Preliminary Report to the Oncologic Drugs Advisory Committee on NDA 21063
Eloxatin (Oxaliplatin) for first line therapy for colorectal cancer
Clinical Considerations

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NDA 21063 Clinical Review

1 Title and General Information

1.1 Title/Heading – Preliminary Report to ODAC on Clinical Considerations
- 1.1.1 NDA # 21063
- 1.1.2 Submission July 22, 1999
- 1.1.3 Review completed February 17, 2000

1.2 Drug name
- 1.2.1 Generic name Oxaliplatin
- 1.2.2 Proposed trade name Eloxatin
- 1.2.3 Chemical name: *cis*-[(1*R,*2*R*)-1,2-cyclohexanediamine-*N,N'*][oxalato(2-)-*O,O'*] platinum.

1.3 Sponsor: Sanofi Pharmaceuticals Inc
9 Greater Valley Parkway
Malvern PA

1.4 Pharmacologic Category: antineoplastic

1.5 Proposed Indication(s): ELOXATIN is indicated for the first-line treatment of patients with advanced colorectal cancer in combination with 5-FU-based chemotherapy.

1.6 Dosage Form(s) and Route(s) of Administration: Intravenous injection

1.7 NDA Drug Classification: Standard

1.8 Important Related Drugs: 5-flurouracil, irinotecan

1.9 Related Reviews: Statisitics, Biopharmaceutics, Pharmacology/Toxicology

2 MATERIAL REVIEWED

NDA Volumes 1.1, 1.45-1.224
Electronic Datasets
FDA Review of NDA 21053
Literature Searches of Grateful Med and CancerLit using keywords colorectal (cancer) and 5-FU, leucovorin, oxaliplatin, irinotecan, levamisole, vincristine, streptozoicin, mitomycin, cisplatin, survival, or randomized controlled trials

3 CHEMISTRY/MANUFACTURING CONTROLS

See chemistry review

4 ANIMAL PHARMACOLOGY/TOXICOLOGY

See pharmacology- toxicology review

5 CLINICAL BACKGROUND

Therapy of metastatic colorectal cancer

Overview
Each year, more than 150,000 people in the United States are diagnosed with colorectal cancer. The incidence of colorectal cancer is second for men next to lung cancer, and is second for women next to breast cancer. Approximately 30-50% of patients have advanced disease when they are diagnosed. Advanced disease is associated with a poor prognosis. Systemic chemotherapy is the major therapeutic option for advanced colorectal cancer. Fluorouracil (5-FU) has been used for over 40 years in a very variety of regimens for the palliative treatment of advanced colorectal cancer. 5-FU has been administered alone or in combination with a variety of modulating agents and/or cytotoxic drugs in numerous clinical trials. However, clinical trials which could demonstrate prolongation of survival are limited and the survival benefits are minimal [1]. In the United States, 5-FU is approved for palliative therapy by the Food and Drug Administration (FDA), and irinotecan (CPT-11) is approved for the treatment of patients with metastatic carcinoma of the colon or rectum whose disease has recurred or progressed following 5-FU-based therapy. Leucovorin is approved for the palliative treatment of patients with advanced colorectal cancer in combination with 5-FU. Levamisole is also approved as adjuvant therapy following surgical resection of Duke's C colon cancer in conjunction with 5-FU. Mitomycin, vincristine, and streptozocin are used off-label.

5-FU
The precise mechanisms of action of 5-FU have not fully characterized, but the drug is thought to act by inhibiting thymidylate synthase (TS), the enzyme that catalyzes the *de novo* formation of thymidine monophosphate (TMP) from deoxyuridine monophosphate (dUMP). TMP is subsequently converted to thymidine triphosphate (TTP), which is needed for DNA synthesis and repair. The conversion of dUMP to TMP requires the transfer of a methyl group from the reduced folate cofactor 5,10-methylenetetrahydrofolate to the 5-position of the uracil moiety. 5-FU is metabolized after entry into the cell via the facilitated uracil transport mechanism to 5-fluorodeoxyuridine monophosphate (FdUMP). In the presence of 5,10-methylenetetrahydrofolate, FdUMP forms a stable covalent complex with TS, and this leads to depletion of TTP and subsequent interference with DNA synthesis and repair. 5-FU may also be converted to fluorouridine monophosphate (FUMP) by the sequential action of uridine phosphorylase and uridine kinase. FUMP is then further metabolized to the triphoshate form which interferes with protein synthesis through incorporation into fraudulent RNA [2].

Best supportive care for advanced colorectal cancer
To determine the survival time of previously untreated advanced colorectal cancer patients with only best supportive care (BCS) is difficult. There are only two published randomized trials that compared BSC with chemotherapy untreated patients with advanced colorectal cancer [3, 4]. An additional study compared the effect of vitamin C with placebo [5]. Table-1 is a summary of these three studies. Scheithauer et al. reported

a randomized study comparing BSC with chemotherapy (5-FU + LV + cisplatin. In this study median survival in the BSC arm was 5 months.

The Nordic Gastrointestinal Tumor Adjuvant Therapy Group allocated 90 out of 192 patients with asymptomatic advanced colorectal cancer to a BSC arm. The median survival in the BSC arm was 9 months and the chemotherapy arm (5-FU + LV + methotrexate) was 14 months, which was not statistically different. Forty-four patients in the BSC arm were treated with chemotherapy when they became symptomatic. This strategy may explain why there was no significant survival benefit for the chemotherapy arm.

Buroker et al. reported the median survival for patients treated with 5-FU/LV regimen was 14.8 months for asymptomatic patients and 8.5 months for symptomatic patients [6]. This difference was significant ($p < 0.0001$). Goldberg et al. also compared the median survival of asymptomatic patients with symptomatic patients in the trial studied 5-FU plus various kinds of leucovorin administration [7]. The median survival of patients with no symptoms was 15.8 months and of patients with symptoms was 9 months ($p < 0.0001$). Moertel et al. reported the double-blind comparison of vitamin C vs. placebo [5]. Patients had no previous chemotherapy, and their performance status were ECOG 0 or 1. Median survival of the placebo group was about 11 months and vitamin C treatment group was about 12months. These outcomes would probably be worse if PS 2 patients had been included. Considering the survival advantage of patients with no symptoms and the patient population (i.e., asymptomatic patient) in the Nordic Gastrointestinal Tumor Adjuvant Therapy Group the median survival of untreated advanced colorectal cancer in general can be estimated to be approximately 9 months.

Table 1: Results of best supportive care in patients with advanced colorectal

Report	Patient #	Median Survival BSC vs. chemotherapy	Comment
Scheithauer (1993) [3]	12	5.0 Mo vs. 11.0Mo (p=0.006)	vs. 5-FU/LV/CDDP (24 pts)
The Nordic Gastrointestinal Tumor Adjuvant Therapy Group (1992) [4]	90 (no symptom)	9 Mo vs. 14Mo (p=0.13)	vs. 5-FU/LV/MTX, 44 of 90 pts with BSC were treated with chemotherapy when became symptomatic
Moertel (1985) [5]	49	11 Mo (placebo) vs. 12Mo (vitamin C)	vs. vitamin C, (50 pts)
Beretta et al. (1997)	163	7.5 vs. 5.5 (p=0.002)	vs. Weekly 5-FULV
Glimelius	21	12 m vs. 6 m (p=0.1)	

5-FU monotherapy

Whether 5-FU monotherapy has the benefit of survival prolongation has been controversial [1, 2]. Many schedules, dosages, and infusion times have been tested for 5-FU monotherapy. The optimal 5-FU monotherapy regimen has yet to be determined. The response rate and the median survival of 5-FU monotherapy arm in randomized trials for untreated advanced colorectal cancer are summarized in Table-2. The response rate ranges from 7% to 30%, and median survival ranges from 6 months to 14.5 months. All 5-FU monotherapy studies showed a better median survival than the 5 months (BSC arm) of the Scheithauer study [3]). Twelve out of 22 studies showed Median Survival greater or equal to 11 months (Placebo arm of Moertel study [5]). On this basis, Moertel concluded that 5-FU monotherapy has no effect on survival [8]. In some reviews 5-FU monotherapy was thought to have marginal survival benefit [1, 2]. The data are summarized in table-2.

Table 2: Results of 5-FU monotherapy

Report	Schedule & study design	Pts # of 5-FU arm	Response Rate	Median Survival (months)
Erlichman (1988) [9]	monthly, vs. 5-FU/LV	61	7%	9.6
Poon (1989) [10]	monthly, 5-FU +/- LV +/- MTX or CDDP	70	10%	7.7

Bobbio-Pallavicini (1993) [11]	monthly, vs. 5-FU/LV	49	10.2%	6
Borner (1998) [12]	monthly, vs. 5-FU/LV	157	9%	10
Di Costanzo (1992) [13]	monthly, vs. 5-FU/LV	78	18%	14.5
Doroshow (1990) [14]	monthly, vs. 5-FU/LV	39	13%	12.9
Labianca (1991) [15]	monthly, vs. 5-FU/LV	90	10%	11
Leichman (1995) [16]	monthly, vs. 5-FU/LV	88	24%	14
	CI, d1-28, q5w	85	18%	15
Valone (1989) [17]	D1-5, then weekly, vs. 5-FU/LV, 5-FU/LV/MTX	52	17.3%	11.5
Petrioli (1995) [18]	monthly, vs. 5-FU/LV	91	18.6%	7.5
Hansen (1996) [19]	bolus D1-5, then biweekly vs. + CDDP	153	18%	10.4
	CI D1-5, then biweekly vs. +CDDP	159	28%	13.0
Lokich (1989) [20]	monthly vs. below	87	7%	10.3
	CI D1 for a protracted time	87	30%	11.2
Machiavelli (1991) [21]	1200mg/m2 D1, q15D vs. same +LV + MTX	58	12%	8.3
Petrelli (1987), [22]	D1-5, then every other day vs. same + MTX	19	11%	11
Bandealy (1998) [23]	D1-5, then weekly vs. same + levamisole	91	12%	11.2
Laufman (1993) [24]	D1-3 x 2w, then weekly vs. same + LV	102	23%	12.6
Petrelli (1989) [25]	Monthly, vs. +LV weekly	107	12.1%	10.7
Hermann (1992) [26]	D 1-5, q3w, vs. + MTX	76	13%	14.2
NGTATG (1989) [27]	D 1,2, q2w x 8, them q3-4w, vs. +MTX	127	3%	6
Buroker (1985) [28]	D 1-5, q5w, vs. other	69	29.7%	Showed by figure
O'Connell (1989) [29]	Monthly, vs. Low dose/High dose LV	70	10%	Not specified

*monthly means the regimen 5-FU day 1 to 5 bolus IV, every 4 or 5 weeks

5-FU and leucovorin (LV)

Various strategies have been studied to increase the efficacy of 5-FU therapy. Leucovorin (LV) modulates the activity of 5-FU by stabilizing the ternary complex formed by TS, 5-FU, and reduced folate. Pharmacologic concentrations of LV expand the intracellular pools of 5,10-methylenetetrahydrofolate, thereby increasing the extent and duration of 5-FU mediated TS inhibition. This strategy for biochemical modulation of 5-FU by LV has improved efficacy in some clinical trials [2].

Many 5-FULV regimens have been studied, but the most well characterized is a monthly regimen consisting of both 5-FU and LV administered days 1 to 5, every 4 or 5 weeks. There are eight published randomized controlled trials comparing 5-FU alone with 5-FU plus LV on a monthly schedule [9-16]. Four studies showed a statistically significant survival difference ($p < 0.05$) with superior median survival time (MS) ranging from 2 to 4.3 months. In the other four studies, two trials showed a longer MS with no significant difference, one had an approximately equal MS, one was shorter. These results overall support the addition of LV to 5-FU. In the United States, the Mayo Clinic/NCCTG regimen is one of the standard regimens for chemo-naïve advanced colorectal cancer. The dose and the schedule of this regimen are the following: 425 mg/m^2 of 5-FU, IV bolus x day 1-5, 20 mg/m^2 of LV IV x day 1-5, every 4 weeks. The MS of monthly intensive 5-FU/LV regimen (5-FU + low dose LV, 5-FU + high dose LV, or Mayo Clinic/NTCCTG regimen) ranges from 8 to 15 months (Table-4). The number of published studies that tested the contribution of LV to other 5-FU regimens are few. It is therefore difficult to quantify the effect of LV, if any, using other 5-FU schedules and doses.

Table 3: Results of randomized studies; 5-FU monotherapy vs. 5-FU/LV regimen

Report	# of pts (5-FU : 5-FU/LV) *	Dose	Response Rate (%) 5-FU vs. FU/LV	Median Survival (months) 5-FU vs. FU/LV
Erlichman (1988) [9]	61 : 63	5-FU: 370 mg/m^2, LV: 200 mg/m^2	7 vs. 33	9.6 vs. 12.6 (overall: p=0.05)
Poon (1989) [10]	70 : 70 (low dose LV) : 68 (high dose LV)	5-FU: 500 mg/m^2 (alone), 370 mg/m^2 (LV arms), LV: 20 mg/m^2 (LD), 200 mg/m^2 (HD).	10 vs. 43 vs. 26	7.7 vs. 12.0 vs. 12.2 (p=0.037/0.05)
Bobbio-Pallavicini (1993) [11]	50 : 100	5-FU: 370 mg/m^2 LV: 200 mg/m^2	10.2 vs. 31.9	6 vs. 8 ($p \leq 0.05$)
Borner (1998) [12]	139 : 134	5-FU: 400 mg/m^2 LV: 20 mg/m^2	9 vs. 22	10 vs. 12.4 (p=0.02)
Di Costanzo (1992) [13]	78 : 77	5-FU: 13.5 mg/kg (alone), 400 mg/m^2 (LV), LV: 200 mg/m^2	18 vs. 16	14.5 vs. 12.4 (p=0.14)
Doroshow (1990) [14]	40 : 36	5-FU: 370 mg/m^2 LV: 500 mg/m^2	13 vs. 44	12.9 vs. 14.4 (p=0.25)
Labianca (1991) [15]	90 : 92	5-FU: 400 mg/m^2 LV: 200 mg/m^2	10 vs. 20.6	11 vs. 11.5 ($p > 0.3$)
Leichman (1995) [16]	88 : 85	5-FU: 500 mg/m^2 (alone), 425 mg/m^2 (LV arm), LV: 20 mg/m^2	29 vs. 27	14 vs. 14

* Number of patients indicated are “evaluable patients”.

The table below suggests the impact of chemotherapy versus best supportive care on survival in advanced colorectal cancer patients who did not have symptoms when entered on study. The Nordic Gastrointestinal Tumor Adjuvant Therapy Group randomized 192 asymptomatic advanced colorectal cancer patients to best supportive care or sequential methotrexate, 5-FU, and leucovorin. The median survival for the chemotherapy arm was 14 months and the median survival for the best supportive arm was 9 months. The survival results were not statistically significant. The reason for the lack of statistical significance may have been due to 44 of the 90 patients randomized to best supportive care being treated with MFL or 5-FU/LV when they became symptomatic.

Table 4: Impact of chemotherapy vs. best supportive care on survival in advanced colorectal cancer patients who did not have symptoms when entered on study

AUTHORS & YEAR	STUDY ARMS	NUMBER OF PATIENTS	% OF PATIENTS SYMPTOMATIC	SURVIVAL, MEDIAN	CROSS-OVER
Nordic 1992 [4]	MFL*	92	0%	14 mo.	
	Best supportive care	90	0%	9 mo. p = 0.13	44 of 90 pts. treated with MFL or 5-FU/LV (when symptomatic)

* MTX 250 mg/m2; 5-FU 500 mg/m2@ 3 hrs and 23 hrs; LV 15 mg x 8 doses starting @ 24 hrs. Cycle repeated q 14 days x 8 then q 3-4 weeks

The table below illustrates the median survivals for symptomatic and asymptomatic advanced colorectal cancer patients treated with effective therapies. First, in a large randomized trial, comparing Mayo Clinic/NCCTG 5-FU/LV and Roswell Park Cancer Institute 5-FU/LV, the median survival for the asymptomatic patients was 14.8 months and for the symptomatic patients was 8.5 months; the difference in the median survivals between the asymptomatic and symptomatic patients was statistically significant. Although there was no statistical difference between the two treatments ($p = 0.26$), the survival curve for the Mayo Clinic/NCCTG 5-FU/LV is to the left of the other treatment arm; the 95% confidence interval for the relative death rate for the Roswell Park 5-FU/LV regimen relative to the Mayo Clinic/NCCTG regimen was 0.72 to 1.09. The small difference in the proportion of symptomatic patients randomized may account for this trend in survival for the Mayo Clinic/NCCTG arm. Second, in a large three arm randomized, comparing Mayo Clinic/NCCTG 5-FU/LV with the leucovorin administered as either standard leucovorin, l-leucovorin, or oral leucovorin, the median survival for the asymptomatic patients was 15.8 months and for the symptomatic patients was 9 months; the difference in the median survivals between the asymptomatic and symptomatic patients was statistically significant. In this case approximately 50% of the patients accrued to each arm had tumor-related symptoms. The survival curves for the three regimens were superimposable. Patients with no symptoms appear to have a 6.3 – 6.9 month advantage in median survival time in comparison to patients with tumor-related symptoms.

Table 5: Median survivals for symptomatic and asymptomatic advanced colorectal cancer patients treated with effective therapies

Authors & year	Study arms	Number of patients	% of patients symptomatic	Covariate predictive for Survival, median
Buroker 1994 [6]	5-FU/LV[1]	183	67%	No symptoms: 14.8 mo.
	5-FU/LV[2]	179	52%	Tumor symptoms: 8.5 mo.
			p = 0.004	P < 0.0001
Goldberg 1997 [7]	5-FU/LV[3]	309	53%	No symptoms: 15.8 mo.
	5-FU/l-LV[4]	308	52%	
	5-FU/PO-LV[5]	310	53%	Tumor symptoms: 9 mo.
				P < 0.0001

[1]5-FU 425 mg/m2 + LV 20 mg/m2; x 5 days; cycle repeated q 4 weeks x 2 then q 5 weeks
[2]5-FU 600 mg/m2 + LV 500 mg/m2 weekly; x 6 weeks; cycle followed by 2 week rest
[3]5-FU 370 mg/m2 + LV 200 mg/m2; x 5 days; cycle repeated q 4 weeks x 2 then q 5 weeks
[4]5-FU 370 mg/m2 + l-LV 100 mg/m2; x 5 days; cycle repeated q 4 weeks x 2 then q 5 weeks5
[5]5-FU 370 mg/m2 + PO-LV 125 mg/m2 (@ 0, 1, 2, & 3 hrs); x 5 days; cycle repeated q 4 weeks x 2 then q 5 wks

With currently available effective therapy, asymptomatic, advanced colorectal cancer appear to achieve median survival times of 14 – 15.8 months; symptomatic patients appear to achieve median survival times of 7.5 – 9 months. Median survival times intermediate between these times occur with differing proportions of asymptomatic and symptomatic patients in the study population.

Contribution of LV to 5-FU Efficacy

To assess equivalence of two treatments we must first know the effect of the control. The best information on the effect of the 5-FU/LV control regimen comes from studies assessing the contribution of LV to 5-FU. 5-FU alone has not shown to have any effect on survival [8]

Table 6: Contribution of LV to 5-FU efficacy

AUTHOR & YEAR	# OF PTS	MEDIAN SURVIVAL TIME (MO) 5-FU vs. FU/LV	MEDIAN SURVIVAL TTIME (MO) EFFECT
Erlichman 1988 [9]	130	9.6 vs. 12.6	3.0* [A]
Poon 1989 [10]	140	7.7 vs. 12.0	4.3*
Pallavincini 1993 [11]	150	6.0 vs. 8.0	2.0*
Borner 1998 [12]	309	10.0 vs. 12.4	2.4*
Meta-Analysis** 1992 [30]	1381	11.0 vs. 11.5	0.5
Doroshow 1990 [14]	79	12.9 vs. 14.4	1.5
Labianca 1991 [15]	182	11.0 vs. 11.5	0.5
DiCostanzo 1992 [13]	181	15.5 vs. 13.3	-2.2
Leichman 1995 [16]	174	14.0 vs. 14.0	0

* $p \leq 0.05$

** some regimens in the meta-analysis differ from the d 1 –5 schedule

A- subsequent analysis (JCO 9:2076) showed no survival advantage with a P value of 0.21

Efficacy enhancement with leucovorin is not universal

The efficacy of 5-FU + LV (425 mg/m2 IV bolus x 5 days + 20 mg/m2 IV x 5 days; repeated q 4 weeks) in advanced colorectal cancer is established. Although there is a potent interaction of 5-FU plus leucovorin through covalent bonding of FdUMP, thymidylate synthetase, and reduced folates, **administering 5-FU plus leucovorin to patients by any dose, by any schedule, and with any malignancy does not consistently translate into an efficacy benefit to patients.**

First, the dose of leucovorin may make a difference in the efficacy of the 5-FU. In metastatic colorectal cancer, the Mayo Clinic/NCCTG 5-FU plus leucovorin (high-dose and low-dose) regimen, enhances response rate and prolongs survival in comparison to 5-FU alone. Roswell Park Cancer Institute weekly 5-FU plus high-dose leucovorin results in comparable response rates and survival when compared to Mayo Clinic/NCCTG 5-FU plus leucovorin (low-dose) [6], but the Roswell Park Cancer Institute low-dose leucovorin regimen was not better than 5-FU alone for both response rate and survival [31].

