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ELOXATINE™ (Oxaliplatin)

**ONCOLOGY DRUG ADVISORY COMMITTEE MEETING
BRIEFING DOCUMENT OF THE
EFFECTIVENESS AND SAFETY OF OXALIPLATIN IN COMBINATION WITH
5-FU-BASED CHEMOTHERAPY IN THE
TREATMENT OF ADVANCED COLORECTAL CANCER**

FINAL VERSION

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AVAILABLE FOR PUBLIC DISCLOSURE WITHOUT REDACTION

TABLE OF CONTENTS

1. INTRODUCTION.....	4
2. BACKGROUND	8
3. PIVOTAL STUDY: EFC2962.....	14
4. SUPPORTIVE STUDIES.....	27
5. SUMMARY OF EFFICACY RESULTS IN CONTROLLED STUDIES.....	43
6. SAFETY RESULTS.....	44
7. CLINICAL BENEFIT	55
8. DISCUSSION	58
9. PRIMARY TABLES.....	62

LIST OF APPENDICES

1. Summary of Efficacy in Secondary Studies in Patients with Advanced Colorectal Cancer.....	68
2. Intergroup Trial Publication.....	76
3. Study EFC2962 - Additional Explanatory Analyses.....	84

LIST OF ABBREVIATIONS

5-FU	5-fluorouracil
ADR	adverse drug reaction
AE	adverse event
ALT/ALAT	alanine aminotransferase
AST/ASAT	aspartate aminotransferase
BUN	blood urea nitrogen
CEA	carcinoembryonic antigen
CI	confidence intervals
CIV	continuous intravenous infusion
CPT-11	irinotecan
CR	complete response
CRF	case report form
CT	computerized tomography
DACH	1,2-diaminocyclohexane
DNA	deoxyribonucleic acid
DRG	dorsal root ganglia
ECOG	Eastern Cooperative Oncology Group
EORTC	European Organization for Research and Treatment of Cancer
FA	folinic acid
FDA	Food and Drug Administration
ITT	intent-to-treat
JCO	<i>Journal of Clinical Oncology</i>
NA	not applicable
NCI	National Cancer Institute
NR	not reported
ODAC	Oncologic Drugs Advisory Committee
ORR	overall response rate (CR + PR)
OS	overall survival
PFS	progression-free survival
PR	partial response
q12w	every 12 weeks
q2w	every two weeks
q3w	every three weeks
q4w	every four weeks
q6w	every six weeks
q8w	every eight weeks
q9w	every nine weeks
SAS	Statistical Analysis System
SGOT	serum glutamate oxaloacetate transaminase
SGPT	serum glutamate pyruvate transaminase
WHO	World Health Organization

1. INTRODUCTION

Requested Indication: “ELOXATINE™ (oxaliplatin) is indicated for the first-line treatment of patients with advanced colorectal cancer in combination with 5-FU-based chemotherapy.”

Proposed Dose and Schedule:

Oxaliplatin: 85 mg/m² (2-hour infusion) Day 1 every two weeks (q2w)
Folinic acid (FA): 200 mg/m² (2-hour infusion) followed by 5-fluorouracil
(5-FU): 400 mg/m² (bolus), 600 mg/m² (22-hour infusion) Days 1-2 q2w

Clinical experience with oxaliplatin is extensive. Originally developed by Roger Bellon (France), a subsidiary of Rhône-Poulenc Rorer, clinical development of oxaliplatin continued under the management of Debiopharm S.A. (Switzerland). Subsequently, Sanofi-Synthelabo licensed oxaliplatin for the United States and Europe, including France and other countries. Oxaliplatin (Eloxatin[®], Eloxatine[®], Dacplat[®]) was marketed in France in April 1996. A Mutual Recognition Procedure, with France serving as the Reference Member State, led to a first-line colorectal cancer approval in Europe in July 1999. Sanofi-Synthelabo entered into a US joint agreement with Eli Lilly and Company for registration, development, and marketing of oxaliplatin in 1999.

The New Drug Application (NDA) consists of 17 clinical investigations of oxaliplatin in patients with advanced colorectal cancer. Of these, eight Phase II/III trials have been designated as Primary Studies, on the basis of study design and conduct, consistent with 21 CFR 314.126 definitions; four are classified as controlled studies and support the efficacy of oxaliplatin in combination with 5-FU-based chemotherapy, and four provide corroborative support of the activity of oxaliplatin as a single agent (Table 1.). Nine clinical investigations in patients with advanced colorectal cancer are designated as Secondary Studies, including five Phase II/III studies and four compassionate-use trials. These studies are summarized in Appendix 1.

Table 1 - Primary Studies of the Efficacy of Oxaliplatin in Advanced Colorectal Cancer

Therapy	Design	Patient Population	Study
<i>Pivotal Trial</i> Oxaliplatin plus 5-FU/FA vs. 5-FU/FA	Controlled, randomized	First-line	EFC2962
<i>Supportive Trials</i> Oxaliplatin plus 5-FU/FA vs. 5-FU/FA	Controlled, randomized	First-line	EFC2961
Oxaliplatin plus 5-FU/FA	Patients act as own control	Second-line	EFC2964 EFC2917
Oxaliplatin monotherapy	Uncontrolled	First-line	EFC2960 EFC2963
		Second-line	EFC3105 EFC3106

5-FU=5-fluorouracil; FA=folinic acid

Based on the May 1998 FDA Guidance for Industry “*Providing Clinical Evidence of Effectiveness for Human Drug and Biological Products*,” the Sponsor has demonstrated the effectiveness of oxaliplatin in a study with independent substantiation from related study data. EFC2962, a multinational, first-line, randomized, Phase III trial, was the pivotal study. There are seven supportive trials that provide independent evidence of efficacy, the preponderance of which supports the pivotal trial, which fulfills the requirements of the guidance. Cross-substantiation of the indicated claim is demonstrated by consistent efficacy in another multinational, first-line, randomized, Phase III trial (EFC2961). Independent substantiation of the indicated claim by other supportive trials was demonstrated by studies in refractory patients (patients with documented evidence of disease progression on 5-FU-based therapy served as their own controls) (EFC2964 and EFC2917) and monotherapy studies of oxaliplatin (first- and second-line) (EFC2963, EFC2960, EFC3105, and EFC3106).

1.1 Epidemiology and current treatment of advanced colorectal cancer

Colorectal cancer is a major public health concern. According to the American Cancer Society, 129400 new cases of colorectal cancer are diagnosed each year, including 94700 cases of colon cancer and 34700 cases of rectal cancer. Although early detection and complete surgical resection can lead to cure in many cases, approximately 40% to 50% of patients ultimately develop unresectable, metastatic disease. Furthermore, 25% of patients present with metastatic disease at their initial diagnosis. In the United States, colorectal cancer is the second leading cause of cancer-related deaths, with annual mortality rates exceeding 50,000 [*Ca Cancer J Clin* (1999); 49:8-64].

Apart from adjuvant therapies that have reduced recurrence and increased survival in patients with nonmetastatic colorectal cancer, chemotherapy is most often used for palliation of metastatic disease. The agent most widely used in the treatment of colorectal

cancer is the antimetabolite, 5-FU. No other approved single agent has demonstrated better efficacy for first-line treatment than 5-FU.

Historically, objective responses to 5-FU monotherapy in previously untreated patients with advanced colorectal cancer have been modest ($\leq 15\%$); however, some studies indicated that 5-FU monotherapy prolonged survival over best supportive care [Bleiberg H. *Semin Oncol* (1996) 23:42-50; Scheithauer W et al. *Brit Med J* (1993); 306:752-755; VanHalteren H et al. *Anticancer Research* (1999); 19:3347-3350]. Modulation of 5-FU by leucovorin (folinic acid, FA) and methotrexate has improved objective response rate (15% to 40%) in patients with advanced colorectal cancer but has provided only modest prolongation of survival [Laufman R, et al. *J Clin Oncol* (1993) 11:1888-1893; Leichman CG, et al. *J Clin Oncol* (1995) 13:1303-1311; Advanced Colorectal Cancer Meta-Analysis Project. *J Clin Oncol* (1992) 10:896-903; Cunningham D. *Br J Cancer* (1998) 77(suppl 2):15-21; Doroshow JH, et al. *J Clin Oncol* (1990) 8:491-501]. The addition of other agents to 5-FU, including α -interferon, and cisplatin, has not produced consistent benefit [Advanced Colorectal Meta-Analysis Project. *J Clin Oncol* (1994) 12:960-969; Wadler S, et al. *J Clin Oncol* (1989) 7:1769-1775; Kemeny N et al. *J Clin Oncol* (1990) 8:313-318; Hansen R et al. *J Clin Oncol* (1996) 88:668-674; Lokich JJ, et al. *Cancer* (1991) 67:14-19; Raderer M, et al. *Eur J Cancer* (1995) 31:1002-1008]. Consequently, most patients develop progressive disease within months, and long-term response or survival remain rare with present standard therapy.

More recently, variations in 5-FU (\pm FA) schedules have been extensively studied in an attempt to improve efficacy. Common bolus schedules (daily bolus for 5 days or weekly bolus) have similar efficacy but different safety profiles [Buroker TR, et al. *J Clin Oncol* (1994) 12:14-20]. In small numbers of patients, antitumor responses have been observed with a continuous infusion of 5-FU after failure on bolus schedules [Mori A, et al. *Cancer Chemother Pharmacol* (1993) 33:179-180; Izzo J, et al. *Proc Am Assoc Cancer Res* (1992) 33:217]; no studies have reported activity of bolus regimens in patients resistant to infusional schedules. Recent meta-analysis of randomized trials [Meta-analysis Group in Cancer. *J Clin Oncol* (1998) 16:301-308] demonstrated that infusional regimens of 5-FU/FA produced higher response rates and slightly longer survival duration (22%, median of 12.1 months) than bolus regimens (14%, median of 11.3 months).

CPT-11 (irinotecan), a topoisomerase I inhibitor, recently received approval from the FDA for the treatment of patients with advanced colorectal cancer whose disease had recurred or progressed following 5-FU-based therapy. In this setting, CPT-11 has produced response rates of 9% to 21% and median survivals of 8.1 to 10.8 months [Product Information: Irinotecan HCl, Camptosar[®], Pharmacia & Upjohn Company], and with an acceptable risk of adverse events, such as myelosuppression and both early-onset and late-onset diarrhea.

Clinical benefits achieved with current 5-FU regimens remain relatively modest. Consequently, there is a need for more effective therapies in the management of patients with advanced colorectal cancer.

1.2 Mechanism of action of oxaliplatin

Oxaliplatin (trans-*l*-diaminocyclohexane oxalatoplatinum) is a novel divalent coordination complex of platinum consisting of an oxalato group and a 1,2-diaminocyclohexane (DACH) ligand (Figure 1.).

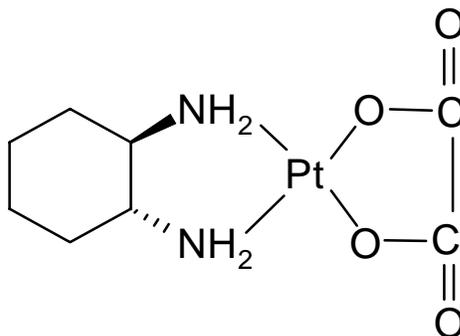


Figure 1 - Oxaliplatin Structure

The mechanism of action of oxaliplatin is dependent of the formation of intrastrand platinum (Pt)-DNA adducts/crosslinks, similar to that of other Pt compounds, including cisplatin. Oxaliplatin forms intrastrand Pt-DNA adducts between two adjacent or close guanines (GG or GNG) or adjacent guanine-adenine (GA) base pairs [Saris CP, et al. *Carcinogenesis* (1996)17:2763-2769]. The formation of these Pt-DNA crosslinks inhibits DNA replication and transcription and activates apoptotic signal transduction pathways which results in cell death. Like other Pt compounds, oxaliplatin can form, to a lesser extent, both Pt-interstrand crosslinks and Pt-DNA-protein crosslinks.

The types of Pt-DNA adducts formed by oxaliplatin are similar to those formed by cisplatin. However, the following nonclinical data suggest several unique attributes related to the cytotoxic/antitumor activity of oxaliplatin compared with cisplatin:

- Experimental data on naked and intracellular DNA demonstrate that oxaliplatin forms 2- to 10-fold less Pt-DNA adducts than cisplatin at equimolar and equitoxic concentrations. This observation suggests that oxaliplatin Pt-DNA adducts may be more cytotoxic than cisplatin Pt-DNA adducts [Woynarowski JM, et al. Institute for Drug Development (1996)].
- DACH-Pt DNA adducts formed by oxaliplatin are bulkier and more hydrophobic than cis-diamine-Pt DNA adducts formed by cisplatin and may be more inhibitory on DNA repair processes [Scheeff E, et al. *Mol Pharmacol* (1999) 56:633-643].
- DNA mismatch-repair complexes do not recognize DACH-Pt DNA adducts [Fink D, et al. *Cancer Res* (1996) 56:4881-4886; Fink D, et al. *Cancer Res* (1997) 57:1841-1845; Vaisman A et al. *Cancer Res* (1998) 58:3579-3585].

In other nonclinical studies, including the NCI Screening panel of 60 human cell lines, oxaliplatin demonstrates a broad spectrum of *in vitro* cytotoxic activity and *in vivo* antitumor activity that differs from that of both cisplatin or carboplatin [Kraker AJ, et al. *Cancer Res* (1988) 48:9-13; Pendyala L, et al. *Cancer Res* (1993) 53:5970-5976; Rixe O, et al. *Biochem Pharmacol* (1996) 52:1855-1865]. Oxaliplatin is active against several cisplatin-resistant cell lines, colon carcinoma, and other solid tumors that are not responsive to cisplatin [Kraker AJ, et al. *Cancer Res* (1988) 48:9-13; Rixe O, et al. *Biochem Pharmacol* (1996) 52:1855-1865; Kidani Y. *DN and P* (1989) 2:50-52; Kidani Y. *Trends Inorg Chem* (1991) 1:107-125; Mathé G, et al. *Biomed Pharmacother* (1989) 43:237-250]. In combination with 5-FU and other agents, oxaliplatin also exhibits *in vitro* and *in vivo* synergistic antiproliferative activity in several tumor models [Raymond E, et al. *Anti-Cancer Drugs* (1997) 8:876-885; Fischel J-L et al. *Clin Cancer Res* (1998) 4:2529-2535].

These results, combined with a favorable toxicology profile, supported the clinical development of oxaliplatin for the treatment of advanced colorectal cancer.

2. BACKGROUND

2.1 Experience with active comparators

2.1.1 5-fluorouracil and folinic acid regimens in previously untreated patients with advanced colorectal cancer

The standard therapy for the treatment of advanced colorectal cancer in previously untreated patients is 5-FU/FA. Two randomized, controlled studies (EFC2962 and EFC2961) compared the efficacy of oxaliplatin and 5-FU/FA with that of 5-FU/FA alone in this patient population. The infusional 5-FU/FA regimens that served as the control arms in these studies differ from the bolus regimens commonly used in the United States. To provide a context for results obtained with 5-FU/FA regimens used in oxaliplatin studies, a literature search was undertaken to survey antitumor responses observed with the daily bolus x 5 days regimen, one of the commonly used regimen in the United States. In addition, the results of a large randomized trial by de Gramont *et al.* [de Gramont A, et al. *J Clin Oncol* 1997;15:808-815] are presented in which the daily bolus x 5 days regimen of 5-FU/FA was directly compared with a bimonthly regimen used in oxaliplatin studies, EFC2962 and EFC2964. As discussed below, these findings will demonstrate that the 5-FU+FA regimens that served as control arms in oxaliplatin investigations are at least as effective as regimens commonly used in the United States. In addition, results of a recent meta-analysis comparing bolus and infusional 5-FU confirm these findings [Meta-analysis Group in Cancer. *J Clin Oncol* (1998) 16:301-308].

2.1.1.1 Historical overview of 5-fluorouracil regimens

The daily bolus x 5 regimen of 5-FU with high- or low-dose FA was one of the first regimens to show patient benefit, and it has very often been used as a control arm in clinical trials. A literature search in MEDLINE and DIALOG was conducted for all reports of randomized trials in which at least one arm contained the daily bolus x 5

regimen of 5-FU with either high- or low-dose FA in previously untreated patients with colorectal cancer.

Efficacy results presented in Table 2 demonstrate that PFS and overall survival have not significantly changed since 1984. Progression-free survival and overall survival ranged from 3.6 to 7.0 months and 9.3 to 14.9 months, respectively. Table 3 displays the percentages of patients surviving at one and two years that were estimated from published survival curves for these same studies. Reported response rates vary significantly between studies (range: 11-44%) as definitions (clinical and/or radiological endpoints), time intervals, methods (nuclear scans, ultrasound, CT scans), and independent/blinded assessments have changed and/or varied. Therefore, comparisons of response rates among clinical trials should be interpreted cautiously.

Table 2 - Studies Evaluating the Daily Bolus x 5 Days Regimen of 5-FU/FA in Previously Untreated Colorectal Cancer, Sorted by Last Year of Patient Enrollment

First Author	Year Last Patient Enrolled	Number of Patients		Response Rate (%)	Median		Method and Timing of Evaluations
		Enrolled	Measurable Disease		PFS (Months)	OS (Months)	
Budd [<i>J Clin Oncol</i> 1987;5:272-277]	1984	63	63	22%	NR	10.3	Scans, q8w
Erlichman [<i>J Clin Oncol</i> 1988;6:469-475]	1986	65	63	33%	5.1	12.6	Scans ^a , q8w
Valone [<i>J Clin Oncol</i> (1989) 7:1427-1436]	1987	107	101	19%	5.5	10.8	Scans ^a , q8w
Doroshov [<i>J Clin Oncol</i> (1990) 8:491-501]	1987	36	36	44%	5.5	14.4	Scans, clinical, q4w
Poon ^b [<i>J Clin Oncol</i> (1989) 7:1407-1418]	1987	73	53	43%	7.0	12	Clinical, q4w
Poon ^c [<i>J Clin Oncol</i> (1989) 7:1407-1418]	1987	69	53	26%	7.0	12.2	Clinical, q4w
Di Costanzo [<i>Ann Oncol</i> (1992) 3(5):371-376]	1989	91	77	16%	5.0	12.2	Scans, q8w
Labianca [<i>Ann Oncol</i> (1991) 2:673-679]	1989	92	92	21%	6.0	11.5	Scans, q12w
Loffler [<i>Dtsch Med Wochenschr (Germany)</i> (1992) 117:1007-1013]	1990	69	69	16%	NR	14.9	Scans, q12w
Buyse [<i>J Clin Oncol</i> (1992) 10:896-903]	1990	803	803	23%	NR	11.5	Meta-analysis
Buroker [<i>J Clin Oncol</i> (1994) 12:14-20]	1990	183	102	35%	5.0	9.3	Clinical, q4w
Corfu-A Group [<i>J Clin Oncol</i> (1995) 13:921-928]	1991	250	236	18%	4.0	11.3	Scans ^a , q8w
Borner [<i>Proc Ann Meet Am Soc Clin Oncol</i> (1992) 11:183]	1991	30	29	28%	NR	13.1	NR
Scheithauer [<i>Cancer</i> (1994) 73:1562-1568]	1992	68	68	19%	5.2	12.6	Clinical, q4w
Mustacchi [<i>Anticancer Res</i> (1994) 14(2B):617-619]	1992	116	105	18%	6.6	12.5	Clinical, NR
Leichman [<i>J Clin Oncol</i> (1995) 13:1303-1311]	1993	85	61	17%	6.0	14	NR, q4w
Valsecchi [<i>Proc Ann Meet Am Soc Clin Oncol</i> (1995) 14:A457]	1994	422	372	11%	6.0	10	NR
Cunningham ^d [<i>Br J Cancer</i> (1998) 77(suppl 2):15-21]	1994	216	204	17%	3.6	10.3	Clinical, q12w
Cunningham ^e [<i>Br J Cancer</i> (1998) 77(suppl 2):15-21]	1994	179	NR	15%	5.1	12.7	Clinical, q12w
Cunningham ^f [<i>Br J Cancer</i> (1998) 77(suppl 2):15-21]	1994	222	NR	18%	3.9	12.3	Clinical, q6w
de Gramont [<i>J Clin Oncol</i> (1997) 15:808-815]	1994	216	173	14%	5.1	13.1	Scans, q12w
Goldberg [<i>J Clin Oncol</i> (1997) 15:3320-3329]	1995	926	514	32%	5.8	12	Clinical, q8w

NR=not reported

^a Blinded assessment^b With low-dose FA^c With high-dose FA^d Data cited from reference 3 in Cunningham D. *Br J Cancer* (1998) 77(suppl 2):15-21^e Data cited from reference 10 in Cunningham D. *Br J Cancer* (1998) 77(suppl 2):15-21^f Data cited from reference 12 in Cunningham D. *Br J Cancer* (1998) 77(suppl 2):15-21

Table 3 - One- and Two-Year Survival Estimates in Studies Evaluating the Daily Bolus x 5 Days Regimen of 5-FU/FA in Previously Untreated Colorectal Cancer

First Author	Year Last Patient Enrolled	Number of Patients Enrolled	One-year Survival (%)	Two-year Survival (%)
Budd [<i>J Clin Oncol</i> 1987;5:272-277]	1984	63	48%	NR ^a
Erlichman [<i>J Clin Oncol</i> 1988;6:469-475]	1986	65	52%	21%
Valone [<i>J Clin Oncol</i> (1989) 7:1427-1436]	1987	107	45%	18%
Doroshov [<i>J Clin Oncol</i> (1990) 8:491-501]	1987	36	55%	22%
Poon ^b [<i>J Clin Oncol</i> (1989) 7:1407-1418]	1987	73	50%	24%
Poon ^c [<i>J Clin Oncol</i> (1989) 7:1407-1418]	1987	69	50%	20%
Di Costanzo [<i>Ann Oncol</i> (1992) 3(5):371-376]	1989	91	52%	16%
Labianca [<i>Ann Oncol</i> (1991) 2:673-679]	1989	92	48%	18%
Loffler [<i>Dtsch Med Wochenschr (Germany)</i> (1992) 117:1007-1013]	1990	69	55%	16%
Buyse [<i>J Clin Oncol</i> (1992) 10:896-903]	1990	803	48%	16%
Buroker [<i>J Clin Oncol</i> (1994) 12:14-20]	1990	183	42%	17%
Corfu-A Group [<i>J Clin Oncol</i> (1995) 13:921-928]	1991	250	47%	16%
Borner [<i>Proc Ann Meet Am Soc Clin Oncol</i> (1992) 11:183]	1991	30	No survival curves	
Scheithauer [<i>Cancer</i> (1994) 73:1562-1568]	1992	68	45%	NR ^a
Mustacchi [<i>Anticancer Res</i> (1994) 14(2B):617-619]	1992	116	No survival curves	
Leichman [<i>J Clin Oncol</i> (1995) 13:1303-1311]	1993	85	55%	22%
Valsecchi [<i>Proc Ann Meet Am Soc Clin Oncol</i> (1995) 14:A457]	1994	422	No survival curves	
Cunningham ^d [<i>Br J Cancer</i> (1998) 77(suppl 2):15-21]	1994	216	45%	NR ^a
Cunningham ^e [<i>Br J Cancer</i> (1998) 77(suppl 2):15-21]	1994	179	No survival curves	
Cunningham ^f [<i>Br J Cancer</i> (1998) 77(suppl 2):15-21]	1994	222	54%	NR ^a
de Gramont [<i>J Clin Oncol</i> (1997) 15:808-815]	1994	216	54%	22%
Goldberg [<i>J Clin Oncol</i> (1997) 15:3320-3329]	1995	926	50%	19%

NR=not reported

^a Could not be estimated from the survival curves

^b With low-dose FA

^c With high-dose FA

^d Data cited from reference 3 in Cunningham D. *Br J Cancer* (1998) 77(suppl 2):15-21

^e Data cited from reference 10 in Cunningham D. *Br J Cancer* (1998) 77(suppl 2):15-21

^f Data cited from reference 12 in Cunningham D. *Br J Cancer* (1998) 77(suppl 2):15-21

REF: Published reports

2.1.1.2 Comparison of daily bolus and bimonthly regimens of 5-fluorouracil and folinic acid

The Bimonthly Bolus+Infusion regimen of 5-FU/FA was directly compared with the Daily x 5 regimen in a large European trial conducted by de Gramont *et al.* [*J Clin Oncol* (1997) 15:808-815]. This report is referred to as the “Intergroup Trial” in this Briefing Document; a copy of this article is included in Appendix 2. A total of 448 patients with measurable advanced colorectal cancer were randomly assigned to receive the Bimonthly Bolus+Infusion regimen (FA: 200 mg/m², 2-hour infusion; 5-FU: 400 mg/m² bolus, followed by 600 mg/m², 22-hour infusion for two days) or the Daily x 5 regimen (FA: 20 mg/m², bolus; 5-FU: 425 mg/m², daily bolus for five days). The Bimonthly Bolus+Infusion regimen of 5-FU/FA was the same as that administered in EFC2962 and in one stratum of EFC2964, and was based on evidence that a combined bolus and continuous infusion schedule of 5-FU was well tolerated and permitted the delivery of

higher 5-FU doses [de Gramont A, et al. *Eur J Cancer Oncol* (1988) 24:1499-1503; Johnson PWM, et al. *Br J Cancer* (1991) 64:603-605]. The Daily x 5 regimen of 5-FU/FA was given every four weeks until progression, instead of at four and eight weeks and every five weeks thereafter, as reported in the original series [Poon MA, et al. *J Clin Oncol* (1989) 7:1407-1418]. Results of this trial as published by de Gramont are displayed in Table 4.

