CENTER FOR DRUG EVALUATION AND RESEARCH

APPROVAL PACKAGE FOR:

APPLICATION NUMBER

NDA 21-492/S-002

Statistical Review(s)

U.S. Department of Health and Human Services
Food and Drug Administration
Center for Drug Evaluation and Research
Office of Pharmacoepidemiology and Statistical Science
Office of Biostatistics

STATISTICAL REVIEW AND EVALUATION

CLINICAL STUDIES

NDA/Serial Number:	21-492/SE1-002
Drug Name:	Eloxatin (Oxaliplatin) injection
Indication(s):	First-line metastatic colorectal cancer
Applicant:	Sanofi-Synthelabo
Date(s):	Submitted July 11, 2003. PDUFA date: January 11, 2004
Review Priority:	Priority
Biometrics Division:	Biometrics 1
Statistical Reviewer:	Dr. Mark Rothmann
Concurring Reviewers:	Dr. Rajeshwari Sridhara Dr. Kooros Mahjoob
Medical Division:	Division of Oncologic Drug Products
Clinical Team:	Dr. Amna Ibrahim Dr. John Johnson
Project Manager:	Ms. Christy Cottrell

Keywords: Active Control/Superiority, Log-rank test, Survival Analysis

Table of Contents

1. EXECUTIVE SUMMARY

This is a review of the s-NDA 21-492 for the use of the drug oxaliplatin (trade name of Eloxatin) in combination with 5-FU/LV (as a regimen known as FOLFOX-4) for patients in metastatic colorectal cancer.

1.1 Conclusions and Recommendations

The FOLFOX-4 regimen demonstrated a survival advantage over IFL, an approved therapy for first-line metastatic colorectal cancer in study EFC7462,supporting a claim of a survival advantage of FOLFOX-4 over IFL. FOLFOX-4 failed to demonstrate a survival advantage over a regimen of 5-FU/LV in study EFC2962. See the section on statistical issues and findings for further discussion.

1.2 Brief Overview of Clinical Studies

Study EFC7462 began as a randomized, 4-arm study. At that time the Mayo Clinic regimen of bolus 5-FU/LV, the control arm in this study, was considered the standard of care for first-line metastatic colorectal cancer. Three arms, each containing oxaliplatin, were later added. Eventually four arms were removed from the study, leaving an arm of an approved treatment in first-line metastatic colorectal cancer known as IFL (bolus 5-FU/LV with irinotecan), an arm known as FOLFOX-4 (a bolus/continuous infusion combination of 5-FU/LV with oxaliplatin) and an arm known as IROX (a combination of irinotecan and oxaliplatin). Data and results were submitted for this trial based on 795 concurrently randomized patients in the IFL, FOLFOX-4 and IROX arms.

For regulatory purposes, the primary comparison was a survival comparison between FOLFOX-4 and IFL. There was a statistically significant survival difference favoring the FOLFOX-4 arm (p-value < 0.0001).

The 5-FU/LV regimen in FOLFOX-4 is known as the "de Gramont regimen." A treatment consisting of the de Gramont regimen of 5-FU/LV with irinotecan, known as FOLFIRI, is also an approved treatment in first-line metastatic colorectal cancer. FOLFIRI and the de Gramont regimen of 5-FU/LV were in separate arms of study v303. In study v303, investigators chose between the AIO and de Gramont regimens of 5-FU/LV, and then the patient was randomized between inclusion of irinotecan vs. exclusion of irinotecan. There was a statistically significant ($p=0.032$) survival advantage favoring the combined irinotecan "sub-arms" over the combined 5-FU/LV sub-arms. The survival hazard ratio estimate was 0.77 with a corresponding 95% confidence interval of 0.60 to 0.98. The survival comparison between the sub-arms of FOLFIRI and the de Gramont regimen of 5-FU/LV yielded a log-rank p-value of 0.01 (the comparison of the other two sub-arms gave a p-value of 0.84).

Study EFC2962 was a phase 3, randomized, multicenter, controlled trial comparing the efficacy and safety of treatment with a combination of oxaliplatin and 5-FU/LV (FOLFOX-4) to treatment with 5-FU/LV alone (de Gramont regimen) in patients with

advanced colorectal carcinoma. This trial had 210 patients in each arm. The FOLFOX-4 versus de Gramont survival hazard ratio estimate (based on updated data with a December 1, 1998 cutoff date; 298 events) was 0.83 with a corresponding 95% C.I. of (0.66, 1.05).

Study EFC2961 was a randomized phase 3 trial that compared chronomodulated 5-FU/LV with oxaliplatin with chronomodulated 5-FU/LV that had 100 patients in each arm. For this study the 5-FU/LV + oxaliplatin vs. 5-FU/LV survival hazard ratio estimate was 1.10 (favoring the 5-FU/LV alone arm) with a corresponding 95% confidence interval of (0.78, 1.55).

Study EFC7233 was a randomized, phase 2/3 multi-center trial of patients with advanced colorectal cancer consisting of 252 patients. Patients were randomized between two arms – a 5-FU/LV with oxaliplatin arm (known as FUFOX) and a 5-FU/LV alone arm (Mayo Clinic regimen). It is important to note that this is not a pure "add-on" study. The two arms involve quite different regimens of 5-FU/LV and quite different planned total exposure of 5-FU/LV. The planned final survival analysis is at the time of the 198th death. A survival comparison based on what appears to be 188 deaths yields a log-rank p-value of 0.19.

The statistical significance of an across trials test for "additive transitivity" (see section 6.1 in the appendix), based on five trials that compared two arms among 5-FU+LV, 5-FU+LV+irinotecan and 5-FU+LV+oxaliplatin, suggests that at least one of the assumptions made,

(1) that different regimens of the same drug or drug combination are substitutable or interchangeable or
(2) the effects of the therapies and therapeutic combinations are constant across trials,

is incorrect.

Study EFC7462 took place at centers in Canada and the United States. Studies EFC2962 and EFC2961 took place at centers in Europe. Study EFC7233 took place at centers in Germany. Data was provided for studies EFC7462, EFC2962 and EFC2961. A summary report without data was provided for study EFC7233.

For study EFC7462, an exploratory analysis without any p-value adjustment gave a statistically significant larger (present interaction) survival advantage of FOLFOX-4 vs. IFL for women than for men. The FOLFOX-4 vs. IFL survival hazard ratio estimate was 0.45 (a 55% reduction in the instantaneous risk of death) among women and the FOLFOX-4 vs. IFL survival hazard ratio estimate was 0.80 (a 20% reduction in the instantaneous risk of death) among men. For both studies EFC2962 and EFC2961, the estimated survival hazard ratio of 5-FU/LV + oxaliplatin vs. 5-FU/LV was slightly smaller among women than among men.

Also, exploratory analyses suggest an interaction effect on survival between primary site (colon vs. rectum) and treatment arm may have been present for studies EFC2962 and EFC2961 (see section 4.2). No data was submitted (or collected) on the primary site of patients in study EFC7462.

1.3 Statistical Issues and Findings

While the arm of FOLFOX-4 demonstrated a survival advantage over the IFL arm in study EFC7462, no results on a direct comparison of survival between FOLFOX-4 and FOLFIRI (an approved treatment of first-line colorectal cancer that has the same 5-FU/LV regimen as FOLFOX-4) were submitted. In indirect survival comparisons with arms of the de Gramont regimen (see section 1.2), FOLFIRI had a larger (and a statistically significant advantage) estimated survival advantage than FOLFOX-4.

Two other studies, EFC2962 and EFC2961, that were "add-on" studies (treatment arm = control arm + oxaliplatin) failed to demonstrate a survival advantage of 5-FU/LV+oxaliplatin over 5-FU/LV. The estimated survival hazard ratio favored the control arm for study EFC2961.

Study center was a stratification factor for study EFC7233 where the average number of patients per study center is four. This is an open-label study. For an open-label study with a few patients per center, having study center as a stratification factor will lead to treatment assignments that may be easily decipherable by the investigators entering the patients. This, in turn may lead to one arm receiving healthier patients than the other arm. This may be a serious flaw to this trial. Also, this trial was not a pure "add-on" trial

2. INTRODUCTION

2.1 Overview

The sponsor is seeking approval of using oxaliplatin (trade name Eloxatin) in combination with 5-fluorouracil with leucovorin (5-FU/LV) for the indication of first-line metastatic colorectal cancer.

The demonstration of efficacy for those past approvals in first-line metastatic colorectal cancer (a regimen of leucovorin with 5-FU, two regimens of irinotecan with 5-FU, and Xeloda) were based primarily on survival comparisons in randomized phase 3 studies. In Spring 2000, two regimens of irinotecan (trade name Camptosar) in combination with 5-FU/LV known by IFL (or the Saltz regimen) and FOLFIRI (or the Douillard regimen) were approved for first-line metastatic colorectal cancer based on studies that had statistically significant survival advantages favoring the irinotecan containing arm. In study 0038, IFL (bolus 5-FU/LV was compared to the Mayo Clinic regimen (bolus 5-FU/LV). IFL is an administration of a total of 2000 mg/m^2 of 5-FU, a total of 80 mg/m^2 of leucovorin, and a total of 500 mg/m^2 of irinotecan per 42 days, while the Mayo Clinic regimen is an administration of a total of 2125 mg/m^2 of 5-FU and a total of 100 mg/m^2 of leucovorin per 28 days. Study 0038 also included a third arm of irinotecan alone. For

study v303, investigators chose between the AIO (500 mg/m^2 LV over 2 hrs followed immediately by 2300 mg/m^2 i.v. 5-FU over 24 hours on days 1,8,15,22,29 and 36 of each 7-week cycle) and de Gramont regimens of 5-FU/LV, and then the patient was randomized between inclusion of irinotecan (trade name Camptosar) vs. exclusion of irinotecan. The statistical significance in survival favoring including irinotecan was driven by the comparison of FOLFIRI (de Gramont regimen of 5-FU/LV plus irinotecan) to the de Gramont regimen of 5-FU/LV. The labeling for Camptosar includes both the IFL and FOLFIRI regimens for first-line metastatic colorectal cancer.

