

Statistical Review and Evaluation - Summary Statement

NDA#: 21-063
Sponsor: Sanofi Pharmaceuticals, Inc.
Name of Drug: Oxaliplatin (Eloxatin for injection)
Indication: Advanced colorectal cancer
Documents Reviewed: Vols. 1.1, 1.226, 1.227, 1.228, 1.235, 1.236, 1.239
Medical Officer: Stephen Hirschfeld, M.D.
Statistical Reviewer: Mark Rothmann, Ph. D.

1. INTRODUCTION

In support of first-line treatment of Eloxatin (oxaliplatin injection) in combination of 5-FU based chemotherapy for patients with advanced colorectal cancer, the sponsor submitted an NDA that includes 33 individual study reports and 17 clinical investigations. Of these, eight Phase II/III trials have been designated as Primary Studies, on the basis of study design and conduct; four are classified as controlled studies –(studies EFC2962, EFC2961, EFC2964 and EFC2917) and four are classified as corroborative, uncontrolled studies (studies EFC2960, EFC2963, EFC3105 and EFC3106). Studies EFC2961 and EFC2962 were randomized, controlled trials in previously untreated patients. Studies EFC2964 and EFC2917 are single-armed studies where patients acted as their own control (patients were refractory to prior a 5-FU/FA regimen). This review will concentrate on studies EFC2961 and EFC2962.

2. MAJOR STATISTICAL ISSUES

“In some instances an adjustment for the influence of covariates or for subgroup effects is an integral part of the analysis plan and hence, should be set out in the protocol. Pre-study deliberations should identify those covariates and factors expected to have an important influence on the primary variable(s), and should consider how to account for these in the analysis in order to improve precision and to compensate for any lack of balance between treatment groups. When the potential value of an adjustment is in doubt, it is often advisable to nominate the unadjusted analysis as one for primary attention, the adjusted analysis being supportive.”

*ICH/FDA Guideline (Draft 2C, 11/96),
Statistical Principles for Clinical Trials*

The following are the major statistical issues:

- For these studies, the sponsor failed to demonstrate a survival benefit for the treatment based upon the protocol specified primary survival analysis (the log-rank test, a p-value of 0.1349 for study EFC2962 and a p-value of 0.5815 for study EFC2961). There were many secondary survival analyses. Some retrospectively investigated baseline factors -

such as, prior radiotherapy, LDH, prior surgery for primary site, prior surgery for metastases, post-study chemotherapy, post-study oxaliplatin, post-study CPT-11 and post-study CPT-11 and/or oxaliplatin, post-study surgery and CEA at baseline. Study objectives and associated statistical analyses should be essentially based on protocol specified study designs. Results based on retrospective adjustment may be biased and not robust. There was no consistency between studies on covariates with low p-values.

- The purpose for adjustments and multiple analyses was to claim a significant survival difference favoring the oxaliplatin arm after the primary survival analyses could not conclude any survival difference. Therefore, the type I error will be inflated.
- Different category defining cutoffs were used for age, WHO performance status at baseline and number of organs involved than specified in the statistical analysis plan. The latter two variables were included in the final Cox forward stepwise regression model. Also, changes were made to how some variables were categorized in different analyses.
- One analysis - disproportionately between the treatment and control groups - redefined a patient's survival time and their censoring indicator. Forty-seven (out of 210) patients in the control group and fifteen (out of 210) patients in the treatment group had their survival time lowered. Another analysis disproportionately (47 vs. 15) removed better (longer surviving) patients from the analysis.

3. BRIEF DESCRIPTION OF STUDIES

Study EPC2962

Study EFC2962 was a phase III, randomized, multicenter, controlled trial comparing the efficacy and safety of treatment with the combination of oxaliplatin and 5-FU + FA to treatment with 5-FU + FA alone in patients with advanced colorectal carcinoma.

According to the sponsor (vol. 1.227 page 1) *“This study forms the primary basis for the approval of oxaliplatin in the first line treatment of patients with advanced colorectal carcinoma in combination with 5-FU/FA based chemotherapy.”* Those patients in the treatment arm received every two weeks 85 mg/m² of oxaliplatin (2-hour infusion) plus 200 mg/m² of FA (2-hour infusion) followed by 400 mg/m² of 5-FU (bolus) and 600 mg/m² of 5-FU (22-hour infusion). Except for the infusion of oxaliplatin, the schedule is the same for patients in the control arm.

Tumor responses were evaluated every four cycles (eight weeks). The planned sample size was chosen to provide 80% power and a Type I error probability of 0.05 using a two-sided test, assuming a median progression free survival of 7 months in the control arm and 10 months in the oxaliplatin arm. To satisfy those assumptions, 123 progressors were required in each arm. Based on this and an expected recruitment rate of 137 patients per year, about 200 eligible

patients were needed per arm. The protocol specified that follow-up would not continue more than 35 months after the first patient was enrolled. Assignment to treatment was centrally done using a minimization technique with stratification by center, performance status (0, 1 versus 2), and number of metastatic sites involved (1 versus >1). Thirty-five centers enrolled 420 patients into the study.

The primary endpoint is progression free survival (PFS). Secondary endpoints were objective response rate (ORR), quality of life (QoL), overall survival (OS) and tolerability.

There were two planned interim analyses on the response rate. The first interim analysis applied a stopping rule after the first 41 evaluable patients in the oxaliplatin arm. If 7 or fewer of the 41 patients were objective responders, then the trial was to stop. The occurrence of 7 or fewer responders would reject at the 0.05 level the null hypothesis that the true response rate was at least 30%.