Second, it remains unproven in prospective randomized trials whether the therapeutic benefit of leucovorin is independent of the schedule of administration of 5-FU (i.e., rapid intravenous injection versus continuous infusion). In a SWOG trial, 88 advanced colorectal cancer patients were randomized to 5-FU 300 mg/m2/day continuous infusion x 28 days and 86 patients were randomized to 5-FU 200 mg/m2/day CI x 28 days plus LV 20 mg/m2 IV q 7 days; all patients were on 35 day cycle [32]. The response rates were 18% and 17%, respectively. The median survivals were 15 months and 14 months, respectively. **The addition of LV appears not to have added to the therapeutic benefit of continuous infusion 5-FU.** Although the response rates and median survivals are not statistically different, the response rate and median survival for the LV arm were tending to be worse.

Third, the table below provides a review that illustrates that the addition of leucovorin to 5-FU is not a guarantee of increased activity in every malignancy. Although a definitive randomized trial in breast cancer comparing 5-FU $\pm$ LV has not been reported, according to the investigators, 5-FU/LV appeared to have activity in breast cancer. 5-FU/LV had marginal activity in gastric cancer and gall bladder cancer. 5-FU/LV

was inactive in pancreatic cancer, non-small cell lung cancer and small cell lung cancer. Although 5-FU/LV may have had no activity in the malignancies, the same spectrum of toxicity appeared in the host as occurred in patients whose malignancies responded to 5-FU/LV.

Table 7: Addition of leucovorin to 5-FU

AUTHORS DATE	TOTAL NUMBER OF PATIENTS	REGIMEN: 5-FU MG/M2 LV MG/M2 CYCLE	RESPONSE	RESPONSE IN PATIENTS WITH PRIOR 5-FU EXPOSURE	MEDIAN TTP SURVIVAL	TOXICITY	COMMENT BY AUTHORS ON PROMISE OF 5-FU + LV
Breast							
Swain et al, 1989 [33]	55 prior treated	375 x 5 days 500 x 5 days q 3 wks	24%	12 of 13		13% grade 3 diarrhea 33% grade 3-4 mucositis 65% grade 3-4 granulocytopenia 19% grade 3-4 thrombocytopenia	Positive
Loprinzi, Ingle, Schaid et al 1991 [34]	36 with $\geq$ 1 prior Rx	375 x 5 days 500 x 5 days q 4 wks	28%	7 of 30 (23%)	3 mo. 12.4 mo.	89% mucositis	LV enhances cytotoxic activity of 5-FU in breast cancer
Margolin et al 1992 [35]	51 1st line pts.	400 x 5days 500 x 5 days	36%			Moderate leukopenia and mucositis	Comparable antitumor activity as anthracyclines in 1st-line
Margolin et al 1994 [36]	21 pre-Rx'ed 36 no prior Rx	370 x 5 days 500 x 5 days	10% pre-Rx-ed 11% no prior Rx			Leukopenia and mucositis	Modest antitumor activity in breast cancer
Fine et al 1994 [37]	33 no prior Rx	370 x 5 days 200 x 5 days q 28 days	41%			16% grade 3 mucositis 88% grade 1-2 diarrhea	Active combination
Pancreatic							
Crown, Casper, Botet, Murray, Kelsen 1991 [38]	22 (18 unRx'ed)	370 x 5 days 500 x 6 days	0%		2.5 months	23% stomatitis $\geq$ grade 2 18% diarrhea stomatitis $\geq$ grade 2 32% hospitalized	Lack of efficacy Associated with moderate to severe toxicity
DeCaprio, Mayer, Gonin, Arbuck 1991 [39]	42 unRx'ed	600 500 q weekly	7%		6.2 mo.	Diarrhea 1 death	Does not appear superior to 5-FU
Bolli et al 1995 [40]	20	370 x 5 200 x 5 methyltetrahydrofolate q 4 weeks	1 PR (5%)			10% grade 3 diarrhea 50% nausea	Appears as little effective as 5-FU alone; exogenous high-dose reduced folates cannot improve therapeutic outcome
Gebbia et al 1996 [41]	40 pancreas 30 gall bladder	600 l-LV 100 hydroxyurea 1000 q weekly	12.5% 30%		5.8 mo. 8 mo.	Grade 1-2 leukopenia G:I toxicity	Pancreas: far from acceptable Gall bladder: active
DiCostanzo et al 1999 [42]	Review article						Biochemical modulation of 5-FU by LV…does not appear to produce better results than 5-FU

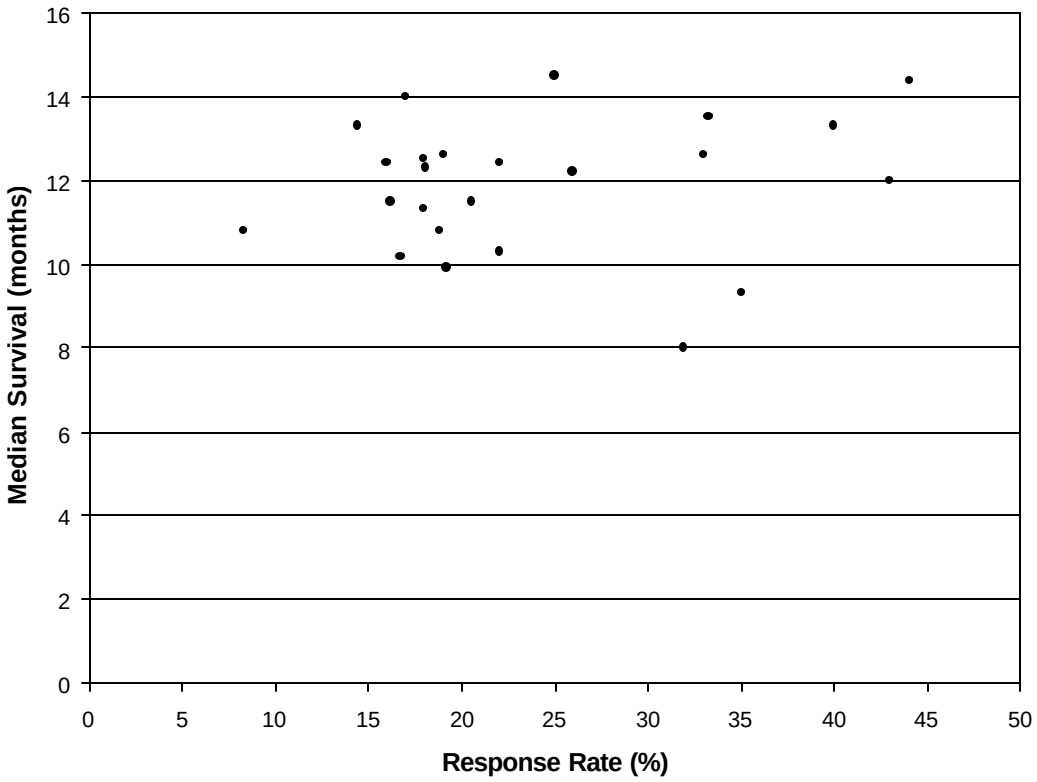
AUTHORS DATE	TOTAL NUMBER OF PATIENTS	REGIMEN: 5-FU MG/M2 LV MG/M2 CYCLE	RESPONSE	RESPONSE IN PATIENTS WITH PRIOR 5-FU EXPOSURE	MEDIAN TTP SURVIVAL	TOXICITY	COMMENT BY AUTHORS ON PROMISE OF 5-FU + LV
							alone
Rubin et al 1996 [43]	31	425 x 5 days 20 x 5 days	0%		5.7 mo.		Ineffective
Mani…Schilsky et al 1998 [44]	14	300 UFT x 28 days 90 LV x 28 days q 35 days	0%		3.5 mo. 3.8 mo.	Grade 3-4 21% hyperbilirubin 7% pain 14% diarrhea 7% transaminitis	Not active Well tolerated and devoid of neutropenia, significant oral mucositis or diarrhea
Gastric							
Pavlidis et al 1994 [45]	20	450 x 4 days 200 x 4 days q 4 weeks	15%		9 mo.	Diarrhea Mild stomatitis, myelosuppression	Median survival appears similar to other more intensive regimens Well-tolerated
Rubin et al 1996 [46]	41	425 x 5 days 20 x 5 days	17.1%		4.8 mo.		modest activity
Tsavaris et al 1996 [47]	Randomized 88 pts.	(Epirubicin + mitomycin C) 5-FU 600 days 1, 8, 29, 36 vs. 5-FU 600 LV 200 days 1, 8, 29, 36	17% 26% p < 0.1		6.9 mo. 7.7 mo.	Toxicity increased with addition of LV	Response rate increased, increased toxicity, and no difference in survival
Non-small cell lung							
Ohe et al 1990 [48]	14	600 500 q weekly	0%			14% grade 2-3 leukopenia 43% skin pigmentation	Ineffective
Evans et al 1990 [49]	30 adenocarcin-oma pts.	370 x 5 days 200 x 5 days q 4 weeks	7%		6.3 mo.	Diarrhea Stomatitis	Less encouraging than in colorectal and breast cancers
Small cell lung							
Stewart et al 1995 [50]	14	370 or 300 x 5 200 x 5	0%		5.8 mo.	Comparable toxicity as in other 5-FU + LV studies	

Table 8: Results of Mayo Clinic/NCCTG regimen randomized studies

Report	# of pts, (design)	Response Rate	Median Survival (months)	Comment
Buroker (1994) [6]	183, (vs. weekly schedule)	35 %	9.3	
Cunningham (1998) [51]	216, (vs. + Tomudex: study 3)	16.7 %	10.2	
	179, (vs. + Tomudex: study 10)	15.2 %	12.7	
Leichman (1995) [16]	61 (vs. other 6 Arms)	17 %	14	PFS: 6M
Aranda (1998) [52]	151, (vs. weekly schedule)	19.2 %	9.9	TTP: 5.5M, duration of response 4.4M
Scheithauer (1994) [53]	69, (vs. + CDDP)	19 %	12.6	TTP or death: 5.2M
de Gramont (1997) [54] study 3840	173, (vs. biweekly)	14.4 %	13.3	PFS: 5.1M

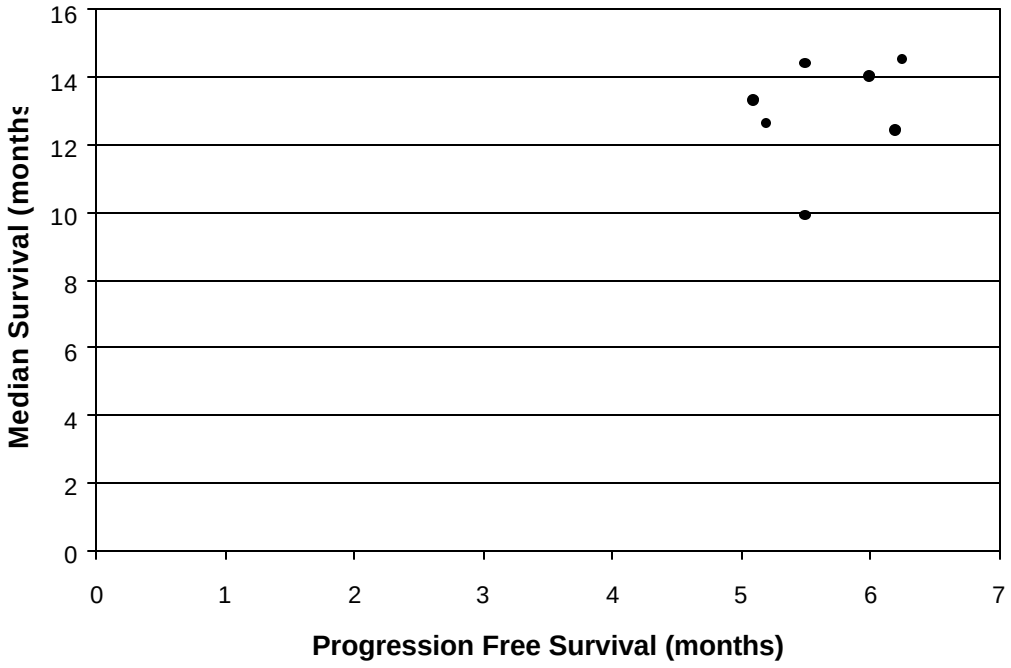
Response rate is considered to be a surrogate endpoint in oncology. Graf et al. reported that there is a relationship between response rate and survival obtained from 4 trials containing 324 patients [55]. In this report, response rate was significantly associated with survival benefit. However, the opinion at Oncology Drug Advisory Committee of UFT was that there is no apparent relationship between response rate and survival in colorectal cancer. We performed an exploratory analysis of the relationship between response rate and median survival. Target studies are prospective, randomized, monthly regimen for not previously treated advanced colorectal cancer. Twenty-four arms of 23 randomized studies were chosen for this analysis [6, 7, 9-16, 28, 51, 54, 56-63]. This is summarized in Figure-1

Figure 1: Relationship between Response Rate and Median Survival



Progression free survival (PFS) has also been used as a clinical endpoint. Seven published studies of prospective, randomized trials that used monthly 5-FU/LV regimen for untreated patients with advanced colorectal cancer [12, 14, 16, 52-54, 61] were compared. In this analysis, the term “time to progression or death” in the literature was considered equivalent to PFS. Time to failure and duration of response were not included in this analysis. This analysis is exploratory, however, there seem to be no apparent relationship between PFS and overall survival as shown in Figure-2.

Figure 2: Relationship between Progression Free survival and Median Survival



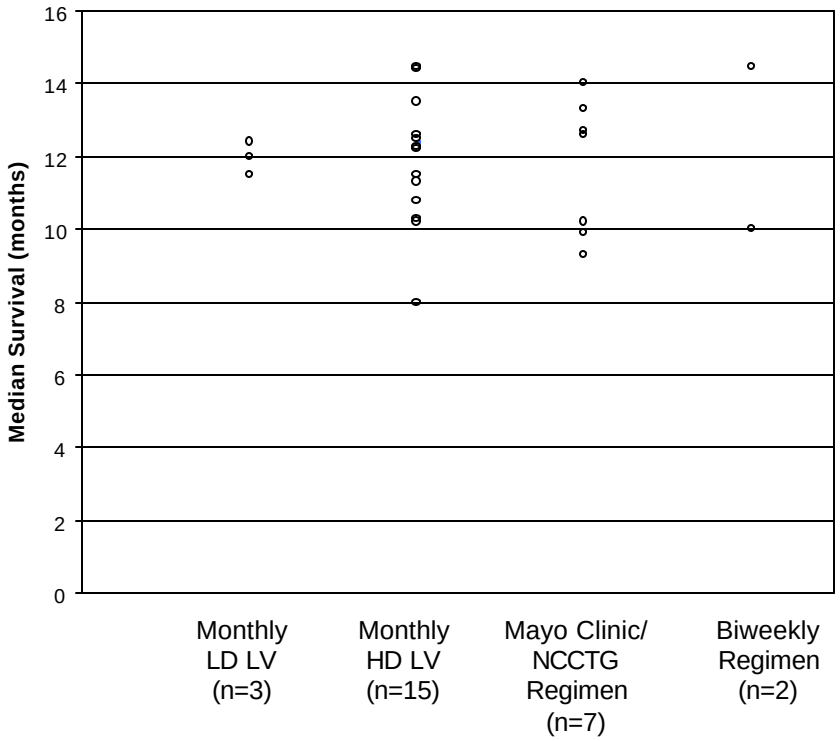
Biweekly regimen

de Gramont, et al. compared the efficacy and the safety between Mayo Clinic regimen and the biweekly high dose LV plus 5-FU regimen [54]. The response rate of this biweekly regimen was significantly greater and less toxicity was observed compared to a Mayo Clinic regimen. However, there was no evidence of survival prolongation in this study. Table-9 shows the results of biweekly regimen. No other trial compared biweekly regimen with other common 5-FU/LV regimens. The pivotal study of this NDA, study 2962, compared this biweekly regimen with oxaliplatin plus biweekly regimen. The sponsor submitted the data of de Gramont study as a bridging study between biweekly 5-FU/LV arm of study 2962 and Mayo Clinic/NCCTG regimen. Another randomized study tested biweekly regimen [64]. Figure-3 compared the median survival for not previously treated patients with advanced colorectal cancer in randomized studies used monthly 5-FU/low dose LV (20 mg/m^2) regimen, monthly 5-FU/high dose LV (≥ 100 mg/m^2) regimen, Mayo Clinic/NCCTG regimen, and biweekly regimen.

Table 9: Results of biweekly regimen

Report	# of Pts and design	Schedule & Dose	Outcome
Hanna (1995) [65]	85 (19: pretreated), phase II study	5-FU: 400mg/m2 IV, then 600mg/m2 22hr x d1-2, q2w, LV: 200mg/m2 x d1-2, q2w	RR: 10.6%, MS: 6M
de Gramont (1988) [66]	37 (chemo-naive), single arm study	5-FU: 300 (to 400) mg/m2 IV, then 300 (to 500) mg/m2 22 hr, d1,2,14,15, q4w, LV: 200mg/m2, d1,2,14,15, q4w	RR: 54.1%, MS: 18M
de Gramont (1997) [54] *Study 3840*	175 (chemo-naïve)	5-FU: 400mg/m2 IV, then 600mg/m2 22hr x d1-2, q2w, LV: 200mg/m2 x d1-2, q2w	RR: 32.6%, MS: 14.5M
Seymour (1996) [64]	104 (chemo-naïve), compared +/- IFN	5-FU: 400mg/m2 IV, then 400mg/m2 22hr x d1-2, q2w, LV: 200mg/m2 x d1-2, q2w	RR: 27%, MS: 10M
Becouarn (1995) [67]	86 (7: pretreated), single arm	5-FU: 400mg/m2 IV, then 600mg/m2 22hr x d1-2, q2w, LV: 200mg/m2 x d1-2, q2w	RR: 38.3%, OS: 10.3M
Ychou (1999) [68]	35 (20: pretreated)	5-FU: same as de Gramont, then escalated based on PK/toxicity, LV: same	RR 23%
Beerblock (1997) [69]	101 (not pretreated)	5-FU: 1.5-2g/m2/d IV x d1-2, q2w, LV: 500 mg/m2 x d1-2, q2w	RR: 33.7%, MS: 18M

Figure 3: Median survival of monthly 5-FU/low dose LV regimen, monthly 5-FU/high dose LV regimen, Mayo Clinic/NCCTG regimen, and biweekly regimen



Chronomodulated regimen

Based on the results of preclinical studies, chronomodulated administration of 5-FU with/without other drugs has been studied [70-73]. Its basis is that chronomodulated therapy can reduce the toxicity of cytotoxic drugs and can increase the dose intensity. Three phase II studies for advanced colorectal cancer have been reported, and two of them showed response rates of 41% and 45% [72, 73]. These reports are abstracts and not published data. Furthermore, these are single arm studies, not controlled comparative study. It is difficult to assess the efficacy and the safety of this regimen. One of pivotal study, study 2961, compared chronomodulated 5-FU/LV therapy with chronomodulated 5-FU/LV plus oxaliplatin therapy.

Irinotecan (CPT-11)

Irinotecan belongs to DNA topoisomerase I inhibitor. Preclinical data had suggested that colon tumors might be uniquely sensitive and its lack of cross-resistance with 5-FU. In phase II trials, CPT-11 showed an objective response rate of approximately 15% for 5-FU refractory patients and 20-30% for not pretreated patients [1, 2]. After accelerated approval for patients with metastatic carcinoma of the colon or rectum whose disease has recurred or progressed following 5-FU-based therapy by FDA, two subsequent studies demonstrated an overall survival benefit. One study compared CPT-11 monotherapy with 5-FU continuous infusion regimen, the other did CPT-11 regimen with best supportive care [74, 75]. Whether this drug has survival benefits as a first line therapy is currently under evaluation.

levamisole

Levamisole has a broad range of immunomodulatory properties including enhancement of specific immune responses in normal hosts and restoration of immunity in immune-deficient host. This drug has no effect on survival when used alone [76]. However, levamisole plus 5-FU therapy showed significant improvement in disease free survival and overall in three of four randomized trials for colorectal cancer as an adjuvant therapy (Table-10) [77-80]. However, two randomized trials which evaluated the addition of levamisole to 5-FU chemotherapy for not previously treated patients with advanced colorectal cancer did not show any improvement in response rate or survival (Table-11) [23, 81].

Table 10: Results of levamisole plus 5-FU adjuvant therapy for colorectal cancer

Report	Treatment	PTS #	5 yr DFS	5 yr OS
Windle (1987) [77]	Control	45	-	55%
	5-FU (po)	42	-	45%
	5-FU/Levamisole	44	-	68% (p=0.046)
Laurie (1989) [78]	Control	135	45%	55%
	Levamisole	130	59%	60%
	5-FU/levamisole	136	59%	62% (p < 0.05 for Dukes C)
Moertel (1990) [79]	Control	159	77%	91%
	5-FU/levamisole	159	84%	85% (N.S.)
Moertel (1990) [79], Rougier (1993) [80]	Control	315	47%	55%
	Levamisole	310	53%	64%
	5-FU/levamisole	304	66%	71% (p=0.006)

Table 11: Randomized studies in advanced colorectal cancer

Report	PTS # and study design	Dosage and schedule	Results
Buroker (1985) [81]	66 (5-FU + levamisole), vs. 5-FU, 5-FU/PALA, 5-FU/thymidine, MOF-strept	5-FU: 500mg/m2 x d1-5, q5w. Levamisole: 50mg q8h, d14-16, 21-23	RR: 22.5% (5-FU + levamisole) vs. 29.7% (5-FU). MS: almost the same (only figure displayed)
Bandealy (1998) [82]	100 (chemo-naïve), 5-FU vs. 5-FU/levamisole	5-FU: 450 mg/m2 x d1-5, then weekly. Levamisole: 50mg q8r for 3 days, q2w for 26 w	RR: 12% (5-FU) vs. 13% (levamisole) Duration of response: 4.2M vs. 4.2M MS: 11.2M vs. 9.6M

Mitomycin

Mitomycin has been used for the treatment of colorectal cancer. Multiple studies have reported a clinical response ranging from zero to 33%. However, cumulative and prolonged myelosuppression as well as infrequent occurrences of hemolytic-uremic syndrome and pulmonary insufficiencies have been prevented its clinical development [76]. The efficacy and safety of mitomycin were tested in two randomized studies. A randomized study compared protracted infusion 5-FU with the same 5-FU administration plus mitomycin for not previously treated colorectal cancer showed a significantly superior response rate (54% vs. 38%) and time to progression (7.9 months vs. 5.4 months), with no difference in quality of life and tolerable toxicity. However, no survival advantage was demonstrated in this study [82]. Another randomized study compared MMF (5-FU + methyl-CCNU + mitomycin) with 5-FU alone for not previously treated patients with advanced colorectal cancer [62]. In this study, MMF showed inferior response rate (7% vs. 16%), and survival (9.5 months vs. 10.3 months).

vincristine

Vincristine was mainly tested as MOF (methyl-CCNU, vincristine, and 5-FU) regimen or MOF-streptozocin regimen. Moertel et al. reported response rate of 43.5% [84]. However, following studies could not show high response rate. Results of MOF regimen and MOF-Strep are summarized in Table-12. In earlier three randomized studies, MOF regimen showed response rates ranging from 5% to 43.5%. Response rate of MOF-Strep regimen was superior to that of MOF regimen [85]. However, the survival of MOF-Strep regimen was equal to that of 5-FU monotherapy [81]. On the other hand, as an adjuvant chemotherapy, this regimen did not show efficacy [86].