Findings from two trials (studies EFC 2961 and EFC 2962) in first-line metastatic colorectal cancer involving treatment arms of 5-FU/LV plus oxaliplatin were presented to the Oncology Division Advisory committee ODAC in March 2000. Study EFC 2961 compared chromodulated 5-FU/LV with and without oxaliplatin. For this study, the treatment versus control survival hazard ratio estimate was 1.10 with a corresponding 95% C.I. of (0.78, 1.55). Study EFC 2962 compared FOLFOX-4 (de Gramont regimen of 5-FU/LV plus oxaliplatin) with the de Gramont regimen of 5-FU/LV. For study EFC 2962, the treatment versus control survival hazard ratio estimate (then based on a July 8, 1998 cutoff date; 251 events) was 0.83 with a corresponding 95% C.I. of (0.65, 1.06). Neither study demonstrated a survival advantage for the 5-FU/LV plus oxaliplatin arm using the protocol specified primary survival analysis. When asked whether the analyses persuasively demonstrated a survival advantage, the committee unanimously voted no (12-0).

Eloxatin in combination with 5-FU/LV (specifically the FOLFOX-4 regimen) received accelerated approval in the Summer of 2002 for the treatment of patients with metastatic colorectal cancer whose disease has recurred or progressed during or within 6 months of completion of a first-line therapy with bolus 5-FU/LV and irinotecan (e.g., IFL). The accelerated approval was supported by statistically significant improvements in response rates and time-to-tumor progression over the de Gramont regimen of 5-FU/LV. A third arm in the study was single agent oxaliplatin. This arm did not demonstrate any improvement over the control arm of 5FU/LV.

This review will cover the results of four trials (studies EFC 2961, EFC 2962, EFC 7233 and EFC 7462) in first-line metastatic colorectal cancer that had treatment arms consisting of combinations of 5-FU/LV and oxaliplatin. A summary without data was provided for study EFC 7233. Study EFC 2961 compared chromodulated 5-FU/LV with and without oxaliplatin. Study EFC 2962 compared FOLFOX-4 with the de Gramont regimen of 5-FU/LV. Study EFC 7233 compared FUFOX (a regimen of continuous infusion 5-FU/LV plus oxaliplatin) with the Mayo Clinic regimen of 5-FU/LV. Study EFC 7462 had arms that included FOLFOX-4, IFL and IROX (a combination of irinotecan and oxaliplatin). No study results were submitted that compared FOLFIRI (an approved therapy in first-line metastatic colorectal cancer) and FOLFOX-4 – both regimens consist in part of the de Gramont regimen of 5-FU/LV.

2.2 Data Sources

Data and electronic documents used for this review are located on the network with path "\\CDSESUB1\N21492\S_002" in the EDR. Submissions to this file occurred on the 7-11-2003, 9-11-2003, 11-07-2003, 11-11-2003 and 11-12-2003.

Reference is also made to the statistical review dated 4-11-2000 and the statistical summary dated 3-9-2000 that was provided to the advisory committee.

3. STATISTICAL EVALUATION

This section will present the efficacy results for those trials in first-line metastatic colorectal cancer that had an experimental arm containing 5-FU/LV and also oxaliplatin.

3.1 Evaluation of Efficacy

3.1.1 Study EFC7462

3.1.1.1 Study Design and Endpoints

Study EFC7462 began on 27 October 1998 as a randomized, 4-arm study (arms A, B, C and D as given in the table below). At that time the Mayo Clinic regimen (arm D in this study) of bolus 5-FU/LV was considered the standard of care for first-line metastatic colorectal cancer.

On April 23, 1999 accrual into arm C was stopped due to toxicities and three oxaliplatin containing arms (E, F and G) were added to the trial. During the trial, two regimens of 5-FU/LV with irinotecan (IFL and FOLFIRI) were approved for first-line metastatic colorectal cancer. Due to the (pending) change in the standard of care accrual into arm D was stopped on April 28, 2000. Accrual into arms B and E was also stopped at that time. Between May 20, 1999 and April 25, 2001, 795 patients were randomized to arms A, F and G. Efficacy results, summaries and data were submitted for these patients and these patients only.

On 25 April 2001 patient accrual was temporarily suspended. On 29 June 2001 patient accrual was re-opened with a lower dose of CPT-11 and 5-FU on Arm A. Patients already on Arm A still taking therapy also had a dose reduction. The reduced dose was: 100 mg/m^2 CPT-11 as a 90-min infusion, followed by 20 mg/m^2 LV as a 15-min infusion or IV push, followed by 400 mg/m^2 IV bolus of 5-FU weekly x 4, every 6 weeks. The proposed sample size was increased to 1705 patients in order to provide adequate statistical power to evaluate reduced Arm A.

The patient accrual for Arm G (IROX) was stopped on 15 March 2002. . The patient accrual for Arm A was stopped on 23 April 2002. The study (Arm F) was closed to patient accrual on 19 July 2002.

The randomization was done centrally and was stratified by the following factors during the study period (795 patients):

- ECOG PS: 0, 1 vs. 2
- Prior adjuvant chemotherapy: yes vs. no
- Prior immunotherapy: yes vs. no
- Age <65 vs. ≥65
- Intergroup vs. EPP patients (however, EPP patients were not analyzed for this report).

The treatment arms and schedules for study EFC7462 are provided in the Tables 1 and 2.

Table 1. Study treatments **Study Arm Treatment Name**

Study Arm	**Treatment Name**
A	IFL; Saltz regimen
B	CPT-11 + Mayo bolus 5-FU/LV
C	Wilke; CPT-11 + infusional 5-FU/LV
D	Mayo bolus 5-FU/LV
E	Oxaliplatin + Mayo bolus 5-FU/LV
F	FOLFOX4 regimen
G	IROX, Wasserman regimen

Table 2. Treatment Schedules

Arms	Schedules
Arm A [1]	CPT-11 125 mg/m^2 as a 90-min infusion LV 20 mg/m^2 as a 15-min infusion or IV push 5-FU 500 mg/m^2 IV bolus weekly x 4, every 6 weeks
Arm B	CPT-11 275 mg/m^2 day 1 as a 90-min infusion LV 20 mg/m^2 IV bolus (days 2, 3, 4, 5) 5-FU 400 mg/m^2 by 90-min infusion (days 2, 3, 4, and 5), every 3 weeks
Arm C	CPT-11 80 mg/m^2 as a 90-min infusion LV 500 mg/m^2 as a 2-hour infusion 5-FU 2000 mg/m^2 as a 24 hour infusion weekly x 6, 1 week rest, then repeat every 7 weeks
Arm D	LV 20 mg/m^2 IV bolus and 5-FU 425 mg/m^2 IV bolus days 1 to 5, every 4 weeks x 2, then every 5 weeks thereafter
Arm E [2]	Oxaliplatin 130 mg/m^2 IV infusion over 120 minutes, day 1 LV 20 mg/m^2 daily IV bolus, days 1 to 5 5-FU 320 mg/m^2 daily IV bolus, days 1 to 5, every 3 weeks

Arm F	Oxaliplatin 85 mg/m^2 IV infusion over 120 minutes, day 1 LV 200 mg/m^2 IV infusion over 120 minutes 5-FU 400 mg/m^2 IV bolus then 600 mg/ m^2 IV infusion over 22 hours on days 1 and 2, every 2 weeks
Arm G	Oxaliplatin 85 mg/m^2 IV infusion over 120 minutes, day 1 CPT-11 200 mg/m^2 IV over 30 minutes, day 1, every 3 weeks

[1] On June 29, 2001 the schedule was modified to: (6-week cycle) CPT-11 100 mg/m^2 as a 90-min infusion; LV 20 mg/m^2 as a 15-min infusion or IV push; 5-FU 400 mg/m^2 IV bolus weekly x 4.

[2] Schedule was later modified to: (3-week cycle) Oxaliplatin 100 mg/m2 IV infusion over 120 minutes, day 1; LV 20 mg/m^2 daily IV bolus days 1 to 5; 5-FU 240 mg/m^2 daily IV bolus, days 1 to 5.

It is stated in the submission that the primary objective of study EFC7462 was to compare the time-to-tumor progression in patients who received FOLFOX-4 (arm F) or IROX (arm G), the 2 experimental regimens, to those receiving IFL (arm A; the control regimen). Each comparison was based on a log-rank test with a two-sided 0.025 significance level. It is stated in the submission that the primary analyses for study EFC7462, was planned to be the date when 326 progression events had occurred in Arm A with an interim analysis planned after 163 progression events in Arm A. These analysis stopping rules were later changed to the date of 234 progression events in Arm A for the final analysis and the date of 117 progression events in Arm A for the interim analysis after the reduction in available sample size. To maintain an overall type I error rate of 0.05, the O'Brien-Fleming stopping bounds were used to determine critical values for interim analyses. The submitted final analysis of TTP has 216 progression events in Arm A. It should be noted that this is an open-label study and that IFL was not regarded as a control therapy until midway through the accrual period for which those data and results were submitted.

Disease progression occurred if

- ≥25% increase in tumor measurements if measurable, or
- an increase in tumor size, if evaluable, or
- after partial response, an increase in tumor measurements exceeding 50% of the previously observed reduction constituted progression, or
- the presence of any new lesion at any time.

Time to tumor progression was calculated from the date of randomization to the first date of documented disease progression (regardless of patient status, administration of other treatments, or protocol compliance). Patients that died without radiological evidence of tumor progression were considered to have progressed at the last date of tumor evaluation, unless death occurred in the absence of progression. Patients who died in the absence of progression or who were lost to follow-up prior to having documented evidence of progression had their TTP classified as censored with the date of their last tumor evaluation used as the ending date.

