Evidence Tables

Citation: Colucci G, Gebbia V, Paoletti G, Giuliani F et al (2005) Phase III Randomised Trial of FOLFIRI versus FOLFOX4 in the treatment of advanced colorectal cancer: a multicentre study of the Gruppo Oncologico Dell'Italia Meridonale Journal of Clinical Oncology 23;22:4866-4875

Design: Randomised Phase III Study

Country: Italy

Setting:

Aim: to compare irinotecan, leucovorin (LV) and fluorouracil (FU) regimen (FOLFIRI) versus oxaliplatin, LV and FU regimen (FOLFOX4) in previously untreated patients with colorectal cancer.

Comparison: FOLFIRI versus FOLFOX4 (first line)

Inclusion criteria
≥18 years and ≤75 years
Histologically confirmed locally advanced and/or metastatic colorectal cancer with bidimensionally measurable disease
Life expectancy of >3 months
ECOG Performance Status of 0-2
Adequate bone marrow, renal and hepatic functions
Adjuvant therapy completed at least 6 months before enrollment

Exclusion criteria
Active of uncontrolled infections
Known brain metastases or carcinomatous meningitis
interstitial pneumonia or interstitial fibrosis
History of myocardial infarction within the previous 6 months or current clinical evidence of congestive heart failure (patients taking medication for congestive heart failure and showing no clinical signs or symptoms were eligible).
Symptoms of coronary artery disease
History of thromboembolic disease in the past 5 years of a prior malignancy, except of adequately treated basal cell or squamous cell skin cancer or in situ cervical cancer
Any psychological or psychiatric conditions that interfere with consent and precluded treatment or adequate follow-up
Pregnant or lactating women

Sample Size
The expected response rates were 35% and 50% for the FOLFIRI and FOLFOX4 regimens respectively, therefore the study was designed to have the power to detect a 15% difference in objective response rate between the two arms using a two-sided log rank test with an α risk of 0.05 and a β risk of 0.02. The number of patients calculated to be included in each arm was 176.

Randomisation Method
Randomisation was performed centrally with a random ratio of 1:1
Stratification factors were size of disease (limited or extensive disease; < or > 10 cm2 respectively) and liver involvement (with or without liver involvement, H+ or H- respectively).

Population
N = 360
Arm A, FOLFIRI N=178
Arm B, FOLFOX N=182

Study Duration
Recruitment Stage: March 199 – November 2002

Interventions
Arm A, FOLFIRI: Irinotecan 180mg/m2 (150mg/m2 for patients ≥70 years and <75 years) only on day 1, with LV 100mg/m2 (L-isomer form) administered as a 2 hour infusion before FU 400mg/m2 administered as an intravenous bolus injection; FU 600mg/m2 was administered as a 22 hour infusion immediately after FU bolus injection. LV and FU were repeated on days 1 and 2 according to a previously recorded schedule.

Arm B, FOLFOX4: Oxaliplatin 85mg/m2 only on day 1, with LV 100mg/m2 (l-isomer form) administered as a 2-hour infusion before FU 400 mg/m2 administered as an intravenous bolus injection; FU 600mg/m2 was administered as a 22 hour infusion immediately after FU bolus injection. LV and FU were repeated on days 1 and 2 according to a previously recorded schedule.

Both schedules were administered at 2 week intervals

Outcomes
Response rate (evaluation of objective response)

Time to progression (determined from the date of first treatment until death or last follow-up and progression)
Overall Survival
Toxicity Profile

Results
The arms were well balanced with respect to stratification factors and baseline characteristics.

336 patients were deemed assessable for response (164 in Arm A and 172 in Arm B) Reasons for patients being unassessable included noneligibility or protocol violation (n=4, arm A, n=4 arm B), patient refusal (n=6 in arm A, n=5 in arm B), toxicity (n=1 in arm B) and early death unrelated to treatment (n=1 in arm A).

A total of 1,264 cycles of the FOLFIRI regimen were administered during the study with a median of 8 cycles per patient (range 1-22 cycles).
A total of 1,321 cycles of the FOLFOX regimen were administered with a median of 8 cycles per patient (range 1-15 cycles).
The average number of cycles (intention to treat analysis) was 7.14 and 7.26 in arms A and B respectively. More than 12 cycles were administered to 4 patients in Arm A and 2 patients in Arm B.

Response Rates
There was no significant difference in the response rates between the two arms (p=0.6 for ITT analysis and p=0.71 for assessable patients only).

Arm	FOLFIRI	FOLFOX4
	Overall response rate (95% CI)	Overall response rate (95% CI)
Assessable Patients	34% (26.9%-41.4%)	36% (28.9%-43.2%)
Intention to Treat Analysis	31% (24.6%-38.3%)	34% (27.2%-41.5%)

Median duration of response was 9 months in arm A and 10 months in arm B (p=0.06) whereas the median time to progression according to ITT analysis was 7 months in both arms.
According to ITT analysis, the median overall survival was 14 and 15 months for patients in Arms A and B respectively (p=0.28).
Median follow-up time was 31 months (range 11-56 months) and the 1 year survival rate was 55% and 62% in arms A and B respectively (p=0.16).

Second line therapy was administered to 61% of patients treated with FOLFIRI and to 58% of patients treated with FOLFOX4 and consisted primarily of oxaliplatin based therapy for patients treated with FOLFIRI and irinotecan based therapy for patients treated with FOLFOX4.
Median overall survival for patients receiving second line therapy was 17 months compared with 10 months for patients that did not receive second line therapy.

	CR + PR	SD	PD
FOLFIRI	18	15	8
FOLFOX4	20	15	9

CR=Complete Response, PR=Partial Response, SD=Stable Disease, PD=Progressive Disease

Table: Median overall survival (months) in arms A and B according to obtained objective response

No difference in response rates was observed between arms A and B for patients with hepatic metastatic disease (33% versus 34% respectively p=0.86 with ITT analysis) whereas patients with lung metastases obtained better results with FOLFOX4 (25% versus 40% for arms A and B respectively) though the difference was not statistically significant. (pp=0.11).
When analysing objective response rates according to primary tumour site response rates were 30% (18/60) in arm A versus 37% (22/59) in arm B for rectal cancer and 32% (38/118) in arm A versus 33% (40/123) in arm B for

colon cancer (ITT analysis).
Objective response was recorded in 41% (26/64) of patients in arm A in whom the liver was the only site of metastases compared with 35% (24/68) in arm B.
23% (15/64) of patients in arm A with liver plus other disease sites showed objective response compared with 32% (21/65) in arm B.
Secondary surgery to remove liver metastases was performed on 9 patients in arm A and 8 patients in arm B.

	FOLFIRI	FOLFOX	P
H+ and tumour > 10cm^2	30%	37%	0.31
H+ and tumour <10cm^2	37.5%	24%	0.25
H- and tumour > 10cm^2	25%	29%	0.76
H- and tumour <10cm^2	36%	43%	0.66

Table; Objective response by stratification group

In patients with only a single site of disease overall response rate was 38% in arm A and 34% in Arm B (p=0.13).

Multivariate analysis of prognostic factors related to response rate did not show statistically significant difference; the only factor predictive of improved overall survival was number of metastatic sites. In the four stratification groups patients with the absence of liver metastases <10cm2 had statistically better survival than patients with liver metastases >10cm2.

Toxicity
All patients were assessable for toxicity; there were 2 treatment related deaths in Arm A (febrile neutropenia), and none in Arm B, one patient in Arm A died of causes unrelated to treatment.
Overall, toxicity in the two arms was mild and grade 3/4 toxicities were uncommon.

	FOLFIRI	FOLFOX	P
Thrombocytopenia	15%	43%	<0.0001
Nausea and vomiting	72%	59%	0.009
Diarrhoea	63.5%	46%	0.007
Hair Loss	42%	19%	<0.0001
Neurologic toxicity	5%	45%	<0.0001

Table 4: Toxicities which were statistically significantly different between the two arms (all grades)

The most frequent toxicity in the FOLFIRI arm was gastrointestinal and more alopecia was observed; toxicities were primarily grade 1 to 2. In the FOLFOX4 more grade 1-2 thrombocytopenia and neurological toxicity was observed.
Hypersensitivity reactions were observed in the FOLFOX4 arm only and occurred primarily as grade 1-2 toxicity following 5 to 6 cycles of treatment.

Death rates within the first 60 days of treatment were 2.8% for patients in the FOLFIRI arm and 1.1% for patients in the FOLFOX4 arm (p=0.24).

Tables

	FOLFIRI (n=178)	FOLFOX4 (n=182)
	N (%)	**N (%)**
Sex		
Male	93(52)	10 (60)
Female	85 (48)	73 (40)
Age, years		
Median	62	62
Range	32-75	31-75
ECOG Performance Status		
Median	0	0
0	108 (60)	106 (58)
1	67 (38)	68 (38)
2	3 (2)	8 (4)
Previous Adjuvant Therapy		
Yes	55 (31)	52 (29)
No	123 (69)	130 (71)

Table: Patient Characteristics (other factors listed include Primary tumour location, metastatic disease, stratification groups, site of disease and no. of sites)

	FOLFIRI	FOLFOX4	P
No. of patients entered	178	182	
No. of patients assessable	164	172	
Response			
Complete Response (CR)			
No. (%)	8 (4.8)	9 (5.2)	
Partial Response (PR)			
No. (%)	48 (29.2)	53 (30.8)	
Stable Disease (SD)			
No. (%)	68 (41.6)	66 (38.3)	
Progressive Disease (PD)			
No. (%)	40 (24.4)	44 (25.7)	
CR + PR No.	56	62	
Response Rate			
Assessable Population			
%	34	36	0.71
95% CI	24.6-38.3	28.9-43.2	
Intent to Treat			
%	31	34	0.6
95% CI	24.6-38.3	27.2-41.5	
Duration, months			
Response			
Median	9	10	0.06
Range	4-47	5-27	
Time to Progression (TTP)			
Median	7	7	0.64
Range	1-47	1-32	
Survival			
Median	14	15	0.28
Range	1-48	1-43	

Table: Response rates for the treatment arms

Variable	HR	95% CI for HR	SE	P
Treatment	1.044	0.798-1.366	0.143	0.752
Age	1.009	0.993-1.024	0.007	0.255
sex	0.946	0.723-1.237	0.129	0.686
Adjuvant Therapy	1.204	0.865-1.676	0.203	0.269
Synchronous/Metachronous metastases	1.055	0.761-1.463	0.175	0.746
Single/Multiple Sites	1.348	1.024-1.774	0.188	0.033
ECOG PS 0 v 1	1.088	0.817-1.449	0.158	0.562
ECOG PS 0 v 2	1.648	0.813-3.341	0.165	0.813
H-, tumour <10cm^2 v H-, tumour >10cm^2	1.201	0.691-2.088	0.338	0.515
H-, tumour <10cm^2 v H+, tumour <10cm^2	1.082	0.616-1.901	0.311	0.782
H-, tumour <10cm^2 v H+ tumour >10cm^2	1.688	1.039-2.743	0.418	0.034