Table 12: Results of MOF/MOF-Strep regimen

Report	Patients	Treatment	Results
Moertel (1975) [84]	Chemo-naïve 41 pts 39 pts	MOF	RR: 43.5%
		5-FU alone	RR: 19.5%
Kemeny (1979) [87]	32 pts 35 pts	MOF (methyl-CCNU d1)	RR: 10%
		MOF (methyl-CCNU d1-5)	RR: 12%
Kemeny (1983) [64]	38 pts 37 pts	MOF	RR: 5%
		MOF-strep	RR: 34%
Weltz (1983) [88]	Chemo-naïve 40 pts	MOF-Strep	RR: 25%
Buroker (1985) [81]	Chemo-naïve 69 pts 68 pts	5-FU	RR: 29.7%
		MOF-Strep	RR: 34.2% no survival difference

streptozocin

Streptozocin is an antineoplastic antibiotic produced by *Streptomyces achromogenes*. The response rate of streptozocin monotherapy for previously treated patients was bout 5-15%. Streptozocin has also been used in combination with methyl-CCNU, vincristine, and 5-FU as MOF-Strep. This regimen showed higher response rate compared with MOF regimen (34% vs. 5%) [85]. However, overall survival of this regimen was almost the same as that of 5-FU monotherapy for not previously treated patients with advanced colorectal cancer (Table 12) [81].

cisplatin

Cisplatin is a platinum compound and possess antitumor activity for various types of cancers. Several randomized studies treated with cisplatin for not previously treated patients with advanced colorectal cancer have been reported. These are summarized in Table-13. Although response rates of 15-33% have been reported with 5-FU (with or without leucovorin) plus cisplatin, no survival benefit has been demonstrated with this combination. This combination therapy has been associated with increased toxicity, such as mucositis, myelotoxicity, and gastrointestinal toxicity, and is not commonly used in clinical studies recently.

Table 13: Results of cisplatin added to 5-FU for advanced colorectal cancer

REPORT	TREATMENT	PATIENTS	RESULTS
Scheithauer (1990) [89]	5-FU/LV/CDDP, single arm	59 (12: pretreated)	RR: 34%, MS: 11.5M
Scheithauer (1994) [52]	5-FU/LV/CDDP	69	RR: 28%, TTP: 8.5M, MS: 14.4M
	5-FU/LV	69	RR: 19%, TTP: 5.2M, MS: 12.6M (p=0.20), severe ADEs
Poon (1989) [10]	5-FU/CDDP	73	RR: 15%, MS: not specified, almost the same as 5-FU alone
	5-FU	70	RR: 10%, MS: 7.7M
	5-FU/LD LV	73	RR: 43%MS: 12.0M
Kemeny (1990) [90]	5-FU/CDDP	63	RR: 25%, MS: 10M, more toxic
	5-FU CI	61	RR: 3%, MS; 12M
Hansen (1996) [19]	5-FU IV	153	RR: 18%, MS: 10.4M
	5-FU IV + CDDP	12	Stopped due to toxicity
	5-FU CI	159	RR: 25%, MS: 13.0M
	5-FU CI + CDDP	154	RR: 28%, MS: 13.0M
Diaz-Rubio (1992) [91]	5-FU/CDDP	80	RR: 18%, MS: 16.6M (p=0.4)
	5-FU	80	RR: 23%, MS: 13.9M
Lokich (1991) [92]	5-FU PI + CDDP	85	RR: 33%, MS: 11.2M
	5-FU PI	83	RR: 35%, MS: 11.8M

History of oxaliplatin

Oxaliplatin is a new 1,2-diaminocyclohexane (DACH) platinum agent that has non-cross resistant characteristics with cisplatin and carboplatin. In early 1970's, while a large number of second and third generation platinum compounds were synthesized, those with DACH carrier ligand have received the most attention [93]. Kidani et al. firstly reported that the stereochemical conformations of the DACH carrier ligand might affect the interactions of DACH-platinum compounds with DNA [94]. This family indicated a different mechanism of activity from cisplatin, as was substantiated in a National Cancer Institute screening test. Activity was demonstrated against cisplatin resistant cell lines, and colon carcinoma cell lines. In preclinical studies, the combination of oxaliplatin with 5-FU demonstrated synergistic activity. Among the DACH-platinum compounds, oxaliplatin was expected to have clinical efficacy. In earlier stage of development, this compound mainly tested in Japan. However, oxaliplatin remained relatively ignored for more than ten years. Amongst the reasons for this long development period was a unique toxicity profile, mainly characterized by an acute sensitive, dose-dependent, and cold-related peripheral neuropathy, whose benign and reversible clinical characteristics were only slowly recognized as such by investigators.

In phase I trials, the dose-limiting toxicity was transient peripheral neuropathy characterized by paresthesia and dysesthesia in hands, feet and the peri-oral area, triggered and/or enhanced by contact with cold. This

neuropathy was cumulative and was reversible within a few months after treatment discontinuation. Oxaliplatin did not display any auditory, renal and hematologic dose-limiting toxicity at the recommended dose of 130 mg/m^2 every three weeks or 85 mg/m^2 every two weeks given as a two-hour IV infusion [74].

Table 14: Phase I studies [93]

Report	Pts #	Dose (mg/m^2)	MTD	RD	DLTs
Mathe	23	0.45-67, IV, q3w	NR	NR	
Extra	44	45-200, 1-2h IV, q3-4w	200	135	neurotoxicity
Caussanel	12	125-300, chronomodulated, q3w	200	125	neurotoxicity
	11	125-300, CI, q3w	175	150	neurotoxicity
Bertheault-Cvitkovic	20	Oxaliplatin: 100, chronomodulated 5-FU: 3300-3900, q2w	100, 3900	100, 3600	Diarrhea, neutropenia

Oxaliplatin was originally developed by Roger Bellon (France), a subsidiary of Rhone-Poulenc Rorer, and clinical development continued under the management of Debiopharm S.A. (Switzerland). Subsequently, Sanofi licensed for France and other countries, including the United States. Oxaliplatin has been marketed in France since April 1996 as second line therapy in combination with fluoropyrimidines. An application for first line therapy, in combination with 5-FU/LV or a single agent when patients are not candidates for 5-FU therapy, was approved in February 1998. As of 21 August 1998, oxaliplatin has been approved in 13 countries (Cameroon, Chile, Colombia, Costa Rica, Dominican Republic, Ecuador, France, Guatemala, Morocco, Panama, Peru, Singapore and South Korea).

Pharmacologic Category: antineoplastic
Oxaliplatin, a 1,2-diaminocyclohexane (DACH) platinum complex, is a third-generation platinum complex. Similar to cisplatin and carboplatin, the main mechanism of action is mediated by the formulation of DNA adducts.

Pharmacology/Pharmacokinetics/Pharmacodynamics
Many DACH carrier ligand have received the most attention during the development of platinum compounds in recent years. The synthesis of DACH platinum complexes was reported in the early 1970s, showing these compounds were more effective against cisplatin-resistant cell lines and xenografts. Kidani et al. were the first to suggest that stereochemical conformations of DACH carrier ligand might affect the interactions of DACH-platinum compounds with DNA. Among the DACH-platinum compounds, oxaliplatin [trans-L dach(1R, 2R-diaminocyclohexane) oxalatoplatinum, L-OHP] might prove to fulfill the original vision of a novel platinum complex with clinical efficacy against cisplatin- and carboplatin-resistant tumors. Early studies of this compound were mainly developed in Japan. However, due to acute sensitive, dose-dependent, and cold-related peripheral neuropathy, this drug had been remained relatively ignored for more than ten years. After the long interval, clinical studies of this compound mainly developed in French.

In preclinical studies, oxaliplatin displayed activity against cisplatin-and carboplatin-resistant cell lines, including human colorectal cells and xenograft models. Oxaliplatin exhibited synergistic antitumor activity with 5-FU *in vitro* and in *vivo* studies.

Pharmacokinetics
The pharmacokinetic (PK) profile of oxaliplatin is characterized by high clearance rates, and a 50-fold higher volume of distribution than cisplatin. Cmax and AUC have proven linear in dose-ranging studies (up to MTD). The relationship between dose/cycle, cumulative dose, and toxicity has been established. The symptoms of acute neurotoxicity have been linked to Cmax, albeit in retrospective studies, which is why a minimum 2-hour infusion time is used with the recommended regimens of 85 mg/m^2 every two weeks or 130 mg/m^2 every three weeks. Patients who receive chronomodulated therapy are exposed to changing levels of oxaliplatin over time. One study assessed the relationship between peak time drug delivery, platinum levels, and toxicity. Free and total plasma platinum levels were determined in 36 patients with chronomodulated oxaliplatin, 5-FU/LV over a 4-day period. Results showed plasma platinum and free platinum levels, as well as overall toxicity, to be dependent on the time of oxaliplatin infusion.

Toxicity

Phase I studies of oxaliplatin with/without 5-FU are summarized as the following table. Oxaliplatin is well tolerated at the recommended dose of 85 mg/m2 every ^{2} weeks or 130 mg/m^2 every 3 weeks, with sporadic mild neutropenia and thrombocytopenia, a high frequency of nausea/vomiting, frequent peripheral transient neurosensory toxicity characterized by parethesia and dysesthesia induced or exacerbated by cold. Some patients reported laryngo-pharyngeal dysesthesia when swallowing cold food and drink. Electromyograms were performed in several patients and showed a sensitive neuropathy with normal nerve conduction. Unlike cisplatin, no ototoxicity or nephrotoxicity were observed. Above toxicities and dose appeared to be related.

Regulatory History

IND [ ] for oxaliplatin was filed by Axion, Inc in February 1993. The IND was transferred to Debiopharm SA , and then to Sanofi in April 1995. The IND was placed on clinical hold due to chemistry manufacturing and control issues and the hold was lifted in May 1997.

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SPONSOR'S QUESTION #4
Does the Agency concur that approval based on European data alone is appropriate while US-based trials are being completed?

FDA RESPONSE:
Yes. If the criteria for approval are met as outlined in the FDA Responses to Sponsor's Questions #1 and #3, and the studies meet the regulations, it does not matter to the Division where the studies were conducted.

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DECISIONS (AGREEMENTS) REACHED:

FDA RESPONSE:
Please refer to our responses to the questions discussed at the October 8, 1997 meeting. The conclusions expressed still apply with the following modifications:

Regarding the previously untreated indication:

- For approval of a first-line indication, it is necessary to demonstrate an advantage in overall survival. Unless the Wilcoxon test is specified in the protocol as the primary analysis, the Division places the greatest weight on the logrank test. [ ]. Progression-free survival will be considered along with other data in the overall analysis.
- Exploratory analyses of survival to assess the effect of crossover or secondary therapies will be considered as appropriate.

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6 CLINICAL STUDIES

The sponsor submitted data and summaries for 33 studies with electronic datasets for 17 studies and electronic study reports for 7 studies. Four of these studies were designated controlled studies (numbers 2917, 2961, 2962, and 2964). The rest of the studies were designated as uncontrolled corroborative studies. Studies 2917 and 2964 were single armed studies in refractory patients and not considered by the FDA to provide evidence that would establish the submitted claim of first line therapy for previously untreated

patients with metastatic colorectal cancer. This report to the committee will therefore focus on the two randomized controlled studies, 2961 and 2962, which enrolled patients who were candidates for first line therapy. Data from an additional study, 3840, that compared a biweekly 5FULV regimen to a monthly regimen, will also be discussed.

Initial review of the primary data revealed only minor discrepancies between what was described in the submission and what could be verified. The FDA believes that these differences do not change the conclusions that may be drawn from the data and therefore will use the summary tables provided by the sponsor in this report.

Structure of protocols

Study 2961

Protocol Description

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

Objectives:
Primary: Response rate
Secondary: Survival time without progression
Toxicity
Overall survival

Eligibility criteria

Inclusion criteria

- Histologically proven adenocarcinoma, of colorectal origin
- No previous chemotherapy and/or radiation therapy for metastases. (more than 6 months from previous adjuvant therapy)
- Performance Status (PS) ≤ 2
- Age < 76
- Anticipated survival > 12 weeks
- At least one measurable lesion $\geq$ 20mm diameter (outside the irradiated zone) documented by US, CT scan and/or MRI done less than 30 days before the start of the 1st cycle
- Complete profile done: clinical, biological and ECG
- Placement of two-lumen P.A.C.
- Consent form

Note: Alkaline phosphatase was not an inclusion/exclusion criterion.

Exclusion criteria

- Cerebral metastasis
- Bone metastases only
- Peripheral sensory neuropathy
- s-Cre > 1.5 x ULN or Ccr < 60mi/min
- Bil > 3 x ULN or PT < 60%
- WBC < 3000 and/or PLT < 100,000/mm^3
- Severe respiratory failure
- Long term corticosteroid treatment
- Uncontrolled hypercalcemia
- Prior history of cancer of other origin, excluding a baso-cellular cancer or in-situ cancer

In case of an apparently single metastasis and normal tumor markers, it is necessary to verify the metastasis histologically by a puncture guided by ultrasound or scanning.

Planned dosing regimen

Both treatment regimes include chronomodulated perfusion of 5-FU and of LV for 5 consecutive days with or without oxaliplatin on day 1, followed by a free interval of 16 days. In each regimen, the perfusion of 5-FU and LV are chronomodulated (given from 10 PM to 11 AM with peak at 4 AM) using a multi-channel portable pump.

Regimen 1: 5-FU: 700 mg/m^2/day, LV: 300 mg/m^2/day,days 1-5
Regimen 2: oxaliplatin: 125 mg/m^{2}by 6 hour infusion prior to FU and LV, day 1
5-FU: 700 mg/m^2/day, LV: 300 mg/m^2/day, days 1-5

Repeat every 21 days

Anti-emetic treatment:
Regimen 1: no treatment or Plitican (2 ampules/day).
Regimen 2: anti-HT3 (Zophren 8 mg or Kitril 3 mg).
Second treatment, if vomiting ≥ grade 2: change to anti-5HT3 not used or increase of Zophren dose to 16 mg ± association with Plitican on *regimen 2*.

Treatment criteria for subsequent courses:
- Complete absence of diarrhea, vomiting, stomatitis, for at least 3 days
- Hematological toxicity ≤ grade 2 on Day 21
- Absence of specific grade 4 sensory neuropathy during the prior cycle

Dose adaptation based on toxicity in the previous cycle:
- A dose reduction will be done in the event of toxicity > grade 2.
- 5-FU: reduction of 500 mg/m2/cycle if stomatitis, diarrhea, neutropenia, or thrombocytopenia > grade 2.
- L-OHP: reduction of 25 mg/m2/cycle if diarrhea, neutropenia, thrombocytopenia, vomiting > grade 2
- L-OHP reduction for Neuropathy:
  Grade 3: reduction of 25 mg/m2/cycle (i.e. give 100mg/m2/cycle)
  If there is persistence of a grade 3 neuropathy in the following cycle, another reduction of 25 mg/m2 (give 75 mg/m2/cycle). If there is persistence of a grade 3 neuropathy despite this reduction: discontinue regimen.
  Grade 4: discontinue the L-OHP (remove from the protocol).

  If a reduction in doses was necessary, then the doses will not ever be increased again at a later time.

Discontinuation of therapy:
- Failure to recover treatment criteria after 6 weeks
- Grade 4 neuropathy
- ≥ 25% progression in comparison with the last evaluation, or appearance of new lesion
- documented progression in one of the groups may cause a switch to the chronomodulated association 5-FU, FA, L-OHP
- minor or objective response allowing complete surgical resection, followed by 6 adjuvant treatment cycles, or complete clinical response, lasting 6 cycles after its start

Scheduled evaluations:
Pre-dosing
- History
- Clinical examinations, PS, weight, height, body surface
- Chest, abdominal, and pelvic scan
- Chest x-ray
- Abdominal US
- MRI, if necessary
- Biological profile (CBC, PLT, UN, Cre, ionogram, Ca, P, Mg, GOT, GPT, γGTP, ALP, LDH, Bil, PT, ACE, CA19-9)
- Bone scintiscan and/or cerebral scan according to the clinical signs

- Colonoscopy less than 12 months prior
- Biology or cytology if necessary

*Scanning, US and biological profile must be done within 30 days preceding the 1st cycle. If the time is longer, the patient is not eligible, or the profile must be redone.

Before each cycle
- Clinical examination, rating of toxicities, PS, weight
- CBC, PLT, blood ionogram, creatinemia, hepatic profile, ACE, CA19-9

Every 3 cycles
- Same as before each cycle
- Scanning of all lesions and/or abdominal US
- In the event of CR, this must be documented by scanning and US and if necessary by MRI.
- Quantity the variation of the markers and of the LDH's in comparison with the values prior to the 1st cycle.

* Only lesions whose greatest diameter is equal to or greater than 20mm will be considered targets. Bone lesions are only for symptomatic effects. If necessary bone lesions can be irradiated without requiring the patient's exit from the protocol.

Planned assessment:

Toxicity: according to WHO criteria (except for diarrhea, nausea/vomiting, parethesia and peripheral neuropathy, mucositis).

Table 15: Planned toxicity assessment

TOXICITY	GRADE 0	GRADE 1	GRADE 2	GRADE 3	GRADE 4
diarrhea	None, ≤ 2 stools per day	3-5 stools/day not requiring treatment	3-5 stools/day requiring treatment (loperamide-Imodium)	> 5 stools/day despite treatment with Imodium	Bloody and/or profuse diarrhea requiring parenteral rehydration
Nausea (N) Vomiting (V)	None	N and/or ≤ 5 V per cycle. No antiemetic other than the one prescribed as a preventive. No effect on food intake	N and/or ≤ 5 V not preventing eating but: Need for additional or different antiemtic treatment; No effect on food intake	> 5V/cycle. Poorly controlled despite additional or different antiemetic treatment	V continues despite all antiemetic treatment. Need for parental feeding and/or rehydration
Paresthesia/peripheral neuropathy	None	Paresthesia during treatment ≤ 8 days without functional effects	Paresthesia, hypoesthesia for 8 to 14 days after the start of chemotherapy	Paresthesia, hypoesthesia, which do not completely regress 21 days after the start of chemotherapy	Paresthesia, hypoesthesia which cause functional impairment > 21 days
Mucositis - Erythema (E) - Ulceration (U)	None	E + minor U without treatment, with no effect on food intake	E + minor U without treatment, with no effect on food intake	E + U preventing intake of solid foods despite of treatment	E + U preventing intake of liquid food despite treatment and/or requiring hospitalization for parenteral feeding

Dose intensity: This will be calculated over 9 weeks (after 3 cycles 0 and 18 weeks, according to Hryniuk's method, modified by Greco et al.

The responses will be classified as objective (reduction by more than 50% of the sum of the surfaces of the measurable tumor lesions outside the previously irradiated area), or complete according to standard method. The date of their occurrence after 3, 6 or 9 cycles will be noted as well as their duration in comparison with the inclusion date. The duration of the lesions' stability will also be specified in comparison with the inclusion date (reduction by less than 50% or increase of less than 25% of the sum of the surfaces of the targets). Tumor progression will be documented according to an increase of 25% or the appearance of a new lesion. If there is an objective response or stabilization of a target tumor, but simultaneous appearance of a new metastasis, the disease will be considered progressive.

Survival without progression and survival: these will be counted starting from the inclusion date.

Particular attention will be paid to neurologic toxicity which will prevent the continuation of the treatment in more than 10% of the patients after a cumulative dose of 800 mg/m^2.

Statistical Considerations

Estimated sample size was 100 patients per arm based on detecting a difference in tumor response rates of 20% (30% in control arm and 50% in Oxaliplatin arm) with alpha 0.05 and beta 0.20.

Two interim analysis of tumor response were planned with p= 0.0005 and 0.014 and a final p=0.045.

The final analysis of overall survival was planned for January 1997, but the actual cut-off date was July 1997

Results of Study 2961

Baseline assessment:

One patient (#10051) on L-OHP arm did not receive oxaliplatin (treated with 5-FU/LV).

Table 16: Age

	5-FU/LV	L-OHP + 5-FU/LV
range	29-74	31-75
mean	59.3	59.3
median	61.0	60.5

- Race: no information, this subject was not required in case-report form.