It is stated in this submission that the main secondary objective of study EFC7462 was to compare overall survival between the FOLFOX4 and the IFL arms. Past approvals for first-line metastatic colorectal cancer have been based on survival results. It should be noted that this is an open-label study and that IFL was not regarded as a control therapy until midway through the accrual period for which data and results were given. Overall survival was calculated from the date of study entry to death or last contact (censoring at last contact).

Other secondary objectives for study EFC7462 stated in this submission are to compare the time to tumor progression [between IROX and FOLFOX-4] and to evaluate toxicity, response rate, time to treatment failure, pharmacogenomics, and quality of life across the 3 treatment arms.

Tumor responses were classified as complete responses if all disease disappeared without any new lesions and as partial responses if there was a ≥50% reduction in the sum of the products of the longest perpendicular diameters of all measurable lesions.

Study EFC7462 was conducted in 301 centers across Canada and the United States.

3.1.1.2 Patient Disposition, Demographic and Baseline Characteristics

For study EFC7462, the patient disposition is given in Table 3.

Table 3. Patient disposition for study EFC7462

	IFL	FOLFOX4	IROX
Number randomized	264	267	264
Number not treated	8	8	6
Number receiving any study drug	256	259	258
Number in ITT population	264	267	264
Number in safety population	256	259	258

For study EFC7462, a summary for the reasons for patient discontinuation is given Table 4.

Table 4. Summary of treatment discontinuation by patient – ITT population

Reason for Discontinuation	IFL (N=264)	FOLFOX4 (N=267)	IROX (N=264)
Died on study	10 (3.8)	6 (2.2)	3 (1.1)
Adverse reactions	22 (8.3)	70 (26.2)	51 (19.3)
Disease progression	159 (60.2)	103 (38.6)	141 (53.4)
Refused further treatment	23 (8.7)	25 (9.4)	24 (9.1)
Alternative treatment	4 (1.5)	4 (1.5)	9 (3.4)
Other medical problems	6 (2.3)	7 (2.6)	4 (1.5)
Other	22 (8.3)	35 (13.1)	26 (9.8)
Not reported	18 (6.8)	17 (6.4)	6 (2.3)

For study EFC7462, a summary of the demographic and baseline characteristics is given in Table 5.

Table 5. Demographic and baseline characteristics for study EFC7462 - ITT population

Parameter		IFL (N=264)	FOLFOX4 (N=267)	IROX (N=264)
Age (years)	N	264	267	264
	Mean	59.7	60.4	60.4
	Median	61.0	61.0	61.0
	St. Dev.	11.3	11.3	10.9
	Min	28.0	27.0	29.0
	Max	88.0	88.0	84.0
Age N (%)	<65	164 (62.1)	163 (61.0)	165 (62.5)
	≥65	100 (37.9)	104 (39.0)	99 (37.5)
Sex N (%)	Male	172 (65.2)	157 (58.8)	161 (61.0)
	Female	92 (34.8)	110 (41.2)	103 (39.0)
Race N (%)	Caucasian	226 (85.6)	238 (89.1)	237 (89.8)
	Black	26 (9.8)	13 (4.9)	17 (6.4)
	Other	12 (4.5)	16 (6.0)	10 (3.8)
ECOG N (%)	0,1	252 (95.5)	252 (94.4)	250 (94.7)
	2	12 (4.5)	15 (5.6)	14 (5.3)
Number of involved organs N (%)	1	98 (37.1)	109 (40.8)	104 (39.4)
	2+	162 (61.4)	156 (58.4)	156 (59.1)
	Not reported	4 (1.5)	2 (0.7)	4 (1.5)
Involved organs N (%)	Primary only (local recurrence)	2 (0.8)	2 (0.7)	1 (0.4)
	Liver only	117 (44.3)	105 (39.3)	103 (39.0)
	Liver + other	102 (38.6)	110 (41.2)	108 (40.9)
	Lung only	10 (3.8)	17 (6.4)	14 (5.3)
	Other (including lymph nodes)	29 (11.0)	31 (11.6)	34 (12.9)
	Not reported	4 (1.5)	2 (0.7)	4 (1.5)
Prior radiation N (%)	Yes	4 (1.5)	8 (3.0)	8 (3.0)
	No	260 (98.5)	259 (97.0)	256 (97.0)
Prior surgery N (%)	Yes	209 (79.2)	199 (74.5)	216 (81.8)
	No	55 (20.8)	68 (25.5)	48 (18.2)
Prior adjuvant chemotherapy N (%)	Yes	39 (14.8)	42 (15.7)	40 (15.2)
	No	225 (85.2)	225 (84.3)	224 (84.8)
Prior immunotherapy N (%)	Yes	2 (0.8)	2 (0.7)	2 (0.8)
	No	262 (99.2)	265 (99.3)	262 (99.2)

3.1.1.3 Statistical Methodologies

Time-to-event endpoints were compared based on the log rank test. Kaplan-Meier methodology was used to describe the distributions for time-to-event endpoints. Toxicity and confirmed response rates were compared using chi-squared tests. For secondary endpoints, p-values <0.05 were considered statistically significant. Efficacy endpoints were analyzed based on the intent-to-treat population – all patients as randomized.

3.1.1.4 Results and Conclusions

Overall Survival has been the basis for all previous approvals in first-line metastatic colorectal cancer. The review of this study will focus on overall survival as the primary regulatory efficacy endpoint. Tables 6 and 7 provide a summary of the descriptive and comparative survival results.

Table 6. Descriptive summary of the results for overall survival

Overall Survival	IFL N=264	FOLFOX4 N=267	IROX N=264
Number of deaths n (%)	192 (72.7)	155 (58.1)	175 (66.3)
Number of events at zero	3	0	0
Median survival (months)	14.6	19.4	17.6
95% confidence interval	(12.4-16.7)	(17.9-21.0)	(15.8-19.6)

Table 7. Comparative summary of the results for overall survival

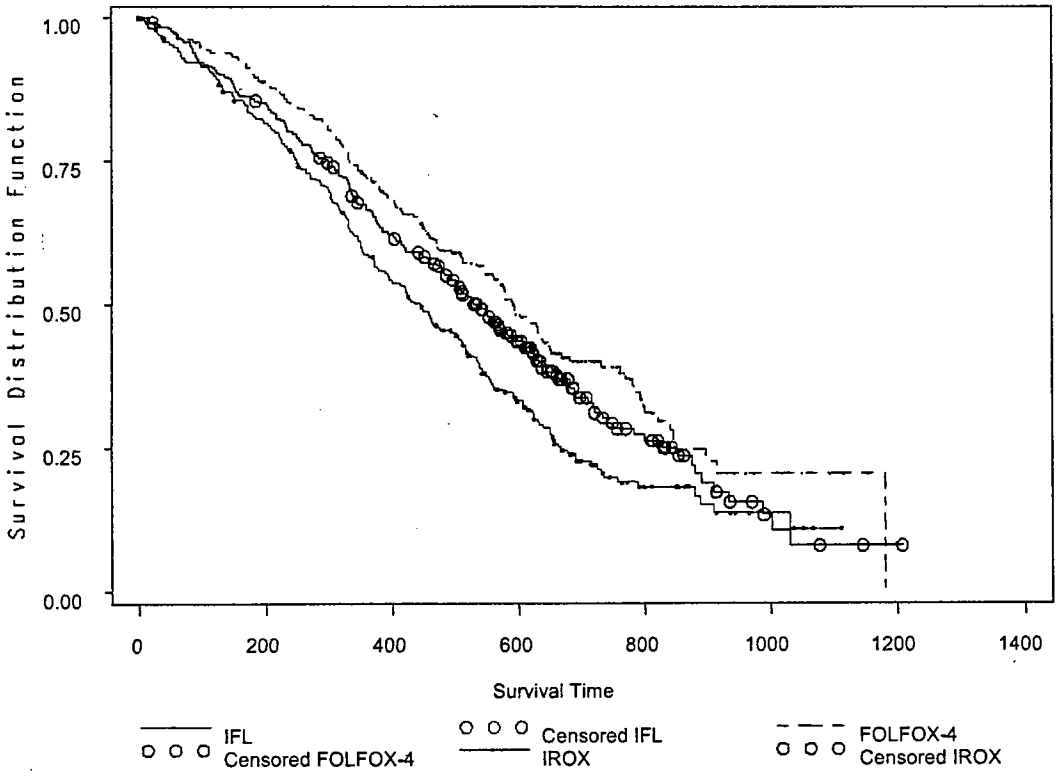
	Hazard ratio 95% C.I.	Log-rank p-value (unadjusted)
FOLFOX-4 vs. IFL	0.65 (0.53, 0.80)	< 0.0001 [1]
IROX vs. IFL	0.79 (0.65, 0.97)	0.0252
FOLFOX-4 vs. IROX [2]	0.83 (0.67, 1.03)	0.094

[1] From this reviewer's calculations the p-value is roughly 0.00007.

[2] Not submitted. - based on this reviewer's calculations.

The FOLFOX-4 arm had a statistically significant superior survival when compared to the IFL arm. The hazard ratio estimate represents a 35% lower instantaneous risk of death for the patients on the FOLFOX-4 arm compared to those patients on the IFL arm. The upper limit of the 95% C.I. for the hazard ratio represents a 20% lower instantaneous risk of death for the patients on the FOLFOX-4 arm compared to those patients on the IFL arm. There was also a "borderline" (adjusting for multiple comparisons) statistically significant survival advantage for the IROX arm versus the IFL arm. The Kaplan-Meier survival functions are given in Figure 1 with time given in days.

Figure 1. Kaplan-Meier survival functions for study EFC7462



Tables 8 and 9 provide a summary of the descriptive and comparative time to progression results.

