Methodology

To study neurotoxicity in study EFC4584, the datatables for adverse events , non-serious adverse events (nsae) and serious adverse events (sae) were combined into a composite table. All events that were mapped to the organ system terms "Central and Peripheral Nervous System" were extracted, and then all events with the terms "Neuropathy", "Sensory Disturbance", and "Paraesthesia" were extracted. Examination of the specific terms used to describe the individual events revealed that the same terms were used for both the "Sensory Disturbance" and "Paraesthesia" categories with some overlap in the "Neuropathy" category. The spectrum of symptoms included numbness, tingling, pain, dysesthesia, paraesthesia, or sensitivity in the distal extremeties, legs, hip, arm, eye, jaw, throat, mouth, gums, lips, or tongue that may or may not be exacerbated or induced by contact with cold temperature including beverages, foods, or objects. A few patients had pharyngo-laryngeal spasms that may be accompanied by a sense of loss of air, shortness of breath, or, as one patient stated, "bees in the throat."

The events could be broadly categorized based on duration. Events that were reversible to baseline status and were of duration less than 14 days or the time between treatment cycles were classified as acute. Events that were not reversible to baseline status or were of duration 14 days or greater were classified as persistent. Using these criteria, the datatables were analyzed to catalog events overall, per treatment cycle, and per study arm.

A chronology was established for each patient to determine when doses were given, when events occurred, event duration, event resolution, the temporal relationship between dosing and events, and the cumulative dose of either oxaliplatin, 5-flurouracil or leucovorin as determined by treatment arm assignment. Dose delays and dose reductions were noted.

The overall experience per study arm was also catalogued with a listing of each patient that had a neurotoxic event in a cross tab table with the number and type of events for each cycle. This data display permitted examination of the pattern of events by type across all cycles for all patients.

Results

1. Neurotoxicity was a common event

Neurotoxicity was prevalent in the study in patients exposed to oxaliplatin as shown in the following table. Although some neurotoxicity was noted in study arm A (5-fluourouracil and leucovorin), it was noted in 25 (17%) of patients and primarily consisted of numbness and tingling in the distal extremities that resolved in all but 6 (4%) patients. Data from Arm A will not be discussed further.

Table 51: Incidence of Neurotoxicity

Arm	Total Patients	Any Neurotox	Acute Neurotox	Persistent Neurotox
B (oxaliplatin alone)	153	116 (76%)	102 (67%)	62 (40%)
C (combination)	150	111 (74%)	87 (58%)	72 (48%)

The number per cycle is summarized in the following table showing total number of patients in each column where Arm B is oxaliplatin alone and Arm C is the oxaliplatin + F-FU/LV combination.

Table 52: Neurotoxicity per Cycle Number of Patients

Cycle	Arm B Total	Arm C Total	Arm B Acute	Arm C Acute	Arm B Persistent	Arm C Persistent
1	153	150	65	35	14	10
2	148	145	69	45	27	20
3	130	134	52	42	31	30
4	74	113	38	31	23	30
5	66	109	31	32	29	30
6	59	98	27	24	27	32
7	35	69	16	22	14	21
8	32	56	14	19	16	18
9	28	43	12	8	13	18
10	16	27	10	4	5	16
11	13	21	3	5	8	16
12	12	15	3	4	9	11
13	6	9	2	1	5	8
14	5	6	2	1	4	5
15	3	4	0	0	3	3
16	2	2	0	0	2	1

The same data expressed as percentages are shown in the following table.

Table 53: Neurotoxicity per Cycle Percentages

Cycle	Arm B Total Pts	Arm C Total Pts	Arm B Acute %	Arm C Acute %	Arm B Persistent %	Arm C Persistent %
1	153	150	43	23	9	7
2	148	145	47	31	18	14
3	130	134	40	31	24	22
4	74	113	51	27	31	26
5	66	109	47	29	44	27
6	59	98	46	25	46	33
7	35	68	46	32	40	30
8	32	55	44	34	50	32
9	28	43	43	19	46	42
10	16	27	62	15	31	59
11	13	19	23	24	61	76
12	12	14	25	27	75	73
13	6	9	33	11	83	89
14	5	5	40	17	80	83
15	3	4	0	0	100	75
16	2	2	0	0	100	50

These results were generated independently by the sponsor, Sanofi-Synthelabo and the FDA and were mutually confirmed as consistent. Comparison of study arms A and B show that there were differences in the incidence of acute neurotoxicity with oxaliplatin alone having a higher incidence than the combination of oxaliplatin and 5-FU/LV. There were 370 incidents of acute neurotoxicity in arm C and 490 in Arm B. The consistency of the observation suggests that there may be methods to mitigate the neurotoxicity.

The totals in each column reflect the number of patients with either acute or persistent toxicity. If a patient had both, the patient was counted once in each category. In sum, for any given cycle of therapy, from 1/3 to 2/3 of the patients will experience some form of neurotoxicity and overall about ¾ of the patients will experience some form of neurotoxicity.

Oxaliplatin alone is not being endorsed by the FDA as a potential therapy for relapsed or refractory colorectal cancer, so further analysis and comments will focus only on the combination regimen.

2. Most of the neurotoxicity was acute

In the combination study arm, there were 370 acute neurotoxic events and 154 persistent events. Eighty-seven patients (58%) had an acute event and 72 (48%) patients had a persistent event. Not

all patients that had a persistent event had an acute event. Thirty-nine patients had acute events without persistent events and 24 patients had persistent events without acute events. The mean number of acute events was 3 per patient with a range of 1 to 12.

Table 54: Neurotoxicity Distribution by Type

Neurotoxicity	# of Pts (n=150)
No event	39 (26%)
Acute only	39 (26%)
Persistent only	24 (16%)
Acute and Persistent	48 (32%)

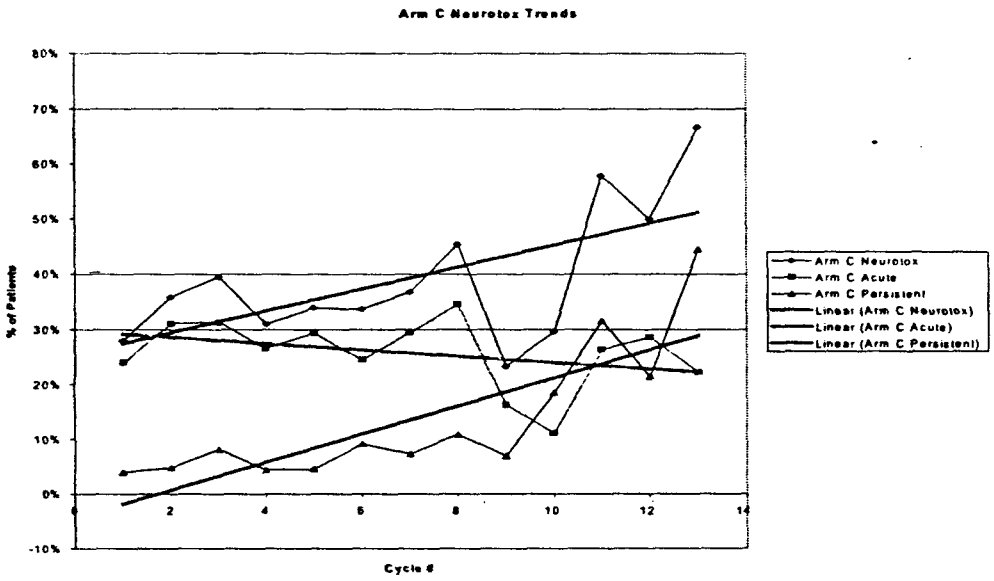
3. The proportion of acute neurotoxicity was relatively stable per cycle while the proportion of persistent neurotoxicity increased with cycle number.

For the first 12 cycles the percentage of patients with new onset acute neurotoxicity had a mean of 25.2 per cent and a median of 27 per cent. There were fewer than 5 patients that completed more than 13 cycles. Patients could have their first acute event during any cycle, although the majority were during the first two cycles. Initial persistent events were less clustered as seen in the following table.

Table 55: Occurrence of First Neurotoxic Event

Cycle #	First acute event pts	First persistent event pts
1	36	6
2	21	8
3	13	13
4	2	4
5	5	5
6	2	6
7	5	4
8	2	3
9	0	5
10	0	4
11	0	2
12	0	1
13	0	1
14	1	0

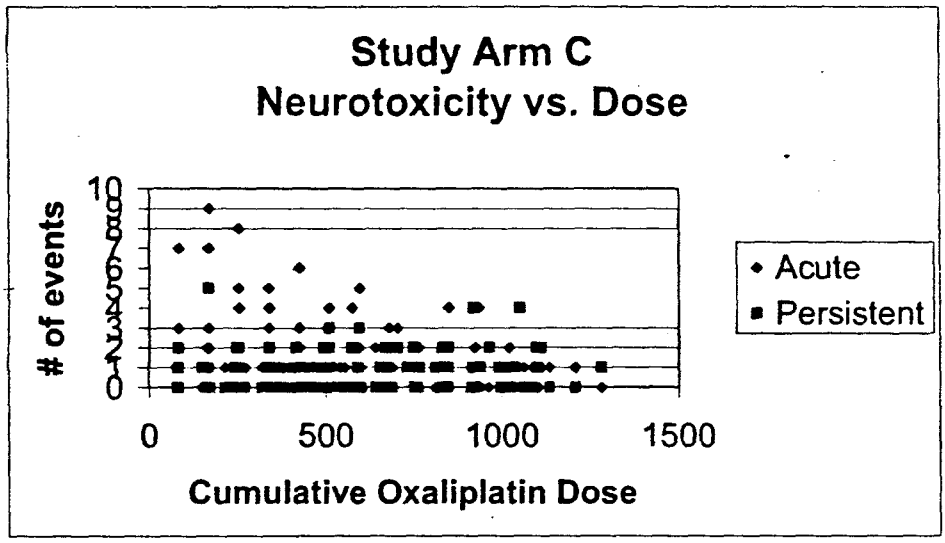
Figure 6: Trends in Neurotoxic Events per Cycle



4. Persistent events could occur without preceding acute events and at any cumulative dose of oxaliplatin.

Of the patients that had neurotoxic events, 24 (21%) had persistent events without any acute events and another 6 (5%) patients had persistent events prior to acute events for a total of 30 patients (27%) who had persistent events without a prior acute event. The following graph shows that persistent and acute events may occur at any cumulative oxaliplatin dose.

Figure 7: Neurotoxicity vs. Dose



5. Higher grade neurotoxicities could occur at any cumulative dose level.

A neurotoxic scale developed for the study was used with Grade 1 defined as reversible and not interfering with function, Grade 2 as interfering with function but not daily activities, Grade 3 as pain or functional impairment that interferes with daily living and Grade 4 as persistent and disabling or life threatening. The following charts show that higher grades (> Grade 1) toxicity can occur at any cumulative dose or study day.

Laryngospasm was noted in two patients in study arm C and also an additional 4 patients in study arm B for a total of 11 episodes. All patients recovered with the median duration 7 days. One patient had 4 episodes, 2 patients had 2 while the other 3 had 1 each. The median day of occurrence was study day 29 .