Table 17: Gender

	5-FU/LV	L-OHP + 5-FU/LV
male	64	66
female	36	34

Table 18: Performance Status

P.S.	5-FU/LV	L-OHP + 5-FU/LV
0	66	69
1	27	20
2	7	11

Table 19: Constitution

		5-FU/LV	L-OHP + 5-FU/LV
weight	range	36-105	37-120
	mean	68.0	69.1
	median	69	67.0

height	range	150-189	146-190
	mean	169.0	168.0
	median	169.5	169.5
BMI	range	14.4-35.2	15.4-37.6
	mean	23.7	24.4
	median	23.2	24.0
BSA	range	1.30-2.15	1.22-2.45
	mean	1.77	1.77
	median	1.82	1.78

Table 20: Center

Center #	Country	total pts #	5-FU/LV pts #	L-OHP + 5-FU/LV pts #
1	France	64	31	33
2	France	12	6	6
4	France	28	14	14
5	France	17	8	9
7	Italy	21	10	11
8	Belgium	20	10	10
11	France	2	1	1
12	France	3	2	1
13	France	4	2	2
14	France	1	1	0
17	France	10	6	4
18	France	4	2	2
19	France	4	2	2
20	France	10	5	5

Age, gender, P.S., constitution, and intra-center are well balanced. 79.5% (159 out of 200) of patients were studied in France. Study center #1 accrued about one-third of participants.

- Pretreatment condition

Table 21: Primary lesion

	5-FU/LV	L-OHP + 5-FU/LV
colon	77	66 (1)
rectum	23	34

The difference of primary lesion was moderate and not statistically significant.

Table 22: Involved organs

ORGAN	5-FU/LV	L-OHP + 5-FU/LV	TOTAL
Liver	86	88	174
Lung	37	35	72
Lymph node	17	21	38
GI tract	8	8	16
Pelvis	6	9	15
Peritoneum	13	7	20
Ovary	0	0	0
Bone	3	0	3
CNS	0	0	0
others	1	2	3

CNS: none. Those who had bone metastasis had other metastatic lesions. Ratio of patients with peritoneum involvement is high in 5-FU/LV arm, however, other lesions are well-balanced.

Table 23: Number of organs per patient

#	5-FU/LV	L-OHP + 5-FU/LV	TOTAL
1	48	51	99
2	40	33	73
3	10	11	21
4	0	5	5
5	0	0	0
6	1	0	1
7	1	0	1

Organs involved and number of involved organ were well-balanced between two arms

Table 24: Prior surgery

Surgery		5-FU/LV	L-OHP + 5-FU/LV	Total
(+)		92	90	182
Dukes	A	2	1	3
	B1	5	4	9
	B2	6	12	18
	C1	22	13	35
	D	57	60	117

- Prior chemotherapy

  Total 33 patients had been treated with adjuvant chemotherapy. All chemotherapies were 5-FU based regimen (bolus: 26, CI: 1, bolus + CI: 4, chronomodulated: 1, continuous infusion: 1, other: 1). Twenty-five patients had been treated with LV. Six patients had received levamisole (5 pts: 5-FU/LV arm; 1 pt: l-OHP arm) and one patient MTX.

  According to the electric data, all previous chemotherapies were adjuvant settings. However, according to the sponsor's report, # 10033 (L-OHP arm) revealed to have received previous chemotherapy for metastatic disease.

Table 25: Prior chemotherapy

	5-FU/LV	L-OHP + 5-FU/LV
Prior chemotherapy	23	10 (1)*

* Ten patients received prior adjuvant chemotherapy, and one patient had been treated with chemotherapy for metastatic disease.

Table 26: List of prior chemotherapy

5-FU/LV arm (n = 23)		L-OHP + 5-FU/LV arm (n = 10)	
Pts #	Adjuvant therapy	Pts #	Adjuvant therapy
10037	5-FU (bolus) + MTX	10103	5-FU (bolus)/LV
10042	5-FU (chronomodulation)/LV	40109	5-FU (bolus)/LV
10169	5-FU (bolus)/LV	50075	5-FU (CI)/LV
20116	5-FU (bolus)/LV	50168	5-FU (bolus)/LV
20173	5-FU (bolus)/LV	70073	5-FU (bolus)/LV
40020	5-FU (bolus & CI)/LV	80035	5-FU (bolus)/LV
40025	5-FU (bolus)/LV	80165	5-FU (bolus) + levamisole
40164	5-FU (other)/LV	80185	5-FU (bolus & CI)
50068	5-FU (bolus) + levamisole	11026	5-FU (bolus & CI)/LV
50144	5-FU (bolus)/LV	200134	5-FU (bolus)/LV
50158	5-FU (bolus)/LV		
70102	5-FU (bolus)/LV		
70112	5-FU (bolus)/LV + levamisole		
70121	5-FU (bolus)/LV		
80053	5-FU (bolus) + levamisole		
80056	5-FU (bolus)		
80084	5-FU (bolus)/LV + levamisole		
80085	5-FU (bolus & CI) + levamisole		
140089	5-FU (bolus)/LV		
190120	5-FU (bolus)/LV		
200122	5-FU (bolus)/LV		
200125	5-FU (bolus)		
200140	5-FU (bolus)/LV + other		

More than twice as many patients had been treated with adjuvant chemotherapy in 5-FU/LV (control) arm in comparison with oxaliplatin plus 5-FU/LV arm. It is an issue whether this imbalance had the influence on the survival.

Interval from previous adjuvant chemotherapy:

The last day of previous chemotherapy of Pt # 40020 was on 3/8/94, and initial date was on 7/2/94. About 4 Mo interval.

The last days of previous chemotherapy were not determined for Pt # 80056 and #200122.

According to the protocol, the interval from the last day of previous chemotherapy to the inclusion date must be more than 6 months.

- Prior radiation

  Total 20 patients had received prior radiation therapy. All radiation therapies were adjuvant settings.

Table 27: Prior radiation

	5-FU/LV	L-OHP + 5-FU/LV
Prior Radiation	8	12

Interval between the end of radiation therapy and the date of inclusion date:

#10016, #50075, and #80056: date of the end of radiation therapy were unknown. The following table is the list of patients whose intervals were less than 6 months.

Table 28: Patients whose intervals were less than 6 months

pts ID	End of radiation	Date of inclusion	interval
40059	6/22/94	10/27/94	4 months
40091	9/5/94	2/7/95	5 months
80057	8/23/94	10/21/94	2 months
200181	12/4/95	1/12/96	1 months

According to the protocol, “more than 6 months from previous adjuvant therapy” is the inclusion criteria.

- Baseline assessment. concomitant illness and medication

  Hearing loss: 2 patients (#10092, #50027: L-OHP arm).
  Peripheral neuropathy: 1 patient (#80157: 5-FU/LV arm).
  Nausea/vomiting: 3 patients on 5-FU arm, 5 pts on L-OHP arm.

Table 29: Baseline assessment: concomitant illness and medication

	5-FU/LV	L-OHP + 5-FU/LV
Hypertension	17	21
Angina pectoris	0	3
Myocardial Infarction	2	2
Rhythm abnormalities	3	4

#40106 (5-FU/LV arm) had the history of non-Hodgkin lymphoma in 1979. #70150 (5-FU/LV arm) had the history of meningioma.
Three patients in oxaliplatin arm had the previous history of myocardial infarction, however, these patients are estimated to have adequate cardiac function.

- Clinical laboratory

  There are no baseline data for patients, #80035 and #180028 (L-OHP arm).

  WBC: All 198 patients showed > 3,000/mm^3 (minimum: 3700/mm^3)
  Platelets count: All 198 patients showed > 100,000/mm^3. (minimum: 101,000/mm^3)
  Creatinine: All 193 patients met criteria. No baseline data for patients #10031, #10037 (5-FU/LV arm) and #10007, #10018, #10079, #80035, #180028 (L-OHP arm).
  Creatinine clearance: no baseline data for any patients. (not required)
  T-bilirubin: All 189 patients met criteria. No baseline data for patients, #10031 (5-FU/LV arm) and #10007, #10018, #10079, #20066, #40163, #50027, #50055, #70073, #80035, #180028 (L-OHP arm).
  Prothrombin time: Baseline of #40005 (L-OHP arm) was 41%, #190117 (L-OHP arm) was 59%. No baseline data for patients #10077, #80053, #80056, #80057, #80127, #200138 (5-FU/LV arm) and #10041, #10079, #10184, #20066, #50019, #70073, #80165, #130148, #180028, #190160, #200134 (L-OHP arm).

  Alkaline phosphatase at baseline is relatively balanced between two treatment arms in this study.

Table 30: Alkaline phosphatase at baseline

Grade	5-FU/LV	L-OHP + 5-FU/LV
0	20	32
1	51	43
2	13	9
3	13	8
4	0	1

- Tumor assessment
  Eligible criteria is "at least one measurable lesion ≥ 20 mm diameter documented by ultrasound and scan and/or MRI done less than 30 days before the start of the first cycle".
  Following patients are against the criteria: #10002 (L-OHP arm: lesions < 20 mm); #10033 (L-OHP arm: lesions < 20 mm); #10042 (5-FU/LV arm: measurable lesion, lymph node, was measured by clinical examination); #10049 (5-FU/LV arm: lesions < 20 mm); #10092 (L-OHP arm: lesions < 20 mm); #50055 (L-OHP arm: lesions < 20 mm); #70112 (5-FU/LV arm: lesions < 20 mm); #80034 (L-OHP arm: lesions < 20 mm); #80076 (L-OHP arm: lesions < 20 mm); #80157 (5-FU/LV arm: colonoscopy only); #110026 (L-OHP arm: lesions < 20 mm).

The sponsor claims: #10049, #70112 (5-FU/LV arm) and #10002, #10092, #80034, #80076 (L-OHP arm) were considered as measurable disease by radiological experts.

The sponsor also claims:
- #80161 (L-OHP arm) had no measurable disease (no target lesion) found by radiological experts.
- #80053, #80157 (5-FU/LV arm) and #10007, #10008, #110026, #20013 (L-OHP arm) had no CT scans available for experts review (CT scans lost).
- #10042, #10094, #20116, #70155 (5-FU/LV arm) and #10009, #10033, #50168 (L-OHP arm) had no radiological assessments performed and were subsequently not possible to review for response by radiologists (early clinical PD).
- #10018 and #70151 (L-OHP arm) died early without radiological tumoral assessment and #10051 withdrew early without radiological tumoral assessment. As per investigators' assessment, only these 3 patients were not evaluable.
- #70126 (L-OHP arm) presented a measurable recurrence at pelvis. However, this patient had prior pelvic radiotherapy.

- Interval from pretreatment evaluation to the start of the first cycle
  Patients whose first cycle was given 30 days or more after the pre-treatment evaluation profile (chemistry, hematological examination, and tumor assessment) were excluded from the study according to the protocol.
  The following table is the summary of patients whose interval from pre-treatment evaluation to the beginning of the first cycle were 30 days or more.

Table 31: Summary of patients whose interval from pre-treatment evaluation to the beginning of the first cycle were 30 days or more

Arm	Chemistry test	Hematological test	Radiological test
5-FU/LV arm	2	2	12
L-OHP arm	8	8	16

- Informed consent
  The sponsor claims that thirty-seven patients signed the informed consent after the start of the randomization procedure, including13 out of 20 Belgian patients (local legal requirements did not oblige to get a signed informed consent). According to the protocol, the signed informed consent is necessary.

- Other inclusion/exclusion criteria
  The sponsor claims: #10042 (5-FU/LV arm) had previously received oxaliplatin 4 years before the inclusion in an adjuvant setting; #50068 (5-FU/LV arm) presented with NSCLC during the study; #80056 (5-FU/LV arm) with hypernephroma; #120152 with prostate adenocarcinoma

- Discontinuation criteria

Documented progressive disease
Following patients were continued on treatment, although they were judged to have progressive disease at the previous cycle.
#20095, #20131, #70012 (5-FU/LV arm), #10067, #40023, #50019, (L-OHP arm).

Table 32: List of patients with protocol violation

Patient #	Treatment arm	Comment/reason	Sponsor's comment
10002	L-OHP	Lesions < 20 mm	measurable by expert
10003	5-FU/LV	34 days from tumor assessment	
10006	L-OHP	41 days from tumor assessment	
10007	L-OHP	No data about baseline Creatinine & Bilirubin, & CT scans lost	inevaluable
10008	L-OHP	44 days from tumor assessment & CT scans lost	inevaluable
10009	L-OHP	No subsequent tumor assessment	inevaluable
10016	L-OHP	Missing data of last date of adjuvant radiation therapy	
10018	L-OHP	No data about baseline Creatinine & bilirubin, & died too early to tumor assessment	inevaluable
10022	L-OHP	Tumor assessment after dosing	
10031	5-FU/LV	No data about baseline Creatinine & bilirubin	
10032	5-FU/LV	31 days from tumor assessment	
10033	L-OHP	Previous chemotherapy for metastatic disease *1 & lesions < 20 mm	ineligible
10036	L-OHP	44 days from tumor assessment	
10037	5-FU/LV	No data about baseline Creatinine	
10041	L-OHP	No data about baseline PT	
10042	5-FU/LV	Lesions < 20 mm & previous treatment with oxaliplatin	inevaluable
10049	5-FU/LV	Lesions < 20 mm	measurable by expert
10051	L-OHP	no dosing of L-OHP (assigned to L-OHP arm)	inevaluable
10067	L-OHP	Continued therapy against PD	
10069	5-FU/LV	46 days from tumor assessment	
10077	5-FU/LV	No data about baseline PT	
10079	L-OHP	No data about baseline Creatinine, bilirubin, PT	
10092	L-OHP	Lesions < 20 mm	measurable by expert
10094	5-FU/LV	No follow-up radiological assessment	inevaluable
10098	L-OHP	32 days from chemistry and hematologic test	
10177	5-FU/LV	No data about baseline PT	
10184	L-OHP	No data about baseline PT	
20013	L-OHP	CT scans lost	inevaluable
20066	L-OHP	No data about baseline bilirubin & PT	
20095	5-FU/LV	Continued therapy against PD	
20116	5-FU/LV	No subsequent radiological assessment	inevaluable
20131	5-FU/LV	Continued therapy against PD	
40005	L-OHP	Baseline PT: 41%	
40020	5-FU/LV	4 Mo interval from adjuvant chemotherapy	minor
40023	L-OHP	Continued therapy against PD	
40059	L-OHP	4 Mo interval from adjuvant radiation therapy	
40062	5-FU/LV	31 days from tumor assessment	
40091	L-OHP	5 Mo interval from adjuvant radiation therapy	
40106	5-FU/LV	History of non-Hodgkin lymphoma	ineligible
40156	5-FU/LV	128 days from chemistry and hematologic test	

40163	L-OHP	No data about baseline bilirubin	
50019	L-OHP	No data about baseline PT & continued therapy against PD	
50027	L-OHP	No data about baseline bilirubin & 33 days from tumor assessment	
50055	L-OHP	No data about baseline bilirubin & lesions < 20 mm	inevaluable
50064	5-FU/LV	32 days from chemistry, hematologic test and tumor assessment	
50068	5-FU/LV	NSCLC during the study	
50075	L-OHP	Missing data of last date of adjuvant radiation therapy	
50168	L-OHP	41 days from tumor assessment & no subsequent tumor assessment	inevaluable
50198	L-OHP	34 days from chemistry and hematologic test	
70012	5-FU/LV	39 days from tumor assessment & continued therapy against PD	
70073	L-OHP	No data about baseline bilirubin & PT	
70112	5-FU/LV	Lesions < 20 mm	measurable by expert
70126	L-OHP	42 days from chemistry and hematologic test, 35 days from tumor assessment	
70150	5-FU/LV	History of meningioma	
70151	L-OHP	31 days from chemistry and hematologic test & died too early to assess tumor	inevaluable
70155	5-FU/LV	No subsequent radiological assessment	inevaluable
70159	L-OHP	41 days from tumor assessment	
70162	5-FU/LV	32 days from tumor assessment	
70171	L-OHP	48 days from chemistry and hematologic test, 42 days from tumor assessment	
70180	L-OHP	31 days from tumor assessment	
80034	L-OHP	Lesions < 20 mm & 33 days from tumor assessment	measurable by expert
80035	L-OHP	No data about baseline hematology & chemistry data	
80053	5-FU/LV	31 days from tumor assessment & CT scans lost	inevaluable
80056	5-FU/LV	Missing data of last date of adjuvant chemotherapy and radiation therapy. No data about baseline PT & hypernephroma during the study	
80057	5-FU/LV	2 Mo interval from adjuvant radiation therapy. No data about baseline PT	
80061	L-OHP	32 days from chemistry and hematologic test	
80076	L-OHP	Lesions < 20 mm	measurable by expert
80127	5-FU/LV	No data about baseline PT	
80145	L-OHP	31 days from tumor assessment	
80157	5-FU/LV	Peripheral neuropathy & colonoscopy only, 49 days from colonoscopy & CT scans lost	inevaluable
80161	L-OHP	No measurable disease by experts	inevaluable
80165	L-OHP	No data about baseline PT	
110004	5-FU/LV	Only ultrasonography assessment	inevaluable
110026	L-OHP	Lesions < 20 mm, 41 days from assessment & CT scans lost	inevaluable
120001	5-FU/LV	32 days from tumor assessment	
120152	L-OHP	Prostate adenocarcinoma during the study	
130088	5-FU/LV	35 days from tumor assessment	

130148	L-OHP	No data about baseline PT & 35 days from tumor assessment	
130179	L-OHP	32 days from tumor assessment	
180028	L-OHP	No data about baseline hematology & chemistry data	
190117	L-OHP	Baseline PT 59%	
190160	L-OHP	No data about baseline PT	
200122	5-FU/LV	Missing data of last date of adjuvant chemotherapy &only ultrasonography assessment	inevaluable
200125	5-FU/LV	This patient presented a sole lung metastasis with a positive cytology. However, this lesion was diagnosed with primary lung adenocarcinoma at a secondary surgery. *2, & 32 days from tumor assessment	ineligible
200134	L-OHP	No data about baseline PT	
200138	5-FU/LV	No data about baseline PT	
200142	L-OHP	No data about baseline PT	
200175	L-OHP	34 days from pretreatment assessment	
200181	5-FU/LV	1 Mo interval from adjuvant radiation therapy	

Minor: minor entry criteria deviation
*1,2: based on the sponsor's report.

Total 89 patients (44.5%) had the protocol violation(s). Thirty-six patients were on 5-FU/LV arm and 53 patients were on oxaliplatin + 5-FU/LV arm. In these groups, two FU/LV patients were judged to have measurable disease by radiological experts, and four L-OHP patients were judged measurable. Considering these patients, total 83 patients had the protocol violation(s); 34 patient in 5-FU/LV (control) arm and 49 patients in oxaliplatin plus 5-FU/LV arm. In this study, analyses are based on intent to treatment (ITT). This high incidence of protocol violations decreases the validity of the data.

Table 33: Total patients with protocol violation

		5-FU/LV arm	L-OHP arm	total
A	Pts # with violation(s)	36	53	89
B	Pts # judged measurable by experts	2	4	6
Pts # (A-B)		34	49	83 (41.5%)

Table 34: Number of Treatment Cycles

Cycle #	5-FU/LV ARM (n = 100)	L-OHP + 5-FU/LV ARM (n = 100)*	
		5-FU/LV	L-OHP
0	0	0	1*
1	3	2	2
2	1	3*	2
3	17	5	5
4	11	4	4
5	7	4	4
6	15	19	19
7	4	12	12
8	4	7	7
9	12	18	18
10	6	9	9
11	1	4	4
12	8	8	8
13	5	1	1
14	1	2	2
15	5	2	2
Total cycle	714	776	774
Mean cycle	7.1	7.8	7.7 (7.8**)
Median cycle	6	8	8

*One patient on L-OHP received 5-FU/LV treatment, but not oxaliplatin.
**Results analyzed by excluding the patient who did not receive oxaliplatin

Table 35: Dose reduction

	5-FU/LV arm		L-OHP arm	
	Patients (n = 100)	Cycles (n = 714)	Patients (n = 100)*	Cycles (n = 774)**
5-FU	9 (9%)	15 (2%)	37 (37%)	123 (16%)
oxaliplatin			52 (52%)	231 (30%)**

* One patient on L-OHP received 5-FU/LV treatment, but not oxaliplatin.
**Results analyzed by excluding the patient who did not receive oxaliplatin

Table 36: Dose Delays

	5-FU/LV arm (n = 100)	L-OHP arm (n = 99)
Dose delay	17 (17%)	36 (36%)

Table 37: Total Dose Delivered

Median dose, mg/m^2	5-FU/LV arm (n=100)	L-OHP arm (n=100)*
5-FU	21000	25110**
oxaliplatin	Not applicable	885**

Table 38: Planned Dose Intensity

Median dose intensity, mg/m^2/week	5-FU/LV arm (n = 100)	L-OHP arm (n = 100)*
5-FU (planned DI = 1170)	1107	1045**
Oxaliplatin (planned DI = 41.8)	Not applicable	36**

* One patient on L-OHP received 5-FU/LV treatment, but not oxaliplatin.
**Results analyzed by excluding the patient who did not receive oxaliplatin

Dose:
5-FU: This table is based on per body, not per mm^2.

Table 39: Dose: 5-FU (based on per body, not per mm^2)

		5-FU/LV ARM	L-OHP ARM
Total dosage: range (mg)		2,500 – 52,500	3,500 – 52,500
Total dose (mg)	< 10,000	6 (pts)	7 (pts)
	10,000 ≤ < 20,000	33	20
	20,000 ≤ < 30,000	22	39
	30,000 ≤ < 40,000	18	25
	40,000 ≤ < 50,000	14	6
	50,000 ≤	7	3
Median total dose(mg)		21,000	25,110
Mean (mg)		25,530	25,800

Both the number of treatment cycle and total dosage of 5-FU in 5-FU/LV arm were less in comparison with those of oxaliplatin plus 5-FU/LV arm. Body surface area of both arms were almost the same. This difference is probably caused by the early termination of therapy in 5-FU/LV arm due to progressive disease.

