

CENTER FOR DRUG EVALUATION AND RESEARCH

APPROVAL PACKAGE FOR:

APPLICATION NUMBER

NDA 21-492/S-002

Medical Review(s)



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

FDA MEDICAL OFFICER REVIEW OF A
NEW DRUG APPLICATION

NDA NUMBER: 21-492
SUPPLEMENT: 002
DRUG NAME: Eloxatin® (oxaliplatin for injection)
INDICATION: Treatment of advanced colorectal cancer
POPULATION: Previously Untreated Patients with Advanced
Colorectal Cancer
SPONSOR: Sanofi-Synthelabo
CLINICAL REVIEWERS: Amna Ibrahim, M.D.
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DATE OF NDA SUBMISSION: July 11th, 2003
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CLINICAL REVIEW

Executive Summary Section

Clinical Review for NDA 21-492

Executive Summary

I. Recommendations

A. Recommendation on Approvability

We recommend the approval of oxaliplatin in combination with infusional 5-FU/LV for the following indication:

"for the treatment of advanced carcinoma of the colon or rectum."

We also recommend conversion of the previous accelerated approval for relapse/refractory advanced colorectal cancer to regular approval.

This recommendation is based on the review of clinical data, which shows a statistically significant improved survival compared to standard chemotherapy, supported by an improvement in time-to-tumor progression. This indication increases the available options for patients previously untreated for advanced colorectal cancer.

B. Recommendation on Phase 4 Studies and/or Risk Management Steps

There are no recommendations for phase 4 studies or risk management steps.

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II. Summary of Clinical Findings

A. Brief Overview of Clinical Program

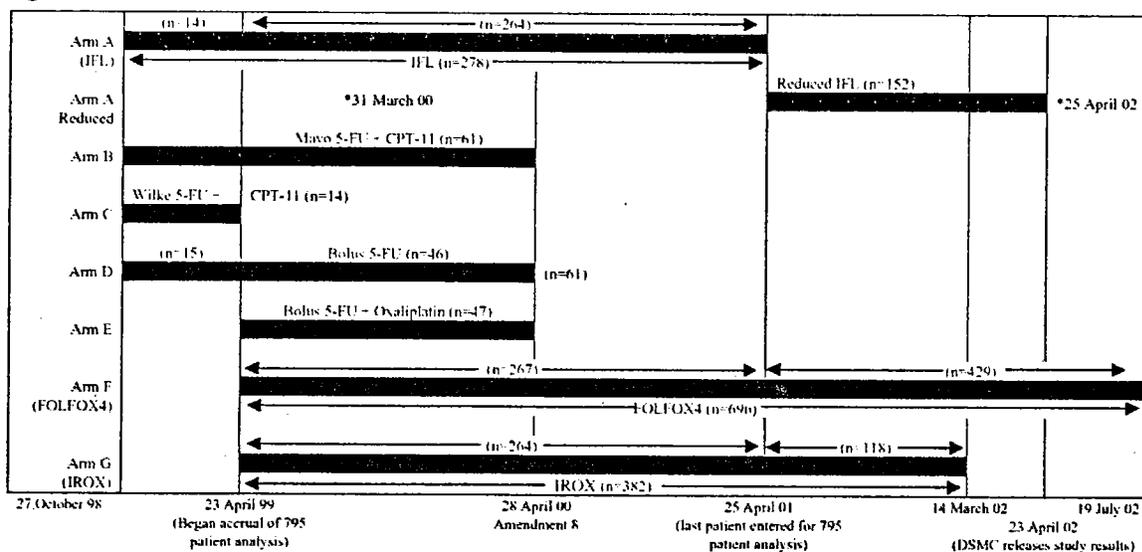
Oxaliplatin is an antineoplastic agent, a platinum analogue, that is administered intravenously. It received accelerated approval in August 2002 for the treatment of patients with metastatic carcinoma of the colon or rectum whose disease has recurred or progressed during or within 6 months of completion of first-line therapy with the combination of bolus 5-FU/LV and irinotecan. A regular approval is sought for patients previously untreated for advanced colorectal cancer who may have received adjuvant therapy without recurrence within 12 months.

A single trial, EFC7462 (N9471), a trial conducted by the NCI as an intergroup study through NCCTG (North Central Cancer Treatment Group) was submitted for evaluation. This was a multicenter, open-label, prospectively randomized, study. The study had 7 arms at different times during its conduct, four of which were closed due to either changes in the standard of care, toxicity, or simplification. (see figure 1). Data on a total of 795 patients concurrently randomized on three arms has been submitted for efficacy and safety evaluation.

B. Efficacy

EFC 7462 (NCI study N9741) was a large, open-label, randomized study conducted in USA and Canada. The primary objective of the study was comparison of Time-to-Tumor Progression (TTP) of the control arm with the investigational arms. The secondary endpoints included evaluation of survival and response rates. The FDA preferred endpoint is overall survival. This trial formed the basis of approval for this NDA.

Figure 1: Time-line of EFC 7462



Data from three arms that concurrently randomized 795 patients were analyzed.

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These arms were:

Arm A: irinotecan plus bolus 5-FU/LV (aka Saltz regimen, IFL)

Arm F: oxaliplatin plus infusional 5-FU/LV (aka FOLFOX 4)

Arm G: irinotecan plus oxaliplatin (IROX)

The dosing regimens are given in table 1 and the FOLFOX 4 regimen recommended for approval is also illustrated in figure 2. Patients were to be treated until CR was confirmed for 2 cycles, or until the patient progressed.

The initial control arm of the Mayo clinic regimen of 5-FU/LV was discontinued on 28th April 2000, after ODAC (Oncology Drug Advisory Committee) recommended IFL as the new standard of care for first-line treatment of metastatic colorectal carcinoma. IFL is the control arm for this submission with the comparison of interest being IFL vs. FOLFOX.

Table 1: Dosing regimens

Treatment Arm	Dose	Regimen
ELOXATIN + 5-FU/LV FOLFOX4 (N=267)	<u>Day 1:</u> ELOXATIN: 85 mg/m ² (2-hour infusion) + LV 200 mg/m ² (2-hour infusion), followed by 5-FU: 400 mg/m ² (bolus), 600 mg/m ² (22-hour infusion) <u>Day 2:</u> LV 200 mg/m ² (2-hour infusion), followed by 5-FU: 400 mg/m ² (bolus), 600 mg/m ² (22-hour infusion)	q2w
irinotecan + 5-FU/LV IFL (N=264)	<u>Day 1:</u> irinotecan 125 mg/m ² as a 90-min infusion +LV 20 mg/m ² as a 15-min infusion or IV push, followed by 5-FU 500 mg/m ² IV bolus weekly x 4	q6w
ELOXATIN + Irinotecan IROX (N=264)	<u>Day 1:</u> ELOXATIN: 85 mg/m ² IV (2-hour infusion) + irinotecan 200 mg/m ² IV over 30 minutes.	q3w

The dose of irinotecan was decreased to 100 mg/m² after all patients were enrolled.

Results:

The median survival was improved by almost 5 months on the FOLFOX 4 arm compared to the control arm of IFL. TTP and response rate were also improved in the FOLFOX arm as reported by the applicant. See table 2.

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Table 2: Efficacy results

	IFL N=264	FOLFOX4 N=267	IROX N=264
Survival (ITT)			
Number of deaths N (%)	192 (72.7)	155 (58.1)	175 (66.3)
Median survival (months)	14.6	19.4	17.6
95% confidence interval	(12.4-16.7)	(17.9-21.0)	(15.8-19.6)
TTP (ITT)			
Percentage of progressors	81.8	82.8	89.4
Median TTP (months)	6.9	8.7	6.5
Response Rate (investigator assessment)			
Patients with measurable disease	212	210	215
Complete response N (%)	5 (2.4)	13 (6.2)	7 (3.3)
Partial response N (%)	64 (30.2)	82 (39.0)	67 (31.2)
Complete and partial response N (%)	69 (32.5)	95 (45.2)	74 (34.4)
95% confidence interval	(26.2-38.9)	(38.5-52.0)	(28.1-40.8)

Response rate and TTP based on investigator assessment only.

Table 3: 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 FDA's Statistical Reviewer's the p-value is roughly 0.00007.

² Not submitted. - based on FDA's Statistical Reviewer's calculations.

Table 4. 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 FDA's Statistical Reviewer's Calculations.

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Table 5: 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 FDA's Statistical Reviewer

There were some weaknesses in this NDA submission.

1. The CRF did not collect some vital information, such as appearance of new lesions, which prevented verification of response rate and TTP.
2. Confirmation of a response at 6 weeks instead of 4 weeks was specified in the protocol.
3. Responses (and TTP) are based on investigator assessment only in an open-label trial.
4. No data on concomitant medications was collected and possibility of concurrent antineoplastic therapy can not be excluded.
5. Certain adverse events could not be completely analyzed because complete information was not collected.
6. Data on doses and methods of administration of 5-FU and LV were not collected uniformly. An audit on 50 patients on the IFL and FOLFOX 4 treatment arms suggested that the regimens were administered appropriately.

Exploratory Analysis for TTP:

The FDA performed an exploratory analysis on all patients with measurable disease. Analysis of TTP based on the measurements submitted was conducted. TTP for FOLFOX 4 was significantly better than IFL in this analysis. Radiology reports were submitted for all progressions. Twenty five patients who were classified as progressors by the applicant, but not on FDA review were audited. Twenty-four of these patients had new lesions, or suspected new lesions. One patient lacked any documentation for that date. These findings lend support to the applicant's claim of improvement of TTP.

No similar exploratory analysis could be performed for response rate because no radiology reports were available for this purpose.

It is observed that IROX did not demonstrate a significant improvement in RR and TTP over that of IFL. In fact TTP on the IROX arm had a poorer trend than IFL. However, IROX was statistically better than IFL for median survival. FOLFOX 4 demonstrated a trend in improvement in median survival over IROX, and was statistically better for RR and TTP.

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Second-line Therapies:

After the treatment on study, the patients could receive other second-line therapies. Oxaliplatin was not approved at that time. Consequently, there was unequal crossover between the treatment arms. See table 6. Fifty eight percent patients on the FOLFOX4 were able to receive irinotecan, whereas only 23% patient on IFL received an oxaliplatin-containing regimen.

Table 6: Second-line therapies.

	IFL (N=256)	FOLFOX4 (N=259)	IROX (N=258)
Any post treatment chemotherapy	164 (64.1)	187 (72.2)	182 (70.5)
5FU (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)

One could argue that the an additional effective second-line therapy contributed to the improved survival. An improved TTP supports the improved survival observed in the FOLFOX 4 arm. Additionally, one can also infer that oxaliplatin plus 5-FU/LV administered sequentially with irinotecan plus 5FU/LV is better than irinotecan plus 5-FU/LV without oxaliplatin. It can be concluded that FOLFOX 4 is an effective regimen.

C. Safety

Oxaliplatin is available widely in the world and is a relatively well-tolerated chemotherapeutic agent. Neurotoxicity (mostly sensory neuropathy including paresthesias and cold-induced dysesthesias) which is generally reversible, is dose or treatment-limiting. It is not associated with renal toxicity or ototoxicity as is cisplatin. Thrombocytopenia is observed but is probably less than that due to carboplatin.

773 patients received at least one dose of the study drugs. A median of 10 cycles of FOLFOX 4 (2-weekly), 4 cycles of IFL (6-weekly) and 4 cycles of IROX (3-weekly) were administered. Twenty seven percent (n=70) patients on the FOLFOX arm, 9% (n=22) on the IFL arm and 20% (n=51) of patients discontinued therapy because of AEs. The time on treatment was similar on the FOLFOX and IFL arms (approximately 23.5 weeks) because of an increase in delays due to toxicity in cycles on the FOLFOX arm. There was a greater number of deaths on the IFL arm in the first 60 days.

Fatigue (all grades: 70%; grade 3 or 4:7%), nausea (all grades:71% ;grade 3 or 4: 6%), vomiting (all grades: 41%; grade 3 or 4:6%), diarrhea with and without colostomy (all grades:69%; grade 3 or 4: 14) on the FOLFOX 4 regimen in the GI system and peripheral neuropathy (all grades: 82%; grade 3 or 4:19%), are the most common non-hematologic adverse events. Neutropenia (all grades: 83%;grade 3 or 4: 54%), and thrombocytopenia (all grades: 71%; grade 3 or 4: 5%), are common hematologic adverse events. Febrile neutropenia or requirement for platelet transfusion was not increased as compared to the other two regimens.

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Approximately 80% of patients had at least one neurotoxicity-related event. It is cumulative. The neurotoxicity is generally reversible and grade 3 or 4 neurotoxicity does not necessarily require discontinuation of treatment. Fifty percent patient had their first sensory neurotoxicity in the first two cycles. Another 25% occurred in cycles 3-10.

Pulmonary fibrosis has been reported as a serious toxicity which may require discontinuation of the treatment drug. Combined incidence of cough, dyspnea or hypoxia was increased in the FOLFOX 4 arm.

Hypersensitivity had an increased incidence on the FOLFOX 4 arm in the submitted randomized trial. This hypersensitivity was manifested as one or more of the following: urticaria, pruritis, flushing of face, diarrhea associated with oxaliplatin infusion, shortness of breath, bronchospasm, diaphoresis, chest pains, hypotension, disorientation and syncope. It did not require immediate discontinuation of oxaliplatin therapy in a few of these patients.

At least one case of HUS has been observed in a Sanofi-Synthelabo sponsored trial. There was one patient in this study who had increased creatinine, prolonged PT, PTT and thrombocytopenia and involvement of multiple systems in his last cycle. This could be consistent with HUS or ARDS.

The number of patients with prolongation of the prothrombin time to greater than twice upper limits of normal was increased in the FOLFOX arm. This is also reflected in the postmarketing surveillance and in literature (a retrospective review). Although concomitant medications were not submitted, all of the patients on the FOLFOX 4 arm had conditions for which anticoagulation would be reasonable. If a possible requirement for closer monitoring of PT /INR is not included in the label, it should be studied formally. Due to the need for a permanent catheter for 5FU infusion, this patient population will be at a higher risk for requiring anticoagulation.

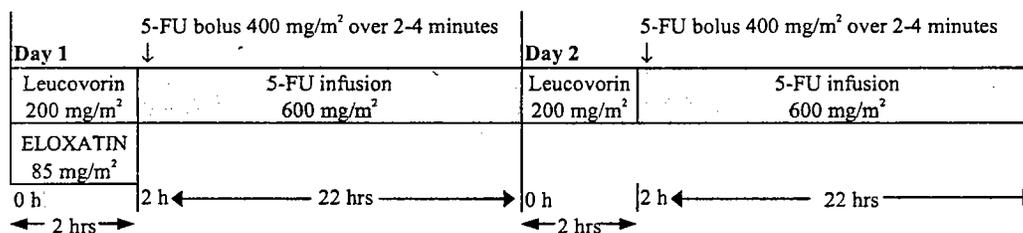
D. Dosing

The recommended dose of oxaliplatin in combination with infusional 5-FU/LV is 85 mg/m² intravenously over 2 hours in 250-500 mL of D5W. Leucovorin 200 mg/m² is administered by an intravenous infusion simultaneously over 2 hours in a separate bag using a Y-line. 5-FU follows the oxaliplatin and leucovorin, first as a bolus injection over 2-4 min in a dose of 400 mg/m², followed then by administration of 600 mg/m² (5-FU) as a continuous infusion in D5W 500 mL over 22 hours. Leucovorin is repeated on Day 2 of the cycle without oxaliplatin. The 5-FU 400 mg/m² bolus and 22 hour infusion of 600 mg/m² is repeated on Day 2 after completion of the Day 2 leucovorin infusion. The cycle is repeated every 2 weeks.

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Figure 2: FOLFOX 4 regimen



Note: Oxaliplatin is administered on day 1 only

Although not evaluated in the current NDA, based on the data submitted with the previously treated patients, following recommendations has been made: Anti-emetics (5HT3 inhibitors) should be used, with or without dexamethasone to prevent nausea and vomiting. No prehydration is required. If cold-induced dysesthesia occurs, prolonging the oxaliplatin infusion time in subsequent cycles may decrease the incidence and severity of symptoms.

E. Special Populations

Age does not affect the efficacy of the FOLFOX 4 regimen. The median overall survival for patient <65 years of age and ≥ 65 years is identical at about 19.5 months. The women demonstrated a trend towards an improved survival when compared to men. The median survival for women was 20.9 months (95% C.I. 18.4-38.8) and was 18.9 months for men (95% C.I. 15.4-20.7).

The applicant performed an analysis on the difference of adverse events by age (<65, ≥65) using Fisher's exact test. The results were reported for all grades and for grades ≥ 3. These results are summarized in table (12.2.3.3)1 of the study report and are attached in the appendix of this document.

Grade 3 or higher events that were greater in the older patients for fatigue, dehydration, leucopenia, syncope and pulmonary events. They were greater for the younger patients for abdominal pain. When all grades are evaluated, patients ≥ 65 years of age had more hypersensitivity, anorexia, and leukopenia. Parasthesias, pharyngo-laryngeal dysesthesias, dysphasia, flatulence, and AST elevations were reported as having an increased incidence in patients <65 years of age with a p value <0.05.

When a similar evaluation was performed by gender, a significantly higher proportion of males experienced depression (all grades), hiccups (all grades), and pulmonary NOS (all grades).

A significantly higher proportion of females experienced alopecia (all grades), urticaria (all grades), hematologic events (any event, Grade = 3), and neutropenia (Grade = 3).

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It is not possible to draw conclusions regarding differences in AE by race. Caucasians constituted 89% of the population on the FOLFOX arm.

Oxaliplatin is a pregnancy category D medicine, and may cause fetal harm when administered to a pregnant woman. If this drug is used during pregnancy or if the patient becomes pregnant while taking this drug, the patient should be apprised of the potential hazard to the fetus. Women of childbearing potential should be advised to avoid becoming pregnant while receiving treatment with oxaliplatin.

The safety and effectiveness of oxaliplatin in pediatric patients have not been established. A pediatric waiver has been granted because of paucity of colorectal cancer in the pediatric population.

The safety and effectiveness of the combination of oxaliplatin and infusional 5-FU/LV in patients with renal impairment has not been evaluated. The combination of oxaliplatin and infusional 5-FU/LV should be used with caution in patients with preexisting renal impairment since the primary route of platinum elimination is renal.

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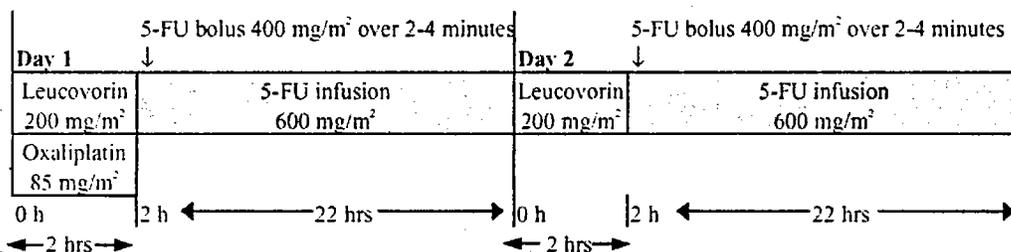
Clinical Review Section

Clinical Review

I. Introduction and Background

A. Drug Established and Proposed Trade Name, Drug Class, Sponsor's Proposed Indication(s), Dose, Regimens, Age Groups

Generic Name: Oxaliplatin
 Proposed Trade Names: Eloxatin
 Established Trade Name: Eloxatin
 Chemical Name: cis-[(1R,2R)-1,2-cyclohexanediamine-N,N] [oxalato(2-)-O,O]platinum
 Pharmacological Category: Antineoplastic agent
 Drug Class: Platinum analogue
 Route of Administration: Intravenous
 Dose and regimen: Oxaliplatin: 85 mg/m² IV infusion in 250-500 mL D5W over 120 min on Day 1 only,
 Leucovorin (LV) 200 mg/m² IV infusion over 120 min., followed by 5-FU 400 mg/m² IV bolus (2 to 4 min.), followed by 5-FU 600 mg/m² IV infusion in 500 mL of D5W (recommended) over 22 hrs on Day 1 & 2



Population studied: Patients with metastatic colorectal carcinoma who have not had any prior treatment for their cancer.

B. State of Armamentarium for Indication

The following drugs are approved for the treatment of metastatic colorectal cancer:

First-line treatment for metastatic carcinoma:

- a- Irinotecan (Camptosar) with 5-fluorouracil and leucovorin (Leucovorin).
- b- Capecitabine (Xeloda) when treatment with fluoropyrimidine alone is preferred.
- c- 5-fluorouracil with leucovorin.

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Table 1: FDA approvals for first-line treatment of colon cancer based on superiority in Survival

Trials	Treatment Arms	N	Result			
			RR (%)	TTP (months)	OS (months)	P value for OS
5FU/ Leucovorin	5-FU	70	10	2.9	7.7	
	5-FU + LV (HD)	69	26	6.7	12.2	0.037*
	5-FU + LV (LD)	73	44	6.7	12	0.05*
	5-FU + MTX + LV rescue					
	5-FU + MTX					
	5-FU + cisplatin					
Study 2 (Study 1 extension)	5-FU + LV (HD)	149	31		12.7	0.04**
	5-FU + LV (LD)	153	42		12.7	0.01**
	5-FU + MTX + LV rescue	155	14		8.4	
Irinotecan			RR (%)	TTP (months)	OS (months)	P value for OS
	Study 1	CPT-11 Wkly x 4, q 6wks (A)	226	18	4.2	12
	CPT-11/ + 5-FU/LV Wkly x 4, q 6 wks (B)	231	39	7	14.8	B vs C <0.05
	5-FU/LV Daily x 5, q 6 wks (C)	226	21	4.3	12.6	
Study 2	CPT-11 + inf 5-FU/LV	198	35	6.7	17.4	<0.05
	5-FU/LV	187	22	4.4	14.1	

* p values are one-sided

** p values are probably one-sided

Calculations used thirty days in each month

Overall survival from first-line treatment with 5FU + LV was approximately 12.5 months and from CPT-11 + 5FU/LV was about 15 months (see table 1).

Second-line treatment for metastatic colorectal carcinoma:

- a- Irinotecan.
- b- Oxaliplatin in combination with 5-fluorouracil with leucovorin. (FOLFOX 4 regimen) after first-line treatment with combination of 5-FU/LV and irinotecan.

C. Important Milestones in Product Development

The IND #41817 for oxaliplatin was initially filed by Axiom, Inc. in February 1993. It was then transferred to Debiopharm SA, and finally to Sanofi-Synthelabo in April 1995. The IND was placed on clinical hold due to chemistry manufacturing and control issues and the hold was lifted in May 1997.

A registration application was submitted for oxaliplatin as NDA # 21063 in February 1999 for first-line treatment of advanced colorectal cancer in combination with infusional 5-fluorouracil-

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based therapy in previously untreated patients. Data from two randomized studies, i.e., EFC 2961 (n=100/arm) and EFC 2962 (n=210/arm) were submitted. These two trials were designed and conducted without FDA advice and neither trial was designed with overall survival as the primary endpoint. EFC 2961 was powered to show a difference in tumor response and EFC 2962 was powered to show a difference in progression-free survival (PFS). For each study (EFC2961 and EFC2962), survival data were premature; too high a proportion of censored survival times at the time of analysis and too few events for sufficient power to detect a difference. The application was presented to the Oncologic Drugs Advisory Committee (ODAC) in March 2000. The Committee noted that although oxaliplatin demonstrated antitumor activity, no benefit in overall survival was observed as a first-line treatment of colon cancer. The data to support a claim for second line or subsequent use was absent. Sanofi-Synthelabo voluntarily withdrew the application from regulatory consideration in May 2000.

Several trials were designed by Sanofi-Synthelabo with the advice of the FDA for the use of oxaliplatin in second-line or subsequent therapy in colon cancer. EFC 4584 was one of these trial. This trial was conducted in patients with metastatic colon cancer progressing on or within 6 months of the Saltz regimen. The interim analysis of this three-arm trial demonstrated an improvement in response rates and time-to-tumor progression of the combination of oxaliplatin and 5-FU and leucovorin (FOLFOX4 regimen) over single agent oxaliplatin or the control regimen of 5-FU and leucovorin. The improved responses and TTP became the basis of accelerated approval of oxaliplatin with 5-FU/leucovorin for the second-line treatment of patients with metastatic colorectal cancer in August 2002. There are several trials in the post-marketing commitment made by the Applicant that can potentially demonstrate clinical benefit and be used to convert the accelerated approval to a standard approval. EFC 7962 is one of these trials.

Meeting Minutes for Applicant study EFC 7962 (NCCTG study N9741)

The results of EFC 7962 will be reviewed in this submission. In October 1998, NCCTG initiated an NCI study N9741 (Sponsor study EFC 7962) in previously untreated patients with metastatic colorectal cancer. NCI and DCTD met with this division on December 17th, 1998 to discuss the trial and possibility of Sanofi-Synthelabo or Pharmacia-Upjohn using this study for oxaliplatin or irinotecan registration for first-line treatment of colon cancer. The questions relevant to oxaliplatin and FDA responses are presented below in Italics:

Q- Would conduct of this trial be acceptable in allowing Sanofi to meet obligations regarding registration for oxaliplatin as 1st line therapy for colorectal cancer?

FDA response:

• A major problem with the study design is that the 5FU/LV regimens used in the six arms are all different and differences in 5-FU dose and/or schedule may account for any differences observed in the outcomes.

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- *To get oxaliplatin and/or CPT-11 approved for this indication we need to have a clear demonstration that the arm is better because of the drug, not because the 5-FU/leucovorin regimen is better. Ideally this would be done by comparing the drug combination to a control arm that is identical except for the addition of oxaliplatin or CPT-11. None of the comparisons of interest appear to have appropriate control arms.*

- *The Division acknowledges the issue of second and third line therapy affecting a survival endpoint. Nevertheless, the Division considers that overall survival remains the most reliable primary endpoint for a first line indication in colorectal cancer at this time and cannot commit to time to progression as a primary endpoint. The sponsor should collect data on second and third line therapies, as planned and the Division will consider such data during the review.*

Q- Does FDA agree that standard cooperative group data monitoring and collection will fulfill the requirements for study evaluations to meet the FDA's requirements to consider this trial as a potential registration trial for the various experimental regimens?

FDA response:

- *Further details will be needed on what data the cooperative groups will be collecting. "Standard" procedures may not be acceptable for unmarketed drugs, e.g., oxaliplatin.*

Q- The U.S. Cooperative Group Chairs have agreed that the study plan is appropriate. Does the FDA have specific concerns regarding the proposed NCI-sponsored study stratification, therapeutic regimens, control arms, patient assessments, primary or secondary endpoints, or statistical methods?

FDA response:

- *Inclusion of patients with evaluable only disease is a problem.*
- *The unequal timing of tumor assessments and the use of QOL endpoints in an unblinded study are problematic.*
- *The definition of progressive disease is unclear.*
- *We have major concerns about the proposed statistical plans, e.g., dropping the control arm based on external data and the second stage.*
- *We have concerns about the use of one-sided p values for analyses of efficacy.*

This NCI study was discontinued early because of DSMB recommendation. The results of the study were presented at the American Society of Oncology's annual meeting in 2002. An improvement in overall survival was demonstrated by the FOLFOX 4 regimen (oxaliplatin and 5-FU and leucovorin) over the control regimen of CPT-11, 5-FU and leucovorin (Saltz regimen or IFL) in an interim analysis, as a first-line treatment of metastatic colorectal carcinoma. This is

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the major study being submitted as EFC-7462 by Sanofi-Synthelabo, Inc., to support registration in first-line treatment of metastatic colorectal carcinoma.

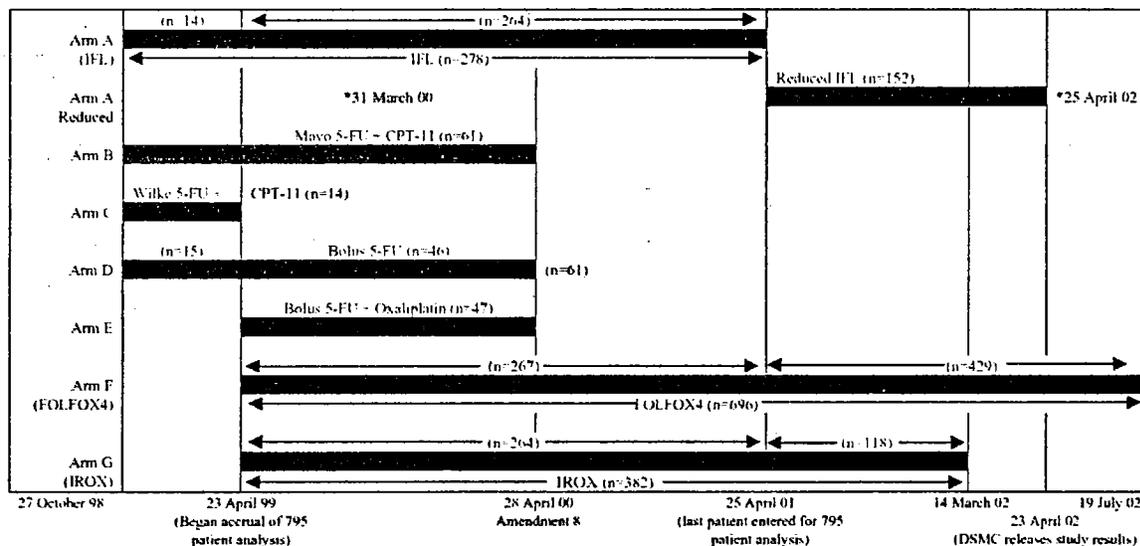
EFC-7462 was activated in 1998 as a 4-arm study when bolus 5-FU/LV was considered the standard of care for first-line treatment of colorectal cancer. Over the course of the trial, IFL became the standard of care for this patient population. An oxaliplatin arm (FOLFOX4) and two other arms were added and some other treatment arms were discontinued because of study simplification and toxicity reasons. The different treatment arms (Table 2) and a time-line of various phases of the study as presented by the applicant (fig 1).