Figure 8: Cumulative Dose vs Toxicity Grade

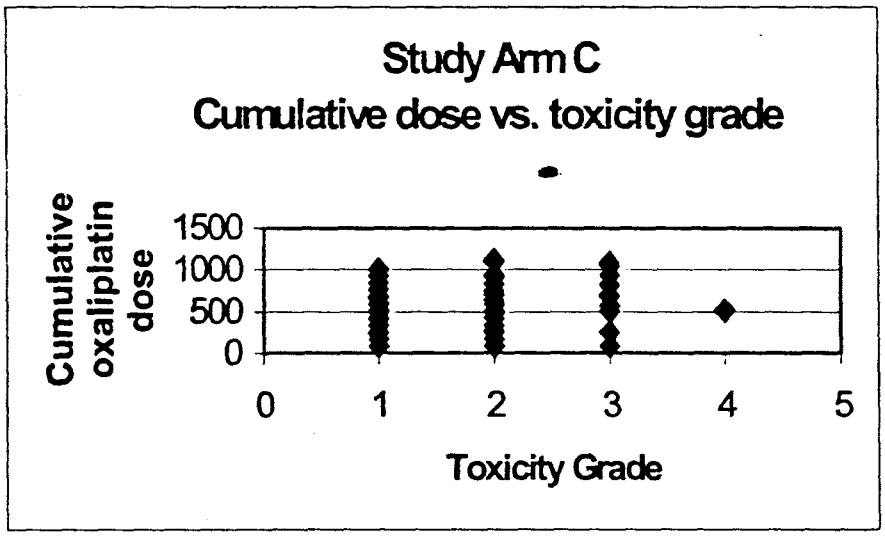
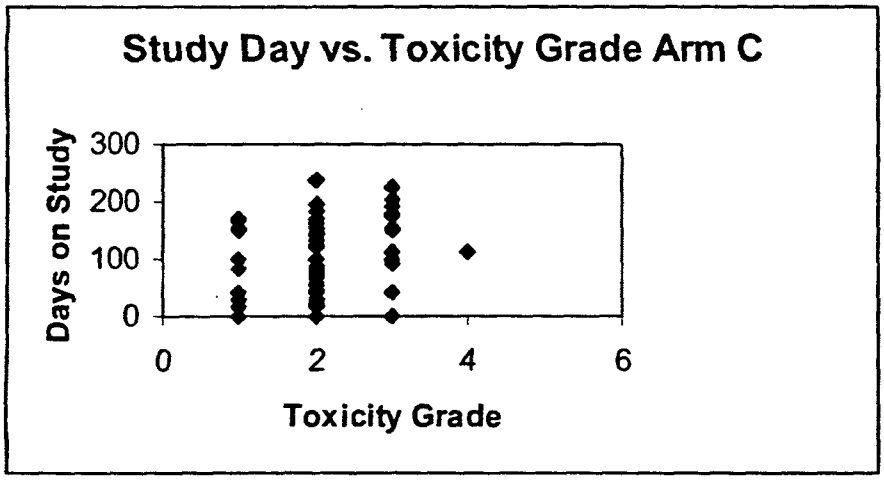


Figure 9: Neurotoxicity vs. Study Day



6. Most patients continued therapy with planned dosage despite the neurotoxicity.

According to the sponsor, only 4 patients had infusion times increased due to neurotoxicity. The following tables were provided by the sponsor and were confirmed by the FDA.

Table 56: Continued oxaliplatin dosing for patients experiencing grade 2 persistent neurotoxicity

Arm	Number of Patients with grade 2 persistent N.T.	Number discontinuing	Number with continued oxaliplatin dosing	Description of continuing oxaliplatin dosing			
				Reduction only	Delay only	Reduction + delay	Neither delay nor reduction
B	8	2 *	6	3	0	0	3
C	15	5 **	10	6	0	1	3
Total	23	7	16	9	0	1	6

* 1 subject for progressive disease, 1 for grade 2 neurotoxicity

** 3 subjects for progressive disease, 1 subject refusal, 1 for grade 2 neurotoxicity

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Table 57: Continued oxaliplatin dosing for patients experiencing grade 3+ persistent neurotoxicity

Arm	Number of Patients with grade 3+ persistent N.T.	Number discontinuing	Number with continued oxaliplatin dosing	Description of continuing oxaliplatin dosing			
				Reduction only	Delay only	Reduction + delay	Neither delay nor reduction
B	3	1 *	2	0	0	0	2
C	8	5 **	3	0	0	2	1
Total	11	6	5	0	0	2	3

* 1 subject for grade 3 neurotoxicity

** 2 subjects for grade 3 neurotoxicity, 2 for disease progression , 1 for granulocytopenia,

In sum, in Arm C 15 (14% of patients with neurotoxicity and 10% of all patients) patients had acute toxicity greater than Grade 1 and 23 (21 % of patients with neurotoxicity and 15% of all patients) had persistent neurotoxicity greater than Grade 1. Of the latter group, 10 left the study for various reasons and 4 continued dosing as before. The number of patients having either dose reduction or dose delay is too small to infer any conclusions; however, of those 9 patients that did receive dose reduction or delay the case report forms indicate that at least 6 continued to have sequelae and persistent toxicity. The patient with Grade 4 neurotoxicity did not receive subsequent doses of oxaliplatin.

Data from other studies analyzed by the sponsor but not confirmed by the FDA show a similar pattern in that the percentage of patients experiencing neurotoxicity in any given cycle was at least 30%. The percentage of patients experiencing new onset acute neurotoxicity was between 25% and 45% for the first 12 cycles while the relative proportion of patients with persistent toxicity continued to increase with cycle number.

Summary and Discussion

Neurotoxicity associated with oxaliplatin infusion is common and in general is reversible and does not interfere with activities of daily living, although adjustments and compensations may have to be made while the neurotoxicity is manifest. The study population was patients with metastatic colorectal cancer that relapsed or was refractory to a first line colorectal regimen and therefore represents a poor prognosis group. The number of cycles of the combination of oxaliplatin, 5-FU, and leucovorin administered in this study may not represent the exposure in clinical practice and therefore extrapolation of findings may be limited.

Prior categorization of neurotoxicity described events based on a combination of symptom cluster and duration with an acute component consisting of cold sensitive spasms and loss of sensation and a chronic component characterized by progressive paraesthesia and dysesthesia, loss of proprioception, and impairment of daily living that was proportional to cumulative dose. The data submitted did not support this schema because either type of symptom could occur as either an acute or persistent event and there was not a demonstrated threshold of cumulative oxaliplatin dose for an event to occur.

In the current analysis, neurotoxicity was categorized as either acute (lasting less than 2 weeks) or persistent (duration of 2 weeks of greater). The onset of persistent neurotoxicity can occur at any cumulative dose and is not necessarily preceded by any episodes of acute toxicity. The spectrum of symptoms included numbness, tingling, pain, dysesthesia, paraesthesia, or sensitivity in the distal extremeties, legs, hip, arm, eye, jaw, throat, mouth, gums, lips, or tongue that may or may not be exacerbated or induced by contact with cold temperature including beverages, foods, or objects. About 2% of patients had pharyngo-laryngeal spasms that may be accompanied by a sense of loss of air, shortness of breath, or, as one patient stated, "bees in the throat" that can occur without warning. All patients in the study survived the laryngospasm toxicity, which had a median duration of 7 days.

In any given cycle at least 30% of patients will have a neurotoxic event. Having an event in one cycle is not predictive of subsequent events, although there were patients who had events with every cycle. For every cycle a different population of patients had an event so that over the course of the study about 75% of all patients had at least one neurotoxic event. The mean number of acute neurotoxic events per patient was 3 with a range of 1 to 12. Of patients that have neurotoxic events, the acute events tend to occur in the earlier cycles. Persistent events and high grade events may occur during any cycle with the net result that proportionately more patients have persistent events during the later cycles.

There are inadequate data to determine if dose adjustment, dose delay, or increasing infusional time are useful to decrease or abrogate neurotoxicity. Absent effective interventions or prophylaxis, the most practical approach will be anticipatory guidance of health care professionals and patients with avoidance of exposure to cold temperature, objects, or liquids such as ice for easing the pain of mucositis.

7.3.5 Cardiovascular Adverse Events

Table 58 summarizes cardiovascular adverse events. Events occurred with similar frequency in all study arms, although thromboembolic disorders were more frequent in Arm C (5-FU/LV/Oxaliplatin) patients. Sinus tachycardia was the most common arrhythmia. Thromboembolic events, which occurred in 13 patients on Arm C, 5 patients on Arm A, and 1 patient on Arm B, included thrombosis, thrombophlebitis (frequently involving the upper extremity and upper body veins), and pulmonary embolism.

Table 58: Cardiovascular Disorders (FDA Analysis)

Adverse Event	Arm A (N = 142)*		Arm B = 153)		Arm C N = 150)	
	All Grades **	Grade 3,4	All Grades	Grade 3,4	All Grades	Grade 3,4
Cardiovascular disorders	10(7.0)	2(1.4)	11(7.2)	2(1.3)	12(8.0)	2(1.3)
Heart rate and rhythm disorders	4(2.8)	2(1.4)	6(3.9)	4(2.6)	9(6.0)	5(3.3)
Thrombophlebitis deep	2(1.4)	1(0.7)	1(0.7)	1(0.7)	8 (5.3)	7(4.7)
Thrombosis	2(1.4)	1 (0.7)	0(0.0)	0(0.0)	1 (0.7)	1 (0.7)
Embolism pulmonary	1(0.7)	1 (0.7)	0(0.0)	0(0.0)	5 (3.3)	5 (3.3)

* Arm A = 5-FU/LV; Arm B = oxaliplatin; Arm C = 5-FU/LV/oxaliplatin
**Number (%) of Treated Patients

Table 59 lists patients who had thromboembolic events. As indicated in the table it was not uncommon to see multiple events in the same patient.