Oxaliplatin: This table is based on per body analyses, not per mm^2.

Table 40: Dose: Oxaliplatin (based on per body analyses, not per mm^2)

		L-OHP ARM (n = 100)*
Total dose: range (mg)		125 – 1,875*
Total dose (mg)	< 500	12 (1)*
	500 ≤ < 1,000	47
	1,000 ≤ 1,500	36
	1,500 ≤	5
Median dose (mg)		875
Mean dose (mg)		885 (894)**

*One patient did not receive oxaliplatin
**Data analyzed by excluding the patient who did not receive oxaliplatin

Over dose experience of oxaliplatin was not observed in this study.

After study therapy:
CPT-11
Total Forty-nine patients received CPT-11 therapy after discontinuation of this study. The number of patients treated with CPT-11 were well-balanced between two arms.

Table 41: Patient receiving after study therapy with CPT-11

	5-FU/LV arm	L-OHP arm	total
CPT-11 (+)	26	23	49

Surgery:
Total 65 patients were performed surgery after discontinuation of study treatment. The number of patients treated with surgery after discontinuation of study treatment was slightly higher in 5-FU/LV arm.

Table 42: Patients undergoing surgery after discontinuing study drug

	5-FU/LV arm	L-OHP arm	total
Surgery (+)	38	27	65

Oxaliplatin

Total 100 patients were treated with oxaliplatin after discontinuation of study treatment. The number of patients treated with oxaliplatin after discontinuation of study was higher in 5-FU/LV arm.

Table 43: Patients receiving after study therapy with oxaliplatin

	5-FU/LV arm	L-OHP arm	total
Oxaliplatin (+)	61	39	100

Efficacy

Response

Assessment of response in this study was performed by investigators and by radiological experts. Differences are summarized in the following table. This table includes all patients. FDA tumor response assessment is based on electronic data (investigators' measurements).

Table 44: Differences in assessment of response for all patients

PTS #	FDA	investigator	experts
10007	NR/SD	NR/SD	missing
10008	PD	PD	missing
10030	NR/SD	missing	PR
10042	PD	PD	missing
10063	PR	PR	NR/SD
20065	NR/SD	PR	NR/SD
40091	PR	PR	PD
40109	PR	PR	NR/SD
40187	NR/SD	NR/SD	PR
50027	PR	PR	NR/SD
50055	PR	PR	NR/SD
50111	PR	PR	NR/SD
70073	CR	CR	PR
80034	PR	PR	NR/SD
80056	PR	PR	NR/SD
80084	PR	PR	NR/SD
80085	PR	PR	PD
80087	PR	PR	NR/SD
80119	PR	PR	NR/SD
80157	NR/SD	NR/SD	missing
80161	PR	PR	missing
110004	NR/SD	NR/SD	missing
110026	NR/SD	NR/SD	missing
120152	NR/SD	missing	PR
170039	NR/SD	missing	NR/SD
170046	NR/SD	NR/SD	PR
170047	NR/SD	PR	NR/SD
170193	NR/SD	NR/SD	PR
200142	NR/SD	PR	PR
200175	NR/SD	NR/SD	PR

Table 45: Response evaluation

Response	5-FU/LV ARM (N=100)			L-OHP + 5-FU/LV ARM (N=100)		
	investigator	expert	FDA	investigator	expert	FDA
CR	0	0	0	2	1	2
PR	13	12	14	37	33	35
NR/SD	51	47	44	42	41	37
PD	35	32	40	13	13	18
Not evaluable	0	0	0	3	2	0
missing	1	1	2	3	0	8
Not done	0	8	0	0	10	0

Table 46: Response rate

Response	5-FU/LV ARM (N=100)			L-OHP + 5-FU/LV ARM (N=100)		
	investigator	expert	FDA	investigator	expert	FDA
RR	13%	12%	14%	39%	34%	37%

($p < 0.001$: investigator's, expert's, and FDA's analyses)

Calculation of response rate was done according to ITT analysis. There was little difference among response rates judged by investigator, expert, or FDA. Response rate in oxaliplatin + 5-FU/LV was significantly superior to 5-FU/LV arm.

Table 47: Relationship between Response Rate and Institute

Institute	5-FU/LV arm			L-OHP + 5-FU/LV arm		
	investigator	expert	FDA	investigator	expert	FDA
1	4/31 (12.9%)	4/31 (12.9%)	6/31 (19.4%)	12/33 (36.4%)	13/33 (39.4%)	11/33 (33.3%)
2	2/6 (33.3%)	1/6 (16.7%)	1/6 (16.7%)	1/6 (16.7%)	1/6 (16.7%)	2/6 (33.3%)
4	1/14 (7.1%)	1/14 (7.1%)	1/14 (7.1%)	4/14 (28.6%)	3/14 (21.4%)	4/14 (28.6%)
5	0/8 (0%)	1/8 (12.5%)	0/8 (0%)	5/9 (55.6%)	2/9 (22.2%)	5/9 (55.6%)
7	0/10 (0%)	0/10 (0%)	0/10 (0%)	3/11 (27.3%)	3/11 (27.3%)	3/11 (27.3%)
8	4/10 (40.0%)	1/10 (10.0%)	4/10 (40.0%)	5/10 (50.0%)	2/10 (20.0%)	5/10 (50.0%)
11	0/1 (0%)	0/1 (0%)	0/1 (0%)	0/1 (0%)	0/1 (0%)	0/1 (0%)
12	1/2 (50.0%)	1/2 (50.0%)	1/2 (50.0%)	0/1 (0%)	1/1 (100%)	0/1 (0%)
13	1/2 (50.0%)	1/2 (50.0%)	1/2 (50.0%)	1/2 (50.0%)	1/2 (50.0%)	1/2 (50.0%)
14	0/1 (0%)	0/1 (0%)	0/1 (0%)	-	-	-
17	0/6 (0%)	2/6 (33.3%)	3/6 (50.0%)	3/4 (75.0%)	2/4 (50.0%)	2/4 (50.0%)
18	0/2 (0%)	0/2 (0%)	0/2 (0%)	0/2 (0%)	0/2 (0%)	0/2 (0%)
19	0/2 (0%)	0/2 (0%)	0/2 (0%)	2/2 (100%)	2/2 (100%)	2/2 (100%)
20	0/5 (0%)	0/5 (0%)	0/5 (0%)	3/5 (60.0%)	4/5 (80.0%)	2/5 (40.0%)

There seems to be no major difference between study institutes and response rates.

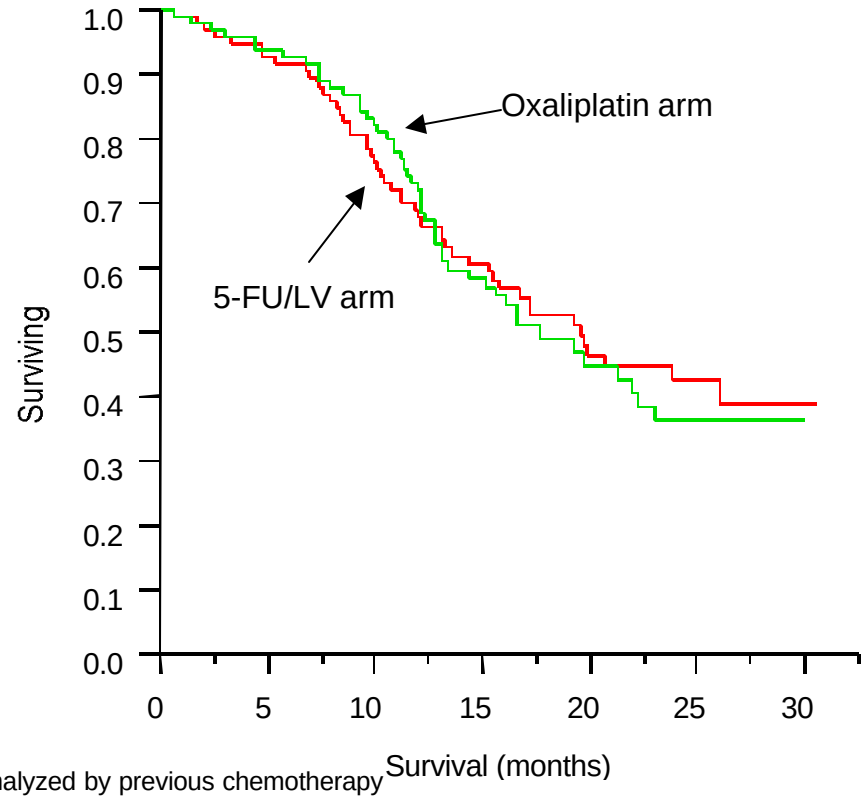
Overall survival

Overall survival is a secondary endpoint of this study. Sample size was based on showing a difference in tumor response rate. The protocol specified cut-off date was January 1997, but the cut-off date for this survival analysis is July 1997.

According to the sponsor's analyses, the median survival was 17.4 months (with a 95% confidence interval of the median of 13.8 months to 22.0 months) for oxaliplatin arm compared to 19.2 months (with a 95% confidence interval of the median of 15.2 months to 26.7 months) for the 5-FU/LV (control) arm. There was no significant difference between two arms per log-rank test ($p = 0.5815$). There was also no significant difference between two arms per Wilcoxon test ($p = 0.7907$). On the control arm 33% of patients were censored for survival and on the Oxaliplatin arm 36% of patients were censored for survival. Thus the study is reasonably mature and there is no indication of a survival difference, not even a trend.

The following figure of Kaplan-Meier survival curve was calculated from electronic data (cut-off date was January, 1997). Median survival was superior in 5-FU/LV (control) arm. There was no significant difference between two arms per log-rank test (p = 0.8209) and per Wilcoxon test (p = 0.9047). Median survival of oxaliplatin arm was 13.2 months and 5-FU/LV (control) arm was 14.4 months. Survival benefit of oxaliplatin arm was not observed in study 2961.

Figure 4: Kaplan-Meier survival curve



Survival analyzed by previous chemotherapy

This analysis was not specified in the protocol. In 5-FU/LV (control) arm, Twenty-three patients out of 100 patients had received previous chemotherapy. All of them were treated with 5-FU containing regimen. By the Kaplan-Meier survival curve analysis, there was no significant difference between previously treated patients and not treated patient in 5-FU/LV arm (log-rank test: p = 0.8695, Wilcoxon test: p = 0.5111).In oxaliplatin arm, ten patients had received previous chemotherapy. By the Kaplan-Meier survival curve analysis, there was no significant difference between the previously treated patients and not previously treated patients in the oxaliplatin arm (log-rank test: p = 0.4192, Wilcoxon test: p = 0.6106).

Survival analyzed by after treatment CPT-11 administration

The analysis of detecting the influence of after study treatment was not stated in the protocol. This subset analysis was performed. The reason why is that CPT-11 was approved for second-line therapy for advanced colorectal cancer, so CPT-11 therapy might influence survival.

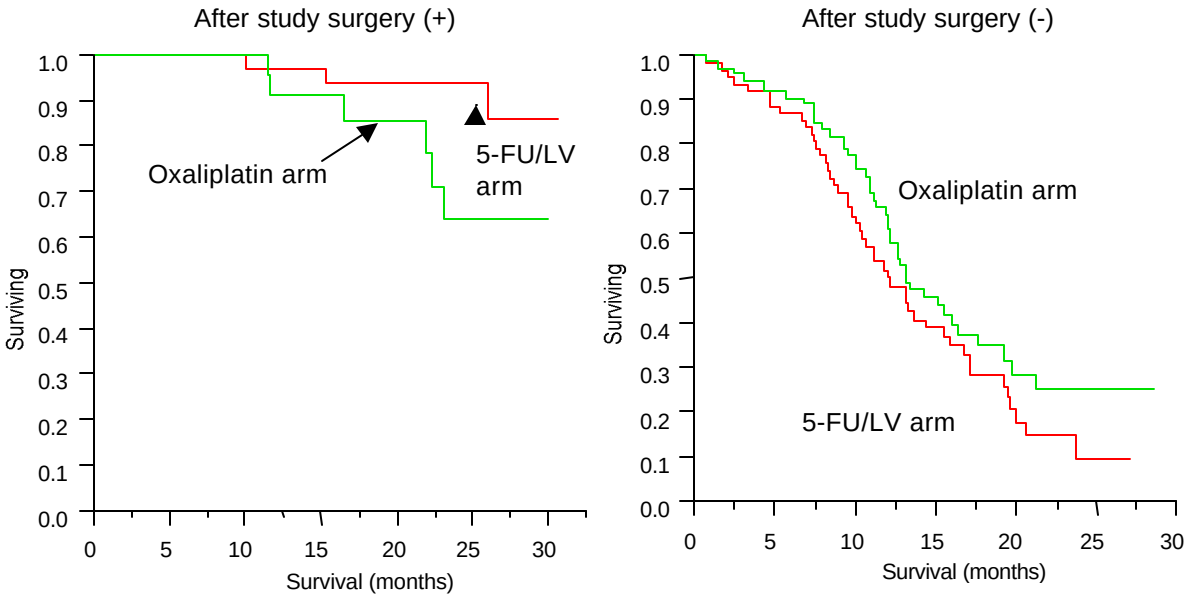
Twenty-six patients in 5-FU/LV (control) arm patients received CPT-11 and 23 patients in oxaliplatin arm received CPT-11. Overall survival between these 26 patients and 23 patients showed no significant difference by Kaplan-Meier survival analysis (log-rank test: p = 0.9488, Wilcoxon test: p = 0.9291).

On the other hand, Seventy-four patients did not receive CPT-11 in 5-FU/LV (control) arm, and 77 patients did not in oxaliplatin arm. Overall survival between these two groups showed no significant difference (log-rank test: p = 0.8582, Wilcoxon test: p = 0.8116).

Overall survival analyzed by after treatment surgery

This analysis was not stated in the protocol. Thirty-eight patients received surgery in 5-FU/LV (control) arm, and 27 patients did in oxaliplatin arm. Overall survival curve of 5-FU/LV arm with surgery exceeds that of oxaliplatin arm with surgery. However, there is no significant difference between the two arms (log-rank test: p = 0.0818, Wilcoxon test: p = 0.1164). On the other hand, the survival curve of oxaliplatin arm without surgery exceeds that of control arm without surgery. However, this difference is not statistically significant (log-rank test: p = 0.1412, Wilcoxon test: p = 0.1725). Although overall survival of two analyses showed no significant differences, survival benefit of surgery could obtain after 5-FU/VL therapy in comparison with oxaliplatin plus 5-FU/LV therapy.

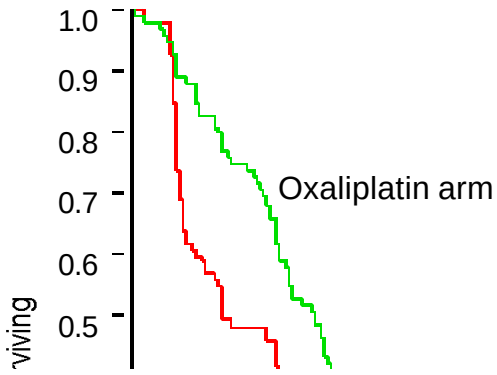
Figure 5: After study surgery (+ and -)



Overall survival analyzed by after administration of oxaliplatin
This analysis is not stated in the protocol. No significant difference was observed between 5-FU/LV arm treated after-study oxaliplatin and oxaliplatin arm treated after-study oxaliplatin (log-rank test: p = 0.9981, Wilcoxon test: p = 0.8518). Also no significant difference was observed between 5-FU/LV arm not treated with oxaliplatin after discontinuation of study and oxaliplatin arm not treated with oxaliplatin again (log-rank test: p = 0.4418, Wilcoxon test: p = 0.1695).

Progression free survival (PFS)
PFS is a secondary endpoint of study 2961.
From the sponsor's analyses, the estimate of median PFS was 8.3 months (95% confidence interval of 6.7 to 9.1 months) for oxaliplatin arm, and 4.2 months (95% confidence interval of 3.2 to 6.7 months) for 5-FU/LV (control) arm. The log-rank test showed a statistically significant difference with a p-value: 0.0455 in favor of oxaliplatin arm, and the Wilcoxon test showed a statistically significant difference in favor of oxaliplatin arm with a p-value: 0.0037.

Figure 6: Progression free survival



The above figure is Kaplan-Meier curve of PFS calculated from electronic data. PFS was statistically significant in favor of oxaliplatin arm. The log-rank test showed a p-value of 0.0455 in favor of oxaliplatin arm, and the Wilcoxon test showed a p-value of 0.0037.

Reasons withdrawn from the study

Table 48: Reasons withdrawn from study

Reason	Patient #					
	5-FU/LV (n=100)		L-OHP (n=100)		Total (n=200)	
	sponsor	FDA	sponsor	FDA	sponsor	FDA
Progressive disease	64	64	38	38	102	102
toxicity	0	0	12	12	12	12
death	3	3	3	3	6	6
surgery	18	18	24	25	42	43
other	12	12	16	15	28	27

Death

Table 49: Withdrawal due to death while on study drugs

Patient #	Treatment	Reason for Death
10009	L-OHP	Disease progression
10018	L-OHP	Respiratory failure following a thrombosis of the CV line
10094	5-FU/LV	Disease progression
20116	5-FU/LV	Disease progression
70151	L-OHP	Gastric hemorrhage without thrombocytopenia
170039	5-FU/LV	Diarrhea due to 5-FU therapy

Adverse Events

Table 50: Adverse Events

Adverse event	Gr	Total incidence			per patient (worst grade)		
		total	5-FU/LV	L-OHP	total	5-FU/LV	L-OHP
anemia	1	167	73	94	47	22	25
	2	48	18	30	20	9	11
	3	6	4	2	5	3	2
leukopenia	1	100	31	69	36	10	26
	2	5	0	5	3	0	3
	3	2	0	2	2	0	2
neutropenia	1	83	18	65	26	6	20
	2	19	1	18	11	1	10
	3	2	1	1	2	1	1
	4	1	0	1	1	0	1
thrombocytopenia	1	35	1	34	14	1	13
	2	11	0	11	7	0	7
	3	1	0	1	1	0	1
diarrhea	1	234	78	156	44	25	19
	2	228	29	199	40	17	23
	3	68	4	64	39	4	35
	4	10	1	9	9	1	8
stomatitis	1	306	161	145	71	36	35
	2	91	49	42	35	19	16
	3	18	6	12	13	4	9
	4	1	0	1	1	0	1
vomiting	1	438	193	245	83	47	36
	2	100	19	81	39	14	25
	3	31	2	29	23	2	21
	4	5	0	5	5	0	5
hepatic disorder	1	385	152	233	68	34	34
	2	111	40	71	42	14	28
	3	36	18	18	13	8	5
	4	11	7	4	8	4	4
renal disorder	1	11	5	6	10	5	5
paresthesia	1	349	28	321	38	18	21
	2	169	1	168	27	1	25
	3	84	0	84	32	0	32
	4	16	0	16	13	0	13
skin disorder	1	155	5	80	52	22	30
	2	43	30	13	23	14	9
	3	2	2	0	1	1	0
Hemorrhage NOS	1	3	3	0	1	1	0
	2	18	5	13	12	5	7
	3	0	0	0	0	0	0
	4	0	0	1	1	0	1

Constipation: grade 3, #50017 (5-FU/LV), #80157 (5-FU/LV), #80170 (5-FU/LV), #190117 (LOHP), #190120 (5-FU/LV).

Hematologic toxicity, diarrhea, vomiting, and paresthesia were observed more frequently in the oxaliplatin plus 5-FU/LV arm.

In this study, peripheral neurotoxicity was recorded by the word “paresthesia” only. Information available in electric data are grade of toxicity, date of onset, and date of end of episode (many missing data). During follow-up examination, more than half of results about neurological toxicity were missing. It is difficult to evaluate the duration of toxicity.

The following figure shows the relationship between cumulative dose of oxaliplatin and the first occurrence of each grade of paresthesia per patient. Vertical axis means cumulative patients number. About half patients showed grade 1 paresthesia after first cycle of treatment, and about half patients had grade 2 paresthesia after 5th cycle of treatment.

Summary

- More than 40% of patients had protocol violation(s). Based on this result, there seems to be a doubt about the validity of this study.
- Both response rate and progression free survival in oxaliplatin plus 5-FU/LV arm were significantly superior to those of control arm. However, this study does not show superiority for overall survival.
- Incidence and grade of hematologic toxicity, diarrhea, vomiting, and paresthesia as adverse events were higher in oxaliplatin arm. Peripheral neuropathy is one of the major toxicities of oxaliplatin. However, all neurological toxicities were expressed as “paresthesia” in this study. Exact toxicity is unknown in this study. Duration of paresthesia is hard to estimate, because more than half of follow-ups were missing.
- By subset analyses post-study administration of CPT-11, oxaliplatin and post-study surgery did not show a significant influence on overall survival.
- Quality of life (QoL) is not an objective of this study. Assessment of QoL was not performed in this study.

Adequate to support approval?

- This study failed to show overall survival benefit.
- This study showed advantages of response rate and progression free survival on oxaliplatin arm. However, these advantages are not generally considered to be associated with the improvement of overall survival.
- There is no bridging study between standard United States 5-FU/LV regimens and the chronomodulated 5-FU/LV regimen. In the literature, the authors claim that the chronomodulated 5-FU/LV regimen is superior to other regimens mainly in terms of response rate.
- Incidence and severity of adverse events, especially paresthesia, in oxaliplatin arm were worse in comparison with 5-FU/LV arm.

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Study 2962

Protocol Description

Name of protocol:

"Phase II-III trial of 5-fluorouracil (bolus and continuous infusion) and folinic acid (LV5FU2) with or without oxaliplatin in metastatic colorectal cancer"

Objectives:

Primary: To demonstrate that the test treatment, which is the combination of LV5FU2 with L-OHP, extends the progression free survival (PFS) by a median of 3 months in comparison to the reference treatment, LV5FU2 alone (i.e. from 7 to 10 months).