Table 4 - Comparison of Daily x 5 and Bolus+Infusion 5-FU/FA Regimens:

Regimen (N)	Response Rate (%)	Median PFS (Weeks)	Median OS (Weeks)	Grade 3-4 Toxicity (%)
Daily x 5 (173)	14.4%	22	56.8	23.9%
Bolus+Infusion (175)	32.6%	27.6	62.0	11.1%
p-value (two-tailed)	p=0.0004 ^a	p=0.001 ^b	p=0.067 ^b	p=0.0004 ^a

PFS=progression-free survival; OS=overall survival

^a Mantel-Haenszel test, with adjustment by stratification criteria [Mantel N, et al. *J Natl Cancer Inst* (1959) 22:719-748]

^b Stratified log-rank test, two-tailed

REF: de Gramont et al. *J Clin Oncol* 1997;15:808-815

The response rate and PFS were significantly better in the Bimonthly Bolus+Infusion arm than in the Daily x 5 arm. In addition, the incidence of Grade 3-4 toxicity was significantly lower in the Bimonthly Bolus+Infusion arm than in the Daily x 5 arm. Although overall survival did not differ significantly between treatment arms (p=0.067, two-tailed, stratified log-rank test), overall survival in the Bimonthly Bolus+Infusion arm was longer than that reported for the Daily x 5 regimen.

The FDA requested that Sanofi-Synthelabo obtain the data for this cooperative group trial as a bridge to demonstrate unequivocally that the Bimonthly Bolus+Infusion 5-FU/FA regimen used as a control in EFC2962 and as previous treatment in EFC2964 was equivalent to or better in efficacy and safety than bolus regimens commonly used in the United States. Sanofi-Synthelabo obtained primary source data for this trial, has independently reviewed each case report form and all available source documents, and has prepared a new database containing all available data. Sanofi-Synthelabo has reanalyzed the data from this trial and the results are displayed in Table 5. The results from this re-analysis are consistent with those published by the Investigator.

Table 5 - Independent Reanalysis of the Intergroup Trial

Regimen (N)	Response Rate (%)	Median PFS (Weeks)	Median OS (Weeks)	Grade 3-4 Toxicity (%)
Daily x 5 (173)	13.3%	23.0	56.9	24.5%
Bolus+Infusion (175)	28.0%	27.4	61.9	12.1%
p-value (two-tailed)	p=0.001 ^a	p=0.0089 ^b	p=0.22 ^b	p < 0.001 ^a

PFS=progression-free survival; OS=overall survival

^a Chi-Squared test

^b Log-rank test, two-tailed

Figure 2 shows the Kaplan-Meier survival curves by treatment group. There were 18 (8.3%) censored Daily x 5 data points and 21 (9.7%) censored Bolus+Infusion data points.

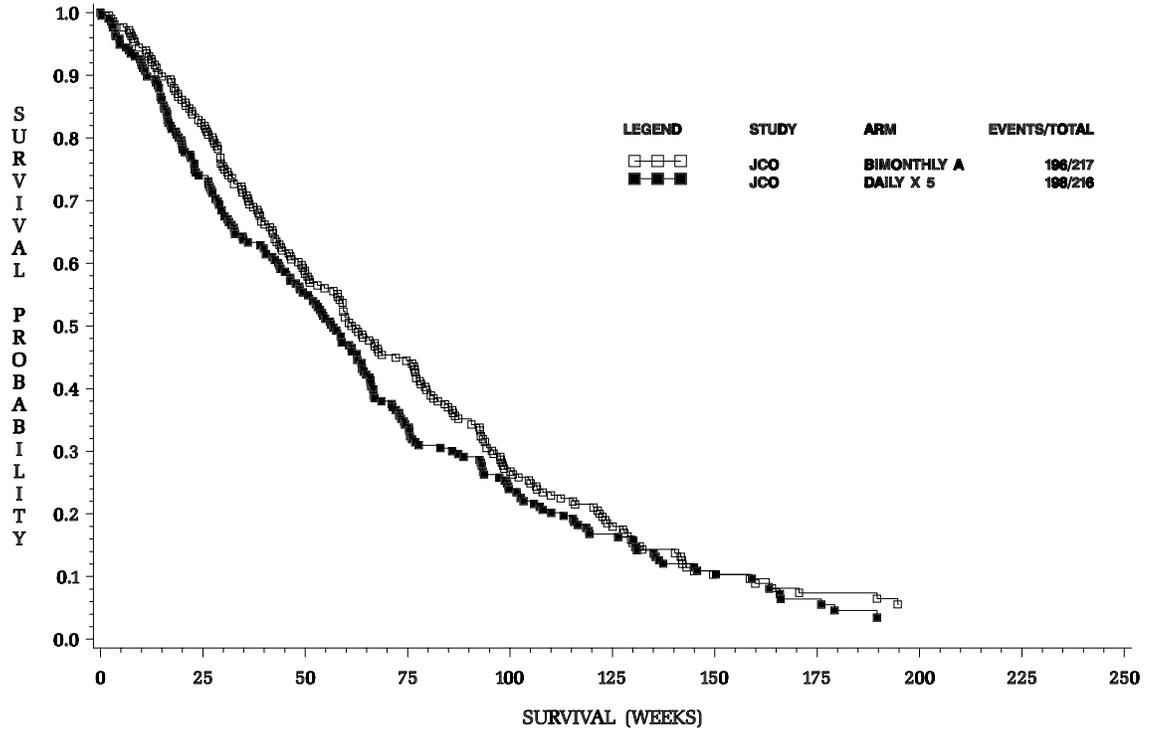


Figure 2 - Inter Group Trial Kaplan-Meier Survival Curve by Treatment Group Based on the Independent Re-analysis

From the Kaplan-Meier analysis of survival for all randomized patients, the estimate of median survival was 56.9 weeks (13.1 months; 95% confidence interval of 48.6 to 63.9 weeks) for the Daily x 5 5-FU/FA patients compared to 61.9 weeks (14.3 months; 95% confidence interval of 53.0 to 76.7 weeks) for the Bolus+Infusion 5-FU/FA patients. The median survival for both treatment arms compares favorably with the results given in the meta-analysis publication [Meta-analysis Group in Cancer. *J Clin Oncol* (1998) 16:301-308]. Therefore, the Bimonthly Bolus+Infusion regimen represents an acceptable control arm for use in clinical trials with oxaliplatin.

2.2 Oxaliplatin dose justification

Two Phase I clinical trials (TDU3099 and TDU3131) explored a wide range of oxaliplatin doses and identified the dose-limiting toxicity and the recommended dose for Phase II/III studies. In study TDU3099, oxaliplatin was given q3w at doses ranging from 45 to 200 mg/m². A dose level of 200 mg/m² of oxaliplatin was found to be the maximum tolerated dose, and a cumulative, reversible sensory neuropathy was identified as the

dose-limiting toxicity. Consistent with these findings, a maximum tolerated dose of 180 mg/m² was reported in study TDU3131, in which oxaliplatin was administered every three to four weeks at doses ranging from 20 to 180 mg/m². The antitumor response and safety profile of oxaliplatin observed in these studies supported the design of Phase II/III studies at a recommended dose of 130 or 135 mg/m² given as a short (2- to 6-hour) intravenous infusion q3w.

The efficacy of oxaliplatin 85 mg/m² administered in combination with 5-FU/FA q2w was also investigated in three Phase II/III studies (EFC2962, EFC2964, and EFC2917). This dose level provided the same dose intensity as the 130 mg/m² q3w regimen and allowed oxaliplatin to be administered in combination with Bimonthly Bolus+Infusion 5-FU/FA regimens. Both dosing regimens of oxaliplatin, either q3w or q2w, exhibited acceptable safety profiles. The two regimens are pharmacokinetically equivalent with respect to cumulative AUC.

3. PIVOTAL STUDY: EFC2962

Study EFC2962 was a multicenter, first-line, randomized, controlled Phase III study that compared the efficacy and safety of oxaliplatin in combination with 5-FU/FA with the efficacy and safety of 5-FU/FA alone. Patients with unresectable, histologically-proven adenocarcinoma of the colon or rectum were eligible to receive 5 FU+FA with or without oxaliplatin. The primary endpoint of the trial was progression-free survival; secondary endpoints included response rate (confirmatory scan obtained at least four weeks), overall survival, safety, and quality of life.

For patients to be included in this study, at least one bidimensionally measurable lesion had to exceed 2 cm. Previous chemotherapy or radiotherapy for metastatic disease was not allowed, although adjuvant chemotherapy or radiotherapy was permitted provided that treatment was completed six months before study enrollment. Only patients aged 18-75 years with a performance status ≤2, a life expectancy >3 months, and adequate chemistries and bone marrow reserve were enrolled. The study design is presented in Figure 3.

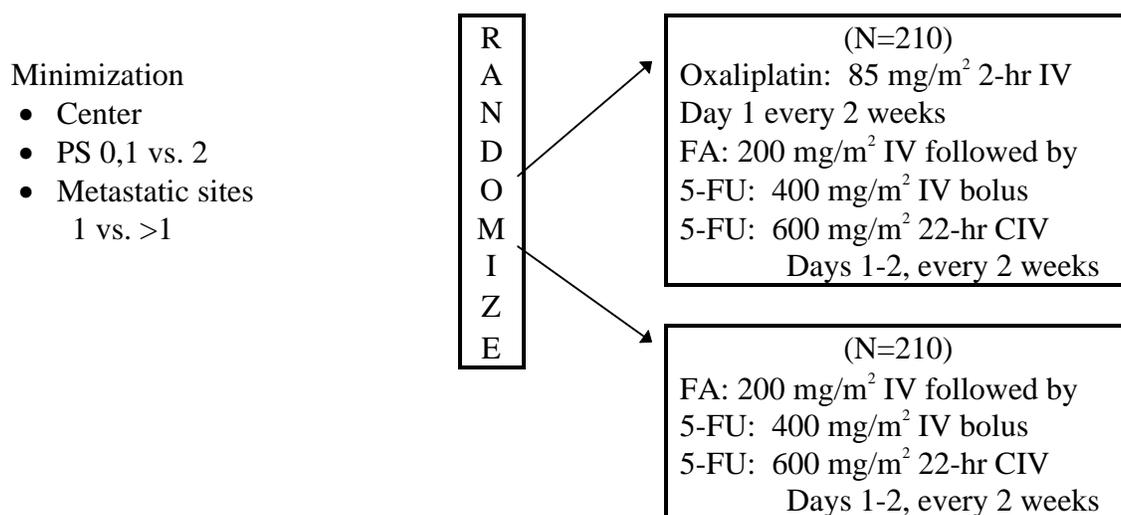


Figure 3 - Phase III Trial of Bimonthly Bolus and Infusion 5-FU/FA With or Without Oxaliplatin Pivotal Trial: EFC2962

The 5-FU/FA regimen used in EFC2962 (Bimonthly Bolus+Infusion) was identical to the Bimonthly Bolus+Infusion regimen used in the Intergroup Trial that was shown to be similar, if not slightly superior to, the Daily x 5 regimen (Section 2.1.1.2). Oxaliplatin was administered on Day 1 as a 2-hour infusion followed by administration of 5-FU. Treatment was continued until withdrawal from the study due to disease progression, a toxicity/adverse event, patient refusal, Investigator decision, loss of patient to follow-up, or death.

The trial methods included an independent assessment of response and progression; use of intent-to-treat (all randomized patients) analyses; and planned adjustment for prospectively defined prognostic factors. Planned disease imaging assessments were to be performed every 8 weeks, i.e., every 4 cycles, with confirmation at 4 weeks.

The statistical design included the following:

- Total study population: Planned N=400 (200 patients per arm)
Enrolled N=420 (210 patients per arm)
- Follow-up for a given patient was not to exceed 35 months
- H₀: No difference in PFS
- H_A: 43% difference in median PFS (from 7 to 10 months)
- Alpha=0.05; power ≥80%
- Two planned interim analyses based on response
 - early stopping rule
 - one formal interim analysis

The final analyses of overall survival in EFC2962 were guided by those described in the protocol and in the more detailed statistical analysis plan submitted to the FDA on 19 February 1998 prior to the 08 July 1998 cut-off date. Specifically, the protocol for EFC2962 stated that overall survival “will be compared between the two treatment arms using the log-rank test. Further explanatory analyses will be performed to adjust the treatment comparison for accidental bias in using multivariate models. Proportional hazard models will include predictive estimates {prognostic factors} at inclusion, such as performance status. Such analyses will complement but not replace the unadjusted analyses.”

3.1 Demographics and other baseline characteristics

Table 6 presents the demographic characteristics at baseline for all patients enrolled in EFC2962. The patients ranged in age from 21 to 76 years, with a median age of 63 years. In this study, 413 (98%) patients were Caucasian and four (1%) patients were non-Caucasian; race was not reported for three (1%) patients. The majority of patients had a baseline performance status of 0 or 1.

Table 6 - Selected Demographic Characteristics: EFC2962

Characteristic	EFC2962		p-Value
	5-FU/FA (N=210)	Oxal 85+ 5-FU/FA (N=210)	
Age			0.97 (t-Test)
Median, years	63.0	63.0	
Minimum, years	23	21	
Maximum, years	76	76	
Gender, n (%)			0.62 (Chi-Square)
Male	122 (58.1%)	127 (60.5%)	
Female	88 (41.9%)	83 (39.5%)	
WHO performance status, n (%)			0.56 (Chi-Square)
0	89 (42.4%)	85 (40.5%)	
1	99 (47.1%)	103 (49.0%)	
2	22 (10.5%)	22 (10.5%)	

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As shown in Table 7, the majority of patients presented with an initial diagnosis of Dukes Stage D colon cancer. At baseline, most patients presented with metastases in the liver, an alkaline phosphatase <Grade 2, and a carcinoembryonic antigen (CEA) value >10 ng/mL. Although not statistically significant, there appears to be more patients with alkaline phosphatase ≥ 2 in the oxaliplatin-containing arm (13.3% vs. 7.6%).

Table 7 - Baseline Characteristics: EFC2962

Characteristic	EFC2962		p-Value
	5-FU/FA (N=210)	Oxal 85+ 5-FU/FA (N=210)	
At study entry			
Primary tumor site, n (%)			0.67 (Chi-Square)
Colon	147 (70.0%)	151 (71.9%)	
Rectum	61 (29.0%)	59 (28.1%)	
Colon+rectum	2 (1.0%)	0	
Dukes stage, n (%)			0.60 (Chi-Square)
A	1 (0.5%)	1 (0.5%)	
B	28 (13.3%)	28 (13.3%)	
C	41 (19.5%)	41 (19.5%)	
D	139 (66.2%)	135 (64.3%)	
Missing	1 (0.5%)	5 (2.4%)	
At baseline			
Number of organs involved, n (%)			0.84 (Chi-Square)
1	84 (40.0%)	90 (42.9%)	
2	83 (39.5%)	76 (36.2%)	
3	31 (14.8%)	34 (16.2%)	
>3	12 (5.7%)	10 (4.8%)	
Organs involved, n (%)			
Liver	173 (82.4%)	182 (86.7%)	0.22 (Chi-Square)
Lung	65 (31.0%)	53 (25.2%)	0.19 (Chi-Square)
Other	103 (49.0%)	107 (51.0%)	0.15 (Chi-Square)
Alkaline phosphatase			0.17 (Chi-Square)
<2	194 (92.4%)	182 (86.7%)	
≥ 2	16 (7.6%)	28 (13.3%)	
Prior adjuvant chemotherapy			0.90 (Chi-Square)
No	167 (79.5%)	168 (80.0%)	
Yes	43 (20.5%)	42 (20.0%)	
CEA, n (%)			0.36 (Chi-Square)
≤ 10 ng/mL	54 (25.7%)	46 (21.9%)	
>10 ng/mL	148 (70.5%)	156 (74.3%)	
Missing	8 (3.8%)	8 (3.8%)	

3.2 Exposure to study treatments

Table 8 presents a summary of dosing in Study EFC2962 by cycle and Table 9 presents a summary of median relative dose intensity and dose reductions/dose delays.

Table 8 - Summary of Exposure by Cycle: Study EFC2962

Cycles	5-FU/FA	Oxal 85+5-FU/FA
Total	2432	2595
Median	11	12
Range	[1-40]	[1-35]

Table 9 - Summary of Median Relative Dose Intensity and Dose Reductions/Delays: Study EFC2962

	5-FU/FA	Oxal 85 + 5-FU/FA
Median relative dose intensity		
Oxaliplatin	—	73%
5-FU bolus	89%	76%
By patient		
Dose reduction	24%	66%
Dose delay	61%	86%
By Cycle		
Dose reduction	9%	39%
Dose delay	13%	29%

3.3 Efficacy

A cut-off date of 08 July 1998 for overall survival had been prospectively determined in the protocol as the date corresponding to the planned duration of the study (i.e., 35 months from the date of first patient randomization).

3.3.1 Progression-free survival

The progression-free survival was defined as the time from randomization until the time that the patient was classified as having progressive disease or death. For patients without a classification of progressive disease or death as of 31 January 1998, the date of last follow-up without progression was used as the date of the terminal event, and the progression-free survival was considered to be right-censored for purposes of these analyses.

Figure 4 shows the Kaplan-Meier progression-free survival curve for all randomized patients by treatment group. At the cutoff date of 31 January 98, 171 (81%) of the patients in the 5-FU/FA arm had progressed while 150 (71%) patients in the oxaliplatin+5-FU/FA arm had progressed.

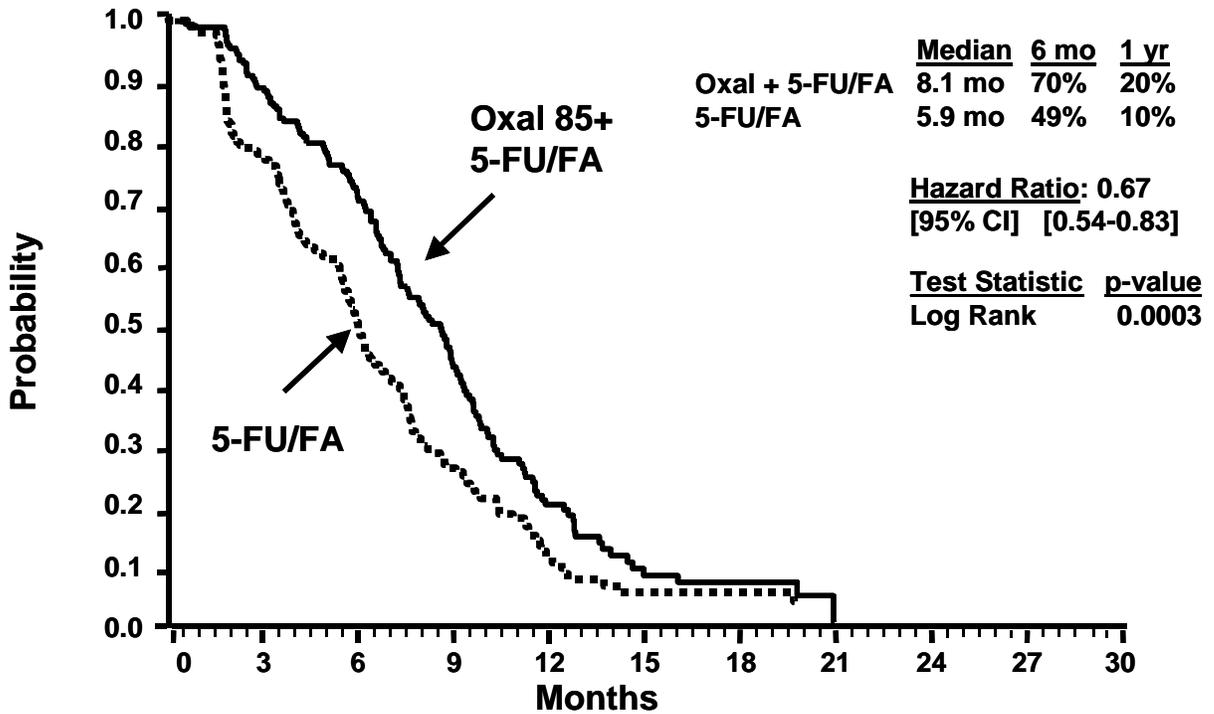


Figure 4 - Study EFC2962 Kaplan-Meier Progression-Free Survival Curve for All Patients by Treatment Group

Progression-free survival is summarized in Table 10. The estimate of median progression-free survival was 5.9 months (95% confidence interval of 5.5 to 6.4 months) for 5-FU/FA patients and 8.1 months (95% confidence interval of 7.1 to 8.8 months) for oxaliplatin plus 5-FU/FA patients, which represents a 37% increase in median survival. The hazard ratio was 0.67 (95% confidence interval of 0.54 to 0.83). The probability of progression-free survival lasting at least 6 months was estimated to be 70% for oxaliplatin plus 5-FU/FA patients and 49% for 5-FU/FA patients. The probability of progression-free survival lasting at least 1 year was estimated to be 20% for oxaliplatin plus 5-FU/FA patients and 10% for 5-FU/FA patients. The Log-Rank test showed a statistically significant difference with a p-value=0.0003 in progression-free survival in favor of oxaliplatin plus 5-FU/FA therapy.

Table 10 - Study EFC2962: Progression-Free Survival Summary (months)

	5-FU/FA (N=210)	Oxal 85+ 5-FU/FA (N=210)
Minimum	0.6	0.3
25 th Percentile	3.4	5.5
Median	5.9	8.1
75 th Percentile	9.1	11.1
Maximum	24 ^a	20.9 ^a
6-month PFS Probability	49%	70%
9-month PFS Probability	25%	41%
12-month PFS Probability	10%	20%

^a Censored

3.3.2 Overall response rate

Radiological evaluations of antitumor responses were performed at baseline and every eight weeks by the Investigators and by at least two independent radiologists. WHO definitions were used for response assessments (CR, PR, SD/NC, or PD) (Primary Table 1.).

Among the 420 randomized patients, radiological scans of 383 patients (91.2%) were reviewed by the independent radiologists; scans were not available for the remaining 37 patients (8.8%). Patients for whom radiological scans were unavailable were included as nonresponders in the analysis. These confirmed response rates were based on two assessments separated by an interval of at least four weeks. Best response rate (defined as confirmed and unconfirmed responses) in the oxaliplatin treatment arm was greater than 50%.

Table 11 summarizes the Independent evaluation of response rate for the ITT population. In both studies, the confirmed response rate (complete and partial responses) was significantly higher for patients who received oxaliplatin and 5-FU/FA than for patients who received 5-FU/FA alone. Oxaliplatin in combination with 5-FU/FA produced a confirmed response rate of 49%, compared with 22% in the control arm, with no overlap in confidence intervals.

Table 11 - Overall Response Rate Based on Independent Assessments: EFC2962

Overall Response Rate	5-FU/FA (N=210)	Oxal 85+ 5-FU/FA (N=210)
Confirmed response rate ^{a,b} , % [95% confidence intervals]	21.9% [16.5-28.2]	49.0% [42.1-56.1]
p-value (chi-square test, two-tailed)	<0.001	
Number of complete responses ^c	1	3
Number of partial responses ^c	45	100
Best response rate ^c , % [95% confidence intervals]	29.0% [23.0-35.7]	55.7% [48.7-62.6]
p-value (chi-square test, two-tailed)	<0.001	

^a Responses observed on at least two consecutive evaluations, separated by four weeks

^b Excludes two patients in EFC2962 whose partial responses were confirmed by CT scan only 23-24 days, rather than 28 days, after the original assessment

^c Confirmed and unconfirmed responses

3.3.3 Overall survival

Figure 5 shows the Kaplan-Meier survival curves for all randomized patients by treatment group. There were 90 (43%) censored oxaliplatin plus 5-FU/FA data points and 79 (38%) censored 5-FU/FA data points. Median follow-up was 20 months.