Table 59: Thromboembolic Events (Applicant & FDA Analysis)

Arm *	Patient	AE Preferred Term	Grade	Date of Onset	Date of Resolution
A	1050007	Thrombophlebitis Deep	1	30-Aug-2001	15-Nov-2001
A	1310004	Thrombophlebitis Deep	3	19-Oct-2001	
A	1500001	Thrombosis	3	13-Apr-2001	14-Apr-2001
A	1900001	Thrombosis	1	17-May-2001	19-Aug-2001
A	1930002	Embolism Pulmonary	4	06-Sep-2001	07-Sep-2001
B	1370004	Thrombophlebitis Deep	4	05-Jul-2001	20-Sep-2001
C	1160001	Thrombophlebitis Deep	2	10-Sep-2001	
C	1200001	Thrombophlebitis Deep	3	17-Mar-2001	10-Apr-2001
C	1260001	Embolism Pulmonary	4	14-Sep-2001	19-Sep-2001
C	1390001	Thrombophlebitis Deep	3	11-May-2001	12-May-2001
C	1390001	Thrombophlebitis Deep	3	26-May-2001	07-Jun-2001
C	1390001	Thrombophlebitis Deep	3	16-Aug-2001	
C	1500004	Embolism Pulmonary	3	14-May-2001	25-Jun-2001
C	1540002	Thrombophlebitis Deep	3	10-Sep-2001	
C	1810001	Embolism Pulmonary	4	02-Jul-2001	08-Jul-2001
C	1910013	Embolism Pulmonary	4	06-Aug-2001	20-Aug-2001
C	1910013	Thrombophlebitis Deep	4	06-Aug-2001	20-Aug-2001
C	1920001	Embolism Pulmonary	4	15-Aug-2001	18-Aug-2001
C	1980004	Thrombosis	3	03-Jun-2001	09-Jun-2001
C	1980004	Thrombosis Venous Arm	3	02-Jun-2001	02-Jun-2001
C	5010003	Thrombophlebitis Deep	3	17-Sep-2001	
C	91180006	Thrombophlebitis Deep	3	14-Nov-2001	14-Nov-2001
C	91180007	Thrombophlebitis Deep	3	10-Oct-2001	24-Oct-2001

* Arm A = 5-FU/LV; Arm B = oxaliplatin; Arm C = 5-FU/LV/oxaliplatin

7.3.6 Respiratory Adverse Events

Respiratory system disorders (any event, all grades) occurred in 48.0% of patients n Arm C (5-FU/LV/Oxaliplatin), compared with 31.7% in Arm A (5-FU/LV), and 33.3% in Arm B (Oxaliplatin). The most common respiratory events in all treatment arms were coughing and dyspnea. Coughing occurred in 18.7% of patients in Arm C compared with 9.2% in Arm A and 11.1% in Arm B. Dyspnea occurred in 20% of patients in Arm C compared with 11.3% in Arm A and 13.1% in Arm B. The rate of Grade 3 or 4 dyspnea was 6.5% in Arm B, compared with 4.0% in Arm C, and 2.1% in Arm A. There were only 2 cases of Grade 3 or 4 coughing and these were in Arm C. Hypoxia, Grade 3, was noted in one patient in Arm C. One patient (#1820001) developed interstitial pneumonitis after 17 cycles of treatment on Arm B. This patient developed dyspnea and coughing during Cycle 17. Despite these symptoms, he was administered Cycle 18 of oxaliplatin and his symptoms worsened. Within 7 days of Cycle 18 he was hospitalized for acute pulmonary symptoms, hypoxic, and CT lung revealed interstitial infiltrates with multiple areas of ground glass appearance, most prominent at the periphery and lung bases. On Day 8 of Cycle 18 he required mechanical ventilation and died 9 days later with ventricular arrhythmia and myocardial infarction.

7.3.7 Special Populations Adverse Events

Age

Adverse events (AEs) were evaluated in patients <65 or 65 and above. The rate of overall toxicities was similar across and within arms in the different age groups. The rate of Grade 3 and 4 toxicities, was higher in Arm C (5-FU/LV/Oxaliplatin) for both age groups. There was a trend toward more reported AEs in the younger age group in the following toxicities across arms: allergic reactions (0.02% in <65 years old vs 0.01% in ≥65 years old), abdominal pain (36% vs 26%), paresthesia (78% vs 67%), stomatitis (21% vs 18%), vomiting (46% vs 29%), and nausea (70% vs 56%). However, diarrhea (62% in <65 years vs 75% in ≥ 65 for overall grades and 10% vs. 15% grade 3/4), dehydration (4% in <65 years vs 15% in ≥ 65 for overall grades and 2% vs. 6% grade 3/4), hypokalemia (7% <65 years vs 13% in ≥65 years old for overall grades), granulocytopenia (32% <65 years vs 38% in ≥65 years for Grade 3/4) chest pain (0.03% in <65 years vs 0.08% in ≥ 65 years), fatigue (60% vs 66%), and dizziness (0.09% vs 0.1%), occurred mostly in the population ≥ 65 years. Six of 12 deaths that occurred within 30 days of administration of oxaliplatin on the single agent arm, Arm B, were ≥65 yo. Four of 7 deaths that occurred within 30 days of administration of the oxaliplatin combination regimen on Arm C were ≥65 yo. (32% of the entire population in Arm B and 36% of Arm C were ≥65 yo.)

Gender

Dizziness, stomatitis, headaches, anemia, urinary tract infections, nausea and vomiting pharyngitis, mucositis, granulocytopenia (42% grade 3/4 in females vs. 28% in males), conjunctivitis, skin exfoliation (hand-foot syndrome), thrombophlebitis, dyspnea (all grades, not grade 3/4) and arthralgiawere more frequently reported in females. Diarrhea, paresthesias, and sensory disturbances were similar across genders. Thrombocytopenia was reported more frequently in oxaliplatin-treated males than in females (4% vs 0.03% for grade 3/4), as was anorexia and dehydration. Fiveof the 12 deaths that occurred within 30 days of treatment on the oxaliplatin single agent arm (Arm B) were female. Three of the 7 deaths within 30 days of treatment in the oxaliplatin combination therapy arm were female. (39% of the entire population in Arm B and 43% of Arm C were female).

Race

There were only a limited number of patients not considered Caucasian per arm (Arm A -19 , Arm B -22 , Arm C -17), which makes further inferences regarding the potential relationship between race and toxicity not evaluable.

Renal impairment

There was a limited number of patients per arm with renal impairment (elevated baseline serum creatinine):Arm A =3, Arm B =5, Arm C =9. Therefore, no assessment was possible.

Hepatic impairment

There did not appear to be an increased number of adverse events in patients with elevated hepatic enzymes or bilirubin, but numbers of patients were small. Only 3 patients receiving 5-FU/LV/oxaliplatin had grade 3,4 hepatic enzyme and/or bilirubin elevation.

7.3.8 Death

There were 7 (5%) deaths within 30 days of treatment on the oxaliplatin/5-FU/LV arm (Arm C), and 12 (8%) deaths on the single agent oxaliplatin arm (Arm B). There were 10 deaths (7%) within 30 days of treatment on the 5-FU/LV arm (Arm A). The applicant reported that 11 patients on Arm B died within 30 days of treatment on study. On review of the narratives submitted for patients who died on study or experienced serious adverse events, the FDA reviewer found an additional patient on Arm B who had died within 30 days of study treatment, Pt.#1180002. The narrative summary for this patient appears below under the *Reviewer Comment, Arm B*. This patient makes the total number of deaths within 30 days of treatment on Arm B 12 (8%)

The sponsor attributed 6 deaths in the overall study population (Arm A –1, Arm B – 3, Arm C –2) to adverse events regardless of relationship to study medication. These deaths are summarized below:

Arm A (5-FU/LV)

Patient #91080003 died on 23 September 2001 from Grade 3 pneumonia that began on 15 September. The patient had a Grade 1 fever from 14 August to 23 September 2001 and Grade 2 granulocytopenia from 27 August to 4 September 2001. Study treatment was temporarily discontinued on 29 August 2001 and the third cycle of treatment was resumed on 4 September 2001. No blood counts were available at the time of death.

Arm B (Oxaliplatin)

Patient #1820001 received 18 cycles of treatment, the last on 29 October 2001. He presented with symptoms of interstitial lung disease – dyspnea and cough - during Cycle 17, that progressed after Cycle 18. He was admitted to the hospital for respiratory distress within 7 days of the last cycle, and required mechanical ventilation. Chest CT revealed changes consistent with interstitial lung disease and he died on 15 November 2001 after experiencing Grade 4 ventricular arrhythmia, Grade 4 myocardial infarction, and cardiogenic shock.

Patient #1840001 received 2 cycles of treatment, the last on 9 August 2001. He died on 25 August 2001 from pneumonia (not graded) and Grade 4 sepsis that began on 12 August 2001. WBC count was 2.5 on 14 August and 10.4 on 25 August. Neutrophil count was normal. On 14 August the patient had Grade 4 AST, Grade 4 hypoglycemia, Grade 3 hypokalemia, and Grade 3 thrombocytopenia; on 23 August 2001 the patient had Grade 3 creatinine and hyperbilirubinemia.

Patient #198008 – this 65 yo female's death was considered treatment related by the applicant, **however, this patient did not receive any chemotherapy on study.**

Arm C (5-FU/LV/Oxaliplatin)

Patient #1810001 - – This 57 year old female was taking hydrochlorothiazide and diltiazem as concomitant medications. She exerienced a pulmonary embolism, complicated by hypokalemia (K=2.4 mg/dL), 10 days after Cycle 2 treatment. Her course was complicated by the development of febrile neutropenia 3 days later. Neutrophils nadired at 100 the day before her death. She died 6 days after admission to the hospital. Autopsy revealed extensive retroperitoneal mass and bilateral pulmonary emboli. Her death was attributed to PE. Contribution of neutropenic infection cannot be excluded and the contribution of the chemotherapy to her development of thromboembolic event cannot be excluded

Patient #1500004 received 3 cycles of treatment, the last on 11 June 2001. He had a pulmonary embolism (Grade 3) on 14 May 2001. The patient died on 25 June 2001. This patient also developed febrile neutropenia on 13 June 2001 that resolved on 15 June 2001. The reason for death was unknown.

Reviewer Comment:

Of the 7 deaths that occurred within 30 days on Arm C, narratives were submitted on 4, of which Pt #1500004 above was one. Of the 12 deaths within 30 days on Arm B, only 4 (including the patient found by the reviewer to be a death that occurred within 30 days of treatment Pt.#1180002) narratives were submitted by the applicant. Patient #1820001 and Patient #1840001 above were 2 of those submitted. The FDA reviewer examined the narratives submitted and the CRF's of patient's without a submitted narrative if the death occurred within 30 days of last treatment. The reviewer believed after review of submitted narratives and CRF's, that contribution of chemotherapy to death could not be excluded in the following additional patients where indicated:

Arm B:

Patient #1180002** was a 67 yo female with a history of COPD, asthma, corpulmonale and atrial fibrillation. Twelve days after Cycle 9 she experiences grade 3 encephalopathy, which was attributed to hepatic encephalopathy from disease progression. She had liver metastastases on CT. She had a urinary tract infection and WBC count was elevated. Her BUN/creatinine was elevated from 8/0.5 at baseline, to 45/1.2(mg/dL), serum sodium was 136 mEq/L, total bilirubin was normal, and AST/ALT had elevated from 14/26 at baseline to 80/193 (IU/L). Three days later (two days before her death) her WBC count continued to climb to 16.6, sodium had increased to 151 mEq/L, BUN/creat increased further to 47/2.8 (mg/dL). Although bilirubin on that date increased from 0.8 to 1.3 mg/dL (ULN for the laboratory was 1.2 mg/dL), the transaminases had declined to ALT/AST of 55/60. Hemoglobin was decreased 1g and serum potassium was slightly elevated at 5.2 mEq/L. No LDH was presented in the narrative. On clinical examination this patient had a left lower facial weakness and "arrhythmic jerking" that was attributed to either a stroke or hepatic encephalopathy. No CT or MRI of the brain was reported. She died 17 days after Cycle 9 treatment with oxaliplatin. This patients death was attributed to disease progression. Her Cycle 9 CT was assessed as stable disease by the investigator. Her neurological symptoms may have been related to brain metastases (undocumented) or encephalopathy related to sepsis, or could have been an atypical presentation of neurologic toxicity related to oxaliplatin. The case for hepatic encephelopathy from tumor progression was not persuasive. **Contribution of oxaliplatin to this patient's death cannot be excluded.