The second interim analysis required testing the null hypothesis of equal response rates in the two arms after 100 patients in each were evaluated for response. Equality of the response rates was tested at the 0.005 alpha level. Using an O'Brien-Fleming adjustment for maintaining an overall Type I error probability of 0.05, the final analysis of response rate was done at the 0.048 level.

Study EPC2961

Study EPC2961 was a phase III, randomized, multicenter, controlled trial comparing the efficacy and safety of treatment with the combination of oxaliplatin and 5-FU + FA to treatment with 5-FU + FA alone.

Those patients in the treatment arm received every three weeks 125 mg/m² of oxaliplatin (6-hour infusion) followed by a 300 mg/m² chronomodulated infusion of FA and a 700 mg/m² chronomodulated infusion of 5-FU. Except for the infusion of oxaliplatin, the schedule is the same for patients in the control arm.

Assignment to treatment was centrally done, stratifying by institution. Fourteen centers enrolled 200 patients into the study. The planned sample size was chosen to provide 80% power and a Type I error probability of 0.05 using a two-sided test, assuming a 30% ORR in the control arm and a 50% ORR in the oxaliplatin arm. Tumor responses were evaluated every three cycles (nine weeks).

The primary endpoint is objective response rate. Secondary endpoints were progression-free survival, overall survival (OS) and tolerability.

The design included a stopping rule and two interim analyses. One responder for each treatment arm among the first nine patients was required for the trial to continue. The first

interim analysis was done after 32 patients in each arm were evaluated (two-sided alpha =0.0005) and the second interim analysis was done after 64 patients in each arm were evaluated (two-sided alpha=0.014). The final analysis of ORR was done at a 0.045 significance level.

4. SUMMARY OF EFFICACY ANALYSES

For each study, the efficacy analysis was based on the intent-to-treat population (all patients as randomized). Statistical tests were two-tailed with alpha = 0.05, except for the interim analyses. Estimates of ORR with 95% confidence intervals based on the binomial distribution were calculated. Confirmed and best response rates were analyzed for each method assessment – Investigator and Expert/Final – using Pearson’s chi-square test.

For each study, median values for time-to-event endpoints were determined using Kaplan-Meier methods and 95% confidence intervals for these medians were determined using Efron’s simple reflected interval. The log-rank test and Wilcoxon rank sum test were used in the analyses of the survival endpoints. The log-rank test was used in the primary analyses and the Wilcoxon test was used for descriptive purposes. Exploratory analyses using Cox proportional hazard regression models were also conducted.

For both studies, further analyses investigated the impact of prognostic factors on the overall survival comparison and the validity of the underlying proportional hazard rate assumption of the log-rank test. Cox and Weibull regression models were used.

For study EFC2962, a self-administered EORTC QLQ-C30 (version 2.0) was used to assess quality of life. This is a cancer-specific instrument that measures functional domains, global health status and symptoms. QoL was assessed at baseline, after every four cycles and at the discontinuation from the study. The Wilcoxon signed-rank test was used for within treatment comparisons and the Mann-Whitney-Wilcoxon test for between treatment comparisons. Because there were 15 different scales in the QLQ-C30, the significance level for each comparison was 0.0033 (0.05/15).

4.1 SURVIVAL ANALYSES

The following table shows the sponsor’s survival results based on unadjusted (primary) and adjusted (supportive) analyses for these two studies.

Table 1. Summary of Survival Analyses results

	(unadjusted log-rank test)	(Cox model)
--	-----------------------------------	--------------------

Study	Primary	Exploratory
EFC2962	0.1349	0.0100 ¹
EFC2961	0.5815	0.4913 ¹

¹ p-value is unadjusted

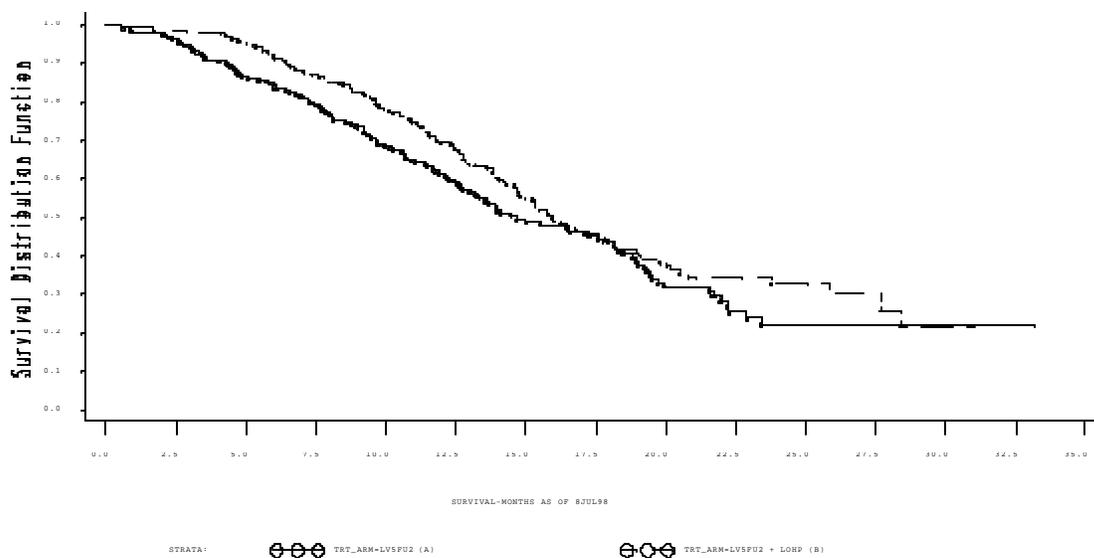
The sponsor made an effort to look into reasons why an oxaliplatin arm survival advantage was not demonstrated. However, because of those results listed in table 1, this reviewer believes that the evidence is not sufficient to demonstrate a survival advantage for the oxaliplatin arms.