Table 2: Treatment Arms

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

Applicant figure from Study report.

Figure 1: Time-line of phases of study



The efficacy and safety results from Arms A (IFL; Saltz regimen), F (FOLFOX4) and G (IROX) in 795 patients who were randomized concurrently from 20th May 1999 through 25th April 2001 have been submitted in this sNDA with supporting safety data from EFC2961 and EFC 2962, which have been submitted previously in NDA # 21063.

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D. Other Relevant Information

According to the Sponsor, as of May 15th, 2003, oxaliplatin has been approved for marketing in 68 countries for first and/or second-line treatment of MCRC and is pending approval in 5 countries. Oxaliplatin has not been withdrawn from the market, or denied approval in any country. France was the first country to approve this drug in April 1996.

Oxaliplatin received accelerated approval by the USFDA for use in combination with 5FU/LV as second-line treatment in metastatic colorectal carcinoma. The current submission claims improved survival over irinotecan, the standard of care for the first-line treatment in patients previously untreated for metastatic MCRC. If approved, this submission will also support the conversion of the prior accelerated approval to a regular approval.

E. Important Issues with Pharmacologically Related Agents

There are two other platinum compounds approved by the FDA. Renal toxicity, neurotoxicity, ototoxicity and myelosuppression are the main side effects of cisplatin. Carboplatin has thrombocytopenia as its most prominent adverse reaction. Oxaliplatin does not share the marked renal, hematological or ototoxicity of these two other platinum drugs.

II. Clinically Relevant Findings From Chemistry, Animal Pharmacology and Toxicology, Microbiology, Biopharmaceutics, Statistics Reviews

Chemistry

The information in this section is obtained from the review of Dr. Haripada Sarker, Ph.D. from the original NDA.

The USAN chemical name of oxaliplatin is: SP-4-2-(1R,2R)-(cyclohexane-1,2-diamine-2 N,N'(oxalato(2-)- 2 O 1 ,O 2]platinum(II). It is a white to off-white powder. Oxaliplatin is an organometallic coordination complex, with the platinum atom chelated with a 1,2-diaminocyclohexane group and an oxalate group. Oxaliplatin is slightly soluble in water, very soluble in methanol, and insoluble in ethanol and acetone. The pKa study on oxaliplatin indicated that the molecule is neutral with no dissociation in solution. Multiple batch records, including the microbiological limits, demonstrate the batch to batch consistency of the oxaliplatin drug substance. Primary and secondary stability studies support the stability of oxaliplatin drug substance in the solid state up to 36 months at normal condition using the commercial container/closure system.

The drug product, oxaliplatin for injection (Eloxatin) is formulated as a sterile lyophilized powder at two strengths 50 mg and 100 mg/vial, for reconstitution with water for injection or 5%. Oxaliplatin lyophilized powder is found to be stable up to 36 months using commercial container/closure systems, and at normal condition. However, the reconstituted drug products are

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stable up to 24 hours at 2-8°C (36-46° F). After final dilution with 250-500 mL of 5% Dextrose Injection, USP, the shelf life is 24 hours at room temperature and at ambient light.

Animal Pharmacology and Toxicology

A summary of the major *in vitro* and *in vivo* findings regarding the antitumor activity of oxaliplatin taken from the year 2000 review of the previous NDA by Dr. Hua Zheng, Ph.D. follows:

Oxaliplatin demonstrates broad spectrum *in vitro* cytotoxic or antiproliferative activity against a variety of murine and human tumor cell lines. In general, the cytotoxic and antitumor activity of oxaliplatin is equal or superior to that observed for cisplatin. In an *in vitro* human tumor cloning assay, oxaliplatin and cisplatin had similar activity against several types of human tumors obtained directly from patients. Oxaliplatin also demonstrates *in vitro* cytotoxic and *in vivo* antitumor activity (including curative activity) in several cell lines/tumor models that are resistant to cisplatin. Oxaliplatin was shown to have additive and/or synergistic cytotoxic and antitumor activity in combination with a variety of standard antineoplastic agents, including 5-fluorouracil, SN-38, gemcitabine, or cisplatin. Oxaliplatin as a single agent demonstrated *in vivo* antitumor activity against a variety of murine tumor models and human xenograft model in athymic mice. Oxaliplatin was more active than cisplatin in the following murine tumors: L1210 leukemia, LGC lymphoma, and MA-16c mammary tumors.

Oxaliplatin was negative in the Ames test, but was positive in all other genotoxicity tests, *i.e.*, mouse lymphoma assay for mammalian cells (TK locus), mouse micronucleus assay, and chromosome aberration assay for human lymphocytes in culture. The relative mutagenicity and clastogenicity of oxaliplatin was comparable to cisplatin within an order of magnitude. Oxaliplatin was mutagenic and clastogenic both in the presence or absence of metabolic activation. Based on net values (≥ 4) obtained from the integrative assessment for assignment of concern, it appears there are significant degrees of concerns for developmental and reproductive toxicity for the endpoints of fertility, developmental mortality, and alterations to growth in humans from the exposure to oxaliplatin at the clinical dose proposed.

The carcinogenicity of oxaliplatin has not been studied in animals. However, based on the similar mechanism of action and genetic toxicity as cisplatin, which has sufficient evidence of carcinogenicity in animals and humans, oxaliplatin should be presumed to be a trans-species carcinogen.

Statistics Review

The statistics review was conducted by Dr. Mark Rothmann Ph.D. for this supplement. His conclusion was that FOLFOX 4 demonstrated a survival advantage over IFL for first-line metastatic colorectal cancer.

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III. Human Pharmacokinetics and Pharmacodynamics

A. Pharmacokinetics

The following information is taken from the Dr. Brian Booth's review of the original NDA 21492, for the Division of Biopharmaceutics.

Using a validated assay, the applicant demonstrated that the pharmacokinetics of platinum from oxaliplatin at a dose of 85 mg/m² are described by a three-compartment open mammalian model with t_{1/2}'s of 0.43, 16.8 and terminal elimination half-life of 391 hours. The pharmacokinetics of oxaliplatin appear to be linear between 40 and 130 mg/m². Oxaliplatin is rapidly hydrolyzed *in vivo* to yield a number of active and inactive platinum species.

The pharmacokinetics of platinum from oxaliplatin are not affected by 5-FU, nor are the pharmacokinetics of 5-FU affected by oxaliplatin at a dosage of 85 mg/m². At the dose of 130 mg/m², oxaliplatin appears to increase the plasma concentration of 5-FU by approximately 20%. Oxaliplatin is extensively protein bound (approximately 90 to 95 % *in vivo*), but it did not mediate displacement interactions with erythromycin, salicylate, valproate, granisetron or paclitaxel.

Cytochrome P-450 isozymes do not metabolize oxaliplatin, and the platinum is excreted predominantly via the renal route (over 50% in 5 days). Oxaliplatin is eliminated primarily by renal excretion. Approximately 50 % of platinum is excreted in the urine after a single dose of oxaliplatin. The applicant conducted a study to assess the effect of renal impairment on the pharmacokinetics of single agent oxaliplatin in patients with a variety of cancers using a dose-escalation scheme and renal impairment criteria that differed from the FDA-promulgated recommendations. Re-analysis by FDA indicated that the AUC_{0-48hr} of platinum in patients with mild, moderate and severe renal impairment increased 59, 138 and 191% respectively, compared to patients with normal renal function. The pharmacokinetic evaluation of oxaliplatin is based on analyses of total platinum ultrafiltrate, and it is unknown what pharmacokinetic changes actually occur in biologically active platinum moieties. There are no PD data available for evaluation. Because the safety data available from this renal impairment study were limited (limited patient numbers) and only single agent oxaliplatin was administered (the combination of oxaliplatin with 5-FU increases the incidence of some of the toxicities associated with 5-FU), no recommendations regarding the relative safety of administering oxaliplatin to patients with varying degrees of renal impairment could be made on the basis of the phase 1 study. There is also no efficacy or safety data available for administration of reduced doses of oxaliplatin to patients with varying degrees of renal impairment. The product label includes cautionary statements regarding administration of oxaliplatin in patients with renal impairment. The following is taken from the Precautions section:

Patients with Renal Impairment

The safety and effectiveness of the combination of ELOXATIN and infusional 5-FU/LV in patients with renal impairment has not been evaluated. The combination of ELOXATIN and

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infusional 5-FU/LV should be used with caution in patients with preexisting renal impairment since the primary route of platinum elimination is renal. Clearance of ultrafilterable platinum is decreased in patients with mild, moderate, and severe renal impairment. A pharmacodynamic relationship between platinum ultrafiltrate levels and clinical safety and effectiveness has not been established. (See CLINICAL PHARMACOLOGY). Age and gender had no apparent effect on the pharmacokinetics of oxaliplatin. The applicant plans to conduct a 40-50 patient, safety study in normal, mild, and moderate renal impairment patient to evaluate any marked difference in these toxicity of oxaliplatin in these patient groups.

B. Pharmacodynamics

Pharmacodynamics data relating efficacy to dose have not been submitted. The only pharmacodynamic correlate to safety is limited information that C_{max} may correlate with cumulative peripheral neuropathy.

IV. Description of Clinical Data and Sources

A. Overall Data

Data was submitted electronically in the EDR. The study reports, annotated CRFs, selected CRFs of patients, and datasets and amendments submitted were reviewed. A literature search was performed using PUBMED. The data was based on a study conducted by the NCI.

B. Tables Listing the Clinical Trials

Tables 3 through 7 below show a list of completed or ongoing controlled clinical trials. Table 3 is the major study submitted in this NDA. Tables 4 and 5 list supportive studies. Tables 6 and 7 are ongoing controlled trials involving oxaliplatin.

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Table 3: Completed Controlled Clinical Trial: Pivotal Safety and Efficacy Study EFC 9762

Applicant Table

	Study Design	Diagnosis and Criteria for Inclusion	Per Treatment Group	Drug Regimen Treatment Duration	Criteria for Evaluation
EFC7462/N9741 795 patient cohort	Phase III, multicenter, open label, randomized three arm study of CPT-11 and 5-FU/LV (IFL) or oxaliplatin and CPT-11 (IROX) or oxaliplatin and 5-FU/LV (FOLFOX4)	Known locally advanced, locally recurrent, or metastatic colorectal adenocarcinoma not curable by surgery or amenable to radiation therapy with curative intent.	ITT population: IFL: 264 FOLFOX4: 267 IROX: 264	IFL: Day 1: CPT-11 125 mg/m ² , LV 20 mg/m ² , 5-FU 500 mg/m ² bolus, weekly x 4, cycle repeated every 6 weeks FOLFOX4: Day 1: Oxaliplatin 85 mg/m ² Day 1 & 2: LV 200mg/m ² 5-FU 400 mg/m ² bolus then 600mg/m ² infusion over 22 hours, cycle repeated every 2 weeks. IROX: Day 1: Oxaliplatin 85 mg/m ² CPT-11 200 mg/m ² cycle repeated every 3 weeks.	Efficacy: Time to Progression (TTP), Overall Survival (OS), Response Rate (RR) Safety

Table 4: Completed Controlled Clinical Trial: Supportive study EFC 2962

Name of finished product: Eloxatin [®]								
Study No. Primary Investigator ¹ Dates of Study Defining Publication	Study Design	Diagnosis and Criteria for Inclusion	Patients			Drug Regimen ⁷ Treatment Duration	Formulation ¹ Batch No.	Criteria for Evaluation
			N (M/F) (B/W/O)	Age Range (years) (Median)	Per Treatment Group			
<i>Supportive Safety Studies</i>								
EFC 2962 (DEB-95-OXA-01) de Gramont, A. Aug 1995 - Jul 1997 (last enrollment) <u>Publications:</u> De Gramont A., et al. J Clin Oncol. 2000; 18:2938-2947 Proc Am Soc Clin Oncol Ann Meet 1998; Abstract 985	Phase II/III, multicenter, controlled, randomized, comparative to 5-FU + FA, in combination with 5-FU + FA	Unresectable, proven adenocarcinoma of colon or rectum, ≥1 measurable lesion, no prior therapy for metastatic disease, no adjuvant chemo- or radio-therapy 6 months prior to inclusion	Total enrolled: 420 Total dosed: 417 Arm 1: (121/87) (206 white/2 non white) Arm 2: (126/83) (1207/1)	Arm 1: 23-76 (63) Arm 2: 21-76 (63)	Arm 1: 208 Arm 2: 209	<i>Regimen:</i> Arm 1: FA 200 mg/m ² (2-hour infusion on Days 1 and 2), 5-FU 1000 mg/m ² (400 mg/m ² IV bolus + 600 mg/m ² 22 hours CIV) on Days 1 and 2, q2w Arm 2: Same as Arm 1, but with addition of 85 mg/m ² of OXAL on Day 1 (2-hour infusion), q2w <i>Duration:</i> Arm 2 - 154 patients greater than 8 cycles	50 mg: 95E16, 95J31 100mg: 94G04, 94G05, 95E23, 95J30, 96E15 2	Efficacy: Progression Free Survival (PFS) (primary), RR, OS, quality of life (QoL) PK results for 9 patients reported in INT3681 Safety

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Table 5: Completed Controlled Clinical Trial: Supportive study EFC 2961

Name of finished product: Eloxatin [®]								
Study No. Primary Investigator ¹ Dates of Study Defining Publication	Study Design	Diagnosis and Criteria for Inclusion	Patients			Drug Regimen ² Treatment Duration	Formulation ³ Batch No.	Criteria for Evaluation
			N (M/F) (B/V/O)	Age Range (years) (Median)	Per Treatment Group			
EFC2961 (DEB-94-OXA-02) Lévi, F. Jun 1994 - Mar 1996 (last enrollment) Addendum cut-off date 31 Jul 1997 Publication <i>Proc Am Soc Clin Oncol Ann Meet</i> 1997; 16: A-805	Phase II/III, multicenter, controlled, randomized, comparing oxaliplatin in combination with chronomodulated 5-FU + FA	Unresectable, proven adenocarcinoma of colon or rectum, ≥1 measurable lesion, no prior therapy for metastatic disease, no adjuvant chemo- or radio-therapy 6 months prior to inclusion	200 Arm 1: (64/36) (Not reported) Arm 2: (65/34) (Not reported)	29-74 (61) 31-75 (60)	Arm 1: 100 Arm 2: 100	<i>Regimen:</i> Arm 1: 5-FU 700 mg/m ² /d and FA 300 mg/m ² /d (Days 1 to 5 chronomodulated) q3w. Arm 2: OXAL 125 mg/m ² (6-hour flat infusion, Day 1 only), followed by 5-FU 700 mg/m ² /d and FA 300 mg/m ² /d (Days 1 to 5 CM) q3w Alternative treatment w/ chronomodulated 5-FU+FA OXAL in either arm in case of disease progression <i>Duration:</i> Arm 2: 44 patients greater than 8 cycles	50 mg: 92L03, 92I29, 92L30, 93F01, 93E16, 95J31, 96I19/1 100 mg: 92J14, 92J15, 92L18, 93E19, 93E24, 94G04, 95E23, 95J30, 96E15/2	Efficacy: confirmed RR (primary), PFS, OS Safety

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Table 6: Ongoing Controlled Clinical Trial: EFC 5337 (LIFE)

Name of finished product: Eloxatin ¹								
Study No. Primary Investigator ² Dates of Study Defining Publication	Study Design	Diagnosis and Criteria for Inclusion	Patients			Drug Regimen ³ Treatment Duration	Formulation ⁴ Batch No.	Criteria for Evaluation
			N (M/F) (B/W/O)	Age Range (years) (Median)	Per Treatment Group			
EFC5337: L8125 (LIFE) Cassidy, J. Mar 2001 – Mar 2002 (last patient enrolled) <u>Publication:</u> <i>Proc Am Soc Clin Oncol Ann Meet.</i> 2003; Abstract 1004	Phase IIIB, multicenter, randomized, open-label evaluating oxaliplatin combined with two different 5-FU regimens	Previously untreated advanced colorectal cancer patients	Total enrolled: 725 Total dosed: 725 Control: 363 (61/39) (Data on race not reported) Oxaliplatin: 362 (66/34) (Data on race not reported)	Control: Data on age ranges not reported (62) Oxaliplatin: Data on age ranges not reported (61)	Oxaliplatin arms: Arm A1: 58 Arm A2: 304 Control arms: Arm B1: 62 Arm B2: 301	<i>Regimen:</i> Oxaliplatin: Arm A1: CIV Oxaliplatin: 85 mg/m ² as a 2-hour IV, Day 1. 5-FU: 250 mg/m ² /day, CIV without interruption during 2 weeks without LV OR Arm A2: FOLFFOX4 Oxaliplatin: 85 mg/m ² in a 2-hour IV, Day 1 5-FU: 400 mg/m ² bolus and 600 mg/m ² 22 hour CIV, Day 1 and Day 2 LV 200 mg/m ² in a 2-hour IV, Day 1 and Day 2 <i>Duration:</i> Administration: every 2 weeks	Not available.	Efficacy: Survival (primary), RR, PFS, TTF, QoL Safety
EFC5337 L8125 (LIFE)						<i>Regimen:</i> Control: Arm B1: Continuous intravenous infusion (CIV) 5-FU: 300 mg/m ² /day, CIV, without LV without interruption during 2 weeks. OR Arm B2: LV5FU2 5-FU: 400 mg/m ² bolus and 600 mg/m ² 22-hour continuous IV, Day 1 and Day 2 and LV 200 mg/m ² in a 2-hour IV, Day 1 and Day 2 <i>Duration:</i> Administration: every 2 weeks		

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Table 7: Ongoing Controlled Clinical Trial: EFC 7233

Name of finished product: Eloxatin ²								
Study No. Primary Investigator ¹ Dates of Study Defining Publication	Study Design	Diagnosis and Criteria for Inclusion	Patients			Drug Regimen ² Treatment Duration	Formulation ¹ Batch No.	Criteria for Evaluation
			N (M/F) (B/W/O)	Age Range (years) (Median)	Per Treatment Group			
E1 C 7233 Schmoll, H-J. Dec 1998 – May 2003 (ongoing) <u>Publication:</u> Grothey A, et al. <i>Proc Am Soc Clin Oncol Ann Meet.</i> 2002; Abstract 512 Grothey A, et al. <i>Proc Am Soc Clin Oncol Ann Meet.</i> 2001; Abstract 496 Buechele T, et al. <i>Proc Am Soc Clin Oncol Ann Meet.</i> 2000; Abstract 984 E1 C 7233	Phase II-III, multicenter, randomized, open-label	Patients with advanced colorectal cancer	Total enrolled: 252 (Data on sex and race not reported)	Data on age not reported	FUFOX: 123 Mayo: 129	<i>Regimen:</i> FUFOX: Oxaliplatin: 50 mg/m ² 2-hour infusion followed by Folinic acid: 500 mg/m ² 2-hour infusion followed by 5-FU: 2000 mg/m ² 24-hour infusion (the dose can be escalated to 2600 mg/m ² at Cycle 2 and thereafter if no gastrointestinal toxicity occurs during Cycle 1) <i>Duration:</i> Days 1, 8, 15, and 22, every 5 weeks for 4 cycles; for subsequent cycles, oxaliplatin given on Days 1 and 15, but 5-FU and folinic acid continue to be given on Days 1, 8, 15, and 22, until disease progression Mayo Regimen: Folinic acid: 20 mg/m ² bolus followed by 5-FU: 425 mg/m ² bolus (injection within 2 minutes) <i>Duration:</i> Days 1 to 5, every 4 weeks for 3 cycles then every 5 weeks until disease progression	Not available	Efficacy: PFS, RR, OS, QOL (EORTC C-30 Questionnaire) Safety: Adverse events and laboratory values

C. Postmarketing Experience

There have been no unexpected postmarketing concerns reported by the applicant or OPDRA.

D. Literature Review

The colorectal cancer has the third highest incidence and mortality in both males and females. Approximately 147,500 new diagnoses of colorectal carcinoma are estimated for year 2003 with about 57,100 deaths¹. The incidence and mortality is slightly greater in blacks.



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Incidence and death rates for all cancer sites and races, 1996–2000. Rates are per 100 000 persons and are age-adjusted to the 2000 U.S. standard population by 5-year age groups².

The most reliable, widely accepted prognostic factor is the stage of disease³. The other prognostic factors proven in large trials are presence of obstruction or perforation⁴, vascular or lymphatic invasion, perineural invasion⁵, peritumoral lymphocytic invasion⁶, character of invasive margin and type of tumor⁷, presence and number of mast cells⁸, age and gender, tumor grade⁹, DNA content¹⁰, increased mitosis and low Bcl-2 expression, low apoptosis rate¹¹, vascular endothelial growth factor (VEGF) levels, and allelic loss of chromosome 18q¹². As noted earlier, Irinotecan (Camptosar) + 5-fluorouracil and leucovorin (Leucovorin), Capecitabine (Xeloda) and 5-fluorouracil with leucovorin are approved for first-line treatment of colorectal cancer. Overall median survival has been reported to be generally approximately 12 – 15 months (background document for regulatory approvals for colorectal endpoints workshop, Nov 03).

Oxaliplatin belongs to the diamminocyclohexane platinum family. Its mechanism of action involves formation of DNA adducts and inhibition of DNA synthesis. Preclinical studies suggested synergy between oxaliplatin and 5-FU¹³. Oxaliplatin may reduce 5-FU catabolism and this may explain the supra-additive interaction between these drugs that has been reported²⁴. It has been postulated that a reason for this observed supra-additive effect in vitro is that sequential administration of oxaliplatin followed by 5-FU results in a significant decrease in thymidylate synthase gene expression. The trial reviewed in the previous NDA suggests synergy between oxaliplatin and 5-FU/LV.

Many different regimens incorporating oxaliplatin have been used. The major ones are given in table 8 on the next page.

The most common adverse reactions are peripheral sensory neuropathies, fatigue, neutropenia, nausea, emesis, and diarrhea in the second-line study leading to the approval of FOLFOX4 regimen. Oxaliplatin hematologic toxicity relative to other chemotherapeutic drugs is moderate, and the neurotoxicity associated with its use was mostly reversible. It is consistently associated with two types of peripheral neuropathy- acute that resolves in 14 days or persistent which lasting more than 14 days, that is, in to the next cycle of chemotherapy. These toxicities are generally reversible.

The study submitted for this NDA has been published recently in the JCO¹⁴.

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Table 8: Major Regimens Incorporating Oxaliplatin

FOLFOX1:

Bimonthly high-dose LV (500 mg/m² on Day 1 & 2) and high dose 5-FU (2 gm/m² on Day 1 & 2) q 2 weeks + oxaliplatin 130 mg/m² in alternate cycles ¹⁵

FOLFOX2:

LV 500 mg/m², + 5-FU 24-h infusion 1.5-2 g/m² Day s1-2 and oxaliplatin 100 mg/m² on Day 1, q 2 weeks ¹⁶.

FOLFOX3:

LV: 500 mg/m², 5-FU: 1.5-2 g/m²/22 hours, Days 1-2, q 2 weeks, oxaliplatin 85 mg/m² q 2 weeks ¹⁷.

FOLFOX4:

LV 200 mg/m², bolus 5-FU 400 mg/m², and CI 5-FU 600 mg/m²/22 hours, Day1, 2 q 2 weeks and 85 mg/m² of oxaliplatin Day 1 q 2 weeks ¹⁸. (This is the combination regimen used in the major study reviewed in this NDA.)

FOLFOX6:

LV 400 mg/m² d 1, 5-FU, bolus 400 mg/m² followed by a 46-h infusion of 2.4-3 g/m² q 2 weeks, and oxaliplatin 100 mg/m² q 2 weeks ¹⁹.

FOLFOX7:

LV 400 mg/m² over 2 hours on Day 1, 5-FU bolus 400 mg/m² and a 46-h infusion 2400 g/m², every 2 weeks and oxaliplatin 130 mg/m² q 2 weeks ²⁰.

OXAF (Oxaliplatin and PVI of 5-FU):

Oxaliplatin (100 mg m²) infusion over 2 hours every 2 weeks, 5-FU (300 mg m²/day) administered as a continuous protracted venous infusion to a maximum of 24 weeks ²¹.

Oxaliplatin with bolus 5-FU and leucovorin:

5-FU and LV 350 mg/m² and 20 mg/m², respectively on Days 1-5, oxaliplatin 130 mg/m² on Day 1, every 21 days ²².

FUFOX:

Infusional 5-FU and LV, 2000 mg/m² over 24 hours and 500 mg/m² respectively, and oxaliplatin 50 mg/m² on Day 1, 8, 15, 22 q 5 weeks. ²³

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V. Clinical Review Methods

A. Overview of Materials Consulted in Review

One trial was submitted for the efficacy and safety review. The study report and electronic datasets were reviewed and analyzed. Questions or further clarifications were requested from the applicant based on the review. Consequently, amendments were submitted on September 11th, November 11th, Nov 12th, December 4th, December 15th, December 16th, and December 19th. The amendments were reviewed and analyzed.

B. Overview of Methods Used to Evaluate Data Quality and Integrity

DSI carried out an inspection. The following sites were selected for inspection:

NAME OF PHYSICIAN	CITY, STATE	COUNTRY	Enrolled	Evaluated
Muhammad Salim, M.D.	Regina, Saskatchewan	Canada	22	22
Robert J. Dalton, M.D.	Duluth, MN	USA	45	13/45

Some irregularities were noted at particularly at the Saskatchewan site, such as:

- Subject #92830/9027596 did not meet inclusion criteria in that he had uncontrolled hypertension.
- Subject # 91091/9026955 was not terminated from the study as required by protocol when he had progression of disease. A new lesion was detected with CT scan.
- Dosing errors of the study drug were noted in review. Subject # 96030/9018610 received full dose of CPT-11 (237mg) and 5-FU (948 mg) instead of reduced dose of CPT-11 (192 mg) and 5-FU (769 mg). When the dosage correction was calculated an incorrect reduced dose was given CPT-11 (144 mg) and 5-FU (576 mg) for 4 doses.
- Adverse events not always reported to the sponsor, specifically:
 - a. Subject 92501/9027466 physician's review notes report gastrointestinal bleeds which were not reported to the sponsor.
 - b. Subject 89397/9026406 had reported swelling in both feet to the nurse which was not reported to the sponsor.

No specific deviations were noted in the 14 records at the 34 subjects in Duluth. Eleven subjects at the Thunder Bay site were not reviewed.

Reviewer's Comments:

The sites that enrolled the largest numbers of patients were reviewed by DSI. Recommendation was made by DSI to exclude the patient who did not meet inclusion criteria, and the one with disease progression. These were not excluded from our analysis. Two patients out of 795 are unlikely to make an impact on the overall results.

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C. Ethical Standards of Trials

The trial was conducted according to accepted ethical standards.

D. Evaluation of Financial Disclosure

The study was conducted by the co-operative group NCCTG. Per applicant: "The investigators conducted study N9741/EFC7462 under the National Cancer Institute (NCI) IND 57,004 according to their standard procedures and that of each participating cooperative group. The North Central Cancer Treatment Group (NCCTG) was the lead group with participation by Cancer and Acute Leukemia Group B (CALGB), Eastern Cooperative Oncology Group (ECOG), Southwestern Oncology Group (SWOG), National Cancer Institute of Canada (NCI-C). Each cooperative group has their own requirements regarding financial disclosure and interest, which are required to be followed by each investigator. A list of participating investigators is listed below. Financial information is not collected by these cooperative groups or the NCI; therefore, this information could not be obtained by Sanofi-Synthelabo."

The Applicant was instructed to submit financial disclosure. Only 1 investigator received amounts in excess of \$50,000.

Reviewer's Assessment of financial disclosure:

If only a small number of investigators received funds from the applicant, it is unlikely that results of a large randomized trial would be affected. Most investigators enrolled and treated less than 5 patients. The investigator who received > \$50,000 enrolled — patient in the study.

VI. Integrated Review of Efficacy

A. Brief Statement of Conclusions

Efficacy data from one large, multicenter, open-label, three-arm randomized trial conducted by the cooperative group NCCTG with support from NCI was submitted to support the efficacy claim. This trial was conducted in the USA and Canada in patients previously untreated for advanced colorectal cancer. The basis for approval is an improvement in survival supported by an improved time-to-tumor progression.