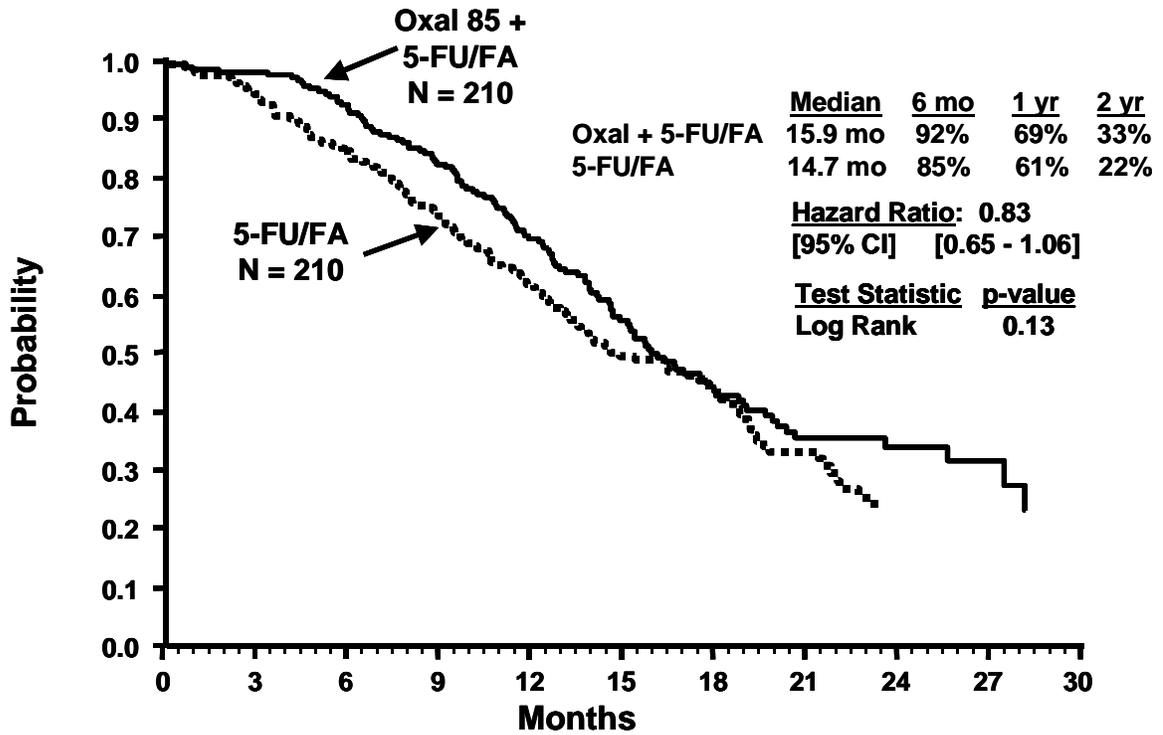


Figure 5 - Study EFC2962 Kaplan-Meier Survival Curves for All Patients by Treatment Group

From Kaplan-Meier analysis of survival for all randomized patients, the estimate of median survival was 15.9 months (95% confidence interval of 14.7 to 18.0 months) for oxaliplatin plus 5-FU/FA patients compared to 14.7 months survival (95% confidence interval of 13.0 to 18.0 months) for 5-FU/FA patients. The hazard ratio was 0.83 (95% confidence interval of 0.65 to 1.06). One-year survival probability was estimated to be 69% for oxaliplatin plus 5-FU/FA patients and 61% for 5-FU/FA patients, while 2-year survival probability was estimated to be 33% for oxaliplatin plus 5-FU/FA patients and 22% for 5-FU/FA patients.

Table 12 presents summary statistics from the output of the Kaplan-Meier survival analysis for all randomized patients.

Table 12 - Study EFC2962 Survival Summary (months)

	5-FU/FA (N=210)	Oxal 85+ 5-FU/FA (N=210)
Minimum	0.6	0.6
25 th Percentile	8.6	10.9
Median	14.7	15.9
75 th Percentile	22.9	28.4
Maximum	33.1 ^a	31.0 ^a
6-month Survival Probability	85%	92%
9-month Survival Probability	73%	82%
12-month Survival Probability	61%	69%
24-month Survival Probability	22%	33%

^a Censored

Despite a survival benefit appearing early in favor of the oxaliplatin arm, the log rank test did not reach significance (p=0.13). However, protocol-planned Cox regression analysis produced a larger and more appropriate estimate of treatment effect. Adjusting for baseline performance status, number of involved organs, and baseline alkaline phosphatase, a significant survival benefit was demonstrated for oxaliplatin+5-FU/FA (p=0.01), with a hazard ratio of 0.70 (95% confidence interval 0.54-0.92). Clinically, this means that patients receiving oxaliplatin+5-FU/FA as first-line treatment experienced a reduction in mortality risk of 30%, with an observable benefit within the first six months of treatment.

The Sponsor believes the results from the Cox regression analysis more accurately estimate the survival benefit with oxaliplatin. Inclusion of the alkaline phosphatase term corrects for a disproportionate number of patients in the oxaliplatin arm with significant elevations at baseline. Details are found in Section 3.3.4.

3.3.4 Cox regression model

The detailed statistical analysis plan for EFC2962 stated that “a multivariate analysis (stepwise procedure) will be provided,” using the predefined prognostic factors shown below and other “pertinent” parameters. Predefined prognostic factors included in the multivariate analyses, with definitions, are shown in Table 13. Explanatory analyses are presented in Appendix 3.

Table 13 - Definitions of Prognostic Factors of Overall Survival in EFC2962

Prognostic Factor	Criteria
Center	per investigator site
Age	<65, ≥65 years of age
Sex	Male, female
WHO performance status at baseline	≤1, 2
Liver metastases at baseline	Yes, no
Astler and Coller's stages at diagnosis ^a	(A, B1, B2, C1, C2) vs. D
Number of organs with metastases	1, ≥2
Primary site	Colon, rectum ^b
Prior chemotherapy	Yes, no
Prior radiotherapy	Yes, no
Liver function tests (NCI toxicity scale)	
SGOT ^c	0, ≥1
SGPT ^c	0, ≥1
Alkaline phosphatase	≤1, ≥2
Renal function (creatinine, NCI toxicity scale) ^c	0, ≥1

Note: Oxaliplatin was commercially available in France (Centers 1-11), but not other countries. This factor potentially represents influence of availability of second line oxaliplatin.

^a Reported here as synchronous metastases (yes, no). Stage D was coded as “yes” and Stages A, B1, B2, C1, and C2 were coded as “no”.

^b Patients with primary site in both the colon and rectum were classified as “rectum”.

^c The original categories were to be Grades ≤1 and Grades ≥2, consistent with the association of clinical impairment with Grades ≥2. Because an insufficient number of patients had a Grade of 2, a cutoff of ≥1 was used.

3.3.4.1 Stepwise multivariate analysis based on the Cox regression model

The results of the stepwise regression analysis, presented in Table 14, included the following factors in the final model for overall survival: treatment arm, WHO performance status at baseline, baseline alkaline phosphatase (NCI grade.), and number of involved organs. The adjusted estimated risk ratio (oxaliplatin/control) was 0.70 (95% confidence limits, 0.54-0.92), yielding a significant effect of oxaliplatin in combination with 5-FU/FA on overall survival at the 0.010 level.

Table 14 - Factors Predictive of Overall Survival in EFC2962

Factor	Risk Ratio	95% CI	p-Value
Treatment arm	0.70	0.54 - 0.92	0.010
WHO performance status	2.31	1.60 - 3.43	0.0001
Baseline alkaline phosphatase	2.40	1.64 - 3.50	0.0001
Number of involved organs	1.49	1.14 - 1.95	0.0038

The results demonstrate that the unadjusted comparison (log-rank test) and the adjusted comparison (stepwise regression model) of overall survival in the two treatment arms of EFC2962 differed; the effect of oxaliplatin and 5-FU/FA on overall survival was not significant using the unadjusted log-rank test, but was significant when adjusted by baseline factors predictive of overall survival (Figure 6.). In addition, the estimated risk ratio is much lower after adjustment (0.70) with 95% confidence limits that do not include 1.0 (0.54-0.92). The unadjusted risk ratio was 0.83, with 95% confidence limits of 0.65-1.06.

Since the two planned analyses produced meaningfully different estimates of the oxaliplatin effect on survival, the Sponsor conducted additional analyses to try to understand the difference. From these analyses it can be seen that: 1) alkaline phosphatase elevation at baseline is an important risk factor for survival; and 2) a moderately greater proportion of patients in the oxaliplatin+5-FU/FA arm had elevated alkaline phosphatase levels at baseline. Inclusion of alkaline phosphatase into the Cox regression model corrects for the imbalance in alkaline phosphatase at baseline. Therefore, it is the Sponsor’s opinion that the survival benefit with oxaliplatin is more accurately estimated in the Cox regression analysis.

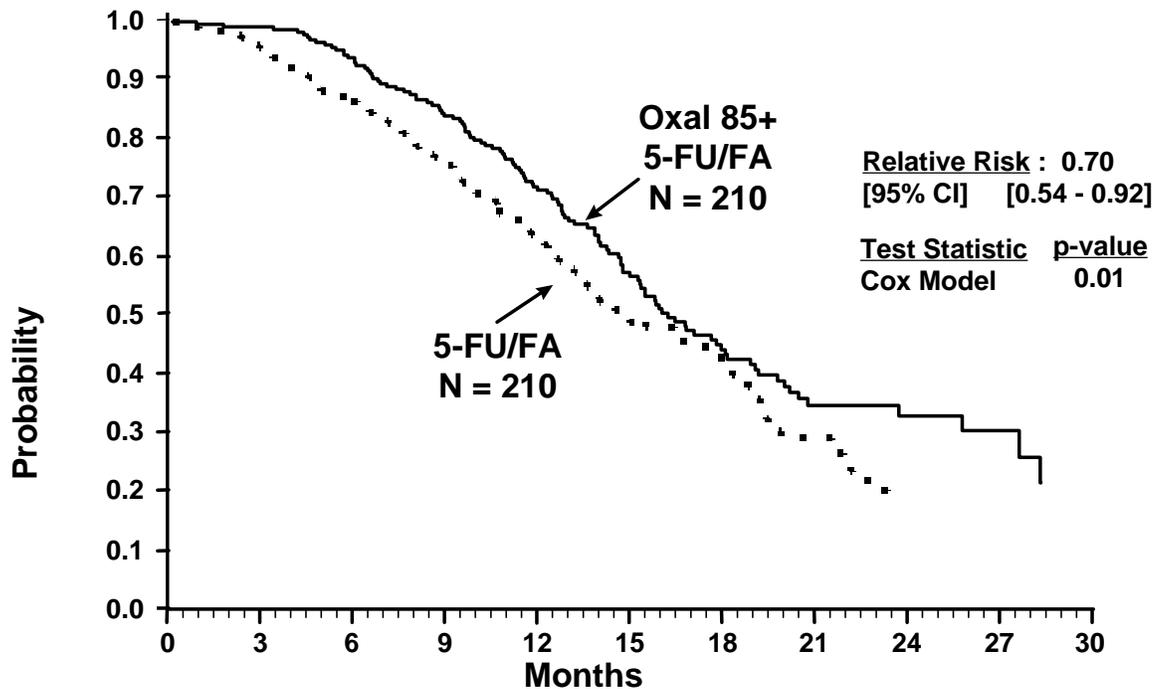


Figure 6 - Study EFC2962 Kaplan-Meier Survival Curves for All Patients by Treatment Group Adjusted for Alkaline Phosphatase, Baseline Performance Status, and Number of Organs Involved

3.3.5 Post-study chemotherapy

During the conduct of EFC2962, effective agents (CPT-11 and oxaliplatin) were approved for use in advanced colorectal cancer. Table 15 shows that 46% of the patients in the 5-FU/FA treatment arm and 41% of patients in the oxaliplatin+5-FU/FA treatment arm received additional post-study chemotherapy. While it is not possible to precisely estimate the effect of post-study chemotherapy in this trial, it is reasonable to infer that the best estimate of survival benefit with oxaliplatin would come from the early part of the survival curves.

Table 15 - Study EFC2962 Distribution of Patients by Post-Study Therapy with Oxaliplatin and or CPT-11

Post Study Therapy	5-FU/FA	Oxal 85 + 5-FU/FA
Post-study chemotherapy (any)	96 (46%)	86 (41%)
Post-study Oxaliplatin	47 (22%)	15 (7%)
Post-study CPT-11	38 (18%)	55 (26%)
Post-study Oxaliplatin and/or CPT-11 ^a	69 (33%)	64 (30%)

^a Includes patients who received CPT-11 or oxaliplatin or CPT-11 plus oxaliplatin at any time post study.

3.3.6 Efficacy summary

The Bimonthly Bolus+Infusion control arm in EFC2962 produced results similar to those achieved with the same regimen in the Intergroup Trial. In the Intergroup Trial the Bimonthly Bolus+Infusion was compared to the Daily x 5 bolus regimen and had slightly longer survival with statistically significant superiority in terms of response rate and PFS. Results from EFC2962 compared to the Intergroup Trial were 1) response rate: 21.9% versus 28.0%; 2) median PFS: 5.9 months versus 6.3 months; and 3) median survival 14.7 months versus 14.2 months. Thus, the control arm for EFC2962 performed at least as well as a daily x 5 bolus 5-FU/FA regimen and provided an adequate test for the addition of oxaliplatin.

In study EFC2962, the addition of oxaliplatin to the Bimonthly Bolus+Infusion regimen of 5-FU/FA demonstrated an improvement in the primary endpoint of PFS, with a median PFS of 8.1 months (95% confidence limits of 7.1 to 8.8 months) versus a median of 5.9 months (95% confidence limits of 5.5 to 6.4 months) in the arm receiving 5-FU/FA. This difference was statistically significant ($p=0.0003$, by the log rank test).

Forty-nine percent (49%) of the patients who were randomized to the oxaliplatin+5-FU/FA arm experienced a confirmed response. This was more than double the confirmed response rate among patients receiving 5-FU/FA alone (21.9%), and this difference was statistically significant ($p<0.001$, by the Chi-squared test).

Addition of oxaliplatin to 5FU/FA was also associated with a survival benefit appearing within the first six months after the start of treatment and continuing beyond 15 months. Median survival was 15.9 months in the oxaliplatin+5-FU/FA arm and 14.7 months in the control arm. Protocol-planned adjustment for baseline prognostic factors produced an estimated mortality hazard ratio of 0.70 (95% confidence limits of 0.54 to 0.92, $p=0.01$). This corresponds to a mortality reduction of 30%.

Together, these data provide compelling evidence that the addition of oxaliplatin to 5-FU/FA as first-line treatment provides a significant clinical advantage to patients. The rapid onset of a high response rate and the low rate of outright progression are associated with an early decrease in the risk of death, which is maintained for over a year. Oxaliplatin offers physicians and their patients a valuable new option in the overall management of this disease.

4. SUPPORTIVE STUDIES

There are seven supportive trials that provide independent evidence of efficacy, the preponderance of which supports the pivotal trial.

Cross-substantiation of the effectiveness of oxaliplatin is demonstrated by another first-line trial with a different primary endpoint and consistent results: EFC2961.

Independent substantiation of the effectiveness of oxaliplatin is demonstrated by the preponderance of evidence in six supportive studies:

- Two studies in other phases of the disease, namely, second-line therapy: EFC2964 and EFC2917
- Four monotherapy studies: EFC2960 and EFC2963 (first-line) and EFC3105 and EFC3106 (second-line)

These studies are discussed in detail in Sections 4.1, 4.2, and 4.3, respectively. In addition, nine studies are considered by the Sponsor to provide secondary support of the indicated claim. These studies provide results consistent with the pivotal and supportive studies and are discussed in Section 4.4.

4.1 Study EFC2961

Study EFC2961 demonstrated the beneficial effect of oxaliplatin using response rate as the primary endpoint. The secondary endpoints of progression-free survival and overall survival were consistent with a beneficial effect of oxaliplatin. Taken together, the results of Study EFC2961 cross-substantiate the indicated claim of effectiveness for oxaliplatin.

Study EFC2961 was a multicenter, first-line, randomized, controlled Phase III study that compared the efficacy and safety of oxaliplatin in combination with 5-FU/FA with the efficacy and safety of 5-FU/FA alone. Patients with unresectable, histologically-proven adenocarcinoma of the colon or rectum were eligible to receive 5 FU/FA with or without

oxaliplatin. The primary objective of the trial was response rate (confirmatory scans were obtained with at least a 9-week interval); secondary objectives included progression-free survival, overall survival, and safety.

For patients to be included in this study, at least one bidimensionally measurable lesion had to exceed 2 cm. Previous chemotherapy or radiotherapy for metastatic disease was not allowed, although adjuvant chemotherapy or radiotherapy was permitted provided that treatment was completed six months before study enrollment. Only patients aged ≤ 75 years with a performance status ≤ 2 , a life expectancy > 3 months, and adequate chemistries and bone marrow reserve were enrolled.

The trial methods included an independent assessment of response and progression; use of intent-to-treat (all randomized patients) analyses.

The study design is displayed in Figure 7.

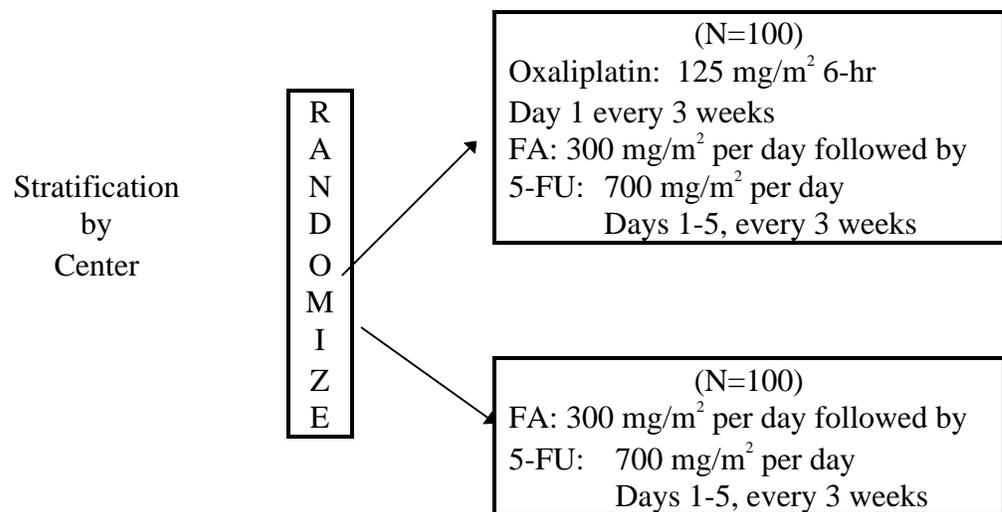


Figure 7 - Phase II/III Study of Oxaliplatin With Chronomodulated 5-FU/FA in Metastatic Colorectal Cancer - Supportive Trial: EFC2961

5-FU and FA were given as a sinusoidal infusion between 10 PM and 10 AM, with a peak at 4 AM on Days 1 through 5 of a 21-day cycle. Oxaliplatin was administered on Day 1 as a 6-hour continuous infusion before administration of 5-FU + FA. Treatment was continued until withdrawal from the study due to disease progression, a toxicity/adverse event, patient refusal, loss of patient to follow-up, or death.

4.1.1 Demographics and other baseline characteristics

Table 16 presents the demographic characteristics at baseline for all patients enrolled in EFC2961. Patients ranged in age from 29 to 75 years, with median ages between 60.5 and 61.0 years. The majority of patients in both arms had a performance status of 0.

Table 16 - Selected Demographic Characteristics: EFC2961

Characteristic	5-FU/FA (N=100)	Oxal 125+5-FU/FA (N=100)	p-Value
Age			0.99 (t-Test)
Median, years	61.0	60.5	
Minimum, years	29	31	
Maximum, years	74	75	
Gender, n (%)			0.77 (Chi-Square)
Male	64 (64.0%)	66 (66.0%)	
Female	36 (36.0%)	34 (34.0%)	
WHO performance status, n (%)			0.37 (Chi-Square)
0	66 (66.0%)	69 (69.0%)	
1	27 (27.0%)	20 (20.0%)	
2	7 (7.0%)	11 (11.0%)	

As seen in Table 17, the majority of patients presented with an initial diagnosis of Dukes Stage D colon cancer. At baseline, most patients presented with metastases in the liver, an alkaline phosphatase <Grade 2, and a CEA value >10 ng/mL.

Table 17 - Baseline Characteristics: EFC2961

Characteristic	5-FU/FA (N=100)	Oxal 125+5-FU/FA (N=100)	p-Value
At study entry			
Primary tumor site, n (%)			0.085 (Chi-Square)
Colon	77 (77.0%)	66 (66.0%)	
Rectum	23 (23.0%)	34 (34.0%)	
Colon+rectum	0	0	
Dukes stage, n (%)			0.26 (Chi-Square)
A	2 (2.0%)	1 (1.0%)	
B	11 (11.0%)	17 (17.0%)	
C	22 (22.0%)	13 (13.0%)	
D	65 (65.0%)	69 (69.0%)	
Missing	0	0	
At baseline			
Number of organs involved, n (%)			0.91 (Chi-Square)
1	48 (48.0%)	50 (50.0%)	
2	37 (37.0%)	34 (34.0%)	
3	12 (12.0%)	11 (11.0%)	
>3	3 (3.0%)	5 (5.0%)	
Organs involved, n (%)			
Liver	86 (86.0%)	88 (88.0%)	0.67 (Chi-Square)
Lung	37 (37.0%)	35 (35.0%)	0.76 (Chi-Square)
Other	34 (34.0%)	34 (34.0%)	1.00 (Chi-Square)
Alkaline phosphatase			0.17 (Chi-Square)
<2	82 (82.0%)	74 (74.0%)	
≥2	18 (18.0%)	26 (26.0%)	
Prior Adjuvant Chemotherapy			0.013 (Chi-Square)
No	77 (77.0%)	90 (90.0%)	
Yes	23 (23.0%)	10 (10.0%)	
CEA, n (%)			0.03 (Chi-Square)
≤10 ng/mL	16 (16.0%)	32 (32.0%)	
>10 ng/mL	79 (79.0%)	65 (65.0%)	
Missing	5 (5.0%)	3 (3.0%)	

4.1.2 Exposure to study treatments

Table 18 presents a summary of exposure in Study EFC2961.

Table 18 - Summary of Exposure: EFC2961

	5-FU/FA (N=100)	Oxal 125+5-FU/FA (N=99)
Cycles		
Total	728	774
Median	6	8
Range	[1-15]	[1-15]
Median Relative Dose Intensity		
Oxaliplatin	---	86%
5-FU	95%	90%
By Patient		
Dose Reduction	14%	64%
Dose Delay	17%	36%

4.1.3 Efficacy

4.1.3.1 Overall response rate

Radiological evaluations of antitumor responses were performed at baseline and every nine weeks by the Investigators and read by at least two independent radiologists. WHO definitions were used for response assessments (CR, PR, SD/NC, or PD).

In EFC2961, radiological scans of 180 (90%) of the 200 randomized patients were evaluated independently. The remaining 20 patients were not evaluated because of early patient withdrawal (one patient), death (two patients), nonmeasurable disease (two patients), or radiological scans that were unavailable or could not be compared across treatment cycles (15 patients). Patients for whom radiological scans were unavailable were included as nonresponders in the analysis. Best response rate (defined as confirmed and unconfirmed responses) in the oxaliplatin treatment arm was greater than 50%.

Table 19 summarizes the Independent evaluation of response rate for the ITT population. The confirmed response rate (complete and partial responses) was significantly higher for patients who received oxaliplatin and 5-FU/FA than for patients who received 5-FU/FA alone. Oxaliplatin in combination with 5-FU/FA produced a confirmed response rate of 34% compared with 12% in the control arm, with no overlap in confidence intervals.

Table 19 - Overall Response Rate Based on Independent Assessments: EFC2961

Overall Response Rate	5-FU/FA (N=100)	Oxal 125+5-FU/FA (N=100)
Confirmed response rate ^{a,b} , % [95% confidence intervals]	12.0% [6.3-20.1]	34.0% [24.8-44.2]
p-value (chi-square test, two-tailed)	<0.001	
Number of complete responses	0	1
Number of partial responses	12	33
Best response rate ^c , % [95% confidence intervals]	16.0% [9.4-24.7]	53.0% [42.7-63.1]
p-value (chi-square test, two-tailed)	<0.001	

^a Responses observed on at least two consecutive evaluations, separated by nine weeks

^b Excludes one patient in EFC2961 who withdrew from study after a partial response was observed at Cycle 3

^c Confirmed and unconfirmed responses

4.1.3.2 Progression-free survival

Progression-free survival was defined as the time from randomization until the time that the patient was classified as having progressive disease or death. For patients without a classification of progressive disease or death as of 20 January 1997, the date of last follow-up without progression was used as the date of progressive disease, and the progression-free survival was considered to be right-censored for purposes of these analyses.