Secondary: Response Rate (including CEA and CA 19-9)
Tolerance and Quality of Life
Overall survival (OS)

Eligibility criteria:

Inclusion:

- Informed consent
- Histologically proven adenocarcinoma of colon or rectum
- Metastatic disease, not eligible for complete surgical resection
- No previous chemotherapy and/or immunotherapy for metastatic disease
- Previous adjuvant chemotherapy allowed only if completed 6 months prior to inclusion, and progression free interval from end of previous adjuvant chemotherapy > 6 months
- At least one bidimensionally measurable lesion as assessed by CT scan or MRI, tumoral target outside of a previously irradiated area and greater than 2 cm in diameter. Histological confirmation required in case of single lesion. A bone metastasis can not be considered as a target lesion.
- $18 \leq$ age ≤ 75
- WHO PS ≤ 2
- Life expectancy > 3 months
- Neutrophils> 2.0×10^9/l, PLT > 100×10^9/l, sCRE $\leq$ 1.5 x ULN, T-Bil $\leq$ 1.5 x ULN, ALP $\leq$ 3 x ULN
- No peripheral sensitive neuropathy (NCI CTC grade 0)
- Regular follow-up feasible
- Ability to fill out EORTC QLQ-30 specific checklist
- Baseline evaluations performed before randomization: clinical and blood evaluations no more than 7 working days prior to planned first course; tumoral assessment (chest x ray, CT scan, or MRI, evaluation of non measurable disease) no more than 21 days prior to planned first course
- First course of treatment planned less than 7 days after randomization

Exclusion:

- Pregnant, lactating, or child bearing potential women not using a contraception
- Previous use of oxaliplatin
- Measurable disease not assessed by CT scan or MRI
- CNS metastasis
- Exclusive bone metastasis
- Uncontrolled hypercalcemia
- Other concomitant or previous malignancy, except adequately treated in situ carcinoma of the uterine cervix or basal or squamous cell carcinoma of the skin
- Concomitant antitumoral treatment (including steroids)
- Participation in another clinical trial with any investigational drug within 30 days prior to randomization
- Symptomatic ascites or pleural effusions not evacuated prior to entry into the study
- Other serious disease: uncontrolled congestive heart disease, angina pectoris, hypertension or arrhythmia; significant neurologic or psychiatric disorders; active infection
- Bowel obstructions or sub-obstruction

Planned dosing regimen:

Every two weeks administration

Arm A: LV5FU2

Day 1: LV 200 mg/m^2 2 hr IV, 5-FU 400 mg/m^2 bolus IV, and then 5-FU 600 mg/m^2 continuous 22 hr IV.
Day 2: same above

Arm B: LV5FU2 + oxaliplatin

Day 1: oxaliplatin 85 mg/m^2 2 hr IV and LV 200 mg/m^2 2 hr IV, 5-FU 400 mg/m^2 bolus IV, and then 5-FU 600 mg/m^2 continuous 22 hr IV
Day 2: LV 200 mg/m^2 2 hr IV, 5-FU 400 mg/m^2 bolus IV, and then 5-FU 600 mg/m^2 continuous 22 hr IV

Treatment modification:

Treatment delay: until

- Recovery of neutrophils> 1.5×10^9/l, PLT > 100×10^9/l
- Recovery from stomatitis, diarrhea
- Recovery of skin toxicity to a grade < 2
- Recovery of other toxicity except for neurological neurosensory toxicity for which dose modification are planned, without delay of treatment

* If treatment has to be delayed for more than 2 weeks, the patient will be dropped out of the study for toxicity, except in case of surgery, where the delay may be prolonged to 6 weeks.

Dose modifications:

Dose modifications will be made according to the worst toxicity. In case of Grade III or IV toxicity after dose modification, the responsible drug(s) will be stopped, except for nausea, vomiting, alopecia and anemia. No dose reescalation is permitted after dose modification. If oxaliplatin is to be stopped for neurological toxicity, the patient will continue to received 5-FU and LV. Oxaliplatin may be reintroduced, according to the regression of the clinical symptoms. If 5-FU and LV are to be stopped, the patient will be considered off study for toxicity.

Table 51: Summary of Dose Modifications for Next Courses in Case of Toxicity

toxicity	5-FU bolus	5-FU CI	oxaliplatin
Neutrophils and/or PLT Grade III	300 x 2	500 x 2	65
Neutrophils and/or PLT Grade IV	300 x 2	500 x 2	65
Nausea and/or Vomiting grade IV despite premedication	Repeat course with adapted antiemetics. If intolerable toxicity is observed, patient off study after agreement of Sponsor and Chairman		
Diarrhea Grade III	300 x 2	500 x 2	none
Diarrhea Grade IV	300 x 2	500 x 2	65
Stomatitis Grade III	300 x 2	500 x 2	none
Stomatitis Grade IV	300 x 2	500 x 2	65
Heart > Grade I	Stop treatment. Patient off study for Toxicity		
Skin Grade III or IV	300 x 2	500 x 2	none
Allergy *1	none	none	none
Neurocerebellar	Stop treatment. Patient off study for Toxicity		
Neurosensory: specific adaptation according to symptomatology	none	none	as described next table
Other Toxicity Grade I and II	none	none	none
Grade III	300 x 2	500 x 2	65
Grade IV	Stop	Stop	Stop

*1: No modification of dose of drugs if in the investigator's opinion. In this case, premedications are dexamethasone 8 mg IV 24, 18, 12 and 6 hrs prior oxaliplatin, diphenylhydramine 50 mg IV, 30 min prior to oxaliplatin, cimetidine 300 mg IV or ranitidine 50 mg IV 30 min prior to oxaliplatin. In addition oxaliplatin will be administered as a 6 hr infusion.

Table 52: Dose Modifications of oxaliplatin for the next course in case of neurosensory toxicity

	Dose modification of oxaliplatin (mg/m^{2}ourse)			
Duration	$\leq$ 1 day	> 1 and $\leq$ 7 days	> 7 days	permanent in between courses
cold related dysesthesia	none	none	none	none
paresthesia	none	none	none	65
Paresthesia with pain	none	none	1st: 65, 2nd: 50	stop until recovery
paresthesia with functional impairment	none	none	50	Stop until improvement

Duration of treatment

- Patients achieving a documented response or with disease stabilization will continue to receive additional treatment until disease progression, or unmanageable toxicity. In case of CR, patients will receive at least 12 additional courses of treatment after documentation.
- Patients who develop progressive disease will be removed from study.
- Patients who are removed from the study because of toxic effects will receive further treatment, if any, at the discretion of the investigator.

Concomitant therapy:

Not allowed:
- steroids (except as antiemetics and antiallergics)
- other experimental drugs and anticancer treatments
- prevention of stomatitis with iced mouth rinses
- prevention of alopecia with cold cap.

Allowed:
- premedication for allergy, nausea and vomiting (including anti 5HT3 drugs and steroids)
- ancillary treatment will be given as medically indicated
- radiation therapy may be given concomitantly for control of bone pain or other reason.

Scheduled evaluations:

Baseline: medical history, physical examination including neurological, PS, ECG, CBC with differentiation, chemistry (Cre, T-Bil, AST, ALT, ALP, LDH, TP, Na^+, K^+, Cl^-, Ca, CEA, and CA 19-9), tumor assessment (chest x-ray, CT scan or MRI), QoL (QLQ-C30).

Every 2 weeks: concomitant medication, toxicity, adverse events, physical examination including neurological, CBC with differentiation.

Every 4 weeks: chemistry, tumor assessment, QoL

End of study: same as baseline

Follow-up: toxicity every 4 weeks

Planned assessments:

Statistical Analysis:
- Safety: analysis of all the patients.
- Efficacy: "intent to treat" and "per protocol" analysis.

“per protocol” are those who: meet eligibility criteria, have no concomitant therapy listed on protocol, and are adequately assessed.

Sample size: sample size is calculated to demonstrate a
median of 3 months superiority of progression free survival on oxaliplatin arm with a two-sided α risk of 0.05 and a β risk of 0.20.
The related number of patients to be recruited to each treatment arm is 200 patients. Assuming a 10% ineligibility rate 220 patients per arm should be recruited.

Interim Statistical Analyses and Stopping Rules:

Two interim analyses with stopping rules are planned. These analyses will be based on the response rate. A first interim analysis is set on the test treatment arm only. A second interim analysis compares both treatment arms.

- First Interim Analysis and Stopping Rule, as One-Arm phase II design
  The null hypothesis (H_0) is that the true response rate is $\leq$ 10% and the alternative hypothesis (H_a) is that true response rate is $\geq$ 30%. The one-sided α risk is set to 0.05 and it represents the probability of rejecting H_0 when it is true and the β risk is set to 0.05 and it represents the probability of rejecting H_a when it is true. Initially, 41 patients will be accrued to each treatment arm. Considering only the L-OHP plus LV5FU2 treatment arm for this first interim analysis in a one-arm procedure:
  if 7 or less objective responses are observed, further accrual will be closed and the trial stopped and the L-OHP plus LV5FU2 combination will be declared insufficiently efficacious at this dose and schedule.

- Second Interim Analysis and Stopping Rules as Group Sequential Phase III Design

The null hypothesis (H_o) is that the true response rate difference is equal to 0% and the alternative hypothesis (H_a) is that there is a true response rate difference is > 0%. In order to preserve the overall two-sided α risk level of 0.05 according to O'Brien and Fleming rule, this interim analysis will be performed at the 0.005 two-sided α risk level and the final analysis at the 0.048 level. The β risk is set to 0.20. Under these assumptions, the interim analysis will have the 80% power to detect an increase of 26% in the response, while the final analysis will have 80% power to detect an increase of 14% in the response rate, as obtained by the formula for comparing two binomial proportions. This second interim analysis will be performed when 100 patients in each treatment arm are available for response rate analysis, that is one half of the total sample size required.

Final analysis was planned to occur thirty-five months after the beginning of the study or about 5 times the reference median PFS time of 7 months.

Baseline assessment: disposition of patients will be presented by center and overall per treatment. Characteristics of baseline continuous parameters will be presented in the form of descriptive statistics per treatment arm in overall and by center. ANOVA will be performed, with treatment, center and treatment x center interaction. Characteristics of baseline categorical parameters, will be presented per treatment arm in overall and by center as contingency tables with absolute and percentage frequencies. Log linear model will be used to analyze the following factors: treatment, center and treatment by center interaction.

Analysis of efficacy: PFS and OS will be estimated as median and 95% CI using Kaplan-Meier method. PFS and OS will be compared with the logrank test. To adjust accidental bias, multivariate models will be used. Proportional hazard models will include predictive estimates at inclusion such as PS. A response rate will present with corresponding 95% CI calculated using the binomial distribution. The two arms will be compared using the chi-square test, with an α risk p-value limit of statistical significance limit of 0.048. Response criteria is the same as WHO criteria.

Evaluable for response: patients must have received at least one course of treatment and have been followed for a minimum of 8 weeks with at least one tumor assessment to be evaluable for response in the “per protocol” analysis.

Table 53: Definition of overall response

Response in Bidimensionally Measurable Lesions	Response in Unidimensionally Measurable Lesions	Response in Non Measurable Lesions	Overall Response
PD	any	any	PD
any	PD	any	PD
NC	any except PD	any except PD	NC
PR	any except PD	any except PD	PR
CR	any except PD	any except PD and CR	PR
CR	CR	CR	CR
any	any	PD or new lesion	PD

Analysis of adverse events: Frequencies of adverse events will be summarized by body system and organs and compared between the treatment arms by the chi-square test or Fisher exact test when numbers are small (<5). Treatment discontinuation due to adverse events will be compared by the chi-square test.

Analysis of laboratory test: Results will be compared by analysis of variance for continuous parameters and by the chi-square test or by Fischer exact test when frequencies are < 5 for categorized parameters.

Analysis of quality of life: Each functional scale and symptom scale of QoL questionnaire (EORTC QLQ C30) will be analyzed separately. The scales will be analyzed by the General Linear Model for repeated measurements.

Table 54: Protocol Amendments

Amendment Number / Date	Description
n° 1 / July 13, 1995	Exclusion criteria : Definition of previous adjuvant chemotherapy with 5-FU continuous infusion more than 500 mg/sqm, and/or administered as an infusion lasting more than 6 hours and/or administered weekly
n° 2 / July 13, 1995	Concomitant administration of oxaliplatin and FA in arm B : method
n° 3 / July 13, 1995	Reduction to 65 mg/sqm instead of no modification for oxaliplatin dosage in case of NCI grade 3 neutropenia and/or thrombocytopenia at previous cycle
n° 4 / July 13, 1995	5-FU continuous infusion in 22 hours instead of 24
n° 5 / July 13, 1995	Administrative change : name and address of Debiopharm S.A. Head Pharmacist
n° 1 / (Israel only) July 18, 1995	Additional blood count on day 7 of the first two cycles
n° 6 / November 2, 1995	Baseline laboratory tests to be performed 7 working days before first course instead of 7 days. First cycle to be administered less than 7 days after randomization instead of less than 3 days.
n° 7 / November 2, 1995	Exclusion criteria : Previous adjuvant chemotherapy with oxaliplatin only.
n° 8 / November 2, 1995	Formal changes in Protocol, related to amendment n° 6 : Baseline evaluation table, chapter 7.3.1
n° 9 / November 2, 1995	Formal changes in Appendix, related to amendment n° 6 : study plan arm A
n° 10 / November 2, 1995	Formal changes in Appendix, related to amendment n° 6 : study plan, arm B

Results of Study 2962

Table 55: Demographics

Demographic Data	Randomized patients (%)	
	Arm A	Arm B
Number of patients	**210**	**210**
Age (years)		
- Median	63	63
- [Range]	[22 - 76]	[20 - 76]
Age by ranges of 10 years		
18 - 29	4 (2 %)	1 (1 %)
30 - 39	3 (1 %)	4 (2 %)
40 - 49	28 (13 %)	24 (12 %)
50 - 59	46 (22 %)	55 (24 %)
60 - 69	90 (43 %)	88 (42 %)
≥ 70	39 (19 %)	38 (18 %)
Sex		
- Male	122 (58 %)	127 (60 %)
- Female	88 (42 %)	83 (40 %)
Performance Status (WHO)		
0	102 (49 %)	91 (43 %)
1	88 (42 %)	97 (46 %)
2	20 (10 %)	22 (10 %)

Table 56: Baseline tumor characteristics

Diagnosis	Randomized patients (%)	
	Arm A	Arm B
Number of patients	**210**	**210**
Primary tumor site		
- colon	147 (70 %)	151 (72 %)
- rectum	61 (29 %)	59 (28 %)
- both	2 (1 %)	0
Original Astler & Coller's stage		
- A	1 (0.5 %)	1 (0.5 %)
- B1	9 (4 %)	6 (3 %)
- B2	19 (9 %)	22 (10 %)
- C1	15 (7 %)	11 (5 %)
- C2	26 (12 %)	30 (14 %)
- D	139 (66 %)	135 (64 %)
- missing	1 (0.5 %)	5 (2 %)

Table 57: Tumor Characteristics

Tumor Characteristics	Randomized patients (%)	
	Arm A	Arm B
Number of patients	**210**	**210**
Number of organs involved		
1	84 (40 %)	90 (43 %)
2	83 (40 %)	76 (36 %)
3	31 (15 %)	34 (16 %)
> 3	12 (6 %)	10 (5 %)
Organs involved		
liver only	68 (32 %)	79 (38 %)
liver + other	105 (50 %)	103 (49 %)
lung only	12 (6 %)	2 (1 %)
lymph nodes only	3 (1 %)	1 (0.5 %)
other	22 (10 %)	25 (12 %)
Liver : number of metastases	N = 172	N = 180*
Median	2	2
Range	[1 - 7]	[1 - 9]
Tumor markers		
CEA		
≤ 5 ng/ml	37 (18 %)	30 (14 %)
> 5. ≤ 10 ng/ml	17 (8 %)	16 (8 %)
> 10 ng/ml	148 (70 %)	156 (74 %)
unknown	8 (4 %)	8 (4 %)
median ng/ml	41.4	51.1
CA 19.9		
≤ 60 IU/L	55 (26 %)	68 (32 %)
> 60 IU/L	88 (42 %)	78 (37 %)
unknown	67 (32 %)	64 (30 %)
median IU/L	140	79

Table 58: Prior Therapy

Prior therapy	Randomized patients (%)	
	Arm A	Arm B
Number of patients	**210**	**210**
Surgery for primary tumor		
No	16 (8 %)	22 (10 %)
Yes	194 (92 %)	188 (90 %)
Primary tumor exeresis (Yes)	179 (85 %)	172 (82 %)
(Neo)adjuvant Radiotherapy		
No	185 (89 %)	191 (91 %)
Yes	23 (11 %)	18 (9 %)
Irradiated Organs		
Pelvis	19	16
Gastro-Intestinal tract	4	2
Adjuvant chemotherapy		
No	167 (80 %)	168 (75 %)
Yes	43 (20 %)	42 (20 %)
5-FU alone	3	5
5-FU/FA	26	24
LV5-FU2	4	4
5-FU/levamisole	2	1
5-FU/other	7	8
Other	1	-
Interval between last chemotherapy and		
median months	17.8	15.6
[range] months	[6.3 - 62.7]	[6.2 - 54.0]

Exposure to therapy

Table 59: Exposure to Therapy

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

Table 60: Dose Reduction

Number of patients and cycles with dose reduction > 10 % by treatment arm	**Arm A**		**Arm B**	
	Patients (N = 208)	**Cycles (N = 2435)**	**Patients (N = 209)**	**Cycles (N = 2594)**
5-FU Bolus	31 (15 %)	179 (7 %)	97 (46 %)	752 (29 %)
5 FU CIV	38 (18 %)	172 (7 %)	102 (49 %)	762 (29 %)
oxaliplatin	Not applicable	Not applicable	121 (58 %)	895 (34 %)

Table 61: Dose Delays

Treatment modification	**Number of patients (%)**		**Number of cycles (%)**	
	Arm A (n = 208)	**Arm B (n = 209)**	**Arm A (n = 2435)**	**Arm B (n = 2594)**
Dose reduction	50 (24 %)	138 (66 %)	219 (9 %)	1025 (39 %)
Dose delay	126 (61 %)	179 (86 %)	291 (13 %*)	695 (29 %*)

Table 62: Total Dose Delivered

Median dose, mg/m^2	**Arm A (N = 208)**	**Arm B (N = 209)**
5-FU bolus	8786	8624
5-FU CIV	13200	13186
oxaliplatin	Not Applicable	837

Table 63: Planned Dose Intensity

Median dose intensity, mg/m^2/week	**Arm A (N = 208)**	**Arm B (N = 209)**
5-FU bolus (planned DI = 400)	354.7	302.4
5-FU CIV (planned DI = 600)	531	458.5
oxaliplatin (planned DI = 42.5)	Not Applicable	31.1

Table 64: Relative Dose Intensity

Relative dose intensity (%)		N Patients (%) Arm A (N = 208)	Arm B (N = 209)
5-FU bolus			
	]90-110 %]	93 (45 %)	31 (15 %)
	]70-90 %]	102 (49 %)	104 (50 %)
	≤ 70 %	13 (6 %)	74 (35 %)
5-FU CIV			
	]90-110 %]	90 (43 %)	25 (12 %)
	]70-90 %]	110 (53 %)	123 (59 %)
	≤ 70 %	8 (4 %)	61 (29 %)
oxaliplatin		Not Applicable	
	]90-110 %]		26 (12 %)
	]70-90 %]		88 (42 %)
	≤ 70 %		95 (45 %)

Primary Endpoint

Table 65: Primary endpoint: Progression Free Survival

ITT Population		Arm A N = 210	Arm B N = 210	p-Value*
Investigator assessment	**Median (months)**	6.2	8.8	p = 0.0001
	95 % CI (months)	[5.5 - 7.3]	[7.9 - 9.5]	
Expert assessment	**Median (months)**	6.0	8.2	p = 0.0003
	95 % CI (months)	[5.5 - 6.5]	[7.2 - 8.8]	

Table 66: Factor

Factor	odds ratio	p-value	
Allocated treatment	1.84	0.0001	(S)
Astler and Coller's grade D	1.57	0.0306	(S)
Number of involved organs	0.80	0.0679	
Liver involvement	1.60	0.1601	

Secondary Endpoints

Table 67: Secondary endpoint: Response Rate

		Treatment Arm	N Total	ORR %	95 % Confidence	p-Value*
Confirmed responses	**Experts**	LV5-FU2	210	22	[16 - 27]	0.0001
		LV5-FU2+ oxaliplatin	210	49	[42 - 56]	

Table 68: Radiological Experts Response Assessment

Radiological Experts Response Assessment	Arm A (N = 210)	Arm B (N = 210)
***CR**	1	3
***PR**	45	100
SD	107	69
PD	34	21
Not Evaluable	3	0
Missing**	20	17

Non evaluable patients

- According to the WHO definition of response (Miller et al 1981 & Beretta et al 1987), patients evaluable for response assessment must have received at least two cycles of treatment, with at least one subsequent tumor assessment unless « early progression » occurred, in which case they are considered evaluable.

  7 patients are non evaluable according to this definition :

  - 2 non treated patients (n°s 0302, 5406, arm A).
  - 1 non treated, early withdrawal in the prospect of metastasis surgery, non eligible patient (n° 6112, arm B).
  - 1 early withdrawal in the prospect of metastasis surgery (n° 1112, arm A).
  - 2 early non-disease related deaths (n°s 0112, 6002, arm B).
  - 1 non eligible patient (n° 6005, arm A).