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Table 9: Summary of efficacy findings

	IFL N=264	FOLFOX4 N=267	IROX N=264
Survival (ITT)			
Number of deaths N (%)	192 (72.7)	155 (58.1)	175 (66.3)
Median survival (months)	14.6	19.4	17.6
95% confidence interval	(12.4-16.7)	(17.9-21.0)	(15.8-19.6)
TTP (ITT)			
Percentage of progressors	81.8	82.8	89.4
Median TTP (months)	6.9	8.7	6.5
95% confidence interval	(6.0-7.5)	(7.8-9.8)	(5.8-7.6)
Response Rate (investigator assessment))			
Patients with measurable disease	212	210	215
Complete response N (%)	5 (2.4)	13 (6.2)	7 (3.3)
Partial response N (%)	64 (30.2)	82 (39.0)	67 (31.2)
Complete and partial response N (%)	69 (32.5)	95 (45.2)	74 (34.4)
95% confidence interval	(26.2-38.9)	(38.5-52.0)	(28.1-40.8)

Table 10: 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 FDA's Statistical Reviewer's the p-value is roughly 0.00007.

² Not submitted. - based on FDA's Statistical Reviewer's calculations.

Table 11: 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 FDA's Statistical Reviewer's Calculations.

Approximately 265 patients were treated in each of the three arms. These arms consisted of irinotecan +5FU/LV (IFL; control regimen), oxaliplatin + 5FU/LV (FOLFOX 4; investigational arm of interest) and irinotecan + oxaliplatin (IROX). Overall survival was improved by almost 5 months from 14.6 months in the IFL arm to 19.4 months in the FOLFOX 4 arm. An improvement in TTP supported the findings of a better overall survival which improved by about

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2 months (IFL: 6.9 months and FOLFOX 4: 8.7 months). The response rate was based on investigator assessment and could not be verified due to incomplete data.

C. Detailed Review of Trials by Indication

Study EFC 7462 (N9741) was submitted as the major trial to support the approval of oxaliplatin in first-line treatment of metastatic colorectal cancer. This protocol was activated on October 27, 1998 as a 4-arm study. The study had accrued 57 patients when three more oxaliplatin combination arms were added. The protocol as submitted to CDER for the first time on March 12, 1999 and salient amendments will be reviewed, followed by analysis of results obtained from the study. The oxaliplatin arm with 5FU/LV in the FOLFOX 4 regimen was added on April 23, 1999, after this amendment.

Whenever possible, the protocol is written verbatim below, and at other times will be paraphrased. If verbatim, the font will be in italics.

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Protocol:**Protocol Title:**

A Randomized Phase III Trial of Two Different Regimens of CPT-11 Plus 5-Fluorouracil and Leucovorin, Two Different Regimens of Oxaliplatin (OXAL) Plus 5-Fluorouracil and Leucovorin, and One Regimen of OXAL and CPT-11 Compared to 5-Fluorouracil and Leucovorin as Initial Treatment of Patients With Advanced Adenocarcinoma of the Colon and Rectum (Addendum 2)

Modified to:

A Randomized Phase III Trial of Combinations of Oxaliplatin (OXAL), 5-Fluorouracil (5-FU), and Irinotecan (CPT-11) as Initial Treatment of Patients With Advanced Adenocarcinoma of the Colon and Rectum (EFC7462/N9741) (Addendum 8)

Study Period:

795 patient cohort

Date first patient enrolled: May 20, 1999

Date last patient enrolled: April 25, 2001

Cut-off date for analysis: February 28 2003

Sites:

Two hundred and ninety one sites in USA and Canada enrolled up to a maximum of 22 patients at one site.

Objectives:**Primary Objective:**

The primary objective of this trial is to compare the time to progression in patients with locally advanced or metastatic colorectal cancer (previously untreated for advanced disease) who receive 1 of 5 experimental regimens, 2 of which are CPT-11 + 5-FU + CF regimens, 2 of which are OXAL + 5-FU + CF, and 1 of which is CPT-11 + OXAL to those receiving standard 5-FU and CF.

[CF: calcium folinate (leucovorin); OXAL: Oxaliplatin]

Secondary Objectives:

- *The secondary objective of this trial is to compare the time to progression of patients receiving each of the 5 experimental regimens.*
- *The other secondary objectives include evaluation of toxicity, response rate, time to treatment failure, and survival.*
- *To compare quality-of-life parameters in patients on these regimens.*

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Reviewer's Comment:

QoL claim is not being made in this NDA and will not be reviewed in detail. The data will be reviewed for survival as a primary endpoint for FDA.

Study Design:

This will be a randomized phase III trial with equal allocation to each of 6 regimens: 5-FU + Leucovorin (the control regimen), 5-FU + Leucovorin+ CPT-11 given in two different combinations, 5-FU + Leucovorin+ OXAL given in two different combinations, and CPT-11 + OXAL. The primary endpoint of this study is time to tumor progression.

As noted in the review, arms were added to and deleted from the study while the study was being conducted. These changes will be described in the protocol amendments section. Only 3 arms (IFL, FOLFOX4, and IROX) will be reviewed as discussed in this document.

Study Population:**Inclusion Criteria:***Required characteristics:*

- *Known locally advanced, locally recurrent, or metastatic colorectal carcinoma not curable by surgery or amenable to radiation therapy with curative intent.*
- *Histologically or cytologically documented locally advanced or metastatic colorectal cancer. The site of the primary lesion must be or have been confirmed endoscopically, radiologically, or surgically to be or have been in the large bowel.*

Patient with a history of colorectal cancer treated by surgical resection who develop radiological or clinical evidence of metastatic cancer do not require histological or cytological confirmation of metastatic disease unless:

1) either an interval of greater than five years has elapsed between the primary surgery and the development of metastatic disease

or

2) the primary cancer was a Duke's A or B1 lesion.

clinicians should consider biopsy of lesion to establish the diagnosis of metastatic colorectal cancer in each case if there is substantial clinical ambiguity regarding the nature or source of apparent metastases.

- *Measurable or evaluable disease.*
- *Life expectancy of ≥ 12 weeks.*

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- *Age >18 years. Ability to complete questionnaire(s) by themselves or with assistance.*
- *All of the following: ≥ 4 weeks must have elapsed from the time of major surgery and patients must have recovered from the effects (e.g., laparotomy) ≥ 2 weeks must have elapsed from the time of minor surgery and patients must have recovered from the operation. (Insertion of a vascular access device is not considered major or minor surgery.) ≥ 4 weeks must have elapsed from the time of major radiotherapy (e.g., chest or bone palliative RT)*
- *Laboratory values obtained ≤ 14 days prior to randomization:*
 - Absolute granulocyte count (AGC) $>1500/\text{mm}^3$ ($\geq 150 \times 10^9/\text{L}$)*
 - Platelets $\geq 100,000/\text{mm}^3$ ($\geq 100 \times 10^9/\text{L}$)*
 - Hemoglobin ≥ 9 gm/dL (patients may be transfused to achieve this requirement) $>90\text{g/L}$*
 - Creatinine $\leq 1.5 \times \text{UNL}$.*
 - Total bilirubin ≤ 1.5 mg/dL ($\leq 25.65 \mu\text{mols/L}$), regardless of whether patients have liver involvement secondary to tumor*
 - Aspartate aminotransferase (AST) $\geq 5 \times \text{UNL}$*
 - Alkaline phosphatase $\geq x \text{ ULN}$.*
- *Patients of childbearing potential must agree to use an effective method of contraception (condoms, diaphragm, birth control pills, injections, foam, intrauterine device IUD), or abstinence, etc.) as there is evidence to demonstrate that this regimen may be to a developing fetus or nursing child.*
- *Patients may have received adjuvant therapy for resected Stage II, III or IV disease with any regimen containing 5-FU or with immunotherapy providing that at least 12 months have elapsed from the time the adjuvant therapy was concluded and that recurrent disease was documented.*
- *For NCIC-CTG Centres: Patient is able (i.e., sufficiently fluent) and willing to complete the quality of life assessments in either English or French. The baseline assessment must already have been completed. Inability (illiteracy in English or French, loss of sight, or other equivalent reason) to complete the assessments will not make the patient ineligible for the study. However, ability but unwillingness to complete the assessments will make the patient ineligible.*

Exclusion Criteria:

Any of the following:

- *Prior chemotherapy for advanced colorectal cancer Prior radiotherapy to greater than 15% of bone marrow (Appendix IV) Concurrent use of other investigational agents*
- *Active or uncontrolled infection.*

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- *Symptomatic sensory peripheral neuropathy.*
- *Any of the following conditions: Uncontrolled high blood pressure Unstable angina Symptomatic congestive heart failure Myocardial infarction ≤ 6 months prior to randomization Serious uncontrolled cardiac arrhythmia New York Heart Association classification III or IV.*
- *Pregnant or nursing women. The effects of OXAL, CPT-11 and 5-FU on a developing human fetus at the recommended therapeutic dose are unknown. For this reason and because DNA alkylating agents are known to be teratogenic, women of childbearing potential and men must agree to use adequate contraception (hormonal or barrier method of birth control) prior to study entry and for the duration of study participation. Should a woman become pregnant or suspect she is pregnant while participating on this study, she should inform her treating physician immediately. Because the risk of toxicity in nursing infants secondary to OXAL, CPT-11 and 5-FU treatment of the mother is unknown but may be harmful, breastfeeding should be discontinued, if the mother is treated with OXAL, CPT-11 and 5-FU.*
- *Prior malignancy, except for adequately treated basal cell or squamous cell skin cancer, adequately treated noninvasive carcinomas, or other cancer from which the patient has been disease-free for at least five years.*
- *Known central nervous system metastases or carcinomatous meningitis.*
- *Interstitial pneumonia or extensive and symptomatic interstitial fibrosis of the lung.*
- *Pleural effusion or ascites which cause respiratory compromise (\geq Grade 2 dyspnea).*
- *Predisposing colonic or small bowel disorders in which the symptoms are uncontrolled as indicated by baseline pattern of >3 loose stools daily in patients without a colostomy or ileostomy. Patients with a colostomy or ileostomy may be entered at investigator discretion.*
- *Medical or psychiatric conditions which, in the opinion of the investigator, make participation in an investigational trial of this nature a poor risk.*

Reviewer's Comments:

Despite TTP being the primary objective, patients with evaluable lesions could be enrolled in to the trial. This may lead to an under-powered trial to evaluate TTP. FDA's primary endpoint has traditionally been an improvement in over all survival for first-line therapy of colon cancer. Enrollment of evaluable disease patients should not present a problem.

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Study Procedures:

As noted before, some treatment arms were added, whereas others were deleted. All treatment arms that were at any time included in the study are given in table 9. Table 10 gives the regimen of Arms A, F and G, which will be reviewed in this submission.

Table 12: All Treatment Arms in Study EFC 7462

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 13: Regimens used in Arms A, F and G

Arm A	IFL	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 F	FOLFOX4	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	IROX	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

Reviewer's Comment:

The IFL dose was modified to CPT-11 100 mg/m² and 5-FU 400 mg/m² at amendment 12 dated 6/29/2001 due to toxicity noted in the first 2 treatment cycles.

Although Arms B and D were ongoing at the time of amendment 2, only the treatment procedures for Arms A, F and G will be given below.

On Arm A (IFL), a cycle is defined as the 6-week period given in the following table.

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Table 14: Procedures on Arm A

Tests and Procedures	≤14 days prior to randomization	Arm A - Saltz Regimen					
		Study Week (Repeat 6 Week Schedule Until PROG)*					
		Week 1	Week 2	Week 3	Week 4	Week 5	Week 6
RX**		d1	d1	d1	d1		
Serum Pregnancy Test ¹	X						
Chest X-ray	X ²	X ³					
Physical Exam: (weight, ECOG PS, Ht, & medical history) ^{4,5}	X	X ⁶					
Serum Chem ⁷	X	X ⁸					
Tumor Measurement	X ¹⁴	X ⁸					
WBC, hgb, Differential, Platelets	X	X	X	X	X	X ⁹	X ⁹
Prothrombin Time (PT) ¹⁰	X	X ⁶	X	X	X	X	X
Interval Eval (Phone or Office Visit) ¹¹			X	X		X	X
OOL ¹²	X	X ¹³					

*If patient has CR confirmed for 2 consecutive cycles, at physician discretion treatment may be discontinued. Patients should continue to follow week of the test schedule for each cycle. Treatment may be initiated at time of progression.

**First day of therapy patient receives patient instructions for preventing and treating diarrhea

1. For females of childbearing potential. Must be done ≤7 days prior to randomization.
2. ≤30 days prior to randomization.
3. If not used to evaluate indicator lesion, start at cycle 4 and repeat every third cycle (cycles 4, 7, 10, etc.).
4. Include baseline # stools, maximum stools per day per cycle, number of stools per day over 24-hour period prior to retreatment.
5. Pretreatment medical history should be complete. At subsequent evaluations directed medical histories (relevant to the colon cancer and other active medical problems) may be done. Ht needed at baseline only.
6. For all cycles, except cycle 1,
7. Chemistries: Alkaline Phosphatase (U/L), AST (SGOT) (U/L), Total Bilirubin (mg/dL) (μmol/L), Creatinine (mg/dL) (μmol/L).
8. For 6 of the first 7 cycles (cycles 2, 3, 4, 5, 6, 7), or until CR or PR Use same imaging method throughout study. All responses (CR, PR) must be confirmed by a 6-week follow-up assessment of indicator lesion(s). Once confirmation of response is obtained or patient is stable for 7 cycles, evaluations may be done as infrequently as every 12 weeks thereafter. Patients who progress go off study.
9. If ANC ≤1000, weekly CBC's until ANC >1000 (NCIC-CTG: If ANC ≤100, weekly CBC's until ANC >100). Once stable dose is established, interim counts are not required thereafter.
10. Required only for patients taking coumadin as therapy such as for DVT, PE, or cardiac disease. Weekly until stable and therapeutic for 2 consecutive cycles. If taking 1 mg/day for prophylaxis of catheter-related thrombosis, no PT is required although PT should be followed at physician discretion.

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11. See Section 10.5. Only required for first 2 cycles.
12. Quality-of-life assessments (see Appendix VII, Administering Quality-of-Life Questionnaires: Instructions for Clinical Research Associates [CRAs]: Symptom Distress Scale, Uniscale, and Supplemental QOL Questions (Appendices VIII, IX, and XIVJ) are to be administered prior to initiation of treatment and prior to every other course of treatment
13. Every other cycle starting prior to cycle 2 (cycles 2, 4, 6, etc.) and at discontinuation of treatment.
14. Pretreatment CT scan allowed ≤ 21 days prior to randomization.

On Arm F (FOLFOX4), a cycle is defined as the 2-week period given in the following table

Table 15: Procedures on Arm F

(Sponsor Table from amendment 2)

Arm F - OXAL Infusion Regimen			
Tests and Procedures	≤ 14 days prior to randomization	Study Week (Repeat 2-Week Schedule Until PROG)*	
		Week 1	Week 2
RX		d1-5	
Serum Pregnancy Test ¹	X		
Chest X-ray	X ²	X ³	
Physical Exam: (weight, ECOG PS, Ht, & medical history) ^{4,5}	X	X ⁶	
Serum Chem ⁷	X	X ⁶	
Tumor Measurement	X ¹⁴	X ⁸	
WBC, hgb, Differential, Platelets	X	X	X ⁹
Prothrombin Time (PT) ¹⁰	X	X ⁶	X
Interval Eval (Phone or Office Visit) ¹¹			X
QOL ¹²	X	X ¹³	

*If patient has CR confirmed for 2 consecutive cycles, at physician discretion treatment may be discontinued. Patient should continue to follow week 1 of the test schedule for each cycle.

Treatment may be initiated at time of progress

1. For females of childbearing potential. Must be done 57 days prior to randomization.
2. ≤ 30 days prior to randomization.
3. If not used to evaluate indicator lesion, start at cycle 10 and repeat every ninth cycle (cycles 10, 19, 28, etc.).
4. Include baseline # stools, maximum stools per day per cycle, number of stools per day over 24-hour period prior to retreatment.
5. Pretreatment medical history should be complete. At subsequent evaluations directed medical histories (relevant to the colon cancer and other active medical problems) may be done. Ht needed at baseline only.
6. For all cycles, except cycle 1.

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7. *Chemistries: Alkaline Phosphatase (U/L), AST (SGOT) (U/L), Total Bilirubin (mg/dL) ($\mu\text{mol/L}$), Creatinine (mg/dL) ($\mu\text{mol/L}$).*
8. *For 6 of the first 19 cycles (cycles 4, 7, 10, 13, 16, 19), or until CR or PR Use same imaging method throughout study. All responses (CR, PR) must be confirmed by a 6-week follow-up assessment of indicator lesion(s). Once confirmation of response is obtained or patient is stable for 19 cycles, evaluations may be done as infrequently as every 12 weeks thereafter. Patients who progress go off study.*
9. *If ANC ≤ 1000 , weekly CBC's until ANC > 1000 (NCIC-CTG: If ANC ≤ 100 , weekly CBC's until ANC > 100). Once stable dose is established, interim counts are not required thereafter.*
10. *Required only for patients taking coumadin as therapy such as for DVT, PE, or cardiac disease. Weekly until stable and therapeutic for 4 consecutive cycles. If taking 1 mg/day for prophylaxis of catheter-related thrombosis, no PT is required although the PT should be followed at physician discretion.*
11. *See Section 10.5. Only required for first 2 cycles.*
12. *Quality-of-life assessments (see Appendix VU, Administering (Quality-of-Life Questionnaires: instructions for Clinical Research Associates [CRAs]: Symptom Distress Scale, Uniscale, and Supplemental QOL Questions [Appendices VIII, IX, and XIVJ) are to be administered prior to initiation of treatment and prior to every other course of treatment.*
13. *Every sixth cycle starting prior to cycle 4 (cycles 4, 10, 16, etc.).*
14. *Pretreatment CT scan allowed & 1 days prior to randomization.*

Reviewer's comment:

Although cycle length is unequal in these arms, IFL (control arm) and OXAL (investigational arm) tumor measurements will be performed every 6 weeks, at intervals intended to be equal in both of these arms.

According to addendum 12, HUS was noted possibly in association with oxaliplatin. Oxaliplatin was to be discontinued for Hct $< 25\%$, plts $< 100,000$ and creatinine ≥ 1.6 mg/dL.

On Arm G(IROX), a cycle is defined as the 3-week period given in the following table
(Sponsor Table from amendment 2)

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Table 16: Procedures on Arm G

Arm G - OXAL & CPT-11 Regimen				
Tests and Procedures	≤14 days prior to randomization	Study Week (Repeat 3-Week Schedule Until PROG)*		
		Week 1	Week 2	Week 3
RX**		d1		
Serum Pregnancy Test ¹	X			
Chest X-ray	X ²	X ³		
Physical Exam: (weight, ECOG PS, Ht, & medical history) ^{4,5}	X	X ⁶		
Serum Chem ⁷	X	X ⁶		
Tumor Measurement	X ¹⁴	X ⁸		
WBC, hgb, Differential, Platelets	X	X	X ⁹	X ⁹
Prothrombin Time (PT) ¹⁰	X	X ⁶	X	X
Interval Eval (Phone or Office Visit) ¹¹			X	X
QOL ¹²	X	X ¹³		

*If patient has CR confirmed for 2 consecutive cycles, at physician discretion treatment may be discontinued. Patients should continue to follow week 1 of the test schedule for each cycle. Treatment may be initiated at time of progression.

**First day of therapy patient receives patient instructions for preventing and treating diarrhea (VI). See Section 9.1.

1. For females of childbearing potential. Must be done ≤7 days prior to randomization.
2. ≤30 days prior to randomization.
3. If not used to evaluate indicator lesion, start at cycle 7 and repeat every sixth cycle (cycles 7, 13, 19, etc.).
4. Include baseline # stools, maximum stools per day per cycle, number of stools per day over 24-hour period prior to retreatment.
5. Pretreatment medical history should be complete. At subsequent evaluations directed medical histories (relevant to the colon cancer and other active medical problems) may be done. Ht needed at baseline only.
6. For all cycles, except cycle 1.
7. Chemistries: Alkaline Phosphatase (U/L), AST (SGOT) (U/L), Total Bilirubin (mg/dL) (μmoUL), Creatinine (mg dL) (μmoUL).
8. For 6 of the first 13 cycles (cycles 3, 5, 7, 9, 11, 13), or until CR or PR. Use same imaging method throughout study. All responses (CR, PR) must be confirmed by a 6-week follow-up assessment of indicator lesion(s). Once confirmation of response is obtained or patient is stable for 14 cycles, evaluations may be done as infrequently as every 12 weeks thereafter. Patients who progress go off study.
9. If ANC ≤1000, weekly CBC's until ANC >1000 (NCIC-CTG: If ANC ≤ 100, weekly CBC's until ANC >100). Once stable dose is established, interim counts are not required thereafter.

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10. Required only for patients taking coumadin as therapy such as for DVT, PE, or cardiac disease. Weekly until stable and therapeutic for 3 consecutive cycles. If taking 1 mg/day for prophylaxis of catheter-related thrombosis, no PT is required although the PT should be followed at physician discretion.

11. See Section 10.5. Only required for first 2 cycles.

12. Quality-of-life assessments (see Appendix VG, Administering Quality-of-Life Questionnaires: Instructions for Clinical Research Associates [CRAsJ: Symptom Distress Scale, Uniscale, and Supplemental QOL Questions [Appendices VIII, IX, and XIVJ) are to be administered prior to initiation of treatment and prior to every other course of treatment. 13. Every fourth cycle starting prior to cycle 3 (cycles 3, 7, 11, etc.).

14. Pretreatment CT scan allowed ≤ 21 days prior to randomization.

Stratification Factors:

ECOG PS: 0, 1 vs. 2.

Prior adjuvant chemotherapy: Yes vs. no.

Prior immunotherapy: Yes vs. no.

Age <65 vs. ≥ 65 .

Membership: Intergroup vs. Expanded Participation Project (EPP).

Dose Modifications:

Table 17: Dose Reduction Steps for Arm A (Saltz Regimen)

Dose Reduction Steps - Arm A*				
	Starting Dose	Dose Level - 1	Dose Level - 2	Dose Level - 3
CPT-11	125 mg/m ²	100 mg/m ²	75 mg/m ²	50 mg/m ²
5-FU	500 mg/m ²	400 mg/m ²	300 mg/m ²	200 mg/m ²

*CF dose remains fixed at 20 mg/m²(not adjusted).

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Table 18: Recommended Dose Modifications on Arm A

Recommended Dose Modifications - Arm A - Saltz Regimen			
Toxicity NCI Grade* (Value)	During a Course of Therapy**	Dose Level for Subsequent Cycles Based on Interval Toxicity***	At Time of Retreatment
No toxicity	Maintain dose level	Maintain dose level	Maintain dose level
Neutropenia (ANC) Grade 1 (1500 to 1999/mm ³) (NCIC: 150 to 199.9 X 10 ³ /L) Grade 2 (1000 to 1499/mm ³) (NCIC: 100 to 149.9 X 10 ³ /L) Grade 3 (500 to 999/mm ³) (NCIC: 50 to 99.9 X 10 ³ /L) Grade 4 (<500/mm ³) (NCIC: < 50 X 10 ³ /L)	Maintain dose level ↓ 1 dose level Omit dose, then ↓ 1 dose level when resolved to ≤Grade 2 Omit dose, then ↓ 2 dose levels when resolved to ≤Grade 2	Maintain dose level Maintain dose level ↓ 1 dose level ↓ 2 dose levels	If ANC <1500 (NCIC: ANC <150) at start of cycle, hold and check weekly then treat based on interval toxicity. If ANC <1500 2 weeks after a new cycle should begin, discontinue therapy.
Neutropenic fever (Grade 4 neutropenia & ≥Grade 2 fever)	Omit dose, then ↓ 2 dose levels when resolved	↓ 2 dose levels	
Other hematologic toxicities	Dose modifications for leukopenia or thrombocytopenia during a course of therapy, at the start of subsequent courses of therapy, and at time of retreatment are also based on NCI toxicity criteria (CTC Version 2.X) and are the same as recommended for neutropenia above.		
Diarrhea Grade 1 Grade 2 Grade 3 Grade 4	Maintain dose level ↓ 1 dose level Omit dose, then ↓ 1 dose level when resolved to ≤Grade 2 Omit dose, then ↓ 2 dose levels when resolved to ≤Grade 2	Maintain dose level Maintain dose level ↓ 1 dose level ↓ 2 dose levels	If Grade ≥2 diarrhea at start of cycle, hold and check weekly then treat based on interval toxicity. If Grade ≥2 diarrhea after 2 weeks, discontinue therapy.
Other nonhematologic toxicities ^{1,2}	Dose modifications for other nonhematologic toxicities during a course of therapy, at the start of subsequent courses of therapy, and at time of retreatment are also based on NCI toxicity criteria (CTC Version 2.X) and are the same as recommended for diarrhea above.		

If the patient experiences significant toxicity requiring a dose reduction at the start of the next course, then the dose will remain lowered for that entire subsequent course. If that course is completed with no further toxicities greater than Grade 2, then the dose may be increased. At the investigator's discretion, one level at a time during an entire course in the following courses until the patient again experiences a toxicity greater than Grade 2. When this occurs, the dose will remain one level lower than the dose that caused the toxicity for all subsequent courses.

If a patient requires omission of the week 2 or week 3 dose, the investigator may decide to consider that one of the two rest weeks. This patient would then receive a 1-week, rather than a 2-week, break after the completion of 4 doses in a 6-week treatment course (three-week treatment, two-week rest). The intention is to maintain greater dose intensity over the treatment period if possible.

Some patients will develop toxicity and require omission of the week 4 dose. In these patients, the investigator may decide to start the next course two weeks later than shortening the course length to 5 weeks (three-week treatment, two-week rest). However, all dose modification conditions still apply.

The dose of CF will not be adjusted due to toxicity. It should remain at 20 mg/m for all courses. CF will be given immediately prior to each 5-FU dose; the, if 5-FU is delayed CF will be delayed.

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Table 19: Dose Reduction Steps - Arm F (FOLFOX)

Dose Reduction - Arm F*				
	Starting Dose	Dose Level - 1	Dose Level - 2	Dose Level - 3
OXAL	85 mg/m ²	65 mg/m ²	65 mg/m ²	50 mg/m ²
5-FU Bolus/Infus.	400-600 mg/m ²	400-600 mg/m ²	300-450 mg/m ²	300-450 mg/m ²

*CF dose remains fixed at 200 mg/m² (not adjusted).

Reviewer's Comment:

Dose reduction to FOLFOX4 arm were changed in addendum 6 on 1/28/2000 as follows

Dose Reduction - Arm F*			
	Starting Dose	Dose Level - 1	Dose Level - 2
OXAL	85 mg/m ²	65 mg/m ²	50 mg/m ²

Dose Reduction - Arm F*			
5-FU	Starting Dose	Dose Level - 1	Dose Level - 2
Bolus	400 mg/m ²	320 mg/m ²	240 mg/m ²
Infusion	600 mg/m ²	500 mg/m ²	400 mg/m ²

By this addendum, absolute values for 5-FU instead of ranges were given.

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Table 20: Recommended Dose Modifications on Arm F

Recommended Dose Modifications - Arm F (OXAL Infusion Regimen)			
Toxicity NCI Grade* (Value)	During a Course of Therapy**	Dose Level for Subsequent Cycles Based on Interval Toxicity***	At Time of Retreatment
No toxicity		Maintain dose level	Maintain dose level
Neutropenia (ANC) Grade 1 (1500 to 1999/mm ³) (NCIC: 150 to 199.9 X 10 ³ /L) Grade 2 (1000 to 1499/mm ³) (NCIC: 100 to 149.9 X 10 ³ /L) Grade 3 (500 to 999/mm ³) (NCIC: 50 to 99.9 X 10 ³ /L) Grade 4 (<500/mm ³) (NCIC: <50 X 10 ³ /L)		Maintain dose level Maintain dose level ↓ 1 dose level ↓ 2 dose levels	If ANC <1500 (NCIC: ANC <150) at start of cycle, hold and check weekly then treat based on interval toxicity. If ANC <1500 after 2 weeks, discontinue therapy.
Neutropenic fever (Grade 4 neutropenia & ≥Grade 2 fever)		↓ 2 dose levels	
Other hematologic toxicities		Dose modifications for leukopenia or thrombocytopenia at the start of subsequent courses of therapy and at time of retreatment are also based on NCI toxicity criteria (CTC Version 2.X) and are the same as recommended for neutropenia above.	
Diarrhea Grade 1 Grade 2 Grade 3 Grade 4		Maintain dose level Maintain dose level ↓ 1 dose level ↓ 2 dose levels	If Grade ≥2 diarrhea at start of cycle, hold and check weekly then treat based on interval toxicity. If Grade ≥2 diarrhea after 2 weeks, discontinue therapy.
Other nonhematologic toxicities ^{1,2}		Dose modifications for other nonhematologic toxicities at the start of subsequent courses of therapy, and at time of retreatment are also based on NCI toxicity criteria (CTC Version 2.X) and are the same as recommended for diarrhea above.	
Neurologic toxicities	See Section 8.8 for toxicity scale and dose modifications.		
If the patient experiences significant toxicity requiring a dose reduction at the start of the next course, then the dose will remain lowered for that entire subsequent course. If that course is completed with no further toxicities greater than Grade 2, then the dose may be increased, at the investigator's discretion, one level at a time during an entire course, in the following courses, until the patient again experiences a toxicity greater than Grade 2. When this occurs, the dose will remain one level lower than the dose that caused the toxicity for all subsequent courses.			
The dose of CF will not be adjusted due to toxicity. It should remain at 200 mg/m ² for all courses. CF will be given immediately prior to each 5-FU dose; thus, if 5-FU is delayed, CF will be delayed.			

* National Cancer Institute Common Toxicity Criteria (CTC Version 2.X).