4.1.1 Primary Survival Analyses.

The following is an excerpt of an FDA response during an October 8, 1998 meeting “*For approval of a first-line indication, it is necessary to demonstrate an advantage in overall survival.*”

For study EFC2962 (from vol. 1.1 pages 273-274), the median OS was 15.9 months (with a 95% confidence interval of the median of 14.7 months to 18.2 months) for the oxaliplatin arm compared to 14.7 months (with a 95% confidence interval of the median of 13.0 months to 18.2 months) for the control arm. The Kaplan-Meier curves are given in figure 1 below. The curve for the oxaliplatin arm is almost entirely above the curve for the control arm. The log-rank test gives a p-value of 0.1349. The Wilcoxon sum rank test gives a p-value of 0.0503. Ninety of 210 values (43%) in the oxaliplatin arm were censored and 79 of 210 values (38%) in the control arm were censored.

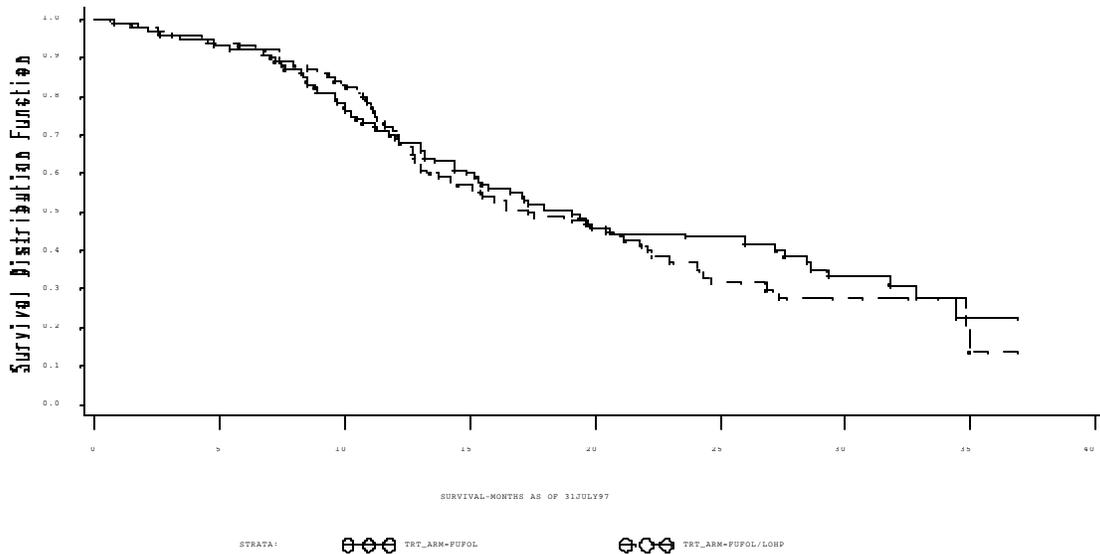
Figure 1. Kaplan-Meier Survival Curves for Study EFC2962



For study EFC2961 (from vol.1.1 page 288-289), the median OS was 17.4 months (with a

95% confidence interval of the median of 13.8 months to 22.0 months) for the oxaliplatin arm compared to 19.2 months (with a 95% confidence interval of the median of 15.2 months to 26.7 months) for the control arm. The Kaplan-Meier curves are given in figure 2 below. The curves cross twice with the curve for the control arm more often on top. The p-value associated with the log-rank test is 0.5815. The p-value associated with the Wilcoxon sum rank test is 0.7907. Thirty-three of 100 values (33%) in the oxaliplatin arm were censored and 36 of 100 values (36%) in the control arm were censored.

Figure 2. Kaplan-Meier Survival Curves for Study EFC2961



4.1.2 Sponsor’s Exploratory Survival Analyses I.

Study EFC2962

The primary survival analysis did not result in a statistically significant difference between these treatment arms. The sponsor performed exploratory analyses on survival involving potential prognostic factors. Most of these prognostic factors were pre-specified in a statistical analysis plan submitted to the FDA on February 19, 1998 - some were not. For many pre-specified prognostic factors the category defining cutoffs used in the analyses are different from what were pre-specified in the statistical analysis plan. The variables included in the final model of the sponsor’s forward stepwise Cox regression model for survival were WHO performance status at baseline, baseline alkaline phosphatase (NCI grade), the number of organs involved and treatment arm. The results are given in Table 2 below (vol. 1.236 pages 245-246). The p-values were based on Wald chi-square tests. Thirty-three patients were excluded from this analysis.