Table: Multivariate analysis of Prognostic factors

	FOLFIRI		FOLFOX	
	Grade 1-2	Grade 3-4	Grade 1-2	Grade 3-4
	No (%)	No (%)	No (%)	No (%)
Anaemia	67 (38)	1 (1)	60 (33)	3 (2)
Leukopenia	65 (37)	5 (3)	70 (38)	5 (3)
Neutropenia	63 (35)	17 (10)	58 (32)	18 (10)
Thrombocytopenia	26 (15)	1 (1)	76 (42)	3 (3)
Nausea/vomiting	120 (67)	8 (4)	102 (56)	5 (3)
Diarrhea	95 (53)	18 (10)	74 (41)	9 (5)
Mucositis	61 (34)	2 (1)	52 (29)	2 (1)
Loss of Hair	75 (42)	-	35 (19)	-
Cholinergic Syndrome	18 (10)	-	-	-
Neurologic	9 (5)	-	74 (41)	8 (4)
Fever	26 (15)	2 (1)	37 (20)	-
Asthenia	28 (16)	-	24 (13)	-
Cardiac	2 (1)	1 (1)	3 (2)	2 (1)
Skin	6 (3)	-	7 (4)	-
Hypersensitivity	-	-	4 (2)	2 (1)

Table: Observed Toxicities for both treatment arms

General comments

Kaplan Meier curves are presented for time to progression and overall survival

Citation: Comella P, Massidda B, Filipelli G, Farris A, Natale D et al (2009) Randomised trial comparing biweekly oxaliplatin plus oral capecitabine versus oxaliplatin plus iv bolus fluorouracil/leucovorin in metastatic colorectal cancer patients: results of the Southern Italy Cooperative Oncology Study 0401
Comparison: Oxaliplatin + FU/FA versus Oxaliplatin + Capecitabine (1st Line)
Design: Randomised Trial **Country**: Italy **Setting:** **Aim**: to compare oxaliplatin combined with either fluorouracil/leucovorin or capecitabine in terms of response rate, safety, progression free survival and quality of life.
Inclusion criteria Histologically proven diagnosis of advanced adenocarcinoma of the colon or rectum Age ≥18 years Life expectancy >3 months **ECOG performance status ≤2** Adjuvant chemotherapy completed at least 6 months before commencing treatment Presence of a bidimensionally measurable lesion Normal renal function Neutrophil count ≥2x10^6/L, platelet count ≥100x10^6/L, haemoglobin level ≥100g/L, serum bilirubin ≤1.25 times the normal upper limit, serum alanine aminotransferase and aspartate aminotransferase ≤2.5 times the normal upper limit in the absence of liver metastases and ≤5 times the normal upper limit in the presence of liver metastasis.
Exclusion criteria None given
Sample Size The study planned an 80% power to demonstrate, with an alpha error =0.05, a minimum difference in response rate between the two arms. Planned accrual was 150 patients per arm, a sample size that also allowed the comparison of progression free survival.
Randomisation Method Not Reported Patients were stratified according to centre, performance status and previous exposure to adjuvant chemotherapy prior to randomisation.
Population N=344 registered N=322 eligible patients randomized (Arm A N=158 and Arm B N=164).
Study Duration Recruitment Stage: May 2004 – April 2007
Interventions Arm A - OXXEL: oxaliplatin 100mg/m^2 iv (2hours) on day 1; capecitabine 1,000mg/m^2 orally twice daily (12-hours apart) from the evening of day 1 to the morning of day 11. Arm B - OXAFAFU: oxaliplatin 85mg/m^2 iv (2hours) on day 1; 6S-leucovorin 250mg/m^2 iv (2hours) followed by fluorouacil 850mg/m^2 iv bolus on day 2. Cycles were repeated every 2 weeks until progression, unacceptable toxicity or patient refusal or for a maximum of 12 cycles.
Outcomes Response Rate Failure Free Survival Progression Free Survival Overall Survival

Safety
Quality of Life

Results

Patient Evaluation

Biochemistry profile, blood cell count and CEA serum level assessment were performed at baseline
Target lesions were measured by CT or MRI not more than 4 weeks before initial therapy.
Toxicity was assessed according to WHO criteria while neuropathy was assessed according to the Levi scale.
Patients' worst toxicity was recorded.
Patients completed the EORTC QLQ-C30 before randomisation and every 8 weeks during treatment.
CT or MRI scan was repeated after every 4 cycles and at the end of treatment.
Response was defined according to WHO criteria and reassessed 8 weeks after the date of their first documentation with only confirmed responses were computed in the activity analysis.

Baseline characteristics were well balanced between the groups apart from more males and more patients with liver metastasis in Arm A and more patients with elevated CEA basal value in Arm B.

Delivered Treatment and Toxicity

A total of 1251 cycles of OXXEL and 1282 cycles of OXAFAFU were delivered with a median number of 8 cycles (range 1-12) in both arms.
Median duration of treatment was 17 weeks (range 1-36) in either arm.

Median cumulative dose was significantly greater for patients treated with OXXEL (739mg/m^2, range 75-1232mg/m^2) compared with OXAFAFU (659mg/m^2, range 63-1069mg/m^2) (p=0.001).
Median dose intensity of oxaliplatin was higher for OXXEL (43mg/m^2 per week, range 14-81mg/m^2 per week) than for OXAFAFU (34mg/m^2 per week, range, 13-78mg/m^2 per week) (p=0.001).
Median relative dose intensities of oxaliplatin were similar in the two arms (84% versus 80%)

Median dose intensity for capecitabine was 8046mg/m^2 per week (range; 5450-12,000mg/m^2) representing 80% of the planned dose intensity (not clear if that is what is meant from the statement made in the paper) and the median dose intensity of fluorouracil was 308m/m^2 (range; 153-406mg/m^2) representing 72% of the intended dose intensity.

Severe neutropenia (10% versus 27%; p<0.001) and febrile neutropenia (6% versus 13%; p=0.043) were significantly lower in the OXXEL arm.
Frequencies of grade ≥3 thrombocytopenia (4% versus 3% and anemia (3% versus 1%) were similar.
13% of patient in the OXXEL arm suffered severe diarrhoea compared to 8% in the OXAFAFU arm, though the difference was not significant.
Gastric intolerance was more common with oral assumption of capecitabine (8% versus 3%; p=0.028).
Other non-haematological side effects were comparable in both arms.
Overall, treatment related adverse events affected significantly fewer patients in the OXXEL arm than the OXAFAFU arm (32% versus 43%, p=0.026).
Deaths within the first 60 days of treatment commencing were similar in both arms (3% in the OXXEL arm versus 4% in the OXAFAFU arm).
There were two toxic deaths in the OXXEL arm in elderly patients, both of whom had received previous cycles of chemotherapy without experiencing severe toxicity and both of whom had normal renal functions.

Response Rates

There were 11 complete responses and 42 partial responses in the OXXEL arm for a response rate of 34%; in the OXAFAFU arm there were 6 complete responses and 48 partial responses for a response rate of 33% (OR=1.03. 95% CI, 0.63-1.68, p=0.999).
An overall disease control (response or stabilisation) was achieved in 68% of patients in the OXXEL arm and in 70% of patients in the OXAFAFU arm.

Response was slightly higher in patients with synchronous metastases (27% vs. 27%) and in patients ≤60 years (40% vs. 30%) irrespective of treatment arm. At multivariate analysis only age of patient adversely affected the probability of response (p<0.001).

Median failure free survival was 4.9 months (95% CL, 4.2-5.6 months) in the OXXEL arm and 4.7 months (95% CL, 4-5.4 months) in the OXAFAFU arm. HR=0.92, 95% CL, 0.73-1.17, p=0.555.

At Cox analysis, number of disease sites was significantly associated with a shorter failure-free survival (p=0.049).

Median progression free survival was 6.6 months (95% CL, 6.0-7.0 months) in the OXXEL arm and 6.5 months (95% CL, 5.4-7.6 months) in the OXAFAFU arm. HR=1.12, 95% CL, 0.88-1.45, p=0.354.
Number of disease sites (p=0.001) and elevated basal CEA value (p=0.036) were negative factors for progression free survival.

Overall Survival
Following a median follow-up of 24 months (range 6-42 months) 50% of patients had died (78 in the OXXEL arm and 84 in the OXAFAFU arm).
Median overall survival was 16 months (95% CL, 11.2-20.2 months) in the OXXEL arm and 17.1 months (95% CL, 13.8 – 20.4 months) in the OXAFAFU; **HR=1.01, 95% CL, 0.74-1.38, p=0.883**).
One, 2 and 3 year probabilities of survival were 59%, 36% and 31% for the OXXEL arm and 63%, 35% and 26% for the OXAFAFU arm.

Quality of Life
97% (n=312) patients, 151 in the OXXEL arm and 161 in the OXAFAFU arm, filled in a baseline questionnaire.
After 8 weeks the questionnaire was available for 78% (225/287) of patients on therapy; after 16 weeks the questionnaire was available for 81% (156/193) of patients on therapy and after 24 weeks questionnaires were available for 79% (72/91) patients on therapy.
Baseline single item and global health status/quality of life scores did not significantly differ between the two arms.
No significant differences in the change of single scores were observed between the two arms apart from constipation (p=0.001) and financial item score (p=0.004).
At the predetermined time point for the comparison , a preservation of the quality of life was observed in 47% of patients in either arm.
A higher proportion of patients in the OXXEL arm showed a deterioration of the global health status/quality of life score after 16 weeks and 24 weeks though the differences were not statistically significant.