** Refers to last dose level received.

*** Refers to initial dose used in previous course.

1. For mucositis/stomatitis decrease only 5-FU, not OXAL.

2. Exceptions: alopecia, fatigue, anorexia, nausea/vomiting if can be controlled by antiemetics, viral infections.

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Table 21: OXAL Dose Modifications for Neurologic Toxicity

Toxicity (Grade)	Duration of Toxicity		Persistent ¹ Between Cycles
	1 - 7 Days	>7 Days	
Paresthesias/dysesthesias ² of short duration that resolve and do not interfere with function (Grade 1)	no change	no change	no change
Paresthesias/dysesthesias ² interfering with function, but not activities of daily living (ADL) (Grade 2)	no change	no change	↓25%
Paresthesias/dysesthesias ² with pain or with functional impairment that also interfere with ADL (Grade 3)	1 st time: ↓25% 2 nd time: ↓25%	1 st time: ↓25% 2 nd time: ↓25%	Stop
Persistent paresthesias/dysesthesias that are disabling or life-threatening (Grade 4)	Stop	Stop	Stop
Pharyngo-laryngeal dysesthesias	no change	↑ duration of infusion to 6 hours	↑ duration of infusion to 6 hours

¹Not resolved by the beginning of the next cycle.

²May be cold-induced.

Table 22: Dose Reduction Steps - Arm G (IROX)

Dose Reduction - Arm G*				
	Starting Dose	Dose Level - 1	Dose Level - 2	Dose Level - 3
OXAL	85 mg/m ²	65 mg/m ²	65 mg/m ²	50 mg/m ²
CPT-11	200 mg/m ²	200 mg/m ²	160 mg/m ²	160 mg/m ²

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Table 23: Recommended Dose Modifications on Arm G

Recommended Dose Modifications - Arm G - (OXAL Plus CPT-11)			
Toxicity NCI Grade* (Value)	During a Course of Therapy**	Dose Level for Subsequent Cycles Based on Interval Toxicity***	At Time of Retreatment
No toxicity			
Neutropenia (ANC) Grade 1 (1500 to 1999/mm ³) (NCIC: 150 to 199.9 X 10 ³ /L) Grade 2 (1000 to 1499/mm ³) (NCIC: 100 to 149.9 X 10 ³ /L) Grade 3 (500 to 999/mm ³) (NCIC: 50 to 99.9 X 10 ³ /L) Grade 4 (<500/mm ³) (NCIC: < 50X 10 ³ /L)		Maintain dose level	Maintain dose level
		Maintain dose level	If ANC <1500 (NCIC: ANC <150) at start of cycle, hold and check weekly then treat based on interval toxicity. If ANC <1500 after 2 weeks, discontinue therapy.
		Maintain dose level	
		↓ 1 dose level	
	↓ 2 dose levels		
Neutropenic fever (Grade 4 neutropenia & ≥Grade 2)		↓ 2 dose levels	
Other hematologic toxicities		Dose modifications for leukopenia or thrombocytopenia during a course of therapy, at the start of subsequent courses of therapy, and at time of retreatment are also based on NCI toxicity criteria (CTC Version 2.X) and are the same as recommended for neutropenia above.	
Diarrhea Grade 1 Grade 2 Grade 3 Grade 4		Maintain dose level	If Grade ≥2 diarrhea at start of cycle, hold and check weekly then treat based on interval toxicity. If Grade ≥2 diarrhea after 2 weeks, discontinue therapy.
		Maintain dose level	
		↓ 1 dose level	
		↓ 2 dose levels	
Other nonhematologic toxicities¹		Dose modifications for other nonhematologic toxicities during a course of therapy, at the start of subsequent courses of therapy, and at time of retreatment are also based on NCI toxicity criteria (CTC Version 2.X) and are the same as recommended for diarrhea above.	
Neurologic toxicities	See Section 8.8 for toxicity scale and dose modifications.		

If the patient experiences significant toxicity requiring a dose reduction at the start of the next course, then the dose will remain lowered for that entire subsequent course. If that course is completed with no further toxicities greater than Grade 2, then the dose may be increased, at the investigator's discretion, one level at a time during an entire course, in the following courses, until the patient again experiences a toxicity greater than Grade 2. When this occurs, the dose will remain one level lower than the dose that caused the toxicity, for all subsequent courses.

* National Cancer Institute Common Toxicity Criteria (CTC Version 2.X).

** Refers to last dose level received.

*** Refers to initial dose used in previous course.

1. Exceptions: alopecia, fatigue, anorexia, nausea/vomiting if can be controlled by antiemetics, viral infections.

Definition of response:

For a patient to qualify for complete response, partial response, or regression, none of the factors constituting progression may be present (see below).

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Complete response (CR): total disappearance of all evidence of tumor.

Partial response (PR)

Bidimensional indicator lesion(s).

>50% reduction in the sum of the products of the largest perpendicular diameters of the indicator lesion(s), single or multiple sites, chosen prior to therapy.

According to the protocol, all responses (CR, PR) must be confirmed by a 6-week follow-up assessment of indicator lesion(s).

Criteria for regression (REGR)

Definite decrease in size of evaluable tumor that can be documented by photographs, x-ray films, ultrasound (US) or other imaging modalities.

Progression (PROG)

Tumor progression will be declared if one or more of the following criteria are met. (It is understood that in the event of equivocal or conflicting observations that the investigator may elect to declare the patient stable and continue therapy on study to gain additional information.)

- *Appearance of new lesion(s).*
- *Increase in tumor size:
Patients with measurable indicator lesion(s) who have met the criteria for partial regression: Significant increase in the size of indicator lesion(s) compared to the smallest measurements while on study. Progression will be declared when the indicator lesion has increased in size from the smallest measurement by at least 50% of the decrease in size between pretreatment measurements and smallest measurement at the point of maximum tumor reduction.*

Example - bidimensional indicator lesion

Pretreatment - Product of perpendicular diameters = 12 cm²

Smallest measurements at the point of maximum tumor reduction = 2 cm².

The reduction in the product of perpendicular diameters is 10 cm² (12 cm² - 2 cm²). 50% of the reduction is 5 cm² (10 cm² divided by 2). Therefore, the product of perpendicular diameters meeting the criteria for progression is 7 cm² (2 cm² + 5 cm²).

Patients with measurable indicator lesion(s) who have met the criteria for complete response: Progression will be declared if a measurable tumor mass meets the criteria in Section 11.1.

According to section 11.1 of the protocol, minimum size for evaluation, i.e., physical examination or chest x-ray 1.0 cm, Liver lesion (by CT scan or MRI scan) 2.0 cm, Intra-

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abdominal mass (by CT scan or MRI scan) 2.0 cm or if new lesions appear. (see footnote 8 of tables on procedures on arm A, F and G).

- *Patients with measurable indicator lesion(s) who have not met the criteria for complete or partial response: >25% increase in measurements of indicator lesion(s) compared to pretreatment measurements.*
- *Patients with evaluable disease who have met the criteria for tumor regression: Definite increase in tumor size compared to the smallest size of the tumor while on study.*
- *Patients with evaluable disease who have not met the criteria for tumor regression: Definite increase in the tumor size compared to pretreatment tumor size.*

Stable (STAB).

Failure to meet the criteria for complete response, partial response, regression, or progression.

Treatment/Follow-up Decision at Evaluation of Patient

If a patient refuses the treatment assignment (and is classified as a cancel), it is necessary to provide follow-up information. The patient will go directly to the event-monitoring phase of the study. On-study material is to be submitted.

Patients with confirmed CR (CR on 2 consecutive cycles) may (at investigator discretion) discontinue therapy. Treatment may be reinitiated at the time of progression (see Section 7.4). Alternatively, such patients may continue to receive treatment until disease progression.

According to section 7.4, "If patient has a CR confirmed for 2 consecutive cycles, at physician discretion, treatment may be discontinued. Patients should continue to follow week 1 of the test schedule for each cycle. At time of progression, treatment may be reinitiated on the same study arm at the same dose level that the patient was receiving at time of discontinuation."

Patients with an objective status of PR or STAB will continue on treatment until disease progression or intolerable toxicity occurs.

Criteria for Removal From Study

- *Progression of disease.*
- *Unacceptable toxicity.*
- *Patient may request to withdraw from the study at any time for any reason.*
- *Intercurrent, noncancer-related illness that prevents continuation of therapy or regular follow-up.*
- *All reasons for discontinuation of treatment must be documented in an off-study note (i.e., progression, toxicity, refusal, etc.).*

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Statistical Considerations and Methodology

Design: This will be a randomized phase III trial with equal allocation to each of 6 regimens: 5-FU + Leucovorin (the control regimen), 5-FU + Leucovorin+ CPT-11 given in two different combinations, 5-FU + Leucovorin+ OXAL given in two different combinations, and CPT- 11 + OXAL.

The primary endpoint of this study is time to tumor progression.

Time-to-tumor progression is defined as the time from start of therapy to documentation of disease progression. Patients who die without documentation of progression will be considered to have had tumor progression at the time of death unless there is documented evidence that no progression occurred before death. Patients who fail to return for evaluation after beginning therapy will be censored for progression on the last day of therapy. Patients who experience major treatment violations will be censored for progression on the date the treatment violation occurred.

In patients with a confirmed CR who discontinue therapy and then restart therapy upon evidence of progression, time to tumor progression will be defined as the time from start of therapy to documentation of further disease progression following the reinitiation of therapy.

Reviewer's Comment:

The above definition of CR for patient who discontinue and restart therapy should be noted as it may affect the TTP.

If at the time of death, there is no documentation of tumor progression, the patient will be considered to have had progression at the time of death. This adds an unknown amount of time to TTP.

Patients who fail to return for evaluation after beginning therapy will be censored for progression on the last day of therapy. This should be the last date of assessment.

Accrual: Accrual to this trial should be rapid. The previous NCCTG study in this patient population (89-46-52) accrued approximately 160 patients a year. As the current trial is an intergroup effort, enrollment should be substantially increased relative to that study. We anticipate that CALGB, SWOG, and ECOG will each contribute a minimum of 150 patients a year, and NCIC will contribute at least 50 patients a year, Therefore we expect to be able to accrue at least 600 patients a year. With this accrual rate we plan to accrue 1710 eligible patients (285 per arm) for the first stage of the trial in 3 years. After the 1710 eligible patients have been accrued for the first stage of the trial, accrual to selected experimental arms may continue for an additional cohort of patients. Accrual will not be suspended between the first and second stages of accrual of this study.

Goals: The primary goal of the study is the comparison of each of the five experimental regimens to control. This comparison will be based on all patients randomized while the control arm is open to accrual (defined to be the first stage of the study). The overall type I error rate for

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comparisons relevant to the primary goal is bounded above by 0.05. The secondary goal of the trial is a comparison of the experimental regimens. The type I error rate for comparisons relevant to the secondary goal is also bounded above by 0.05.

Analysis plans and power: In the most recent NCCTG randomized phase III trial in this patient population (89-46-52), the median time to tumor progression on 5-FU + Leucovorin was 6 months. Several other recent trials have reported median times to progression in this patient population ranging from 4 to 6 months. In this trial, we will assume a median time progression of 5 months for the control group, and base our power calculations on an exponential hazard model. Based on the calculations below, a total of 1710 eligible patients (285 per arm) will be required for the analysis comparing each experimental arm to control. After the initial 1710 patients are enrolled, accrual to the control arm will cease. These 1710 patients will constitute the first stage of the trial. Accrual may continue to the experimental arms for an additional cohort of patients to provide sufficient power for comparisons between the experimental arms. Sample size for the comparisons between experimental arms will be based on an analysis which will occur when the 1710 patients necessary for the analyses of the primary goal have been entered. The purpose of this analysis will be to determine whether the second stage of the trial should occur, and its sample size, not to compare the experimental regimens to control.

Analysis and power considerations for the primary goal: The primary goal of this trial is to compare each of the five experimental regimens to control. The primary analysis for this goal will be a comparison of each of the five experimental regimens to the control regimen using a one-sided (unstratified) log-rank test at level 0.01. This insures that the total type I error rate for comparisons with control is bounded above by 0.05. Allowing for a 2% rate of lost to follow-up, if we accrue 285 eligible patients per arm over 3 years, and conduct the final analysis for the first stage of the study after 258 progressions have been observed in the control group (at which time all patients will have been followed for a minimum of approximately 6 months), each test will have 90% power to detect an increase in the median time to progression from 5 months to 7 months (corresponding to a hazard ratio of progression of 1.4 comparing control to each experimental regimen), and 80% power to detect an increase in median time to progression from 5 months to 6.7 months (corresponding to a hazard ratio of progression of 1.33 comparing control to each experimental regimen).

Interim analysis for the primary goal: In this study we will conduct a single interim analysis designed to provide information relevant to the primary goal. This analysis will occur after one-half of the required number of events for the primary analysis have occurred (i.e. after 129 progressions have been observed in the control group). This interim analysis is designed to A) possibly remove experimental arms, and B) possibly remove the control.

A). At the time of the interim analysis, we will compare each experimental arm to the control arm. If at the time of the interim analysis the ratio of the observed hazard rate on the experimental regimen divided by the observed hazard rate on the standard regimen equals or exceeds one, we will consider terminating accrual to that experimental regimen and conclude that an advantage for that experimental regimen has not been established. Removing an

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experimental arm from the trial at this interim analysis will result in minimal loss of power ($\leq 2\%$).

B). At the time of the interim analysis we will compare the distribution of time to progression on the control arm to the distribution on each experimental arm using a one-sided log-rank test. If the one-sided p-value for any of the comparisons is smaller than 0.0005 in favor of the experimental regimen, we will consider closing the control arm of the study. This is based on the multiple-arm version of the O'Brien-Fleming stopping bounds. This method of analysis also shows that the extra conservatism induced by the Bonferroni p-value adjustment assures that the final analysis plan for the first stage has proper type I error rates despite the interim analysis. If this interim analysis results in dropping the control arm, we will conclude that the experimental arm that tested superior to the control arm is superior to the control arm, but not that this experimental arm is superior to the other experimental arms. No conclusions regarding the secondary goal of the trial (the comparison between experimental arms) will be drawn from this interim analysis.

If this interim analysis results in the closing of the control arm of the study, each experimental arm will be compared to the control arm using only those patients randomized while the control arm was open. This analysis would occur approximately six months after the control arm was closed. Each comparison would be conducted using a one-sided log-rank test at level 0.01).

If the interim analysis for the primary goal results in the closing of the control arm, and in addition an experimental arm has been recommended for closure based on a comparison with the control arm, then both the experimental arm and the control arm will be closed.

Release of data at the conclusion of the first stage: At the conclusion of the first stage of the trial and after review by the NCCTG External Data Monitoring Committee, the results of the comparisons of each of the experimental arms to the control arm will be released to the study team to report as appropriate. Comparisons between any experimental arms continued into the second stage of accrual will not be released until the conclusion of the second stage of the trial.

Analysis and power considerations for the secondary goal: The secondary goal of the trial is a comparison of the experimental regimens. To provide sufficient power for these comparisons, after the 1710 patients necessary to satisfy the primary goal of the trial have been accrued, accrual may be continued to two or more experimental regimens (details are specified below). Accrual to the control arm will not continue to the second stage. The potential sample size for the second stage will be based providing sufficient power for the planned comparisons specified in the analysis of the second stage section below, and the median time to progression in the arm with the lowest hazard rate at the conclusion of the first stage. Specifically, sufficient patients will be accrued to provide 90% power to detect a hazard ratio of progression of 1.4 for each planned pairwise comparison, using the lowest observed hazard rate at the conclusion of the first stage as the basis for comparison. The necessary additional sample size for various combinations of time to progression and the number of arms carried forward to the second stage are given in Table 4.

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Accrual to the second stage: An analysis will be conducted at the time at which the 1710 patients necessary for the first stage of the trial have been accrued. This will be considered an interim analysis for the secondary goal of the study, as accrual may continue beyond this analysis based on the results of this analysis. The goal of this analysis will be to determine if the second stage of accrual is necessary. This analysis will focus only on whether the trial should continue to the second stage, and will not be used to make any comparisons relevant to the primary goal of the study. This analysis will be blinded to the study team and will be presented to the NCCTG External Data Monitoring Committee.

Analysis at the conclusion of the first stage: At the time of the closing of the control arm (i.e., the conclusion of the first stage of the study), the potential final comparisons for the secondary goal of the trial will be known (based on the first-stage interim analysis), and are listed in Sections 16.4221-16.4224. Also, at this time the potential sample size for the second stage will be known (also based on the first-stage interim analysis), and is shown in Table 4. At this time two analyses will be conducted. First, each of the planned final comparisons for the secondary goal (selected from Sections 16.4221- 16.4224) will be made. Statistical significance at this interim analysis will be based on a Lan-Demets version of the O'Brien-Fleming boundaries, assuming that this is an interim analysis in a trial with the current number of events designed to proceed to the number of events that coincides with the appropriate total sample size listed in Table 4. If any of these pairwise comparisons reach statistical significance, then the inferior arm in that pairwise comparison will not continue to the second stage. In addition, if five arms were continued at the time of the first-stage interim analysis (therefore, Section 16.4224 applies for the final analysis), for the purpose of determining which arms will continue to the second stage of accrual, the following testing procedure will be used in addition to the tests specified in Section 16.4224. If Test 3, 4, or 5 of Section 16.4224, conducted at the time of the close of the first stage of accrual (with significance levels based on a Lan-Demets versions of the O'Brien-Fleming boundaries) require that the best regimen from either Test 1 or 2 of Section 16.4224 is not continued to the second stage of accrual, then the inferior regimen from that test will also not continue to the second stage of accrual. Second, we will compute the conditional power for each of the planned final comparisons for the secondary goal (listed in Sections 16.4221-16.4224). If the conditional power for at least one of the comparisons is not at least 50%, accrual will not continue to the second stage.

Analyses for the secondary goal: The secondary goal of this study is a comparison of the experimental regimens. No comparisons will be made between experimental regimens dropped at the first-stage interim analysis and those continued at the time of the first-stage interim analysis. Comparisons between arms that did not continue to the second stage based on the analysis conducted at the conclusion of the first stage and those that continue to the second stage will use all patients entered while both arms were open to randomization. These comparisons are protected by the use of appropriately adjusted p-values at the time of the second-stage interim analysis (the analysis conducted at the end of the first stage). Comparisons between the experimental arms will be made using both the initial 285 per arm patients accrued in the first stage, and the additional patients accrued in the second stage. Experimental arms will be compared using a stratified two-sided log-rank test. In conducting this test, patients will be stratified according to the stage of the study to which they were accrued (first vs. second).

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If two experimental arms are continued at the time of the first-stage interim analysis, the interim and final analysis of the second stage will be based on a two-sided log-rank test at level 0.05 comparing those two regimens continued to the second stage.

If three experimental arms are continued at the time of the first-stage interim analysis, the interim and final analysis of the second stage will be based on three pairwise two-sided log-rank tests at level 0.0167 comparing each of the three experimental regimens continued to the second stage.

If four experimental arms are continued at the time of the first-stage interim analysis, the interim and final analysis of the second stage will be based on six pairwise two-sided log-rank tests at level 0.0083 comparing each of the four experimental regimens continued to the second stage.

If five experimental arms are continued at the time of the first-stage interim analysis, the interim and final analysis of the second stage will be based on five pairwise two-sided log-rank tests at level 0.01 each, as specified below:

- 1. Test 1: CPT-11 sequential regimen vs. CPT-11 simultaneous regimen.*
- 2. Test 2: 0 infusional regimen vs. OXAL bolus regimen.*
- 3. Test 3: Best arm from Test 1 vs. best arm from Test 2.*
- 4. Test 4: Best arm from Test 1 vs. CPT-11 + OXAL regimen.*
- 5. Test 5: Best arm from Test 2 vs. CPT-11 + OXAL regimen.*

Secondary endpoints and analyses.

Secondary endpoints include overall survival, time-to-treatment failure, objective tumor response, toxicity, and quality of life.

- Survival: Overall survival will be compared between arms using log-rank tests. The type I error rates for each survival comparison will be identical to the corresponding time-to-progression comparisons as outlined in Sections 16.31 and 16.32. Overall survival and analyses may be greatly influenced by second and third line therapies, therefore, attempts will be made to document any treatments received after tumor progression. Cox proportional hazards analyses (including time-varying coefficient models) will be used to adjust for covariates for analyses of both time to progression and overall survival.

Time-to-treat failure is defined to be the time from the date of randomization to the date at which the patient is removed from treatment due to progression, toxicity, refusal or death. If the patient is considered to be a major treatment violation or is taken off study as a non-protocol failure, the patient will be censored on the date they are removed from treatment.

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Objective tumor response: Tumor response will be reported only in patients with measurable disease. An objective tumor response is defined as an objective status of CR or PR that is maintained for at least 4 weeks,

Quality of Life: All QOL total scores will be translated into percentages representing the relative position of an individual along the theoretical dimension specified by the QOL instrument. Normality testing via the Shapiro-Wilk (72) procedure will determine whether or not parametric or nonparametric procedures will form the basis for analysis.

Sloan et al., (73) set out a procedure for estimating clinically relevant effects for QOL endpoints involving an algorithm using the empirical rule and a framework due to Cohen (74) for effect sizes pertaining to sociobehavioral endpoints. From this framework, we define small, moderate, and large effect sizes of 3, 8, and 13 units on the transformed scale of 0-100 for each of the QOL tools. These are representative of effects equivalent to 0.2, 0.5, and 0.8 standard deviations of the transformed tool scores respectively.

Comparison of the QOL tools (UNISCALE, SPS) between the 5 treatment groups and control will have approximately 85% power to detect a difference of 0.3 standard deviations and approximately 99% power to detect a difference of 0.4 standard deviations (moderately small effect sizes, [74], p. 37) using a two-sided procedure and a 1% type I error rate. We use a two-sided procedure here because the addition of CPT-11 or 03GC, to 5-FU + CF may result in increased toxicity and thus decreased quality of life.

Missing data will be handled in a number of ways. First, all analyses will be run using only the data that is available. Second, imputation will be carried out by use of last-value-carried-forward (LVCF) and average-value-carried-forward (AVCF) and the analyses run again. Collectively, these three approaches have been demonstrated to be useful for identifying the impact of missing data on results as long as the amount of missing data is no more than 20% (75).

Toxicity and dose intensity: Toxicity and dose intensity will be tabulated for each arm. Of particular interest is whether each CPT-11-containing arm is being administered according to the treatment schedule.

The statistical section required major changes after addendum 8. For ease of review, these changes are given below:

16.5 Revised design as of Addendum 8:

16.51 This is a randomized phase III trial with equal allocation to each of 3 regimens: 5-FU + Leucovorin + CPT-11 (the control regimen), 5-FU + Leucovorin + OXAL, and CPT-11 + OXAL. The primary endpoint of this study is time to tumor progression.

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16.52 *Accrual to this trial should be rapid. As of the implementation of Addendum 8, accrual from NCCTG, CALGB, and NCIC CTG was 50 patients a month. SWOG and ECOG are in the process of opening the study; therefore, we expect accrual to rise to at least 75 patients a month (at least 900 patients a year). As of Addendum 8, approximately 135 patients have been randomized to the three study arms. With this accrual rate, we plan to accrue the remaining 990 required patients (330 per arm) necessary to meet the total accrual goal of 1125 patients in just over one year.*

16.53 *Goals: The primary goal of the study is the comparison of each of the two experimental regimens to the control regimen (Arm A). This comparison will be based on concurrently randomized patients only. The overall type I error rate for comparisons relevant to the primary goal is bounded above by 0.05. The secondary goal of the trial is a comparison of the two experimental regimens.*

16.54 *Analysis plans and power: In the Pharmacia & Upjohn trial that supported the approval of the Arm-A regimen as first-line treatment in advanced colon cancer, the median time to progression on the CPT-11 + 5-FU+ CF regimen was 5 months. In this trial, we will assume a median time to progression of 5 months for the control group, and base our power calculations on an exponential hazard model. Based on the calculations below, a total of 1125 eligible patients (375 per arm) will be required for the analysis comparing each experimental arm to control.*

16.541 *Analysis and power considerations for the primary goal: The primary goal of this trial is to compare each of the two experimental regimens to control. The primary analysis for this goal will be a comparison of each of the experimental regimens to the control regimen using a two-sided log-rank test stratified by the stratification factors listed in Section 5.0 at level 0.025. This insures that the total type I error rate for comparisons with control is bounded above by 0.05. Allowing for a 2% rate of lost to follow-up, if we accrue 375 eligible patients per arm over 2 years, and conduct the final analysis for the first stage of the study after 326 progressions have been observed in the control group (at which time all patients will have been followed for a minimum of approximately 6 months), each test will have 90% power to detect an increase in the median time to progression from 5 months to 6.66 months (corresponding to a hazard ratio of progression of 1.33 comparing control to each experimental regimen).*

16.5411 *Interim analysis for the primary goal: In this study we will conduct a single interim analysis designed to provide information relevant to the primary goal. This analysis will occur after one-half of the required number of events for the primary analysis have occurred (i.e., after 163 progressions have been observed in the control group). This interim analysis is designed to A) possibly remove experimental arms. and B) possibly remove the control arm.*

16.54111 *A), At the time of the interim analysis, we will compare each experimental arm to the control arm. If at the time of the interim analysis the ratio of the observed hazard rate on the experimental regimen divided by the observed hazard rate on the standard regimen equals or exceeds one, we will consider terminating accrual to that experimental regimen and conclude that an advantage for that experimental regimen has not been established. Removing an*

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experimental arm from the trial at this interim analysis results in minimal loss of power (2%).

16.54112 B), At the time of the interim analysis, we will compare the distribution of time to progression on the control arm to the distribution on each experimental arm using a one-sided log-rank test. If the one-sided p-value for any of the comparisons is smaller than 0.0004 in favor of the experimental regimen, we will consider closing the control arm of the study. This is based on the O'Brien-Fleming stopping bounds (78).

16.5412 If this interim analysis results in the closing of the control arm of the study, the other experimental arm will be compared to the control arm using only those patients randomized while the control arm was open. This analysis would occur approximately six months after the control arm was closed. This comparison would be conducted using a two-sided log-rank test at level 0.025.

16.5413 If the interim analysis for the primary goal results in the closing of the control arm, and in addition an experimental arm has been recommended for closure based on a comparison with the control arm, then the study will be closed.

16.5414 Release of data at the conclusion of the first analysis: At the conclusion of the first analysis of the trial (the time at which time to tumor progression is formally analyzed), and after review by the NCCTG External Data Monitoring Committee, the results of the comparisons of each of the experimental arms to the control arm for the primary endpoint of time to tumor progression will be released to the study team to report as appropriate.

16.542 Analysis and power considerations for the secondary goal: The secondary goal of the trial is a comparison of the experimental regimens. This analysis will be based on a two-sided logrank test at level 0.05, and will occur at the time at which the primary analysis for time to tumor progression occurs. This analysis will have >90% power to detect a hazard ratio of 1.33 between the two experimental arms.

16.6 Secondary endpoints and analyses.

Secondary endpoints include overall survival, time-to-treatment failure, objective tumor response, toxicity, and quality of life.

16.61 Survival

16.611 Overall survival will be compared between arms using log-rank tests, The type I error rates for each survival comparison will be identical to the corresponding time-to-progression comparisons as outlined in Section 16.5. Overall survival may be greatly influenced by second and third line therapies, therefore, attempts will be made to document any treatments received after tumor progression. Cox proportional hazards analyses (including time-varying coefficient models) will be used to adjust for covariates for analyses of both time to progression and overall survival.

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16.612 *The comparison of the survival endpoints for this study will require additional follow-up. In particular, the final analysis for the secondary endpoint of overall survival will occur when 280 deaths have been observed on the control arm (approximately 18 months after the close of enrollment). Assuming a median survival in the control group of 14 months, this analysis will have 85% power to detect a hazard ratio for survival of 1.33 comparing each experimental regimen to the control regimen.*

16.613 *Interim analysis for overall survival. An interim analysis for overall survival will be conducted at the time of the primary analysis for time to tumor progression. The significance levels for this analysis will be based on the Lan-DeMets version of the O'Brien-Fleming stopping bounds, based on the proportion of the required number of deaths (280) that have been observed at the time of the interim analysis (79).*

16.62 *Time-to-treat failure is defined to be the time from the date of randomization to the date at which the patient is removed from treatment due to progression, toxicity, refusal or death. If the patient is considered to be a major treatment violation or is taken off study as a non-protocol failure, the patient will be censored on the date they are removed from treatment.*

16.63 *Objective tumor response: Tumor response will be reported only in patients with measurable disease. An objective tumor response is defined as an objective status of CR or PR that is maintained for at least 4 weeks.*

Missing data will be handled in a number of ways. First, all analyses will be run using only the data that is available. Second, imputation will be carried out by use of last-value-carried-forward (LVCF) and average-value-carried-forward (AVCF) and the analyses run again. Collectively, these three approaches have been demonstrated to be useful for identifying the impact of missing data on results as long as the amount of missing data is no more than 20% (75).