Table 8. Descriptive summary of the results for time to progression

Time to Progression	IFL N=264	FOLFOX4 N=267	IROX N=264
Number of events n (%)	216 (81.8)	221 (82.8)	236 (66.3)
Number of events at time zero	2	2	8
Number of times censored at zero	17	2	2
Median (days)	209	264	198
95% confidence interval	(184-227)	(238-299)	(178-230)

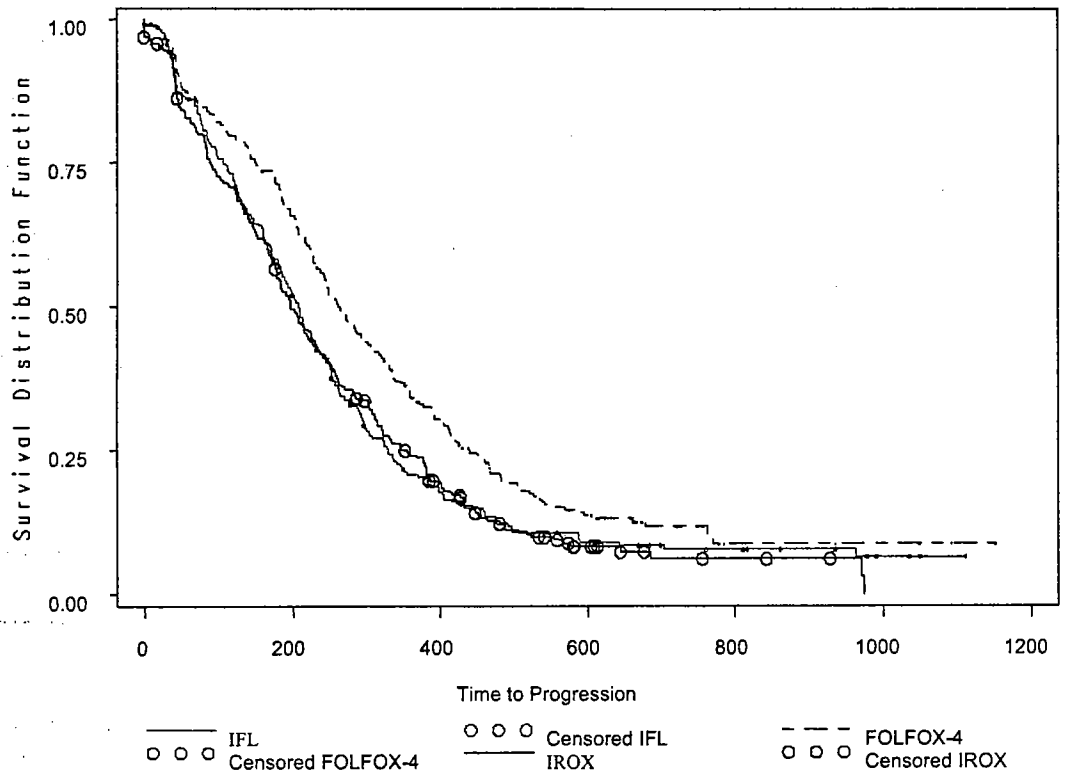
Table 9. Comparative summary of the results for time to progression

	Hazard ratio 95% C.I.	Log-rank p-value (unadjusted)
FOLFOX-4 vs. IFL	0.74 (0.61, 0.89)	0.0014
IROX vs. IFL	1.02 (0.85, 1.23)	0.8295
FOLFOX-4 vs. IROX [1]	0.72 (0.60, 0.87)	0.0005

[1] Not submitted. - based on this reviewer's calculations.

The time to progression Kaplan-Meier functions are given in Figure 2 with time given in days.

Figure 2. Time to progression Kaplan-Meier functions for study EFC7462



A disproportionate number of observations were censored at time zero and a disproportionate number of times were events at time zero. The FOLFOX-4 arm had a statistically significant superior time-to-progression when compared to the IFL arm. The hazard ratio estimate represents a 26% lower instantaneous risk of death for the patients on the FOLFOX-4 arm compared to those patients on the IFL arm. The upper limit of the 95% C.I. for the hazard ratio represents an 11% lower instantaneous risk of death for the patients on the FOLFOX-4 arm compared to those patients on the IFL arm. Unlike overall survival, the estimated (non-statistically significant) time-to-progression hazard ratio favored (slightly) the IFL arm over the IROX arm.

Tables 10 - 13 summarize the results for response rate for both the ITT population and for the subgroup of patients that had measurable disease. Thirteen percent of patients did not have the required tumor measurements to determine a best overall response. Therefore, the results should be interpreted with caution.

Table 10. Summary of best overall response - ITT population

	IFL (N=264) n (%)	FOLFOX4 (N=267) n (%)	IROX (N=264) n (%)
Complete or partial response (95% confidence interval)	76 (28.8) (23.3-34.2)	107 (40.1) (34.2-46.0)	79 (29.9) (24.4-35.4)
Complete response	7 (2.7)	19 (7.1)	10 (3.8)
Partial response	69 (26.1)	88 (33.0)	69 (26.1)
Regression	4 (1.5)	13 (4.9)	12 (4.5)
Stable disease	112 (42.4)	92 (34.5)	108 (40.9)
Progression	34 (12.9)	26 (9.7)	31 (11.7)
Not reported	38 (14.4)	29 (10.9)	34 (12.9)

Table 11. Summary of unadjusted p-values for response rate comparisons - ITT population

	Chi-squared p-value	Fisher's exact test p-value [1]
FOLFOX4 vs. IFL	0.0062	0.0080
IROX vs. IFL	0.7743	0.8485
FOLFOX-4 vs. IROX	--	0.0179

[1] Calculated by this reviewer, not provided by sponsor

Table 12. Confirmed overall response rate - Patients with measurable disease at baseline

	IFL (N=212) n (%)	FOLFOX4 (N=210) n (%)	IROX (N=215) n (%)
Complete or partial response (95% confidence interval)	69 (32.5) (26.2-38.9)	95 (45.2) (38.5-52.0)	74 (34.4) (28.1-40.8)
Complete response	5 (2.4)	13 (6.2)	7 (3.3)
Partial response	64 (30.2)	82 (39.0)	67 (31.2)
Regression	0	3 (1.4)	1 (0.5)
Stable disease	94 (44.3)	75 (35.7)	86 (40.0)
Progression	28 (13.2)	18 (8.6)	25 (11.6)
Not reported	21 (9.9)	19 (9.0)	29 (13.5)

[1] Patients with measurable disease at randomization that became too small to measure during the study were classified as regression and not partial response in this study.

Table 13. Summary of unadjusted p-values for response rate comparisons - patients with measurable disease at baseline

	Chi-squared p-value	Fisher's exact test p-value [1]
FOLFOX4 vs. IFL	0.0075	0.0093
IROX vs. IFL	0.6820	0.7584
FOLFOX-4 vs. IROX	--	0.0291

[1] Calculated by this reviewer, not provided by sponsor

Table 14 provides a summary of the post-study treatments for each arm. Post study chemotherapy was received by 64.1% 72.2%, and 70.5% of the treated patients respectively on the IFL, FOLFOX-4 and IROX arms. Evaluation of the impact of the different distributions of post-study treatment on the differences in overall survival should be done with caution. The relationship between post-study therapy and overall survival is "circular." In order to receive post-study therapy, a patient must first survive to post-study (which may depend on the arm the patient was randomized with the best arm having more patients eligible for post study treatment). Then, the remaining survival time may depend on both the post-study therapy and the initial therapy (and possible "crossover" effects). Twenty-seven more patients (236 vs. 209) in the FOLFOX-4 arm had censored or uncensored survival times of at least six months compare to the IFL arm. Also, thirty-five more patients (215 vs. 180) in the FOLFOX-4 arm had censored or uncensored survival times of at least nine months compare to the IFL arm. In addition, thirty-eight more patients (182 vs. 144) in the FOLFOX-4 arm had censored or uncensored survival times of at least twelve months compare to the IFL arm. The upshot is that there were sufficiently more candidates for both first and second post-study treatment in the FOLFOX-4 arm than in the IFL arm.

Table 14. Any post-study treatment for colorectal cancer - Number (%) of treated patients

	IFL (N=256)	**FOLFOX-4 (N=259)**	**IROX (N=258)**
Any post treatment chemotherapy	164 (64.1)	187 (72.2)	182 (70.5)
5-FU (may include other agents)	99 (38.7)	99 (38.2)	129 (50.0)
CPT-11 (may include other agents)	58 (22.7)	151 (58.3)	80 (31.0)
Oxaliplatin (may include other agents)	60 (23.4)	21 (8.1)	22 (8.5)
Other	103 (40.2)	84 (32.4)	111 (43.0)

3.1.2 Study EFC2962

3.1.2.1 Study Design and Endpoints

Study EFC2962 was a phase III, randomized, multicenter, controlled trial comparing the efficacy and safety of treatment with a combination of oxaliplatin and 5-FU/LV (FOLFOX-4) to treatment with 5-FU/LV alone (de Gramont regimen) in patients with advanced colorectal carcinoma.

Those patients in the treatment arm received on days 1 and 2 every two weeks, 85 mg/m^2 of oxaliplatin (2-hour infusion) plus 200 mg/m^2 of LV (2-hour infusion) followed by 400 mg/m^2 of 5-FU (bolus) and 600 mg/m^2 of 5-FU (22-hour infusion). Except for the infusion of oxaliplatin, the schedule is the same for patients in the control arm.

Assignment to treatment was centrally done using a minimization technique with stratification by center (37 centers), performance status (0, 1 versus 2), and number of metastatic sites involved (1 versus >1). Four hundred twenty patients (210 per arm) were enrolled into this study.

This study was powered for the primary endpoint of progression-free survival (PFS). The planned sample size (of 400) was chosen to provide 80% power (assuming a median progression free survival of 7 months in the control arm and 10 months in the oxaliplatin arm) with a type I error probability of 0.05 using a two-sided test. To satisfy those assumptions, 123 progression events 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. Tumor responses were evaluated every four cycles (eight weeks).

Secondary endpoints are objective response rate (ORR), quality of life (QoL), overall survival (OS) and tolerability.