Tables

Arm Characteristics	OXAFAFU	Fisher's Test	OXXEL	Total
	No (%)		No (%)	No (%)
Eligible Patients	164 (100)		158 (100)	322 (100)
Males	89 (54)	0.023	104 (66)	193 (58)
Females	75 (46)		54 (34)	129 (42)
Median age	65 (range: 37-79)		64 (range: 39-84)	63 (range: 37-84)
Aged ≥70 years	65 (40)		51 (32)	116 (36
ECOG Performance Status				
0	99 (60)		96 (61)	195 (61)
1	59 (36)		57 (36)	116 (36)
2	6 (4)		5(3)	87 (3)
Previous Surgery	125 (76)		114 (72)	239 (74)
Previous Adjuvant Chemotherapy	41 (25)		39 (25)	80 (25)

Table 1: Baseline characteristics (other reported factors include primary tumour location, tumour grading, no. of disease sites and metastases)

Arm Characteristics	OXAFAFU	Fisher's Test	OXXEL	Total
	No (%)		No (%)	No (%)
Eligible Patients	164 (100)		158 (100)	322 (100)
Total number of cycles	1,272		1,243	2,515
Median cycles/patient	8 (range 1-12)		8 (1-12)	8 (1-12)
Patients treated with:				
≥ 4 cycles	146 (89)		141 (89)	287 (89)
≥ 8 cycles	97 (59)		96 (61)	193 (60)
≥ 12 cycles	46 (28)		45 (28)	91 (28)
Patients still on therapy	7 (4)		7 (4)	14 (4)
Patients off treatment for:				
Protocol	110 (67)		101 (64)	210 (65)
Refusal	13 (8)		16 (10)	29 (9)
Toxicity	10 (6)	0.015	21 (13)	32 (10)
Disease Complications	14 (8)		5 (3)	19 (6)
Physicians decisions	10 (6)		8 (5)	18 (5)

Table 2: Treatment profiles

Arm	OXAFAFU		OXXEL		Fishers Test	
WHO toxicity %	**All Grades**	**Grade ≥ 3**	**All Grades**	**Grade ≥ 3**	**All Grades**	**Grade ≥ 3**
Neutropenia	49	27	15	10	0.001	0.001
Febrile Neutropenia		13		6		0.043
Anemia	30	1	23	3	N/S	N/S
Thrombocytopenia	21	3	24	4	N/S	N/S
Diarrhoea	43	8	36	13	N/S	N/S
Neuropathy	43	7	48	10	N/S	N/S
Gastric Symptoms	41	3	50	8	N/S	0.028
Stomatitis	18	2	15	2	N/S	N/S
Liver Toxicity	15	1	22	0	N/S	N/S
Hair Loss	14	0	7	0.6	N/S	N/S
Hand & Foot Syndrome	10	1	15	4	N/S	N/S
Renal Toxicity	4	0.6	8	2	N/S	N/S
Allergic Reactions	4	3	3	0.6	N/S	N/S
Fatigue	4	1	5	1	N/S	N/S

Table 3: Frequencies of main side effects

	Baseline Assessment		8 weeks		16 weeks		24 weeks	
	OXXEL	**OXAFAFU**	**OXXEL**	**OXAFAFU**	**OXXEL**	**OXAFAFU**	**OXXEL**	**OXAFAFU**
N	151	161	107	118	83	73	33	39
Physical	81 (1.4)	80 (1.5)	79 (2.1)	75 (1.8)	80 (2.1)	74 (2.6)	83 (4.6)	74 (2.6)
Role	76 (2.4)	75 (2.1)	76 (2.7)	68 (3.4)	79 (2.5)	76 (3.6)	77 (5.7)	85 (3.6)
Emotional	72 (1.7)	68 (1.7)	70 (2.2)	71 (2.1)	74 (2.1)	72 (2.9)	72 (3.8)	75 (3.7)
Cognitive	87 (1.7)	85 (1.5)	82 (2.7)	83 (1.8)	85 (2.3)	82 (3.0)	86 (4.2)	77 (9.0)
Social	82 (1.8)	80 (2.1)	78 (2.5)	77 (2.1)	77 (2.9)	79 (3.1)	78 (5.2)	87 (3.1)
Fatigue	28 (1.9)	30 (1.9)	31 (2.5)	37 (2.4)	30 (2.2)	38 (3.9)	34 (5.1)	28 (3.6)
Nausea/Vomiting	5 (0.9)	6 (1.3)	15 (2.3)	13 (1.6)	12 (1.7)	12 (2.4)	10 (3.8)	4 (1.5)
Pain	18 (1.9)	13 (1.5)	23 (4.1)	21 (2.2)	15 (2.5)	16 (2.9)	23 (4.8)	13 (2.9)
Dyspnoea	9 (1.4)	13 (1.6)	12 (2.3)	14 (1.6)	11 (2.2)	12 (2.5)	19 (4.7)	9 (2.9)
Insomnia	25 (2.3)	31 (2.4)	26 (2.9)	24 (2.4)	20 (2.8)	23 (3.3)	29 (5.5)	16 (3.7)
Appetite Loss	16 (2.1)	18 (1.9)	23 (2.1)	21 (1.9)	19 (2.9)	22 (3.4)	16 (4.5)	11 (3.1)
Constipation	20 (2.4)	20 (2.1)	16 (2.6)	22 (2.7)	13 (2.6)	27 (3.5)	10 (3.2)	15 (3.4)
Diarrhoea	9 (1.5)	10 (1.5)	16 (2.4)	20 (2.5)	14 (2.2)	15 (2.8)	10 (3.6)	11 (3.3)
Financial Difficulties	17 (2.2)	20 (2.1)	19 (2.8)	18 (1.8)	19 (3.0)	21 (3.9)	25 (5.5)	19 (2.9)
General Health Status	66 (1.8)	65 (1.7)	65 (2.2)	65 (1.8)	70 (2.2)	67 (2.5)	67 (5.1)	69 (2.9)

Table 4: Quality of Life (means and standard errors)

Arm	After 8 weeks		
	Improved[1]	**Stable**	**Deteriorated[2]**
OXXEL	24 (23%)	50 (47%)	30 (30%)
OXAFAFU	25 (22%)	56 (47%)	37 (31%)
Arm	**After 16 weeks**		
	Improved[1]	**Stable**	**Deteriorated[2]**
OXXEL	30 (37%)	29 (35%)	23 (28%)
OXAFAFU	17 (24%)	40 (57%)	13 (19%)
Arm	**After 24 weeks**		
	Improved[1]	**Stable**	**Deteriorated[2]**
OXXEL	5 (17%)	2 (7%)	47 (76%)
OXAFAFU	1 (3%)	7 (18%)	30 (79%)

[1]≥10 pt increment of baseline score
[2]≤10 pt decrease of baseline score

Table 5: Patients showing significant change in the quality of life score during treatment

General comments

After first line treatment was discontinued, patients were followed every 2 months to assess the disease status and survival.

Further treatment was not planned and the decision was left to single investigator choice.

Kaplan Meier Curves are given for progression free survival and overall survival.

Citation: Comella P, Massidda B, Filippelli G, Palmeri S, Natale D (2005) Oxaliplating plus high dose folinic acid and 5 fluorouracil i.v. bolus (OXAFAFU) versus irinotecan plus high dose folinic acid and 5-fluorouracil i.v. bolus (IRIFAFU) in patients with metastatic colorectal carcinoma: a Southern Italy Cooperative Oncology Group phase III trial *Annals of Oncology* 16;6:878-886

Comparison: Oxaliplatin + FA/FU versus Irinotecan + FA/FU (1st line)

Design: Randomised Trial

Country: Italy

Setting: Multicentre

Aim: to assess the activity and toxicity of OXAFAFU compared with IRIFAFU in metastatic colorectal cancer patients

Inclusion criteria
Histologically proven diagnosis of adenocarcinoma of the colon or rectum
Age ≥18 years
Life expectancy of >3 months
ECOG performance status of ≤2
Metastatic unresectable disease
At least one bideminsionally measurable lesion
Normal renal function
Neutrophil count ≥2,000/mm^3
Platelet count ≥100,000/mm^3,
Bilirubin ≤1.25x upper normal limit
Alanine aminotransferase and aspartate aminotransferase ≤5x upper normal limit

Exclusion criteria
Patients with previous palliative chemotherapy
Patients receiving adjuvant chemotherapy within 6 months of starting therapy
Inflammatory bowel disease or significant diarrhoea
Previous total colectomy or ileostomy
Bowel obstruction
Uncontrolled metabolic disorders or active infections
Severe cardiac arrhythmia or acute myocardial infarction within 6 months of starting therapy
Symptomatic cerebral metastasis
Concomitant or previous malignant tumour

Sample Size
It was assumed that the OXAFAFU regimen might increase by 50% (From 5-7.5 months) the median failure free survival in comparison with the IRIFAFU regimen.
With 257 events on the whole series of patients there is an 80% power to demonstrate this difference with a 0.05 alpha error.
A recruitment of 280 patients was planned for the comparative analysis; a number of patients may also give an 80% power to detect a 15% difference in response rates between OXAFAFU and IRIFAFU.

Randomisation Method
Randomisation method not reported
Patients were stratified according to centre, previous adjuvant chemotherapy and performance status

Population
N=288
N=276 eligible patients randomized
Arm A (IRIFAFU): 74 patients randomised prior to amendment and 62 patients randomised after
Arm B (OXAFAFU): 71 patients randomised to receive high dose regimen prior to amendment and 69 patients randomised to low dose regimen

Study Duration
Recruitment Stage: January 2001 – June 2003

Interventions

Arm A (IRIFAFU): Irinotecan 200mg/m^2 i.v. (90 min) on day 1, *l*-FA 250mg/m^2 i.v. (2h), 5-FU 850mg/m^2 i.v. bolus on day 2
Arm B (OXAFAFU): Oxaliplatin 100 mg/m^2 i.v. (2h) on day 1, *l*-FA 250 mg/m^2 i.v. (2h), 5-FU 1,050 mg/m^2 i.v. bolus on day 2 (OXAFAFU, high dose), later amended to Oxaliplatin 85mg/m^2 and 5-FU 850mg/m^2(OXAFAFU, low dose).

Cycles were repeated every 2 weeks in both arms

Outcomes
Not clear, reported as being activity and toxicity

Results
One patient in each arm refused the assigned regimen (does not say what happened to these patients).
The median number of cycles was 6 (range: 1-16) in the IRIFAFU arm and 8 (range 1-12) in the OXAFAFU (both high dose and low dose); patients in the IRIFAFU arm stayed on study for a median of 16 weeks (range 2-44) and in the OXAFAFU arm patients stayed on study for a median of 18 weeks (range 2-40) in the high dose group and for a median of 22 weeks (range 2-39) in the low dose group.
19% of patients treated with IRIFAFU dropped out for refusal or toxicity compared with 11% of OXAFAFU (high dose) and 12% of OXAFAFU (low dose).

Dose Intensity and OXA Cumulative Dosage

	4 Week		8 Week		12 Week	
	Irinotecan/Oxaliplatin	**5-FU**	**Irinotecan/Oxaliplatin**	**5-FU**	**Irinotecan/Oxaliplatin**	**5-FU**
IRIFAFU	88mg/m^2/week	372 mg/m^2/week	82 mg/m^2/week	343 mg/m^2/week	76 mg/m^2/week	346 mg/m^2/week
OXAFAFU (high dose)	41 mg/m^2/week	426 mg/m^2/week	37 mg/m^2/week	374 mg/m^2/week	39 mg/m^2/week	354 mg/m^2/week
OXAFAFU (low dose)	39 mg/m^2/week	417 mg/m^2/week	34 mg/m^2/week	344 mg/m^2/week	35 mg/m^2/week	327 mg/m^2/week

Table 1: Median dose intensity for each treatment regimen and cycle

Cumulative Oxaliplatin dosage was 705 mg/m^2 (range 100-1200) with OXAFAFU high dose and 780 mg/m^2 (range 82-1114) with OXAFAFU low dose.