16.65 *Toxicity and dose intensity: Toxicity and dose intensity will be tabulated for each arm.*

16.72 *There is no information currently available regarding differential effects of OXAL, 5-FU or CPT-11-based treatment in subsets defined by race, gender, or ethnicity, and there is no reason to expect such differences exist. Therefore, although the planned analysis will, as always, look for differences in treatment effect based on racial and gender groupings, the sample size is not increased in order to provide additional power for ethnic subset analyses.*

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Reviewer's Comments:

The primary comparison after the addendum 8 is each experimental arm with the control arm at a significance level of 0.025, which is acceptable. However, the primary endpoint remains TTP and not survival, although data on survival will be collected. An interim analysis is planned at 163 progressions. If the one-sided p-value for any of the comparisons is smaller than 0.0004 in favor of the experimental regimen, closure of the control arm will be considered. The other experimental arm will be compared to the control arm using only those patients randomized while the control arm was open. This analysis would occur approximately six months after the control arm was closed. This comparison would be conducted using a two-sided log-rank test at level 0.025. This analysis at 6 months does not account for alpha-spending for the initial interim analysis.

Major Amendments to the Protocol after Addendum 2:

During the course of the study, 18 amendments were made. The relevant amendments will be given briefly in this section. A list of a summary of all addendums as submitted by the applicant are given in appendix X.

Addendums 6, 7, 8, 9, 11, 12 and 15 are given below.

Addendum 6. January 2000

Dose modification table for Arm F (FOLFOX4) was changed to

Dose Reduction - Arm F*			
5-FU	Starting Dose	Dose Level - 1	Dose Level - 2
Bolus	400 mg/m ²	320 mg/m ²	240 mg/m ²
Infusion	600 mg/m ²	500 mg/m ²	400 mg/m ²

*CF dose remains fixed at 200 mg/m² (not adjusted).

The previous table was combined with oxaliplatin modifications and ranges were given for dose levels instead of absolute numbers.

Dose modification table for Arm G (IROX) was changed to

Dose Reduction - Arm G*			
	Starting Dose	Dose Level - 1	Dose Level - 2
CPT-11	200 mg/m ²	160 mg/m ²	120 mg/m ²

New doses for the modified level were given in this new table.

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Addendum 7. March 24, 2000.

Study was temporarily closed after March 23rd, 2000 based on a study comparing Saltz regimen (combination of CPT 11 and bolus 5-FU/LV or IFL) to standard 5FU/LV regimen, which demonstrated superiority of the Saltz regimen in first-line treatment of patients with metastatic colorectal carcinoma. Saltz regimen became the new control arm. Patients on Arm D of this protocol will be treated at investigator's discretion.

Addendum 8. April 28, 2000

Study re-opened to accrual. Six arms were collapsed to three arms. Arm B (CPT-11 + bolus 5FU/LV), Arm D (bolus 5FU/LV) and Arm E (Oxaliplatin + bolus 5-FU) were deleted. Arms B (5 deaths of 61 randomized patients) and E (4deaths of 47 randomized patients) were more toxic of the six choices, and Arm D was no longer the control regimen.

Addendum 9. November 24th, 2000

Arm A-Saltz Regimen was modified to include IV push of LV as well as a 15-minute infusion. It read as:

CPT-11 125 mg/m² as a 90-min infusion + CF 20 mg/m² as a 15-minute infusion or **IV push & 5-FU 500 mg/m² IV bolus weekly x 4, Q6 wks.**

Addendum 11. April 25, 2001

Due to increased toxicities and deaths (3%) in the first cycle of Arm A, the study was temporarily suspended as of April 25, 2001. Patients on cycle 1 treatment on Arm A had dose level reduced to -1. Patients on treatment post cycle 1 with acceptable toxicity were to continue to be treated and followed per protocol.

Addendum 12. June 29, 2001

Study was re-opened. The starting doses on Arm A were reduced to **CPT-11 100 mg/m² and 5-FU 400 mg/m²**. To retain the maximum dose intensity on a patient-by-patient basis, provision for a single-dose escalation to the original regimen was specified for patients who experience grade 1 or less toxicity during cycle 1. In order to provide adequate statistical power to evaluate the modified Arm A, the sample size has been increased to a total of 1705 patients.

Re-escalation of CPT-11 may be done as follows:

Arm A dose escalation of CPT-11 and 5-FU is permitted and could only occur at the beginning of cycle 2, provided that there were no toxicities \geq Grade 1 present. The leucovorin dose was not escalated or de-escalated.

Addendum 14. March 15, 2002

Arm G was closed to patient to patient accrual on March 15, 2002 because the accrual objective was met.

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Addendum 15. April 23 2002.

Study was closed to accrual on Arm A. Outcome of Arm F appears to be superior to those on Arm A. Accrual to Arm F was continued.

Reviewer's Comments:

This study had a complicated design with three arms deleted and three arms added. The control arm was one of the arms deleted. The second control arm (IFL) required decreased dosing midway during the conduct of the study. This will require several adjustments to the statistical design and will be commented in detail in the statistics review.

The planned conduct of the study was changed several times. Addendums 6 and 9 had changes to dose modifications in FOLFOX4 and IROX arms and IFL administration. Addendums 7 and 10 resulted in temporary study closure. Addendums 8 and 12 had major modifications in study on reopening the study. The arms in the study were collapsed to three in addendum 8. In addendum 12, CPT-11 starting dose was decreased to 100 mg/m², with an option to increasing the dose at the beginning of cycle 2. HUS was recognized as a possible AE. In addendum 18, new toxicities i.e. fatigue and hyponatremia were included in the consent form in January 2003.

Tumors were measured every 6 weeks for the first 42 weeks or until a tumor response was confirmed at a subsequent measurement. Measurements thereafter were required every 12 weeks.

The study was ended early based on interim analysis in which an improved TTP and OS were noted. The planned accrual was approximately 330 patients per arm, and about 265 were randomized to each arm by the time the study was closed.

If patient has CR confirmed for 2 consecutive cycles, at physician discretion treatment may have been discontinued. The difference in duration of treatment once CR has been reached will be reviewed.

Out of all the drugs used in the study, only oxaliplatin was not marketed while the study was being conducted. The patients would be able to get benefit from secondary treatment with CPT-11 and 5FU/LV if they were on the FOLFOX4 arm, possibly skewing the results of OS in favor FOLFOX4.

Safety Concerns in the Protocol Amendments:

Following safety concerns were added to the protocol in different addendums:

Addendum 6:

Life threatening enteric sepsis secondary to neutropenia and diarrhea was recognized as a possible toxicity secondary to bolus 5FU/LV/OXAL.

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Per addendum:

"The bolus infusion of OXAL/5-FU/LV may increase the risk of developing life-threatening enteric sepsis secondary to neutropenia and diarrhea. Patients with grade 4 ANC and grade 3 diarrhea should be monitored closely and hospitalization considered for appropriate hydration; treatment with antibiotics, appropriate for gram negative or anaerobic sepsis, should be instituted for fever or clinical deterioration. Patients should be monitored closely and provided with aggressive supportive care until neutropenia and diarrhea resolve."

Addendum 9:

Additionally, respiratory problems, particularly pulmonary fibrosis was recognized as a possible AE.

"As of Addendum 9: Respiratory: Among over 50,000 patients that have been treated with oxaliplatin, there have been 11 patients that have developed respiratory problems. Four deaths occurred in these 11 patients, 2 of which were due to pulmonary fibrosis. As the relationship of such toxicity to oxaliplatin cannot be confirmed, you must closely monitor patients for unexplained respiratory problems (i.e., pulmonary fibrosis, cough, dyspnea, rales, pulmonary infiltrates, hypoxia, and tachypnea) and hold oxaliplatin until interstitial lung disease is ruled out for cases of Grade ≥ 3 ."

Respiratory problems (i.e., pulmonary fibrosis, cough, dyspnea, rales, pulmonary infiltrates, hypoxia, air hunger, and tachypnea) have been observed in patients administered oxaliplatin. In rare cases, death has occurred due to pulmonary fibrosis. Please monitor and instruct the patient to report any respiratory difficulties and hold oxaliplatin until interstitial lung disease is ruled out for cases of Grade ≥ 3 . If patient is experiencing shortness of breath, a chest x-ray and assessment of oxygenation via either finger oximetry or arterial blood gas evaluation are required to confirm the absence or presence of pulmonary infiltrates and/or hypoxia (treat accordingly: no intervention, steroids, diuretics, oxygen, or assisted ventilation)."

Ileus secondary to oxaliplatin/5FU/LV in the 9th addendum was added in the consent form.

Addendum 10:

Confusion or mental changes in addendum 10 was added as an AE in the consent form.

Addendum 12:

HUS was recognized as a possible toxicity of oxaliplatin. Patients with HCT <25%, PLTs <100,000, and creatinine ≥ 1.6 mg/dL should be evaluated in and treatment with oxaliplatin should be held if HUS is confirmed. SVTs, Tumor Lysis Syndrome and acute vein irritation have also been reported.

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Efficacy Results:

Study Period:

795 patient cohort

Date first patient enrolled: May 20, 1999

Date last patient enrolled: April 25, 2001

Cut-off date for analysis: February 28 2003

Patient Disposition:

Arms A (IFL), F (FOLFOX4) and G (IROX) will be analyzed for this NDA. Seven hundred and ninety five patients were randomized and will be evaluated for efficacy. Out of these, 773 were treated and will be evaluated for safety. An approximately equal number of patients dropped out from each arm before being treated.

Table 24: Patient Disposition

Applicant Table from Synopsis of the Study Report.

	IFL N=264	FOLFOX4 N=267	IROX N=264
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

Table 25: Summary of patients randomized but not treated

Applicant table (10.1) 3

Reason for Discontinuation	IFL (N=8)	FOLFOX4 (N=8)	IROX (N=6)
Disease progression	1 (12.5)	0	0
Refused further treatment	0	3 (37.5)	1 (16.7)
Other	0	2 (25.0)	2 (33.3)
Not reported	7 (87.5)	3 (37.5)	3 (50.0)

Treatment Discontinuations:

The most common reason for treatment discontinuation was disease progression, and they were the least in the FOLFOX4 arms compared to the IFL and IROX. Deaths on study and disease progressions were the most in the IFL arm, which surprisingly had the least number of adverse events as a reason for treatment discontinuation. Prior to decreasing the starting dose, there were 4.8% treatment-related deaths in the first 60 days with IFL. An equal number of patients refused further treatment in each arm.

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The absolute numbers for reasons for treatment discontinuations are identical for the applicant and this reviewer. The applicant table is given below.

Table 26: Summary of treatment discontinuation by patient - Number (%) of ITT

Applicant table (10.1)2

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)

The applicant provided a detailed table for "alternate treatment", refused further treatment and other medical problems in table (15.1)2 of study report. Per applicant, this was obtained after review of CRF and the dataset comments. Most of these could be audited using the dataset 'COMMENTS', and the applicants table (15.1)2 of the study report.

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Table 27: Reason for Discontinuations

(Refused further treatment, alternative treatment, other medical problems, and other reasons)

Adapted from applicant table (15.1)2

Reason of Discontinuation	Applicant Comments	IFL	FOLFOX4	IROX
Alternate Treatment	Post study metastatectomy	2	3	8
	Other	1	0	0
	Post study Chemotherapy	1	1	0
	Post study radiotherapy	0	0	1
Other	Complete Response	6	17	6
	Progression	3	3	7
	Adverse Event	6	4	2
	Other	4	5	2
	Maximum benefit achieved	2	3	4
	Patient Refusal	0	4	1
	Post study metastatectomy	1	0	3
Other Medical Problems	Adverse Event	4	6	3
	Progression	2	0	1
	Maximum benefit achieved	0	1	0
Refused Further Treatment	Adverse Event	7	8	8
		7	8	7
	Patient Refusal	6	7	8
	Other	0	1	1
	Progression	2	0	0
	Post study metastatectomy	1	0	0

The reasons for discontinuation due to 'adverse events', 'medical problems', 'treatment refusal' and 'other' are similar across arms. More patients discontinued treatment due to CR and adverse events on FOLFOX4 arm, and because of progression on the IROX arm. This table only gives an idea of what kind of reasons was the reason for discontinuation when it came to the three vague terms such as 'adverse events', 'medical problems', 'treatment refusal' and 'other'.

Reviewer's comment:

There does not appear to be any major imbalance in reasons discontinuation of therapy across the 3 arms except for discontinuation because patients had achieved CR. These patients were greatest in number on the FOLFOX4 arm.

Protocol Violations:

Seven hundred and sixty-nine patients had at least 1 AE reported in the datasets (CYTOXNCI and CYTOX). Four patients had no reported adverse events. One received no treatment. Major violations were assigned to 2 patients and 3 were ineligible (084723, 095060, 090972, 091873,

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092140) by the NCCTG QC. Additionally, On DSI inspection, patient with ID 092830 did not meet all inclusion criteria because of uncontrolled hypertension.

The study report was misleading for the enrollment criteria. According to the study report, all randomized patients were included in the primary analysis and that there were no violations reported for inclusion/ exclusion criteria at baseline. No statements were included in this section of any protocol violations.

The data submitted for enrollment criteria were incomplete. The enrollment criteria could not be verified using the dataset "CHKLST". Many patients had data missing in various inclusion and exclusion criteria columns. One hundred and sixteen patients had missing values for all inclusion or exclusion criteria. Only 579 patient (IFL: n=191; FOLFOX4: n=196; IROX: n=192) patients had complete information on all inclusion criteria. Exclusion criteria were given for 679 patients. There were no violations for patients who had values submitted for the inclusion and exclusion criteria. Some patients were not required to complete the QoL questionnaires.

Per applicant, all of the 116 patients with the missing values for all inclusion and exclusion criteria belonged to SWOG, a member of NCCTG. The FDA was told that SWOG does not complete the eligibility checklist due to cutbacks, but that any errors are found during the audit process. The applicant was then asked to provide the percentage of CRFs that were audited. Per applicant, SWOG generally audits 10% of the CRFs, but could not confirm the number of CRFs audited for this study. Later in the review, the applicant confirmed that 42 of the 116 patients were audited.

Table 28: Protocol Violations

Reason	Randomized Arm
Violations	
received 5FU infusion for the first day only of each cycle	FOLFOX4
received standard adjuvant rectal cancer chemoradiation prior to study entry	None
Assigned to receive IROX, but given IFL	IROX
Ineligible	
prior RT to >15% of bone marrow	IROX
Diabetic neuropathy at baseline, and PS of 3	None
Pancreatic cancer was primary	None

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Reviewer's Comments:

The finding of ineligible patients or protocol violations is not surprising in an 800-patient study, but it does reinforce the need to have the ability to verify the data and results submitted. The study report opening statement in the 'Protocol Deviation' section reporting no violations at baseline, is misleading. The 5 patients with violations/ineligibility were not given in this section of the study report, but the information was available from the datasets. Additionally, on DSI inspection of a relatively small sample size, a patient was found to have violated the inclusion criteria because of uncontrolled hypertension.

These irregularities reflect only on the quality of data and the study report submitted. By themselves the irregularities cited will not affect the study results.

Demography:

The patients were fairly well-balanced for age, number of organs involved and the organs involved. There were slightly more women and less blacks in the FOLFOX4 arm.

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Table 29: Demography and baseline characteristics

Applicant table 11.2.1

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)
	Not reported	0 (0.0)	0 (0.0)	0 (0.0)
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)

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Table 30: Stratification factors at randomization

Applicant table 11.2.3.1

	IFL (N=264)	FOLFOX4 (N=267)	IROX (N=264)
ECOG N (%)			
0,1	252 (95.5)	252 (94.4)	250 (94.7)
2	12 (4.5)	15 (5.6)	14 (5.3)
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)
Age N (%)			
<65	164 (62.1)	163 (61.0)	165 (62.5)
≥65	100 (37.9)	104 (39.0)	99 (37.5)

The applicant performed a nice analysis on the lab tests at randomization. More patients in the IROX arms had anemia, and the IFL arm had the fewest patients with anemia. Patients with decreased neutrophils, platelets, alkaline phosphatase, AST and creatinine were well-balanced.

Table 31: Summary of baseline laboratory tests by NCI grade

Applicant table (11.2.3.2)1

Inclusion Criteria	IFL (N=264)		FOLFOX4 (N=267)		IROX (N=264)	
	All Grades	Grades 3,4	All Grades	Grades 3,4	All Grades	Grades 3,4
Hemoglobin	113 (42.8)	0	106 (39.7)	0	99 (37.5)	0
Neutrophils	1 (0.4)	0	0	0	3 (1.1)	0
Platelet count	2 (0.8)	0	3 (1.1)	0	2 (0.8)	0
Alkaline phosphatase	106 (40.2)	0	104 (39.0)	0	105 (39.8)	0
AST (SGOT)	52 (19.7)	0	58 (21.7)	0	53 (20.1)	0
Creatinine	13 (4.9)	0	9 (3.4)	0	8 (3.0)	0

Reviewer's Comment:

The FOLFOX4 patients had slightly poorer performance status an older age group , and more black patients. No major imbalances could be identified in the study population at randomization that would skew the results in favor of the FOLFOX4 population.

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Second-line therapy for colorectal cancer:

After enrollment to the IFL arm was suspended on 23 April 2002, any patients choosing to continue their current treatment could have crossed over onto the FOLFOX4 arm. There was no other planned crossover on this study. Table X from the applicant and X published in JCO by the cooperative group NCCTG that conducted the study summarize patients having any post-study treatment for colorectal cancer.

Second-line therapies were similar across treatment arms. More patients on the FOLFOX arm received irinotecan (~60%) whereas fewer patients on the IFL (~25%) arm received oxaliplatin, because oxaliplatin was not commercially available at that time.

Table 32: Any poststudy treatment for colorectal cancer - Number (%) of treated

Applicant Table (11.2.4) 1

	IFL (N=256)	FOLFOX4 (N=259)	IROX (N=258)
Any post treatment chemotherapy	164 (64.1)	187 (72.2)	182 (70.5)
5FU (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)

Table 33: Second-line therapies reported by NCCTG in JCO

Second-Line Therapy	% of Patients		
	Irinotecan and Fluorouracil Plus Leucovorin n = 2511	Oxaliplatin and Fluorouracil Plus Leucovorin n = 2591	Oxaliplatin and Irinotecan n = 2621
Any			
Overall	67	75	70
Before progression	32	26	26
Irinotecan			
Overall	25	60	32
Before progression	9	25	10
Oxaliplatin			
Overall	24	8	9
Before progression	17	3	3
Fluorouracil			
Overall	41	40	50
Before progression	18	14	21

from "A Randomized Controlled Trial of Fluorouracil Plus Leucovorin, Irinotecan, and Oxaliplatin Combinations in Patients With Previously Untreated Metastatic Colorectal Cancer. Goldberg et al; JCO Jan 1 2004; 23-30"

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Reviewer's Comment:

The unequal crossover may affect overall survival. Hence the improvement in overall survival on the FOLFOX arm could be at least partially due to second-line irinotecan.

Survival Analysis:

Overall survival has been the primary endpoint for FDA for first-line treatment of advanced colorectal cancer but was a secondary endpoint per protocol. Both the oxaliplatin arms had a significantly longer survival than the IFL arm. Per Applicant, FOLFOX 4 arm had a significantly longer median survival of 19.4 months than the control arm of IFL which had a median survival of 14.6 months ($p < 0.0001$, HR: 0.65 with 95% CI of 0.53 to 0.80). The median survival in the IROX arm was also better than IFL by approx 3 months than IFL ($p = 0.025$). See table below. These findings were duplicated by this reviewer. See figure and table below.

Table 34: Overall Survival

From Applicant table (11.5.4)1 of the study report

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

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Figure 2: Kaplan Meier Curve for Survival

Applicant figure

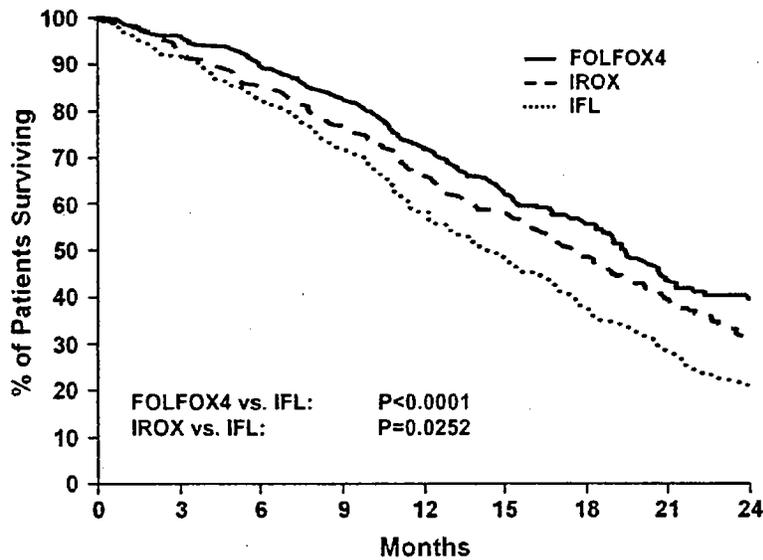


Table 35: Survival

FDA Analysis

	IFL N=264	FOLFOX4 N=267	IROX N=264
# of Deaths (N)	192	155	175
Median Time (months)	14.6	19.4	17.6
95% Confidence Interval	12.4- 16.6	17.9- 21	15.8-19.6
25% Failures (months)	8.2	11.1	9.8
75% Failures (months)	21.9	27.8	28

Table 36: P value comparison between treatment arm for survival

	P value by Log Rank
FOLFOX vs IFL	0.0003
IROX vs IFL	0.025
FOLFOX vs IROX	0.09

Both FOLFOX 4 and IROX had better OS than the control arm of IFL. There was no statistical difference between the two oxaliplatin-containing arms for an improvement in survival.

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Table 37: Summary of CPT 11 exposure affected by addendum 12

	# of cycles	# of cycles pre & post add 12
Dates not known	6	6 (1%)
Before addendum 12 in >110 mg/m ²	589	929
Before addendum 12 in <110 mg/m ²	340	(83%)
After addendum 12 in >110 mg/m ²	136	179
After addendum in <110 mg/m ²	43	(16%)
	CPT-11 dose mg/m²	
Median CPT 11 exposure/cycle before addendum 12		95
Median CPT 11 exposure/cycle after addendum 12		76

Reviewer's Comment:

All patients were enrolled in this trial by the time addendum 12 was instituted, reducing the dose of CPT-11. Eighty percent of the cycles were administered prior to the amendment with a median CPT-11 dose of 95 mg/m². It is relatively unlikely that dose reduction had a great impact on the overall survival of the control arm, considering the number of cycles administered pre-versus post amendment 12.

Response and Time to Tumor Progression Evaluation:

The review team had the following concerns about the TTP and RR analyses:

1. The information on new lesions was not captured on the CRF as a requirement. There may be an unknown number of new lesions in each treatment arm that have remained uncaptured. Supporting documents for validation of progression were given by NCCTG to applicant only for the submitted date of progression. Per applicant it may not be possible to get all the radiology reports on all patients because many institutions destroy scans of patients who have expired. The FDA is not able to confirm the reported tumor response and progression results because of a large amount of incomplete data.
2. Response and tumor progression were based on investigator assessment in an unblinded trial. In the trial for previously treated patients, patients had investigator as well as independent, blinded assessment
3. For analysis of response rate, per applicant, NCCTG has chosen to analyze only those patients who have been treated for at least 18 weeks (9 cycles on FOLFOX arm and 3 cycles on the IFL arm) for response rate. There was no such requirement in the protocol and reason for this time period is not clear. This is an unusual criteria. The response rate should be evaluated as an intent-to-treat analysis. Furthermore, responses as defined in

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the protocol should have been confirmed at 6 weeks. The applicant has submitted response rates based on confirmation of tumor responses at 4 weeks. At the end of review period, the applicant has assured us that responses were recorded regardless of duration of therapy received by the patients.

4. In the late 5th month of the FDA review, a hard copy submission of 40 patients dated 12/3/2003, identified 40 patients (15 Arm A, 15 Arm F, 10 Arm G) These 40 patients were selected based on potential discrepancies in the dataset that Sanofi-Synthelabo found on their review for progression dates. This example illustrates the difficulty verifying the response rate and TTP.

Response Rate:

The response rate as submitted by the applicant are given in table 38. This response rate could not be verified by the FDA because of absence of information about new lesion in the CRFs.

Table 38: Response Rates submitted by the Applicant
(for patients with measurable disease at baseline)

	IFL (N=212) n (%)	FOLFOX4 (N=210) n (%)	IROX (N=215) n (%)
CR	5 (2.4)	13 (6.2)	7 (3.3)
PR	64 (30.2)	82 (39.0)	67 (31.2)
CR and PR	69 (32.5)	95 (45.2)	74 (34.4)
(95% C.I.)	(26.2-38.9)	(38.5-52.0)	(28.1-40.8)
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)

Fisher's exact test p-values for FOLFOX vs IFL: 0.0093

for IROX vs IFL: 0.7584

for IROX vs FOLFOX: 0.029

According to the study report, a patents had to be treated for at least 18 weeks for evaluation of a response. Regardless of the methodology, whether as above, or as an ITT analysis, the the RR remains exactly the same. When the applicant was asked about this lack of difference, they found that RR occurring before week 18 were durable and lasted until at least week 18 of treatment. This was verified by this reviewer using the dataset TUMEVAL.

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Time to Tumor Progression:

Per applicant, the median TTP on the IFL arm was 6.9 months (95%C.I. 6.0-7.5), 8.7 months on the FOLFOX 4 arm (95%C.I. 7.8-9.8), and 6.5 months on the IROX arm (95%C.I. 5.8-7.6) See table 39 and 40.. This was based on the investigator assessment, which was not blinded. The presence of new lesions was used for evaluation of response (or progression) but because the data on new lesions was not captured on the CRF, the TTP and tumor responses could not be verified by the FDA. An exploratory analysis was performed.

Table 39: Progression rate and Median months of 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)	6.9	8.7	6.5
95% confidence interval	(6.0-7.5)	(7.8-9.8)	(5.8-7.6)

Table 40: 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 FDA's Statistical Reviewer's Calculations.

Exploratory Analysis for TTP by the FDA:

An exploratory analysis was conducted by the FDA on all measurable disease patients. This analysis was performed only on the basis of the documented target lesions and not the evaluable lesions or new lesions. FOLFOX arm was superior to IFL with a p value of 0.0043.

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Table 41: Exploratory Analysis for TTP

(FDA analysis)

	FOLFOX	IFL
Measurable disease	215	218
Progressors (FDA exploratory analysis)	42 (19.5)	67 (30.7)
Applicant analysis on same subset of patients	70 (32.5)	100 (45.9)

Table 42: Comparison of Original Applicant and FDA Analysis for patients with measurable disease- Exploratory Analysis

FDA Analysis	Applicant Analysis	N	FOLFOX4 N=215	IFL N=218	IROX N=210
Progression	Progression	140	33 (15.3)	61(28)	46
None*	Progression*	110	37 (17.2)	39(17.8)	33
Progression	None	27	9 (4.2)	6 (2.7)	12

*25 radiology reports audited. 24 of these reported a new lesion or suspicion of one. 1 report reported SD in the previous cycle but no documentation for the current cycle.

In this analysis, it was found that there was a similar number of patients (FOLFOX: 37, IFL: 39 and IROX: 33) in each treatment arm that the Applicant labeled as progressors, but this reviewer did not. Because Radiology reports were submitted for the cycles in which the patient progressed, this reviewer audited 25 reports where applicant analysis labeled a patient as a progressor, but this reviewer did not. The radiology reports for 24 of these patients concluded that new lesions or a suspicion of new lesions were observed. There was no radiologic documentation of progression (0008 089500) for one patient because the report of interest was absent.

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Figure 3: TTP- Exploratory Analysis by the FDA

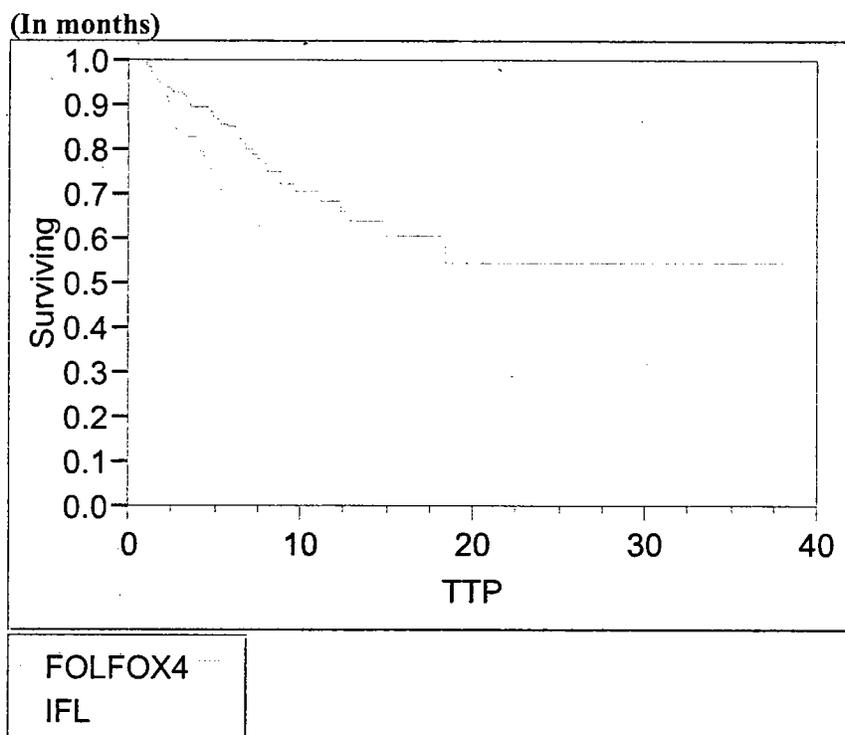


Table 43: TTP- FDA Exploratory Analysis

Arm	N Failed	N Censored	Median Time
FOLFOX 4	42	173	-
IFL	67	151	15.367

P value 0.0043

Methodology for the FDA Exploratory Analysis of TTP:

Only patients with at least one documented lesion from dataset DZ TYPE were chosen as patients with measurable disease. Rows where total # of lesions were less than at baseline were excluded. Progression were assigned by using formula $“(pretreatment\ sum - nadir / 2) + nadir”$ to get progression as defined by the protocol for responders. For patients who did not meet the criteria for CR or PR, a $>25\%$ increase in measurements of indicator lesion(s) compared to pretreatment measurements were classified as progressors. There were no patients who had progression by this second criteria without meeting the criteria by the formula given earlier. All patient who did not progress were censored at last date of assessment, or if missing, last follow up date (available from dataset CSECRSE).