- Five additional patients are considered non evaluable. These patients were assessed by the investigators as being stable (2 patients) or responders (3 patients), but CT-scans could not be retrieved and reviewed (n° 6206, arm A; n°s 5311, 5312, 6305, 6405, arm B).

Response Rate Conclusions

The number of evaluable patients is therefore 205 and 203 patients in arm A and B, respectively; the number of responders is therefore 46 (unchanged) and 105 patients in arm A and B, respectively, resulting in a response rate of 22.4 % in arm A and 51.7 % in arm B (p = 0.0001).

Overall Survival

The median overall survival was 15.9 months (95% CI 14.7 to 18.2 months) for the oxaliplatin arm and 14.7 (95% CI 13.0 to 18.2 months) for the control arm. The p-value using the log-rank test is 0.1349. Forty-three per cent (90/210) of the patients in the oxaliplatin arm were censored and 38% (79/210) of the patients in the control arm were censored.

Several exploratory analyses of overall survival were conducted by Sanofi using various prognostic factors. Some of these exploratory analyses show a statistically significant advantage for oxaliplatin. For a description and discussion of these analyses see Dr. Rothman's FDA Statistical review.

Additional Therapy

Follow-up treatments

- Surgery:
  The number of patients in each arm who underwent secondary surgery for metastectomy after the 1st line chemotherapy, was as follows:
  - 7 / 208 (3 %) in arm A
  - 14 / 209 (7 %) in arm B

Complete surgical response was achieved in 5 (2 %) patients in arm A, and in 12 (6 %) in arm B.

- Chemotherapy :

This table displays the status of chemotherapy administered to the patients during the follow-up period after study withdrawal, as of cut-off date.

Table 69: Chemotherapy during follow-up

	Arm A	Arm B
N withdrawals	190	181
N followed-up as of cut-off date (% withdrawals)	154 (81 %)	158 (87 %)
N received chemotherapy during follow-up (% withdrawals)	83 (44 %)	65 (36 %)
N received oxaliplatin during follow-up (% withdrawals)	34 (18 %)	7 (4 %)

Nearly 20 % (i.e. 34 / 190) of patients who withdrew from the LV5-FU2 arm A received oxaliplatin as further chemotherapy (22 % of patients with follow-up data : 34 / 154), as opposed to only 4 % of patients (i.e. 7 / 181) first treated in the LV5-FU2 + oxaliplatin arm B.

Clinical Benefit

Clinical benefit was analyzed with regard to amelioration from baseline of performance status, pain level and weight.

Performance status amelioration

Overall, 227 patients had a baseline PS ≥ 1 (i.e. PS 1 or 2).

The table below presents the proportions of patients in both groups who had a lower PS recorded at any cycle on-study, compared to baseline (i.e. grade 1 to 0, grade 2 to 1 or 0).

Table 70: Patients with PS amelioration during the study

Number of patients :	Arm A N = 208	Arm B N = 209
With PS ≥ 1 at baseline	108	119
With improved PS	59	71

(Appendix C1, pages 114 and 115-123)

The majority of patients of both arms with PS ≥ 1 at baseline, improved at some point during the study: 59 / 108 (55 %) in arm A, 71 / 119 (60 %) in arm B.

Pain level amelioration

Overall, 111 patients had at least mild pain at baseline, mostly related to the disease.
Table (10.4.8.2).1 displays the proportions of patients in both groups who experienced an alleviation of their baseline pain level at any cycle on-study (i.e. grade 1 to 0, grade 2 to 1 or 0 and grade 3 to 2, 1 or 0).

Table 71: Patients with Pain improvement during the study

Number of patients :	Arm A N = 208	Arm B N = 209
With pain ≥ mild at baseline	57	56
With improved pain	11	9

(Appendix C1, page 114)

A similar proportion of patients in both treatment arms had some amelioration of pain during the study compared to baseline: 11 / 57 patients in arm A, 9 / 56 in arm B.

Weight increase
This analysis considered the evolution of the actual weight of the patients from baseline.
Table (10.4.8.3).1 presents the proportion in both groups of the patients who exhibited a weight increase of at least 5 % compared to baseline, at any cycle throughout study.

Table 72: Patients with weight increase during the study

Number of patients	Arm A N = 208	Arm B N = 209
N patients with weight increase	83 (40 %)	90 (43 %)

A total of 40 % of patients in arm A, and of 43 % in arm B had an increase of weight during the study, as compared to baseline.

Quality of Life
Quality of life was assessed using the patient self administered EORTC QLQ-C 30 (version 2). The Sponsor reports no significant difference in quality of life between the two treatment arms of this study.

Efficacy Conclusions
There were significant differences in response rate and progression free survival that favored the addition of oxaliplatin. There were no significant differences in overall survival, performance status, pain, weight gain or quality of life. Some exploratory analyses showed a favorable effect of oxaliplatin on survival (See Dr. Rothman's FDA Statistical Review). The interpretation of overall survival results may be confounded by cross over of patients on the 5FULV arm who subsequently received oxaliplatin and treatment of patients on the oxaliplatin arm who received irinotecan as second line therapy. Irinotecan has been demonstrated to prolong survival in patients with colorectal cancer.

Safety

Table 73: Safety: Adverse Event

Adverse Event (Preprinted in the	Number of Patients (%)					
	Arm A (N = 208)			Arm B (N = 209)		
	All grades	G3 (%)	G4 (%)	All grades	G3 (%)	G4 (%)
Neurosensory	25 (12 %)	-	NA	142 (68 %)	38 (18 %)	NA
Anemia	169 (81 %)	3 (1 %)	2 (1 %)	181 (87 %)	7 (3 %)	-
Leucopenia	48 (23 %)	2 (1 %)	3 (1 %)	145 (69 %)	19 (9 %)	-
Neutropenia	63 (30 %)	8 (4 %)	3 (1 %)	147 (70 %)	62 (30 %)	25 (12 %)
Thrombocytopenia	61 (29 %)	1(0.5 %)	-	159 (76 %)	4 (2 %)	1 (0.5 %)
Hemorrhage	27 (13 %)	1(0.5 %)	-	24 (11 %)	-	-
Nausea	111 (53 %)	3 (1 %)	NA	151 (72 %)	12 (6 %)	NA
Vomiting	61 (29 %)	3 (1 %)	1(0.5 %)	113 (54 %)	9 (4 %)	3 (1 %)
Diarrhea	91 (44 %)	8 (4 %)	3 (1 %)	123 (59 %)	18 (9 %)	7 (3 %)
Stomatitis	74 (36 %)	3 (1 %)	-	91 (44 %)	11 (5 %)	1 (0.5 %)
Fever w/o infection	31 (15 %)	-	-	69 (33 %)	-	-
Infection	48 (23 %)	2 (1 %)	1(0.5 %)	54 (26 %)	3 (1 %)	-
Skin toxicity	65 (31 %)	-	1 (0.5 %)	60 (29 %)	-	-
Alopecia	39 (19 %)	NA	NA	37 (18 %)	NA	NA

Table 74: Safety: Neurological sign/symptom

Neurological sign / symptom	Number of patients (%)			
	Arm A (N = 208)		Arm B (N = 209)	
	All grades (%)	G3 (%)	All grades (%)	G3 (%)
Global specific grade	23 (11 %)	-	173 (83 %)	36 (17 %)
Cold-related dysesthesia	1 (0.5 %)	-	141 (67 %)	1 (0.5 %)
Paresthesia without pain	23 (11%)	-	136 (65 %)	5 (2 %)
Paresthesia with pain	-	-	22 (11 %)	1 (0.5 %)
Paresthesia with functional impairment	-	-	34 (16 %)	34 (16 %)
	All severity levels (%)	**Severe (%)**	**All severity levels (%)**	**Severe (%)**
Laryngeal spasm (syndrome)	-	-	2 (1 %)	-
Cramps	3 (1 %)	-	12 (6 %)	2 (1 %)
Pharyngo-laryngeal dysesthesia	1 (0.5 %)	-	47 (22 %)	1 (0.5 %)
Lhermitte's sign	-	-	7 (3 %)	-
Loss of deep tendon reflexes	1 (0.5 %)	-	24 (11 %)	-

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

Table 75: Safety: Drug-related SAEs

Drug-related SAEs (preferred term)	Number of patients (%)			
	Arm A - N = 208		Arm B - N = 209	
Diarrhea	3[1]	(1 %)	9[2,2]	(4 %)
Vomiting	-		2	(1 %)
Mucositis	-		1	(0.5 %)
Haemolysis	-		1	(0.5 %)
Granulocytopenia	2	(1 %)	1	(0.5 %)
Leucopenia	1[1]	(0.5 %)	-	
Fever	-		2	(1 %)
Infection	1[1]	(0.5 %)	2	(1 %)
Chest pain, chest pain precordial	2	(1 %)	-	
Myocardial infarction	1	(0.5 %)	-	
Bradycardia	-		1	(0.5 %)
Cardiac failure	-		1	(0.5 %)
Allergic reaction	-		4	(2 %)
Depression	-		1	(0.5 %)
Headache	1	(0.5 %)	-	
Dysaesthesia	-		1	(0.5 %)
Venous thrombosis (arm)	1[2]	(0.5 %)	-	
Thrombosis	1	(0.5 %)	-	
Dyspnea	1	(0.5 %)	1[2]	(0.5 %)
Malaise	1	(0.5 %)	-	
GI haemorrhage	1	(0.5 %)	-	
Asthenia	-		2	(1 %)
Implantation complication	1	(0.5 %)	-	
Haemorrhage*			1	(0.5 %)

- 12 patients were hospitalized for 14 episodes of severe diarrhea (n°[S] 2103, 5311, 6204, 6432, 7001, 8009, 8102, 8115, 8203, 8217, 8223, 8309). Diarrhea was complicated with vomiting in 5 cases, mucositis in 2 cases, dehydration in 2 cases and signs of bowel obstruction in 2 cases. It occurred in the first 4 cycles in 9 patients, typically 1 week after treatment course. Treatment was symptomatic with recovery in a few days and discharge from hospital after 1 - 6 days, except for 2 patients with bowel obstruction and grade IV diarrhea, respectively. All events were related to 5-FU administration ; among the 11 events which occurred in patients treated with oxaliplatin, 2 were not related to its administration. Diarrhea resulted in a withdrawal for toxicity for 1 patient.

Table 76: Safety: Diarrhea

Diarrhea	**Number of patients (%)**			
Worst NCI-CTC grade	**Arm A (N = 208)**		**Arm B (N = 209)**	
³ 1	91	(44 %)	123	(59 %)
3	8	(4 %)	18	(9 %)
4	3	(1 %)	7	(3 %)

The table below presents the incidence and severity of diarrhea observed by cycle for each treatment arm during the study.

Table 77: Incidence and severity of diarrhea by cycle and by treatment arm during study

Diarrhea	Number of cycles (%)			
NCI-CTC	Arm A (N = 2435)		Arm B (N = 2594)	
≥ 1	306	(13 %)	441	(17 %)
3	9	(0.4 %)	31	(1 %)
4	3	(0.1 %)	7	(0.3 %)

Vomiting

2 patients, (n°s 1109, 5401), both in arm B were hospitalized for vomiting, of whom one had concomitant diarrhea and dehydration and in the other vomiting was incoercible. Events occurred at 4th and 8th cycle. Treatment was symptomatic ; both patients recovered (in 2 and 5 days), and went on with the trial. Both events were related to both drugs.

Table 78: Safety: Nausea

Nausea	**Number of patients (%)**			
Worst NCI-CTC grade	**Arm A (N = 208)**		**Arm B (N = 209)**	
³ 1	111	(53 %)	151	(72 %)
3	3	(1 %)	12	(6 %)
4	NA		NA	

NA : not applicable

Table 79: Incidence and severity of nausea by cycle by treatment arm during study

Nausea	**Number of cycles (%)**			
NCI-CTC grade	**Arm A (N = 2435)**		**Arm B (N = 2594)**	
³ 1	402	(17 %)	632	(24 %)
3	4	(0.2 %)	13	(0.5 %)
4	NA		NA	

Table 80: Incidence and severity of vomiting

Vomiting	Number of patients (%)			
Worst NCI-CTC grade	Arm A (N = 208)		Arm B (N = 209)	
³ 1	61	(29 %)	113	(54 %)
3	3	(1 %)	9	(4 %)
4	1	(0.5 %)	3	(1 %)

Table 81: Incidence and severity of vomiting by cycle by treatment arm during study

Vomiting	Number of cycles (%)			
NCI-CTC grade	Arm A (N = 2435)		Arm B (N = 2594)	
³ 1	135	(6 %)	288	(11 %)
3	3	(0.1 %)	13	(0.5 %)
4	2	(0.1 %)	3	(0.1 %)

Mucositis

Mucositis occurred in 1 patient (n° 8309) 10 days after first cycle and was complicated by thrush. Patient recovered in 10 days with local treatment. The event was related to both drugs.

Table 82: Incidence and severity of anemia

Anemia	Number of patients (%)			
Worst NCI-CTC grade	Arm A (N = 208)		Arm B (N = 209)	
³ 1	169	(81 %)	181	(87 %)
3	3	(1 %)	7	(3 %)
4	2	(1 %)	0	

Table 83: Anemia, NCI-CTC grade by arm and by cycle during study

Anemia	Number of cycles (%)			
NCI-CTC grade	Arm A (N = 2435)		Arm B (N = 2594)	
³ 1	1247	(51 %)	1395	(54 %)
3	3	(0.1 %)	14	(0.6 %)
4	2	(0.1 %)	0	

Table 84: Stomatitis

Stomatitis Worst NCI-CTC grade	Number of patients (%)	
	Arm A (N = 208)	Arm B (N = 209)
³ 1	74 (36 %)	91 (44 %)
3	3 (1 %)	11 (5 %)
4	0	1 (0.5 %)

The Table below displays the incidence and severity of stomatitis by cycle and by treatment arm during the study.

Table 85: Incidence and severity of stomatitis by cycle and by treatment arm during study

Stomatitis NCI-CTC grade	Number of cycles (%)	
	Arm A (N = 2435)	Arm B (N = 2594)
³ 1	202 (8 %)	277 (11 %)
3	3 (0.1 %)	14 (0.5 %)
4	0	1 (0.04 %)

Hemolysis

Mild hemolysis occurred in one patient (n°3004) after 19 cycles; total bilirubin went up to 2.3 mg / 100 ml. Direct Coombs test was negative.
Recovery was obtained in 5 days after discontinuation of treatment. The event was related to both drugs.

Table 86: Leukopenia and Neutropenia

	Number of patients (%)					
	Arm A (N = 208)			Arm B (N = 209)		
NCI-CTC grade	≥ 1	3	4	≥ 1	3	4
Leukopenia	48 (23 %)	2 (1 %)	3 (1 %)	145 (69 %)	19 (9 %)	0
Neutropenia	63 (30 %)	8 (4 %)	3 (1 %)	147 (70 %)	62 (30 %)	25 (12 %)

Table 87: Leuco-neutropenia, NCI-CTC grade by treatment arm, by cycle during study

	Number of cycles (%)					
	Arm A (N = 2435)			Arm B (N = 2594)		
NCI-CTC grade	≥ 1	3	4	≥ 1	3	4
Leukopenia	146 (6 %)	3 (0.1 %)	3 (0.1 %)	623 (24 %)	28 (1 %)	0
Neutropenia	162 (7 %)	8 (0.3 %)	3 (0.1 %)	689 (27 %)	119 (5 %)	35 (1 %)

Table 88: Thrombocytopenia

Thrombocytopenia Worst NCI-CTC grade	Number of patients (%)	
	Arm A (N = 208)	Arm B (N = 209)
³ 1	61 (29 %)	159 (76 %)
3	1 (0.5 %)	4 (2 %)
4	0	1 (0.5 %)

Granulocytopenia
3 patients suffered from grade III and IV granulocytopenia (n°^{s} 4213, 6106, 6433), 3, 4 and 16 days after last treatment course. All patients were treated with GCSF and antibiotics and recovered. All events were related to administered drugs, and no patient withdrew from trial.
Leucopenia
This patient (arm A, n°8203) had concomitant diarrhea, was treated with GCSF and antibiotics and recovered in 6 days. The patient went on with study.

Fever
2 patients (n°^{s} 1110, 7003) exhibited fever on the first day of the 6th course, one after oxaliplatin infusion. Both events were related to oxaliplatin infusion and both patients went on with study.
Infection
2 patients (n°^{s} 8202, 8203) presented with fever and infection ; one had an infection possibly related to the implanted infusion system (Port-a-Cath), the other a viral chest infection with dyspnea. Both patients quickly recovered and went on with study. Both events were related to administered drugs.

Table 89: Incidence of fever with and without infection

Fever without infection worst NCI-CTC grade	Number of patients (%)	
	Arm A (N = 208)	Arm B (N = 209)
³ 1	31 (15 %)	69 (33 %)
3	0	0
4	0	0
Infection	**Arm A (N = 208)**	**Arm B (N = 209)**
³ 1	48 (23 %)	54 (26 %)
3	2 (1 %)	3 (1 %)
4	1 (0.5 %)	0

The table below displays the incidence and severity of fever without infection and infection by cycle and treatment arm during the study.

Table 90: Incidence and severity of fever without infection and of infection by cycle and by treatment arm

Fever without infection NCI-CTC grade	Number of cycles (%)			
	Arm A (N = 2435)		Arm B (N = 2594)	
³ 1	56	(2 %)	130	(5 %)
3	0		0	
4	0		0	
Infection	**Arm A (N = 2435)**		**Arm B (N = 2594)**	
³ 1	75	(3 %)	97	(4 %)
3	3	(0.1 %)	3	(0.1 %)
4	2	(0.1 %)	0	

Related thrombosis SAEs

1 patient (n°8306, arm A) had 2 occurrences of thrombosis of an arm vein, of which he recovered.

1 patient (n° 1102, arm A) had a possible lung infarction (coded « thrombosis »). The patient was subsequently withdrawn from the study due to disease progression.

Related allergic SAEs

Four patients (n°s 3007, 3008, 5411, 6430) presented with severe oxaliplatin-related allergic reaction (1 anaphylactoid reaction) with skin symptoms (erythroderma, rash, itching), dyspnea, hypotension and syncope (patient with anaphylactoid reaction).

These events appeared after 7 to 13 cycles when infusing oxaliplatin on the first day of the treatment course.

In all cases, infusion was stopped and infused doses ranged from 14 to 38 mg.

All patients recovered ; 4 patients went on with study, of whom 2 received preventive therapy prior to oxaliplatin administration at subsequent cycles without recurrence of allergic symptoms, and 2 received further courses without oxaliplatin ; the patient with the anaphylactoid reaction was withdrawn from study.

Neurologic Events

- Patient n° 1114 (arm B) complained of mnesic disorders identified as depressive symptoms, possibly related to 5-FU, which was not withdrawn.
- Patient n°8220 (arm A) presented with headaches possibly related to 5-FU, not withdrawn as well.
- Patient n°6302 (arm B) exhibited an acute laryngo-pharyngeal dysesthesia with feeling of suffocation 30 minutes after completion of the oxaliplatin infusion of 9th cycle. She quickly recovered on the same day, was not withdrawn from study and no recurrence was observed at subsequent cycles, as oxaliplatin was infused in 6 hours instead of 2.

  The event was probably related to oxaliplatin administration.

Table 91: Assessment of severity of neurologic events

GRADE 0	GRADE 1	GRADE 2	GRADE 3
Absent	Short lasting paresthesia and/or dysesthesia with complete regression at next cycle	Paresthesia and/or dysesthesia persistent between 2 cycles without functional impairment	Permanent functional impairment

Table 92: Peripheral neuropathy [neurosensory]

Peripheral neuropathy « Neurosensory » Worst NCI-CTC grade	Number of patients (%)	
	Arm A (N = 208)	Arm B (N =209)
³ 1	25 (12 %)	142 (68 %)
3	0	38 (18 %)
4	NA	NA

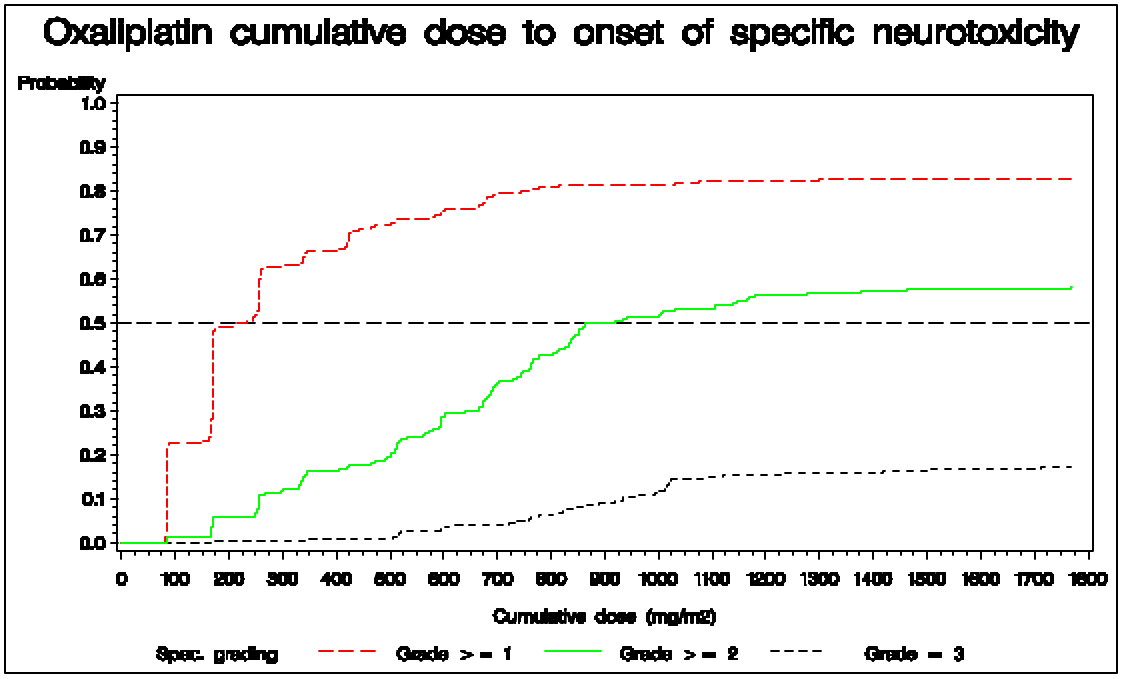
Table 93: Peripheral neuropathy symptom

Peripheral neuropathy symptom Worst specific grade	Number of patients (%)	
Cold-related dysesthesia	Arm A (N = 208)	Arm B (N = 209)
³ 1	1 (0.5 %)	141 (67 %)
3	0	1 (0.5 %)
Paresthesia without pain		
³ 1	23 (11 %)	136 (65 %)
3	0	5 (2 %)
Paresthesia with pain		
³ 1	0	22 (11 %)
3	0	1 (0.5 %)
Paresthesia with functional impairment		
3	0	34 (16 %)
Worst global grade		
³ 1	23 (11 %)	173 (83 %)
3	0	36 (17 %)

Cold-related dysesthesias were frequent (67 % of arm B patients) but mild or moderate in intensity and duration (i.e. acute symptom) as only one patient (0.5 %) suffered from grade 3 dysesthesia for 1 cycle. Also frequent were acute paresthesias (65 % of patients in arm B), they led to functional impairment persistent for at least 1 cycle interval, in 34 patients (16 %) of arm B for a total of 138 cycles (5 % of the total of cycles in arm B).