This study was conducted in 32 centers across Europe and five centers in Israel.

3.1.2.2 Patient Disposition, Demographic and Baseline Characteristics

For study EFC2962, a summary for the reasons for patient disposition is given in the Table 15.

Table 15. Patient Disposition Summary for study EFC2962

	Total	**5-FU/LV**	**5-FU/LV + oxaliplatin**
Randomized	420	210	210
Treated	417	208	209
Eligible	418	209	209
Withdrawn for toxicity	29	7	22
Withdrawn for P.D.	240	137	103
Withdrawn for death	6	3	3
Other reason for discontinuation	96	43	53
Still on-study as of Jan. 31, 1998	49	20	29

For study EFC2962, a summary of the demographic and baseline characteristics is given in Table 16.

Table 16. Summary of Patient Characteristics at Baseline for study EFC2962

Patient Characteristics at Baseline		**5-FU/LV**	**5-FU/LV + oxaliplatin**
Sex M/F		122/88	127/83
Median Age (years)		63	63
WHO PS	0	102	91
	1	88	97
	2	20	22
Colon/Rectum/both		147/61/2	151/59/0
Aster-Coller grade D		139	135
Prior Adjuvant chemotherapy (Yes)		43	42
Number of organs involved	1	84	90
	≥ 2	126	120
Liver involvement (Yes)		173	182
CEA mg/m	≤ 5	37	30
	> 5	165	172
	Missing	8	8

3.1.2.3 Statistical Methodologies

Median values for time-to-event endpoints are determined using Kaplan-Meier methods and 95% confidence intervals for these medians are 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 is used in the primary analyses and the Wilcoxon test is used for descriptive purposes. Exploratory analyses using Cox proportional hazard regression models are also conducted. Only those unadjusted log-rank test results will be discussed in this review. For discussion and results for other analyses refer to the statistical review dated 4-11-2000 or the statistical summary dated 3-9-2000 that was provided to the advisory committee.

3.1.2.4 Results and Conclusions

Table 17 provides descriptive and comparative efficacy results for study EFC2962. A survival difference or advantage was not statistically demonstrated. There was marked statistical significance favoring the 5-FU/LV + oxaliplatin arm in the comparisons of both progression-free survival and response rate.

Table 17. Summary of the Efficacy Results for Study EFC2962 (December 1, 1998 cutoff date for survival)

Endpoint	**5-FU/LV**	**5-FU/LV+Oxaliplatin**
Survival		
Median in months (95% CI)	14.7 (13.0, 17.7)	16.2 (14.7, 18.9)
Number of events	155	143
Log-rank p-value	0.1160	
Hazard Ratio (95% C.I.) [1]	0.83 (0.66, 1.05)	
Progression-free survival		
Median in months (95% CI)	5.9 (5.5, 6.4)	8.1 (7.1, 8.8)
Number of events	171	150
Log-rank p-value	0.0003	
Hazard Ratio (95% C.I.) [1]	0.67 (0.54, 0.83)	
Tumor response		
Response rate [2]	22% (46/210)	49% (103/210)
95% C.I.	(16.5%, 28.2%)	(42.1%, 56.1%)
p-value	< 0.001	

[1] Hazard Ratios are treatment/control

[2] Patients with unavailable radiological scans were counted as nonresponders

The Kaplan-Meier survival functions are given in Figure 3 with time given in days.

Figure 3. Kaplan-Meier survival functions for study EFC2962

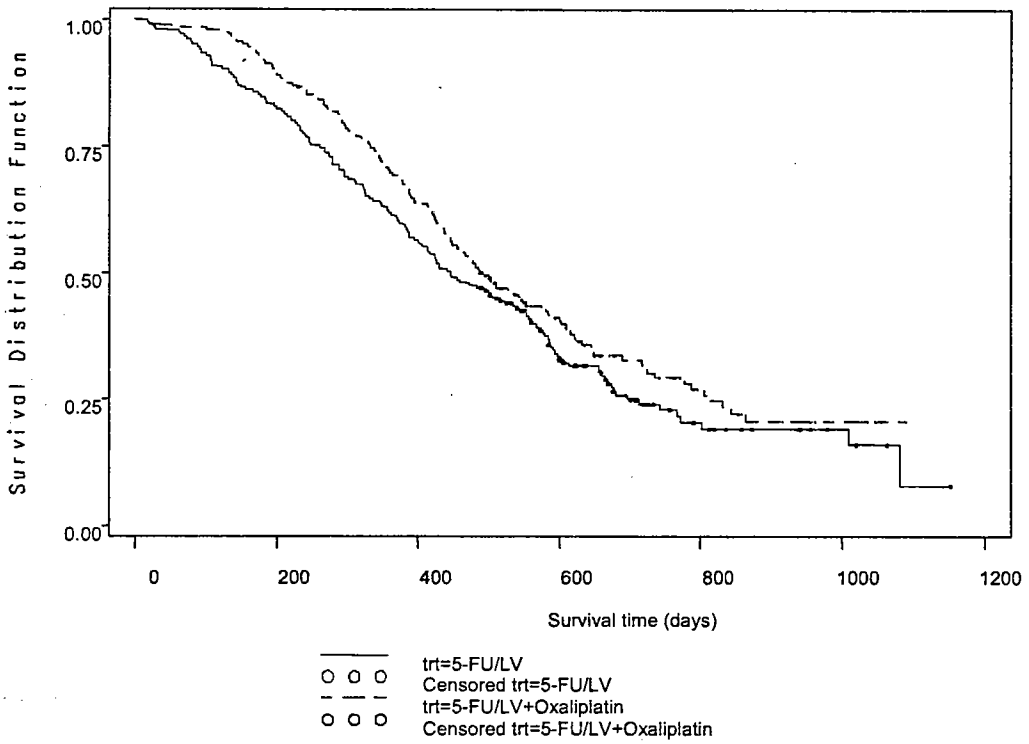


Table 18 below gives the distribution of patients by treatment and post-study chemotherapy.

Table 18. Distribution of Patients by Treatment and Post-Study Therapy for study EFC2962

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%)

3.1.3 Study EFC2961

3.1.3.1 Study Design and Endpoints

Study EFC2961 was a randomized phase 3 trial that compared chronomodulated 5-FU/LV with oxaliplatin with chronomodulated 5-FU/LV that had 100 patients in each arm. This study was conducted in 13 centers in France, one center in Belgium and one center in Italy. The treatment schedules are given in Table 19.

Table 19. Treatment schedules for study EFC2961

Arm	Schedule
Control Arm	5-FU+LV - administered on days 1-5 of every three weeks (1 cycle) as follows: 300 mg/m^2/day LV chronomodulated continuous infusion with 700 mg/m^2/day 5-FU chronomodulated continuous infusion.
Treatment Arm	Oxaliplatin administered on day 1 of the 3-week cycle as a 125 mg/m2 6-hour IV infusion (from 10:00 am to 4 pm) followed by 5-FU+LV - administered on days 1-5 of every three weeks (1 cycle) as follows: 300 mg/m^2/day LV chronomodulated continuous infusion with 700 mg/m^2/day 5-FU chronomodulated continuous infusion.

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

Secondary endpoints are 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 the 0.045 significance level.

3.1.3.2 Patient Disposition, Demographic and Baseline Characteristics

For study EFC2961, a summary for the reasons for patient disposition is given in Table 20.

Table 20. Patient Disposition Summary for study EFC2961

Number of patients	Total	5-FU/LV	5-FU/LV + oxaliplatin
Randomized	200	100	100
Treated	200	100	100
Eligible	197	98	99
Evaluable for Efficacy	180	92	88
Evaluable for Safety	199	100	99
Still on-study as of Sept. 30, 1996	10	3	7

For study EFC2961, a summary of the demographic and baseline characteristics is given in Table 21.

Table 21. Patient Characteristics at Baseline Summary for study EFC2961

Patient Characteristics at Baseline	5-FU/LV	5-FU/LV + oxaliplatin
Sex M/F	64/36	66/34
Median Age (years)	60.7	60.7
WHO PS 0	66	69
1	27	20
2	7	11
Colon/Rectum	77/23	66/34
Aster-Coller grade D		
Prior Adjuvant chemotherapy (Yes)	23	10
Number of organs involved 1	48	50
≥ 2	52	50
CEA mg/m ≤ 10 mg/ml	16	32
> 10 mg/ml	79	65
Missing	5	3

3.1.3.3 Statistical Methodologies

For this study, median values for time-to-event endpoints are determined using Kaplan-Meier methods and 95% confidence intervals for these medians are determined using Efron's simple reflected interval. The log-rank test and Wilcoxon rank sum test are used in the analyses of the survival endpoints. The log-rank test is used in the primary analyses and the Wilcoxon test is used for descriptive purposes. Exploratory analyses using Cox proportional hazard regression models are also conducted. Only those unadjusted log-rank test results will be discussed in this review. For discussion and results for other analyses refer to the statistical review dated 4-11-2000 or the statistical summary dated 3-9-2000 that was provided to the advisory committee.

3.1.3.4 Results and Conclusions

Table 22 provides descriptive and comparative efficacy results for study EFC2961. A survival difference or advantage was not statistically demonstration. There was a marginal statistically significant difference favoring the 5-FU/LV + oxaliplatin arm in the comparison of progression-free survival and a statistically significant difference favoring the 5-FU/LV + oxaliplatin arm in the comparison of response rates.

Table 22. Summary of the Efficacy Results for Study EFC2961

Endpoint	5-FU/LV	5-FU/LV+Oxaliplatin
Survival		
Median in months (95% CI)	19.2 (15.2, 26.7)	17.4 (13.8, 22.0)
Number of events	64	67
Log-rank p-value	0.5815	
Hazard Ratio (95% C.I.) [1]	1.10 (0.78, 1.55)	
Progression-free survival		
Median in months (95% CI)	4.2 (3.2, 6.7)	8.3 (6.7, 9.1)
Number of events	91	80
Log-rank p-value	0.0455	
Hazard Ratio (95% C.I.) [1]	0.74 (0.54, 1.00)	
Tumor response		
Response rate [2]	12%	34%
95% C.I.	(6.3%, 20.1%)	(24.8%, 44.2%)
p-value	< 0.001	

[1] Hazard Ratios are treatment/control
[2] Patients with unavailable radiological scans were counted as nonresponders

The Kaplan-Meier survival functions are given in Figure 4 with time given in days.