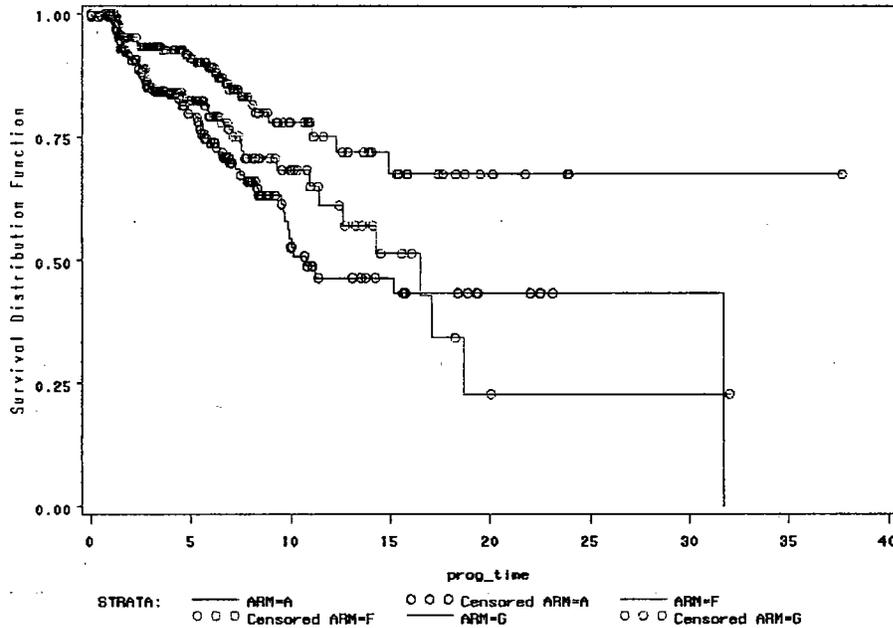
A similar analysis was requested from the applicant.

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Exploratory analysis on TTP performed by the Applicant:

Figure 4: Time to Progression Curves (in Months)
(Subset of patients with baseline measurable lesion)



Progression rate and Median months of Time to Progression

	IFL	FOLFOX 4	IROX
Number of patients with baseline measurable lesions	220	218	214
Number of patients whose disease progressed based on the measurable lesions in the DZ_TYPE	60 (27.3%)	28(12.8%)	45(21.0%)
Time to progression (months): Median	10.8	Curve above 0.50 level	16.5
95% Confidence interval	(9.6, 31.7)	NA	(11.4 18.7)

Per applicant, the above curves were created based on measurable tumor assessments reported on tumor measurement form of the CRF. Tumor Progression reported during the follow up period captured on EVENT pages but not the tumor measurement form was not used in the analysis. Therefore, progressions occurring during follow up period were not reflected on the above curves.

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Reviewer's Comment:

The new lesions were taken in to account when the response rate was evaluated by the NCCTG. Unfortunately this data was not collected in the CRF making the verification of the response rate and TTP impossible. An exploratory analysis was performed for patients with measurable disease. In this subset of patients, again the FOLFOX arm had a longer TTP. More over, patient who progressed per applicant analysis, but not this reviewer's analysis were audited. Almost all of the 25 patients audited had documentation of a new lesion or a suspicious new lesion, giving credibility to the applicant's analysis.

Exploratory analysis for dosing on the IFL arm after addendum 12:

According to addendum 12 dated 6/29/2001, the starting doses on Arm A were reduced to CPT-11: 100 mg/m² and 5-FU: 400 mg/m². To retain the maximum dose intensity on a patient-by-patient basis, provision for a single-dose escalation to the original regimen was specified for patients who experience grade 1 or less toxicity during cycle 1. Arm A dose escalation of CPT-11 and 5-FU was permitted and could only occur at the beginning of cycle 2, provided that there were no toxicities \geq Grade 1 present. The leucovorin dose was not escalated or de-escalated.

All patients had been randomized by end of April 2001. Nine hundred and twenty nine (83%) cycles on IFL arm were administered before addendum 12 and 179 (16%) in 61 of 264 patients (23% of all patient on IFL) were administered after the institution of this addendum. Dates of 6 cycles (approx 1%) were not known. Six hundred and eighty cycles (61%) were given in doses greater than 90 mg/m² and 434 (39%) cycles were given in doses lower than 90 mg/m². Median dose administered before the amendment was 95 mg/m². After 6/29/2001, a median dose of 76 mg/m² was administered per cycle.

Reviewer's Comment:

The amendment decreasing the dose of IFL came late in the study when all patients had received at least one dose as originally proposed in the protocol. The median dose of IFL decreased as expected, but the number of cycles administered after the amendment are small (16%). It is difficult to say what effect this decrease had on the efficacy of the control arm.

D. Efficacy Conclusions

Seven hundred and ninety-five patients were randomized to three arms- IFL (N=264), FOLFOX 4: (N=267) and IROX (N=264). For the purpose of this NDA, IFL was the control arm. Although the protocol-defined primary endpoint was TTP, FDA's primary endpoint was survival.

The overall survival in the FOLFOX 4 arm (median survival of 19.4 months) and IROX (median survival of 17.6 months) are better than the control arm of IFL (median survival of 14.6 months). There is no significant difference between the two oxaliplatin-containing arm, in terms of overall survival. As will be seen later in the review, the IROX arm has a greater toxicity. Interestingly,

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the RR and TTP for IROX were inferior to that of FOLFOX and no statistical difference existed for these analyses for IFL and IROX, as submitted by the applicant.

One cannot be entirely certain that the survival improvement in the FOLFOX arm is not due to an effective second-line therapy. Fifty-eight percent patients on the FOLFOX arm received irinotecan later while only 23 % of patients on the IFL arm received oxaliplatin.

The OS for the first-line study that led to the approval of irinotecan had an identical OS as the IFL arm of the current study (approximately 14.5 months). Additionally, the RR and TTP were likely improved with FOLFOX 4 (although the actual numbers can not be verified). In the current trial as well as previously reported randomized trials in the first-line setting, improved RR and PFS have been observed. One can conclude that oxaliplatin + infusional 5-FU + irinotecan containing regimen is better than IFL without an oxaliplatin-containing regimen in improving OS. Whether FOLFOX 4 is superior to IFL for first-line treatment of colorectal cancer is not known.

Issues with electronic data for efficacy findings:

The trial was conducted by the NCCTG under NCI sponsorship, and it is noted that the datasets were constructed keeping restrictions of resources in mind. An EOP2 meeting with the FDA took place early during the trial and it was realized that the current study could be a registration trial. The data collection was not complete so that response rates and TTP cannot be verified. Critical data on new lesions was not identified on the CRF. Dosages and method of administration of study drugs was not recorded consistently and the CRF was changed several times. Whether NCCTG audited the data is not known. Incorrect data on patients were noted in the electronic datasets, such as dates and cycles numbers. Such discrepancies should be corrected prior to an NDA submission. Dates of follow up after completion of treatment were not updated in all datasets. Datasets which were 'incomplete' because they were not updated were not identified. Repeating the same analysis after conducting them once on another dataset added considerable time to the review of this NDA by the FDA.

If a trial is recognized as a possible registration trial, datasets and CRFs should be well-constructed to allow validation, as required for FDA review. When evaluating responses, having an independent review of data is important as suggested by Therasse et al (New Guidelines to Evaluate the Response to Treatment in Solid Tumors: JNCI, Vol. 92, No. 3, February 2, 2000). This is particularly important when response evaluation (as in RR and TTP) is a primary endpoint, or response evaluation is required to provide support as in the case of this trial where unequal crossover could confound the OS results. A CRF with all the requirements for responses (if TTP or RR are major endpoints), previous best responses to treatment if applicable, dosages and method of drug administration in the proposed trial, dates of tumor evaluation rather than date of drug administration (if TTP is a major endpoint) would be some of the major items that should be carefully recorded. Concomitant medications should be collected to see if there may be other therapies influencing the outcome.

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VII. Integrated Review of Safety

A. Brief Statement of Conclusions

Oxaliplatin is available widely in the world and is a relatively well-tolerated chemotherapeutic agent. Neurotoxicity (mostly sensory neuropathy including paresthesias and cold-induced dysesthesias) is generally reversible and is dose or treatment-limiting. It is not associated with renal toxicity or ototoxicity as is cisplatin. Thrombocytopenia is observed but is probably less than that due to carboplatin.

773 patients received at least one dose of the study drugs. A median of 10 cycles of FOLFOX 4 (2-weekly), 4 cycles of IFL (6-weekly) and 4 cycles of IROX (3-weekly) were administered. Twenty seven percent (n=70) patients on the FOLFOX arm, 9% (n=22) on the IFL arm and 20% (n=51) of patients discontinued therapy because of AEs. The time on treatment was similar on the FOLFOX and IFL arms (approximately 23.5 weeks) because of an increase in delays due to toxicity in cycles on the FOLFOX arm. There were a greater number of deaths on the IFL arm in the first 60 days.

For FOLFOX 4, fatigue (all grades: 70%; grade 3 or 4:7%), nausea (all grades:71% ;grade 3 or 4: 6%), vomiting (all grades: 41%; grade 3 or 4:6%), diarrhea with and without colostomy (all grades:69%; grade 3 or 4: 14) and peripheral neuropathy (all grades: 82%; grade 3 or 4:19%), are the most common non-hematologic adverse events. Neutropenia (all grades: 83%;grade 3 or 4: 54%), and thrombocytopenia (all grades: 71%; grade 3 or 4: 5%), are common hematologic adverse events. Febrile neutropenia or requirement for platelet transfusion were not increased on FOLFOX 4 as compared to the other two regimens.

Approximately 80% of patients had at least one neurotoxicity-related event. This neurotoxicity is cumulative. It is generally reversible and grade 3 or 4 neurotoxicity does not necessarily require discontinuation of treatment. Fifty percent of patients had their first sensory neurotoxicity in the first two cycles. Another 25% occurred in cycles 3 through 10.

Pulmonary fibrosis has been reported as a serious toxicity which may require discontinuation of oxaliplatin. Combined incidence of cough, dyspnea or hypoxia was increased in the FOLFOX 4 arm. At least one case of HUS has been observed in a Sanofi-Synthelabo sponsored trial. There was one patient in this study who had increased creatinine, prolonged PT, PTT and thrombocytopenia and involvement of multiple systems in his last cycle. This could be consistent with HUS or ARDS. Definitive relationship of HUS with oxaliplatin was not observed in this study. Hypersensitivity had an increased incidence on the FOLFOX 4 arm in the submitted randomized trial. This hypersensitivity was manifested as one or more of the following: urticaria, pruritis, flushing of face, diarrhea associated with oxaliplatin infusion, shortness of breath, bronchospasm, diaphoresis, chest pains, hypotension, disorientation and syncope. Immediate discontinuation of oxaliplatin therapy was not required in a few of these patients. See table 73 in the Appendix.

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B. Description of Patient Exposure

The doses of each agent and its method of administration was not captured for 5FU or LV for most patients because the CRF was changed several times during the conduct of study. The applicant was asked to provide this information for leucovorin, and if applicable for 5-FU from the clinic or hospital records on a pre-specified 50 responders on each of the IFL and FOLFOX4 arms. Information on all cycles up to a maximum 10 cycles was requested.

Table 44: Regimens of Arms A, F and G

Arm A	IFL	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 F	FOLFOX4	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	IROX	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

Audit of selected patients:

FOLFOX 4:

In the fifty patients on the FOLFOX 4 arm for whom information was obtained from the medical records, a total of 463 cycles were recorded with a median of 10 cycles/patient (range 2-10). Forty nine patients (98%) received at least one appropriate dose of all drugs in the regimen, with a median of 9 cycles in recommended doses.

Appropriate dose range for the purpose of this analysis included starting and dose level 2. For the purpose of this analysis, they were as follows: OXAL: 45-90 mg/m², LV: 375-425 mg/m², bolus 5FU: 450-850 mg/m², and infusional 5FU: 750-1250 mg/m².

In 18 patients (36%), 45 cycles (median of 1.5 cycles in the 18 patients) were not administered in recommended doses. Most of the violations were because of administering a decreased dose of LV (around 200 mg), and less often, a decreased dose of 5FU (bolus and infusional). One patient had all 10 cycles in the recommended doses except for LV which was given in 200 mg/m² doses on only 1 day in each cycle.

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Table 45: Summary of inadequate dosing in the 50 audit patients on the FOLFOX 4 arm.

Number of cycles	Oxaliplatin dose adequate	LV dose adequate	Bolus FU dose adequate	infusional FU dose adequate
1	No	Yes	No	No
1	No	No	No	No
1	No	Yes	No	No
2	No	Yes	Yes	Yes
13	Yes	No	No	No
10	Yes	No	Yes	Yes
8	Yes	Yes	No	No
3	Yes	Yes	No	Yes
6	Yes	Yes	Yes	No

Adequate dose range for the purpose of this analysis included starting and modified dose levels defined by the protocol

IFL:

Fifty patients were pre-selected by the FDA for an audit of dosages administered on the IFL arm. Data on forty-nine patients was submitted by the sponsor. In the 49 patients on the IFL arm for whom information was obtained from the medical records for an audit, a total of 344 cycles were recorded with a median of 7 cycles/patient (range 3-10). Forty nine patients (100%) received at least one appropriate dose of the regimen, with a median of 6 cycles in recommended doses.

Appropriate dose range for the purpose of this analysis included starting and dose level 3. They were as follows: CPT 11: 135 - 45 mg/m², LV: 15 - 25 mg/m², 5FU: 175 - 550 mg/m². In 14 patients (29%), 20 cycles (median of 4 cycles) were not administered in recommended doses. Most of the violations were because of administering an incorrect dose of CPT-11.

Reviewers Comments:

All patients received at least one appropriate dose of the regimen, (median of 6 cycles in an appropriate dose). From this audit, it appears that most patients received the recommended doses on the FOLFOX 4 and IFL regimen.

Analysis of all patients on the FOLFOX 4 Arm:

The information about drug exposure for all patients from the original dataset is as follows:

A median of 10 cycles of oxaliplatin were administered per patient (range 1- 47 cycles) in the FOLFOX 4 arm. Fourteen cycles did not have a BSA recorded. They were excluded from the median oxaliplatin dose/cycle calculation because only the total dose of the agent was submitted.

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Average total dose/cycle of oxaliplatin was 155 and the median BSA was 1.9. The median dose of oxaliplatin was 85 mg/m².

Table 46: Exposure to Oxaliplatin and CPT -11

	Range	Median
Cycles oxaliplatin administered in FOLFOX 4 arm		
2755	1 – 47 cycles	10 cycles
Cycles CPT-11 administered in IFL arm		
1115	1 – 23 cycles	4 cycles
Cycles oxaliplatin & CPT-11 administered in IROX arm		
1894	1 – 38 cycles	6 cycles

Dataset: PROTDATA

Table 47: Time to complete median # of cycles

Regimen	Time to complete 1 cycle	Median # of cycles	Time to complete median # of cycles	Actual treatment Duration
IFL	6 weeks	4	24 weeks	23.6 weeks
FOLFOX	2 weeks	10	20 weeks	23.9 weeks
IROX	3 weeks	6	18 weeks	21 weeks

Reviewer's comments:

As will be observed below, there were fewer delays on the IFL arm as compared to the oxaliplatin-containing regimens. This is likely why time to complete median # of cycles is more in IFL, despite a longer TTP on the FOLFOX 4 and IROX arms.

Table 48: Dose of oxaliplatin administered per cycle in mg/m²*

Oxaliplatin dose mg/m ²	# of cycles (%)
75 - 95	2108 (77)
60 - 74	377 (14)
45 - 59	163 (6)
Other	93 (3)

*In cycles where BSA has been submitted. N=2741

In approximately three quarter of cycles, 75-95 mg/m² (no dose reduction) of oxaliplatin were administered. Fourteen percent cycles were administered in dose level -1 (60-74 mg/m²) and 6 % in dose level -2 (45-59 mg/m²). Two thousand seven hundred and fifty five cycles were administered on the FOLFOX 4 arm. A record of bolus and infusional 5FU is provided for 2531 cycles. Ninety nine percent (n=2505) of the patients received 5FU in recommended starting dose

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to dose level -2. In 23 cycles > 850 mg/m² (greater than starting dose) of bolus 5FU were administered and in 3 less than 200 mg/m² (less than level 2).

Reviewer's Comments:

Full dose of oxaliplatin was administered to 75% of patients on the FOLFOX 4 arm. However, more dose delays were required due to toxicity on the FOLFOX arm as compared to the IFL arm.

Information regarding 5FU and LV were submitted for 92% all treatment cycles on this arm. In most of these cycles, 5FU was administered in doses ranging from starting level to dose level -2.

Table 49: Delay in drug administration

No Delay (cycles)	Delayed (cycles)	Not Reported (cycles)
FOLFOX 4		
2141	580	19
78%	21%	1%
IFL		
978	127	10
88%	11%	1%
IROX		
1520	366	8
80%	19%	1%

The next 9 tables, from 50-59 give the Applicant's analysis of number of cycles, drug exposure, cycle delays and dose reductions for each of the three arms.

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Table 50: Number of cycles administered - IFL - Treated patients

Applicant Table (12.1.1) 1

		IFL (N=256)
Number of cycles administered	Total	1138
	Median	4
	Min	1
	Max	23
Duration of treatment (weeks)	N	256
	Mean	26.6
	SD	20.3
	Median	23.6
	Min	6.0
Number of patients grouped by cycle; N (%)	Max	137.0
	1 - 3	119 (46.5)
	4 - 6	86 (33.6)
	7 - 9	30 (11.7)
	10 - 12	15 (5.9)
	13 - 18	5 (2.0)
	19 - 24	1 (0.4)
25 + Cycles	0	

Table 51: Extent of exposure on IFL

Applicant table (12.1.1)2

		CPT-11	5-FU
Total cumulative dose (mg/m ²)	N	256	256
	Mean	1621.2	6492.3
	Median	1376.4	5450.4
	St. Dev	1306.1	5222.7
	Min	122.2	500.0
	Max	6995.4	27977.3
Relative dose intensity (%)	N	256	256
	Mean	72.8	72.9
	Median	75.0	75.0
	St. Dev	20.2	20.4
	Min	23.7	22.2
	Max	115.2	115.2

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Table 52: Summary of cycle delays in IFL arm

Adapted from Applicant Table: Table (12.1.1)3

	IFL
Parameter	(N=256)
Number of patients who received more than 1 cycle of study treatment	203
Number of patients with at least 1 delay; N (%)	91 (44.8)
Delay	
Number of cycles that could be delayed (excluding cycle 1)	883
Number of cycles that were delayed; N (%)	129 (14.6)
Number of cycles delayed due to toxicity	44 (5%)
Number of cycles delayed due to other reasons	82
Number of delayed cycles with no reason reported	3

Table 53: Summary of cycle delays in IFL arm

Adapted from Applicant table (12.1.2) 3

	IFL
Parameter	(N=256)
Number of patients who received more than 1 cycle of study treatment	203
Number of patients with at least 1 delay; N (%)	91 (44.8)
Delay	
Number of cycles that could be delayed (excluding cycle 1)	883
Number of cycles that were delayed; N (%)	129 (14.6)
Number of cycles delayed due to toxicity	44
Number of cycles delayed due to other reasons	82
Number of delayed cycles with no reason reported	3
CPT-11 reduction	
Number of patients who received CPT-11	256 ^a
Number of patients with at least 1 cycle of CPT-11 dose reduced; N (%)	139 (54.3)
Number of cycles of CPT-11	1112
Number of cycles where CPT-11 dose level was reduced; N (%)	254 (22.8)
Number of cycles where dose was reduced due to AE	202
Number of cycles where dose was reduced due to other reasons	50
Number of reduced cycles with no reason reported	2
5-FU reduction	
Number of patients who received 5-FU	256 ^a
Number of patients with at least 1 cycle of 5-FU dose reduced; N (%)	141 (55.1)
Number of cycles of 5-FU	1110
Number of cycles where 5-FU dose was reduced; N (%)	255 (23.0)
Number of cycles where dose was reduced due to AE	203
Number of cycles where dose was reduced due to other reasons	50
Number of reduced cycles with no reason reported	2

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Table 54: Number of cycles administered - FOLFOX4 - Treated patients

Applicant table (12.1.2)1

		FOLFOX4
		(N=259)
Number of cycles administered	Total	2949
	Median	10
	Min	1
	Max	47
Duration of treatment (weeks)	N	259
	Mean	25.8
	SD	18.6
	Median	23.9
	Min	2.0
Number of patients grouped by cycle; N (%)	Max	98.0
	1 - 3	45 (17.4)
	4 - 6	41 (15.8)
	7 - 9	40 (15.4)
	10 - 12	41 (15.8)
	13 - 18	49 (18.9)
	19 - 24	26 (10.0)
25 + Cycles	17 (6.6)	

Table 55: Extent of exposure in FOLFOX4 - Treated patients

		Oxaliplatin	5-FU
Total cumulative dose (mg/m ²)	N	259	259
	Mean	836.3	19845.6
	Median	764.8	17917.9
	St. Dev	542.6	14289.1
	Min	83.7	800.0
	Max	2958.6	92839.2
Relative dose intensity (%)	N	259	259
	Mean	82.3	79.8
	Median	84.0	81.0
	St. Dev	16.1	16.3
	Min	20.7	16.5
	Max	118.4	105.8

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Table 56: Summary of cycle delays and dose reductions in FOLFOX4 arm

Applicant Table (12.1.2) 3

Parameter	FOLFOX (N=259)
Number of patients who received more than 1 cycle of study treatment	250
Number of patients with at least 1 delay; N (%)	198 (79.2)
Delay	
Number of cycles that could be delayed (excluding cycle 1)	2690
Number of cycles that were delayed; N (%)	610 (22.7)
Number of cycles delayed due to toxicity	396
Number of cycles delayed due to other reasons	210
Number of delayed cycles with no reason reported	4
Oxaliplatin reduction	
Number of patients who received OXAL	259
Number of patients with at least 1 cycle of OXAL dose reduced; N (%)	98 (37.8)
Number of cycles of OXAL	2762
Number of cycles where OXAL dose level was reduced; N (%)	176 (6.4)
Number of cycles where dose was reduced due to AE	153
Number of cycles where dose was reduced due to other reasons	22
Number of reduced cycles with no reason reported	1
5-FU reduction	
Number of patients who received 5-FU	259
Number of patients with at least 1 cycle of 5-FU dose reduced; N (%)	126 (48.6)
Number of cycles of 5-FU	2884
Number of cycles where 5-FU dose was reduced; N (%)	259 (9.0)
Number of cycles where dose was reduced due to AE	220
Number of cycles where dose was reduced due to other reasons	38
Number of reduced cycles with no reason reported	1

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Table 57: Number of cycles administered - IROX - Treated patients

Applicant Table (12.1.3) 1

		IROX (N=258)
Number of cycles administered	Total	1948
	Median	7
	Min	1
	Max	38
Duration of treatment (weeks)	N	258
	Mean	24.1
	SD	19.2
	Median	21.0
	Min	3.0
	Max	138.0
Number of patients grouped by cycle; N (%)	1 - 3	72 (27.9)
	4 - 6	55 (21.3)
	7 - 9	52 (20.2)
	10 - 12	45 (17.4)
	13 - 18	23 (8.9)
	19 - 24	7 (2.7)
	25 + Cycles	4 (1.6)

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Table 58: Extent of exposure in IROX - Treated patients

Applicant Table (12.1.3) 2

		CPT-11	Oxaliplatin
Total cumulative dose (mg/m ²)	N	258	258
	Mean	1372.3	594.6
	Median	1199.3	513.3
	St. Dev	1073.6	467.0
	Min	0.0 ^a	0.0
	Max	7502.2	3229.7
Relative dose intensity (%)	N	258	258
	Mean	87.1	89.2
	Median	91.0	94.3
	St. Dev	14.1	14.1
	Min	0.0 ^a	0.0
	Max	123.4	104.7

Table 59: Summary of cycle delays and dose reductions in IROX arm

Adapted from Applicant table (12.1.3) 3

Parameter	IROX (N=258)
Number of patients who received more than 1 cycle of study treatment	240
Number of patients with at least 1 delay; N (%)	138 (57.5)
Delay	
Number of cycles that could be delayed (excluding cycle 1)	1689
Number of cycles that were delayed; N (%)	373 (22.1)
Number of cycles delayed due to toxicity	182
Number of cycles delayed due to other reasons	189
Number of delayed cycles with no reason reported	2
Oxaliplatin reduction	
Number of patients who received OXAL	257 ^a
Number of patients with at least 1 cycle of OXAL dose reduced; N (%)	69 (26.8)
Number of cycles of OXAL	1904
Number of cycles where OXAL dose level was reduced; N (%)	113 (5.9)
CPT-11 reduction	
Number of patients who received CPT-11	257
Number of patients with at least 1 cycle of CPT-11 dose reduced; N (%)	114 (44.4)
Number of cycles of CPT-11	1924
Number of cycles where CPT-11 dose level was reduced; N (%)	191 (9.9)

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C. Methods and Specific Findings of Safety Review

Seven hundred and seventy-three patient were dosed on study. Seven hundred and sixty-nine patients had at least 1 AÉ reported in the datasets (CYTOXNCI and CYTOX). Four patients had no reported adverse events. Twenty seven percent (n=70) in the FOLFOX arm, 9% (n=22) on the IFL arm and 20% (n=51) of patients discontinued therapy because of AEs.

Table 60: Adverse events greater than 5% all grades and greater than 1% grade 3 or 4

Adverse Event	FOLFOX4	FOLFOX 4	IFL	IFL	IROX	IROX
	All Grades (%)	Grades 3/4 (%)	All Grades (%)	Grades 3/4 (%)	All Grades (%)	Grades 3/4 (%)
Allergy/Immunology						
Hypersensitivity	12	2	5	0	6	1
Cardiovascular						
Thrombosis	6	5	7	7	3	3
Hypotension	5	3	5	3	4	3
Constitutional Symptoms						
Fatigue	70	7	60	11	67	16
Gastrointestinal						
Nausea	71	6	69	16	84	19
Diarrhea-no colostomy	56	12	66	29	77	25
Vomiting	41	3	46	14	65	23
Stomatitis	38	0	25	1	19	0
Anorexia	35	2	26	5	28	5
Constipation	32	5	29	4	21	2
Diarrhea-colostomy	13	2	16	8	16	3
Dehydration	9	5	16	11	15	7
Ileus	3	2	6	5	4	3
Hematology						
Leukopenia	87	20	86	24	79	26
Neutropenia	83	54	82	47	74	40
Thrombocytopenia	71	5	28	3	47	5
Anemia	27	3	29	5	25	3
Lymphopenia	6	2	4	1	5	2
Hepatic						
SGOT (AST)	17	1	4	0	11	1
Alkaline Phostphatase	16	0	9	0	17	2
Hypoalbuminemia	8	0	5	2	9	0
SGPT (ALT)	6	1	3	0	5	2
Infection/Febrile Neutropenia						

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Adverse Event	FOLFOX4	FOLFOX 4	IFL	IFL	IROX	IROX
	All Grades (%)	Grades 3/4 (%)	All Grades (%)	Grades 3/4 (%)	All Grades (%)	Grades 3/4 (%)
Infection-no ANC	10	3	6	2	7	2
Infection-ANC	8	8	12	11	9	8
Febrile neutropenia	4	4	15	14	12	11
Metabolic/Laboratory						
Hyperglycemia	14	2	12	4	12	3
Hypokalemia	12	4	7	4	6	2
Hyponatremia	8	2	7	4	5	1
Neurology						
Paresthesias	77	18	17	3	62	7
Pharyngo-laryngeal dysesthesias	38	2	2	0	29	1
Depression	8	1	5	0	7	1
Pain						
Pain-abdominal	30	8	32	8	40	11
Myalgia	14	2	6	0	9	2
Pain	7	1	5	2	6	1
Pulmonary						
Cough	36	1	27	2	19	0
Dyspnea	18	7	15	4	12	2

Datasets: CYTOX and CYTOXNCI

Individual toxicities:

Four toxicities were identified while the study was ongoing, and the CRF was modified to include them specifically in the database. These four toxicities are pulmonary fibrosis, ileus, HUS and hyponatremia and will be discussed in greater detail with their organ systems. These AEs will be analyzed realizing that trials are powered for efficacy. Particularly for relatively uncommon AEs, a larger number of patients would be required to find a difference in treatment arms. In addition there is the problem of multiple comparisons.