Pt.# 1020003 –was a 70 year old female with a history of vena cava thrombosis and hypertension who started treatment on study on August 13, 2001. Her last dose on study was administered on 9/11/2001. She developed weakness, grade 3 diarrhea, and grade 3

dehydration on that date, and died in the hospital on September 20, 9 days after last treatment. ***Contribution of the treatment to her death could not be excluded from information reviewed in the CRF.***

Pt.# 1250001 *– was a 72 year old female who started treatment on April 27, 2001 and 2 days later had uncontrolled nausea and vomiting and dehydration. She reportedly had uncontrolled pain on April 29. She died on May 9 of cardiopulmonary arrest.* ***Although the pain control difficulties suggest PD was responsible for her death, one cannot exclude a role for treatment, given the other symptoms she was having and the fact that her death occurred only 12 days after first treatment.*** *(CRF was the source document for review.)*

Pt.#1860004 *– was a 45 year old male who started treatment on June 13, 2001 and had a history of melena. He had a history of GI bleed on June 11, and he started treatment on study on June 13. GI bleed grade 3 presented June 18 and he required transfusion support, including fresh frozen plasma. He died on July 9, 26 days after last treatment. His death was attributed to PD. This is the most likely cause of death, but recovery from GI bleed could have been complicated by his chemotherapy. (CRF was the source document for review.)*

Arm C:

Pt.# 1560006 *–This was a 72 yo male with a history of coronary artery disease, hypertension and hypercholesterolemia, was taking concominant medications that included simvastatin, isosrbide, celecoxib, aspirin, hydrochlorothiazide and diltiazem. He experienced grade 4 T wave inversions on ECG one day into cycle 1, during the 5-FU infusion and 5-FU was discontinued completely (subsequent cycles were oxaliplatin as a single agent). Blood tests that day reveled that the BUN and creatinine were elevated from baseline (creatinine increased from 1.4 to 1.8 mg//dL and BUN increased from 18 to 42 mg/dL). Cycle 2 was complicated with grade 3 diarrhea, grade 3 nausea and grade 2 vomiting, and the dose of oxaliplatin in Cycle 3 was reduced. His KPS was 60. Ten days after Cycle 3 oxaliplatin the patient experienced a cardiopulmonary arrest and died.* ***Given the patient's history of poor tolerance of chemotherapy in previous cycles and the lack of clinical data to exclude that he was neutropenic or dehydrated, one cannot exclude that this death was related to his treatment with oxaliplatin.***

Pt. #1590006 *- This 66 year old man's death 25 days after Cycle 1 was attributed to disease progression. No radiographic evidence of PD was submitted. This patient was admitted to the hospital 4 days after Cycle 1 for pain related to an injury from a fall. He had intractable left chest wall pain and a left apical hydropneumothorax on chest X-ray. No clinical information is provided to exclude the possibility that the fall occurred secondary to orthostasis or acute neurosensory deficit related to chemotherapy.*

Pt.# 1320001- Review of electronic CRF (no submitted narrative found) reveals this female patient entered the study with a KPS of 70. Her chemotherapy was interrupted by generalized weakness, lower extremity weakness and Grade 1 dyspnea. She developed agitation, ascites, Grade 4 lower extremity edema (described as "weeping"), urinary incontinence, and pain. Her treatment was stopped because the investigator believed she had PD. Target lesion increase did not correlated with PD. New lesions were marked as reason for PD, but it was unclear where those new lesions were noted. CEA markedly increased. She was admitted to hospice and died. This patient's death was attributed to PD and the CRF provides evidence that this is in fact the cause of death.

Pt.# 1680012 – Review of electronic CRF (no narrative found) revealed that this patient was a 60 year old male who began treatment in late June 2001 with normal LFT's and a performance status of 90, developed jaundice after 2 cycles and underwent an ERCP for stent placement, but remained with bilirubin ≥4.0 on subsequent examinations. Treatment continued x 2 cycles beyond radiographic documentation of progressive disease, including interval development of ascites. The patient was admitted 3 days after his last chemotherapy (10/16/01 – 10/17/01) to the hospital for nausea and vomiting, complicated by the development of hematemesis. His protime was 22.3, bilirubin was 12 and he was neutropenic, with an ANC of 680. His ANC increased to normal range with G-CSF, but he died in the hospital. His death was attributed to disease progression. This patient's death was likely related to PD, although the upper GI bleed was presumed secondary to a Mallory-Weiss tear, which could have been secondary to chemotherapy-induced nausea.

Pt.# 1970006 – Review of electronic CRF (no narrative found) revealed that this patient was a 44 yo female who had multiple ill-defined lung metastases and a cough at study entry. She received 2 cycles of chemotherapy on study – last dose July 26, 2001, and went off study on 8/10 for disease progression. She had progressive dyspnea and cough. A CT chest reportedly was consistent with lymphagitic spread of disease. Review of electronic CRF confirms most likely cause of death is disease progression.

Based on the narratives above, the FDA review believed that 5 deaths on Arm B (3%) and 3 deaths on Arm C (2%) were treatment related. The applicant has proposed that the label state in the ADVERSE EVENTS section that the incidence of treatment related deaths from oxaliplatin administered in combination with 5-FU/LV was <1%. The assignment of attribution of death is subject to bias. The FDA has utilized evaluation and comparisons of rate of death within 30 days of treatment as a less biased method of comparing potentially toxicity related deaths. Granted, deaths within 30 days will also capture deaths related to progressive disease and other medical illness, but it is not subject to the bias introduced by the investigator/applicant in making an assignment of attribution to their drug or to the comparator drug/regimen. The applicant agreed to revise the label to delete reference to death rates based on applicant/investigator attribution and to add the comparison of rate of deaths within 30 days of treatment.

7.3.9 Serious Adverse Events

The applicant reported an overall incidence of SAEs of 31.3% in Arm C (5-FU/LV/Oxaliplatin) patients compared with 2 8.2% in Arm A, (5-FU/LV) patients and 26.1% in Arm B (Oxaliplatin) patients. Corresponding numbers from the FDA analysis are 34.0%, 27.5% and 28.2%.

In all 3 arms "malignant aggravated neoplasm" was the most common SAE. This is a wastebasket term including a wide spectrum of disorders and provides little useful information. Excluding this category in Arm C, the most common SAE's were pulmonary embolism (3.3%), febrile neutropenia (2.7%), diarrhea (2.7%), deep thrombophlebitis, injection site reaction, nausea, vomiting, and dehydration (2.0% each). In Arm A, the most common SAE's were dehydration (2.8%), intestinal obstruction (2.1 %), and pneumonia (2. 1 %), and in Arm B, the most common SAE's were dehydration (3.3%), fatigue (2.6%) intestinal obstruction, ileus, and urinary tract infection (2.0% each).

7.3.10 Hospitalizations

A total of 129 patients were hospitalized - 38/153 (24.8%) in Arm A, 42/157 (26.8%) in Arm B, and 49/153 (32.0%) in Arm C.

7.3.11 Supportive studies

Of the five clinical trials submitted in this NDA (listed in the table below), the trials submitted to provide supportive safety data for EFC 4584 (the major study submitted for review) were either randomized phase 3 trials that enrolled a different patient population (first-line treatment of colorectal carcinoma) or were phase 2 studies that utilized different doses and schedules of administration of the drugs in the combination regimen (despite enrolling a comparable patient population – second-line treatment). One of the phase 2 trials, EFC 2964, did have an arm that duplicated the treatment regimen studied in EFC4584. One of the randomized studies, EFC 2961, also differed from EFC 4584, not only by the patient population enrolled, but because it utilized a chronomodulated infusion of 5-FU and a higher dose of oxaliplatin, 125 mg/m^2. Studies EFC2962 and EFC2961 were submitted and reviewed in a previous NDA. Both of these studies will be briefly summarized from a safety standpoint in this review. The safety data from only one of the phase 2 trials, EFC 2964, will be presented because one arm contained the oxaliplatin and 5-FU/LV regimen utilized in EFC 4584.

Table 60: Clinical Studies Submitted in NDA 21-492

Study No.	Study Design	Population	N	Objective
EFC4584	**Phase 3, 3-arm RCT**	**Second-line therapy for MCRC following Saltz regimen**	**463**	**RR (for accelerated approval), OS (primary)**
EFC2962	Phase 3, 2-arm RCT	First-line therapy for MCRC	420	PFS (primary)
EFC2961	Phase 3, 2-arm RCT	First-line therapy for MCRC	200	RR (primary)
EFC2964	Phase 2, multicenter, open-label trial	Second-line therapy for MCRC after progression from one 5-FU/LV	100	RR (primary)
EFC2917	Phase 2, multicenter, open-label trial	Second-line therapy for MCRC after progression from one 5-FU/LV	115	RR (primary)

MCRC: metastatic colorectal carcinoma
RCT: randomized controlled trial
OS: overall survival
RR: response rate
PFS: progression-free survival

Study EFC2964

Title of the study: Multicenter Phase 2 Study of a Combination of 5-Fluorouracil - Folinic Acid - Oxaliplatin in Colorectal Cancer Resistant to 5-Fluorouracil in Combination With Folinic Acid (FOLFOX 3-4). Drug doses and schedules are indicated below. The FOLFOX 4 regimen below is identical to the FOLFOX regimen used in the phase 3 trial submitted for review in this NDA, Study EFC4584.

FOLFOX 4 treatment regimen: Oxaliplatin + LV5FU
Day 1 Hr 0-Hr 2: oxaliplatin 85 mg/m^2 over 2 hours in 500 mL of 5% glucose
Hr 0-Hr 2: LV 200 mg/m^2 over 2 hours in 250 mL 5% glucose
Hr 2: bolus 5-FU 400 mg/m^2 over 10 minutes in 5% glucose
Hr 2-Hr 24: continuous 5-FU infusion 600 mg/m^2 in 5% glucose over 22 hours, protected from light
Day 2 Hr 0-Hr 2: LV 200 mg/m^2 over 2 hours in 250 mL of 5% glucose
Hr 2: bolus 5-FU 400 mg/m^2 over 10 minutes in 5% glucose
Hr 2-Hr 24: continuous 5-FU infusion 600 mg/m^2 in 5% glucose over 22 hours, protected from light
FOLFOX 3 treatment regimen: Oxaliplatin + FOLFUFORT
Day 1 Hr 0-Hr 2: oxaliplatin 85 mg/m^2 over 2 hours in 500 mL of 5% glucose
Hr 0-Hr 2: LV 500 mg/m^2 over 2 hours in 250 mL of 5% glucose
Hr 2-Hr 24: continuous 5-FU infusion 1500 mg/m^2 in 5% glucose over 22 hours, protected from light
Day 2 Hr 0-Hr 2: LV 500 mg/m^2 over 2 hours in 250 mL of 5% glucose
Hr 2-Hr 24: continuous 5-FU infusion 1500 mg/m^2 over 22 hours in 5% glucose, protected from light
The cycle was repeated every 2 weeks.