Appears This Way
On Original

Figure 4. Kaplan-Meier survival functions for study EFC2961

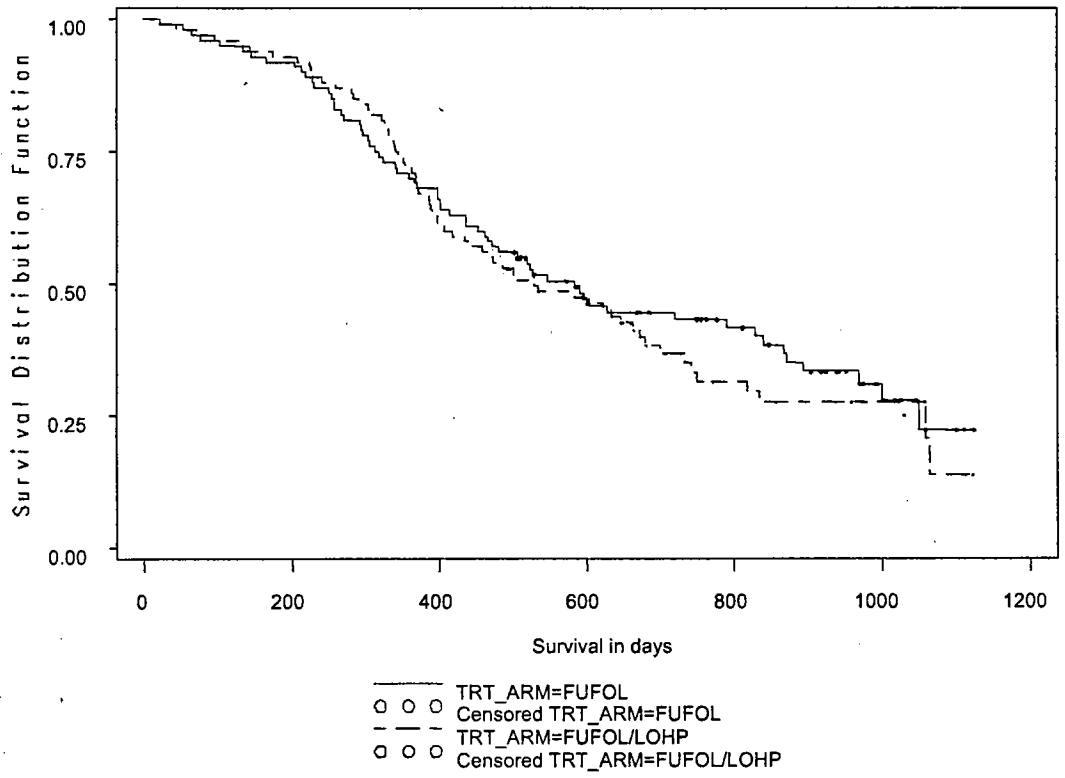


Table 23 gives the distribution of patients by treatment and post-study chemotherapy and/or surgery.

Table 23. 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

3.1.4 Study EFC7233

3.1.4.1 Study Design and Endpoints

Study EFC7233 was a randomized, phase II/III multi-center trial of patients with advanced colorectal cancer. Patients were randomized between two arms – a 5-FU/LV with oxaliplatin arm (known as FUFOX) and a 5-FU/LV alone arm (Mayo Clinic

regimen). The randomization was stratified by study center and ECOG performance status. The study involved 60 centers in Germany. The first patient was entered into the study December 15, 1998. The treatment schedules are given in Table 24. It is important to note that this is not a pure "add-on" study. The two arms involve quite different regimens of 5-FU/LV and quite different planned total exposure of 5-FU/LV.

Table 24. Treatment Schedules for study EFC7233

Arm	Schedule
Control Arm (Mayo Clinic regimen)	5-FU+LV - administered on days 1-5 of every four weeks (1 cycle) as follows: 20 mg/m^2 LV bolus 425 mg/m^2 5-FU bolus (injection within 2 minutes) Duration: three 4-week cycles then every 5 weeks until disease progression.
Treatment Arm (FUFOX)	Oxaliplatin administered on days 1, 8, 15 and 22 of the 5-week cycle as a 50 mg/m^2 2-hour infusion followed by 500 mg/m^2 LV by a 2-hour infusion followed by 2000 mg/m^2 5-FU IV 24-hour infusion. Repeat for four cycles. After which oxaliplatin just given on days 1 and 15 of each cycle.

For the design of study EFC7233, the primary endpoint was time to progression (TTP). The primary analysis for TTP was the log-rank test based on the intent-to-treat population. A sample size of 250 patients was believed to provide better than 95% power at an alternative of a 60% increase in the median TTP. The calculation was based on a one-sided significance level of 0.05, a recruitment period of 12 months, a 15% rate of patients who non-evaluable or lost to follow-up, and a maximum study period of 36 months. It was determined that at least 103 evaluable patients per arm would be needed.

Per protocol amendment 2 (dated July 30, 1999), the primary analysis will be performed for progression-free survival instead of TTP with this analysis occurring at 11 months after the last patient was enrolled.

Secondary endpoints included response rate, overall survival and QOL (EORTC C-30 questionnaire). Patients were to be followed to death or until the time of the 198th death.

No data was provided to the Agency for Study EFC7233. A summary report was provided for Study EFC7233.

3.1.4.2 Patient Disposition, Demographic and Baseline Characteristics

For study EFC7233, a summary for the reasons for patient disposition is given in the Table 25.

Table 25. Patient Disposition for Study EFC7233

Parameter	FUFOX	Mayo
Total randomized	123	129
Dropouts prior to therapy	5	5
Evaluable for safety	**118**	**124**
Did not receive 1 full cycle of therapy	3	0
No malignant disease	1	0
Evaluable for efficacy	**114 (92.7%)**	**124 (96.1%)**

No summary of patient demographics or baseline characteristics was provided for study EFC7233.

3.1.4.3 Statistical Methodologies

According to the study report, the analysis would be based on the intention to treat principle. Based on all of the submitted information, this reviewer believes that five patients enrolled in the study were not included in the intent-to-treat analyses – that the ITT analyses were based on 120 (not 123) patients in the FUFOX arm and 127 (not 129) patients in the Mayo Clinic arm (see section 3.1.4.4 Results and Conclusions for further discussion on this).

A log-rank test with a one-sided 0.05 significance level was the planned analysis for each of time to progression and overall survival. According to the report for study EFC7233: "For the time to tumor progression, the missing observation is replaced by the time between startpoint and death or adverse event."

Inferences in the difference in response rates will be based on a one-sided 95% confidence interval. Only patients with measurable tumor response were included in the analysis. According to the report for study EFC7333: "For the response rate the Last-Observation-Carry-Forward principle (LOCF) will be applied. If a bias in using this principle is detected in the analysis, another appropriate strategy will be applied."

3.1.4.4 Results and Conclusions

Table 26 provides the submitted summary for progression-free survival. The numbers of events were not provided in the summary report for the progression analysis.

Table 26. Progression-free survival summary from the submitted study report for study EFC7233

Category	FUFOX	Mayo
N	123	129
Median PFS (months)	7.8	5.3
P-value (Log-rank test)	0.0001	

In response to a reviewer question about the number of events in each, on December 16, 2003 the sponsor submitted some SAS output of the progression-free survival analysis

via the "CRO responsible for study EFC7233." The output consisted entirely of a Cox regression analysis with treatment arm as the sole factor. The progression-free survival results of 120 patients in the FUFOX arm and 127 patients in the Mayo Clinic regimen arm were used in this analysis. There were 116 events in the FUFOX arm and 125 events in the Mayo Clinic regimen arm. The estimate of the FUFOX vs. Mayo progression-free survival hazard ratio was 0.62 with a corresponding confidence interval of (0.48, 0.80). The two-sided Wald's p-value is 0.00024.

Table 27 provides the submitted summary for overall survival.

Table 27. Overall survival summary from the submitted study report for study EFC7233

Category	FUFOX	Mayo
N	123	129
% censored [1]	25.8	22.0
Median Survival (months)	19.7	16.1
Median followup (months)	32.5	
P-value (Log-rank test) [2]	0.19	

[1] Provided in the submitted summary report – see further comments

[2] While one cannot be certain, since the time to event analyses were planned for one-sided significance levels and the data for this study were not provided, this reviewer believes that this is a p-value for a two-sided test.

The number of patients in each arm and the percent censored in each arm cannot coincide. There is no number of censored observations that represents 25.8% of 123 (22.0% of 129). Based on the December 16, 2003 submission from the sponsor for PFS and the fact that 31 is 25.8% of 120 and 28 is 22.0% of 127, this reviewer believes that the submitted survival analysis was based on the survival results of 247 patients (120 in the FUFOX arm and 127 in the Mayo arm) where there were 89 deaths in the FUFOX arm and 99 deaths in the Mayo arm. This would give a total of 188 deaths, ten deaths short of the planned stopping time for follow-up. This trial is listed in the study report as "ongoing."

Table 28 provides the submitted summary for tumor response for the evaluable patients.

Table 28. Tumor response

Response	FUFOX N = 114	Mayo N = 124	P-value (Fisher's Exact Test)
CR (complete response)	7.9	0.8	0.003
PR (partial response)	41.2	21.8	0.003
CR/PR	**49.1**	**22.6**	**<0.0001**
Stable disease	32.5	47.6	0.024
Progressive disease	14.0	24.2	0.050
Early toxic death	0.9	3.2	--
Not available	3.5	2.4	--

Tumor response is an ordinal variable. The p-values listed above are for comparisons of nominal variables. Computing such p-values for partial response and for stable disease is not meaningful. From this reviewer's calculations, the 95% exact confidence intervals for the response rates were (39.3%, 58.7%) for the FUFOX arm and (15.6%, 31.0%) for the Mayo arm.