Figure 8 shows the Kaplan-Meier progression-free survival curve for all randomized patients by treatment group. There were 20 of 100 (20%) censored oxaliplatin plus 5 FU+FA data points and 9 of 100 (9%) censored 5-FU/FA data points in this figure.

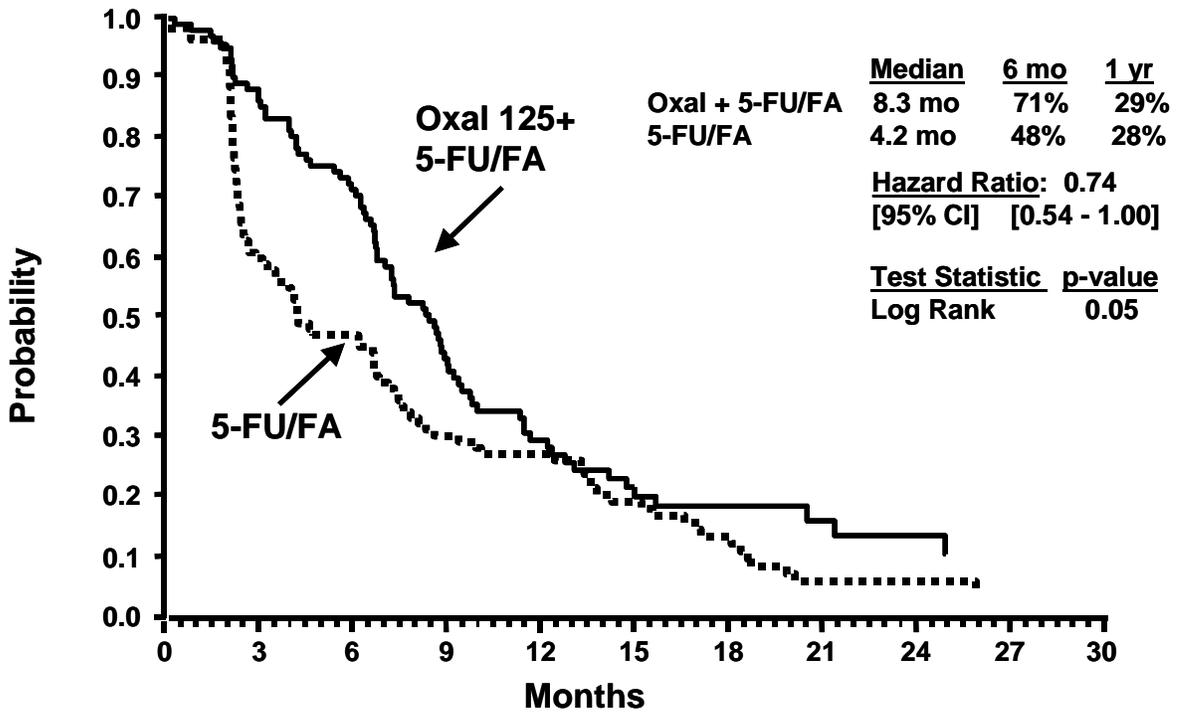


Figure 8 - Study EFC2961 Kaplan-Meier Progression-Free Survival Curve for All Patients by Treatment Group

The estimate of median progression-free survival was 8.3 months (95% confidence interval of 6.7 to 9.1 months) for oxaliplatin plus 5-FU/FA patients. This represents a 98% increase in the median progression-free survival of 4.2 months (95% confidence interval of 3.2 to 6.7 months) for 5-FU/FA patients. The probability of progression-free survival lasting at least 6 months was estimated to be 71% for oxaliplatin plus 5-FU/FA patients and 48% for 5-FU/FA patients. The probability of progression-free survival lasting at least 1 year was estimated to be 29% for oxaliplatin plus 5-FU/FA patients and 28% for 5-FU/FA patients. The Log-Rank test showed a statistically significant difference with a p-value=0.05 in progression-free survival in favor of oxaliplatin plus 5-FU/FA therapy. The hazard ratio was 0.74 (95% confidence intervals of 0.54 to 1.00).

Table 20 presents summary statistics from the output of the Kaplan-Meier progression-free survival analysis for all randomized patients.

Table 20 - Study EFC2961 Progression-Free Survival Summary (months)

	5-FU/FA N=100	Oxal 125+ 5-FU/FA N=100
Minimum	0.7	0.2
25 th Percentile	2.2	4.6
Median	4.2	8.3
75 th Percentile	13.4	12.7
Maximum	26.7 ^a	29.8 ^a
6-month PFS Probability	48%	71%
9-month PFS Probability	31%	41%
12-month PFS Probability	28%	29%

^a Alive without progression

4.1.3.3 Overall survival

Survival time was specified as the time from the date of randomization until the date of death from any cause. For patients who were confirmed as alive on 20 July 1997, the time from randomization to 20 July 1997 was used as their survival time, and the observation was considered to be right-censored for purposes of these analyses. For patients alive at last follow-up prior to 20 July 1997, the date when the patient was last known to be alive was used for determination of survival time, and the observation was also considered to be right censored for purposes of these analyses.

Figure 9 shows the Kaplan-Meier survival curves for all randomized patients by treatment group. There were 33 (33%) censored oxaliplatin plus 5-FU/FA data points and 36 (36%) censored 5-FU/FA data points.

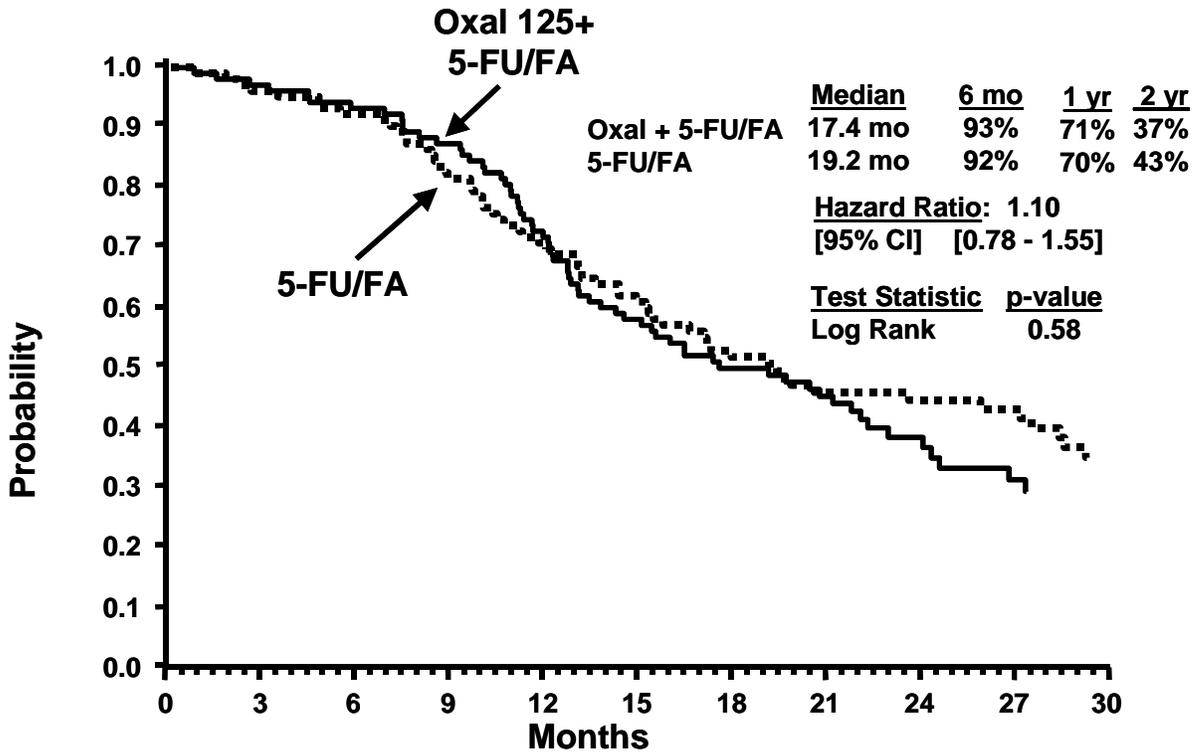


Figure 9 - Study EFC2961 Kaplan-Meier Survival Curves for All Patients by Treatment Group

From Kaplan-Meier analysis of survival for all randomized patients, the estimate of median survival was 17.4 months (95% confidence interval of 13.8 to 22.0 months) for oxaliplatin plus 5-FU/FA patients compared to 19.2 months (95% confidence interval of 15.2 to 26.7 months) for 5-FU/FA patients. One-year survival probability was estimated to be 71% for oxaliplatin plus 5-FU/FA patients and 70% for 5-FU/FA patients. There was no significant difference between treatment arms per log-rank test (p-value=0.58). The hazard ratio was 1.10 (95% confidence interval of 0.78 to 1.55).

Table 21 presents the summary statistics from the output of the Kaplan-Meier survival analysis for all randomized patients.

Table 21 - Study EFC2961 Survival Summary (months)

	5-FU/FA N=100	Oxal 125+ 5-FU/FA N=100
Minimum	0.7	0.7
25 th Percentile	10.3	11.2
Median	19.2	17.4
75 th Percentile	34.5	34.8
Maximum	37.0 ^a	36.9 ^a
6-month Survival Probability	92%	93%
9-month Survival Probability	81%	87%
12-month Survival Probability	70%	71%

^a Censored

4.1.3.4 Post-study therapy

Patients in EFC2961 received extensive post-study therapy (chemotherapy and/or surgery) as encouraged by the protocol (Table 22.). This may have contributed to the long survival observed in both treatment arms. The timing of surgery in this study was related to exposure to oxaliplatin. More patients in the experimental arm received surgery following treatment with oxaliplatin plus 5-FU/FA. Conversely, more patients in the control arm received surgery following post-study treatment with oxaliplatin. The prolonged survival observed in both arms suggests that the combination of oxaliplatin-based chemotherapy plus surgery may offer additional benefits over chemotherapy alone. Overall, subsequent therapy makes it impossible to accurately interpret differences in survival between the two arms in this trial. However, the overall results are consistent with those of EFC2962.

Table 22 - Study EFC2961 Distribution of Patients by Post-Study Therapy with Oxaliplatin, CPT-11, and/or Surgery

Post-Study Therapy	5-FU/FA	Oxal 125+ 5-FU/FA
Post-study Chemotherapy (any) and/or Surgery for metastases	81 (81%)	78 (78%)
Post-study Oxaliplatin	64 (64%)	39 (39%)
Post-study CPT-11	26 (26%)	23 (23%)
Post-study Surgery for metastases	32 (32%)	33 (33%)

4.2 Second-line therapy: EFC2964 and EFC2917

Independent substantiation of the effectiveness of oxaliplatin was demonstrated by the two studies in second-line therapy: EFC2964 and EFC2917.

These multicenter, open-label, Phase II studies were conducted in patients with colorectal adenocarcinoma who had been treated previously with 5-FU/FA. In both studies, patients

were to be proven refractory to 5-FU, having progressed while receiving 5-FU or within two months after 5-FU discontinuation; objective verification of progression on the previous regimen was obtained. Intravenous oxaliplatin was added to the same 5-FU/FA treatment regimen on which each patient had previously experienced documented disease progression. In EFC2964, patients could have failed two previous 5-FU-based regimens; all patients in EFC2917 were required to have failed one and only one prior 5-FU-based chemotherapy regimen.

In EFC2964, patients were stratified into two treatment regimens according to the 5-FU-based regimen on which disease progression had occurred (Table 23.). One of these regimens (Bimonthly Bolus+Infusion) was identical to that used in EFC2962 and the Intergroup Trial; the other was a similar q2w regimen. Patients were to receive a minimum of six two-week treatment cycles (12 weeks), and they could remain on treatment for up to one year.

In EFC2917, patients could receive a maximum of eight treatment cycles for the three-week oxaliplatin schedule and 12 cycles for the two-week schedule, yielding a maximum 24-week duration of treatment (Table 23.). The Daily x 5 regimen of 5-FU/FA prior to study was administered every four weeks; therefore, to maintain a consistent dose intensity for the three-week regimen of oxaliplatin, the dose of 5-FU administered in the Daily x 5 regimen was decreased by 25% relative to the last cycle on which disease progression was documented. All patients were followed until disease progression was documented.

Table 23 - Treatment Regimens: EFC2964 and EFC2917

Study	Regimen	Dose	Regimen
EFC2964	Oxal 85+ Bolus+Infusion (N=57)	Oxaliplatin: 85 mg/m ² (2-hour infusion) FA: 200 mg/m ² (2-hour infusion) followed by 5-FU: 400 mg/m ² (bolus), 600 mg/m ² (22-hour infusion)	Day 1 q2w Days 1-2 q2w
	Oxal 85+ Bolus+Infusion (N=40)	Oxaliplatin: 85 mg/m ² (2-hour infusion) FA: 500 mg/m ² (2-hour infusion) followed by 5-FU: 1500 mg/m ² (22-hour infusion)	Day 1 q2w Days 1-2 q2w
EFC2917	Oxal 130+ Daily x 5 (N=115)	Oxaliplatin: 130 mg/m ² (2-hour infusion) FA: previous dose and infusion rate 5-FU: previous dose (bolus) decreased by 25%	Day 1, q3w Days 1-5 q3w
	Oxal 85 + Weekly 24 Hr (N=57)	Oxaliplatin: 85 mg/m ² (2-hour infusion) FA: previous dose and infusion rate 5-FU: previous dose (24-hour infusion)	Day 1, q2w Weekly for 6 of 8 weeks

In EFC2964, tumor response was evaluated every six cycles (12 weeks). Patients who discontinued treatment were monitored every three months until their death. In EFC2917, tumor response was assessed at Weeks 6, 12, and 18 and during the 28-day post-treatment follow-up observation. After completion of treatment, for all patients who achieved complete response, partial response, or no response/stable disease, disease status was evaluated at approximately two-month intervals until one year after study enrollment and

every three months thereafter until death or two years after study enrollment, disease progression, or initiation of another anticancer treatment, whichever came first.

Tumor response was evaluated by the Investigator and an independent third-party radiological review panel (Independent Assessment). In each study, a review panel was composed of independent radiologists who specialized in tumor imaging and who were blinded to study treatment and the Investigators' antitumor-activity assessments.

The primary efficacy endpoint was considered overall response rate. Secondary efficacy criteria were PFS (based on Independent assessment of progression, if available) and overall survival.

4.2.1 Demographics and other baseline characteristics

Table 24 presents the demographic characteristics at baseline for EFC2964 and EFC2917. The study populations were similar in the two studies. The patients ranged in age from 27 to 77 years, with median ages between 59.5 and 64.0 years.

Table 24 - Selected Demographic Characteristics: Second-Line Therapy

Characteristic	EFC2964		EFC2917	
	Oxal 85 + Bolus+Infusion (N=57)	Oxal 85 + Bolus+Infusion (N=40)	Oxal 130 + Daily x 5 (N=115)	Oxal 85 + Weekly 24-Hr (N=57)
Age				
Median, years	64.0	59.5	61.0	60.0
Minimum, years	35	34	27	29
Maximum, years	75	74	77	76
Sex, n (%)				
Male	37 (64.9%)	26 (65.0%)	72 (62.6%)	36 (63.2%)
Female	20 (35.1%)	14 (35.0%)	43 (37.4%)	21 (36.8%)
Performance status, n (%)				
0	25 (43.9%) ^a	25 (62.5%) ^a	75 (65.2%) ^b	46 (80.7%) ^b
1	25 (43.9%) ^a	13 (32.5%) ^a	38 (33.0%) ^b	10 (17.5%) ^b
2	7 (12.3%) ^a	2 (5.0%) ^a	2 (1.7%) ^b	1 (1.8%) ^b

^a Based on the ECOG (Eastern Cooperative Oncology Group) scale, considered to be equivalent to the WHO scale

^b Based on the Karnofsky scale [converted to the WHO scale]

Table 25 displays the tumor characteristics of previously treated patients. The majority of patients had a primary diagnosis of colon cancer and presented at baseline with liver metastases. CEA values were not reported in EFC2917.

Table 25 - Second-Line Therapy: Tumor Characteristics

Characteristic	EFC2964		EFC2917	
	Oxal 85 + Bolus+Infusion (N=57)	Oxal 85 + Bolus+Infusion (N=40)	Oxal 130 + Daily x 5 (N=115)	Oxal 85 + Weekly 24-Hr (N=57)
At initial diagnosis				
Primary tumor site, n (%)				
Colon	37 (64.9%)	24 (60.0%)	66 (57.4%)	30 (52.6%)
Rectum	20 (35.1%)	16 (40.0%)	47 (40.9%)	24 (42.1%)
Colon rectum	0	0	2 (1.7%)	3 (5.3%)
Dukes stage, n (%)				
A	1 (1.8%)	1 (2.5%)	1 (0.9%)	0
B	4 (7.0%)	4 (10.0%)	21 (18.3%)	9 (15.8%)
C	16 (28.1%)	10 (25.0%)	38 (33.0%)	13 (22.8%)
D	36 (63.2%)	25 (62.5%)	55 (47.8%)	33 (57.9%)
Missing	0	0	0 (0.0%)	2 (3.5%)
At baseline				
Number of organs involved, n (%)				
1	26 (45.6%)	16 (40.0%)	44 (38.3%)	28 (49.1%)
2	16 (28.1%)	13 (32.5%)	34 (29.6%)	19 (33.3%)
3	4 (7.0%)	8 (20.0%)	24 (20.9%)	8 (14.0%)
>3	11 (19.3%)	3 (7.5%)	11 (9.6%)	2 (3.5%)
Organs involved, n (%)				
Liver	49 (86.0%)	32 (80.0%)	88 (76.5%)	44 (77.2%)
Lung	17 (29.8%)	20 (50.0%)	39 (33.9%)	22 (38.6%)
Other	27 (47.4%)	18 (45.0%)	67 (58.3%)	21 (36.8%)
CEA, n (%)				
N	57 (100.0%)	40 (100.0%)	115 (100.0%)	57 (100.0%)
≤10 ng/mL	9 (15.8%)	11 (27.5%)	NR	NR
>10 ng/mL	43 (75.4%)	28 (70.0%)	NR	NR
Median	195.0	40.4	NR	NR

NR=not reported

4.2.2 Efficacy

EFC2964 and EFC2917 provide independent evidence of the activity of oxaliplatin in another stage of disease (recurrent disease post 5-FU) for the approval of the use of oxaliplatin in combination with 5-FU/FA regimens. In these studies, oxaliplatin was added to the 5-FU/FA regimen on which patients had previously progressed within two months of study enrollment, thereby allowing patients to act as their own controls. Overall response rate was the primary efficacy endpoint for both of these studies, with PFS, overall survival, and clinical benefit as secondary endpoints. Results demonstrated a consistent benefit of oxaliplatin for all efficacy parameters in both studies and were supportive of the findings in the two studies in first-line patients (EFC2962 and EFC2961). Of note, the Bolus+Infusion regimen of oxaliplatin in combination with

5-FU/FA administered in EFC2964 was the same as the Bimonthly Bolus+Infusion regimen used in EFC2962, the randomized study in previously untreated patients. The 5-FU/FA dose and schedule used in these regimens was the same bolus+continuous infusion regimen as that compared directly to the Daily x 5 regimen in a randomized trial (Intergroup Trial).

4.2.2.1 Progression-free survival

Table 26 summarizes the PFS results of EFC2964 and EFC2917. Median PFS was similar in both studies in previously treated patients, ranging from four to five months.

Table 26 - Progression-Free Survival: Second-Line Therapy

Parameter	EFC2964		EFC2917	
	Oxal 85 + Bolus+Infusion (N=57)	Oxal 85 + Bolus+Infusion (N=40)	Oxal 130 + Daily x 5 (N=115)	Oxal 85 + Weekly 24-Hr (N=57)
Disease Progression	98.2%	100%	90.4%	87.7%
Median PFS, months [95% confidence intervals]	5.3 [3.2-5.7]	4.6 [3.0-5.5]	4.3 [3.1-5.1]	4.1 [3.4-4.8]

4.2.2.2 Overall response rate

Table 27 summarizes confirmed response rates based on the Independent assessments for EFC2964 and EFC2917, in which all patients had previously received a 5-FU-based regimen and had experienced disease progression. The Investigators' assessment of each patient's failure on the previous 5-FU-based regimen was confirmed in both studies. Scans were submitted to the FDA for verification of refractory status and response.

Across these studies, confirmed response rates ranged between 7% (EFC2917, oxaliplatin+Weekly 24-hour regimen) and 22.8% (EFC2964, oxaliplatin plus de Gramont regimen) in patients who had previously failed the same 5-FU/FA regimen to which oxaliplatin was added.

Table 27 - Response Rate Based on Independent Assessments: Second-Line Therapy

Parameter	EFC2964		EFC2917	
	Oxal 85 + de Gramont (N=57)	Oxal 85 + modified de Gramont (N=40)	Oxal 130 + Daily x 5 (N=115)	Oxal 85 + Weekly 24-Hr (N=57)
Confirmed response rate ^a , % [95% confidence intervals]	22.8% [12.7-35.9]	17.5% [7.3-32.8]	13.0% [7.4-20.6]	7.0% [1.9-17.1]
Number of complete responses	0	0	0	1
Number of partial responses	13 ^b	7	15	3
Best response rate ^c , % [95% confidence intervals]	24.6% [14.1-37.8]	25.0% [12.6-41.2]	19.1% [12.3-27.6]	14.0% [6.2-25.8]

^a Responses observed on at least two consecutive evaluations, separated by 12 weeks (EFC2964) and 6 weeks (EFC2917).

^b Includes one patient (Patient 60003) who was determined to be stable on previous chemotherapy.

^c Confirmed and unconfirmed responses.

Table 28 summarizes the number of patients not progressing at 4 and 6 months after study entry. In both studies, nearly one-half of all patients were stabilized at 4 months after study entry and one-quarter to one-third of patients were stabilized at 6 months after study entry.

Table 28 - Stabilization of Disease: Patients not Progressing at Four and Six Months After Study Entry

Parameter	EFC2964		EFC2917	
	Oxal 85 + de Gramont (N=57)	Oxal 85 + modified de Gramont (N=40)	Oxal 130 + Daily x 5 (N=115)	Oxal 85 + Weekly 24-Hr (N=57)
Stabilization of disease, n (%)				
4 months	27 (47%)	22 (55%)	59 (51%)	28 (49%)
6 months	19 (33%)	12 (30%)	29 (25%)	12 (21%)

4.2.2.3 Overall survival

Table 29 summarizes the overall survival of patients in EFC2964 and EFC2917. Consistent with the findings for PFS, median overall survival was similar in the two studies, ranging from 10 to 11 months. At one year, 40% to 47% of patients in these studies were alive.

Table 29 - Overall Survival: Second-Line Therapy

Parameter	EFC2964		EFC2917	
	Oxal 85 + de Gramont (N=57)	Oxal 85 + modified de Gramont (N=40)	Oxal 130 + Daily x 5 (N=115)	Oxal 85 + Weekly 24-Hr (N=57)
Deaths, %	75.4%	75.0%	53.9%	56.1%
One-year survival, % [95% confidence intervals]	45.0% [32.0-58.1]	41.9% [26.4-57.4]	39.8% [28.8-50.7]	47.3% [33.3-61.4]
Median, months [95% confidence intervals]	11.1 [8.3-13.0]	10.5 [8.6-13.4]	10.8 [9.1-12.3]	10.1 [6.6-13.1]

Addition of oxaliplatin to 5-FU/FA-resistant patients in these two studies has resulted in disease control for more than a year in 40% of the patients with a median survival of 10-11 months.

4.3 Monotherapy studies: EFC2960, EFC2963, EFC3105, EFC3106

Independent substantiation of the effectiveness of oxaliplatin was demonstrated by four monotherapy studies: EFC2960 and EFC2963 (first-line) and EFC3105 and EFC3106 (second-line).

Oxaliplatin monotherapy was administered at 130 mg/m² q3w in two Phase II studies each in first-line patients (EFC2960 and EFC2963) and second-line patients (EFC3105 and EFC3106) with advanced colorectal cancer. In second-line patients, disease progression on 5-FU chemotherapy, documented by radiological scans or clinical evidence, was required for inclusion. Only patients who had discontinued previous chemotherapy for at least four weeks were included in EFC3105 and EFC3106.

Table 30 summarizes the efficacy results based on the Independent assessments for the monotherapy studies. Confirmed response rate is not reported in this Briefing Document for EFC3105 and EFC3106 because supporting documentation of the Independent assessments was incomplete. Progression-free survival was not measured in EFC3105 and EFC3106. Overall survival in study EFC3106 could not be estimated because 33 patients (65%) were alive at the time the analyses were performed.

