 4 positive nodes	60 / 277	66 / 284	0.93	(0.66 – 1.32)
<b>Hormonal Receptor Status</b>				
Negative	40 / 178	58 / 181	0.66	(0.44 – 0.98)
Positive	50 / 566	71 / 561	0.69	(0.48 – 0.99)

## 5. SUMMARY AND CONCLUSIONS

### 5.1 STATISTICAL ISSUES AND COLLECTIVE EVIDENCE

Although the statistical reviewer confirmed the sponsor's analysis results for the primary and secondary endpoints, the issue about the censoring scheme that the sponsor used for patients who received delayed further anti-cancer therapy before their relapse or discontinuation was raised and discussed since it was different from the method originally proposed in the statistical analysis plan. In addition, the medical reviewer found sixteen patients who had severe protocol violations in the study and some patients who should be censored instead of being counted as events, so analyses by excluding patients and/or using different censoring schemes were performed and reported.

All the reanalysis results showed p-values greater than 0.001, the interim significance level by the Peto's stopping rule. That implies the differences between the TAC and FAC were not statistically significant based on the Peto's stopping rule. However, we notice that if the O'Brien-Fleming procedure was used for this sequential design instead, then all the reanalysis results showed that TAC had statistically significant effect. When the sponsor submitted the original protocol to the FDA, the agency indeed suggested the sponsor consider to use the O'Brien-Fleming procedure to replace the proposed Peto's stopping rule.

On the other hand, for the second interim data, p-values of analysis results on both primary and secondary endpoints should be compared with a same interim significance level. Since the p-value for the analysis results of the secondary endpoint, i.e., overall survival, was 0.008 (>0.001), the sponsor's conclusion that the significant finding is observed in the overall survival analysis based on the Peto's stopping rule was not correct. For this secondary endpoint, overall survival, the data did not show TAC's efficacy based on either the Peto's stopping rule or the O'Brien's Fleming procedure. However, the data do suggest a trend favoring TAC over FAC with respect to OS.

## 5.2 CONCLUSIONS AND RECOMMENDATIONS

In this reviewer's opinion the results of the single study, TAX 316 appear to demonstrate efficacy of Taxotere® in combination with doxorubicin and cyclophosphamide (TAC) over 5-fluorouracil in combination with doxorubicin and cyclophosphamide (FAC) for the adjuvant treatment of patients with operable node-positive breast cancer. The results presented are based on a second planned interim analysis with 399 DFS events and a median follow-up of 55 months.

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Yeh-Fong Chen, Ph.D.  
Mathematical Statistician

cc: NDA 20-449  
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HFD-120/Dr. Dagher  
HFD-120/Dr. Cortazar  
HFD-700/Dr. Anello  
HFD-710/Dr. Mahjoob  
HFD-710/Dr. Sridhara

This review consists of 19 pages. MS Word: C:/yfchen/NDA20449/review.doc.

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/s/

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