The average number of patients per study center is four. This is an open-label study. For an open-label study with a few patients per center, having study center as a stratification factor will lead to treatment assignments that may be easily decipherable by the investigators entering the patients. This, in turn may lead to one arm receiving healthier patients than the other arm. This may be a serious flaw to this trial.

3.2 Evaluation of Safety

Safety will not be discussed in this review. For an evaluation of safety, see the clinical reviewer's review.

4. FINDINGS IN SPECIAL/SUBGROUP POPULATIONS

This section will provide survival results for various subgroups for studies EFC7462, EFC2962, and EFC2961. No survival subgroup summaries or data were provided for study EFC7233.

4.1 Gender, Race and Age

4.1.1 Results by Gender

Tables 29 and 30 provide the survival results by gender for study EFC7462.

Table 29. Overall Survival summary for male patients for study EFC7462

Arm	Deaths/Number	Median (95% C.I.) [1]
IFL	120/172	462 [378, 542]
FOLFOX-4	101/157	576 [470, 630]
IROX	106/161	562 [481, 637]

[1] Medians are given in days

Table 30. Overall Survival summary for female patients for study EFC7462

Arm	Deaths/Number	Median (95% C.I.) [1]
IFL	72/92	428 [331, 511]
FOLFOX-4	54/110	635 [559, 1180]
IROX	69/103	508 [402, 571]

[1] Medians are given in days

For study EFC7462, an exploratory analysis without any p-value adjustment (p-vlaue = 0.012) gave a statistically significant larger (present interaction) survival advantage of FOLFOX-4 vs. IFL for women than for men. The FOLFOX-4 vs. IFL survival hazard

ratio estimate was 0.45 (a 55% reduction in the instantaneous risk of death) among women and the FOLFOX-4 vs. IFL survival hazard ratio estimate was 0.80 (a 20% reduction in the instantaneous risk of death) among men.

Tables 31 and 32 provide the survival results by gender for study EFC2962. The results were not inconsistent across gender subgroups.

Table 31. Overall Survival summary for male patients for study EFC2962 (December 1998 cutoff)

Arm	Deaths/Number	Median (95% C.I.) [1]
de Gramont (control)	88/122	14.8 [12.2, 18.4]
FOLFOX-4	87/127	16.8 [14.7, 19.7]

[1] Medians are given in months

Table 32. Overall Survival summary for female patients for study EFC2962 (December 1998 cutoff)

Arm	Deaths/Number	Median (95% C.I.) [1]
de Gramont (control)	67/88	14.6 [12.6, 18.7]
FOLFOX-4	56/83	15.4 [13.7, 20.0]

[1] Medians are given in months

Tables 33 and 34 provide the survival results by gender for study EFC2961. The results were not inconsistent across gender subgroups.

Table 33. Overall Survival summary for male patients for study EFC2961

Arm	Deaths/Number	Median (95% C.I.) [1]
5-FU/LV	24/36	14.4 [12.2, 31.8]
5-FU/LV+Oxaliplatin	22/34	17.4 [12.8, 24.6]

[1] Medians are given in months

Table 34. Overall Survival summary for female patients for study EFC2961

Arm	Deaths/Number	Median (95% C.I.) [1]
5-FU/LV	40/64	20.6 [16.6, 28.4]
5-FU/LV+Oxaliplatin	45/66	16.5 [13.8, 23.0]

[1] Medians are given in months

4.1.2 Results by Race

Almost all the patients in studies EFC2962 and EFC2961 were Caucasian. Survival results by race will only be given for study EFC7462. The results were not inconsistent across race subgroups.

Tables 35 and 36 provide the survival results by race for study EFC7462.

Table 35. Overall Survival summary for those patients with race listed as black for study EFC7462

Arm	Deaths/Number	Median (95% C.I.) [1]
IFL	23/26	412 [346, 509]
FOLFOX-4	9/13	630 [332, 840]
IROX	8/17	583 [370, ∞)

[1] Medians are given in days

Table 36. Overall Survival summary for those patients with race listed as white for study EFC7462

Arm	Deaths/Number	Median (95% C.I.) [1]
IFL	160/226	462 [393, 533]
FOLFOX-4	141/238	580 [511, 635]
IROX	158/237	524 [478, 607]

[1] Medians are given in days

4.1.3 Results by Age Group

Tables 37 and 38 provide the survival results by age group for study EFC7462.The results were not inconsistent across age subgroups.

Table 37. Overall Survival summary for those patients with age < 65 for study EFC7462

Arm	Deaths/Number	Median (95% C.I.) [1]
IFL	111/164	500 [419, 538]
FOLFOX-4	89/163	594 [474, 780]
IROX	106/165	550 [482, 624]

[1] Medians are given in days

Table 38. Overall Survival summary for those patients with age ≥ 65 for study EFC7462

Arm	Deaths/Number	Median (95% C.I.) [1]
IFL	81/100	352 [315, 462]
FOLFOX-4	66/104	590 [511, 669]
IROX	69/99	512 [407, 637]

[1] Medians are given in days

Tables 39 and 40 provide the survival results by age group for study EFC2962. The results were not inconsistent across age subgroups.

Table 39. Overall Survival summary for those patients with age < 65 for study EFC2962 (December 1998 cutoff)

Arm	Deaths/Number	Median (95% C.I.) [1]
de Gramont (control)	86/114	14.0 [12.5, 16.5]
FOLFOX-4	82/120	16.8 [14.6, 19.7]

[1] Medians are given in months

Table 40. Overall Survival summary for those patients with age ≥ 65 for study EFC2962 (December 1998 cutoff)

Arm	Deaths/Number	Median (95% C.I.) [1]
de Gramont (control)	69/96	17.0 [12.4, 18.7]
FOLFOX-4	61/90	15.7 [13.8, 20.2]

[1] Medians are given in months

Tables 41 and 42 provide the survival results by age group for study EFC2961. The results were not inconsistent across age subgroups.

Table 41. Overall Survival summary for those patients with age < 65 for study EFC2961

Arm	Deaths/Number	Median (95% C.I.) [1]
5-FU/LV	44/73	20.6 [15.3, 31.8]
5-FU/LV+Oxaliplatin	37/58	17.6 [14.3, 24.6]

[1] Medians are given in months

Table 42. Overall Survival summary for those patients with age ≥ 65 for study EFC2961

Arm	Deaths/Number	Median (95% C.I.) [1]
5-FU/LV	20/27	15.8 [9.7, 28.5]
5-FU/LV+Oxaliplatin	30/42	15.8 [12.1, 23.0]

[1] Medians are given in months

4.2 Other Special/Subgroup Populations

This section contains the results of analyses by primary site (colon or rectum). This reviewer requested data from the sponsor that lists the primary site for each patient in the EFC7462 study. The response from the sponsor stated that they checked with NCCTG and confirmed that the information on the primary site was not collected for those patients in study EFC7462. This subsection will thus concentrate on the results of studies EFC2961 and EFC2962. Subgroup analyses by primary site were also provided in the statistical review dated April 10, 2000. The data cutoff for survival for study EFC2962 for that review was July 8, 1998. For this summary, the updated survival data for study EFC2962 will be used (December 1, 1998 cutoff).

Tables 43 and 44 provide survival analyses by primary site for studies EFC2962 and EFC2961.

Table 43. Analyses for the primary site of the Rectum for studies EFC2962 and EFC2961

Study	Log-rank P-value	Hazard Ratio [1]	95% C.I.	Control Median [2]	Treatment Median [2]
EFC 2962	0.0196	0.60	0.39-0.93	14.1	20.0
EFC 2961	0.0708	0.55	0.29-1.06	15.3	24.1

[1] Hazard ratio is 5-FU/LV+oxaliplatin ÷ 5-FU/LV.
[2] Medians are in months.

Table 44. Analyses for the primary site of the Colon for studies EFC2962 and EFC2961

Study	Log-rank P-value	Hazard Ratio [1]	95% C.I.	Control Median [2]	Treatment Median [2]
EFC 2962	0.6961	0.95	0.73-1.24	14.9	15.3
EFC 2961	0.0486	1.50	1.00-2.26	19.5	14.0

[1] Hazard ratio is 5-FU/LV+oxaliplatin ÷ 5-FU/LV.
[2] Medians are in months.

For study EFC 2961, the p-value for an interaction effect between therapeutic arm and the primary site on survival was 0.011. For study EFC 2962, the p-value for an interaction effect between therapeutic arm and the primary site on survival was 0.078.

For the primary site of the rectum, a fixed effects meta-analysis (equivalent to a stratified analysis) gives an estimate of the 5-FU/LV+Oxaliplatin vs. 5-FU/LV survival hazard ratio of 0.58 with a corresponding 95% C.I. of (0.40, 0.84) and a p-value of 0.004. For the primary site of the colon, a fixed effects meta-analysis (equivalent to a stratified analysis) gives an estimate of the 5-FU/LV+Oxaliplatin vs. 5-FU/LV survival hazard ratio of 1.09 with a corresponding 95% C.I. of (0.87, 1.36) and a p-value of 0.458. The corresponding p-value for an interaction effect between therapy arm and the primary site on survival was 0.004.

5. SUMMARY AND CONCLUSIONS

5.1 Statistical Issues and Collective Evidence

The arm of FOLFOX-4 (a regimen of a bolus-continuous infusion combination of 5-FU/LV plus oxaliplatin) demonstrated a survival advantage over the IFL (a regimen of bolus 5-FU/LV plus irinotecan) arm in study EFC7462. The survival results are summarized in Table 45.