Pulmonary Adverse Events and Pulmonary fibrosis:

Pulmonary fibrosis was added as a possible AE in addendum 9, at a time when 11 deaths were reported due to this complication in over 50,000 patients treated with oxaliplatin. There was one reported case of pulmonary fibrosis on the FOLFOX4 arm in this trial.

Symptoms that may be part of pulmonary fibrosis such as cough, hypoxia, dyspnea were increased in the oxaliplatin-containing arm as compared to IFL (see below for details). There also appears to be a higher incidence of most of the other pulmonary toxicities in the FOLFOX4 arm. There were 4% cases of pneumonitis of any grade and 1% grade 3 or 4 in the IFL arm, 4%

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and 2% in the FOLFOX4 arm, and 3% and 1% in the IROX arm. There was one patient who died from grade 5 pneumonitis in the IFL arm.

Table 61: Pulmonary Toxicity*

Grade	IFL N	FOLFOX4 N	IROX N	IFL %	FOLFOX4 %	IROX %
Dyspnea						
4	3	3	2	1	1	1
3	7	14	4	3	5	2
2	27	27	24	11	10	9
1	2	3	1	1	1	0
Cough						
3	5	2	1	2	1	0
2	9	10	6	4	4	2
1	54	80	41	21	31	16
Hypoxia						
4	1	0	2	0	0	1
3	2	6	3	1	2	1
2	0	0	1	0	0	0
1	1	0	0	0	0	0
Pneumonitis						
5	1	0	0	0	0	0
4	2	0	0	1	0	0
3	1	6	3	0	2	1
2	2	0	2	1	0	1
1	4	4	2	2	2	1
Pulmonary fibrosis						
3	0	1	0	0	0	0
Pulmonary NOS						
4	1	0	0	0	0	0
3	0	1	0	0	0	0
2	0	2	1	0	1	0
1	2	5	3	1	2	1
Hiccups						
3	0	2	2	0	1	1
2	1	4	5	0	2	2
1	4	6	3	2	2	1

*Toxicities > 2% any grade on any arm

Unexplained respiratory symptoms such as non-productive cough, dyspnea, crackles, or radiological pulmonary infiltrates may be signs of pulmonary fibrosis. When cough, dyspnea and hypoxia are combine together, the overall and grade 3 and 4 events incidence were increased in the FOLFOX 4 arm (IFL all: 34%, grade 3-4: 5%; FOLFOX 4 all: 43%, grade 3-4: 7, IROX all:

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28% and grade 3-4:3%). Information about auditory findings on chest examination and radiological examination of patients were not available.

Table 62: Combined incidence of Cough, Dyspnea and Hypoxia.

Grade	IFL N=256 (%)	FOLFOX4 N=259 (%)	IROX N=258 (%)
3 & 4	13 (5)	18 (7)	9 (3)
all	87 (34)	111 (43)	71 (28)

HUS, Coagulation and Hemorrhage:

HUS:

No cases of HUS per se were reported in this study. However, 3 patients discussed below had increased creatinine along with PT and one of them also had hemolysis. All of these occurred in oxaliplatin-containing arms. These case will be further discussed below. As will be seen, one of these patient may have had HUS. Hemolysis is not reported in the table 48 because it is classified as a hematology AE.

Patient 7462 1036 092353 on the FOLFOX arm had a combination of grade 2 creatinine elevation, grade 3 PT prolongation and grade 2 thrombocytopenia in the 21st and last cycle. Apparently the patient had multiple organs affected in that cycle and had grade 3 bilirubin elevation, grade 3 cardiac troponin elevation. HUS can affect multiple systems. The CRF for this patient was requested on 12/12/2003.

The patient 7462 0163 080390 on the IROX arm had PT, PTT prolongation, increased creatinine and hemolysis only in cycle 1. He subsequently had many more cycles without the hemolysis. This patient does not appear to have had HUS.

Patient 7462 1278 093732 on the FOLFOX arm had PT prolongation, thrombocytopenia, and creatinine increase but they occurred in different cycles. This case is not likely to be HUS.

PT PTT prolongation:

PT and PTT were more prolonged on the FOLFOX arm, and are clinically meaningful only if the patient was on anticoagulation. Information on concomitant medications were not captured in the CRF. One can only attempt to get clues about the relationship of the AE with the PT prolongation. There were 13 patients with any increase in PT. Five patients on the FOLFOX arm, 2 on the IFL arm and 1 on the IROX arm reported grade 3 toxicity (i.e > x 2 ULN). All patients on the FOLFOX arm had reason to be on anticoagulation. PT prolongation is not uncommon while a patient is being adjusted on coumadin.

In the postmarketing reports, there are 18 reports of abnormal or prolonged PT, and 24 of increased INR (17 and 21 of these, respectively, were termed serious). For the sake of a

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perspective, only anemia, leucopenia, , thrombocytopenia, hypokalemia and hyperglycemia have a higher number of cases reported for investigations in the post-marketing reporting.

INR prolongation in patients treated with coumadin has been reported in literature. In this retrospective review, 12 of 21 (57%) patients on the FOLFOX regimen had prolonged INR on 1 mg/d dose of coumadin. (Minidose warfarin prophylaxis for catheter-associated thrombosis in cancer patients: can it be safely associated with fluorouracil-based chemotherapy? Masci G, Magagnoli M, Zucali PA, Castagna L, Carnaghi C, Sarina B, Pedicini V, Fallini M, Santoro A.; J Clin Oncol. 2003 Feb 15;21(4):736-9.)

The summary submitted by the applicant on request for patients with grade 3 PT toxicity is given in the table 63 below.

Table 63: Applicant summary of patients with PT Grade 3 toxicity

Treatment Arm	Subject ID	Sponsors Review of CRF's
IFL	92595	On Coumadin for Atrial Fibrillation. Increase in PT cycle 1
	88138	Gr. 3 increase in PT cycle 1. No other details
FOLFOX4	90165	Patient on chronic anticoagulation for Atrial valve replacement
	90647	Patient experienced a thrombo-embolic event. Increase in PT cycle 4
	91312	Patient had DVT. Increase in PT cycles 2 to 12
	92353	On anticoagulants, reason not available. Increase in PT cycle 21
	95223	Thrombosis in PICC line cycle 2 and cycle 3. Started on anti-coagulants. Increase in PT cycles 3 and 6
IROX	80390	Gr. 3 increase in PT cycle 1. No other details

Grade 1 toxicity is >ULN-1.5xULN, Grade 2 is >1.5-2xULN and grade 3 is >2xULN. There is no grade 4 for PT in the NCI CTC v2

Hemorrhage:

Grade 1 epistaxis was greater in the FOLFOX arm (10%) vs on IFL (2%) and IROX (1%), and this probably translated into overall greater hemorrhagic events seen in table 64.

Table 64: Hemorrhage-Any

Grade	IFL N	FOLFOX4 N	IROX N	IFL %	FOLFOX4 %	IROX %
4	0	0	2	0	0	1
3	3	2	2	1	1	1
2	5	3	3	2	1	1
1	18	46	14	7	18	5

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GI system and Ileus:

Gastrointestinal:

Diarrhea without colostomy, nausea, vomiting and dehydration were the most common GI toxicities with an incidence of >5% in the FOLFOX4 arm. The incidence of constipation was the same as in the IFL arm.

Ileus was recognized as a possible AE related to the FOLFOX arm at addendum 9. When evaluated in the database, ileus was greater in the CPT-11 containing arms.

Dehydration caused grade 5 AE in all arms. In general, the incidence of dehydration was greater in the CPT-11 containing arms. Grade 1 and 2 alteration in taste, dyspepsia and flatulence was greater in the FOLFOX arm.

Table 65: Selected GI Adverse Events*

Grade	IFL N	FOLFOX4 N	IROX N	IFL %	FOLFOX4 %	IROX %
Diarrhea-no colostomy						
4	8	2	6	3	1	2
3	67	30	59	26	12	23
2	40	39	53	16	15	21
1	54	74	80	21	29	31
Diarrhea-colostomy						
5	1	0	0	0	0	0
4	2	0	1	1	0	0
3	18	6	8	7	2	3
2	8	11	12	3	4	5
Nausea						
3	40	16	50	16	6	19
2	46	45	78	18	17	30
1	90	123	88	35	47	34
Stomatitis						
4	1	0	0	0	0	0
3	1	0	1	0	0	0
2	14	28	9	5	11	3
1	50	70	42	20	27	16
Vomiting						
4	5	0	4	2	0	2
3	32	9	55	13	3	21

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Grade	IFL N	FOLFOX4 N	IROX N	IFL %	FOLFOX4 %	IROX %
2	33	39	53	13	15	21
1	47	58	56	18	22	22
Dehydration						
5	1	1	1	0	0	0
4	5	1	1	2	0	0
3	22	11	18	9	4	7
2	13	7	14	5	3	5
1	1	4	4	0	2	2
Anorexia						
4	3	0	0	1	0	0
3	11	4	12	4	2	5
2	17	27	25	7	10	10
1	36	60	34	14	23	13
Ileus						
4	5	1	4	2	0	2
3	9	5	5	4	2	2
2	1	1	2	0	0	1
Constipation						
4	3	3	1	1	1	0
3	6	9	3	2	3	1
2	14	19	20	5	7	8
1	51	51	30	20	20	12
Mouth dryness						
2	1	0	3	0	0	1
1	4	14	6	2	5	2
Taste						
3	0	0	1	0	0	0
2	3	4	8	1	2	3
1	12	32	13	5	12	5
Dyspepsia						
3	0	0	1	0	0	0
2	5	5	7	2	2	3
1	13	25	7	5	10	3

*Toxicities > 2% any grade on any arm

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Hematological Toxicity:

Infection /Fever:

Fever and /or infection could have been reported in several ways in the database. Febrile neutropenia (defined as fever $\geq 38.5^{\circ}$ C of unknown origin with ANC $< 1 \times 10^9/L$), infection with or without decreased ANC were uniformly lower in the oxaliplatin-containing arms. Catheter-related infection were higher in the FOLFOX arm, probably because of the need for permanent catheter for FU infusion in the FOLFOX 4 regimen. Please see table below.

Table 66: All infections under preferred term infection/febrile neutropenia.

Grade	IFL N	FOLFOX4 N	IROX N	IFL %	FOLFOX4 %	IROX %
Febrile neutropenia						
5	2	0	1	1	0	0
4	8	3	8	3	1	3
3	28	8	21	11	3	8
1	0	0	1	0	0	0
Infection						
5	1	0	0	0	0	0
4	2	0	0	1	0	0
3	2	0	0	1	0	0
2	4	2	2	2	1	1
1	1	2	0	0	1	0
Infection-ANC						
5	2	0	2	1	0	1
4	8	2	3	3	1	1
3	21	18	18	8	7	7
Infection-catheter						
4	0	1	0	0	0	0
3	2	1	0	1	0	0
2	0	7	0	0	3	0
Infection-no ANC						
5	0	1	0	0	0	0
4	0	1	2	0	0	1
3	4	8	4	2	3	2
2	8	13	9	3	5	3
1	3	2	4	1	1	2
Infection-						

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Unk ANC						
3	5	6	5	2	2	2
1	0	0	1	0	0	0

Myelosuppression:

Myelosuppression was common in all 3 arms. Overall, all arms had similar myelosuppression, except FOLFOX4 had a greater incidence of thrombocytopenia of any grade. Grade 3 or 4 thrombocytopenia was similar across treatment arms. In general other grade 3 or 4 myelosuppression AE were similar except for neutropenia. As noted above, febrile neutropenias was not increased in the FOLFOX4 arm. Platelet transfusions were not greater in the FOLFOX 4 arm.

Table 67: AE all grades ($\leq 5\%$) and grade 3 or 4 AEs ($\leq 1\%$)

Grade	IFL N	FOLFOX4 N	IROX N	IFL %	FOLFOX4 %	IROX %
Leukopenia						
4	14	2	22	5	1	9
3	48	49	45	19	19	17
2	86	110	69	34	42	27
1	71	64	68	28	25	26
Neutropenia						
4	50	48	55	20	19	21
3	71	92	48	28	36	19
2	51	52	52	20	20	20
1	37	22	36	14	8	14
Anemia						
4	2	0	1	1	0	0
3	10	7	7	4	3	3
2	33	19	29	13	7	11
1	30	44	28	12	17	11
Anemia-leukemia*						
3	1	0	0	0	0	0
1	1	0	1	0	0	0
Blood/bone marrow						
4	0	0	1	0	0	0
3	0	1	0	0	0	0
Hemolysis						
2	0	1	1	0	0	0
1	2	1	3	1	0	1
Thrombocytopenia						
4	1	2	1	0	1	0

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Grade	IFL N	FOLFOX4 N	IROX N	IFL %	FOLFOX4 %	IROX %
3	7	10	12	3	4	5
2	3	59	13	1	23	5
1	60	114	95	23	44	37
Lymphopenia						
3	3	4	4	1	2	2
2	5	9	9	2	3	3
1	3	2	1	1	1	0
Transfusion-Plt						
3	1	0	1	0	0	0
Transfusion-PRBC						
3	2	1	3	1	0	1

*as submitted in the electronic datasets

Neuropathy:

Neurotoxicity is the main non-hematologic dose limiting toxicity. The major neurotoxicity is sensory neuropathies (including parasthesias and pharyngo-laryngeal dysesthesia). In the original NDA, the duration of toxicity was collected and analyzed. However, this was not done in this cooperative group study. Consequently, the neurotoxicity can not be analyzed as acute or persistent. The neurotoxicity was graded by the oxaliplatin neurotoxicity scale as in the previous NDA. The grading scale for paresthesias/dysesthesias was: Grade 1, resolved and did not interfere with functioning; Grade 2, interfered with function but not daily activities; Grade 3, pain or functional impairment that interfered with daily activities; Grade 4, persistent impairment that is disabling or life-threatening..

The overall incidence of any neurotoxicity was approximately 82% (19% grade 3 or 4) in the FOLFOX arm, 70% (7% grade 3 or 4) in the IROX arm and 19% (2% grade 3 or 4) in the IFL arm. It is generally reversible. Of the patients who had grade 3 or 4 neurotoxicity, half of the patients received further therapy. Per protocol, treatment was supposed to discontinue for grade 3 or 4 toxicity persistent between cycles. Duration of treatment was not captured in the CRF, and discontinuation of treatment due to persistent grade 3 or 4 treatment can not be verified.

Pharyngo-laryngeal dysesthesia is characterized by subjective sensation of dysphagia or dyspnea, without any laryngospasm or bronchospasm. Its grade 3 or 4 incidence of 2% is the same as that reported in literature. It occurred as a grade 1 toxicity in a third of the patients on the FOLFOX arm.

Neurosensory and neuromotor toxicities were more in the oxaliplatin arm, as expected. Anxiety, depression and insomnia were also increased with FOLFOX 4.

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Table 68: Neurotoxicities*

Grade	IFL N=256	FOLFOX4 N=259	IROX N=258	IFL %	FOLFOX4 %	IROX %
Paresthesias						
4	1	0	1	0	0	0
3	6	46	16	2	18	6
2	3	58	37	1	22	14
1	34	96	107	13	37	41
Pharyngo-laryngeal dysesthesias						
3	0	4	2	0	2	1
2	0	13	10	0	5	4
1	4	82	62	2	32	24
Neuro-sensory						
3	0	2	2	0	1	1
2	1	9	2	0	3	1
1	5	20	20	2	8	8
Anxiety						
3	0	0	1	0	0	0
2	0	3	6	0	1	2
1	7	11	9	3	4	3
Ataxia						
3	0	1	0	0	0	0
2	0	2	1	0	1	0
1	0	1	1	0	0	0
Depression						
3	1	2	3	0	1	1
2	3	11	6	1	4	2
1	9	9	9	4	3	3
Dizziness						
3	0	1	2	0	0	1
2	7	2	6	3	1	2
1	9	18	18	4	7	7
Hallucinations						
3	1	2	1	0	1	0
Insomnia						
2	4	9	8	2	3	3
1	20	25	19	8	10	7
Neuro-motor						
3	0	2	1	0	1	0

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2	1	3	3	0	1	1
1	0	1	2	0	0	1
Syncope						
3	4	7	2	2	3	1
2	0	1	0	0	0	0
Vertigo						
3	1	0	0	0	0	0
2	0	3	1	0	1	0
1	0	6	3	0	2	1

*Toxicities > 2% any grade on any arm

In order to evaluate cumulative toxicity of sensory neuropathy, parasthesias and neurosensory adverse events were combined. In literature, as well as in the previous NDA for oxaliplatin, paresthesia was shown to be cumulative. To analyze the cumulative sensory neurotoxicity (neurosensory AE and paresthesias) in the current trial for this NDA, the incidence of sensory neurotoxicity reported in the trial by number of patients in that cycle was evaluated. The percentage of patients with neurotoxicity increased with increasing cycles on treatment. In any given cycle, 30% -75% of patients suffered from sensory neuropathy (when number of patients treated in cycle >10). Sensory neuropathy occurred in largest numbers in the FOLFOX arm. See table 71

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Table 69: Incidence of sensory neuropathy by number of patients in cycle.

(for cycles in which at least 10% of enrolled patients continued on the FOLFOX arm)

CYCLE	IFL		FOLFOX4		IROX		% pts with neurosensory AE and paresthesias		
	Pts (N)	AE (N)	Pts (N)	AE (N)	Pts (N)	AE (N)	IFL (%)	FOLFOX4 (%)	IROX (%)
1	255	17	259	77	258	75	7	30	29
2	203	14	250	118	240	96	7	47	40
3	169	14	236	130	207	87	8	55	42
4	139	7	214	110	186	89	5	51	48
5	101	6	203	111	164	78	6	55	48
6	77	7	192	101	151	68	9	53	45
7	51	3	173	96	131	53	6	55	40
8	39	5	163	97	118	51	13	60	43
9	27	5	152	104	90	47	19	68	52
10	21	2	133	96	80	44	10	72	55
11	18	1	125	90	60	35	6	72	58
12	16	2	114	89	51	28	13	78	55
13	10	2	92	68	34	19	20	74	56
14	9	2	85	62	30	17	22	73	57
15	7	2	74	56	24	16	29	76	67
16	7	2	62	46	20	13	29	74	65
17	6	2	54	40	15	10	33	74	67
18	6	2	52	36	12	6	33	69	50
19	5	1	43	29	11	6	20	67	55
20	5	1	39	23	8	4	20	59	50
21	5	2	32	23	7	1	40	72	14
22	5	4	28	22	5	2	80	79	40

Methodology: Dataset PROTDATA for cycle #s. Dataset CYTOX and CYTOXNCI concatenated. Zero or missing grades excluded. Paresthesia and neurosensory AE joined with cycle #s. If both the toxicities were present in one cycle, only one was used. Percentages were then calculated for number of events/number of patients in that cycles.

Sensory neuropathy is one of the most important toxicities of oxaliplatin. The codes neurosens, paresthesia, dysesthesias and neuropathy nos were combined by the applicant to analyze the incidence of sensory neuropathy by grade.

Sensory neuropathy including paresthesias generally started with grade 1 toxicity. Seventy four percent of all patients had sensory neuropathy present as a grade 1 toxicity and 5% as a grade 2 toxicity (table 71). This neuropathy often started early in the course of treatment on the FOLFOX4 arm, but late first appearances were not uncommon. Fifty percent of sensory neurotoxicity appeared in the first two cycles. Another 25% occurred in cycles 3-10.

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Table 70: Cycle at first occurrence of paresthesia and neurosensory adverse event

Cycle	IFL N=256	FOLFOX4 N=259	IROX N=258	IFL %	FOLFOX4 %	IROX %
1	17	77	75	7	30	29
2	8	60	41	3	23	16
3-10	8	24	19	8	25	21
11-20	0	1	1	0	2	0

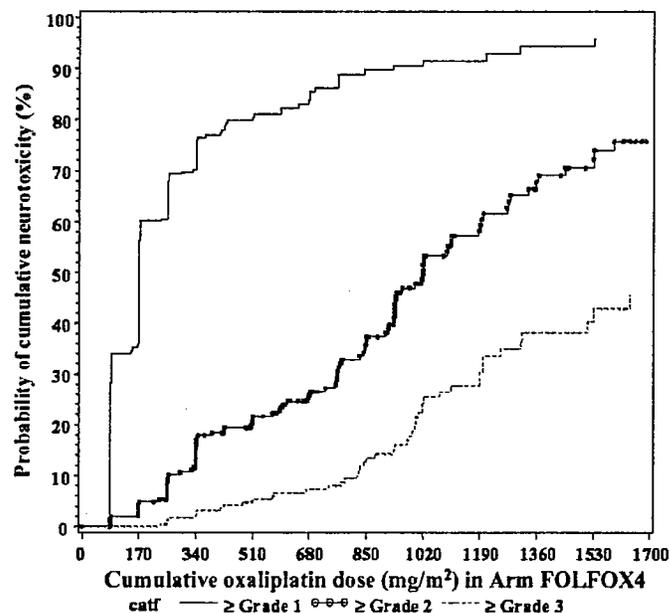
Truncated at 20 cycles

Table 71: Grade at first occurrence of paresthesia and neurosensory adverse event

Grade at initial presentation	IFL	FOLFOX4	IROX	IFL	FOLFOX4	IROX
	N=256	N=259	N=258	%	%	%
1	36	192	152	14	74	59
2	3	14	16	1	5	6
3	5	1	3	2	0	1
4	1	0	1	0	0	0

The above findings on cumulative toxicity and grade at first occurrence are similar to those presented in the applicant figure below.

Figure 5: - Kaplan-Meier Plots of the Cumulative Rate of the First Occurrence of Different Grades of Cumulative Neurotoxicity - FOLFOX4 arm
Applicant Figure (12.2.3.1.4) 1



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Hypersensitivity:

More patients in the oxaliplatin arms experienced hypersensitivity (IFL: 5%; FOLFOX4: 12%; IROX: 6%). Grade 3 or 4 incidence was 0% for IFL, 2% for FOLFOX 4 and 1% for the IROX arm. Treatment discontinuation due to hypersensitivity as a reason were not available from the dataset. According to the applicant, twelve patients in the FOLFOX arm discontinued treatment because of hypersensitivity. Hypersensitivity in these patients manifested as urticaria, pruritis, flushing of face, diarrhea associated with oxaliplatin infusion, shortness of breath, bronchospasm, diaphoresis, chest pains, hypotension, disorientation and syncope. Some patient were administered up to 3 cycles depending on the severity of the hypersensitivity reactions before treatment was discontinued. A summary of patients who discontinued FOLFOX 4 due to hypersensitivity as submitted by the applicant is in the appendix.

Table 72: Hypersensitivity reactions by grade

Grade	IFL N=256	FOLFOX N=259	IROX N=258
4	1	0	0
3	0	4	2
2	1	7	2
1	11	21	12

Tumor Lysis Syndrome:

Two patients on IROX and 1 patient on FOLFOX 4 suffered from tumor lysis syndrome. Both are oxaliplatin-containing arms.

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Hepatic Adverse Events:

Although the transaminases were higher in the oxaliplatin containing arms, grade 3/4 toxicities, or hepatic failures were few if any.

Table 73: Hepatotoxicity

Grade	IFL N	FOLFOX4 N	IROX N	IFL %	FOLFOX4 %	IROX %
Alk phos						
3	0	0	6	0	0	2
2	6	8	11	2	3	4
1	16	34	27	6	13	10
Bilirubin						
4	1	1	0	0	0	0
3	3	0	4	1	0	2
2	1	4	1	0	2	0
1	5	11	2	2	4	1
SGOT (AST)						
4	0	0	1	0	0	0
3	1	3	2	0	1	1
2	1	6	5	0	2	2
1	7	36	21	3	14	8
SGPT (ALT)						
3	0	2	4	0	1	2
2	2	3	1	1	1	0
1	5	11	9	2	4	3
Hepatic failure						
4	0	1	0	0	0	0
3	1	0	1	0	0	0

There is no indication from this trial that there is an increased incidence of hepatic failure in the FOLFOX arm. An initial review by Dr Kathleen Phelan PhD (ODS) found no strong support for oxaliplatin as a cause for hepatic failure from the post-marketing reports, although an association could not be excluded.

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Renal:

There were two grade 5 renal failure events, 1 each on the IFL and the FOLFOX arms. There does not appear to be an increased incidence of renal failure with FOLFOX 4.

Table 74: Selected Renal & Urogenital Adverse Events*

Grade	IFL N	FOLFOX4 N	IROX N	IFL %	FOLFOX4 %	IROX %
Creatinine						
3	1	0	0	0	0	0
2	3	4	6	1	2	2
1	5	7	6	2	3	2
Renal NOS						
4	1	0	0	0	0	0
2	4	1	1	2	0	0
1	2	1	3	1	0	1
Dysuria						
3	0	1	0	0	0	0
2	1	1	2	0	0	1
1	5	5	3	2	2	1
Urinary frequency						
3	1	2	2	0	1	1
2	0	2	2	0	1	1
1	4	11	4	2	4	2

*Toxicities \geq 2% any grade on any arm

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Cardiac:

The incidence of any cardiac event was greater in the IFL arm, probably due to bolus 5FU known to have infrequent cardiac toxicity, as well as CPT-11 which can cause ischemia. Only VTs were increased in FOLFOX 4. However, the overall numbers are too few to make any definitive conclusions. Grade 5 events were greater in IFL arm, although one patient of the FOLFOX arm had grade 5 thrombosis.

Table 75: Cardiac Events-Any grade*

Grade	IFL N=256	FOLFOX4 N=259	IROX N=258	IFL %	FOLFOX4 %	IROX %
Arrhythmia-SVT						
3	8	1	0	3	0	0
Edema						
4	0	0	1	0	0	0
3	1	0	1	0	0	0
2	13	13	5	5	5	2
1	20	25	19	8	10	7
Hypotension						
4	2	0	1	1	0	0
3	5	9	7	2	3	3
2	6	4	1	2	2	0
1	0	0	1	0	0	0
Thrombosis						
5	1	1	0	0	0	0
4	5	1	3	2	0	1
3	12	13	4	5	5	2
2	0	1	1	0	0	0

*Toxicities > 2% any grade on any arm

Table 76: Grade 5 cardiac events

Toxicity	IFL	FOLFOX
Arrhythmia	1	0
Cardiovascular nos	0	1
Hypotension	1	0
Ischemia/infarction	2	0
Thrombosis	1	1

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Constitutional Symptoms:

Fatigue was by far the most common constitutional symptom reported. Grade 3 or 4 events were more in the CPT-11 containing arms.

Table 77: Fatigue

Grade	IFL N=256 (%)	FOLFOX4 N=259(%)	IROX N=258(%)
1	65 (25)	78 (30)	61 (24)
2	60 (23)	87 (34)	70 (27)
3	25 (10)	16 (6)	39 (15)
4	3 (1)	1 (0)	3 (1)

Pain:

Myalgias, neuralgias and headaches are increased in the FOLFOX arm .

Table 78: Pain

(continued on next page)

Grade	IFL N	FOLFOX4 N	IROX N	IFL %	FOLFOX4 %	IROX %
Arthralgia						
3	1	1	1	0	0	0
2	2	5	5	1	2	2
1	11	7	15	4	3	6
Headache						
3	1	1	1	0	0	0
2	4	13	5	2	5	2
1	10	20	17	4	8	7
Myalgia						
3	1	4	5	0	2	2
2	6	13	6	2	5	2
1	8	19	12	3	7	5
Neuralgia						
3	1	0	2	0	0	1
2	0	5	0	0	2	0
1	0	7	2	0	3	1
Pain						
4	2	0	0	1	0	0
3	2	2	3	1	1	1
2	2	7	4	1	3	2
1	8	10	9	3	4	3
Pain-						

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Grade	IFL N	FOLFOX4 N	IROX N	IFL %	FOLFOX4 %	IROX %
abdominal						
4	1	2	0	0	1	0
3	19	18	28	7	7	11
2	22	20	37	9	8	14
1	39	38	39	15	15	15

Metabolic and Laboratory

There appears to be an increase in hypokalemia in the FOLFOX 4 arm, as well as hypoglycemia in both the oxaliplatin-containing arms. The hypokalemia was mostly associated with diarrhea, See table 80. One patient died from acidosis in the IFL arm. Hyponatremia was recognized as a toxicity late in the study (amendment 18), but the results shown in table 80 do not support this.

Table 79: Selected metabolic and Laboratory Adverse Events

Grade	IFL N	FOLFOX4 N	IROX N	IFL %	FOLFOX4 %	IROX %
Acidosis						
5	1	0	0	0	0	0
4	1	1	0	0	0	0
3	1	0	0	0	0	0
1	1	0	0	0	0	0
Hyperglycemia						
4	4	1	0	2	0	0
3	5	5	7	2	2	3
2	9	12	11	4	5	4
1	12	17	14	5	7	5
Hypoglycemia						
3	1	1	1	0	0	0
1	0	3	2	0	1	1
Hypokalemia						
5	0	1	0	0	0	0
4	1	2	1	0	1	0
3	9	7	4	4	3	2
2	1	0	1	0	0	0
1	8	20	9	3	8	3
Hypomagnesemia						
2	1	0	2	0	0	1
1	4	4	4	2	2	2
Hyponatremia						
4	2	0	0	1	0	0

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Grade	IFL N	FOLFOX4 N	IROX N	IFL %	FOLFOX4 %	IROX %
3	9	6	3	4	2	1
2	1	0	0	0	0	0
1	9	15	9	2	7	3

Table 80: Incidence of Hypokalemia accompanying Diarrhea

Adverse Event	IFL N=256	FOLFOX N=259	IROX N=258
Either Hypokalemia or Diarrhea	2	5	3
Both*	17	25	12

*Hypokalemia and diarrhea occurred in the same cycle

Deaths on Study:

The Applicant analyzed deaths within 60 days of first dosing, within 30 days of last dosing and during the entire study. FOLFOX 4 arm consistently had the lowest number of deaths. The applicant table is given below.