Table 30 - Efficacy Results Based on Independent Assessments: Monotherapy Studies

Parameter	First-line Patients		Second-line Patients	
	EFC2960 (N=25)	EFC2963 (N=38)	EFC3105 (N=58)	EFC3106 (N=51)
Overall response rate				
Confirmed response rate [95% confidence intervals]	8.0% [0.9-26.1]	23.7% [11.4-40.3]	- -	- -
Number of complete responses	0	0		
Number of partial responses	2	9	-	-
Best response rate, n (%) [95% confidence intervals]	3 (12%) [2.6-31.2]	10 (27.0%) [13.8-44.1]	10.3% NR	7.8% ^{a,b} NR
Progression-free survival, months				
Median [95% confidence intervals]	4 ^c [2-7]	4.1 [2.1-5.5]	NR	NR
Overall survival, months				
Median [95% confidence intervals]	14.5 [10-20]	13.3 [9.8-18.9]	8.2 NR	Median not reached yet

NR=not reported

^a Excludes one patient (Patient 44) for whom supporting documentation of a partial response was unavailable.

^b For two patients with partial responses (Patients 1 and 13), radiological documentation of disease progression on previous 5-FU chemotherapy was not available.

^c Based on the Investigator's assessment of date of progression.

Oxaliplatin monotherapy, administered at a dose of 130 mg/m² q3w, produced confirmed response rates of 8% and 23.7% in first-line patients and best response rates (confirmed and unconfirmed responses) of 7.8% and 10.3% in second-line patients. In EFC2963, patients were to continue treatment until disease progression or withdrawal for other reasons. In EFC2960, patients who were stable or responding could continue beyond six cycles at the discretion of the Investigator, but subsequent tumor evaluations were not mandatory. Together, the results of these studies provide clear evidence of the single agent activity of oxaliplatin, corroborating the evidence for the efficacy of oxaliplatin in combination with 5-FU-based therapy.

5. SUMMARY OF EFFICACY RESULTS IN CONTROLLED STUDIES

The data presented in the Sponsor's dossier demonstrates the effectiveness of oxaliplatin in a single pivotal study (EFC2962) with independent substantiation from related study data (seven supportive trials) (Table 31.). In first-line patients, the addition of oxaliplatin to 5-FU/FA significantly improved confirmed response rate and PFS above values observed with 5-FU/FA alone, despite differences in treatment regimens. In second-line patients, oxaliplatin produced confirmed response rates between 7% and 22.8% when combined with the same 5-FU regimens on which patients had progressed. Overall survival duration of patients who received oxaliplatin was approximately 16-17 months in

previously untreated patients and 10 months in previously treated patients across controlled studies.

Table 31 - Summary of Efficacy Results in Primary Studies

	Response Rate	Median PFS	Median OS	1-Year Survival
Pivotal Trial: EFC2962				
5-FU/FA	21.9%	5.3 mo.	14.7 mo.	61%
Oxal + 5-FU/FA	49.0%	8.1 mo.	15.9 mo.	69%
<i>Supportive Trials</i>				
First-line trial: EFC2961				
Oxal + 5-FU/FA	34%	8.3 mo.	17.4 mo.	71%
5-FU/FA	12%	4.2 mo.	19.2 mo.	70%
Second-line trials				
EFC2964: Oxal + 5-FU/FA	17.5 - 22.8%	4.6 - 5.3 mo.	10.5 - 11.1 mo.	42-45%
EFC2917: Oxal + 5-FU/FA	13.0 - 7.0%	4.1 - 4.3 mo.	10.1 - 10.8 mo.	40-47%
Monotherapy trials				
EFC2960, 2963: First line	8.0 - 23.7%	4.0 - 4.1 mo.	13.3 - 14.5 mo.	--
EFC3105, 3106: Second line	7.8 - 10.3%	NR	8.2 mo.	--

The data on the effectiveness of oxaliplatin plus 5-FU/FA in advanced colorectal cancer represents a significant advance in the treatment of this disease, which has not been seen in the last 20 years.

6. SAFETY RESULTS

More than 1900 patients with advanced colorectal cancer have been treated with oxaliplatin during its clinical development. These include 1174 patients treated in Phase II/III studies and 734 patients treated in compassionate-use series. Among the 1174 patients in Phase II/III studies, 700 were previously untreated patients and 474 were previously treated patients.

6.1 Prelisted toxicities and adverse events in first- and second-line studies

Administration of oxaliplatin as a single-agent at a dose of 130 mg/m² q3w has been associated with gastrointestinal reactions (nausea/vomiting and diarrhea), hematological events (neutropenia and thrombocytopenia), and neurological symptoms (paresthesias). There was no significant alopecia, renal toxicity, or ototoxicity.

The trials described in this section used different toxicity scales to report adverse events. In addition, different preprinted checklists of adverse events in complement to free-text reporting of adverse events were used.

As prelisted toxicities were not identical across the studies, these were mapped into common terms. For producing the overall summaries of AE incidence, prelisted toxicities and spontaneously reported AEs were coded according to the WHO dictionary and combined. Thus, a given patient is counted as having an AE whether the event was recorded as a prelisted toxicity or on the AE page of the CRF.

The most frequently reported adverse events regardless of grade in the oxaliplatin arms were nausea/vomiting, paresthesia, and diarrhea, granulocytopenia, thrombocytopenia and elevated hepatic transaminases. Each of these events was reported more frequently in the oxaliplatin plus 5-FU/FA treatment groups than in the control groups. The most frequent Grade 3-4 events in the oxaliplatin plus 5-FU/FA treatment groups were diarrhea, neuritis sensory, paresthesia, and granulocytopenia.

Primary Tables 2 and 3 summarize the incidence of prelisted toxicities and all other occurring adverse events in at least 5% of the patients in any treatment arm in studies EFC2962, EFC2961, EFC2917, and EFC2964.

6.2 All deaths within 30 days of treatment, all deaths after 30 days of treatment (unless due to disease progression), and all adverse events with an outcome of death

In the Primary Studies, 32 patients died while receiving oxaliplatin plus 5-FU/FA treatment; four were attributed to study treatment (all four were toxicity to the study drug) by the Investigators, resulting in an overall study treatment-related death rate of 0.5% (4/749). Although considered by the Investigator to be unrelated to study treatment, the Sponsor noted that one patient died due to hypotension/renal failure 21 days after receiving the last dose of oxaliplatin. Therefore, the Sponsor is of the opinion that the fully reconciled, treatment-related death rate (≤ 30 days) is 0.7% (5/749).

In the Secondary Studies, a total of 17 deaths appeared to be potentially related to study treatment, resulting in an overall study treatment-related death rate of 0.9% (17/1996). Further review of these data revealed that only two of the 17 deaths (carotid rupture and acute heart failure/severe hypoglycemia) were attributed to oxaliplatin monotherapy; the remaining 15 were attributed to oxaliplatin therapy in combination with 5-FU/FA (12), cisplatin (2), and cisplatin/epirubicin/ifosfamide-bleomycin (1).

Across the 33 completed studies, the treatment-related death rate (for Primary and Secondary Studies combined) was 0.76% (21/2745) for patients receiving oxaliplatin plus 5-FU/FA. Treatment-related deaths were often attributed to multiple events in different body systems.

The Sponsor also reviewed all deaths considered unrelated to study treatment by the Investigators and concluded, based on overall pooled data, that no other potentially treatment-related deaths were identifiable. In addition, the Sponsor reviewed the data regarding deaths in all ongoing studies, where similar results were observed as of the

cut off date. One death was reported in the post-marketing experience of oxaliplatin in France. This death, due to anaphylactoid shock, was possibly attributed to study treatment by the Investigator; the patient also received ondansetron.

6.3 120-Day Safety Update

In the 120-day safety update to the NDA, the Sponsor noted that the review of deaths “while on study” supports that there is no increase in deaths associated with oxaliplatin plus 5-FU/FA at the proposed dose and regimen of 85 mg/m² oxaliplatin plus Bimonthly Bolus+Infusion of 5-FU/FA.

However, review of data provided from five first-line studies (ROC95, EFC3327, EFC7031, EFC7140, and EFC7462) using 130 mg/m² oxaliplatin plus a modified bolus Mayo Clinic regimen revealed a higher than expected incidence of severe neutropenia and diarrhea, and an apparent increase in the number of deaths (12/281 patients [4.3%]) associated with this regimen. In addition, review of limited data provided from three first-line studies (EFC2977, EFC7132, and INT3010) using a Roswell Park regimen with oxaliplatin 85 mg/m² every two weeks revealed an apparent increase in the number of deaths (3/71 patients [4.2%]) associated with this regimen. The significance of these findings is currently under review.

6.4 Review of systems

This section provides a summary of the most important toxicities within body systems for EFC2962 and EFC2961. Other noteworthy adverse events from review of the clinical database are also briefly described.

The following body systems are presented in the review of systems: Body as a Whole, Gastrointestinal, Hematologic, Hepatic, and Nervous.

6.4.1 Body as a whole

The overall incidence of body as a whole disorders (Table 32.) was lower in the oxaliplatin arm than in the control arm in EFC2961 and higher in the oxaliplatin arm than in the control arm in EFC2962.

Table 32 - *Body as a Whole* Prelisted Toxicities and Adverse Events Reported for $\geq 5\%$ of Patients in Any Treatment Arm: Studies EFC2962 and EFC2961- Number (%) of Patients

Body System/ Preferred Term	EFC2962				EFC2961			
	5-FU/FA N=208 ^a		Oxal 85+5-FU/FA N=209 ^a		5-FU/FA N=100		Oxal 125 + 5-FU/FA N=99 ^a	
	All Grades	Grades 3 and 4	All Grades	Grades 3 and 4	All Grades	Grades 3 and 4	All Grades	Grades 3 and 4
Allergic reaction	0 (0.0)	0 (0.0)	12 (5.7)	3 (1.4)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Asthenia	45 (21.6)	7 (3.4)	49 (23.4)	9 (4.3)	6 (6.0)	4 (4.0)	3 (3.0)	1 (1.0)
Chest pain	7 (3.4)	1 (0.5)	11 (5.3)	0 (0.0)	6 (6.0)	0 (0.0)	3 (3.0)	1 (1.0)
Fatigue	15 (7.2)	1 (0.5)	27 (12.9)	2 (1.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Fever	31 (14.9)	0 (0.0)	69 (33.0)	0 (0.0)	19 (19.0)	5 (5.0)	12 (12.1)	7 (7.1)
Pain	21 (10.1)	2 (1.0)	24 (11.5)	5 (2.4)	12 (12.0)	3 (3.0)	6 (6.1)	2 (2.0)

Allergic reaction

Hypersensitivity reactions to oxaliplatin were similar in nature and severity to those reported with other platinum-containing compounds, i.e., rash, urticaria, pruritis, bronchospasm, and hypotension. These reactions are usually managed with standard epinephrine, corticosteroid, and antihistamine therapy.

6.4.2 Gastrointestinal

A summary of gastrointestinal system disorders is presented in Table 33.

Table 33 - *Gastrointestinal System* Disorders Prelisted Toxicities and Adverse Events Reported for $\geq 5\%$ of Patients in Any Treatment Arm: Studies EFC2962 and EFC2961- Number (%) of Patients

Body System/ Preferred Term	EFC2962				EFC2961			
	5-FU/FA N=208 ^a		Oxal 85+5-FU/FA N=209 ^a		5-FU/FA N=100		Oxal 125 + 5-FU/FA N=99 ^a	
	All Grades	Grades 3 and 4	All Grades	Grades 3 and 4	All Grades	Grades 3 and 4	All Grades	Grades 3 and 4
Abdominal pain	31 (14.9)	2 (1.0)	42 (20.1)	0 (0.0)	21 (21.0)	7 (7.0)	17 (17.2)	3 (3.0)
Anorexia	12 (5.8)	0 (0.0)	12 (5.7)	2 (1.0)	5 (5.0)	3 (3.0)	7 (7.1)	3 (3.0)
Constipation	27 (13.0)	1 (0.5)	46 (22.0)	1 (0.5)	5 (5.0)	1 (1.0)	4 (4.0)	0 (0.0)
Diarrhea	91 (43.8)	11 (5.3)	123 (58.9)	25 (12.0)	49 (49.0)	5 (5.0)	85 (85.9)	43 (43.4)
Dyspepsia	16 (7.7)	1 (0.5)	9 (4.3)	0 (0.0)	0 (0.0)	0 (0.0)	1 (1.0)	0 (0.0)
Intestinal obstruction	9 (4.3)	7 (3.4)	5 (2.4)	4 (1.9)	1 (1.0)	1 (1.0)	8 (8.1)	6 (6.1)
Nausea	111 (53.4)	4 (1.9)	151 (72.2)	12 (5.7)	0 (0.0) ^b	0 (0.0) ^b	0 (0.0) ^b	0 (0.0) ^b
Stomatitis	74 (35.6)	3 (1.4)	92 (44.0)	12 (5.7)	59 (59.0)	4 (4.0)	61 (61.6)	10 (10.1)
Vomiting	61 (29.3)	4 (1.9)	113 (54.1)	12 (5.7)	64 (64.0)	2 (2.0)	88 (88.9)	25 (25.3)

^a Two patients in the control arm and one patient in the oxaliplatin arm of EFC2962 and one patient in the oxaliplatin of EFC2961 were not dosed.

^b Nausea was not reported as separate event in this study but was reported as nausea/vomiting.

Diarrhea

The incidence of diarrhea associated with the addition of oxaliplatin to the bimonthly Bolus+Infusion regimens of 5-FU/FA is modest.

Nausea/Vomiting

The incidence of nausea/vomiting was higher in the 130 mg/m² oxaliplatin plus 5-FU/FA treatment groups than in the 85 mg/m² oxaliplatin plus 5-FU/FA treatment groups.

Mucositis/stomatitis

The incidence of mucositis/stomatitis was slightly greater in the oxaliplatin plus 5-FU/FA treatment groups in both EFC2962 and EFC2961.

6.4.3 Hematologic

A summary of hematologic disorders is presented in Table 34.

Table 34 - *Hematologic System Findings: Studies EFC2962 and EFC2961- Number (%) of Patients*

Toxicity	EFC2962				EFC2961			
	5-FU/FA N=208 ^a		Oxal 85+5-FU/FA N=209 ^a		5-FU/FA N=100		Oxal 125+5-FU/FA N=99 ^a	
	All Grades	Grades 3 and 4	All Grades	Grades 3 and 4	All Grades	Grades 3 and 4	All Grades	Grades 3 and 4
Anemia	168 (80.8)	5 (2.4)	178 (85.2)	7 (3.3)	74 (74.0)	2 (2.0)	83 (83.8)	3 (3.0)
Leukopenia	48 (23.1)	5 (2.4)	145 (69.4)	19 (9.1)	10 (10.0)	0	27 (27.3)	2 (2.0)
Lymphopenia	181 (87.0)	15 (7.2)	182 (87.1)	30 (14.4)	83 (83.0)	4 (4.0)	83 (83.8)	6 (6.1)
Neutropenia	64 (30.8)	15 (7.2)	156 (74.6)	90 (43.1) ^b	8 (8.0)	1 (1.0)	30 (30.3)	2 (2.0)
Thrombocytopenia	60 (28.8)	0	158 (75.6)	5 (2.4)	0	0	7 (7.1)	0

^a Two patients in the control arm and one patient in the oxaliplatin arm of EFC2962 and one patient in the oxaliplatin of EFC2961 were not dosed.

^b 30.6% Grade 3 and 12.4% Grade 4.

Anemia

The overall incidence of anemia was high, but did not differ between the oxaliplatin+5-FU/FA and 5-FU/FA alone groups. The incidence of anemia was similar and did not differ between the 130 mg/m² and 85 mg/m² regimens of oxaliplatin. This event is likely related to the underlying disease state.

Thrombocytopenia

In EFC2962, the incidence of all grades of thrombocytopenia was higher in the oxaliplatin plus 5-FU/FA treatment group compared with the 5-FU/FA treatment group. The incidence of Grade 3/4 thrombocytopenia was low (2.4%).

Neutropenia

In EFC2962, neutropenia was more frequent in the oxaliplatin plus 5-FU/FA treatment group (all grades, 74.6%; Grade 3, 30.6%; Grade 4, 12.4%) compared with the control arm (all grades, 30.8%; Grades 3 and 4, 7.2%). In EFC2961, using a less myelosuppressive chronomodulated regimen of 5-FU, the incidence of neutropenia (all grades) was 30.3% in the oxaliplatin arm and 8.0% in the control arm.

Using the conservative definition of febrile neutropenia as fever \geq Grade 2 in combination with neutropenia of Grade 3 or 4, 12 of 577 (2.1%) patients treated with oxaliplatin experienced this event (Table 35.).

Table 35 - Number (%) of Patients With Fever \geq Grade 2 and Grade 3 or 4 Neutropenia During the Same Cycle

Regimen	Fever \geqGrade 2 with Grade 3 Neutropenia	Fever \geqGrade 2 with Grade 4 Neutropenia
EFC2962		
5-FU/FA (N=208)	1 (0.5)	0
Oxal+5-FU/FA (N=209)	1 (0.5)	1 (0.5)
EFC2961		
5-FU/FA (N=100)	0	0
Oxal+5-FU/FA (N=99)	0	0
EFC2917		
Oxal 130+Daily x 5 (N=115)	2 (1.7)	4 (3.5)
Oxal 85+Weekly 24-Hr (N=57)	0	0
EFC2964		
Oxal 85+Bimonthly (de Gramont) (N=57)	1 (1.8)	3 (5.3)
Oxal 85+Bimonthly (modified de Gramont) (N=40)	0	0
Total receiving Oxal (N=577)	4 (0.7)	8 (1.4)

6.4.4 Hepatic

A summary of liver function abnormalities is presented in Table 36.

Table 36 - *Liver Function Test Abnormalities: Studies EFC2962 and EFC2961-
Number (%) of Patients*

Toxicity	EFC2962				EFC2961			
	5-FU/FA N=208 ^a		Oxal 85+5-FU/FA N=209 ^a		5-FU/FA N=100		Oxal 125+5-FU/FA N=99 ^a	
	All Grades	Grades 3 and 4	All Grades	Grades 3 and 4	All Grades	Grades 3 and 4	All Grades	Grades 3 and 4
Hyperbilirubinemia	38 (18.3)	16 (7.7)	34 (16.3)	7 (3.3)	18 (18.0)	2 (2.0)	17 (17.2)	7 (7.1)
Increased SGOT (ASAT)	48 (23.1)	0	97 (46.4)	1 (0.5)	75 (75.0)	1 (1.0)	91 (91.9)	5 (5.1)
Increased SGPT (ALAT)	45 (21.6)	0	61 (29.2)	2 (1.0)	22 (22.0)	1 (1.0)	47 (47.5)	1 (1.0)
Increased alkaline phosphatase	83 (39.9)	3 (1.4)	118 (56.5)	3 (1.4)	85 (85.0)	14 (14.0)	82 (82.8)	19 (19.2)

^a Two patients in the control arm and one patient in the oxaliplatin arm of EFC2962 and one patient in the oxaliplatin arm of EFC2961 were not dosed.

Increased SGOT and SGPT

In the EFC2962 Study, the incidence of Grade 1 or 2 elevations in SGOT and SGPT were more common in the oxaliplatin plus 5-FU/FA treatment group than in the 5-FU/FA treatment group. The incidence of Grade 3/4 enzyme elevations was similar in the two treatment groups.

6.4.5 Nervous System

EFC2962, EFC2964, and EFC2917 used 3 distinct prelisted fields to capture neurotoxicity data; using 3 different neurotoxicity scales (Table 37.).

- Using the NCI scale, in particular, for neurosensory toxicity
- Using a trial-specific scale for the different manifestations of paresthesia known to occur with oxaliplatin
- Using a mild, moderate, severe scale in particular for pharyngolaryngeal manifestations.

Since there is overlap between these fields, after a given cycle, the same event could be captured as an NCI Grade 3 neurosensory toxicity as well as a trial-specific Grade 3 paresthesia, for instance.

In addition, the following conventions were used to summarize the prelisted toxicities to WHO terms shown in the summary table of adverse events.

Neuritis sensory:	Neurosensory from the NCI scale panel.
Paresthesia:	Paresthesia from the trial-specific scale panel - paresthesia without pain, paresthesia with pain, paresthesia with functional impairment.
Sensory disturbance:	Cold-related dysesthesia, pharyngolaryngeal dysesthesia.

Study EFC2961 used a fourth distinct 4-grade scale.

Table 37 - Peripheral Neurotoxicity-Specific Grading Scales (Including NCI Common Toxicity Scale)

Study	Grade				
	0	1	2	3	4
NCI Common Toxicity Scale ^a					
EFC2962, EFC2917, and EFC2964	None or no change	Mild paresthesias, loss of deep tendon reflexes	Mild or moderate objective sensory loss; moderate paresthesias	Severe objective sensory loss or paresthesias that interfere with function	—
Trial-Specific Grading Scales					
EFC2962, EFC2917, and EFC2964 (Scale for other peripheral neurotoxicity events ^b)	Absent	Mild	Moderate	Severe	—
EFC2962, EFC2917, and EFC2964 (Scale for paresthesia ^c)	Absent	Short lasting paresthesia and/or dysesthesia with complete regression at next cycle or prior to next cycle	Paresthesia and/or dysesthesia persistent between two cycles without functional impairment	Permanent (persistent) functional impairment	—
EFC2961	None	Paresthesias during treatment or lasting \leq 8 days, without functional impairment	Paresthesias, hypothesias lasting for 8 to 14 days after start of chemotherapy	Paresthesias, hypothesias without complete recovery 21 days after start of chemotherapy	Paresthesias, hypothesias causing functional impairment for more than 21 days

— Not applicable

^a Scale used for the terms: neurosensory, neuromotor, neurocortical, neurocerebellar, neuromood.

^b Scale used for the following terms: laryngeal spasm (syndrome), cramps, pharyngolaryngeal dysesthesia, Lhermitte's sign, and loss of deep tendon reflex

^c Scale used for the following terms: cold-related dysesthesia, paresthesia (without pain), paresthesia with pain, paresthesia with functional impairment

A summary of nervous system disorders is presented in Table 38.

Table 38 - *Nervous System* Prelisted Toxicities and Adverse Events Reported for $\geq 5\%$ of Patients in Any Treatment Arm: Studies EFC2962 and EFC2961- Number (%) of Patients

Body System/ Preferred Term	EFC2962				EFC2961			
	5-FU/FA N=208 ^a		Oxal 85+5-FU/FA N=209 ^a		5-FU/FA N=100		Oxal 125 + 5-FU/FA N=99 ^a	
	All Grades	Grades 3 and 4	All Grades	Grades 3 and 4	All Grades	Grades 3 and 4	All Grades	Grades 3 and 4
Headache	10 (4.8)	0 (0.0)	13 (6.2)	1 (0.5)	6 (6.0)	0 (0.0)	3 (3.0)	1 (1.0)
Muscle contractions involuntary	3 (1.4)	0 (0.0)	12 (5.7)	2 (1.0)	2 (2.0) ^b	0 (0.0) ^b	1 (1.0) ^b	0 (0.0) ^b
Neuritis motor	1 (0.5)	1 (0.5)	15 (7.2)	5 (2.4)	0 (0.0) ^b	0 (0.0) ^b	0 (0.0) ^b	0 (0.0) ^b
Neuritis sensory	25 (12.0)	0 (0.0)	142 (67.9) ^c	39 (18.7)	0 (0.0) ^b	0 (0.0) ^b	0 (0.0) ^b	0 (0.0) ^b
Paraesthesia	24 (11.5)	0 (0.0)	140 (67.0) ^c	35 (16.7)	20 (20.0)	0 (0.0)	91 (91.9)	45 (45.5) ^d
Sensory disturbance	2 (1.0)	0 (0.0)	142 (67.9) ^c	1 (0.5)	0 (0.0) ^b	0 (0.0) ^b	0 (0.0) ^b	0 (0.0) ^b

^a Two patients in the control arm and one patient in the oxaliplatin arm of EFC2962 and one patient in the oxaliplatin of EFC2961 were not dosed.

^b Neurotoxicity reported uniquely under “paresthesia” in EFC2961.

^c Grade 3 only.

The preferred term “sensory disturbance” includes the prelisted toxicities of “cold-related dysesthesia” and “pharyngo-laryngeal dysesthesia” and is equivalent to the class of “acute neurosensory symptoms” that will be described below. These neurosensory symptoms were frequently reported in oxaliplatin monotherapy studies, as well as in the oxaliplatin arm (67.9%) of EFC2962 when compared with the 5-FU control arm (1.0%).