Table 2. Final Results of the Forward Stepwise Cox Regression Model

Factor	Risk ratio	95% C.I.	P-value
Treatment arm	0.70	0.54-0.92	0.0100
WHO performance status	2.31	1.60-3.43	0.0001
Baseline alkaline phosphatase	2.40	1.64-3.50	0.0001
Number of involved organs	1.49	1.14-1.95	0.0038

In another approach (vol. 1.236 pages 246-250), important prognostic factors were identified by examining the product of two standard normal statistics - Z_d and Z_i . Z_d is a test statistic measuring the disparity of the prognostic factor between the treatment arms at baseline and Z_i is a test statistic measuring the association between the prognostic factor and survival. The factor with the greatest Z-product was baseline alkaline phosphatase. Twenty patients in the control group and twenty-nine patients in the oxaliplatin group had baseline alkaline phosphatase grades ≥ 2 . When baseline alkaline phosphatase is included in the Cox regression model with treatment arm, the estimated risk ratio for the treatment arm (oxaliplatin/control) was 0.76 (95% confidence interval of (0.59, 0.98)), with an associated p-value of 0.032 (Wald's chi-square test).

The sponsor argues that since patients were allowed to receive subsequent therapies including those in the other treatment arm, there may be a violation of the proportional hazard assumption that underlies the log-rank test. A Cox regression model with a treatment-by-time interaction term was used to assess the proportional hazards assumption (vol. 1.236 pages 250-251). The associated p-value of 0.086 was regarded as significant at the 0.10 level. The sponsor states the following (vol. 1.236 page 252) “*The above findings suggest that a model which is not based on the proportional hazards assumption may better represent the observed survival functions in EFC2962.*”

For each treatment group and the combined group, the sponsor fit a two-parameter Weibull model to log-survival (vol. 1.236 pages 252-253). A Wald test for the equality of Weibull models for the treatment groups yielded a chi-square value of 6.12 (with two degrees of freedom) and a p-value of 0.047. The sponsor concluded that this indicates a significant benefit of the oxaliplatin treatment arm for overall survival (vol. 1.236 page 256).

Reviewer’s Comments:

- Due to the exploratory nature of these Cox regression analyses, interpretation of their results (p-values) should be with caution.
- A Cox proportional hazards model is still fit despite the sponsor’s conclusion (vol. 1.236 page 252) “... *that a model which is not based on the proportional hazards assumption may better represent the observed survival functions in EFC2962.*” In addition to the sponsor’s analysis involving a time by treatment interaction, when time is replaced by log(time) in the interaction, the associated p-value is 0.0389. These analyses

on the proportional hazards assumption suggest that the hazard rate ratio may be decreasing over time. The hazard rates cross at 15.95 months (14.99 months) based on the sponsor's analysis (log(time) analysis).

- From this reviewer's analysis, only two patients (due to missing values for prognostic factors) - not thirty-three patients - should have been excluded from the final Cox regression model (through the stepwise procedure). In any case, the p-values are fairly similar.
- Prognostic factors on overall survival not specified in the statistical analysis plan were investigated. These include prior radiotherapy, LDH, prior surgery for primary site, prior surgery for metastases and CEA at baseline. These factors were not included in the final Cox regression model and their exclusion would not have changed the final model.
- Different category defining cutoffs were used for age, WHO performance status at baseline and number of organs involved than specified in the statistical analysis plan. The latter two variables were included in the final Cox forward stepwise regression model. When the cutoffs in the statistical analysis plan are used, the results are similar.
- The sponsor's Weibull analysis is difficult to interpret, since the test (test statistic) used does not test to detect the desired alternative hypothesis. In this analysis, the simultaneous equality (between groups) of both parameters (scale and shape) is being tested. The alternative hypothesis spans many possibilities: the survival distributions may be ordered - for example, a stochastic ordering or hazard rate ordering - or there may be no ordering whatsoever. Here, the estimated survival functions cross (at 29.38 months with a 16.5% survival probability) and the hazard rate functions cross (at 15.97 months). To test for an ordering, the maximum likelihood estimates (m.l.e.'s) based on the ordering would replace the unrestricted m.l.e.'s in computing the value of the test statistic. The underlying distribution under the equality assumption will no longer be a chi-square distribution. The eventual p-value will change, quite possibly increase.

Study EFC2961

The sponsor performed exploratory analyses on survival involving potential prognostic factors. A Cox regression model with a treatment-by-time interaction term was used to assess the proportional hazards assumption that underlies the log-rank test. The associated p-value is 0.4268 (Appendix 6.9.2 vol. 1.239 page 133). For each treatment group and the combined group, the sponsor fit a two-parameter Weibull model to log-survival. A Wald test for the equality of Weibull models for the treatment groups yielded a chi-square value of 0.73 (with two degrees of freedom) and a p-value of 0.694 (Appendix 6.10.2 vol. 1.239 page 139-143).

When baseline alkaline phosphatase is the sole factor in the Cox regression model for survival, the p-value is 0.0789 (Wald's chi-square test; vol. 1.239 page 202).

Reviewer's Comments:

- These Cox and Weibull regression analyses are exploratory and results are consistent with those based on unadjusted analysis.
- For study EFC2961, an association between baseline alkaline phosphatase and overall survival was not demonstrated (p-value > 0.05).

4.1.3 Sponsor's Exploratory Survival Analyses II.

Study EFC2962

The sponsor performed two additional log-rank tests that made adjustments for patients receiving post-study oxaliplatin. These analyses were motivated by the log-rank test not demonstrating a survival advantage for the oxaliplatin arm and the results of two Cox regressions on survival involving many prognostic factors.

Results of a Cox regression analysis on survival (vol. 1.1 page 279) are given in Table 3. The p-values are based on Likelihood-Ratio Chi-square tests.