The patient population treated and evaluable for safety included 57 patients and 40 patients on the FOLFOX 3 and 4 arms, respectively.

Table 61 summarizes the extent of exposure for oxaliplatin. The total cumulative dose (mg/m^2) was calculated as the sum of the actual dose administered in all cycles while the patient was on study. The duration of dosing (weeks) was calculated as the [(start date of last cycle) - (start date of first cycle) + 14]/7. The dose intensity (mg/m^2/week) was calculated as the (total cumulative dose) / (duration of dosing). The relative dose intensity (RDI) (%) was calculated as 100 x (dose intensity)/(planned dose intensity). The planned oxaliplatin dose intensity (mg/m^2/week) is 42.5.

Table 61: Study EFC2964 Extent of Oxaliplatin Exposure (Applicant Analysis)

	FOLFOX4 N=57	FOLFOX3 N=40	All Treated Patients N=97
Number of cycles administered	526	370	896
Median cycles per patient [range]	10 [1-18]	10 [1-22]	10 [1-22]
Mean cumulative oxaliplatin dose (mg/m2)	755 ± 380	761 ± 292	757 ± 345
Mean relative oxaliplatin dose intensity (%)	87 ± 12	90 ± 10	88 ± 11
Median cumulative oxaliplatin dose (mg/m^2)	787.5	847.5	827.7
Median dose intensity of oxaliplatin (mg/m^2 per week)	37.1	39.4	38.0
Cycles delayed >7 days	9.1%	4.8%	7.3%
Cycles given at oxaliplatin target dose (85 mg/m^2)	87.3%	89.5%	88.2

Table 62 summarizes Study EFC2964 Grade 3/4 adverse events. As indicated, the FOLFOX4 regimen used in this trial was identical to the regimen used in the phase 3 trial submitted to support this NDA, Study EFC4584. The folinic acid and 5-FU doses administered in FOLFOX3 were higher than those administered in Study EFC4584.

Table 62: Study 2964 Grade 3/4 Adverse Events (FDA Analysis)

Grade 3-4 (NCI Scale)	FOLFOX4 N=57	FOLFOX3 N=40	All Treated Patients N=97
Toxicities	% of Patients		
Anemia	7.1	2.5	5.1
Leukopenia	17.5	12.5	15.5
Neutropenia	36.8	15.0	27.8
Thrombocytopenia	7.0	7.5	7.2
Vomiting	5.3	5.0	5.2
Diarrhea	5.3	5.0	5.1
Mucositis	5.3	17.5	10.3
Neurological	15.8	27.5	20.6
Cutaneous	0	0	0

The incidence of Grade 3/4 adverse events listed in the table above is similar to that observed in the major study reviewed in this NDA, EFC4584. Neutropenia,vomiting and diarrhea were observed somewhat more frequently in EFC4584 (44%, 9% and 11%, respectively).

The applicant in the ISS examined overall all reports of peripheral neurotoxicity (without attempt to separate acute and persistent neuropathy symptoms) and reported that in EFC2964 the incidence of all grades was 84 % compared to 75% in EFC

4584, and the incidence of Grade 3/4 was 18% vs. 8 % in EFC 4584. All rates were higher in EFC 2964. In an effort to separate acute from persistent neurological toxicity , the applicant reported a category of "Any Acute Neurotoxicity" (which included cold-related dysesthesia, pharyngolaryngeal dysesthesai, jaw pain , and "other acute symptoms." Again the all grades incidence for this pooled acute category was higher in study EFC 2964 than in EFC 4584 – 77% vs. 54%, and the incidence of Grade 3/4 events was similar – 5% vs. 3%. An analysis of persistent "cumulative" neurotoxicity was also presented, and although the overall incidence of these persistent events was more similar between studies than the acute events (51% reported in EFC 4584 vs. 58%), the incidence of Grade ¾ "cumulative" neurotoxicity events in EFC 2964appears higher – 16% vs. 3% in EFC 4584. This has been attributed to the higher median number of cycles of chemotherapy delivered in EFC 2964 (10 vs. 6 on EFC 4584) but could also be secondary to different coding of neurotoxicity between the two studies. (See Section 7.5 below for a further discussion of the correlation between cumulative exposure to oxaliplatin and neurotoxicity.)

Study EFC2962

Title of the study: "Phase 2-3 trial of 5-fluorouracil (bolus and continuous infusion) and folinic acid (LV5FU2) with or without oxaliplatin in metastatic colorectal cancer". The treatment regimen is identical to the regimen administered in the phase 3 trial submitted to this NDA, Study EFC4584. Arm A is 5-FU/LV and Arm B is 5-FU/LV/Oxaliplatin This study was submitted in a previous NDA for oxaliplatin first line treatment of metastatic colorectal carcinoma.

Exposure to therapy for patients enrolled in Study EFC2962 is indicated below in **Table 63.**

Table 63: Study EFC 2962 Exposure to Therapy

	Arm A*	Arm B
Number of patients treated	208	209
Number of cycles given	2435	2594
Median number of cycles per patient	11	12
[Range]	[1 - 40]	[1 - 35]

* Arm A = 5-FU/LV; arm B = 5-FU/LV/Oxaliplatin

Table 64 indicates the median and relative dose intensities of 5-FU and oxaliplatin received by Study EFC2962 patients.

Table 64: Study EFC2962 Treatment Dose Intensity Delivered

Median dose intensity, mg/m^2/week	Arm A* (N = 208)	Arm B (N = 209)
5-FU bolus (planned Dose Intensity = 400)	354.7	302.4
5-FU CIV** (planned Dose Intensity = 600)	531	458.5
oxaliplatin (planned Dose Intensity = 42.5)	Not Applicable	31.1
Relative dose intensity		
5-FU bolus		
[90-110%]	93 (45%)	31 (15%)
[70-90 %]	102 (49%)	104 (50%)
≤ 70 %	13 (6%)	74 (35%)
5-FU CIV		
[90-110 %]	90 (43%)	25 (12%)
[70-90 %]	110 (53 %)	123 (59%)
≤ 70 %	8 (4 %)	61 (29%)
oxaliplatin		
[90-110%]	Not Applicable	26 (12%)
[70-90%]		88 (42%)
≤ 70%		95 (45%)

* Arm A = 5-FU/LV; Arm B = 5-FU/LV/Oxaliplatin

** CIV=Continuous IV infusion

A summary of Study EFC2962 adverse events(AEs) appears in **Table 65**. **Table 66** summarizes Study EFC2962 neurologic AEs.

Table 65: Study EFC 2962 Adverse Events (FDA Analysis)

Adverse Event	Arm A* (N = 208)			Arm B (N = 209)		
	All grades (%)	G3 (%)	G4 (%)	All grades (%)	G3 (%)	G4 (%)
Nausea	111(53 %)	3(1 %)	NA	151(72 %)	12(6 %)	NA
Vomiting	61(29 %)	3(1 %)	1(0.5 %)	113(54 %)	9(4 %)	3(1%)
Diarrhea	91(44 %)	8(4 %)	3(1 %)	123(59 %)	18(9 %)	7(3%)
Stomatitis	74(36 %)	3(1 %)	-	91(44 %)	11(5 %)	1(0.5%)
Fever w/o infection	31(15 %)	-	-	69(33 %)	-	-
Infection	48(23 %)	2(1 %)	1(0.5 %)	54(26 %)	3(1 %)	-
Skin toxicity	65(31 %)	-	1(0.5 %)	60(29 %)	-	-
Alopecia	39(19 %)	NA	NA	37(18 %)	NA	NA

* Arm A = 5-FU/LV; arm B = 5-FU/LV/oxaliplatin

The incidence of adverse events in Arm B was similar to that observed in the major study reviewed in this NDA, EFC4584. The incidence of Grade 3/4 nausea and vomiting was somewhat higher in that study (11% Grade 3/4 nausea and 9% Grade 3/4 vomiting), skin toxicity and alopecia were somewhat higher in incidence in EFC 2962.

Table 66: Study 2962 Neurological Adverse Events (FDA Analysis)

Neurological sign / symptom	Arm A* (N = 208)		Arm B (N = 209)	
	All grades (%)	G3 (%)	All grades (%)	G3 (%)
Cold-related dysesthesia	1(0.5 %)	-	141(67)	1(0.5%)
Paresthesia without pain	23(11%)	-	136 (65%)	5 (2%)
Paresthesia with pain	-	-	22 (11%)	1(0.5%)
Paresthesia with functional impairment	-	-	34 (16%)	34(16%)
Cramps	3(1%)	-	12 (6%)	2(1%)
Pharyngo-laryngeal dysesthesia	1(0.5 %)	-	47 (22%)	1(0.5%)
Lhermitte's sign**	-	-	7 (3%)	-
Loss of deep tendon reflexes	1(0.5%)	-	24(11%)	-

* Arm A = 5-FU/LV; Arm B = 5-FU/LV/Oxaliplatin

** Lhermitte's sign, a shock-like or electric sensation, transmitted down the spine, which occurred during neck flexion or rotation.

A higher incidence of cold-related dysesthesia is reported in Arm B of this study compared to EFC 4584 (48% overall grades). The incidence of grade 3 cold-related dysesthesia and pharyngeal dysesthesia is similar between trials, however the incidence of overall .pharyngolaryngeal dysesthesia reported by the applicant in Study EFC4584 was lower, 3%. Investigators could only grade the latter as Grade 3 in EFC 4584, but could assign any grade to this toxicity in EFC 2962.

The applicant in the ISS examined overall all reports of peripheral neurotoxicity (without attempt to separate acute and persistent neuropathy symptoms) and reported that in EFC2962 the incidence of all grades was 83 % compared to 75% in EFC 4584, and the incidence of Grade 3/4 was 20% vs. 8 % in EFC 4584. All rates were higher in EFC 2962. In an effort to separate acute from persistent neurological toxicity , the applicant reported a category of "Any Acute Neurotoxicity" (which included cold-related dysesthesia, pharyngolaryngeal dysesthesai, jaw pain , and "other acute symptom"). Again the all grades incidence for this pooled acute category was higher in study EFC 2964 than in EFC 4584 – 70% vs. 54%, and the incidence of Grade 3/4 events was similar – 1% vs. 3%. An analysis of persistent neurotoxicity was also presented, and the incidence of overall grades and Grade ¾ for these persistent neurotoxicity events were higher in study EFC 2964 (51% and 3% for EFC 4584 vs. 68% and 17% in EFC 2962). This difference has been attributed to the higher median number of cycles of chemotherapy delivered in EFC 2964 (10 vs. 6 on EFC 4584) but could also be secondary to different coding of neurotoxicity between the two studies. (See Section 7.5 below for a further discussion of the correlation between cumulative exposure to oxaliplatin and neurotoxicity.)