Table 81: Summary of number of deaths - Number (%) of patients - Safety population

Applicant Table (12.3.1) 1

	IFL (N=256)	FOLFOX4 (N=259)	IROX (N=258)
Number of deaths within 30 days of last dose	12 (4.7)	8 (3.1)	8 (3.1)
Number of deaths within 60 days of first dose	13 (5.1)	6 (2.3)	8 (3.1)
Number of deaths during the entire study	189 (73.8)	149 (57.5)	170 (65.9)

D. Adequacy of Safety Testing

Safety findings from a large randomized study have been evaluated in this submission. The findings are generally consistent with those reported previously for oxaliplatin.

E. Summary of Critical Safety Findings and Limitations of Data

Oxaliplatin in combination with infusional 5FU/LV has an acceptable toxicity profile. It is similar to the adverse events noted in the previous NDA for pretreated patients. Seven hundred and seventy-three patients were dosed with study drugs in this study. Twenty-seven percent discontinued therapy on the FOLFOX arm due to adverse events, as compared to IFL (9%) and IROX (20%). Fifteen percent cycles on the FOLFOX arm were delayed due to toxicity compared

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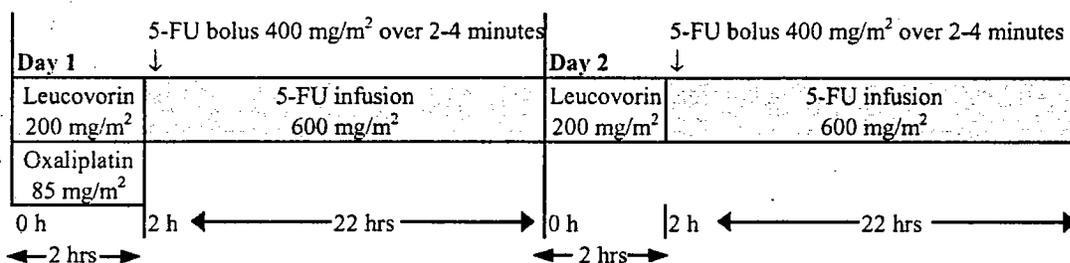
to 5% on the IFL arm. Deaths within 30 or 60 days were highest on the IFL arm. The most common non-hematologic toxicities were fatigue, GI symptoms (nausea, vomiting, abdominal pain, diarrhea, constipation and anorexia) and paresthesias. Oxaliplatin causes myelosuppression. However, the incidence of febrile neutropenia does not appear to be markedly increased and transfusions were not increased in the FOLFOX 4 arm. There appears to be an increase in pulmonary events, but only one case of pulmonary fibrosis was noted. PT/PTT may require closer monitoring. However, data on concomitant medications was not collected, and these findings are not conclusive. There has been one reported case of HUS with possible association with oxaliplatin from postmarketing reporting. No cases of HUS were reported for this study.

Approximately 80% of patients had at least one neurotoxicity-related event. The neurotoxicity is cumulative. It is generally reversible, and grade 3 or 4 neurotoxicity did not always require discontinuation of treatment. Fifty percent of patients had their first sensory neurotoxicity in the first two cycles. Another 25% occurred in cycles 3-10.

The NCCTG did not collect data on concomitant medications or on duration of AEs which prevented evaluation of whether an AE such as neuropathy was reversible in this study, or whether persistent grade 3 – 4 toxicity led to discontinuation of therapy and its consequences. It was assumed that if neurotoxicity was not reported in later cycles, it was reversible. These features of oxaliplatin have been studied in literature and in the previous NDA. Association of PT prolongation with warfarin administration could not be made because data on concomitant medications was not collected.

VIII. Dosing, Regimen, and Administration Issues

The recommended dose of oxaliplatin in combination with infusional 5-FU/LV is 85 mg/m² intravenously over 2 hours in 250-500 mL of D5W. Leucovorin 200 mg/m² is administered by an intravenous infusion simultaneously over 2 hours in a separate bag using a Y-line. 5-FU follows the oxaliplatin and leucovorin, first as a bolus injection over 2-4 min in a dose of 400 mg/m², followed then by administration of 600 mg/m² (5-FU) as a continuous infusion in D5W 500 mL over 22 hours. Leucovorin is repeated on Day 2 of the cycle without oxaliplatin. The 5-FU 400 mg/m² bolus and 22 hour infusion of 600 mg/m² is repeated on Day 2 after completion of the Day 2 leucovorin infusion. The cycle is repeated every 2 weeks.



Although not evaluated in the current NDA, based on the data submitted with the previously treated patients, following recommendations have been made: Anti-emetics (5HT3 inhibitors) should be used, with or without dexamethasone to prevent nausea and vomiting. No prehydration

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is required. If cold-induced dysesthesia occurs, prolonging the oxaliplatin infusion time in subsequent cycles may decrease the incidence and severity of symptoms.

IX. Use in Special Populations

A. Evaluation of Evidence for Age, Race, Gender or Ethnicity Effects on Safety or Efficacy

Age does not affect the efficacy of the FOLFOX 4 regimen. The median overall survival for patient <65 years of age and ≥ 65 years is identical at about 19.5 months. The women demonstrated a trend towards an improved survival when compared to men. The median survival for women was 20.9 months (95% C.I. 18.4-38.8) and was 18.9 months for men (95% C.I. 15.4-20.7).

The applicant performed an analysis on the difference of adverse events by age (<65, ≥ 65) using Fisher's exact test. The results were reported for all grades and for grades ≥ 3 . These results are summarized in table (12.2.3.3)1 of the study report and are attached in the appendix of this document.

Grade 3 or higher events that had an increased incidence in the older patients were fatigue, dehydration, leucopenia, syncope and pulmonary events. The incidence was greater for the younger patients for abdominal pain. When all grades are evaluated, patients ≥ 65 years of age had more hypersensitivity, anorexia, and leukopenia. Parasthesias, pharyngo-laryngeal dysesthesias, dysphasia, flatulence, and AST elevations were reported as having an increased incidence in patients <65 years of age with a p value <0.05.

When a similar evaluation was performed by gender, a significantly higher proportion of males experienced depression (all grades), hiccups (all grades), and pulmonary NOS (all grades).

A significantly higher proportion of females experienced alopecia (all grades), urticaria (all grades), hematologic events (any event, Grade = 3), and neutropenia (Grade = 3).

It is not possible to draw conclusions regarding differences in AE by race. Caucasians constituted 89% of the population on the FOLFOX arm.

B. Evaluation of Pediatric Program

Colorectal cancer is extremely rare, if it occurs at all in the pediatric population. A waiver from pediatric studies was granted.

C. Comments on Data Available or Needed in Other Populations

The applicant has analyzed the special populations well. A phase 4 commitment from the time of the previous NDA is pending. A special protocol assessment has been submitted for this study the objective of which is to evaluate the safety of oxaliplatin in combination with

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bolus/infusional 5-FU/LV (FOLFOX4) in adult patients with advanced gastrointestinal (GI) cancer with varying degrees of renal dysfunction (normal, mild, moderate and severe renal impairment).

The patients on the FOLFOX arm require a permanent catheter placement and may be more susceptible to thrombosis. Prolonged prothrombin time was more common on the FOLFOX arm but due to incomplete information on concomitant medications (specifically anticoagulation), no conclusions can be made. An study should be conducted to evaluate the effect of oxaliplatin on anticoagulation.

X. Conclusions and Recommendations

A. Conclusions

Oxaliplatin in combination with infusional 5FU/LV demonstrated an improvement in overall survival in patients previously untreated for advanced colorectal cancer, and an improvement in TTP in a large, randomized, multicenter trial. It has a well-documented, acceptable safety profile.

B. Recommendations

Oxaliplatin in combination with infusional 5FU/LV should be approved for patients previously untreated for advanced colorectal cancer. The previous accelerated approval for relapsed/refractory advanced colorectal cancer should be converted to a regular approval.

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XI. Appendix

A. Other Studies submitted

EFC2961:

Title:

"Contribution of oxaliplatin to the treatment of metastatic colorectal carcinoma in combination with chronomodulated 5-fluorouracil and folinic acid. Phase II-III multicentric randomized study."

This study was reviewed in the original supplement of oxaliplatin in 2000. A chronomodulated infusion was employed, different from the one used in the major (NCCTG) study or the approved regimen. This study can not be used for safety or efficacy analysis.

EFC 2962:

Title:

"A phase II-III trial of 5- fluoro uracil (bolus and continuous infusion) and folinic acid (LV5FU2) with or without oxaliplatin in metastatic colorectal cancer. An open randomized European multicenter study."

This study was also reviewed in NDA 21063 in year 2000. 210 patients were enrolled in each arm. The primary endpoint was PFS (progression-free survival). FOLFOX 4, the approved regimen of oxaliplatin was used.

Table 82: Efficacy of Study 2962

	5FU/LV (De Gramont Regimen) N=208	FOLFOX 4 N=209
Median PFS	6.0	8.2
95% CI	(5.5-6.5)	(7.2-8.8)
Response Rate	22%	49%
95% CI	(16%-27%)	(42%-56%)

Table adapted form summary submitted by the Applicant for the study

OS not evaluated because less than 50% patients were dead in both treatment groups by the cut-off dates.

The following conclusion is taken from Dr. Steven Hirschfelds's review of EFC 2961 and EFC 2962:

"The data to support a first line indication for oxaliplatin in combination with 5- FU/ LV in the treatment of advanced metastatic colorectal cancer is weak. Data from two randomized clinical trials are submitted adding Oxaliplatin to different 5- FULV regimens. Addition of Oxaliplatin

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shows better tumor response rate and better progression free survival. However, there is no clear improvement in overall survival. Study 2962 shows a survival benefit for oxaliplatin only after exploratory adjusted analysis. This is not reflected in any improvement in patient clinical benefit or quality of life. Study 2961 does not even show a trend toward a survival benefit. Oxaliplatin adds significant adverse effects, especially peripheral neurotoxicity."

EFC5337 (LIFE)

Title:

A Randomized Trial Evaluating Eloxatin (Oxaliplatin) Combined With Two Different 5-Fluorouracil Regimens in Patients With Previously Untreated Advanced Colorectal Cancer (ACC)

The primary endpoint of this study conducted in Europe, Australia, New Zealand, Hong Kong and Taiwan, is survival. This study is ongoing. The last patient was enrolled on March 22, 2002. An abstract of the interim results were published in Proc. ASCO 2003; Abstract 1064. Patients were randomized to receive either continuous (CIV) 5-FU (350mg/m²/day) or De Gramont regimen (leucovorin 200mg/m² as a 2-hour infusion, 5-FU bolus 400mg/m² and 600mg/m² 22-hours continuous infusion, d1 and 2) versus the same regimens plus oxaliplatin 85mg/m² d1 every 2 weeks (FOLFOX4 or 5-FU CIV 300mg/m²/day+ OXA).

Table 83: Best Responses of EFC 5337 (LIFE) per Investigator

Response	Control (%)	Oxaliplatin (%)
CR (complete response)	2	6
PR (partial response)	28	46
CR + PR	30	52
Stable Disease	34	21
Progressive Disease	23	10
Not Evaluable	1	2
Missing data	12	16

Based on Investigator assessment only.

PFS, TTF, QoL, and OS are not yet available.

At time of this report no efficacy data are available for the irinotecan treatment period.

EFC 7233:

Title:

"5-FU Plus Low-Dose Folinic Acid Bolus-Application (Mayo-Clinic) Versus Weekly Highdose 5-FU 24 Hour Infusion Plus Folinic Acid in Combination With Oxaliplatin in Patients With Advanced Colorectal Cancer."

The primary endpoint of this study are to demonstrate increase in PFS. RR, OS and QoL are secondary endpoints. Two hundred and fifty two patients were randomized and 238 were

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evaluable for efficacy. The control regimen was the Mayo Clinic regimen of 5FU/LV, and the investigational regimen was FUFOX (Oxaliplatin: 50 mg/m² 2-hour infusion followed by Folinic acid: 500 mg/m² 2-hour infusion followed by 5-FU: 2000 mg/m² 24-hour infusion on Days 1, 8, 15, and 22). The RR on the FUFOX arm was 49% and on the 5FU/LV arm was 23%. The doses of oxaliplatin and 5FU/LV used in this study are different from the FOLFOX 4 regimen.

Conclusion of Supportive Studies:

The results of the above supportive studies (EFC 2961, EFC 2962, EFC 5337 and EFC 7233) as submitted by the applicant are consistent with the observation of the major study (EFC 7264), that oxaliplatin is effective when used in first-line therapy of metastatic colorectal cancer in previously untreated patients. Although likely, it is not known whether oxaliplatin-containing regimens improve survival of these patients because of availability of effective second-line agents.

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B. More Detailed Study Tables

Table 84: All Protocol Amendments

Applicant table (7.2)2

Amendment Number	Date	Changes
1	04 December 1998	The protocol was opened to participants in the EPP.
2	23 April 1999	<ul style="list-style-type: none"> • Patient enrollment to the Wilke Regimen (Arm C) was discontinued for logistical reasons and to reduce the number of treatment arms; patients were followed according to the protocol. • The trial design was modified to add two treatment regimens containing OXAL + 5-FU/LV (Arm E and Arm F), and one treatment regimen containing CPT-11 + OXAL (Arm G). There were a total of 6 arms in the study. • This was the start of enrollment for the 795 patient cohort. (See Figure (7.2) 1).
3	04 June 1999	<ul style="list-style-type: none"> • Clarified primary and secondary quality of life (QoL) endpoints • Indicated that supplemental QoL items will be compared across treatment groups on a per item basis only.
4	02 July 1999	Administrative changes and corrections; procedure clarifications
5	08 October 1999	Due to excessive toxicities experienced at the starting dose levels on Arm E, patients randomized to this arm and patients currently receiving treatment started/continued treatment at a lower dose level oxaliplatin and 5-FU.
6	28 January 2000	<ul style="list-style-type: none"> • Patient consent form was updated. • Based on additional data provided by Sanofi Research combined with initial patient experience on Arms E, F, and G of this trial, dose reduction and dose modification tables were altered. Modifications included reducing dose levels for each agent individually and further focusing of dose reduction steps to specific toxicities (neutropenia, thrombocytopenia, and diarrhea) and agents (OXAL, 5-FU, and CPT-11). • Changes in administrative procedures
7	24 March 2000	<ul style="list-style-type: none"> • The study was temporarily closed to patient accrual effective 24 March 2000 due to unexpectedly high early mortality in Arms B and E. • Data presented on 16 March 2000 to ODAC, based on a study comparing Arm A (Saltz regimen; IFL) of the current trial to Arm D (standard 5-FU/LV regimen) of the current trial demonstrated a statistically significant survival advantage for patients treated with Arm A compared with Arm D. On the basis of this data, enrollment was temporarily closed to all arms of this trial to allow for modification of the protocol and the consent form to reflect this new data. • Patients currently enrolled to Arm D were taken off the trial and treated at Investigator discretion because 5-FU/LV was no longer considered the standard of care.

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Amendment Number	Date	Changes
8	28 April 2000	<ul style="list-style-type: none"> • On 17 March 2000, ODAC voted to recommend the approval of CPT-11 plus 5-FU and LV as the new standard first-line therapy in this setting replacing the Mayo 5-FU plus LV regimen. • A decision was made to collapse the trial from 6 to 3 arms. The arms eliminated were: Arm B, Arm D, (the former standard therapy arm), and Arm E. • The study was re-opened to accrual
9	24 November 2000	<ul style="list-style-type: none"> • An optional pharmacogenomic component was added to the study • Changes made based on reports of pulmonary fibrosis associated with oxaliplatin administration.
10	16 February 2001	Additional risks were identified for oxaliplatin (inflammation or infection of the bowel; rarely, patients have had confusion or other mental changes).
11	25 April 2001	<ul style="list-style-type: none"> • Patient accrual was temporarily suspended due to a high death rate on Arm A • This was the end of enrollment for the 795 patient cohort. (See Figure (7.2) 1)
12	29 June 2001	<ul style="list-style-type: none"> • Arm A doses were decreased for CPT-11 and 5-FU • The possible association of hemolytic uremic syndrome with oxaliplatin was reported; the protocol and consent form were revised. • Administrative changes were made • The study was re-opened to accrual
13	19 October 2001	As a result of an external review, several additional changes to the protocol were made, including more sensitive criteria for dose delay/reduction, more intense monitoring of fluid and electrolyte levels, and recommendations for antibiotics and octreotide.
14	15 March 2002	Closed Arm G to patient accrual because planned enrollment was completed.
15	23 April 2002	Because the outcome of patients treated on Arm F appeared to be superior to the outcome of patients treated on Arm A, Arm A was closed to patient accrual based on DSMC recommendation
16	12 July 2002	<ul style="list-style-type: none"> • Additional genetic variants were to be studied • Procedural changes
17	19 July 2002	The study was closed to all patient accrual
18	17 January 2003	Additional risks for oxaliplatin (fatigue and hyponatremia) were added to the protocol and informed consent.

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Table 85: Listing of patients in the FOLFOX4 arm who discontinued the study due to allergy, hypersensitivity reactions, and possible hypersensitivity reactions

Applicant Table (12.2.3.1.6) 1

Patient ID	Age	Sex	Preferred Terms and Grades	Cycle of Occurrence	Case Summary
9025448 83255	47	F	Hypersensitivity Grade 2, Pruritus Grade 1, Truncal erythema Grade 3, tongue swelling Grade 2, urticaria Grade 2 Flushing Grade 1, itchy hand Grade 2	Cycle 5 Cycle 6	15 minutes into oxaliplatin infusion on Cycle 5, the patient experienced a hypersensitivity reaction which consisted of pruritus (Grade 1), truncal erythema (Grade 3), tongue swelling (Grade 2), and generalized urticaria (Grade 2). Corrective treatments were not reported. The patient was re-challenged for Cycle 6 and dosing of oxaliplatin was withheld once again due to the occurrence of flushing of the face (Grade 1) and itchy hands (Grade 2). Study treatment was permanently discontinued.
9025471 84079	67	M	Autoimmune disorder Grade 3, Hypotension Grade 3, Diaphoresis Grade 3, Syncope Grade 3, Diarrhea Grade 3 Autoimmune disorder Grade 3, Hypotension Grade 3, Diarrhea Grade 3, Vomiting Grade 3, Sweating Grade 2	Cycle 6 Cycle 7	On Day 1 of Cycle 6, the patient received oxaliplatin over 2 hours and 30 minutes of leucovorin when he began feeling queasy. He began having watery diarrhea followed by a syncopal episode (Grade 3) where he passed out briefly. He was shaky and diaphoretic (Grade 3). Blood pressure was 90/40 mmHg. The patient was treated with IV hydration. On Day 1 of Cycle 7, the patient was almost finished receiving oxaliplatin when he became dizzy and developed diarrhea (Grade 3), diaphoresis, chills, fever, and vomiting (Grade 3). Blood pressure was 80/36 mmHg. The patient was treated with IV hydration, vancomycin, and cefazidime. The investigator believed these 2 episodes were allergic reactions to oxaliplatin. Study treatment was permanently discontinued.
9026972 90244	64	M	Lymphoma rash Grade 2, Flushing Grade 2	Cycle 9	Reported as hypersensitivity reaction to oxaliplatin in investigator comments. No precise clinical information was reported. Study treatment was permanently discontinued.
9026729 90647	68	F	Hypersensitivity Grade 3, Diarrhea Grade 4	Cycle 10	Fifteen minutes into oxaliplatin infusion on Cycle 10 patient had chest pain and shortness of breath. Study treatment was permanently discontinued.
9026946 90736	50	F	Hypersensitivity Grade 3	Cycle 9	Thirty minutes into oxaliplatin infusion on Cycle 9, the patient experienced nausea, flushing, swelling of face and eyes. Oxaliplatin infusion was stopped and the patient rapidly improved with diphenhydramine and lorazepam. The investigator reported these events were hypersensitivity reaction to oxaliplatin. Study treatment was permanently discontinued.
9026944 91073	69	F	Dyspnea/shortness of breath Grade 3, vasovagal episode Grade 3, incontinence Grade 3, Hypotension Grade 3, Urticaria Grade 2	Cycle 14	Thirteen minutes into oxaliplatin infusion on Cycle 14, the patient became unresponsive and was incontinent during the 1 or 2 min of no response. Upon awaking she was not oriented to place or time, BP was 98/48 and O ₂ saturation was 87%. The patient simultaneously reported a Grade 2 urticaria. Study treatment was permanently discontinued.
9026949 91081	77	F	Not reported in AE panel	Cycle 28	Treatment was discontinued due to Grade 2 allergic reaction at the time of oxaliplatin infusion of Cycle 28. A similar Grade 1 episode has been also reported on Cycle 27. Study treatment was permanently discontinued.
9027530 92080	73	M	Not reported in AE panel	Cycle 19	4 minutes after initiation of oxaliplatin on Cycle 19, the patient reported "the left rear hand". He was extremely diaphoretic, BP was 88/50, pulse 92, respirations 4/min, O ₂ saturation 83%, brad (3-4 seconds) episodes of consciousness were reported. Oxaliplatin was stopped immediately. IV push corticosteroid was administered and O ₂ initiated. The patient condition rapidly improved. Study treatment was permanently discontinued.
9027699 93142	64	F	Allergy Grade 1, Allergy Grade 2, Allergy Grade 2	Cycle 22, Cycle 23, Cycle 24	This patient reported 3 consecutive episodes of allergy on Cycles 22, 23, and 24. A bronchospasm was reported on Cycle 24 but no specific symptoms were reported for Cycles 22 and 23. Chronology of events were not reported, the patient received full dose of oxaliplatin on Cycle 22 (130 mg) but only 15 and 15 mg on Cycles 23 and 24 respectively. Study treatment was permanently discontinued. This patient was reported off study for progression on Cycle 21.
(continued)					
9027736 93243	66	M	Rash Grade 3	Cycle 4	No toxicity was reported for this patient up to Cycle 4. On Cycle 4 the patient reported a rash on 60 to 70% of the body surface area (chronology: oxaliplatin infusion unknown). Persistence of the rash and simultaneous Grade 3 thrombocytopenia at the time of Cycle 5 led to withheld treatment for 3 weeks which has been finally permanently discontinued due to persistence of symptoms.
9028013 94159	58	F	Hypersensitivity Grade 3	Cycle 6	Infusion of oxaliplatin for Cycle 6 has been stopped due to what was reported as "extreme hypersensitivity". For the same treatment cycle dyspnea Grade 3, hypoxia Grade 3, diaphoresis Grade 2, tachycardia Grade 3, Hypotension Grade 3, chills Grade 1, flushing Grade 1 were reported on the CRF. Study treatment was permanently discontinued.
9028324 95327	52	M	Hypersensitivity Grade 1, Hypersensitivity Grade 2, Hypersensitivity Grade 1	Cycle 9 Cycle 10 Cycle 11	Patient experienced a Grade 1 rash on Cycle 9. Hypersensitivity reactions (No specific symptoms reported) were also reported early into oxaliplatin infusion on Cycles 10 and 11. In both cases infusions of oxaliplatin were stopped. Study treatment was permanently discontinued.

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Table 86: Summary of statistically significant differences in adverse events by age
Applicant Table (12.2.3.3) 1 -

		Adverse Event	Inc. dir. Code	IMI (N=256)			T0140X1 (N=259)			T0140X1 (N=259)		
				Avg.55 (N=93)	60-65 (N=91)	PN Value (N=184)	Avg.25 (N=92)	30-35 (N=92)	PN Value (N=184)	Avg.55 (N=93)	Avg.66 (N=93)	PN Value (N=184)
High Severity	Hypertension	Al. event	5.511	2.6211	1.00100	27.1669	5.012	0.00681	110.531	10.110	0.23191	
		Al. event	33.2233	15.02270	0.00709	42.0369	29.0963	0.5752	5.41031	20.2225	0.57109	
Moderate	Acute Myocardial Infarction	Al. event	1.061	6.0111	0.01360	3	1.01	0.09211	0	0		
		Al. event	1.061	6.0111	0.01360	3	1.01	0.09211	0	0		
Overall and Synonyms	Hypertension	Al. event	1.061	19.01940	0.00147	21.0141	7.11231	0.00228	15.031	11.01110	0.07065	
		Al. event	12.074	21.0124	0.01192	3.631	11.111	0.00339	22.01570	22.02270	0.00856	
Hypertension	Hypertension	Al. event	5.511	18.0184	0.00231	6.0380	1.111	0.00338	2.01800	20.02230	0.11321	
		Al. event	31.5130	25.02510	0.02812	35.0650	44.04410	0.00117	21.07640	65.06410	0.00312	
Hypertension	Hypertension	Al. event	55.2113	26.02640	0.00899	42.02617	24.04650	0.00222	67.0670	27.02750	0.03812	
		Al. event	11.074	17.0174	0.01256	4.0251	9.012	0.00501	14.0571	1.0670	0.04175	
Hypertension	Hypertension	Al. event	37.2113	16.01670	0.00258	5.941	5.0523	0.06717	11.02651	41.02270	0.00392	
		Al. event	4.231	7.0711	0.00001	3.811	1.01	0.00013	1.025	1.021	0.0000	
Hypertension	Hypertension	Al. event	5.381	9.024	0.00208	19.01110	4.021	0.00445	16.01521	2.021	0.0000	
		Al. event	71.4523	39.03881	0.02813	72.0400	34.04130	0.00228	16.02260	19.02550	0.00007	
Hypertension	Hypertension	Al. event	160.08160	59.05939	0.00897	42.08480	91.01190	0.00045	30.0452	95.00750	0.00009	
		Al. event	71.4451	56.05716	0.01171	20.05909	63.00361	0.00988	29.01661	34.05531	0.00046	
Hypertension	Hypertension	Al. event	2.131	9.0521	0.00250	7.1131	1.021	0.0137	6.021	2.021	0.0182	
		Al. event	14.08290	57.08270	0.07355	12.08259	91.00290	1.0039	18.0741	21.08290	0.01720	
Hypertension	Hypertension	Al. event	21.1110	15.0271	0.01478	19.01110	23.0221	0.0002	29.01800	17.02210	0.00101	
		Al. event	120.07730	57.08270	0.01507	27.0210	25.00600	0.01555	20.01512	21.02510	0.00009	
Hypertension	Hypertension	Al. event	61.1153	51.05110	0.00826	81.0524	54.04661	0.00726	29.02010	31.02250	0.00057	
		Al. event	31.1523	37.07780	0.01123	38.06250	77.07780	0.00951	19.01561	27.02550	0.00075	
Hypertension	Hypertension	Al. event	1.191	7.0271	0.00001	21.0164	1.1621	0.00228	29.01800	19.01550	0.01439	
		Al. event	23.1543	30.03060	0.00209	21.0164	1.1621	0.00228	29.01800	19.01550	0.01439	
Hypertension	Hypertension	Al. event	13.1451	21.0124	0.00598	4.0251	7.074	0.01073	8.01131	18.01130	0.00311	
		Al. event	17.1450	21.0124	0.00598	4.0251	7.074	0.01073	7.01060	18.01130	0.00916	
Hypertension	Hypertension	Al. event	15.082	17.01730	0.01106	1.691	9.012	0.00281	13.0511	10.01130	0.00387	
		Al. event	15.082	17.01730	0.01106	1.691	9.012	0.00281	13.0511	10.01130	0.00387	

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**FDA MEDICAL OFFICER MEMO TO A
NEW DRUG APPLICATION**

NDA NUMBER: 21-492
SUPPLEMENT: 002
DRUG NAME: Eloxatin® (oxaliplatin for injection)
INDICATION: Treatment of advanced colorectal cancer
POPULATION: Previously Untreated Patients with Advanced Colorectal
Cancer
SPONSOR: Sanofi-Synthelabo
CLINICAL REVIEWERS: Amna Ibrahim, M.D.
CLINICAL TEAM LEADER: John Johnson, M.D.
DATE OF NDA SUBMISSION: July 11th, 2003
DATE REVIEW COMPLETED: January 8th, 2004

120-Day Safety Update

Updated adverse events, serious and non-serious were submitted by the applicant for IND Studies EFC 4585, EFC 4760, EFC 7462 and non-IND studies EFC 7103 for a safety update. There were no unexpected adverse events or adverse events of an unexpected frequency.

According to the applicant, no additional patients entered into the previously untreated colorectal cancer pivotal study (EFC7462) met the criteria to require a narrative and/or case report form submission due to SAE, withdrawals due to toxicity, or death within 30 days of last treatment other than due to progressive disease. No serious treatment-emergent adverse events were reported during the reporting period for IND studies EFC4584, EFC4759 and LTS4897. No serious treatment-emergent adverse events were reported during the reporting period for non-IND studies EFC3313 and EFC4692.

Amna Ibrahim M.D.
Clinical Reviewer

John Johnson M.D.
Clinical Team Leader

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Amna Ibrahim
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