Table 3. Cox Regression on Survival

Prognostic Factor	p-value	Hazard ratio
Treatment	0.0170	1.19
Gender	0.4702	
Age	0.2723	
Performance status at randomization	0.0118	0.74
Disease stage	0.3267	
Disease localization	0.1862	
Liver metastases	0.7073	
Number of organs involved	0.0007	1.34
Prior Radiotherapy	0.7417	
Prior Adjuvant Chemotherapy	0.5688	
SGOT (NCI Grade)	0.8653	
SGPT (NCI Grade)	0.8387	
Alkaline Phosphatase (NCI Grade)	0.0103 ¹	
LDH (Actual Laboratory Values)	0.0010 ¹	
Creatinine (NCI Grade)	0.6779	
Post-study Chemotherapy (any)	0.0009	1.28

¹ Since this variable was not a binary variable, no hazard ratio is given.

Based on the p-value of 0.0009 for post-study chemotherapy and the availability of second-line therapies, the sponsor believed that (vol. 1.1 page 280) “*it was important to carefully assess the full impact of post-study chemotherapy on survival.*” Table 4 below gives the distribution of patients by treatment and post-study chemotherapy (vol. 1.1 page 280).

Table 4. Distribution of Patients by Treatment and Post-Study Therapy

PS Therapy	Control	Treatment
Oxaliplatin	47 (22%)	15 (7%)
CPT-11	38 (18%)	55 (26%)
Oxaliplatin and/or CPT-11	69 (33%)	64 (30%)
Chemotherapy	96 (46%)	86 (41%)

When post-study oxaliplatin therapy, post-study CPT-11 therapy and post-study oxaliplatin and/or CPT-11 were included in a Cox regression model along with post-study chemotherapy (any), post-study oxaliplatin was deemed “statistically significant” (p-value = 0.0268) and post-study CPT-11 was deemed “borderline significant” (p-value=0.0664). Results of this Cox regression analysis on survival are given in Table 5 below (vol. 1.1 page 281). The p-values are based on Likelihood-Ratio chi-square tests.

Table 5. Cox Regression on Survival

Prognostic Factor	p-value	Hazard ratio
--------------------------	----------------	---------------------

Treatment	0.0063	1.23
Gender	0.3570	
Age	0.1765	
Performance status at randomization	0.0160	0.75
Disease stage	0.5870	
Disease localization	0.2799	
Liver metastases	0.8276	
Number of organs involved	0.0003	1.37
Prior Radiotherapy	0.6509	
Prior Adjuvant Chemotherapy	0.7238	
SGOT (NCI Grade)	0.8072	
SGPT (NCI Grade)	0.7519	
Alkaline Phosphatase (NCI Grade)	0.0163 ¹	
LDH (Actual Laboratory Values)	0.0012 ¹	
Creatinine (NCI Grade)	0.8310	
Post-study Chemotherapy (any)	0.9223	
Post-study Oxaliplatin	0.0268	1.62
Post-study CPT-11	0.0664	
Post-study Oxaliplatin and/or CPT-11	0.6064	

¹ Since this variable was not a binary variable, no hazard ratio is given.

Results of this Cox regression led the sponsor to perform two additional log-rank tests – one altering the survival time and censoring status for patients that received post-study oxaliplatin and the other entirely removing those patients that received post-study oxaliplatin from the analyses.

Reviewer’s Comments:

- Non pre-specified covariates (i.e. prior radiotherapy, LDH, post-study chemotherapy, post-study oxaliplatin, post-study CPT-11 and post-study CPT-11 and/or oxaliplatin) were included in these Cox regression models.
- The results from using “post-study” covariates are difficult to interpret. Patients were coded as ‘1’ if the post-study characteristic (post-study oxaliplatin, etc.) was satisfied and as ‘0’ otherwise (whether or not the patient made it to “post-study”). The group of patients who received any (or a particular) post-study therapy is a subgroup of all post-study patients. Thus, any apparent post-study therapy effect on survival may reflect the relationship between surviving to post-study and overall survival. See the note following table 6.
- Here, the hazard rate ratios for many factors (including treatment) are incorrect due to improper coding. The hazard rates for treatment should be the square of what is listed in tables 3 and 5.

Two approaches studying the impact of post-study oxaliplatin therapy on survival were undertaken. In the first approach, survival time was specified as the time from the date of randomization until the date of death from any cause for patients who did not receive oxaliplatin post-study. For patients alive as of 08 July 1998 but who did not receive oxaliplatin post-study, the time from randomization to the date of last follow-up was used as their survival time and the observation was considered to be right-censored for purposes of these analyses. For patients receiving oxaliplatin post-study, survival was specified as the time from the date of randomization until the date off-study with the observation being considered as right censored. The sponsor recognizes that a limitation of this analysis is that it violates the underlying statistical assumption of independence between the time-to-event variable and the censoring mechanism.

With this first approach (vol. 1.1 page 282), the log-rank test showed a difference in survival with a p-value = 0.0331 in favor of oxaliplatin plus 5-FU+FA therapy. The Wilcoxon test gives a p-value=0.0184.

The second approach excludes those 62 patients treated with oxaliplatin post-study from the analysis. The sponsor recognizes that the retrospective exclusion of a subset of patients may introduce an imbalance between the treatment arms with respect to other important baseline characteristics.