Table 45. Survival comparison summary of FOLFOX-4 vs. IFL for study EFC7462

Arms	Hazard Ratio (95% C.I.)	Log-rank p-value
FOLFOX-4 vs. IFL	0.65 (0.53, 0.80)	0.00007

Formally (without referring to any historical comparisons), the impact of the difference in the regimens of 5-FU/LV on overall survival and the impact of the substitution of oxaliplatin for irinotecan on overall survival are confounded.

A meta-analysis of trials in first-line metastatic colorectal cancer that compared bolus 5-FU with continuous infusion 5-FU (J Clin Oncol, vol 16, no. 1, January 1998, pp. 301-308) yielded a statistically significant survival advantage (HR=0.88; 95% CI 0.78-0.99; p=0.04) in favor of the continuous infusion schedules. Tumor response rates also favored the continuous infusion regimens (22% vs. 14%; p=0.0002). Grade 3 or 4 hematologic toxicity was more frequent among the bolus regimens (31% vs. 4%; $p < 10^{-16}$) and hand-

foot syndrome was more frequent among the continuous infusion regimens (34% vs. 13%; $p < 10^{-7}$).

Another study in first-line metastatic colorectal cancer (J Clin Oncol, vol 15, no. 2, February 1997, pp. 808-815) compared an arm of the Mayo Clinic regimen of 5-FU/LV with an arm of the de Gramont regimen of 5-FU/LV. The de Gramont regimen had a statistically significant greater tumor response rate (p=0.0004) and progression-free survival (p=0.0012). The estimated survival advantage favored the de Gramont regimen arm (median survival of 62 weeks vs. 56.8 weeks), but the survival difference was not statistically significant (p=0.067).

These two arms (the Mayo Clinic regimen of 5-FU/LV and the de Gramont regimen of 5-FU/LV) were also compared in a study in adjuvant colorectal cancer (J Clin Oncol, vol 21, no. 15, August 2003, pp. 2896-2903). Comparisons on the disease-free survival and overall survival were not statistically significant. The estimated advantage for each of these endpoints favored the Mayo Clinic regimen. The disease-free survival hazard ratio estimate was 1.04 (95% CI: 0.81-1.34; p=0.74; 251 events) and the survival hazard ratio estimate was 1.26 (95% CI: 0.90-1.78; p=0.18, 132 events).

The statistical significance of an across trials test for "additive transitivity" (see section 6.1 in the appendix), based on five trials that compared two arms among 5-FU+LV, 5-FU+LV+irinotecan and 5-FU+LV+oxaliplatin, suggests that at least one of the assumptions made,

(3) that different regimens of the same drug or drug combination are substitutable or interchangeable or
(4) the effects of the therapies and therapeutic combinations are constant across trials,

is incorrect.

There were no results submitted for first-line metastatic colorectal cancer on a direct comparison of survival between FOLFOX-4 and FOLFIRI (an approved treatment of first-line colorectal cancer that has the same 5-FU/LV regimen as FOLFOX-4). In indirect survival comparisons with arms of the de Gramont regimen (see section 1.2), FOLFIRI had a larger (and a statistically significant advantage) estimated survival advantage than FOLFOX-4.

For this study, the IFL arm was one of the three original arms in the study. During the study four addition arms, including FOLFOX-4 and IROX, were added. Four arms were removed from further study. It should be noted that this is an open-label study and that IFL was not regarded as a control therapy until midway through the accrual period for which those data and results were submitted.

Two other studies, EFC2962 and EFC2961, that were "add-on" studies (treatment arm = control arm + oxaliplatin) failed to demonstrate a survival advantage of 5-FU/LV+oxaliplatin over 5-FU/LV. For each of these studies, the treatment arm and the

control arm had the same regimen of 5-FU/LV. The survival results for these studies are summarized in Table 46. The estimated survival hazard ratio favored the control arm for study EFC2961.

Table 46. Survival comparison summary for studies EFC2962 and EFC2961

Study	Hazard Ratio (95% C.I.)	Log-rank p-value
EFC2962	0.83 (0.66, 1.05)	0.1160
EFC2961	1.10 (0.78, 1.55)	0.5815

Exploratory analyses suggest an interaction effect on survival between primary site (colon vs. rectum) and treatment arm may have been present for studies EFC2962 and EFC2961 (see section 4.2).

Study EFC7233 was not a pure "add-on" trial – the treatment arm had a different regimen of 5-FU/LV. Study center was a stratification factor where the average number of patients per study center is four. For such an open-label study with a few patients per center, having study center as a stratification factor will lead to treatment assignments that may be easily decipherable by the investigators entering the patients. This, in turn may lead to one arm receiving healthier patients than the other arm. Data was not provided for this study. The survival results are summarized in Table 47.

Table 47. Survival comparison summary for study EFC7233

Arms	Hazard Ratio (95% C.I.)	Log-rank p-value
5-FU/LV + oxaliplatin vs. 5-FU/LV	Not provided	0.19

5.2 Conclusions and Recommendations

The FOLFOX-4 regimen demonstrated a marked survival advantage over IFL, an approved therapy for first-line metastatic colorectal cancer in study EFC7462. The regimens of 5-FU/LV were different in these arms. IFL consisted of bolus 5-FU/LV with irinotecan and FOLFOX-4 consisted of a bolus/continuous infusion combination of 5-FU/LV with oxaliplatin. Great caution should be taken in drawing survival conclusion between FOLFOX-4 and other therapeutic treatments in first-line metastatic colorectal cancer.

There were no results submitted for first-line metastatic colorectal cancer on a direct comparison of survival between FOLFOX-4 and FOLFIRI (an approved treatment of first-line colorectal cancer that has the same 5-FU/LV regimen as FOLFOX-4). In indirect survival comparisons with arms of the de Gramont regimen of 5-FU/LV, FOLFIRI had a larger (and a statistically significant advantage) estimated survival advantage than FOLFOX-4. Also, FOLFOX-4 failed to demonstrate a survival advantage over the de Gramont regimen of 5-FU/LV in study EFC2962. Another add-on trial

(EFC2961) of oxaliplatin also failed to demonstrate a survival advantage over the 5-FU/LV alone arm.

APPENDIX

Testing for additive transitivity

Table 48 gives a summary of the survival log-hazard ratios and their standard errors for five studies that compared two arms among 5-FU+LV, 5-FU+LV+irinotecan and 5-FU+LV+oxaliplatin. Studies EFC2962, EFC2961, 0038 and v303 are true "add-on" trials.

Table 48. Summary of survival log-hazard ratios and their standard errors

Study EFC2962	Log HR(5-FU+LV/5-FU+LV+oxaliplatin) = 0.1824 SE = 0.1161
Study EFC2961	Log HR(5-FU+LV/5-FU+LV+oxaliplatin) = -0.0966 SE = 0.1754
Fixed effects Meta-analysis of studies (EFC2962 and EFC2961)	**Log HR(5-FU+LV/5-FU+LV+oxaliplatin) = 0.0974** **SE = 0.0968**
Study 0038 [1]	Log HR(5-FU+LV+irinotecan/5-FU+LV) = -0.2164 SE = 0.1064
Study v303 [2]	Log HR(5-FU+LV+irinotecan/5-FU+LV) = -0.2652 SE = 0.1237
Fixed effects Meta-analysis of studies (0038 and v303)	**Log HR(5-FU+LV+irinotecan/5-FU+LV) = -0.2372** **SE = 0.0807**
Study EFC7462	Log HR(5-FU+LV+oxaliplatin /5-FU+LV+irinotecan) = -0.4316 SE = 0.1083

[1] Estimates based on a p-value of 0.042 with 169 and 185 events in the respective arms
[2] Estimates based on a p-value of 0.032 with 126 and 136 events in the respective arms

Consider a single trial that has three arms of 5-FU+LV, 5-FU+LV+irinotecan, and 5-FU+LV+oxaliplatin. Then under the assumptions of proportional hazards for the three survival functions, we have log HR(5-FU+LV/5-FU+LV+oxaliplatin) + log HR(5-FU+LV+irinotecan/5-FU+LV) + log HR(5-FU+LV+oxaliplatin /5-FU+LV+irinotecan) = 0. If different 5-FU+LV regimens were regarded as substitutable (having equal benefit), different regimens of 5-FU+LV+irinotecan were regarded as substitutable, and different regimens of 5-FU+LV+oxaliplatin were regarded as substitutable and if the effects of the therapies and therapeutic combinations were constant across trials, then log HR(5-FU+LV/5-FU+LV+oxaliplatin) + log HR(5-FU+LV+irinotecan/5-FU+LV) + log HR(5-FU+LV+oxaliplatin /5-FU+LV+irinotecan) = 0 across trials. If we test across trials the null hypothesis log HR(5-FU+LV/5-FU+LV+oxaliplatin) + log HR(5-FU+LV+irinotecan/5-FU+LV) + log HR(5-FU+LV+oxaliplatin /5-FU+LV+irinotecan) =

0, the two-sided p-value is 0.0006 ($Z = \frac{-0.2372 + -0.4316 + 0.0974}{\sqrt{(0.0807)^2 + (0.1083)^2 + (0.0968)^2}} = -3.439$), if study EFC2961 is included in the analysis and the two-sided p-value is 0.006 ($Z = \frac{-0.2372 + -0.4316 + 0.1824}{\sqrt{(0.0807)^2 + (0.1083)^2 + (0.1161)^2}} = -2.731$), if study EFC2961 is not included in the analysis.

A conclusion that additive transitivity does not hold (based on the statistical significance of the test) means that at least one of the assumptions made,

(1) different regimens are substitutable or interchangeable or
(2) the effects of the therapies and therapeutic combinations are constant across trials,

is incorrect.

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

Mark Rothmann
1/6/04 03:00:46 PM
BIOMETRICS

Rajeshwari Sridhara
1/6/04 03:08:34 PM
BIOMETRICS

Kooros Mahjoob
1/8/04 02:47:27 PM
BIOMETRICS