Globally, 83 % (173 patients) of patients in arm B suffered from paresthesias and / or dysesthesias which were cumulative (grade 3) with some sort of functional impairment for the patient in 17 % (36 patients) of patients and for 5 % of the total number of cycles.

Figure 7: Oxaliplatin cumulative dose to onset of specific neurotoxicity



The above Figure displays the probability of occurrence of the first experience of grade 1, 2, 3 neurotoxicity (specific grading) when increasing the cumulative dose of oxaliplatin. Median dose to onset for the 173 patients who experienced at least a grade 1 neurotoxicity was 170 mg / m² (2 cycles) ; median cumulative dose to onset for the 122 patients who experienced at least a grade 2 was 603 mg / m² (circa 7 cycles) ; median cumulative dose to onset for the 36 patients who experienced grade 3 was 874 mg / m² (circa 10 cycles).

Table 94: Other neurotoxicity symptom/signs

Other neurotoxicity symptom/signs severity scale	Number of patients (%)			
Pharyngo-laryngeal dysesthesia	**Arm A (N = 208)**		**Arm B (N = 209)**	
³ **mild**	1	(0.5 %)	47	(22 %)
severe	0		1	(0.5 %)
Laryngeal spasm (syndrome)				
³ **mild**	0		2	(1 %)
severe	0		0	
Cramps				
³ **mild**	3	(1 %)	12	(6 %)
severe	0		2	(1 %)
Loss of deep tendon reflexes				
³ **mild**	1	(0.5 %)	24	(11 %)
severe	0		0	
Lhermitte's sign				
³ **mild**	0		7	(3 %)
severe	0		0	

The most frequent symptom was pharyngo-laryngeal dysesthesia (22 % of arm B patients, 1 was severe and serious, n° 6302). The typical oxaliplatin «laryngeal spasm-syndrome » was observed in only 2 patients.

Table 95: Adverse Event: System Organ Class

Adverse Event (AE) SYSTEM ORGAN CLASS preferred term	Number of patients with drug-related AEs (%)							
	Arm A (N = 208)				Arm B (N = 209)			
	All grades		severe*		All grades		severe*	
BODY AS A WHOLE								
Asthenia	44	(21 %)	4	(2 %)	63	(30 %)	10	(5 %)
Allergy	0		0		14	(7 %)	4	(2 %)
GASTRO-INTESTINAL								
Constipation	11	(5 %)	0		25	(12 %)	1	(0.5 %)
PSYCHIATRIC								
Anorexia	7	(3 %)	0		10	(5 %)	1	(0.5 %)
SPECIAL SENSES								
Taste perversion	6	(3 %)	0		11	(5 %)	0	
VISION								
Conjunctivitis	22	(11 %)	3	(1 %)	12	(6 %)	0	

Toxicity in Elderly Patients
The table below presents the incidence of most frequent toxicities (preprinted AEs of the CRF) by patient, in patients aged 60 years and older, as compared with that of overall population.

Table 96: Toxicity frequency by patient in elderly and all patients

Toxicity	Arm A				Arm B			
	Elderly patients N = 128 (%)		All patients N = 208 (%)		Elderly patients N = 126 (%)		All patients N = 209 (%)	
Leukopenia	29	(23 %)	48	(23 %)	87	(69 %)	145	(69 %)
Neutropenia	38	(30 %)	63	(30 %)	92	(73 %)	147	(70 %)
Thrombocytopenia	45	(35 %)	61	(29 %)	92	(73 %)	159	(76 %)
Anemia	105	(82 %)	169	(81 %)	113	(90 %)	181	(87 %)
Nausea	70	(55 %)	111	(53 %)	89	(71 %)	151	(72 %)
Vomiting	40	(31 %)	61	(29 %)	62	(49 %)	113	(54 %)
Diarrhea	56	(44 %)	91	(44 %)	72	(57 %)	123	(59 %)
Stomatitis	45	(35 %)	74	(36 %)	55	(44 %)	91	(44 %)
Fever without infection	17	(13 %)	31	(15 %)	41	(33 %)	69	(33 %)
Infection	29	(23 %)	48	(23 %)	30	(24 %)	54	(26 %)
Alopecia	25	(20 %)	39	(19 %)	24	(19 %)	37	(18 %)
Skin	39	(30 %)	65	(31 %)	33	(26 %)	60	(29 %)
Peripheral neuropathy								
• NCI « neurosensory » Worst NCI grade	11	(9 %)	25	(12 %)	79	(63 %)	142	(68 %)
• Peripheral neuropathy Worst global Specific grade	9	(7 %)	23	(11 %)	104	(83 %)	173	(83 %)

There was no increase in the frequency of toxicity symptoms between the elderly population and the overall population.

Deaths within 30 days of last treatment administration

16 patients died within 30 days of last treatment administration, 11 in arm A and 5 in arm B. No death was related to trial drugs, except for patient n° 6002 whose death was related to both drugs (toxic death, see paragraph 10.2.1).

- 11 patients died from disease progression: n°s 0109, 0911, 3005, 4003, 5007, 5018, 5101, 6401, 6429, 8216 and 9202.
- 1 patient (n° 0912) died from toxicity of second line chemotherapy: diarrhea, febrile neutropenia and renal failure due to irinotecan (CPT 11) administration.
- 1 patient died suddenly without relationship with either treatment drugs or disease, in the investigator's opinion (n° 4212). In this arm B patient, the dose of oxaliplatin administered at last cycle was 0.
- 1 patient (n° 0112) died from renal failure, neither related to treatment drugs, nor to disease in the investigator's opinion.
- 1 patient (n° 6413) died from deep venous thrombosis, complicated of sepsis.

Related thrombosis SAEs

1 patient (n°8306, arm A) had 2 occurrences of thrombosis of an arm vein, of which he recovered.

1 patient (n° 1102, arm A) had a possible lung infarction (coded « thrombosis »). The patient was subsequently withdrawn from the study due to disease progression.

Safety Conclusions
There were significant differences in hematologic, gastorintestinal and neurologic toxicities between the study arms. Those patients that received oxaliplatin had more frequent and more severe toxicities. The neurologic toxicity was cumulative.

Overall Study Conclusions
The study was well run and results were adequately documented for regulatory review. The patient population was representative of other published series and was balanced between treatment arms with regard to age, gender, performance status and disease characteristics. Oxaliplatin resulted in significantly more toxicity and morbidity without a significant increase in overall survival, improvement in performance status, alleviation of pain, weight gain, or quality of life.

Study 3840

The following is quoted from the sponsor's study report.

Dates of Study:	February 1991 through March 1996
Objectives:	Primary Objective: To compare the survival time of pts treated with a monthly schedule of 5-Fluorouracil (5-FU) bolus plus low-dose Leucovorin (FA) for 5 consecutive days versus pts treated with the Bimonthly A schedule of 5-FU bolus plus continuous infusion plus high-dose FA. Secondary Objectives: To compare the toxicity of the two regimens; To compare response rates in pts with measurable tumors.
Methodology:	Multi-center, open-label, randomized study.
Number of Enrolled Patients:	Total: 441 patients; Bimonthly A: Total 221, Daily × 5: Total 220
Number of Evaluable Patients:	Total: 433 patients; Bimonthly A: Male 135, Female 82, Total 217 Daily × 5: Male 145, Female 71, Total 216
Diagnosis and Inclusion Criteria:	Histologically documented colorectal cancer with nonresectable metastases; WHO performance status 0 – 2; no chemotherapy in last 6 months; no previous chemotherapy with folinic acid; aged ≤ 75 years; no brain metastases or exclusively bone metastases; no second, uncured malignancy; life expectancy > 2 months; metastases outside the radiation field in patients who have previously received radiotherapy for colorectal cancer; initial evaluation < 2 weeks prior to inclusion; neutrophils >1500/mm^3, platelets > 100,000/mm^3, creatinine < 3 fold above normal, prothrombin ≥ 50%, signed informed consent, follow-up feasible.
Dosage and Administration:	<u>Bimonthly A Arm</u>

	FA: 200 mg/m^2/day, 5-FU bolus: 400 mg/m^2/day, continuous 5-FU: 600 mg/m^2/day, Day 1 – Day 2 treatment repeated every 14 days <u>Daily × 5 Arm</u> FA: 20 mg/m^2/day, 5-FU bolus: 425 mg/m^2/day, Day 1 – Day 5 treatment repeated every 28 days
Duration of Treatment:	Continue until tumor progression, unless Grade 4 toxicity. If complete response (CR) noted, continue treatment for at least one year.
Stratification Criteria:	WHO performance status 0 or 1-2 Synchronous or metachronous metastases Measurable or nonmeasurable disease
Randomization:	All patients were randomized by the Scientific Secretariat of the FFCD by telephone. To randomize patients, investigators had to provide complete officially registered personal information and all inclusion and exclusion criteria.
Cooperative Group Statistical Methods:	The study was designed with enough power to detect a 15% difference in survival between the two arms at 18 months using a two-sided log-rank test. The Mantel-Haenszel test, with stratification criteria adjusted, was used for population, response rate and toxicity comparisons. Response duration, progression-free survival, and survival were calculated using the Kaplan-Meier method. The stratified log-rank test and Cox proportional hazard model were used for testing the association between treatment and outcome.

"Efficacy data (response rate, PFS, and survival) are analyzed separately as reported on case report forms and based on Sanofi adjudication. Response rate is estimated and compared for the two treatment arms using the population of eligible patients with measurable disease (n = 348). PFS and survival comparisons for the two treatment arms are done for the eligible population (n=433). Statistical comparison for the two treatment arms is done with the Chi-squared test for response rate. For the time-dependent parameters of PFS and survival, results from the log rank test and the Wilcoxon test are presented. The influence of individual baseline prognostic factors on probability of response, PFS, and survival is also assessed. A model was fitted for each of the baseline prognostic factors (Appendix 10.3), including the factor and allocated treatment as independent variables. Logistic regression was used for probability of response. The Cox proportional hazard model was used for PFS and survival.

Overall survival was calculated as number of weeks from randomization to date of death. PFS was calculated as the number of weeks from randomization to the progression date. When progression date was not specified on the case report form, an algorithm described in Appendix 10.5 was used to determine the date of progression and PFS. This algorithm is similar to an algorithm provided by the Cooperative Group and has been modified to cover the case 3c (patient known dead, but no further information on progression beyond date of randomization). Sanofi's review included an adjudication of all reported progression dates. If the reviewing oncologist indicated agreement with the reported progression date, adjudicated PFS was the same as Cooperative Group-determined PFS. In those cases where Sanofi did not agree with the reported progression date, adjudicated PFS was calculated using Sanofi's adjudicated assessment of progression date."

Reviewer's Comments

The abstract from the investigator's publication in the Journal of Clinical Oncology, 1997 Feb;15(2):808-15

states "The bimonthly regimen was more effective and less toxic than the monthly regimen and definitely increased the therapeutic ratio. However, there was no evidence of increased survival." There were sufficient differences in tolerance, toxicity, and response rate in the two arms that it would be difficult to know what the effects of varying a parameter in one regimen would predict about the other.

7 OVERVIEW OF EFFICACY

Data for the use of oxaliplatin in the first line chemotherapy of advanced metastatic colorectal cancer was submitted for 2 randomized controlled clinical trials. The clinical endpoint of interest for registration of a product as first line therapy is survival. This principle has been established on the basis of discussions with the Oncologic Drug Advisory Committee and has been communicated to all sponsors with an interest in developing products for colorectal cancer. The FDA/Sanofi meeting minutes for meetings prior to the submission of NDA 21063 reflect this perspective.

Of the two randomized controlled clinical trials submitted, one, study 2961, did not show a survival advantage or even a trend toward better survival for the Oxaliplatin arm. The second study, 2962, did not show a survival advantage in the primary unadjusted analysis using the Log Rank test. Some exploratory adjusted analyses did show a survival advantage for oxaliplatin. See Dr. Rothmann's FDA statistical review for a description and discussion of these exploratory analyses. One of the adjusted analyses was on the basis of alkaline phosphatase levels at baseline. The use of alkaline phosphatase levels has been considered in some published studies to be of prognostic value, but is not universally accepted. It is noteworthy that alkaline phosphatase was not a prognostic factor for survival in study 2061 (p=0.99).

The sponsor's conclusion that oxaliplatin will prolong survival as part of a 5-FULV regimen administered as first line therapy for metastatic colorectal cancer is at best tentative, and would require confirmatory studies (preferably using standard United States 5-FULV regimens) before it would satisfy the intent of CFR 21 314 and the principles in ICH documents E-8 and E-9 with regard to evidence from adequate and well controlled studies. This is not a reflection on deficiencies in the specific design and conduct of studies 2961 and 2962. These studies were intended to answer different questions for specific regimens.

8 OVERVIEW OF SAFETY

Examining the results of only the controlled randomized studies in previously untreated patients with metastatic colorectal cancer, studies 2961 and 2962, the combination of oxaliplatin plus 5-FUL:V increased significantly the rates and severity of hematologic (hemolysis, leukopenia, thrombocytopenia) , gastrointestinal (diarrhea, emesis, mucositis) , and neurologic adverse events. The neurologic adverse events were characterized by paraesthesias (with and without pain and with and without functional impairment), temperature sensitive dysesthesia, laryngospasm, pharyngo-laryngeal dysesthesia, cramps, and Lhermitte's sign (electric shock sensations in the spine upon turning of the neck).

The incidence of fever and neutropenia was also higher on the Oxaliplatin arm, but not the incidence of infection, when compared to 5-FULV without Oxaliplatin.

The incidence of adverse events varied in details between the two studies for both the oxaliplatin 5-FULV combination and for 5-FULV. This suggests that the adverse event profile will vary depending upon the 5-FULV regimen used. There did not seem to be any age dependent differences in severity or profile of adverse events. An analysis based upon whether patients were symptomatic or asymptomatic at baseline was not performed by the FDA.

9 LABELING REVIEW

The labeling review is postponed pending the results and recommendations of the advisory committee.

10 CONCLUSIONS

The data to support a first line indication for oxaliplatin in combination with 5-FU/LV in the treatment of advanced metastatic colorectal cancer is weak. Data from two randomized clinical trials are submitted adding Oxaliplatin to different 5-FULV regimens. Addition of Oxaliplatin shows better tumor response rate and better progression free survival. However, there is no clear improvement in overall survival. Study 2962 shows a survival benefit for oxaliplatin only after exploratory adjusted analysis. This is not reflected in any

improvement in patient clinical benefit or quality of life. Study 2961 does not even show a trend toward a survival benefit. Oxaliplatin adds significant adverse effects, especially peripheral neurotoxicity.

Neither of the randomized clinical trials (2961 and 2962) was conducted in the United States. Both trials added Oxaliplatin to complex 5-FULV regimens requiring infusion pumps. These complex 5-FULV regimens are completely unlike the 5-FULV regimens used in the United States. Realistically they are not likely to be used in the United States. There is no data on the efficacy or toxicity of Oxaliplatin when added to the standard 5-FULV regimens used in the United States.

11 RECOMMENDATIONS

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12 REFERENCES

1. Cancer –Principles & Practice of Oncology 5th edition, Lippincott-Raven, Philadelphia, PA, U.S.A.
2. Cancer Medicine 4th edition, Williams & Wilkins, Baltimore, MD, U.S.A.
3. BMJ 306: 752-755, 1993
4. J Clin Oncol 10: 904-911, 1992
5. New Engl J Med 312: 137-141, 1985
6. J Clin Oncl 12: 14-20, 1994
7. J Clin Oncol 15: 3320-3329, 1997
8. Cancer 36: 675-682, 1975
9. J Clin Oncol 6: 469-475, 1988
10. J Clin Oncol 7: 1407-1418, 1989
11. J Chemother 5: 52-55, 1993
12. Ann Oncol 9: 535-541, 1998
13. Ann Oncol 3: 371-376, 1992
14. J Clin Oncol 8: 491-501, 1990
15. Ann Oncol 2: 673-679, 1991
16. J Clin Oncol 13: 1303-1311, 1995
17. J Clin Oncol 7: 1427, 1989
18. Eur J Cancer 21A: 2105, 1995
19. J Natl Cancer Inst 88: 668-674, 1996
20. J Clin Oncol 7: 425-432, 1989
21. Am J Clin Oncol 14: 211-217, 1991
22. J Clin Oncol 5: 1559-1565, 1987
23. Clin Cancer Res 4: 935-939, 1998
24. J Clin Oncol 11: 1888-1893, 1993
25. J Clin Oncol 7: 1419-1426, 1989
26. Ann Oncol 3: 539-543, 1992
27. J Clin Oncol 7: 1437-1446, 1989
28. J Clin Oncol 15: 908-914, 1997
29. Cancer 63(6 suppl): 1026, 1989
30. J Clin Oncol 10: 896-903, 1992
31. N Engl J Med. 330:1136-1142, 1994
32. Cancer. 85: (letter) 1866-7, 1999
33. J Clin Oncol. 7:890-9, 1989
34. Am J Clin Oncol. 14:30-2, 1991
35. J Clin Oncol. 10:1278-83, 1992
36. Am J Clin Oncol. 17:175-80, 1994
37. Breast Cancer Res Treat. 30:205-9, 1994
38. J Clin Oncol. 9:1682-6, 1991
39. J Clin Oncol 9:2128-33, 1991
40. J Clin Oncol 35: 339-42, 1995
41. Cancer 78: 1300-1307, 1996
42. Tumori 85(1 suppl): S47-53
43. Cancer 78: 1888-1891, 1996
44. Ann Oncol 9: 1035-1037, 1998
45. J Chemother. 6:417-22, 1994
46. Cancer. 78:1888-91, 1996
47. Am J Clin Oncol. 19:517-21, 1996
48. Jpn J Clin Oncol. 20:364-8, 1990
49. Cancer Invest. 8:345-6, 1990
50. Am L Clin Oncol 18: 130-132, 1995
51. Br J Cancer 77(suppl 2): 15, 1998
52. Ann Oncol 9: 121, 1998
53. Cancer 73: 1562-1568, 1994
54. J Clin Oncol 15: 808, 1997
55. Br J Cancer 70: 559-563, 1994

56. Am J Clin Oncol 21: 233, 1998
57. J Clin Oncol: 7: 1427, 198
58. Am J Clin Oncol 19: 301, 1996
59. J Clin Oncol 16: 2943, 1998
60. Eur J Cancer 21A: 2105, 1995
61. Anticancer Res 14(2B): 617-619, 1994
62. J Clin Oncol 5: 272, 1987
63. J Clin Oncol 13: 921, 1995
64. J Clin Oncol 14: 2280, 1996
65. Br J Cancer 72: 774, 1995
66. Eur J Cancer Oncol 24: 1499, 1998
67. Cancer 76: 1126, 1995
68. Anticancer Res 19: 2229, 1999
69. Cancer 79: 1100, 1994
70. Eur J Cancer 31A: 1264-1270, 1995
71. Proc 6th Inter Conf Chronopharm Chronother, Amelia Island FL, July 5-9, Abst VIIIb-4
72. Proc ASCO, #1048, 1998
73. Proc ASCO, #1058, 1998
74. Lancet 352: 1407-1412, 1998
75. Lancet 352: 1413-1418, 1998
76. Cancer Chemother Pharmacol 33: 415-419, 1994
77. Br J Surg 74: 569-572, 1987
78. J Clin Oncol 7: 1447-1456, 1989
79. N Engl J Med 322: 352-358, 1990
80. Ann Oncol 4(suppl.2): S21-S28, 1993
81. J Clin Oncol 3: 1624-1631, 1985
82. Ann Oncol 8: 995-1001, 1997
83. J Clin Oncol 4: 565-570, 1986
84. J Nat Cancer Inst 54: 69-71, 1975
85. Cancer 51: 20-24, 1983
86. Br J Surg 77: 1345-1348, 1990
87. Cancer 43: 78-82, 1979
88. J Clin Oncol 1: 135-137, 1983
89. Cancer 67: 1294-1298, 1991
90. J Clin Oncol 8: 313-318, 1990
91. Am J Clin Oncol 15: 56-60, 1992
92. Cancer 67: 14-19, 1991
93. Semin Oncol 6: 647-662, 1999
94. Gann 67: 921-922, 1976
95. Ann Oncol 9: 1053-1071, 1998