This term was not captured in EFC2961 which used a different neurotoxicity scale. Sensory disturbance was generally reported more frequently in studies of previously treated patients (76.5% to 92.5%), but was not related to oxaliplatin dose.

The preferred term “paresthesia” includes the prelisted toxicities of “paresthesia”, “paresthesia without pain”, “paresthesia with pain”, and “paresthesia with functional impairment”, and is equivalent to the “cumulative neurosensory symptoms” that is discussed below. These cumulative neurosensory symptoms were frequently reported in oxaliplatin monotherapy studies and were more frequent in the oxaliplatin arm of EFC2962 when compared with the control arm (all grades, 67.0% vs. 11.5%; Grade 3, 16.7% vs. 0%).

Although the same term was used in the context of a different neurotoxicity scale in EFC2961, the same incidence of cumulative neurosensory symptoms was associated with oxaliplatin, particularly for Grade 4 (13.1%).

The incidence of this toxicity was generally similar in the combination-therapy studies in previously treated patients.

A high incidence of neurosensory symptoms was observed across all oxaliplatin clinical trials. In all studies, two distinct patterns of oxaliplatin-related neurosensory symptoms were observed: an acute neurosensory syndrome and a cumulative neurosensory syndrome.

Acute neurosensory syndrome

An acute neurosensory syndrome of early onset that occurred within one to two days of oxaliplatin administration, was the most commonly reported type of neurosensory symptoms and was manifested principally as dysesthesia. This dysesthesia was more prominent in the upper extremities and pharyngolaryngeal area and was commonly triggered or exacerbated by exposure to cold. This acute neurosensory syndrome had a short duration, with most events resolving within one week or less; it includes rare Grade 3 events referred to as “pharyngolaryngeal syndrome,” consisting of subjective dysphagia and dyspnea, with no obstruction and normal blood gases, but of sufficient intensity to be worrisome to the patients or physicians.

Acute neurosensory symptoms are presented in Table 39. The clinical management of the acute neurosensory symptoms are through patient education and awareness. Patients should be instructed to avoid cold drinks and foods for a few days and to wear gloves if exposure to the cold is unavoidable. Additionally, ice chips should not be given during chemotherapy. In a similar fashion, the treating physician and his/her staff should be aware of the pharyngo-laryngeal symptoms.

Table 39 - Acute Neurosensory Symptoms: Studies EFC2962, EFC2964, and EFC2917

	EFC2962 (N=209)		EFC2964, EFC2917 (N=269)	
	All Grades	Grade 3	All Grades	Grade 3
Cold-Related Paresthesias				
Distal extremities	68%	0.5%	78%	2.6%
Pharyngo-laryngeal area	23%	0.5%	19%	1.5%

Cumulative neurosensory syndrome

The second pattern was seen as late-onset, cumulative neurosensory symptoms that could progress to proprioception and sensory deficits (difficulty in writing, holding objects, performing ordinary manual activities, weakness of hands, and intermittent disability of using hands for mechanical work). Their incidence is <10% at cumulative doses below 850 mg/m² by which time tumor responses have occurred (see Figure 10.). Thus, the decision to continue, reduce, or stop oxaliplatin dosing can be individualized on the basis of the quality of the observed response to treatment and of the emerging neurosensory symptoms. Cumulative neurosensory symptoms typically improve noticeably within months of oxaliplatin interruption.

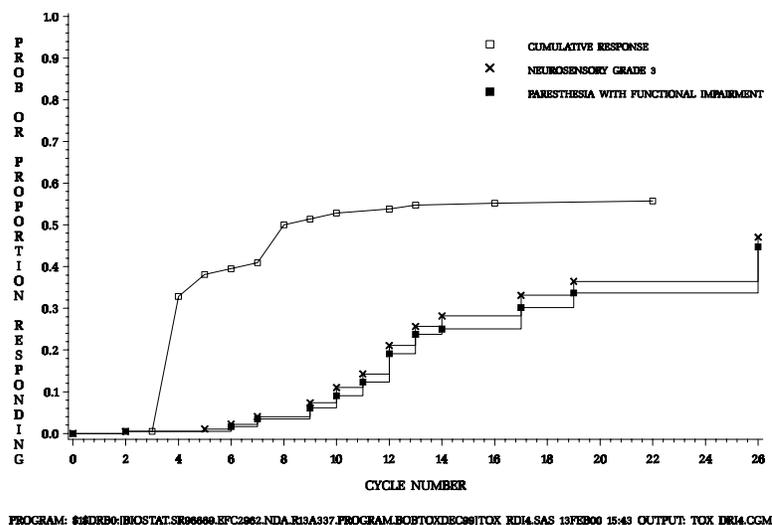


Figure 10 - Onset of Response and Grade 3 Neurotoxicity by Cycle

The cumulative dose associated with >10% incidence of Grade 3 neurosensory symptoms was comparable in all studies, with no evidence of a shift in risk between the 85 mg/m² dose regimens and the 125-130 mg/m² dose regimens.

7. CLINICAL BENEFIT

The clinical benefit of oxaliplatin was evaluated in the pivotal trial, EFC2962, using three endpoints:

- Quality of life as assessed by EORTC QLQ-C30
- Rate of change in performance status
- Time to treatment failure as assessed by the SWOG criteria (defined as “the time from registration to the first observation of disease progression, death due to any cause, or discontinuation of treatment”)

These endpoints are discussed in Sections 7.1, 7.2, and 7.3, respectively.

7.1 Quality of life

Quality of life (QoL) was assessed in Study EFC2962 using the self-administered EORTC QLQ-C30 (version 2.0), a validated, cancer-specific instrument. The QLQ-C30 measures functional domains (i.e., physical, role, emotional, cognitive, social), global health status, and symptoms (i.e., fatigue, nausea/vomiting, pain, dyspnea, insomnia, appetite loss, constipation, diarrhea). QoL was assessed at baseline, after every four cycles of therapy, and at discontinuation from study. QoL data were analyzed with a Wilcoxon signed rank test for within treatment comparisons and with a Mann-Whitney-Wilcoxon test for between treatment comparisons. Since there are 15 scales in the QLQ-C30, the statistical significance level was adjusted with Bonferroni’s procedure such that a p-value less than or equal to 0.0033 (0.05/15) was considered significant.

Three hundred fifty-one patients (178/210 patients in the control arm and 173/210 in the oxaliplatin arm) completed a baseline questionnaire within 30 days of the start of treatment. The number of completed questionnaires decreased during the study due to discontinuation of patients. Two hundred fifty-four of the 351 patients (127 patients in each arm) completed a questionnaire after 4 cycles of therapy. One hundred forty-one patients of the 351 patients (63 patients in the control arm and 78 in the oxaliplatin arm) completed questionnaires after both 4 and 8 cycles of therapy. Sixty-five of the 351 patients (32 patients in the control arm and 33 in the oxaliplatin arm) completed questionnaires after 4, 8, and 12 cycles of therapy. Twenty-six of the 351 patients (13 in each arm) completed questionnaires after 4, 8, 12, and 16 cycles of therapy. Because there were relatively few observations beyond 8 cycles of therapy, the analyses focused on the data from cycles 4 and 8.

The treatment groups were not significantly different at baseline. After both 4 and 8 cycles of therapy, the median change from baseline within most scales was 0 for both treatment groups. There were no statistically significant differences in change from baseline between treatment groups. Addition of oxaliplatin did not result in any difference in QoL as compared to the control arm.

7.2 Performance status

This analysis was performed to ascertain whether the addition of oxaliplatin to a 5-FU/FA regimen is associated with a more rapid decline in performance status in Study EFC2962. In this analysis, patients were censored on the date of the last documented performance status if it had not yet declined by a level of 1.

Figure 11 shows that the probability of experiencing a decline in performance status was the same in the two treatment arms. The addition of oxaliplatin did not result in any difference in the risk of decreased performance status compared to the control arm.

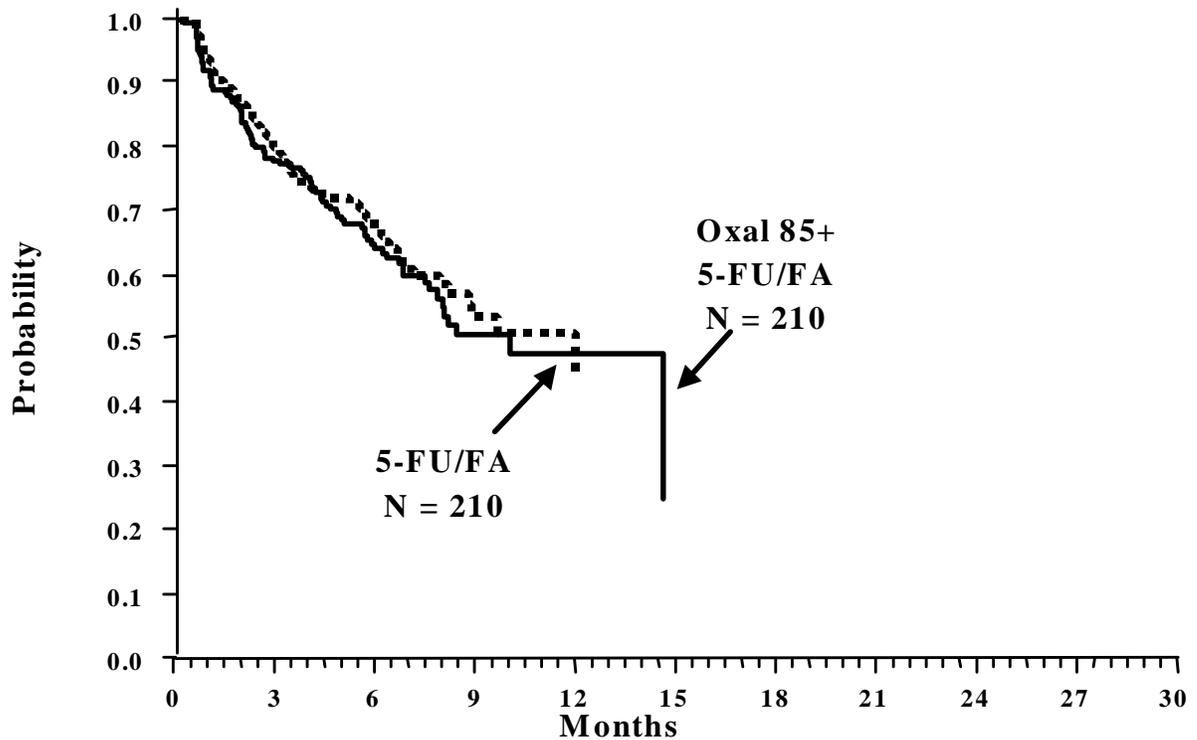


Figure 11 - Study EFC2962: Decline in Performance Status

7.3 Time to treatment failure

In terms of objective measures (tumor response, progression free survival, and survival) study EFC2962 showed a clear positive effect for oxaliplatin when added to 5FU/FA. However, the addition of oxaliplatin did result in excess gastrointestinal and neurosensory toxicity over what is normally observed with 5-FU/FA. While the toxicities resulting from oxaliplatin treatment have been reported to be manageable, it is clinically important to construct an endpoint which weighs the benefit from oxaliplatin anti-tumor activity against the effects of toxicity.

Neither the quality of life results from EFC2962 nor the time to first decline in performance status showed a statistical difference between the two treatment arms. Both analyses have limitations, however. The compliance in completion of the quality of life form was low, and performance status was collected prior to the start of each cycle, generally when patients had recovered sufficiently from toxicity resulting from the previous cycle.

For reasons stated above the Sponsor has constructed an ad hoc time to treatment failure (TTF) endpoint, using the SWOG definition published in 1992 [*Investigational New Drugs* (1992) 10:239-252]. TTF is defined in that publication as “the time from registration to the first observation of disease progression, death due to any cause, or discontinuation of

treatment.” The Sponsor has interpreted “discontinuation” to mean ‘discontinuation due to toxicity, adverse experience, or patient/investigator refusal to continue’.

Results of the TTF analysis, Figure 12, show a statistically significant benefit for the oxaliplatin + 5FU/FA patients (p=0.003 by the log rank test). This indicates that the objective benefit resulting from oxaliplatin treatment is not outweighed by excess toxicities.

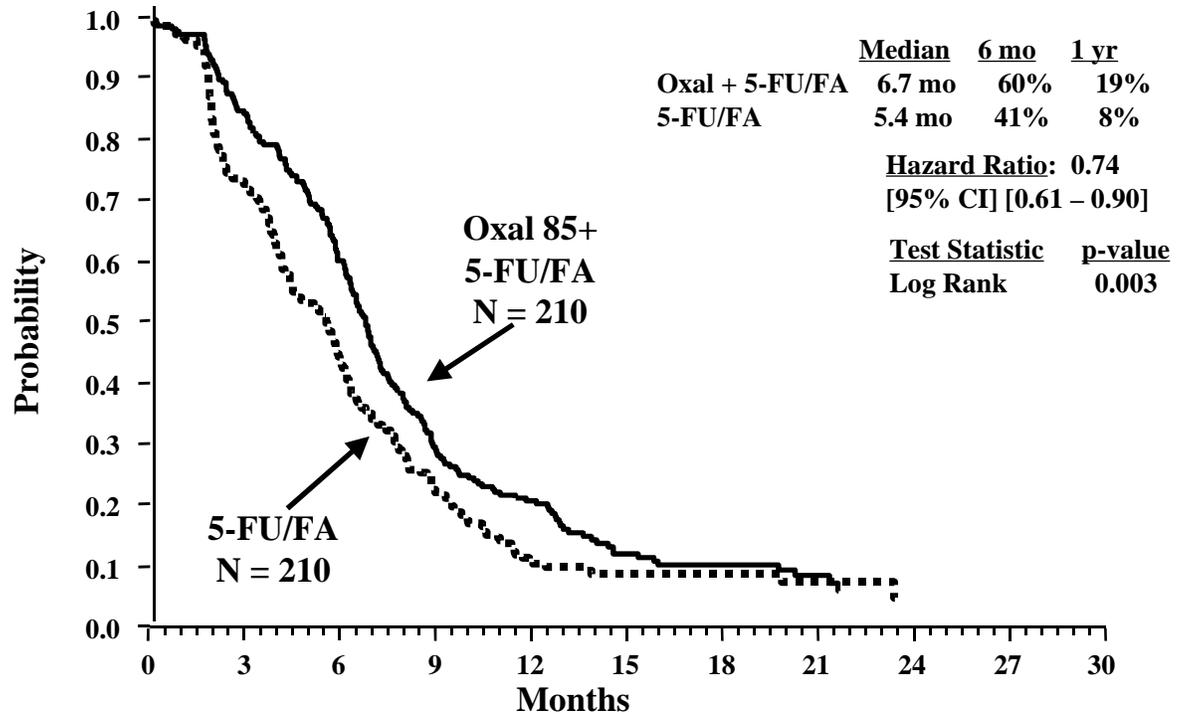


Figure 12 - Study EFC2962: Time to Treatment Failure

8. DISCUSSION

Oxaliplatin is a new intravenous oncolytic agent seeking recommendation for approval of the indication: “ELOXATINE (oxaliplatin) is indicated for the first-line treatment of patients with advanced colorectal cancer in combination with 5-FU-based chemotherapy.”

Based on the May 1998 FDA Guidance for Industry “*Providing Clinical Evidence of Effectiveness for Human Drug and Biological Products*,” the Sponsor has demonstrated the effectiveness of oxaliplatin in a study with independent substantiation from related study data. EFC2962, a multinational, first-line, randomized, Phase III trial, was the pivotal study. There are seven supportive trials that provide independent evidence of efficacy, the preponderance of which supports the pivotal trial, which fulfills the requirements of the guidance. Cross-substantiation of the indicated claim is demonstrated

by consistent efficacy in another multinational, first-line, randomized, Phase III trial (EFC2961). Independent substantiation of the indicated claim by other supportive trials was demonstrated by studies in refractory patients (patients with documented evidence of disease progression on 5-FU/FA-based therapy served as their own controls) (EFC2964 and EFC2917) and monotherapy studies of oxaliplatin (first- and second-line) (EFC2963, EFC2960, EFC3105, and EFC3106).

The Bimonthly Bolus+Infusion control arm in EFC2962 produced results similar to those achieved with the same regimen in the Intergroup Trial. In the Intergroup Trial the Bimonthly Bolus+Infusion was compared to the Daily x 5 bolus regimen and had slightly longer survival with statistically significant superiority in terms of response rate and PFS. Results from EFC2962 compared to the Intergroup Trial were 1) response rate: 21.9% versus 28.0%; 2) median PFS: 5.9 months versus 6.3 months; and 3) median survival 14.7 months versus 14.2 months. Thus, the control arm for EFC2962 performed at least as well as a daily x 5 bolus 5-FU/FA regimen and provided an adequate test for the addition of oxaliplatin.

In study EFC2962, the addition of oxaliplatin to the Bimonthly Bolus+Infusion regimen of 5-FU/FA demonstrated an improvement in the primary endpoint of PFS, with a median PFS of 8.1 months (95% confidence limits of 7.1 to 8.8 months) versus a median of 5.9 months (95% confidence limits of 5.5 to 6.4 months) in the arm receiving 5-FU/FA. This difference was statistically significant ($p=0.0003$, by the log rank test).

Forty-nine percent (49%) of the patients who were randomized to the oxaliplatin+5-FU/FA arm experienced a confirmed response. This was more than double the confirmed response rate among patients receiving 5-FU/FA alone (21.9%), and this difference was statistically significant ($p<0.001$, by the Chi-squared test).

Addition of oxaliplatin to 5FU/FA was also associated with a survival benefit appearing within the first six months after the start of treatment and continuing beyond 15 months. Median survival was 15.9 months in the oxaliplatin+5-FU/FA arm and 14.7 months in the control arm. Protocol-planned adjustment for baseline prognostic factors produced an estimated mortality hazard ratio of 0.70 (95% confidence limits of 0.54 to 0.92, $p=0.01$). This corresponds to a mortality reduction of 30%.

Together, these data provide compelling evidence that the addition of oxaliplatin to 5-FU/FA as first-line treatment provides a significant clinical advantage to patients. The rapid onset of a high response rate and the low rate of outright progression are associated with an early decrease in the risk of death, which is maintained for over a year. Oxaliplatin offers physicians and their patients a valuable new option in the overall management of this disease.

In Study EFC2961, the estimate of median survival was 17.4 months for oxaliplatin plus 5-FU/FA patients compared to 19.2 months for 5-FU/FA patients. There was no significant difference between treatment arms per log-rank test ($p\text{-value}=0.58$).

The timing of surgery in this study was related to exposure to oxaliplatin. More patients in the experimental arm received surgery following their treatment with oxaliplatin plus 5-FU/FA. Conversely, more patients in the control arm received surgery following post-study treatment with oxaliplatin. The prolonged survival observed in both arms suggests that the combination of oxaliplatin-based chemotherapy plus surgery may offer additional benefits over chemotherapy alone. Overall, subsequent therapy makes it impossible to accurately interpret differences between the two arms in survival in this trial. However, the overall results are consistent with those of EFC2962.

The studies in previously untreated advanced colorectal cancer patients were statistically significant for the per-protocol primary efficacy endpoints of progression-free survival (in EFC2962) and response rate (in EFC2961). Statistical significance was also demonstrated for the secondary endpoints of response rate (in EFC2962) and progression-free survival (in EFC2961). In these two studies, oxaliplatin produced confirmed response rates (34% to 49%) that were two to three times higher than those observed with 5-FU/FA alone (12% to 22%) and increased progression-free survival by approximately three months (medians of approximately eight and five months for oxaliplatin and control regimens, respectively).

In patients who were demonstrated to be refractory to 5-FU chemotherapy, oxaliplatin produced confirmed response rates of 7% to 22.8% when combined with the same 5-FU regimens on which patients had progressed. Oxaliplatin produced progression-free survival durations of approximately 4 to 5 months and overall survival durations of approximately 10 to 11 months.

Oxaliplatin monotherapy, administered at a dose of 130 mg/m² q3w, produced confirmed response rates of 8% and 23.7% in previously untreated patients and best response rates (confirmed and unconfirmed responses) of 7.8% and 10.3% in patients who were refractory to 5-FU chemotherapy. Progression-free survival and overall survival of previously untreated patients were approximately 4 months and 14 months, respectively; overall survival in patients who were refractory to 5-FU chemotherapy was approximately eight months. Together, the results of these studies provide clear evidence of the single agent activity of oxaliplatin, corroborating evidence for the safety and efficacy of oxaliplatin in combination with 5-FU-based therapy.

The safety profile of oxaliplatin was established from the Phase II-III studies previously described, with oxaliplatin given as single-agent or in combination with 5-FU, using several doses, schedules, and modes of administration in various tumor types.

The hematotoxicity of oxaliplatin given as monotherapy was usually mild; neutropenia and thrombocytopenia were more pronounced in combination with 5-FU/FA without clinical consequence. Nausea and/or vomiting were observed in the majority of patients; diarrhea was common in combination with 5-FU/FA; mucositis occurred mainly when oxaliplatin was associated with 5-FU.

Neurological toxicity is dose-limiting for oxaliplatin, characterized primarily by a peripheral sensory neuropathy, with dysesthesias and or distal paresthesias often triggered or exacerbated by cold. This toxicity generally regresses between cycles of treatment, but tends to last longer with subsequent cycles. Functional impairment (proprioception and sensory deficit), including difficulty with activities requiring fine motor coordination, may occur as a result of the sensory impairment. The risk of functional impairment is less than 10% at a cumulative dose of approximately 850 mg/m² (ten cycles at the recommended dose and regimen). However, almost all tumor responses are observed to occur before this point. Thus, the decision to continue, reduce, or stop oxaliplatin dosing can be individualized on the basis of the quality of the observed response to treatment and of the emerging neurosensory symptoms. Cumulative neurosensory symptoms typically improve noticeably within months of oxaliplatin interruption.

Of note, the specific adverse event profile of oxaliplatin did not lead to a compromise in quality of life parameters, in performance status, or in time to treatment failure. Furthermore, the risk of treatment-related mortality is low (<1%).

Thus, the safety and efficacy of oxaliplatin for the first-line treatment of patients with advanced colorectal cancer in combination with 5-FU-based chemotherapy represent an important advantage over currently available therapies since oxaliplatin doubles overall tumor response rate, decreases by 33% the risk of disease progression, and decreases by 24-30% the risk of death with manageable, reversible toxicities.

9. PRIMARY TABLES

Primary Table 1 - WHO Criteria Used to Evaluate Objective Tumor Responses

Overall responses	Definitions
Complete response (CR) ^a	Disappearance of all evidence of measurable and evaluable disease that persists for at least four weeks without the appearance of any new lesions.
Partial response (PR) ^a	Decrease of $\geq 50\%$ in the sum of the products of the largest perpendicular diameters (bidimensional disease) or in the sum of the lengths (unidimensional disease) of all measurable lesions that persists for at least four weeks.
No change (NC) ^a = Stable disease (SD)	Decrease of $< 50\%$ or an increase of $< 25\%$ in the sum of the products of the largest perpendicular diameters (bidimensional disease) or in the sum of the lengths (unidimensional disease) of all measurable lesions.
Progressive disease (PD) ^b = Disease progression (DP)	Increase of $\geq 25\%$ in the total area of measurable disease, the appearance of a new lesion, or the occurrence of pleural effusion or ascites substantiated by positive cytology.
Confirmed response	Complete or partial responses confirmed on at least two consecutive evaluations, separated by an interval greater than four weeks.
Best response	Complete or partial responses (confirmed and unconfirmed)
Overall response rate (ORR)	Number of complete and partial responses divided by the total number of enrolled patients.
Progression-free survival (PFS) ^c	Calculated from the date of study enrollment to the date of documented disease progression or death.
Overall survival (OS) ^c	Calculated from the date of study enrollment to the date of death.
Quality of life ^d	Measured by the EORTC QLQ-C30 questionnaire.