Activity
There were 42 confirmed responses (16 complete responses and 26 partial responses) in the IRIFAFU group, 29 in the OXAFAFU high dose group (7 complete responses and 22 partial responses) and 32 in the OXAFAFU low dose group (13 complete responses and 19 partial responses).
12/16 complete respsonses in the IRAFAFU group were achieved in patients with only one involved organ; 6/7 complete responses in the OXAFAFU high dose group were in patients with only one site of disease and 8/13 complete responses in the OXAFAFU low dose group were in patients with a single metastatic site.

OXAFAFU yielded a significantly higher response rate (44%, 95% CI 35%-52%) compared to IRIFAFU (31%, 95% CI 23% - 40%) (p=0.029).
The proportion of patients achieving a partial response was greater among patients treated with OXAFAFU (29% versus 19%; p=0.002) and no difference was observed in complete response (14% versus 12%)
There was a significant difference in response rate between IRIFAFU and OXAFAFU low dose (p=0.032).
The rate of disease control (response or stabilisation) was greater with Oxaliplatin (66%) than with Irinotecan (58%).

Response rates were adversely affected by a number of baseline characteristics including performance status ≥1, presences of symptoms of disease, loss of body weight, CEA baseline value >100ng/ml, no primary surgery and more than one disease site.
Including these factors together with treatment type in multivariate analysis good performance status (p=0.000), the OXAFAFU regimen (p=0.011) and a low CEA baseline value (p=0.035) showed significant correlation with response rates

Time to response achievement was 2.9 months (range 1.6-9 months) for IRIFAFU and 3.2 months (range 1.7-9.3) for OXAFAFU.
Median duration of complete responses was 5.2 months (range 2-19 months) in the IRIFAFU group, 17.2 months (range 2.3-25.3 months) in the OXAFAFU high dose group and 8.5 months (range 2-16.4 months) in the

OXAFAFU low dose group.
Median duration of all responses was 7.9 months (range 1.9-20.8 months) treated with irinotecan and 8.5 months (range, 1.5-22.1 months) for patients treated with oxaliplatin (10.5 months for OXAFAFU high dose and 7.9 months for OXAFAFU low dose).

Toxicity
At interim analysis, neutropenia was more pronounced with OXAFAFU high dose than with IRIFAFU (grade ≥3 toxicity was 55% versus 39%; p=0.029) and febrile neutropenia was more frequent (19% versus 9%, p=0.041).
After dosage amendment, there was no difference in sever haematological toxicity between OXAFAFU low dose and IRIFAFU.
Occurrence of diarrhoea was significantly lower among patients treated with OXAFAFU low dose and grade ≥3 was less frequent (12% versus 28%, p=0.005).
The proportion of patients complaining of severe emesis was more than halved (4% versus 10%, p=0.113) and hair loss was less pronounced with OXAFAFU based treatment.
Grade 3 neuropathy was recorded in 14% of patients treated with OXAFAFU high dose and in 3% of patients treated with OXAFAFU low dose.
Overall 44% of patients treated with OXAFAFU low dose and 53% of patients treated with IRIFAFU suffered at least one episode of grade ≥3 toxicity.

Early deaths (within 60 days of initial therapy) were 4% in both IRIFAFU and OXAFAFU groups.
5 patients died due to severe adverse events possibly related to received treatment; 3 patients died as a consequence of severe diarrhoea, 1 died of myocardial infarction following the first course of IRIFAFU and 1 patient had a gastric haemorrhage after the first course of OXAFAFU low dose.

Failure Free Survival and Overall Survival
Median follow-up was 24 months (range 10-36), 252 (91%) patients had an induction failure and 150 (54% patients died.
According to treatment, median failure free survival was 5.8 months (95% CI 4.4 - 7.2 months) for patients treated with IRIFAFU, 6 months (95% CI 5.9 – 9.3 months) for patients treated with OXAFAFU high dose and 7.6 months (95% CI 5.9-9.3) for patients treated with OXAFAFU low dose.

Median overall survival was 15.6 months (95% CI 13.5 – 17.9) for IRIFAFU and 18.9 months (95% CI 15.3 – 22.5) for OXAFAFU. Median overall survival for patients treated with OXAFAFU high dose was 17.6 months (95% CI 13.1 – 22.1) and exceeded 23 months for patients treated with OXAFAFU low dose.

Failure free survival was 8.3 months for patients with performance status 0 compared with 3.4 months for patients with performance status ≥1 and overall survival was 20.5 months compared with 11.1 months.
The difference in failure free survival for patients treated with irinotecan and oxaliplatin was statistically significant when adjusted for performance status (p=0.046).
Comparison of overall survival between irinotecan and oxaliplatin treated patients was significant when adjusted for performance status (p=0.032)

Survival probability for OXAFAFU treated patients compared to IRIFAFU treated patients was 60% versus 65% at 12 months, 42% versus 52% at 18 months and 23% versus 39% at 24 months.

Overall survival for patients treated sequentially with all three active drugs (5-FU, Irinotecan and oxaliplatin) was significantly longer than that of patients not receiving all three drugs (median 16.6 months versus 13 months, p=0.009).

Off-study treatments
9 patients with partial response were rendered disease free by surgical resection of liver metastases (3 in the IRIFAFU group and 6 in the OXAFAFU group).

At progression following 1st line IRIFAFU 57% (n=77) of patients went on to receive second line treatments, 62 of whom received Oxaliplatin associated with 5-FU or capecitabine.
Local treatment of liver metastases was performed in 5 patients.
13% (n=18) of patients received a third line treatment in the form of oral fluoropyrimidines.
Salvage treatments were delivered to 56% (n=78) of patients receiving OXAFAFU front line consisting of irinotecan alone or combined with 5-FU or mitomycin C in 52 patients, local management of liver metastases in 6 patients and third line treatment with oral fluoropyrimidines in 20 patients.

Tables

	IRIFAFU	OXAFAFU high dose	OXAFAFU low dose	OXAFAFU
	n (%)	n (%)	n (%)	n (%)
Eligible Patients	136 (100)	71 (100)	69 (100)	140 (100)
Males	72 (53)	46 (65)	35 (51)	81 (58)
Females	64 (47)	25 (35)	34 (49)	59 (42)
Median Age, years	62 (range: 38-80)	62 (range: 41-79)	63 (37-76)	62 (37-79)
Aged ≥70 years	22 (16)	16 (22)	12 (17)	28 (20)
Previous Surgery	111 (82)	49 (69)	55 (80)	104 (74)
Previous Adjuvant Chemotherapy	34 (25)	19 (27)	15 (22)	34 (24)
ECOG Performance Status				
0	82 (60)	33 (47)	42 (61)	75 (54)
1	50 (36)	35 (49)	26 (38)	61 (44)
2	4 (4)	3 (4)	1 (1)	4 (3)

Table 2: Patient Characteristics (other reported details included Primary tumour site, no. of metastatic sites, liver involvement, synchronous metastasis, symptoms of disease, CEA values and weight loss)

Treatment	IRIFAFU	OXAFAFU high dose	OXAFAFU low dose
Total number of cycles	1022	549	572
Median cycles/ patient (range)	8 (1-16)	8 (1-12)	8 1-12)
No. of patients receiving (%)			
≥4 cycles	117 (87)	63 (89)	61 (90)
≥8 cycles	77 (57)	40 (56)	46 (68)
≥12 cycles	41 (30)	18 (25)	23 (34)
No. of patients off treatment (%)			
As per protocol	96 (71)	54 (76)	50 (74)
Refusal	15 (11)	6 (8)	6 (9)
Toxicity	11 (8)	2 (3)	2 (3)
Disease Complication	3 (2)	5 (7)	5 (7)
Physician Decision	10 (7)	4 (6)	5 (7)

Table 3: Summary of treatment

	IRIFAFU	OXAFAFU high dose	OXAFAFU low dose	OXAFAFU
	n (%)	n (%)	n (%)	n (%)
Complete Response	16 (12)	7 (10)	13 (19)	20 (14)
Partial Response	26 (19)	22 (31)	19 (28)	41 (29)
Stable Disease	36 (27)	15 (21)	15 (22)	30 (22)
Progressive Disease	38 (28)	19 (27)	14 (21)	33 (24)
Not Assessed	19 (14)	8 (11)	7 (10)	15 (11)
Treated Patients	135 (100)	71 (100)	68 (100)	1139 (100)

Table 4: Activity according to treatment

	IRIFAFU n=135	OXAFAFU high dose n=71	OXAFAFU low dose n=68	OXAFAFU n=139
Grade	Any (≥3)	Any (≥3)	Any (≥3)	Any (≥3)
Neutropenia	59 (31)	78 (55)	49 (29)	65 (40)
Febrile neutropenia/infections	9 (7)	19 (13)	3 (3)	11 (7)
Anaemia	33 (1)	35 (2)	35 (1)	35 (3)
Thrombocytopenia	10 (1)	32 (4)	29 (3)	32 (4)
Emesis	62 (10)	54 (4)	53 (4)	54 (6)
Diarrhoea	66 (28)	44 (13)	32 (12)	39 (11)
Stomatitis	23 (3)	35 (6)	15 (4)	26 (4)
Fatigue	5 (2)	6 (4)	7 (3)	6 (3)
Neuropathy	5 (1)	48 (14)	47 (3)	48 (7)
Cholinergic	10 (2)	0 (0)	0 (0)	0(0)
Hair Loss	49 (23)	23 (1)	9 (2)	16 (1)
Allergic	1 (0)	4 (1)	7 (1)	5 (1)
Treatment related death	- (2)	-(1)	-(1)	-(1)

Table 5: Frequency of Toxicity

General comments
After progressive disease a crossover policy (IRIFAFU second line for the OXAFAFU arm and OXAFAFU second line for the IRIFAFU arm) was advised but not mandatory.

Kaplan Meier curves for failure free survival and overall survival are presented

There is a table comparing the efficacy and toxicity of 5-FU/FA with either oxaliplatin or irinotecan in advanced colorectal cancer with 2 other randomised trials (Tournigand, 2004 and Goldberg, 2004).

Citation: Cunningham D, Sirohi B, Pluzanska A, et al (2009) Two different first line 5 fluorouracil regimens with or without oxaliplatin in patients with metastatic colorectal cancer *Annals of Oncology* 20;244-250

Design: Open label Phase IIIb randomised trial

Country: Multiple

Setting: Multicentre

Aim: to evaluate two 5-FU regimens ± Oxaliplatin followed by Irinotecan on progression

Inclusion criteria
Patients with histologically proven colorectal cancer with distant metastases
Age ≥18 years
No prior chemotherapy for metastatic disease
WHO performance status ≤2
No major biochemical/haematologic abnormalities
Unidimensionally measurable lesions
Prior chemotherapy to be completed ≥6 months before study entry.