Hematology abnormalities occurring during treatment in Study EFC2962 are summarized in **Table 67.**

Table 67: Study 2962 Hematologic Toxicity (FDA Analysis)

	Arm A* (N = 208)			Arm B (N = 209)		
NCI-CTC grade	≥ 1	3	4	≥ 1	3	4
Anemia	169(81%)	3(1%)	2(1%)	181(87%)	7(3%)	0
Leukopenia	48(23%)	2(1%)	3(1%)	145(69%)	19(9 %)	0
Neutropenia	63(30%)	8(4 %)	3(1%)	147(70%)	62(30%)	25(12%)
Thrombocytopenia	61(29%)	1(1%)	0	159(76%)	4(2%)	1(1%)

* Arm A = 5-FU/LV; arm B = 5-FU/LV/Oxaliplatin

The incidence of hematological toxicity was similar between studies (EFC 4584).

Study EFC2961

Title of the study: "Role of L-OHP in metastatic colo-rectal cancers treated with the association of chronomodulated 5-fluorouracil and folinic acid"

This is one of the randomized, controlled trials that was previously submitted in an NDA to support oxaliplatin first-line treatment of advanced colorectal carcinoma.

Planned dosing regimen:

Both treatment regimens include chronomodulated perfusion of 5-FU and of LV for 5 consecutive days with or without oxaliplatin on Day 1, followed by a free interval of 16 days. In each regimen, the infusion of 5-FU and LV are chronomodulated (given from 10 PM to 11 AM with peak at 4 AM) using a multi-channel portable pump. The oxaliplatin dose is higher than that used in EFC 4584.

Regimen 1: 5-FU: 700 mg/m^2/day, LV: 300 mg/m^2/day,Days 1-5
Regimen 2: oxaliplatin: **125** mg/m^2 by 6 hour infusion prior to 5-FU and LV, Day 1
5-FU: 700 mg/m^2/day, LV: 300 mg/m2/day, Days 1-5

Repeat every 21 days

Adverse events recorded in patients participating in Study EFC2961 are summarized in **Table 68**.

Table 68: Study EFC2961 Adverse Events (FDA Analysis)

AE	Grade	Total	5-FU/LV (N = 100)	5-FU/LV/Oxaliplatin (N = 99)
Anemia	1	47	22	25
	2	20	9	11
	3	5	3	2
Leukopenia	1	36	10	26
	2	3	0	3
	3	2	0	2
Neutropenia	1	26	6	20
	2	11	1	10
	3	2	1	1
	4	1	0	1
Thrombocytopenia	1	14	1	13
	2	7	0	7
	3	1	0	1
Diarrhea	1	44	25	19
	2	40	17	23
	3	39	4	35
	4	9	1	8
Stomatitis	1	71	36	35
	2	35	19	16
	3	13	4	9
	4	1	0	1
Vomiting	1	83	47	36
	2	39	14	25
	3	23	2	21
	4	5	0	5
Hepatic Disorder	1	68	34	34
	2	42	14	28
	3	13	8	5
	4	8	4	4
Renal Disorder	1	10	5	5
Paresthesia	1	38	18	21
	2	27	1	25
	3	32	0	32
	4	13	0	13
Skin Disorder	1	52	22	30
	2	23	14	9
	3	1	1	0
Hemorrhage NOS	1	1	1	0
	2	12	5	7
	3	0	0	0
	4	1	0	1

The incidence of diarrhea, stomatitis, vomiting, and skin disorder were higher in this dosing and administration regimen for oxaliplatin and 5-FU compared to that observed in the major study reviewed in this NDA, EFC 4584. There were two toxic deaths in Study EFC2961. One patient (Arm 1) died of drug related diarrhea and 1 patient (Arm 2) died of catheter associated thrombosis. (See Section 7.5 below for a discussion of the neurotoxicity observed in this study.)

7.4 Adequacy of Safety Testing

Safety data reported from studies submitted as part of NDA 21-492 are consistent with safety data reported from previously published oxaliplatin study results that include over 1,500 patients.

7.5 Summary of Critical Safety Findings and Limitations of Data

The safety results with oxaliplatin seen in the major study reviewed in this NDA, Study EFC 4584, are consistent with results seen in other studies of oxaliplatin alone or in combination in previously treated or untreated patients with metastatic colorectal cancer.

On Arm C (5-FU/LV/oxaliplatin) of Study EFC4584, the exposure to study treatment was greater (median 6 cycles) compared to either Arm A (5-FU/LV) (median: 3 cycles) or Arm B (oxaliplatin) (median: 3 cycles), while a high median RDI (Relative Dose Intensity) of oxaliplatin and 5-FU/LV (89%) was maintained on Arm C. Dose reductions, as expected, occurred more frequently in Arm C. Patients in Arm C also had more dose delays, predominantly of 5-14 days, primarily due to AE's.

The incidence of hematologic toxicity was higher in Arm C compared with Arm A. The addition of oxaliplatin to the infusional 5-FU/LV regimen was associated with an increase in the incidence of neutropenia. Febrile neutropenia occurred only in 10 patients on the study, 9 of whom were in Arm C ($\leq$ 1% of cycles) and 1 in Arm A. For patients with febrile neutropenia treated on Arm C, the oxaliplatin dose was either reduced or temporarily discontinued. Eight patients in Arm C were treated with antibiotics and all patients recovered. The incidence of Grade 1 and 2 thrombocytopenia in Arm C was almost 3 times as high as that seen in Arm A, however, none of the patients had clinically significant complications.

Almost all patients had at least 1 adverse event. Across all treatment arms, most events were gastrointestinal in nature. The incidence of nausea, vomiting, and diarrhea in patients treated with combination therapy of oxaliplatin and 5-FU/LV (Arm C) is additive to that resulting from 5-FU therapy alone. The combined incidence of stomatitis and mucositis and pharyngitis (the case report form captured both stomatitis and pharyngitis under one category on the "checkoff" sheet) was comparable in Arms A and C, indicating that the addition of oxaliplatin does not substantially increase oral mucosal toxicity associated with infusional 5-FU and leucovorin.

Sensory peripheral neurotoxicity is a known toxicity of oxaliplatin, and as expected, the incidence was similar in Arms B and C but more common compared with Arm A. The fact that the incidence of observed severe paresthesias in this study was low (<5%) relative to prior study reports is likely due to the shorter median duration of treatment in this study. The median number of cycles of treatment on Arm C (pivotal study) was 6 and the median total cumulative dose of oxaliplatin was 510 mg/m^2. In the ISS of the NDA, the applicant presented an analysis correlating grade of neurotoxicity with number of cycles of treatment, utilizing data from the two supportive studies that utilized the same dosing regimen and schedule administered in EFC 4584.

Allergic reactions and allergy (all grades) were infrequent but were reported slightly more often in Arm C compared with Arm A and Arm B. Except for 1 patient in Arm C who developed a Grade 3 allergic reaction leading to treatment discontinuation, all other patients had Grade 1 or 2 allergic reactions.

Elevated liver enzymes are common in patients with colorectal cancer. At baseline, the incidence of AST and ALT elevations were 20-30% (all grades) in Arm C and 30-40% (all grades) in Arm A. At the time of this analysis, the incidence of AST and ALT elevations ranged from 40-50% (all grades) in both Arm A and Arm C; suggesting that oxaliplatin did not have an marked adverse effect on these liver function parameters.

Patients in Arm C had more SAEs (Serious Adverse Events) than patients in Arm A or B, but most of these were attributed to disease progression. The number of patients withdrawing from the study due to adverse events was comparable across arms. Patients in Arm C had the lowest death rates, both due to PD and other reasons. The applicant attributed only 2 deaths to adverse events on Arm C, compared to 1 on Arm A, and 3 on Arm B. The FDA has utilized evaluation and comparisons of rate of death within 30 days of treatment as a less biased method of comparing potentially toxicity related deaths. Granted, deaths within 30 days will also capture deaths related to progressive disease and other medical illness, but it is not subject to the bias introduced by the investigator/applicant in making an assignment of attribution to their drug or to the comparator drug/regimen. There were 7 (5%) deaths within 30 days of treatment on the oxaliplatin/5-FU/LV arm (Arm C), and 12 (8%) deaths on the single agent oxaliplatin arm (Arm B). There were 10 deaths (7%) within 30 days of treatment on the 5-FU/LV arm (Arm A).

Adverse events (CTC Grade 3/4), from published oxaliplatin therapy reports, are summarized in **Table 69**. **Table 70** summarizes the various 5-FU, folinic acid and oxaliplatin (FOLFOX) treatment regimens that have been reported. It is evident that toxicity observed in the NDA 21-492 studies is comparable to previously reported oxaliplatin toxicity. Cross study comparisons are difficult in some cases, since oxaliplatin doses and/or 5-FU doses were higher in some regimens or utilized chronomodulation of 5-FU (compared to the major study reviewed in this NDA, EFC4584). The higher incidence of nausea/vomiting, diarrhea and mucositis observed in those trials may be secondary to these differences.

The safety profile of oxaliplatin and infusional 5-FU appears to be predictable and manageable and is not expected to limit the usefulness of this drug combination.

Table 69: Grade 3/4 Toxicities In Advanced Colorectal Carcinoma Patients Treated in Second-Line Oxaliplatin/5-FU/LV Studies§

NCI-CTC Toxicity		No. of Patients	Neutro penia	Thrombo cytopenia	Neurosens Ory	Nausea/ Vorniting	Diarrhea	Muco stitis	Alopecia
Chronomodulated Infusions									
Levi		42			11%	8%	5%	2%	NA
Garufi		25			NA	25%	16%	8%	NA
Brienza		57	NA	NA	NA	8%	6%	<1%	NA
Bertheault-Cvitkovic		37	-	2%	-	36%	40%	28%	NA
Flat-rate infusions									
de Gramont	FOLFOX 1	13	23%	15%	8%	15%	-	15%	31%
Andre	FOLFOX 2	46	40%	11%	9%	4%	9%	13%	9%
Andre	FOLFOX 3&4	60	11%	11%	7%	7%	2%	13%	NA
Maindrault-Goebel	FOLFOX 6	60	24%	2%	16%	7%	YT	5%	NA
Maindrault-Goebel	FOLIFOX 7	38	9%	12%	9%	6%	12%	-	-
Gerard		36	8%	8%	6%	5%	11%	NA	NA
Meyer		38	NA	NA	NA	NA	NA	NA	NA
Buechele		14	-	NA	-	18%	37%	4%	NA
Compassionate use programs (short IV)									
French 14 Ox/5-FU		492	16%	5%	11%	10%	16%	5%	3%
Europe 15 Ox/5-FU		206	21%	7%	15%	16%	28%	6%	NA

§ Cvitkovic E, and Bekradda M. Oxaliplatin: A new therapeutic option in colorectal cancer. Semin Oncol 1999;26:647-662.