WHO=World Health Organization; EORTC QLQ-C30=European Organization for Research and Treatment of Cancer Quality of Life Questionnaire

^a Measured relative to baseline

^b Measured relative to the smallest total area of measurable disease

^c Based on Kaplan-Meier methods

^d Assessed only in EFC2962

Primary Table 2 - Prelisted Toxicities and All Other Adverse Events Reported for ≥5% of Patients in Any Treatment Arm: Studies EFC2962 and EFC2961- Number (%) of Patients

Body System/ Preferred Term	EFC2962				EFC2961			
	5-FU/FA N=208 ^a		Oxal 85+5-FU/FA N=209 ^a		5-FU/FA N=100		Oxal 125 + 5-FU/FA N=99 ^a	
	All Grades	Grades 3 and 4	All Grades	Grades 3 and 4	All Grades	Grades 3 and 4	All Grades	Grades 3 and 4
Body as a whole - general disorders								
Allergic reaction	0 (0.0)	0 (0.0)	12 (5.7)	3 (1.4)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Asthenia	45 (21.6)	7 (3.4)	49 (23.4)	9 (4.3)	6 (6.0)	4 (4.0)	3 (3.0)	1 (1.0)
Chest pain	7 (3.4)	1 (0.5)	11 (5.3)	0 (0.0)	6 (6.0)	0 (0.0)	3 (3.0)	1 (1.0)
Fatigue	15 (7.2)	1 (0.5)	27 (12.9)	2 (1.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Fever	31 (14.9)	0 (0.0)	69 (33.0)	0 (0.0)	19 (19.0)	5 (5.0)	12 (12.1)	7 (7.1)
Pain	21 (10.1)	2 (1.0)	24 (11.5)	5 (2.4)	12 (12.0)	3 (3.0)	6 (6.1)	2 (2.0)
Central & peripheral nervous system disorders								
Headache	10 (4.8)	0 (0.0)	13 (6.2)	1 (0.5)	6 (6.0)	0 (0.0)	3 (3.0)	1 (1.0)
Muscle contractions involuntary	3 (1.4)	0 (0.0)	12 (5.7)	2 (1.0)	2 (2.0) ^b	0 (0.0) ^b	1 (1.0) ^b	0 (0.0) ^b
Neuritis motor	1 (0.5)	1 (0.5)	15 (7.2)	5 (2.4)	0 (0.0) ^b	0 (0.0) ^b	0 (0.0) ^b	0 (0.0) ^b
Neuritis sensory	25 (12.0)	0 (0.0)	142 (67.9) ^c	39 (18.7)	0 (0.0) ^b	0 (0.0) ^b	0 (0.0) ^b	0 (0.0) ^b
Paraesthesia	24 (11.5)	0 (0.0)	140 (67.0) ^c	35 (16.7)	20 (20.0)	0 (0.0)	91 (91.9)	45 (45.5) ^d
Sensory disturbance	2 (1.0)	0 (0.0)	142 (67.9) ^c	1 (0.5)	0 (0.0) ^b	0 (0.0) ^b	0 (0.0) ^b	0 (0.0) ^b
Gastrointestinal system disorders								
Abdominal pain	31 (14.9)	2 (1.0)	42 (20.1)	0 (0.0)	21 (21.0)	7 (7.0)	17 (17.2)	3 (3.0)
Anorexia	12 (5.8)	0 (0.0)	12 (5.7)	2 (1.0)	5 (5.0)	3 (3.0)	7 (7.1)	3 (3.0)
Constipation	27 (13.0)	1 (0.5)	46 (22.0)	1 (0.5)	5 (5.0)	1 (1.0)	4 (4.0)	0 (0.0)
Diarrhoea	91 (43.8)	11 (5.3)	123 (58.9)	25 (12.0)	49 (49.0)	5 (5.0)	85 (85.9)	43 (43.4)
Dyspepsia	16 (7.7)	1 (0.5)	9 (4.3)	0 (0.0)	0 (0.0)	0 (0.0)	1 (1.0)	0 (0.0)
Intestinal obstruction	9 (4.3)	7 (3.4)	5 (2.4)	4 (1.9)	1 (1.0)	1 (1.0)	8 (8.1)	6 (6.1)
Nausea	111 (53.4)	4 (1.9)	151 (72.2)	12 (5.7)	0 (0.0) ^c	0 (0.0) ^c	0 (0.0) ^c	0 (0.0) ^c
Stomatitis	74 (35.6)	3 (1.4)	92 (44.0)	12 (5.7)	59 (59.0)	4 (4.0)	61 (61.6)	10 (10.1)
Vomiting	61 (29.3)	4 (1.9)	113 (54.1)	12 (5.7)	64 (64.0)	2 (2.0)	88 (88.9)	25 (25.3)
Musculo-skeletal system disorders								
Back pain	19 (9.1)	1 (0.5)	14 (6.7)	2 (1.0)	7 (7.0)	3 (3.0)	6 (6.1)	2 (2.0)
Skeletal pain	13 (6.3)	0 (0.0)	8 (3.8)	2 (1.0)	1 (1.0)	1 (1.0)	2 (2.0)	0 (0.0)
Platelet, bleeding & clotting disorders								
Haemorrhage NOS	28 (13.5)	1 (0.5)	24 (11.5)	0 (0.0)	6 (6.0)	0 (0.0)	9 (9.1)	1 (1.0)
Thrombosis	3 (1.4)	2 (1.0)	2 (1.0)	1 (0.5)	6 (6.0)	1 (1.0)	3 (3.0)	1 (1.0)
Psychiatric disorders								
Depression	11 (5.3)	2 (1.0)	15 (7.2)	3 (1.4)	1 (1.0)	0 (0.0)	1 (1.0)	1 (1.0)
Resistance mechanism disorders								
Infection	58 (27.9)	2 (1.0)	66 (31.6)	2 (1.0)	5 (5.0)	4 (4.0)	2 (2.0)	0 (0.0)

(Continued)

Body System/ Preferred Term	EFC2962				EFC2961			
	5-FU/FA N=208 ^a		Oxal 85+5-FU/FA N=209 ^a		5-FU/FA N=100		Oxal 125 + 5-FU/FA N=99 ^a	
	All Grades	Grades 3 and 4	All Grades	Grades 3 and 4	All Grades	Grades 3 and 4	All Grades	Grades 3 and 4
Respiratory system disorders								
Coughing	14 (6.7)	0 (0.0)	10 (4.8)	0 (0.0)	3 (3.0)	0 (0.0)	4 (4.0)	0 (0.0)
Rhinitis	11 (5.3)	0 (0.0)	12 (5.7)	0 (0.0)	2 (2.0)	0 (0.0)	1 (1.0)	0 (0.0)
Upper resp tract infection	7 (3.4)	0 (0.0)	13 (6.2)	0 (0.0)	1 (1.0)	0 (0.0)	0 (0.0)	0 (0.0)
Skin and appendage disorders								
Alopecia	40 (19.2)	0 (0.0)	37 (17.7)	0 (0.0)	4 (4.0)	0 (0.0)	4 (4.0)	0 (0.0)
Skin disorder	67 (32.2)	1 (0.5)	60 (28.7)	0 (0.0)	38 (38.0)	1 (1.0)	39 (39.4)	0 (0.0)
Special senses other, disorders								
Taste perversion	7 (3.4)	0 (0.0)	12 (5.7)	0 (0.0)	0 (0.0)	0 (0.0)	1 (1.0)	0 (0.0)
Urinary system disorders								
Urinary tract infection	6 (2.9)	0 (0.0)	8 (3.8)	0 (0.0)	4 (4.0)	1 (1.0)	5 (5.1)	1 (1.0)
Vision disorders								
Conjunctivitis	25 (12.0)	3 (1.4)	14 (6.7)	0 (0.0)	1 (1.0)	0 (0.0)	1 (1.0)	0 (0.0)

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^a Two patients in the control arm and one patient in the oxaliplatin arm of EFC2962 and one patient in the oxaliplatin of EFC2961 were not dosed.

^b Neurotoxicity reported uniquely under "paresthesia" in EFC2961.

^c Grade 3 only

^d Grade 3 and 4 (see scale on Table 37.); Grade 4=13.1%.

^e Nausea was not reported as separate event in this study but was reported as nausea/vomiting.

Primary Table 3 - Prelisted Toxicities and All Other Adverse Events Reported for ≥5% of Patients in Any Treatment Arm: Previously Treated Patients Receiving Combination Therapy - Number (%) of Patients

Body System/ Preferred Term	EFC2917				EFC2964			
	Oxal 130 + Daily x 5 N=115		Oxal 85 + Weekly 24-Hr N=57		Oxal 85 + Bimonthly A N=57		Oxal 85 + Bimonthly B N=40	
	All Grades	Grades 3 and 4	All Grades	Grades 3 and 4	All Grades	Grades 3 and 4	All Grades	Grades 3 and 4
Body as a whole - general disorders								
Allergy	1 (0.9)	0 (0.0)	0 (0.0)	0 (0.0)	3 (5.3)	1 (1.8)	1 (2.5)	0 (0.0)
Asthenia	14 (12.2)	2 (1.7)	12 (21.1)	3 (5.3)	39 (68.4)	13 (22.8)	22 (55.0)	1 (2.5)
Chest pain	6 (5.2)	1 (0.9)	1 (1.8)	0 (0.0)	5 (8.8)	0 (0.0)	2 (5.0)	0 (0.0)
Condition aggravated	2 (1.7)	2 (1.7)	1 (1.8)	1 (1.8)	4 (7.0)	2 (3.5)	1 (2.5)	0 (0.0)
Fatigue	37 (32.2)	4 (3.5)	11 (19.3)	1 (1.8)	2 (3.5)	0 (0.0)	1 (2.5)	1 (2.5)
Fever	34 (29.6)	1 (0.9)	13 (22.8)	0 (0.0)	29 (50.9)	1 (1.8)	11 (27.5)	1 (2.5)
Hot flushes	0 (0.0)	0 (0.0)	3 (5.3)	0 (0.0)	1 (1.8)	0 (0.0)	0 (0.0)	0 (0.0)
Influenza-like symptoms	9 (7.8)	0 (0.0)	5 (8.8)	0 (0.0)	2 (3.5)	0 (0.0)	4 (10.0)	0 (0.0)
Pain	7 (6.1)	1 (0.9)	5 (8.8)	0 (0.0)	11 (19.3)	3 (5.3)	5 (12.5)	1 (2.5)
Rigors	1 (0.9)	0 (0.0)	3 (5.3)	1 (1.8)	1 (1.8)	0 (0.0)	1 (2.5)	0 (0.0)
Weight decrease	12 (10.4)	0 (0.0)	12 (21.1)	1 (1.8)	9 (15.8)	0 (0.0)	2 (5.0)	0 (0.0)
Weight increase	0 (0.0)	0 (0.0)	1 (1.8)	0 (0.0)	4 (7.0)	0 (0.0)	0 (0.0)	0 (0.0)
Cardiovascular disorders, general								
Hypertension	3 (2.6)	1 (0.9)	1 (1.8)	0 (0.0)	4 (7.0)	1 (1.8)	1 (2.5)	0 (0.0)
Hypotension	2 (1.7)	1 (0.9)	1 (1.8)	0 (0.0)	2 (3.5)	0 (0.0)	2 (5.0)	1 (2.5)
Oedema	2 (1.7)	0 (0.0)	3 (5.3)	0 (0.0)	2 (3.5)	1 (1.8)	2 (5.0)	0 (0.0)
Oedema legs	10 (8.7)	0 (0.0)	0 (0.0)	0 (0.0)	5 (8.8)	1 (1.8)	1 (2.5)	0 (0.0)
Central & peripheral nervous system disorders								
Ataxia	0 (0.0)	0 (0.0)	1 (1.8)	0 (0.0)	3 (5.3)	1 (1.8)	1 (2.5)	0 (0.0)
Dizziness	6 (5.2)	0 (0.0)	3 (5.3)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Headache	12 (10.4)	0 (0.0)	7 (12.3)	0 (0.0)	8 (14.0)	1 (1.8)	8 (20.0)	0 (0.0)
Muscle contractions involuntary	16 (13.9)	1 (0.9)	3 (5.3)	0 (0.0)	13 (22.8)	1 (1.8)	10 (25.0)	0 (0.0)
Neuralgia	2 (1.7)	1 (0.9)	1 (1.8)	0 (0.0)	3 (5.3)	1 (1.8)	1 (2.5)	1 (2.5)
Neuritis motor	13 (11.3)	2 (1.7)	2 (3.5)	2 (3.5)	1 (1.8)	0 (0.0)	1 (2.5)	1 (2.5)
Neuritis sensory	26 (22.6)	2 (1.7)	14 (24.6)	3 (5.3)	47 (82.5)	9 (15.8)	39 (97.5)	12 (30.0)
Paraesthesia	82 (71.3)	9 (7.8)	41 (71.9)	4 (7.0)	32 (56.1)	9 (15.8)	18 (45.0)	11 (27.5)
Sensory disturbance	88 (76.5)	2 (1.7)	45 (78.9)	2 (3.5)	44 (77.2)	2 (3.5)	37 (92.5)	3 (7.5)
Vertigo	2 (1.7)	0 (0.0)	0 (0.0)	0 (0.0)	8 (14.0)	1 (1.8)	2 (5.0)	0 (0.0)
Gastrointestinal system disorders								
Abdominal pain	28 (24.3)	1 (0.9)	13 (22.8)	3 (5.3)	35 (61.4)	6 (10.5)	20 (50.0)	2 (5.0)
Anorexia	27 (23.5)	2 (1.7)	13 (22.8)	4 (7.0)	17 (29.8)	3 (5.3)	10 (25.0)	0 (0.0)
Constipation	32 (27.8)	2 (1.7)	13 (22.8)	0 (0.0)	19 (33.3)	2 (3.5)	9 (22.5)	0 (0.0)
Diarrhoea	84 (73.0)	23 (20.0)	32 (56.1)	12 (21.1)	30 (52.6)	3 (5.3)	23 (57.5)	2 (5.0)
Dyspepsia	7 (6.1)	0 (0.0)	1 (1.8)	0 (0.0)	3 (5.3)	0 (0.0)	1 (2.5)	1 (2.5)
Flatulence	2 (1.7)	0 (0.0)	3 (5.3)	1 (1.8)	8 (14.0)	1 (1.8)	2 (5.0)	0 (0.0)
Gastroesophageal reflux	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	4 (7.0)	0 (0.0)	0 (0.0)	0 (0.0)
Haemorrhoids	0 (0.0)	0 (0.0)	4 (7.0)	0 (0.0)	1 (1.8)	0 (0.0)	0 (0.0)	0 (0.0)
Nausea	85 (73.9)	11 (9.6)	38 (66.7)	5 (8.8)	39 (68.4)	4 (7.0)	28 (70.0)	2 (5.0)
Stomatitis	26 (22.6)	4 (3.5)	9 (15.8)	2 (3.5)	18 (31.6)	3 (5.3)	22 (55.0)	7 (17.5)
Vomiting	72 (62.6)	12 (10.4)	27 (47.4)	3 (5.3)	32 (56.1)	3 (5.3)	17 (42.5)	2 (5.0)

(Continued)

Body System/ Preferred Term	EFC2917				EFC2964			
	Oxal 130 + Daily x 5 N=115		Oxal 85 + Weekly 24-Hr N=57		Oxal 85 + Bimonthly A N=57		Oxal 85 + Bimonthly B N=40	
	All Grades	Grades 3 and 4	All Grades	Grades 3 and 4	All Grades	Grades 3 and 4	All Grades	Grades 3 and 4
Heart rate and rhythm disorders								
Tachycardia	0 (0.0)	0 (0.0)	1 (1.8)	0 (0.0)	2 (3.5)	0 (0.0)	2 (5.0)	0 (0.0)
Metabolic and nutritional disorders								
Gout	0 (0.0)	0 (0.0)	3 (5.3)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Musculo-skeletal system disorders								
Arthralgia	5 (4.3)	0 (0.0)	2 (3.5)	0 (0.0)	3 (5.3)	0 (0.0)	3 (7.5)	0 (0.0)
Back pain	10 (8.7)	0 (0.0)	4 (7.0)	0 (0.0)	10 (17.5)	0 (0.0)	3 (7.5)	0 (0.0)
Myalgia	3 (2.6)	0 (0.0)	1 (1.8)	0 (0.0)	4 (7.0)	0 (0.0)	1 (2.5)	0 (0.0)
Skeletal pain	3 (2.6)	0 (0.0)	4 (7.0)	0 (0.0)	7 (12.3)	2 (3.5)	2 (5.0)	0 (0.0)
Neoplasms								
Neoplasm malignant aggravated	8 (7.0)	5 (4.3)	6 (10.5)	5 (8.8)	2 (3.5)	1 (1.8)	1 (2.5)	0 (0.0)
Platelet, bleeding & clotting disorders								
Epistaxis	5 (4.3)	0 (0.0)	2 (3.5)	0 (0.0)	1 (1.8)	0 (0.0)	4 (10.0)	0 (0.0)
Haemorrhage NOS	13 (11.3)	2 (1.7)	4 (7.0)	1 (1.8)	12 (21.1)	0 (0.0)	6 (15.0)	0 (0.0)
Psychiatric disorders								
Depression	8 (7.0)	1 (0.9)	5 (8.8)	1 (1.8)	11 (19.3)	1 (1.8)	8 (20.0)	0 (0.0)
Insomnia	4 (3.5)	0 (0.0)	1 (1.8)	0 (0.0)	5 (8.8)	0 (0.0)	6 (15.0)	0 (0.0)
Nervousness	6 (5.2)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Resistance mechanism disorders								
Herpes simplex	3 (2.6)	0 (0.0)	1 (1.8)	0 (0.0)	3 (5.3)	0 (0.0)	0 (0.0)	0 (0.0)
Infection	11 (9.6)	2 (1.7)	2 (3.5)	0 (0.0)	15 (26.3)	0 (0.0)	10 (25.0)	2 (5.0)
Infection fungal	1 (0.9)	0 (0.0)	0 (0.0)	0 (0.0)	3 (5.3)	0 (0.0)	0 (0.0)	0 (0.0)
Sepsis	3 (2.6)	2 (1.7)	1 (1.8)	1 (1.8)	1 (1.8)	1 (1.8)	2 (5.0)	2 (5.0)
Respiratory system disorders								
Bronchitis	3 (2.6)	1 (0.9)	3 (5.3)	0 (0.0)	7 (12.3)	1 (1.8)	2 (5.0)	0 (0.0)
Coughing	10 (8.7)	0 (0.0)	7 (12.3)	0 (0.0)	5 (8.8)	0 (0.0)	3 (7.5)	0 (0.0)
Dyspnoea	16 (13.9)	4 (3.5)	7 (12.3)	1 (1.8)	7 (12.3)	5 (8.8)	5 (12.5)	1 (2.5)
Laryngismus	14 (12.2)	3 (2.6)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (2.5)	0 (0.0)
Pharyngitis	2 (1.7)	0 (0.0)	1 (1.8)	0 (0.0)	0 (0.0)	0 (0.0)	3 (7.5)	0 (0.0)
Rhinitis	4 (3.5)	0 (0.0)	4 (7.0)	0 (0.0)	3 (5.3)	0 (0.0)	6 (15.0)	0 (0.0)
Sputum increased	1 (0.9)	0 (0.0)	1 (1.8)	0 (0.0)	3 (5.3)	0 (0.0)	2 (5.0)	0 (0.0)
Upper resp tract infection	6 (5.2)	0 (0.0)	4 (7.0)	0 (0.0)	3 (5.3)	0 (0.0)	2 (5.0)	0 (0.0)

(Continued)

Body System/ Preferred Term	EFC2917				EFC2964			
	Oxal 130 + Daily x 5 N=115		Oxal 85 + Weekly 24-Hr N=57		Oxal 85 + Bimonthly A N=57		Oxal 85 + Bimonthly B N=40	
	All Grades	Grades 3 and 4	All Grades	Grades 3 and 4	All Grades	Grades 3 and 4	All Grades	Grades 3 and 4
Secondary terms								
Procedural site reaction	1 (0.9)	0 (0.0)	1 (1.8)	1 (1.8)	3 (5.3)	0 (0.0)	1 (2.5)	0 (0.0)
Skin and appendage disorders								
Alopecia	9 (7.8)	0 (0.0)	6 (10.5)	0 (0.0)	10 (17.5)	0 (0.0)	10 (25.0)	0 (0.0)
Nail disorder	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (1.8)	0 (0.0)	2 (5.0)	0 (0.0)
Pruritus	3 (2.6)	0 (0.0)	0 (0.0)	0 (0.0)	3 (5.3)	0 (0.0)	0 (0.0)	0 (0.0)
Rash erythematous	1 (0.9)	0 (0.0)	0 (0.0)	0 (0.0)	2 (3.5)	0 (0.0)	2 (5.0)	0 (0.0)
Skin disorder	14 (12.2)	0 (0.0)	20 (35.1)	0 (0.0)	16 (28.1)	0 (0.0)	15 (37.5)	0 (0.0)
Skin exfoliation	2 (1.7)	1 (0.9)	6 (10.5)	0 (0.0)	1 (1.8)	0 (0.0)	0 (0.0)	0 (0.0)
Sweating increased	7 (6.1)	0 (0.0)	4 (7.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Special senses other, disorders								
Taste loss	2 (1.7)	0 (0.0)	1 (1.8)	0 (0.0)	0 (0.0)	0 (0.0)	2 (5.0)	1 (2.5)
Taste perversion	4 (3.5)	0 (0.0)	3 (5.3)	0 (0.0)	1 (1.8)	0 (0.0)	4 (10.0)	0 (0.0)
Urinary system disorders								
Micturition frequency abnormal	1 (0.9)	0 (0.0)	1 (1.8)	0 (0.0)	2 (3.5)	0 (0.0)	2 (5.0)	0 (0.0)
Urinary tract infection	3 (2.6)	0 (0.0)	4 (7.0)	0 (0.0)	3 (5.3)	0 (0.0)	1 (2.5)	0 (0.0)
Vision disorders								
Conjunctivitis	1 (0.9)	0 (0.0)	0 (0.0)	0 (0.0)	6 (10.5)	1 (1.8)	5 (12.5)	0 (0.0)
Lacrimation abnormal	1 (0.9)	0 (0.0)	0 (0.0)	0 (0.0)	2 (3.5)	0 (0.0)	2 (5.0)	0 (0.0)
Vision abnormal	5 (4.3)	1 (0.9)	1 (1.8)	1 (1.8)	1 (1.8)	0 (0.0)	2 (5.0)	0 (0.0)

APPENDIX 1 - SUMMARY OF EFFICACY IN SECONDARY STUDIES IN PATIENTS WITH ADVANCED COLORECTAL CANCER

Nine uncontrolled Secondary Studies of oxaliplatin were conducted in patients with colorectal cancer. These included studies of oxaliplatin in combination with 5-FU+FA in previously untreated and/or previously treated patients and studies of oxaliplatin as monotherapy. The study designs and enrollment information are summarized in the following table.

Study Designs of Uncontrolled Secondary Studies of Oxaliplatin

Study No. Primary Investigator Dates of Study Defining Publication	Study Design	Diagnosis and Criteria for Inclusion	Patients			Drug Regimen ¹ Treatment Duration	Criteria for Evaluation
			N (M/F) (B/W/O)	Age Range (years) (Median)	Per Treatment Group		
<i>Previously Untreated Patients, Chronomodulated Oxaliplatin + 5-FU+FA</i>							
EFC3111 Lévi, F. May 90-May 91 Publication: <i>J Natl Cancer Inst</i> 1994; 86(21):1608-1617.	Phase III, multicenter, open-label, randomized, in combination with 5-FU+FA, chronomodulation compared to constant drug delivery	Measurable recurrent or metastatic colorectal cancer, prior therapy allowed only if disease- and treatment-free for 6 months	Total enrolled: 92 Dosed with OXAL + 5-FU: 90 (45/45) (Not reported)	31-73 (60)	CIV: 45 CM: 45	<i>Regimen:</i> CIV: [OXAL 20-25 mg/m ² /d, 5-FU 600-700 mg/m ² /d, and FA 300 mg/m ² /d (24-h infusion)] x 5 days; q3w CM: [OXAL 20-25 mg/m ² /d (12-h infusion), then 5-FU 600-700 mg/m ² /d (12-h infusion) simultaneous with FA 300 mg/m ² /d (12-h infusion)] x 5 days; q3w <i>Duration:</i> up to 20 cycles	Efficacy: every 3 cycles, reviewed by radiologists: response rate, time to disease progression, OS Safety
EFC3112 Lévi, F. May 91-Feb 93 Publication: <i>Lancet</i> 1997;350(9087): 1325-1326.	Phase III, multicenter, open-label, randomized, in combination with 5-FU+FA, chronomodulation compared to constant drug delivery	Measurable recurrent or metastatic colorectal cancer, prior therapy allowed only if disease- and treatment-free for 6 months (unless cisplatin >300 mg/m ² total dose), ≥1 measurable lesion	Total enrolled: 186 Total dosed: 183 CIV: 92 (59/33) CM: 91 (51/40)	CIV: 29-75 (61) ² CM: 22-75 (61) ³	CIV: 92 CM: 91	<i>Regimen:</i> CIV: [OXAL 20-25 mg/m ² /d, 5-FU 600-700 mg/m ² /d ⁴ , and FA 300 mg/m ² /d ⁴ (24-h infusion)] x 5 days; q3w CM: [OXAL 20-25 mg/m ² /d ⁴ (12-h infusion), then 5-FU 600-700 mg/m ² /d ⁴ (12-h infusion) simultaneous with FA 300 mg/m ² /d (12-h infusion)] x 5 days; q3w <i>Duration:</i> up to 24 cycles	Efficacy: every 3 cycles, reviewed by radiologists: response rate, PFS, OS Safety

¹ All drugs administered intravenously unless specified otherwise² Includes one patient enrolled but not dosed.³ Includes two patients enrolled but not dosed.