With this second approach (vol. 1.1 page 283), the log-rank test showed a difference in survival with a p-value=0.0124 in favor of oxaliplatin plus 5-FU+FA therapy. The Wilcoxon test gives a p-value = 0.0052.

According to the sponsor (vol. 1.1 page 284): *“These exploratory analyses have shown that secondary chemotherapy potentially increases overall survival. The fact that nearly 50% of the patients in each treatment arm received post-study chemotherapy likely reduced the sensitivity of the log-rank test in detecting a survival difference between two arms. Unfortunately, effective secondary therapies became available during the conduct of EPC2962, after the log-rank test had been specified in the protocol. Despite this limitation, data from EPC2962 demonstrate that there is a clear benefit with the combination of oxaliplatin and 5-FU+FA in terms of reduced mortality.”*

Reviewer’s Comments:

- In these two post hoc log-rank analyses, patients with better survival times were disproportionately censored or removed among the two groups. This appears to be why the p-values for the “adjusted” log-rank analyses were smaller than the p-value from the log-rank test. Post-study oxaliplatin was not randomly assigned to patients. An imbalance of 47 patients in the control group and 15 patients in the oxaliplatin group received oxaliplatin post-study. The group of patients that made it to “post-study” appear to have better survival times than those who did not survive to “post-study.” See the note following table 6.

Log-rank analyses which apply the sponsor’s post-study oxaliplatin log-rank test approaches were applied individually to post-study CPT-11 (alone), post-study oxaliplatin and/or CPT-11 and post-study chemotherapy (any). Results are given in the table 6 below. This table gives the p-values (Wald’s test), the hazard rate ratio and corresponding 95% C.I.’s (Cox proportional hazards model) and the Kaplan-Meier medians. When an “adjustment” is made according to a post-study therapy (therapies) other than oxaliplatin, the resulting p-value is greater than 0.05.

Table 6. Log-Rank Analyses

	Log-rank P-value	Hazard Rate Ratio	95% C.I.	Control Median	Treatment Median
Unadjusted Analysis	0.1349	1.208	(0.94, 1.55)	14.7	15.9
Approach One: Censoring According To Post Study Therapy					
Oxaliplatin (only)	0.0331	1.331	(1.02, 1.73)	14.1	15.8
CPT-11 (only)	0.1161	1.244	(0.95, 1.63)	14.0	15.9
Oxaliplatin & CPT-11	0.0611	1.316	(0.99, 1.76)	13.7	15.9
Chemotherapy (any)	0.1787	1.245	(0.90, 1.71)	14.7	15.9
Approach Two: Removing Patients According To Post Study Therapy					
Oxaliplatin (only)	0.0124	1.398	(1.07, 1.82)	13.2	15.8
CPT-11 (only)	0.2342	1.180	(0.90, 1.55)	13.3	15.0
Oxaliplatin & CPT-11	0.0664	1.308	(0.98, 1.75)	12.6	15.2
Chemotherapy (any)	0.1682	1.251	(0.91, 1.72)	12.1	14.8

Note when every patient that received post-study chemotherapy is removed from the analysis the control median is reduced from 14.7 months to 12.1 months and the treatment median is reduced from 15.9 months to 14.8 months.

The sponsor submitted an analysis (vol. 1.236 page 215) entitled “Survival benefit predicted by an improved response in colorectal cancer.” In this analysis the hazard rate ratio (HR) of 0.87 (and a corresponding 95% confidence interval of (0.76,0.98)) was calculated from the response odds ratio (OR; (0.51/0.49)/(0.78/0.22)) of 0.294 and an estimated relative effect of 0.11 by $\log(\text{HR}) = \text{RE}/\log(\text{OR})$ (Buyse and Molenberghs (1998)). Where the relative effect estimate is from a re-analysis of data from 3,898 patients in 28 randomized trials testing various treatments for colorectal cancer (Buyse *et. al.* Submitted).

References

Buyse, M. and Molenberghs, G (1998), “Validation of surrogate endpoints in randomized clinical trial,” *Biometrics* **54** (3)

Buyse, M., Piedbois, P., Carlson, R.W. and Molenberghs, G (1998), “Is tumor response a valid surrogate for survival in advanced colorectal cancer?” Submitted for publication.

Reviewer Comment:

- Responder analyses is unacceptable for describing or analyzing other characteristics – for example, overall survival. Besides that, extrapolating from previous results relating OR and HR from 28 non-oxaliplatin trials to a controlled trial involving oxaliplatin is very risky. No rationale was given to why oxaliplatin should have a similar toxicity profile as those other “various treatments.”

Study EFC2961

Cox regressions involving many prognostic factors were performed on survival. Table 7 below gives the results of a Cox regression analysis on survival. The p-values are based on Likelihood-Ratio chi-square tests (vol. 1.1 page 292).

Table 7. Cox Regression on Survival

Prognostic Factor	p-value	Hazard ratio
-------------------	---------	--------------

Treatment	0.6278	
Gender	0.0780	
Age	0.8481	
Performance status at randomization	0.2299	
Disease stage	0.7152	
Disease localization	0.1382	
Liver metastases	0.4688	
Number of organs involved	0.0777	
Prior Radiotherapy	0.1326	
Prior Chemotherapy	0.2595	
SGOT (Actual Laboratory Values)	0.0027 ¹	
SGPT (Actual Laboratory Values)	0.0352 ¹	
Alkaline Phosphatase (NCI Grade)	0.9949	
LDH (Actual Laboratory Values)	0.9652	
Creatinine (Actual Laboratory Values)	0.1266	
Post-study Chemotherapy (any) and/or surgery	<0.0001	2.07

¹ Since this variable was not a binary variable, no hazard ratio is given.