Exclusion criteria
Patients with resectable disease
Unresolved bowel obstruction/diarrhea
Peripheral neuropathy
Prior malignancies
History of hyper sensitivity or intolerance to previous 5-FU
Pregnant/lactating females

Sample Size
A sample size of 700 patients was required in order to provide ≥90% power to detect a difference between the two arms using a two-sided log-rank test at the 0.05 level on the basis of the assumption that two year survival would be 30% in arm A and 20% in arm B.

Randomisation Method
Patients were randomly allocated to arm A or arm B and then further subdivided into arm A1 or A2 and Arm B1 or B2.
No further details are given.

Population
N=725 (Intention to Treat)
N=720 (Safety)
N=5 (Not Treated)

Study Duration

Interventions
Arm A1: Oxaliplatin very 2 weeks (85mg/m^2 2hour i.v. infusion on D1 + 5-FU 250mg/m^2/day CIV given continuously without interruption for the two week duration of the treatment cycle).

Arm A2: Oxaliplatin every 2 weeks (85mg/m^2 2hour i.v. infusion on D1 + 5-FU 400mg/m^2 bolus + 600mg/m^2 22-hour CIV on D1, 2 + LV, 200mg/m^2 2hour infusion on D1, 2) (FOLFOX4)

Arm B1: 5-FU 300mg/m^2/day CIV (5-FU CIV) without interruption

Arm B2: 5-FU 400mg/m^2 bolus + 600mg/m^2 22hour CIV on D1,2 + LV 200mg/m^2 2hour infusion on D1, 2)

Outcomes
Survival (defined as percentage of patients still alive at 2 years)

Progression free survival
Time to treatment failure
Safety

Results
Reasons for not treating patients included physician decision,intercurrent medical problem, voluntary withdrawal and death before treatment.

362 patients were randomised to Arm A and 363 were randomised to Arm B
Arm A1=58
Arm A2=304
Arm B1=62
Arm B2=301

A total of 7908 cycles were administered to 720 patients with a median of 10 cycles per patient
Mean planned 5-FU dose intensity was 78.3% in Arm A1, 83.6% in Arm A2, 76.7% in Arm B1 and 91% in Arm B2.
Mean planned oxaliplatin dose intensity was 77% in Arm A1 and 83% in Arm A2
5-FU dose reductions were more common with the CIV regimen (Arm A, 61%; Arm B69%) compared to the two weekly regimens (Arm A 41%; Arm B, 16%).
Oxaliplatin reductions were required in 34% of patients in Arm A1 and in 39% of patients in Arm A2.

196 in Arm A patients and 220 patients in Arm B received second line chemotherapy; 150 patients in Arm A and 177 patients in Arm B received Irinotecan. Details of second line treatment received by the remaining patients in each arm are not provided.

2 year survival rates were similar between the two arms; 27.3% in Arm A versus 24.8% in Arm B.
Median overall survival was 15.9 months (95% CI, 15.0-17.3) in Arm A and 15.2 months (95% CI, 14.0-16.1) in Arm B.
Hazard Ratio for survival: HR=0.93 (95% CI, 0.78-1.10; p=0.155)

1 year survival rates were 62.6% (95% CI, 57.6-67.7%) in Arm A and 61.5% (95% CI, 56.5-66.5%) in Arm B.
The study reported a numerically greater probability of survival in Arm A compared with Arm B at all time points (assumed that this meant that the number of patients still alive at any given time point was greater in Arm A compared with Arm B).

Survival analysis conducted 2 years after the last patient was randomised showed no significant difference between the two arms: **HR=0.92 (95% CI, 0.78-1.08, p=0.106)**.
Overall survival was higher for patients on oxaliplatin compared with 5-FU±LV alone (Relative Risk: RR=0.93; 95% CI, 0.79-1.09) and for patients who received the 5-FU CIV regimen compared with 5-FU+LV (RR=0.84; 95% CI, 0.67-1.05).
Retrospective analysis showed that median overall survival appeared to be longer in centres where >50% of patients received Irinotecan second line (19.9 months in Arm A and 16.4 months in Arm B).

Overall response rate (CR+PR) was significantly higher in Arm A (54.1%; 95% CI, 48.9-59.45%) than in Arm B (29.8%; 95% CI, 25.1-34.7%), p<0.0001).
Median progression free survival was significantly longer in Arm A compared with Arm B (7.9 months (95% CI 7.3-9.0) versus 5.9 months (95% CI 5.1-6.8). **HR=0.67 (95% CI, 0.58-0.79, p<0.0001)**.
The probability of being alive without disease progression was greatest in Arm A at all time points.
Median TTF was 5.5 months in Arm A (95% CI, 5.2-6.1) and 4.9 months in Arm B (95% CI, 4.7-5.3). **HR=0.9 (95% CI 0.77-1.04, p=0.053)**.

Oxaliplatin versus non-oxaliplatin: 77% of patients in Arm A versus 51% of patients in Arm B experienced at least one episode of grades 3-4 toxicity.
Treatment discontinuation occurred in 17% of patients in Arm A and 5% in Arm B.

CIV versus two weekly schedule: In arm A, the incidence of several grade 3-4 toxic effects differed according to the administered 5-FU schedule including diarrhoea, neutropenia, febrile neutropenia, infection without neutropenia, skin exfoliation, fatigue and vomiting.
In Arm B, the incidence of grade 3-4 toxicities was similar for both treatment regimens with the exception of skin exfoliation which was more common with the 5-FU CIV regimen (15% versus 1%).

Serious Adverse Events: The total number of serious adverse events leading to hospitalisation, prolonged hospitalisation, death or considered medically important was 424 for Arm A and 310 for Arm B.
40 patients died between date of randomisation and 30 days after completion of chemotherapy, mostly as a result

of disease progression.
The number of patients requiring hospitalisation during the study was 146 (40%) in Arm A and 125 (34%) in Arm B.

Tables

Response Category	Patients, n (%)	
	Arm A: Oxaliplatin +5-FU (n=362)	Arm B: 5-FU (n=363)
Complete Response	24 (6.6)	6 (1.7)
Partial Response	172 (47.5)	102 (28.1)
Stable Disease	76 (21)	128 (35.3)
Progressive Disease	46 (12.7)	89 (24.5)
Not Evaluable	8 (2.2)	4 (1.1)
Not Done/Missing Data	36 (9.9)	34 (9.4)

Toxicity	Patients, n (%)			
	Arm A: oxaliplatin + 5-FU (n=358)		Arm B: 5-FU (n=362)	
	Any Grade	Any Grade 3-4	Any Grade	Any Grade 3-4
Neutropenia	223 (62)	117 (33)	82 (23)	17 (5)
Diarrhoea	209 (58)	50 (14)	172 (48)	29 (8)
Fatigue	262 (73)	32 (9)	228 (63)	29 (8)
Pain	182 (51)	27 (8)	203 (56)	27 (7)
Infection without neutropenia	113 (32)	28 (8)	111 (31)	24 (7)
Sensory Neuropathy	267 (75)	45 (13)	69 (19)	5 (1)
Vomiting	163 (46)	22 (6)	100 (28)	11 (3)
Injection Site Reaction	77 (22)	17 (5)	74 (20)	12 (3)
Chest Pain	6 (2)	1 (<1)	6 (2)	2 (1)
Myocardial Ischaemia	1 (<1)	1 (<1)	3 (1)	2 (1)

Toxicity (Arm A)	Patients, n (%)	
	CIV	2 weekly schedule
	Any Grade 3-4	Any Grade 3-4
Neutropenia	2%	39%
Diarrhoea	28%	11%
Febrile Neutropenia	0%	3%
Infection without neutropenia	19%	6%
Skin Exfoliation	11%	1%
Vomiting	12%	5%
Fatigue	4%	10%

Citation: Diaz-Rubio E, Tabernero J, Gomez-Espana A et al (2007) Phase III study of Capecitabine plus oxaliplatin compared with continuous infusion fluorouracil as first line therapy in metastatic colorectal cancer: final report of the Spanish Cooperative Group for the treatment if digestive tumours trial *Journal of Clinical Oncology* 25;27:4224-4230

Comparison: XELOX versus FUOX (1st line)

Design: Multi-centre Open Label Randomised Trial

Country: Spain

Setting: Outpatients

Aim: to compare the efficacy and safety of Capecitabine plus oxaliplatin versus Spanish-based continuous infusion high-dose fluorouracil plus oxaliplatin regimens and first line therapy for metastatic colorectal cancer

Inclusion criteria
Age ≥18 years
Histological confirmed MCRC
Karnofsky performance status ≥70%
Life expectancy >3 months
At least one measurable lesion according to Response Evaluation Criteria in Solid Tumours Group criteria
Chemotherapy to have been completed at least 1 year before study entry
Adequate haematological, hepatic and renal function

Exclusion criteria
Pregnant or breast feeding women
Clinically significant cardiac disease or myocardial infarction within the 12 months prior to study inclusion
Severe renal failure
Lack of physical integrity of the upper GI tract
Peripheral neuropathy
History of other malignant disease apart from cured basal cell carcinoma or in situ cervical carcinoma or CNS metastases

Sample Size
Sample size determination was based on the results of a previously published study which showed a median time to progression of approximately 7 months.
A noninferiority hypothesis was considered when the median time to progression in the XELOX arm was not lower than 5.5 months (corresponding to a Hazard Ratio <1.27).
The sample size estimated for noninferiority with an α=0.05 and an 80% power was 165 patients in each treatment arm.
Assuming a 5% loss of patients to follow-up, the total number of patients to be enrolled needed to be 174 per treatment arm.

Randomisation Method
Centrally generated computer randomisation code

Population
N=348 (intention to treat population) , 174 to each arm

6 patients (3 in each arm) did not initiate study treatment leaving 342 patients (per protocol population), 171 in each arm.

Study Duration
Recruitment Phase: April 2002 to August 2004
Cut-off date for analysis was June 15, 2006

Interventions
Arm A, XELOX: oral Capecitabine 1,000mg/m^2 bid for 14 days plus oxaliplatin 130 mg/m^2 on day 1 every 3 weeks.
Arm B, FUOX: FU 2,250 mg/m^2 diluted in saline, administered by CIV during 48 hours on days 1, 8, 15, 22, 29 and 36, plus oxaliplatin 85mg/m^2 on days 1, 15 and 29 every 6 weeks.

Oxaliplatin was administered as a 120 minute intravenous infusion in 5% dextrose

Outcomes
Time to progression between groups in the per protocol (no definition)

Safety
Response Rate
Time to Treatment Failure
Overall Survival
Duration of Response

Results
Baseline demographics and clinical characteristics were well balanced between the two arms, though significantly more patients in the XELOX arm (26%) than the FUOX arm (16%) had received previous adjuvant chemotherapy (p=0.032) which consisted of fluoropyrimidine therapy with or without leucovorin.