Study No. Primary Investigator Dates of Study Defining Publication	Study Design	Diagnosis and Criteria for Inclusion	Patients			Drug Regimen ¹ Treatment Duration	Criteria for Evaluation
			N (M/F) (B/W/O)	Age Range (years) (Median)	Per Treatment Group		
Previously Treated and Previously Untreated Patients, Oxaliplatin + 5-FU+FA							
EFC3110 Lévi, F. Apr 88-Sep 90 Publication: <i>Cancer</i> (Phila) 1992;69(4):893-900.	Phase II, single-center, open-label, noncontrolled, in combination with 5-FU+FA	Advanced recurrent and/or metastatic colorectal cancer, ≥1 measurable lesion	93 (58/35) (Not reported)	28-74 (53)	N/A	<i>Regimen:</i> CM [OXAL 25 mg/m ² /d (Cycle 1) or 30 mg/m ² /d (subsequent cycles) (12-h infusion), then 5-FU 700 mg/m ² /d (Cycle 1) or 800 mg/m ² /d (subsequent cycles) (12-h infusion) simultaneous with FA 300 mg/m ² /d (12-h infusion)] x 5 days; q3w <i>Duration:</i> up to 27 cycles	Efficacy: every 3 cycles, reviewed by radiologists: response, PFS, OS Safety
Previously Treated Patients, Oxaliplatin + 5-FU+FA							
EFC3108 (93-OXA-05) de Gramont, A. Jun 93-May 94 Publication: <i>Eur J Cancer</i> 1997; 33(2):214-219.	Phase II, single-center, open-label, noncontrolled, in combination with 5 FU+FA	Histologically proven colorectal cancer, nonresectable metastases, ≥1 measurable lesion outside the irradiated zone, refractory to prior 5-FU+FA therapy for metastases	28 (20/8) (Not reported)	37-75 (61)	N/A	<i>Regimen:</i> OXAL 100 mg/m ² (2-h infusion) and FA 500 mg/m ² (2-h infusion) D1, then 5-FU (24-h continuous infusion) D1, FA 500 mg/m ² (2-h infusion) D2, simultaneous with 5-FU (24-h continuous infusion) D2; q2w 5-FU dose was 1500 mg/m ² Cycles 1-2, and 2000 mg/m ² cycles ≥3 <i>Duration:</i> up to 18 cycles (36 weeks)	Efficacy: Response (every 12 weeks), PFS, OS Safety

⁴ For the first cycle, daily dose of oxaliplatin was 20 mg/m²/d and 5-FU was 600 mg/m²/d.

Study No. Primary Investigator Dates of Study Defining Publication	Study Design	Diagnosis and Criteria for Inclusion	Patients			Drug Regimen ¹ Treatment Duration	Criteria for Evaluation
			N (M/F) (B/W/O)	Age Range (years) (Median)	Per Treatment Group		
Previously Treated Patients, Compassionate-Use Program, Oxaliplatin + 5-FU+FA							
EFC3107 de Gramont, A. Oct 92-Apr 93 Publication: <i>Proc Am Soc Clin Oncol Ann Meet</i> 1994;13(30 Meet):220.	Phase II, compassionate-use, single-center, open-label, in combination with 5-FU+FA	Histologically proven colorectal cancer, metastases or progressive disease refractory to 5-FU therapy	13 (10/3) (Not reported)	44-72 (60)	N/A	<i>Regimen:</i> OXAL 130 mg/m ² (2-h infusion) D1 only and FA 500 mg/m ² (2-h infusion) D1 and D15, then 5-FU 2000 mg/m ² (24-h continuous infusion) and FA 100 mg/m ² (oral) D1 and D15, FA 500 mg/m ² (2-h infusion) D2 and D16, simultaneous with 5 FU 2000 mg/m ² (24-h continuous infusion) D2 and D16, then 2 h later by FA 100 mg/m ² (oral) D2 and D16; q4w <i>Duration:</i> up to 16 cycles (64 weeks)	Efficacy: Response (every 12 weeks), PFS, OS Safety
EFC3109 Garufi, C. Oct 91-Sep 94 Publication: <i>Proc Am Soc Clin Oncol Ann Meet</i> 1995;14(31 Meet): 192.	Phase II compassionate-use, multicenter	Advanced colorectal cancer, refractory to chronotherapy with 5-FU+FA, measurable lesion not undergone radiotherapy	25 (10/15) (Not reported)	25-75 (59)	N/A	<i>Regimen:</i> CM [OXAL 20 or 25 mg/m ² /d (6-h infusion), then 5-FU 600/900 mg/m ² /d (12-h continuous infusion) simultaneous with FA 150 or 300 mg/m ² /d (12-h infusion)] x 4 or 5 days; q2w or q3w <i>Duration:</i> up to 15 cycles	Efficacy: RR, OS, PFS, duration of response
Previously Treated Patients, Previously Untreated Patients, Single-Agent, Oxaliplatin							
EFC3104 (9005) Lévi, F. May 90-May 91 Publication: <i>Eur J Cancer</i> 1993; 29A(9):1280-1284.	Phase II, multicenter, open-label, dose-escalating, noncomparative	Recurrent or metastatic histologically proven colorectal cancer, ≥1 measurable, non-irradiated lesion	Total enrolled: 30 Dosed with OXAL alone: 29 (24/5) (Not reported)	34-75 (61)	N/A	<i>Regimen:</i> OXAL (24-hr CM) q3w as below: Cycle 1: 30 mg/m ² /day x 5 days Cycle 2: 35 mg/m ² /day x 5 days Cycle 3: 40 mg/m ² /day x 5 days <i>Duration:</i> up to 9 cycles at 40 mg/m ² /day x 5 days q3w	Efficacy: response assessed every 3 cycles by investigator team and Independent radiologists for PFS & OS Safety

Study No. Primary Investigator Dates of Study Defining Publication	Study Design	Diagnosis and Criteria for Inclusion	Patients			Drug Regimen ¹ Treatment Duration	Criteria for Evaluation
			N (M/F) (B/W/O)	Age Range (years) (Median)	Per Treatment Group		
<i>Previously Treated Patients, Compassionate-Use Program</i>							
EFC3094 (SWL-OHP-95-01) Cvitkovic E. Jun 95-Apr 96 Publication: None	Compassionate-use, multicenter, noncomparative, open-label, single-agent, or in combination with 5-FU+FA	Metastatic histologically-documented colorectal cancer, measurable disease in non-irradiated areas, documented progression with fluoropyrimidine therapy, inability to participate in oxaliplatin trial	Total enrolled: 514 Dosed with OXAL alone: 18 (12/6) (Not reported)	Dosed with OXAL alone: 40-75 (62)	OXAL alone: 18 OXAL + 5-FU+FA: 476 Not treated: 20	<i>Regimen:</i> OXAL 130 mg/m ² /cycle (2-hour IV infusion) q3w, alone or in combination with mixed 5-FU/FA regimens <i>Duration:</i> up to 9 cycles	Safety
			Total enrolled: 514 Dosed with OXAL + 5-FU: 476 ⁵ (294/178) ⁶ (Not reported)	Dosed with OXAL + 5-FU: 21-79 ⁷ (62) ⁷	OXAL alone: 18 OXAL + 5-FU+FA: 476 Unknown: 20		

⁵ Two patients did not have colorectal cancer, one patient presented with metastatic lesions attributable to a second concomitant malignancy, and one patient was not dosed.

⁶ Data unavailable for four patients.

⁷ Data unavailable for four patients.

Study No. Primary Investigator Dates of Study Defining Publication	Study Design	Diagnosis and Criteria for Inclusion	Patients			Drug Regimen ¹ Treatment Duration	Criteria for Evaluation
			N (M/F) (B/W/O)	Age Range (years) (Median)	Per Treatment Group		
EFC3113 (includes Jul 97 update) Cvitkovic E. Jan 94-Jan 95 Publication: <i>Proc Am Soc Clin Oncol Ann Meet</i> 1996; 15(32 Meet):206.	Compassionate-use, multicenter, retrospective, open-label, single-agent or in combination with 5-FU+FA	Refractory advanced colorectal cancer resistance to fluoropyrimidines for groups B & C	Total enrolled: 206 Dosed with OXAL alone: 29 (17/12) (Not reported)	Dosed with OXAL alone: 31-76 (57)	A: 29 B: 49 C: 62 D: 66	<i>Retrospectively assigned to Regimen Groups:</i> A: OXAL ≥100 mg/m ² (1- to 6-hour infusion) q3w B: OXAL ≥80 mg/m ² (1-6 hour infusion) q2w and 5-FU+FA C: OXAL ≥100 mg/m ² (1- to 6-hour infusion) q3w and 5-FU/FA D: Variable dose <i>Duration:</i> up to 14 cycles	Efficacy: RR, duration of response. External radiological review Safety
			Total enrolled: 206 Dosed with OXAL + 5-FU: 177 (101/76) (Not reported)	Dosed with OXAL + 5-FU: 16-82 (Mean: 57.5)	A: 29 B: 49 C: 62 D: 66	<i>Retrospectively assigned to Regimen Groups:</i> A: Oxaliplatin ≥100 mg/m ² (1- to 6-hour infusion) q3w B: Oxaliplatin ≥80 mg/m ² (1-6 hour infusion) q2w and 5-FU+FA C: Oxaliplatin ≥100 mg/m ² (1- to 6-hour infusion) q3w and 5-FU/FA D: Variable dose <i>Duration:</i> up to 24 cycles	Efficacy: RR, duration of response. External radiological review Safety

List of Abbreviations for Table (1) 1 - Study Designs of Uncontrolled Secondary Studies of Oxaliplatin

B	Black	N/A	not applicable	Pt	platinum
CIV	constant-rate infusion	NDA	New Drug Application	RF	renal function
CM	chronomodulated infusion	No.	number	RR	response rate
d, D	day(s)	O	Other	tx	treatment
F	female	OS	objective survival	W	White
IV	intravenous	PFS	progression-free survival		
M	male	PK	pharmacokinetic		

The efficacy results of the nine uncontrolled Secondary Studies are summarized in the following table. The response rates in these studies for both single-agent oxaliplatin (response rates of 6% to 10% in previously treated patients) and oxaliplatin plus 5-FU+FA (response rates ranging from 15% to 50% in previously treated patients) were consistent with those in the Primary Studies. Similar response rates were also obtained with oxaliplatin in two compassionate-use series: EFC3113 was a retrospective study, whereas in EFC3094, patients with a history of failure on multiple prior therapies were prospectively enrolled. Response rates of 17% (EFC3113) and 15% (EFC3094) were consistent with those observed in the controlled studies in refractory patients (EFC2964 and EFC2917), and support the effectiveness of oxaliplatin in this clinical setting.

Efficacy Results of Uncontrolled Secondary Studies in Colorectal Cancer

Study Treatment Group	Number - CR ^a	Number - PR ^a	Response Rate (95% CI) ^a	Median PFS (months)	Median OS (months)
Previously untreated patients, chronomodulated oxaliplatin + 5-FU+FA					
EFC3111					
All treated (N=90) ^b	5	34	43%	NR	NR
CIV (N=45) ^b	2	13	33%	8	15
CM (N=45)	3	21	53%	11	20
EFC3112 (All treated, N=183) ^c					
CIV (N=92) ^c	3	24	29% ^d	8 (95% CI: 6-10)	17 (95% CI: 14-20)
CM (N=91) ^c	5	42	52% ^d	10 (95% CI: 8-12)	17 (95% CI: 12-20)
Previously treated and previously untreated patients, oxaliplatin + 5-FU+FA					
EFC3110					
All patients (N=93)	4	45	53% (43-63%)	NR	NR
Previously untreated (N=51)	4	24	55% (41-69%)	10.5	16
Previously treated (N=42)	0	21	50% (35-65%)	8.5	15
Previously treated patients, oxaliplatin + 5-FU+FA					
EFC3108 (N=28)	1	10	39% ^d	10	NR
Previously treated patients, compassionate-use program, oxaliplatin + 5-FU+FA					
EFC3107 (N=13)	0	3	23% ^d	NR	10
EFC3109 (N=25)	0	7	28%	5.8 (range: 0-13.5)	12 (range: 1.4-32.4)
Previously treated patients, previously untreated patients, single-agent oxaliplatin					
EFC3104 (N=29)	0	3	10%	NR	8.8
Previously treated patients, compassionate-use program					
EFC3094					
Oxaliplatin alone (N=18)	0	1	5.6% (0-17%)	1.6 (95% CI:0.7-1.9)	3.7 (95% CI: 2.5-7.0)
Oxaliplatin + 5-FU (N=472)	3	68	15.0% (12-18%)	4.4 (95% CI:4.0-4.7)	10 (95% CI: 8.9-11.1)
All treated (N=490)	3	69	14.7% (12-18%)	4.3 (95% CI:4.0-4.6)	9.7 (95% CI: 8.6-10.8)
EFC3113 (N=206)	1	35	17%	NR	NR

CR=complete response; PR=partial response; CI=confidence interval; PFS=progression-free survival; OS=overall survival; CIV=continuous intravenous infusion; NR=not reported; CM=chronomodulated infusion; 5-FU=5-fluorouracil; FA=folinic acid

^a Investigators' assessment unless otherwise noted

^b Excludes two patients assigned to the CIV regimen who were not dosed

^c Excludes one patient assigned to the CIV regimen and two patients assigned to CM regimen who were not dosed

^d Independent assessment

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APPENDIX 3 ADDITIONAL EXPLANATORY ANALYSES

Adjustment for important baseline prognostic factors

It is recommended that the analysis of overall survival data from controlled trials be adjusted by prognostic factors associated with overall survival that differ between treatment arms [Piantadosi S. *Clinical Trials: A Methodologic Perspective*. 1997:352-356]. Important prognostic factors were identified by examining the product of two z statistics, Z_d and Z_i . Z_d is the z statistic resulting from the test of disparity at baseline, and Z_i is the z statistic for association of the prognostic factor with overall survival. Z_d was calculated as the square root of the chi-square value for disparity. Z_i was calculated as the square root of the test for association of the prognostic factor with overall survival. Adjusting for factors that have a large Z_d , Z_i product may reduce bias in the comparison of treatment arms [Beach ML. *Cont Clin Trials* 1989;10:1615-1755.].

Predetermined prognostic factors displayed in Table 13 (of the text.) were used in this analysis. Other pertinent prognostic factors included in the analysis are summarized in Table 1.

Table 1 - Other Pertinent Prognostic Factors of Overall Survival in EFC2962

Prognostic Factor	Levels
Lung metastases at baseline	yes, no
Other metastases (non-liver and non-lung) at baseline	yes, no
Prior surgery for primary disease	yes, no
Prior surgery for metastases	yes, no
Carcinoembryonic antigen (CEA) values at baseline	<10 ng/mL, ≥10 ng/mL

To determine whether an imbalance between treatment arms existed in factors associated with overall survival, baseline prognostic factors were subsequently examined by treatment arm. A moderate imbalance was observed between the two treatment arms in baseline alkaline phosphatase grades (chi-square=1.87, p=0.17); baseline alkaline phosphatase was Grade ≥2 for 13.9% and 9.6% of the patients in the oxaliplatin and control arms, respectively.

An imbalance was also observed for SGOT grade ≥1 (28.5% in the oxaliplatin arm versus 23.4% in the control arm) and for the proportion of patients with liver metastases at baseline (86.7% in the oxaliplatin arm versus 82.4% in the control arm). The proportion of patients with baseline SGPT grade ≥1 was only slightly larger in the oxaliplatin arm (20.9% versus 19.4% in the control arm).

The distribution of baseline prognostic factors shown in Table 2 indicates that the oxaliplatin containing treatment arm had relatively more patients with extensive liver involvement at baseline than the controls. This is further confirmed by review of the distribution of baseline LDH, a known predictor of survival in patients with colorectal

cancer. Among the 359 patients with baseline LDH determinations, more patients in the oxaliplatin arm had grade 2 or higher LDH elevations (19.8% versus 11.5% in the control arm; chi squared=4.62, p=0.03).

Inclusion of baseline alkaline phosphatase in the Cox regression model is likely correcting for the bias against the oxaliplatin arm which results from having relatively more patients with extensive liver involvement at baseline.

Table 2 - Distribution of Prognostic Factors by Treatment Arm in EFC2962

Prognostic Factor	Treatment Arm		Chi-square	p-Value
	5-FU/FA N (%) ^a	Oxal +5-FU/FA N (%) ^a		
NON LIVER RELATED				
Center				
Centers 1-11	53 (25.2%)	60 (28.6%)	0.59	0.44
Other centers	157 (74.8%)	150 (71.4%)		
Age (years)				
<65	114 (54.3%)	120 (57.1%)	0.35	0.56
≥65	96 (45.7%)	90 (42.9%)		
Creatinine (NCI grade) ^d				
0	198 (94.3%)	199 (95.7%)	0.42	0.52
≥1	12 (5.7%)	9 (4.3%)		
CEA at baseline				
≤10 ng/mL	54 (26.7%)	46 (22.8%)	0.66	0.42
>10 ng/mL	148 (73.3%)	156 (77.2%)		
Prior chemotherapy				
Yes	44 (21.0%)	42 (20.0%)	0.06	0.81
No	166 (79.0%)	168 (80.0%)		
Lung metastases at baseline				
Yes	65 (31.0%)	53 (25.2%)	1.70	0.19
No	145 (69.0%)	157 (74.8%)		
Number of organs with metastases				
≤1	84 (40.0%)	90 (42.9%)	0.35	0.55
≥2	126 (60.0%)	120 (57.1%)		
Other metastases (non-liver and non-lung) at baseline				
Yes	103 (49.0%)	107 (51.0%)	0.15	0.70
No	107 (51.0%)	103 (49.0%)		
Primary site				
Colon	147 (70.0%)	151 (71.9%)	0.18	0.67
Rectum ^e	63 (30.0%)	59 (28.1%)		
Prior radiotherapy				
Yes	24 (11.4%)	18 (8.6%)	0.95	0.33
No	186 (88.6%)	192 (91.4%)		
Sex				
Male	122 (58.1%)	127 (60.5%)	0.25	0.62
Female	88 (41.9%)	83 (39.5%)		
Prior surgery for metastases				
Yes	16 (7.8%)	14 (6.8%)	0.18	0.67
No	188 (92.2%)	193 (93.2%)		

Prognostic Factor	Treatment Arm		Chi-square	p-Value
	5-FU/FA N (%) ^a	Oxal +5-FU/FA N (%) ^a		
Prior surgery for primary disease				
Yes	181 (89.6%)	177 (88.1%)	0.24	0.62
No	21 (10.4%)	24 (11.9%)		
Synchronous metastases ^b				
Yes	139 (66.2%)	135 (64.3%)	0.17	0.68
No	71 (33.8%)	75 (35.7%)		
WHO PS at baseline				
≤1	188 (89.5%)	188 (89.5%)	0.00	1.00
2	22 (10.5%)	22 (10.5%)		
LIVER RELATED				
Alkaline phosphatase (NCI grade)				
≤1	189 (90.4%)	180 (86.1%)	1.87	0.17
≥2	20 (9.6%)	29 (13.9%)		
SGPT (NCI grade) ^d				
0	162 (80.6%)	159 (79.1%)	0.14	0.71
≥1	39 (19.4%)	42 (20.9%)		
SGOT (NCI grade) ^d				
0	154 (76.6%)	143 (71.5%)	1.37	0.24
≥1	47 (23.4%)	57 (28.5%)		
LDH ^e				
≤1	161 (88.5%)	142 (80.2%)	4.62	0.03
≥2	21 (11.5%)	35 (19.8%)		
Liver metastases at baseline				
Yes	173 (82.4%)	182 (86.7%)	1.47	0.22
No	37 (17.6%)	28 (13.3%)		

^a Percentages were based on the number of patients with data rather than the ITT population.

^b Coded as “yes” for Astler and Coller’s Stage D and “no” for Stages A, B1, B2, C1, or C2.

^c Patients with a primary site in both the colon and rectum were classified as “rectum”.

^d The original categories were to be Grades ≤1 and Grades ≥2, consistent with the association of clinical impairment with Grades ≥2. Because an insufficient number of patients had a Grade of 2, a cutoff of ≥1 was used.

^e LDH was measured at baseline in 359 (85%) of the 420 patients randomized. LDH was not prespecified as a prognostic factor in the statistical analysis plan.

The impact of the distribution of prognostic factors between treatment arms on overall survival in EFC2962 was next evaluated by examining the product of the two z-statistics, Z_d and Z_i . Z_d is a measure of the disparity between treatment arms at baseline, and Z_i is a measure of the association of the prognostic factor with overall survival. Table 3 shows the individual values for Z_d and Z_i , and the product of Z_d , Z_i for each of the prognostic factors. The largest Z_d , Z_i product was 7.36 for alkaline phosphatase at baseline, indicating an imbalance between treatment arms with a factor strongly associated with overall survival. Subsequent testing indicated that baseline alkaline phosphatase of Grade ≥2 was negatively associated with overall survival (risk ratio=2.5, p=0.0001), which produced a bias against the oxaliplatin treatment arm. This finding supported an analysis of treatment effects on overall survival, adjusted by baseline alkaline phosphatase grade.

Table 3 - Z-Statistics for Prognostic Factors of Overall Survival in EFC2962

Factor	Z _a	Z _i	Product (Z _a , Z _i)
Center	0.77	3.52	2.71
Age	0.59	0.23	0.13
Sex	0.50	0.56	0.28
WHO PS at baseline	0.00	5.46	0.00
Liver metastases at baseline	1.21	0.14	0.18
Synchronous metastases ^a	0.41	1.63	0.67
Number of organs with metastases	0.59	2.98	1.77
Primary site ^b	0.43	0.92	0.40
Prior chemotherapy	0.24	1.00	0.24
Prior radiotherapy	0.98	1.77	1.73
SGOT ^c	1.17	2.92	3.41
SGPT ^c	0.37	1.37	0.51
Alkaline phosphatase	1.37	5.38	7.36
Creatinine ^c	0.65	0.45	0.29
Lung metastases at baseline	1.30	1.09	1.42
Other metastases (non-liver and non-lung) at baseline	0.39	3.66	1.43
Prior surgery for primary site	0.49	3.12	1.54
Prior surgery for metastases	0.42	0.19	0.08
CEA at baseline	0.92	3.67	3.38

^a Coded as yes for Astler and Coller's Stage D and no for Stages A, B1, B2, C1, or C2.

^b Patients with a primary site in both the colon and rectum were classified as "rectum".

^c The original categories were to be Grades ≤ 1 and Grades ≥ 2 , consistent with the association of clinical impairment with Grades ≥ 2 . Because an insufficient number of patients had a Grade of 2, a cutoff of ≥ 1 was used.

Table 4 displays the results of the analysis of treatment effects on overall survival in EFC2962, adjusted by baseline alkaline phosphatase. The estimated relative risk of death (oxaliplatin/control) was 0.76, indicating a significant effect of oxaliplatin and 5-FU + FA therapy on overall survival (p=0.032).

Table 4 - Treatment Effects on Overall Survival, Adjusted by Baseline Alkaline Phosphatase Grade in EFC2962

Factor	Risk Ratio	95% CI	p-Value
Treatment arm	0.76	0.59 - 0.98	0.032
Baseline alkaline phosphatase	2.62	1.85 - 3.72	0.0001

The association between baseline alkaline phosphatase and overall survival was independently validated in the other controlled study, EFC2961. As shown in Table 5, the negative association of alkaline phosphatase at baseline and overall survival duration was

confirmed in EFC2961, as indicated by an estimated risk ratio of 1.51 ($p = 0.079$). Further confirmation of the validity of alkaline phosphatase as a prognostic factor for survival comes from the Intergroup Trial where baseline elevations of Grade 2 or higher were significantly associated with reduced survival ($p < 0.0001$, risk ratio 2.52, 95% confidence limits 1.95 – 3.27).

Table 5 - Association of Baseline Alkaline Phosphatase and Overall Survival in EFC2961 and the Intergroup Trial

Study/Factor	Risk Ratio	95% CI	p-value
EFC2961/Baseline alkaline phosphatase	1.51	0.95 - 2.40	0.079
Intergroup Trial/Baseline alkaline phosphatase	2.52	1.95 - 3.27	<0.0001

The conclusions of these analyses show that the highly significant improvement in PFS when oxaliplatin is added to 5-FU+FA is associated with a risk reduction for mortality in the range of 24–30% compared to 5-FU+FA alone.