Post-study chemotherapy (any) and/or surgery was identified by the sponsor as a highly statistically significant factor for patient overall survival. The sponsor believed that (vol. 1.1 page 293) *“Because of availability of second line therapies in this disease, including CPT-11 and oxaliplatin, it was important to carefully assess the full impact of post study chemotherapy and/or surgery on survival.”* Table 8 below gives the distribution of patients by treatment and post-study chemotherapy and/or surgery (vol. 1.1 page 293).

Table 8. Distribution of Patients by Treatment and Post-Study Therapy

PS Therapy	Control	Treatment
Oxaliplatin	64	39
CPT-11	26	23
Surgery	32	33
Chemotherapy (any) and/or Surgery	81	78

Post-study oxaliplatin therapy, post-study CPT-11 therapy and post-study surgery were included in a Cox regression model. Results of this Cox regression analysis on survival are given in Table 9 below (vol. 1.1 page 294). The p-values are based on Likelihood-Ratio Chi-square tests.

Table 9. Cox Regression on Survival

Prognostic Factor	p-value	Hazard ratio
Treatment	0.4913	
Gender	0.0219	0.75
Age	0.2549	
Performance status at randomization	0.4438	
Disease stage	0.4635	
Disease localization	0.0324	0.75
Liver metastases	0.2441	
Number of organs involved	0.0656	
Prior Radiotherapy	0.0463	1.52
Prior Chemotherapy	0.2040	
SGOT (Actual Laboratory Values)	0.0115 ¹	
SGPT (Actual Laboratory Values)	0.5353	
Alkaline Phosphatase (NCI Grade)	0.9311	
LDH (Actual Laboratory Values)	0.5493	
Creatinine (Actual Laboratory Values)	0.0198 ¹	
Post-study Chemotherapy (any) and/or surgery	0.0355	1.44
Post-study Oxaliplatin	0.1494	
Post-study CPT-11	0.2640	
Post-study Surgery	<0.0001	2.21

¹ Since this variable was not a binary variable, no hazard ratio is given.

Post-study surgery was deemed to have a statistically significant impact on survival. The sponsor states the following (vol. 1.1 page 294): *“The timing of surgery in this study was related to exposure of oxaliplatin. More patients in the experimental arm received surgery following their treatment with oxaliplatin plus 5-FU+FA (see ISE Appendix 4.1). Conversely, more patients in the control arm received surgery following post-study treatment with oxaliplatin. The prolonged survival observed in both arms suggests that the combination of oxaliplatin-based chemotherapy plus surgery may offer additional benefits over chemotherapy alone.”*

Reviewer’s Comments:

- These Cox regression analyses are exploratory and results are consistent with those based on unadjusted analyses.
- This analysis is not valid with regards to conclusions made about post-study surgery (or any post-study therapy). The results from using “post-study” covariates are difficult to interpret. Patients were coded as ‘1’ if the post-study characteristic was satisfied and as ‘0’ otherwise (whether or not the patient made it to “post-study”). The group of patients who received post-study surgery (or a particular therapy) is a subgroup of all post-study patients. Thus, any apparent post-study therapy effect on survival may reflect the

relationship between surviving to post-study and overall survival. A necessity for drawing such conclusions would involve randomizing post-study patients to surgery or no surgery and studying the survival solely of these patients.

- Here, the hazard rate ratios for many factors (including treatment) are incorrect due to improper coding. The hazard rates for treatment should be the square of what is listed in tables 7 and 9.

Other Comments:

- There was no consistency for low p-values among prognostic factors in the Cox regression models between studies EFC2962 and EFC2961 – for example, baseline alkaline phosphatase had rather low p-values for study EFC2962 and rather high p-values for study EFC2961.
- Some covariates (i.e. age, baseline SGOT, baseline SGPT and baseline alkaline phosphatase) used in these Cox analyses had different categorizations for studies EFC2961 and EFC2962.

4.2 ANALYSES OF OTHER ENDPOINTS

4.2.1 Progression Free Survival Analyses

For study EFC2962, the median PFS was 8.1 months (with a 95% confidence interval of the median of 7.1 months to 8.8 months) for the oxaliplatin arm compared to 5.9 months (with a 95% confidence interval of the median of 5.5 months to 6.4 months) for the control arm. The p-value associated with the log-rank test is 0.0003. Sixty of 210 values (29%) in the oxaliplatin arm were censored and 39 of 210 values (19%) in the control arm were censored.

For study EFC2961, the median PFS was 8.3 months (with a 95% confidence interval of the median of 6.7 months to 9.1 months) for the oxaliplatin arm compared to 4.2 months (with a 95% confidence interval of the median of 3.2 months to 6.7 months) for the control arm. The p-value associated with the log-rank test is 0.0455. Twenty of 100 values (20%) in the oxaliplatin arm were censored and nine of 100 values (9%) in the control arm were censored.

Cox regressions involving many prognostic factors were performed on progression-free survival. Table 10 below gives the results of a Cox regression analysis on progression-free survival for study EFC2962 (vol. 1.1 page 278). The p-values are based on Likelihood-Ratio chi-square tests.