Table 70: 5-FU/LV/Oxaliplatin (Folfox) Treatment §

	Cycle length (wks)	Hour 0	2	24	26 ——— 48
Folfox 1	2	LV –500 OXA 130 (q2cycles)	5-FU CI : 2000	LV : 500	5-FU CI :2000
Folfox2	2	LV –500 OXA 100	5-FU CI: 1500 - 2000	LV : 500	5-FU CI :2000
Folfox 3	2	LV –500 OXA 85	5-FU CI: 1500	LV : 500	5-FU CI :1500
Folfox 4	2	LV –200 OXA 85	5-FU bolus 400 5-FU CI : 600	LV : 200	5-FU CI :600
Folfox 6	2	LV –400 OXA 100	5-FU bolus 400 5-FU CI : 2400-3000 (H2-H48)		
Folfox 7	3*	LV –400 OXA 130	5-FU bolus 400 5-FU CI : 2400 (H2-H48)		

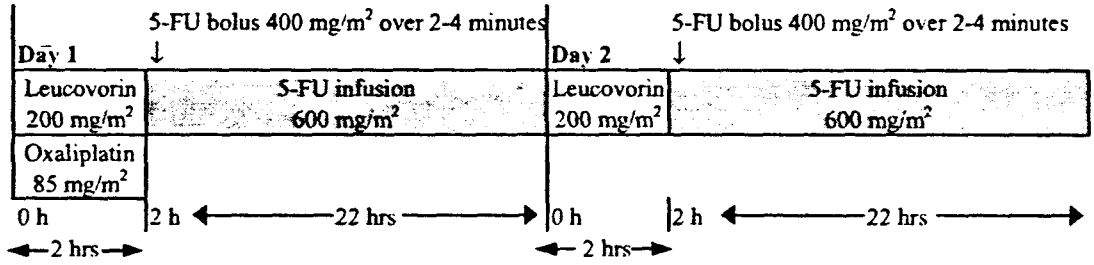
§ Misset JL, Bleiberg H, Sutherland W, et al. Oxaliplatin clinical activity: a review. Clin Rev Oncol/Hematol 2000;35:75-93.

*The first 2 cycles were administered q3 weeks, subsequent cycles q 2-3 weeks, according to tolerance.

CI = continuous infusion

8 Dosing, Regimen, and Administration Issues

The recommended dose of oxaliplatin in combination with infusional 5-FU/LV is 85 mg/m^2 intravenously over 2 hours in 250-500 mL of D5W. Leucovorin 200 mg/m^2 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/m^2, followed then by administration of 600 mg/m^2 (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/m^2 bolus and 22 hour infusion of 600 mg/m^2 is repeated on Day 2 after completion of the Day 2 leucovorin infusion. The cycle is repeated every 2 weeks.



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.

9 Use in Special population

9.1 Analysis of efficacy and safety of effects of, Age, Gender and Race

Age

The age of patients on the combination arm (oxaliplatin and infusional 5-FU with leucovorin) of the major study that was submitted for review in this NDA ranged from 22 to 88 years (54 patients were ≥ 65 years of age). Among the responders on the oxaliplatin combination arm, the age range was 30 to 80 years, with a median of 56 years.

For the more commonly occurring AE's in the 5/FU/LV/oxaliplatin arm, patients < 65 when compared to patients ≥ 65 had more frequent (all grades) paresthesias, 78% vs 67%, nausea, 70% vs 56%, vomiting 46% vs 29%, and sensory disturbance, 59% versus 42%, and less frequent fatigue 6% vs 75%, and diarrhea, 62% vs 75%. Fever was comparable in the two age groups, 27% and 28%, respectively.

In addition to the higher incidence of diarrhea and fatigue in patients ≥65 yo, dehydration (4% in <65 yo vs 15% in ≥ 65 for overall grades and 2% vs. 6% grade 3/4), hypokalemia (7% <65 yo vs 13% in ≥65 yo for overall grades), and Grade ¾ granulocytopenia (32% <65 yo vs 38% in ≥65 yo) occurred more frequently in this older population. Four of 7 deaths that occurred within 30 days of

administration of the oxaliplatin and 5-fluorouracil/leucovorin combination regimen were in patients ≥65 yo. (36% of patients on the oxaliplatin combination treatment arm were ≥65 yo.)

Sex

Of the 13 responders in Arm C (oxaliplatin combination arm), 5 were females and 8 were males. There do not appear to be any differences in efficacy based on sex.

Some adverse events were reported more frequently in females, such as dizziness, stomatitis, headaches, anemia, urinary tract infections, nausea and vomiting pharyngitis, mucositis, granulocytopenia (42% grade 3/4 in females vs. 28% in males), conjunctivitis, and skin exfoliation (hand-foot syndrome). Rates of diarrhea, paresthesias, and sensory disturbances were similar between males and females. Thrombocytopenia was reported more frequently in oxaliplatin combination regimen-treated males than in females (4% vs 0.03% for grade 3/4), as was anorexia and dehydration. Three of the 7 patients who died within 30 days of treatment in the oxaliplatin and 5-fluorouracil/leucovorin combination regimen were female. (43% of the oxaliplatin combination treatment arm were female).

Race

There were only a limited number of patients not considered Caucasian per arm (Arm A -19, Arm B -22, Arm C -17), which makes a meaningful analysis of differences in efficacy and safety among races impossible.

9.2 Pediatric Program (e.g., pediatric waivers, deferrals, written requests)

A pediatric waiver was granted since colorectal cancer in a pediatric population is a rare occurrence.

9.3 Renal or Hepatic Compromised Patients, and Use in Pregnancy.

Patients with Renal Impairment:

There was a limited number of patients per arm with renal impairment (elevated baseline serum creatinine) (Arm A -3, Arm B -5, Arm C -9). Therefore, no assessment was possible. The applicant will conduct a study on patients with minimal and moderate renal imppairment to evaluate for toxicity (see Section 10).

Patients with Hepatic Insufficiency:

There did not appear to be an increased number of adverse events in patients with elevated hepatic enzymes or bilirubin, but numbers of patients were small. Only 3 patients receiving 5-FU/LV/Oxaliplatin had grade 3,4 hepatic enzyme and/or bilirubin elevation.

Use in Pregnancy:

Oxaliplatin may cause fetal harm when administered to a pregnant woman. Women of childbearing potential should be advised to avoid becoming pregnant while receiving treatment with oxaliplatin.

10 Labeling Safety Issues and Postmarketing Commitments

10.1 Labeling issues:

The major issues negotiated with the applicant regarding the product label included, regarding efficacy, whether to include the time to progression analysis with K-M curve, p-value, medians and confidence intervals; regarding biopharmaceutics, the content and extent of information to provide on dosage and administration of oxaliplatin in patients with renal impairment, and; regarding safety, inclusion of a black box warning and presentation of complete available safety data on oxaliplatin overdosage.

Although the pre-specified analysis of the secondary endpoint time to progression, which by definition was limited to radiographic progression based on independent radiology review, demonstrated improvement in time to radiographic progression in an analysis of 49% of the events available at the time of data cut-off, this analysis did not represent a valid intent to treat analysis because 20% of the patients were excluded from the analysis by censoring them at time zero. For that reason, the FDA could not justify inclusion of the detailed analysis of this secondary endpoint. The FDA agreed that the sponsor could include a statement that a prolongation in median time to progression was observed, as long as the caveats regarding the limitations of the validity of the analysis were presented, and the confidence intervals, p-value and K-M curves were not.

Re-analysis of the data submitted by the applicant from a study conducted to evaluate pharmacokinetics of single agent oxaliplatin in patients with renal impairment was performed by the FDA. This re-analysis indicated that the $AUC_{0\text{-}48hr}$ 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 the individual biologically active platinum moieties. There are no PD data available for evaluation. Because the safety data available from this renal impairment study was 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 revisions were made in the Precautions section of the product label:

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 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)

The label submitted by the applicant did not include a black box warning for anaphylactic reactions associated with platinum products. Hypersensitivity reactions have been observed with administration of oxaliplatin. The label was revised to include a black box warning about the potential for anaphylactic reactions.

Neurotoxicity

The sponsor revised the neuropathy categories based on the FDA suggested classification and analysis. The categories used were acute (duration less than 14 days) and persistent (duration 2 weeks or longer). The adverse event tables were revised to reflect the reclassification and figures were recalculated. The dose reduction and modification sections were revised to impart the protocol recommendations but with the understanding that the protocol recommendations were not followed in the study resulting in a dearth of data to support those recommendations.

The applicant's ISS included information on 4 patients that had been administered oxaliplatin overdoses. Two errors were attributed to mistakenly substituting oxaliplatin for carboplatin, at carboplatin doses. One of the patients, a 70 year old female who was administered 500 mg of oxaliplatin with paclitaxel 250 mg, developed respiratory failure and severe bradycardia the same day as drug administration. She died despite efforts at cardiopulmonary resuscitation. Another female, 51 years old, was administered a similar overdose, 650 mg of oxaliplatin, in combination with paclitaxel and survived. She was hospitalized, but no clinical symptoms are provided, other than those of anxiety, paresthesia, and emesis. The label's Overdosage section will be revised to include information on these patients. In addition, the phase 4 commitments will include a requirement that the applicant develop a post-marketing medical errors education program, specifically targeting prevention of mistaken substitution of oxaliplatin for carboplatin, and to moniter post-marketing safety reports specifically for these types of errors.

The FDA requested that the applicant provide a Patient Package Insert with the product label because of the unique and potentially distressing neurological toxicities associated with oxaliplatin and because of the potential for diarrhea complicated by dehydration and enteric sepsis. The PPI was submitted and the FDA, after negotiation with the applicant, agreed with its content.

10.2 Phase 4 commitments for accelerated approval of Eloxatin

There are several post-marketing commitments agreed upon as a condition for accelerated approval of Eloxatin. The following trials have the potential for verifying and describing clinical benefit associated with oxaliplatin:

1. Complete the study that was submitted for review in NDA 21-492, EFC4584 (Multi-center, Randomized, Three Arm Study of 5-Fluorouracil/Leucovorin or Oxaliplatin or a Combination of 5-Fluorouracil and Oxaliplatin as Second-Line Treatment of Metastatic Colorectal Carcinoma). Submit the mature survival data and analysis in a final study report for review by 2004, second quarter.

2. Complete the study EFC4585 (Multi-center, Randomized, Two Arm Study of Irinotecan versus the Combination of Oxaliplatin with Irinotecan as Second Line Treatment of

Metastatic Colorectal Cancer). Submit the mature survival data in a full study report for review by 2005, third quarter.

3. Complete the study EFC7462 (Randomized, Phase 3 trial of Combinations of Oxaliplatin, 5-Fluorouracil and Irinotecan as Initial Treatment of Patients with Advanced Adenocarcinoma of the Colon and Rectum). Submit the full study report for review by 2003, first quarter.

4. Complete the study L8125 (Randomized Trial Evaluating Oxaliplatin Combined with Two Different 5-Fluorouracil Regimens in Patients with Previously Untreated Advanced Colorectal Cancer). Submit the full study report for review by 2005, second quarter.

5. Complete the adjuvant treatment study EFC3313 (Multicenter International Study of Oxaliplatin/5FU/LV in the Adjuvant Treatment of Colon Cancer – MOSAIC TRIAL). Submit the full study report for review by 2004, third quarter.