Efficacy
Median duration of follow-up was 17.5 months.
Median time to progression was 8.9 months (95% CI, 7.8-9.9 months) in the XELOX arm versus 9.5 months (95% CI, 7.8-9.9 months) in the FUOX arm **(Hazard Ratio, 1.18; 95% CI 0.9 to 1.5; p=0.153)**.
There were no statistically significant differences in the median time to progression whether patients received adjuvant chemotherapy or not (p=0.527).
Median overall survival was 18.1 months (95% CI, 15.5-20.4 months) in the XELOX arm versus 20.8 months (95% CI, 16.6-25 months) in the FUOX arm **(Hazard Ratio, 1.22; 95% CI 0.9 to 1.6, p=0.145)**.
One and 2 year survival rates were 66.3% (95% CI, 59%-73.6%) and 35.7% (95% CI, 28.1%-43.3%) for XELOX and 71.5% (95% CI, 64.6%-78.4%) and 44% (95% CI, 37%-51.7%) for FUOX respectively.
There was no statistically significant difference between the arms in relation to time to treatment failure; median time to treatment failure was 6 months (95% CI 5.1-6.8 months) in the XELOX arm and 6.9 months (95% CI, 6.2-7.6 months) in the FUOX arm **(Hazard Ratio, 1.15; 95% CI, 0.9 to 1.4; p=0.204)**.

Confirmed objective response rate was 37% (95% CI, 30.2-44.7%) in the XELOX arm and 46% (95% CI, 38.1%-53.1%) in the FUOX arm(Fishers exact test P=0.154).
Median duration of response was 9.2 months (95% CI, 7.6-11 months) in the XELOX arm and 9.4 months (95% CI, 7.6-11.2 months) in the FUOX arm (p=0.430).
Tumour control rate was similar in both arms: 66% (95% CI, 59-73.2%) in the XELOX arm and 71% (95% CI, 63.9-77.5%) in the FUOX arm.

22 patients in the XELOX arm and 15 patients in the FUOX arm were not assessed for response; these patients withdrew from the study before the scheduled response evaluation (established by protocol at 12 weeks after the start of treatment).
Reasons for not evaluating patients included adverse events, death as a result of different reasons, consent withdrawal or protocol violation, loss to follow-up, major surgery and patient withdrawn and discretion of investigator.

Poststudy Treatment
58.2% (n=199) of patients received second line therapy; 57.9% (n=99) in the XELOX arm and 58.5% (n=100) in the FUOX group. The most common second line treatment was irinotecan (80.4%, n=160), either in combination with FU with or without LV or with Capecitabine, cetuximab or raltitrexed (52.7%, n=105) or in monotherapy (27.6%, n=55).
There was no statistically significant difference between the two arms in the second line treatment rate (>0.999).
11.4% (39/342) of patients receiving chemotherapy underwent surgery for metastasectomy, 38 for liver metastases and 1 for lung metastasis.
10% (n=17) of the surgeries were on patients in the XELOX arm and 12.9% (n=22) on patients in the FUOX arm.
An R0 liver resection was performed in 71% (27/38) of patients: 13/16 in the XELOX group and 14/22 in the FUOX group (p=0.296).
Median time to progression in patients with R0 resections was 16.9 months in the XELOX arm and 18.8 months in the FUOX arm.
Median overall survival in patient with R0 resections was 31.1 months for patients receiving XELOX and had not been reached for patients in the FUOX arm and the time of publication.

Safety
Safety was evaluated in all patients receiving treatment and the safety profiles were generally similar.

There were significantly lower rates of grade 3/4 diarrhoea (14% v 24%, p=0.027) and grade 1/2 mucositis (28% v 43%, p=0.005) and significantly higher rates of grade 1/2 hyperbilirubinemia (37% v 21%, p=0.001) and grade 1/2 hand-foot syndrome (14% v 5%, p=0.009) in the XELOX arm compared with the FUOX arm.
There was a similar rate of venous thrombotic events (4% (n=7) in each arm). In the XELOX arm, two serious events were deemed possibly treatment related and in the FUOX arm one event was deemed treatment related but not seious.
27% of patients in each arm (n=45) discontinued treatment because of adverse events with the main reason for discontinuation including neurological toxicity, oxaliplatin intolerance, allergic reactions, pharyngolaryngeal dysesthesias or gastrointestinal disorders, haemototoxicity, diarrhoea, asthenia, hepatic toxicity and cerbrovascular events.

Deaths were considered to be treatment related in 4 patients (one receiving XELOX and 3 receiving FUOX); cause of death was febrile neutropenia, stomatitis and thrombocytopenia in the patient receiving XELOX and pneumonia (n=2) and septic shock (n=1) in the patients receiving FUOX).
60 day mortality rates were 2% (n=3) with XELOX and 3% (n=5) with FUOX).

Tables

	XELOX (n=171)	**FUOX (n=171)**	**P**
	N (%)	**N (%)**	
Sex			
Male	107 (63)	100 (58)	0.507
Female	64 (37)	71 (42)	
Age, years			
Median	64	65	0.485
Range	32-80	35-81	
Karnofsky Performance Status			
≤70	18 (11)	17 (10)	0.99
>70	153 (89)	154 (90)	
Previous Treatment			
Surgery	138 (81)	142 (83)	0.674
Chemotherapy	44 (26)	27 (16)	0.032
Radiotherapy	16 (9)	27 (16)	0.102

Table 1: Patient Characteristics (other factors reported include Body weight, primary tumour site, tumour stage at initial diagnosis, tumour status, metastatic site)

	XELOX (n=171)	**FUOX (n=171)**
	N (%)	**N (%)**
Objective Response (CR +PR)	64 (37)	78 (46)
Complete Response (CR)	8(5)	10 (6)
Partial Reponse (PR)	56 (32)	68 (40)
Stable Disease	49 (29)	43 (25)
Tumour Control (CR+PR+SD)	113 (66)	121(71)
Progressive Disease	36 (21)	35 (20)
Not Assessable	22 (13)	15 (9)

Table 2: Antitumour Efficacy (per protocol)

Chemotherapy	**XELOX (n=99**	**FUOX (n=100)**
	N (%)	**N (%)**
FU±LV	2 (2)	1 (1)
FU±LV+Irinotecan	32 (32.3)	42 (42)
FU±LV+Oxaliplatin	1 (1)	6 (6)
Capecitabine	1 (1)	8 (8)
Capecitabine+Oxaliplatin	5 (5.1)	
Capecitabine+Irinotecan	15 (15.2)	4 (4)
Irinotecan	27 (27.3)	28 (28)
Irinotecan+Cetuximab	5 (5.1)	5 (5)
Irinotecan+Raltitrexed	2 (2)	
Oxaliplatin+Raltitrexed	3 (3)	2 (2)
Others	6 (6.1)	4 (4)

Table 3: Chemotherapy after withdrawal from study treatment

	XELOX		FUOX	
	Grade 1/2	**Grade 3/4**	**Grade 1/2**	**Grade 3/4**
	N (%)	**N (%)**	**N (%)**	**N (%)**

Haematologic				
Anaemia	114 (67)	5 (3)	131 (77)	3 (2)
Leukopenia	68 (40)	4 (2)	77 (45)	7 (4)
Thrombocytopenia	80 (47)	6 (4)	81 (47)	6 (4)
Neutropenia	78 (46)	12 (7)	80 (47)	18 (11)
Non Haematologic				
Paresthesia	108 (63)	31 (18)	113 (66)	28 (16)
Asthenia	86 (50)	21 (12)	86 (50)	29 (17)
Transaminases Increase	101 (59)	3 (2)	106 (62)	4 (2)
Diarrhoea	61 936)	24 (14)	74 (43)	41 (24)
Nausea	73 (43)	5 (3)	75 (44)	9 (5)
Vomiting	63 (37)	9 (5)	59 (35)	13 (8)
Hyperbilirubinemia	63 (37)	5 (3)	35 (21)	6 (4)
Mucositis	48 (28)	4 (2)	74 (43)	7 (4)
Anorexia	44 (26)	5 (3)	56 (33)	4 (2)
Constipation	39 (23)	1 (<1)	42 (25)	3 (2)
Abdominal Pain	36 (21)	1 (<1)	42 (25)	4 (2)
Fever	34 (20)	0 (0)	34 (20)	1 (<1)
Hand-Foot Syndrome	24 (14)	4 (2)	9 (5)	2 (1)
Increased Creatinine	16 (9)	0 (0)	20 (12)	2 (1)
Rash	13 (8)	3 (2)	16 (9)	1 (<1)
Dysgeusia	14 (8)	0 (0)	16 (9)	1 (<1)
Allergic Reaction	2 (1)	2 (1)	12 (7)	1 (<1)
Alopecia	4 (2)	0 (0)	15 (9)	0 (0)
Dyspepsia	2 (1)	0 (0)	19 (11)	1 (<1)
Epistaxis	3 (1)	0 (0)	12 (7)	0 (0)

Table 4: Most Common Adverse Events (>5% of patients)

General comments

Patients were scheduled to receive a total of 12 cycles of XELOX and 6 cycles of FUOX (36 weeks in each group) or until disease progression, intolerable adverse events or patient refusal. Patients with stable disease could continue to receive treatment after this period at the discretion of the individual investigator. Patients could also continue Capecitabine or FU single agent therapy after discontinuation of oxaliplatin due to toxicity.

Kaplan Meier curves are presented for time to progression and overall survival

Citation: Douillard J, Cunnigham D, Roth A, Navarro, James R et al (2000) Irinotecan combined with fluorouracil compared with fluorouracil alone as first-line treatment for metastatic colorectal cancer: a multicentre randomised trial *Lancet* 355;9209:1041-1047

Design: Randomised Trial

Country:

Setting:

Aim: to assess whether the addition of irinotecan to fluorouracil and calcium folinate would benefit patients previously untreated with chemotherapy for metastatic colorectal cancer.

Inclusion criteria
Histologically proven adenocarcinoma of the colon/rectum
Age 18-75 years
WHO performance status 0-2
Life expectancy >3 months
Previous chemotherapy to be completed more than 6 months before randomisation

Exclusion criteria
Central nervous system metastasis
Unresolved bowel obstruction or diarrhea
Known contraindications to fluorouracil (angina pectoris, myocardial infarction)

Sample Size
338 evaluable patients were needed to show a significant difference in response rates between the two treatment groups assuming response rates of 35% in the no irinotecan group and 50% in the irinotecan group by use of two tailed X^2 tests (α=0.05, power 0.8).