Table 10. Cox Regression on Progression Free Survival

Prognostic Factor	p-value	Hazard ratio
Treatment	<0.0001	1.33
Gender	0.4370	
Age	0.2097	
Performance status at randomization	0.8053	
Disease stage	0.6022	
Disease localization	0.7440	
Liver metastases	0.3803	
Number of organs involved	0.0073	1.22
Prior Radiotherapy	0.7205	
Prior Adjuvant Chemotherapy	0.1405	
SGOT (NCI Grade)	0.6294	
SGPT (NCI Grade)	0.4973	
Alkaline Phosphatase (NCI Grade)	0.6707	
LDH (Actual Laboratory Values)	0.2094	
Creatinine (NCI Grade)	0.5712	

Table 11 below (vol. 1.1 page 291) gives the results of a Cox regression analysis on progression-free survival for study EFC2961. The p-values are based on Likelihood-Ratio chi-square tests.

Table 11. Cox Regression on Progression Free Survival

Prognostic Factor	p-value	Hazard ratio
Treatment	0.0175	1.24
Gender	0.1239	
Age	0.7321	
Performance status at randomization	0.4592	
Disease stage	0.7214	
Disease localization	0.3256	
Liver metastases	0.8009	
Number of organs involved	0.1157	
Prior Radiotherapy	0.5569	
Prior Adjuvant Chemotherapy	0.6605	
SGOT (NCI Grade)	0.0025 ¹	
SGPT (NCI Grade)	0.0662 ¹	
Alkaline Phosphatase (NCI Grade)	0.2518	
LDH (Actual Laboratory Values)	0.8594	
Creatinine (NCI Grade)	0.1633	

¹ Since this variable was not a binary variable, no hazard ratio is given.

Reviewer's Comments:

- These Cox regression analyses confirm those results from the unadjusted analyses.
- Here, the hazard rate ratios for treatment are incorrect due to improper coding. The hazard rates for treatment should be the square of what is listed in tables 10 and 11.

4.2.2 Objective Response Rate

For study EFC2962, oxaliplatin in combination with 5-FU/FA produced a confirmed response rate of 49% (103/210; a 95% C.I. of 42.1% to 56.1%) compared with 22% (46/210; a 95% C.I. of 16.5% to 28.2%) for 5-FU/FA alone with no overlap of the 95% confidence intervals. Patients with unavailable radiological scans were included as nonresponders. Best response rates in the oxaliplatin treatment arm were 56% (117/210; a 95% C.I. of 48.7% to 62.6%) compared with 29% (61/210; a 95% C.I. of 23.0% to 35.7%) for 5-FU/FA alone with no overlap of the 95% confidence intervals.

For study EFC2961, oxaliplatin in combination with 5-FU/FA produced a confirmed response rate of 34% (34/100; a 95% C.I. of 24.8% to 44.2%) compared with 12% (12/100; a 95% C.I. of 6.3% to 20.1%) for 5-FU/FA alone with no overlap of the 95% confidence intervals. Patients with unavailable radiological scans were included as nonresponders. Best response rates in the oxaliplatin treatment arm were 53% (53/100; a 95% C.I. of 42.7% to 63.1%) compared with 16% (16/100; a 95% C.I. of 9.4% to 24.7%) for 5-FU/FA alone with no overlap of the 95% confidence intervals.

4.2.3 Quality of Life

Quality of life (QoL) was assessed in study EFC2962 using the self administered EORTC QLQ-C30 (version 2.0), a cancer-specific instrument that measures functional domains (i.e. physical, role, emotional, cognitive, social), global health status, and symptoms (i.e. fatigue, nausea/vomiting, pain, dyspnea, insomnia, appetite loss, constipation, diarrhea). A detailed QoL analysis was not included in the statistical submission.

5. SUMMARY AND CONCLUSIONS

For study EFC2962, the median survival was 15.9 for the oxaliplatin arm compared to 14.7 months for the control arm. The p-value associated with the log-rank test is 0.1349. For study EFC2961, the median survival was 17.4 months for the oxaliplatin arm compared to 19.2 months for the control arm. The p-value associated with the log-rank test is 0.5815.

Table 1 reappears below. This table shows the sponsor’s survival results based on unadjusted (primary) and adjusted (supportive) analyses for these two studies.

Table 1. Summary of Survival Analyses results

	(unadjusted log-rank test)	(Cox model)
Study	Primary	Exploratory
EFC2962	0.1349	0.0100 ¹
EFC2961	0.5815	0.4913 ¹

¹ p-value is unadjusted

Adjusted survival analyses were performed for both studies retrospectively. For study EFC2962 the p-values were < 0.05 and for study EFC2961 the p-values were > 0.05. Due to the exploratory nature of the Cox regression analyses, p-values should be interpreted with caution. Because of those results listed in table 1, this reviewer believes that a survival advantage has not been sufficiently demonstrated in either study EFC2962 or study EFC2961 for the oxaliplatin arm.

Mark D Rothmann, Ph.D.
Mathematical Statistician

Concur: Dr. Chen

Dr. Mahjoob

cc:

Archival NDA #21-063
HFD-150/Ms. Wilson
HFD-150/Dr. Johnson
HFD-150/Dr. Hirschfeld
HFD-710/Dr. Chi
HFD-710/Dr. Mahjoob
HFD-710/Dr. Chen
HFD-710/Dr. Rothmann
HFD-710/Chron

ROTHMANN/2-16-00/MSWD-'c:\fda.pro\NDA_21063\Statistical_Review.doc

This review consists of nineteen pages of text.