6. Complete the adjuvant treatment study EFC7112 (Clinical Trial Comparing 5-FU plus Leucovorin and Oxaliplatin with 5-FU/LV for the Treatment of Patients with Stage 2 and 3 Carcinoma of the Colon). Submit the full study report for review by 2007, first quarter.

Additional proposals by the applicant, acknowledged by the FDA are as follows:

7. Design and conduct a study to examine the safety of administering repeated doses of oxaliplatin 85 mg/m^2 in combination with 5-FU/LV, at the doses and schedule recommended in the product label, in patients with varying degrees of renal impairment. This study should include patients with normal renal function, minimally impaired renal function and moderately impaired renal function. The study should be designed to assess whether there are differences in safety between each of the different subgroups of renal impairment compared to a control group with normal renal function. Differences in proportions of patients with all grades and grade 3/4 gastrointestinal, neurological, renal and hematological toxicities, differences in time to onset and duration of grade ¾ neurotoxicity, and differences in proportions of patients who require dose reductions should be evaluated. A subgroup of patients with severe renal toxicity should also be considered for study, possibly at a lower starting dose.

8. Submit reports of all medication errors, both potential and actual, that occur within the United States with oxaliplatin for two years following the date of approval. Potential errors should be reported and summarized quarterly. All actual errors should be submitted within 15 days regardless of patient outcome. Yearly reports of potential and actual errors occurring with oxaliiplatin should be submitted for two years following the date of approval.

9. To decrease potential medication errors of substitution of oxaliplatin for other platinum drugs, you should redesign the oxaliplatin product packaging so that the "oxali-" prefix to the name appears in a different font color and/or size.

10. Complete the study EFC4759 (Single Arm Phase 2 study of Oxaliplatin as Third-Line Treatment of Metastatic Colorectal Carcinoma). Submit the full study report for review by 2004, third quarter.

Complete the study EFC 4760 (Randomized, Phase 2 Trial of Infusional 5-FU versus Infusional 5FU/Oxaliplatin in 3rd line Treatment of Metastatic Colorectal Carcinoma). Submit the full study report for review by 2004, first quarter.

11 Conclusions

11.1 Conclusions Regarding Safety and Efficacy

EFC 4584 is a well-designed, well-conducted trial that continues to accrue data for the primary endpoint of overall survival. The patients enrolled in this study are heavily pre-treated, without any further options for treatment.

As prespecified in the original protocol, data was submitted for consideration for accelerated approval of oxaliplatin in combination with infusional 5-FU and leucovorin (LV) for treatment of patients with advanced colorectal cancer that had progressed on or relapsed after first-line treatment with 5-FU and irinotecan. The surrogate endpoint proposed as a basis for accelerated approval was response rate. A statistically significant improvement in response rate was shown to be associated with the combination oxaliplatin and 5-FU/LV regimen in comparison to the 5-FU/LV control arm. Although the pre-specified analysis of time to progression, which by definition was limited to radiographic progression based on independent radiology review, demonstrated improvement in time to radiographic progression in an analysis of 49% of the events available at the time of data cut-off, this analysis did not represent a valid intent to treat analysis because 20% of the patients were excluded from the analysis by censoring them at time zero.

Neuropathy is the dose limiting toxicity of the oxaliplatin and infusional 5-FU/LV regimen. Neutropenia is the most prominent hematologic adverse event. Febrile neutropenia was observed in 6% of patients. The number of adverse events was re higher in the oxaliplatin combination arm, in which the patients received twice the median number of cycles of therapy compared to the 5-FU/LV arm and the single agent oxaliplatin arm. Patients treated with the combination regimen had a higher incidence of diarrhea, neutropenia, nausea, vomiting, febrile neutropenia, and neurosensory toxicity than on the 5-FU/LV control arm. There was also a higher incidence of thrombosis and embolic events on the combination therapy arm that is of uncertain significance. Five percent of patients treated on the oxaliplatin combination regimen arm died within 30 days of treatment, compared to 8% on the control arm. .
This application has provided persuasive is evidence that oxaliplatin when combined with infusional 5FU/LV has efficacy and a tolerable safety profile in patients with metastatic colorectal carcinoma who have progressed during, or recurred after a combination of irinotecan, andbolus 5-FU/LV, the approved regimen for first-line treatment.

11.2 Recommendations on Approvability

We recommend accelerated approval of oxaliplatin in combination with infusional 5-FU/LV for patients with metastatic colorectal cancer, who have progressed or recurred after first-line therapy with irinotecan, bolus 5-FU and leucovorin.

11.3 Labeling

Pending approval

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APPENDIX

In any given cycle at least 30% of patients will have a neurotoxic event. Having an event in one cycle is not predictive of subsequent events, although there were patients who had events with every cycle. The population of patients having an event varied, so that over the course of the study about 75% of all patients had at least one neurotoxic event.

The following two tables give the number of persisitent and acute neurologic events (not grade) per cycle per patient, that occurred in the study (EFC4584) submitted in this NDA.

Appendix Table: Persistent Neurotoxicity per Patient per Cycle

(Continued on the next page)

Patient ID	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15
04584 0101 0001	1														
04584 0102 0005															
04584 0103 0003										1		1			
04584 0104 0002									1						
04584 0105 0001				1		1									
04584 0105 0004	2					1			2			1			
04584 0110 0002				1											
04584 0112 0004					1										
04584 0113 0002								2							
04584 0119 0003							1								
04584 0119 0005															
04584 0121 0001															
04584 0126 0001													1	2	
04584 0126 0002												1			
04584 0127 0004					1										
04584 0131 0005			1												
04584 0133 0003						1									
04584 0139 0001			1												
04584 0141 0001		2					1				1				
04584 0153 0004										1	1				
04584 0154 0002									1						
04584 0156 0001									1						
04584 0157 0001			1												
04584 0162 0001							2								
04584 0162 0003		1		1											
04584 0165 0001		1									2		2		
04584 0166 0010															
04584 0167 0004						1	2				2				
04584 0168 0012	1														
04584 0176 0001											1				
04584 0180 0001	1														
04584 0186 0003			1												
04584 0187 0004		1													

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Patient ID	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15
04584 0189 0003			2						1						
04584 0191 0013		1													
04584 0191 0014										2					
04584 0191 0015															
04584 0191 0017						1									
04584 0191 0020			1												
04584 0192 0001				1				1							
04584 0197 0006	1	1													
04584 0197 0007					2										
04584 0198 0002			2												
04584 0501 0001										1					
04584 0501 0003						1		1							
04584 0502 0002			2												
04584 0505 0003								1		1	1				1
04584 0506 0001							3	2			4		4		
04584 0508 0001				1											
04584 0508 0002			1												
04584 0511 0013			1			2									
04584 0511 0014									1	1			1		
04584 0511 0020							1								
04584 0511 0024	1														
04584 0515 0001		1	1												
04584 0515 0002					1	1									
04584 9101 0007		1				2									
04584 9101 0008						2		2	2						
04584 9104 0002					1										
04584 9105 0001											1				
04584 9108 0002									2			1			
04584 9108 0005			1												
04584 9109 0001															
04584 9110 0001			1					1							
04584 9113 0004	1														
04584 9113 0005															
04584 9114 0002		1		1	1										
04584 9114 0007															
04584 9117 0002															
04584 9118 0003								2							
04584 9118 0006						1									
04584 9128 0001			2												

Appendix Table: Acute Neurotoxicity per Patient per Cycle
(continued on next page)

Patient ID	1	2	3	4	5	6	7	8	9	10	11	12	13	14
04584 0102 0001								1						
04584 0102 0005	1		1											
04584 0103 0003			1				1				2	1	1	
04584 0104 0002		2	1	1	1	1	1	1	1					
04584 0105 0001	2	1	1	1		1								
04584 0105 0004					1			2						
04584 0107 0002	1	1	1	1	1									
04584 0109 0002		1	1											
04584 0109 0006	2	1												
04584 0112 0002					3									
04584 0112 0004		1		1										
04584 0112 0005			1	1		1	1	1						
04584 0116 0001	1													
04584 0119 0005							1							
04584 0121 0001		1												
04584 0126 0001														1
04584 0128 0003		1			1									
04584 0133 0003	1	1	1											
04584 0133 0004		1												
04584 0134 0002	2													
04584 0141 0001	1													
04584 0142 0003	1	3	2	2			2	2						
04584 0142 0005		1	2											
04584 0146 0002	1	3	1											
04584 0148 0003							1							
04584 0153 0002			1											
04584 0153 0004	3	1		1	1	1					1			
04584 0154 0001		1	1											
04584 0154 0002							1	1	2					
04584 0156 0001	1	1	2	2	1	4	4	2	2					
04584 0156 0004	1		1											
04584 0156 0006		1												
04584 0157 0001	1	1		1										
04584 0162 0001	2	2	2	2	2	3								
04584 0165 0001	1													
04584 0167 0004	1	1												
04584 0169 0001		1												
04584 0170 0001					1	1								
04584 0176 0001							1	1						
04584 0180 0001			1		1		1							
04584 0180 0002			2											
04584 0181 0001		1												

Clinical Review Section

Patient ID	1	2	3	4	5	6	7	8	9	10	11	12	13	14
04584 0186 0002	1													
04584 0186 0003	1													
04584 0187 0002		1												
04584 0189 0003	3	4	3	2	3	2	2	2	2	4	4	2		
04584 0191 0004			2	2			1	1						
04584 0191 0013	1	3	1		1	1	1	1						
04584 0191 0014		1	3	2	1	1	1	1	2					
04584 0191 0015	1	3	1	1	1	2		1						
04584 0191 0020		1		1	1									
04584 0197 0002			1	2	1	1								
04584 0197 0007	1		2	1		2								
04584 0198 0004			1		1	1								
04584 0501 0001	1	1	1											
04584 0501 0003		1	1		1									
04584 0502 0002	2													
04584 0502 0003	2													
04584 0505 0001	1													
04584 0505 0003	1	1	1	1	1	1		1		1	1	1	1	1
04584 0506 0001				1	1	2	5							
04584 0508 0001		1												
04584 0508 0002			1											
04584 0511 0003			1											
04584 0511 0006			2											
04584 0511 0010			1											
04584 0511 0013						1								
04584 0511 0014	1	1	1		1				1					
04584 0511 0020	1	1	1	1										
04584 0511 0024	1	1	2	1	1	1								
04584 0515 0001	1	1	1	1	1	1								
04584 0515 0002			1	2	1									
04584 9101 0006		1		1										
04584 9101 0007					2									
04584 9101 0008					2		2	1						
04584 9102 0002	1	1	1	1	1	1	1	1	1	1	1	1		
04584 9103 0003		1		1	1	1								
04584 9104 0001								1						
04584 9105 0001		1	1	1	1	1	1							
04584 9108 0002				1	1	3		2						
04584 9114 0004		1												
04584 9114 0007							1	1						
04584 9118 0003	2	3	1	2	1		1							
04584 9118 0006	1	2	2	2	1									
04584 9118 0007						1								
04584 9124 0004		2												
04584 9128 0001	1	2												

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