Randomisation Method
Central randomisation by a computer generated random scheme and stratified by centre

Population
387 patients randomised
Irinotecan + FU = 199
FU = 188

Study Duration

Interventions
Irinotecan 80mg/m^2 with fluorouracil 2300mg/m^2 by 24hour infusion plus calcium folinate 500mg/m^2 once weekly (n=54) or irinotecan 180mg/m^2 on day 1 with fluorouracil 400mg/m^2 bolus and 600mg/m^2 by 22 hour infusion plus calcium folinate 200mg/m^2 on day 1 and 2 every two weeks (n=145).

Once weekly fluorouracil 2600mg/m^2 by 24 hour infusion plus calcium folinate 500mg/m^2 (n=43) or every two weeks, fluorouracil and calcium folinate fluorouracil 400mg/m^2 bolus and 600mg/m^2 by 22 hour infusion plus calcium folinate 200mg/m^2 on day 1 and 2 (n=143).

Outcomes
Response Rate

Time to Progression (defined as time from randomisation to progression)
Duration of Response (time from first infusion to progression in responding patients)
Time to treatment failure (time from randomization to treatment discontinuation or disease progression)
Overall Survival (date of randomization to date of death)

Results
Median duration of treatment was longer in the irinotecan versus no irinotecan arm irrespective of regimen (24 weeks versus 21 weeks for the weekly regimen and 24.6 weeks versus 18 weeks for the two week regimen). Relative dose intensity was 0.82 for irinotecan and 0.81 for fluorouracil in the weekly regimen and 0.93 and 0.92 respectively in the 2 weekly regimen.

39.4% of patients in the Irinotecan group and 58.3% in the no-irinotecan group received further chemotherapy with 31% of the no-irinotecan group receiving irinotecan. Similar proportions of patients in each group received further treatment with oxaliplatin (15.7 in the irinotecan arm versus 12.8% in the no irinotecan arm).

Efficacy
In the evaluable population the response rate was 49% in the irinotecan arm and 31% in the no irinotecan arm (p<0.001). Confirmed responses (after 6-7 weeks) resulted in response rates of 41% (95% CI 33.3-48.6) and 23% (17-30.2) respectively.
In the intent to treat population, response rate was significantly higher in the irinotecan group than the no-irinotecan group (34.8 [28.2-41.9] versus 21.9% [16.2-28.5], p=0.005).
Median time to onset of response was 8.9 (range: 4.7-25.4) weeks in the irinotecan group and 11.4 (5.3-29.6) in the no-irinotecan group.
Median response duration was 9.3 (2.8-13.1) months in the irinotecan group and 8.8 (3.7-11.8) months in the no-irinotecan group (p=0.08). Duration of response and stabilisation was longer in the irinotecan group than the no irinotecan group (median 6.7 [0+ to 13.8+] versus 4.4 [0+ to 11.8+] months, p<0.001. The interaction between treatment and regimen was not significant. The log rank, stratified by regimen (p<0.001) and that stratified by country (p<0.001) were significant.

Median follow-up was 23.3 (20.0-29.7) months.

Survival in the irinotecan group was significantly longer than in the no-irinotecan group (median 17.4 [0.4-28.4+] versus 14.1 [0.5-27.6+] months, p=0.031). The probability of survival in the irinotecan group was 82.1% at 9 months and 69.1% at 12 months and in the no-irinotecan group the probability of survival was 71.6% at 9 months and 59.1% at 12 months.
The interaction between treatment and regimen was not significant, supporting the hypothesis that the difference in the two regimens would be similar in both groups and therefore allow pooling of the data.
The log rank test stratified by regimen was significant (p=0.03) as was that stratified by country (p=0.04).

Intent to treat analysis showed that for the weekly regimen, the response rates in the irinotecan and no irinotecan groups did not differ significantly (39.6 [95% CI 26.5 -54] versus 25% [13.2-40.3]).
Median time to progression was 7.2 (range 0+-13.8) months and 6.5 (0+-12.3+) month.
Probability of survival in the irinotecan group was 84.9% at 9 months and 75.5% at 12 months and in the no-irinotecan group was 773% at 9 months and 62.7% at 12 months.
In the intent to treat analysis of the 2 weekly regimen, the response rate was 33.1% (95% CI 25.5-41.4) in the irinotecan group and 21% (95% CI 14.6-28.6) in the no-irinotecan group (p=0.021).
Median time to progression was 6.5 (range 0+-13.2) in the irinotecan group and 3.7 (0+-13.1+) months in the no irinotecan group (p=0.001) and median survival was 17.4 (0.4-28.3+) months in the irinotecan and 13.0 (0.5-27.6+) months in the no-irinotecan group. The log rank p was significant (p=0.0098).
The probability of survival in the irinotecan group was 81% at 9 months and 66.7% at 12 months and in the irinotecan group and 69.8% at 9 months and 54.8% at 12 months in the no-irinotecan group.

In Cox's multivariate analysis of time to progression, age and number of organs involved were significant predictors. In patients younger than 58 years, the risk of progression increased by about 28% with all other variables fixed. If 3 or more organs were involved, the risk of progression was increased by about 56%. The treatment effect was significant (p<0.001). The risk of progression for a patient in the no irinotecan group was increased by about 69% compared with that for a patient in the irinotecan group when all other variables were equal.

The median time to treatment failure was 5.3 (0.4-15.7+) months in the irinotecan group and 3.8 (0.4-11.5+) in the no-irinotecan group.
Time to definitive deterioration in performance status was significantly longer in the irinotecan group than in the no-irinotecan group (median 11.2 [0.1+-15.7+] versus 9.9 [0+-13.6+] months (p=0.046).

Safety
In the irinotecan group the most common side effects were diarrhoea and neutropenia and were significantly more frequent and severe than in the no-irinotecan group.
Doses were reduced because of toxic effects more frequently for the weekly regimen and more in the irinotecan group than the no-irinotecan group. Doses were reduced in 29.6% of patients on the weekly regimen and in 18.6% of patients on the two weekly regimen in the irinotecan and no-irinotecan groups respectively. Most dose

reductions occurred during the first two cycles in the weekly regimen. One patient treated with the irinotecan combination on the 2-weekly regimen did not receive appropriate therapy for the management of diarrhoea and died early in the first cycle.
Despite the high frequency of side-effects in the irinotecan group, the relative dose intensity was preserved compared with the no-irinotecan group.

Quality of Life
1161 questionnaires were obtained from the 385 patients in the intent to treat population and the rate of return was similar in the two treatment groups (62% in the irinotecan group and 59% in the no-irinotecan group), the two groups did not differ significantly at baseline apart from cognitive function (mean 89.9, SE, 1.1 versus 86.1, SE 1.5 (p=0.05)).
QoL did not differ significantly between groups; when missing data for death, progressive disease or grade 3-4 adverse events were taken into account with the two imputation methods, results were biased towards the no-irinotecan group. The analysis of variance on QoL showed significantly better quality of life in the irinotecan group after the first imputation method was used (p=0.03) with the same trend seen with the second imputation method. Definitive deterioration in quality of life occurred consistently later in the irinotecan for a deterioration from baseline of 5% (p=0.03), 10% (p=0.06), 20% (p=0.04) and 30% (p=0.03).

Tables

	Irinotecan (n=198)	No Irinotecan (n=187)
	N (%)	N (%)
Sex		
Male	132 (66.7)	99 (52.9)
Female	66 (33.3)	88 (47.1)
Age		
Median	62	59
Range	27-75	24-75
WHO Performance Status		
0	102 (51.5)	96 (51.3)
1	83 (41.9)	77 (41.2)
2	13 (6.6)	14 (7.5)
Synchronous Metastases	110 (55.6)	121 (64.7)
Previous Adjuvant Chemotherapy	51 (25.8)	44 (23.5)
At least one tumour related symptom at baseline	95 (48)	96 (51.3)
At least one abnormal laboratory value at baseline	177 (89.4)	157 (84)

Table 1: Patient Characteristics at baseline

	Evaluable Population (n=338)		Intent to treat population (n=385)	
	Irinotecan (n=169)	No Irinotecan (n=169)	Irinotecan (n=198)	No Irinotecan (n=187)
	N (%)	N (%)	N (%)	N (%)
Complete Response	6 (3.6)	0	6 (3)	0
Partial Response	63 (37.3)	39 (23.1)	63 (31.8)	41 (21.9)
Overall Response	69 (40.8)	39 (23.1)	69 (34.8)	41 (21.9)
Stable Disease	64 (37.9)	84 (49.7)	70 (35.4)	86 (46)
Progressive Disease	36 (21.3)	46 (27.2)	38 (19.2)	49 (26.2)
Not Evaluable	0	0	21 (10.6)	11 (5.9)

Table 2: Response Rates

Covariate	Parameter Estimate	Wald X^2	p	Hazard Ratio (95% CI)
Treatment Group				
No Irinotecan				1.00
Irinotecan	0.780	9.558	0.002	2.18 (1.33-3.58)
Weight Loss				
>5%				1.00
≤5%	0.804	6.829	0.009	2.23 (1.22-4.08)
Time between first diagnosis and first metastasis (months)				
>12				1.00
3-12	1.001	4.689	0.030	2.72 (1.10-6.73)
0-3	1.063	11.831	0.001	2.9 (1.58-5.31)

Table 3: Logistic Regression of predictive factors for response rate

Covariate	Parameter Estimate	Wald X^2	p	Hazard Ratio (95% CI)
Treatment Group				
Irinotecan				1.00
No Irinotecan	0.522	15.731	<0.001	1.69 (1.3-2.18)

Number of organs involved				
>3				1.00
≤3	0.443	5.776	0.016	1.56 (1.09-2.23)
Age (years)				
≥58				1.00
<58	0.248	3.643	0.056	1.28 (0.99-1.65)

Table 4: Cox's Model for Time to Progression

	Irinotecan group (n=54)		**No Irinotecan group (n=43)**		**p***
	Total	**Grade 3-4**	**Total**	**Grade 3-4**	
	N (%)	**N (%)**	**N (%)**	**N (%)**	
Non Haematological toxic effects					
Diarrhoea	48 (88.9)	24 (44.4)	28 (65.1)	11 (25.6)	0.055
Nausea	39 (72.2)	4 (7.4)	25 (58.1)	2 (4.7)	0.57
Vomiting	30 (55.6)	6 (11.1)	19 (44.2)	2 (4.7)	0.25
Asthenia	23 (42.6)	4 (7.4)	6 (14)		0.068
Alopecia	20 (37)		7 (16.3)		
Anorexia	16 (29.6)	4 (7.4)	6 (14)	1 (2.3)	0.26
Mucositis	14 (25.9)		15 (34.9)	1 (2.3)	0.26
Abdominal Pain	12 (22.2)	3 (5.6)	1 (2.3)	1 (2.3)	0.47
Cholinergic Syndrome	11 (20.4)	1 (1.9)			0.37
Hand and Foot Syndrome	9 (16.7)		17 (39.5)	2 (4.7)	0.11
Fever in absence of infection without concomitant grade 3-4 neutropenia	6 (11.3)		4 (9.3)		
Cutaneous signs	4 (7.4)		4 (9.3)		
Pain	4 (7.4)	1 (1.9)	6 (14)	1 (2.3)	0.87
Weight Loss	4 (7.4)	1 (1.9)			0.37
Infection without concomitant grade 3-4 neutropenia	2 (3.7)		2 (4.7)		
Haematological Toxic Effects					
Anaemia	51 (94.4)	3 (5.6)	41 (97.6)		0.12
Neutropenia	37 (71.2)	15 (28.8)	9 (21.4)	1 (2.4)	0.001
Leukopenia	40 (74.1)	11 (20.4)	16 (38.1)	1 (2.4)	0.009
Fever in absence of infection with concomitant grade 3-4 neutropenia	5 (9.3)	5 (9.3)	1 (2.3)	1 (2.4)	0.16
Infection with concomitant grade 3-4 neutropenia	1 (1.9)	1 (1.9)			0.37

*based on comparison of frequency of grade 3 or 4 toxic effects

Table 5: Patients with any adverse event and with grade 3-4 adverse event related to study treatment (weekly regimen)

	Irinotecan group (n=145)		**No Irinotecan group (n=143)**		**p***
	Total	**Grade 3-4**	**Total**	**Grade 3-4**	
	N (%)	**N (%)**	**N (%)**	**N (%)**	
Non Haematological toxic effects					
Diarrhoea	99 (68.3)	19 (13.1)	8 (5.6)	8 (5.6)	0.028
Nausea	85 (58.6)	3 (2.1)	2 (1.4)	2 (1.4)	0.66
Alopecia	82 (56.6)				
Asthenia	65 (44.8)	9 (6.2)	1 (0.7)	1 (0.7)	0.011
Vomiting	60 (41.4)	4 (2.8)	1 (0.7)	1 (0.7)	0.18
Mucositis	56 (38.6)	6 (4.1)	3 (2.1)	3 (2.1)	0.32
Cholinergic Syndrome	41 (28.3)	2 (1.4)			0.16
Anorexia	25 (17.2)	3 (2.1)	1 (0.7)	1 (0.7)	0.32
Cutaneous signs	16 (11)	1 (0.7)			0.32
Abdominal Pain	14 (9.7)	1 (0.7)			0.32
Hand and Foot Syndrome	13 (9)	1 (0.7)	1 (0.7)	1 (0.7)	0.99
Pain	12 (8.3)		1 (0.7)	1 (0.7)	0.31
Fever in absence of infection without concomitant grade 3-4 neutropenia	9 (6.2)		1 (0.7)	1 (0.7)	
Infection without concomitant grade 3-4 neutropenia	7 (4.8)	4 (2.8)			0.045
Weight Loss	6 (4.1)	2 (1.4)			0.16
Haematological Toxic Effects					
Anaemia	140 (97.2)	3 (2.1)	130 (90.9)	3 (2.1)	0.99
Neutropenia	118 (82.5)	66 (46.2)	68 (47.9)	19 (13.4)	0.001
Leukopenia	117 (81.3)	25 (17.4)	60 (42)	5 (3.5)	0.001
Fever in absence of infection with concomitant grade 3-4 neutropenia	5 (3.4)	5 (3.4)	1 (0.7)	1 (0.7)	0.10

Infection with concomitant grade 3-4 neutropenia	3 (2.1)	3 (2.1)			0.08

Table 6: Patients with any adverse event and with grade 3-4 adverse event related to study treatment (2 weekly regimen).

General comments

Kaplan Meier curves for time to progression, survival and time to definitive deterioration in performance status.

Citation: Ducreux M, Bennouna J, Hebbar M et al (2010) Capecitabine plus oxaliplatin (XELOX) versus 5-fluorouracil/leucovorin plus oxaliplatin (FOLFOX-6) as first line treatments for metastatic colorectal cancer *International Journal of Cancer* 128;3:682-690

Design: Randomised Control Trial

Country: France

Setting: Multicentre

Aim: to demonstrate non-inferiority of capecitabine plus oxaliplatin (XELOX) versus FOLFOX-6 for patients with advanced metastatic colorectal cancer

Inclusion criteria
Aged ≥18 years
Previously untreated, histologically confirmed metastatic colorectal cancer
ECOG performance status ≤2
Life expectancy ≥3 months
Normal renal function
Adequate haematological and hepatic function

Exclusion criteria
Pregnant or breast feeding women
Patients who had received (neo) adjuvant therapy <6 months previously containing oxaliplatin, 5-FU or capecitabine.
Patients with a history of neuropathy or uncontrolled congestive heart failure, angina pectoris, hypertension or myocardial infarction within the 12 months previous to study inclusion.

Sample Size
Assuming that 55% of patients in each arm would respond to treatment at 6-8 weeks and allowing for approximately 10% of patients to be excluded from the per protocol population, it was planned that 304 patients (152 per arm) would be recruited to ensure 80% power to demonstrate non-inferiority of XELOX versus FOLFOX-6 with a non-inferiority margin of 15% and a one-sided type 1 error of 5%.

Randomisation Method
Minimisation method with stratification for centre, age, Kohnes predictive risk factors (low, intermediate and high) and previous chemotherapy.

Population
N=306 patients (XELOX=156; FOLFOX-6=150)

Study Duration
Recruitment: May 16th 2003-August 31st 2004
Trial Ended: December 2006 (18 months after recruitment of the last randomised patient)

Interventions
XELOX: 2hour intravenous infusion of oxaliplatin 130mg/m^2 on day 1 plus oral capecitabine 1,000mg/m^2 twice daily on days 1-14 every 3 weeks.

FOLFOX-6: 2hour intravenous infusion of oxaliplatin 100mg/m^2 followed by a 2hour infusion of LV 400mg/m^2 followed by 5-FU 400mg/m^2 iv bolus injection then 5-FU 2,400-3,000 mg/m^2 as a 46hour continuous infusion every 2 weeks.

Outcomes
Non-inferiority in relation to tumour response
Tumour response assessed by investigators

Progression Free Survival Overall Survival Time to response Duration of Response Time to Treatment Failure
Results The baseline characteristics for both arms were generally well balanced Mean treatment duration was 19 weeks (±8 weeks) in the XELOX arm and 21 weeks (±8 weeks) in the FOLFOX-6 group. Median number of cycles was 8 (range: 0-8) in the XELOX arm and 11 (range 0-12) in the FOLFOX-6 arm. Mean cumulative dose of oxaliplatin was higher in the FOLFOX-6 group (1,508±538mg) compared with the XELOX arm (1,330±520mg). Median relative dose intensity of oxaliplatin was 93.8% in the XELOX group and 83.3% in the FOLFOX-6 group. Median relative dose intensity of capecitabine was 93.7% and for infusional 5-FU was 77.5%. Dose modifications were performed in 93.5% of patients in the FOLFOX-6 group compared with 80.1% of patients in the XELOX group. Median duration of follow-up was 18.8 months (range, 0.1-41.6) in the intention to treat population *Efficacy* The overall response rate was 42% in the XELOX group and 46% in the FOLFOX-6 group. The difference between the groups was 4.7%, the upper limit of the unilateral 95% confidence interval (14.4%) was below the non-inferiority margin of 15%. Independent review resulted in an overall response rate for the intention to treat population of 39% for the XELOX group and 46% for the FOLFOX-6 group. The difference between the groups was 6.9%, the upper limit of the unilateral 95% CI (16.2%) exceeded the non-inferiority margin of 15%. According to assessment of investigators, the overall response rate in the per protocol population was 46% in the XELOX group and 45% in the FOLFOX-6 group and in the intention to treat group it was 44% in both groups. *Secondary Endpoints* Median progression free survival was 8.8 months in the XELOX group and 9.3 months in the FOLFOX group **(HR=1.00, 90% CI 0.82-1.22)** in the intention to treat population. The upper limit of the 90% CI was below the predefined non-inferiority limit of 1.75. Median overall survival was 19.9 months in the XELOX arm and 20.5 months in the FOLFOX-6 arm **(HR=1.02, 90% CI 0.81-1.30)**. The upper limit of the 90% CI was below the predefined non-inferiority limit of 1.75. In total, 30 patients in the XELOX arm and 34 patients in the FOLFOX-6 group underwent potentially curative resection of lung, liver or lymph node metastases. *Safety* The safety population consisted of 304 patients (XELOX n=155; FOLFOX-6 n=149). XELOX was associated with more hand-foot syndrome (20% versus 13%) though the difference was not significant (p=0.088). Considering all grade events, there was significantly less nausea (57% versus 70%, p=0.019), asthenia (45% versus 59%, p=0.011), alopecia (8% versus 26%, p<0.001), neutropenia (27% versus 62%; p<0.001) and thrombocytopenia (27% versus 50%, p<0.001) recorded in the XELOX group compared with the FOLFOX-6 group.

Considering only grade 3-4 adverse events, XELOX was associated with significantly less grade 3/4 neuropathly (11% versus 26%, p<0.001), neutropenia (5% versus 47%, p<0.001) and febrile neutropenia (0% versus 6%; p=0.001) compared with FOLFOX-6.
XELOX was associated with more grade 3/4 diarrhoea (14% versus 7%, p=0.034) and thrombocytopenia (12% versus 5%, p=0.052).
20% of patients in the XELOX arm and 22% of patients in the FOLFOX arm discontinued treatment due to toxicity.

There were 193 deaths in the over the course of the study (98 n the XELOX group and 95 in the FOLFOX-6 group) with the main cause of death being disease progression.
The 60 day mortality rate in the per protocol population was 4.2% (4/144 patients, 90% CI: 1.3-6.4) in the XELOX arm and 2.1% (3/140 patients; 90% CI: 0.01-3.9) in the FOLFOX-6 group.

Tables

Endpoint	Per Protocol		Intention to Treat	
	XELOX (n=144)	FOLFOX-6 (n=140)	XELOX (n=156)	FOLFOX-6 (n=150)
Primary Endpoint				
Overall Response Rate (independent review)	42	46	39	46
Difference (upper limit of unilateral 95% CI)	4.7% (14.4%)[1]		6.9% (16.2%)[1]	
Complete Response	2	<1	2	1
Partial Response	40	46	37	45
Secondary Endpoints				
Median PFS (months)	8.9	9.3	8.8	9.3
Hazard Ratio (90% CI)	0.98 (0.8-1.21)[2]		1.00 (0.82-1.22)[2]	
Median OS (months)	20.1	18.9	19.9	20.5
Hazard Ratio (90% CI)	1.02 (0.79-1.30)[2]		1.02 (0.81-1.30)[2]	
Median Time to Treatment Failure (months)	5.9	6.8	6.1	6.8
Hazard Ratio (90% CI)	1.29 (0.97-1.73)[2]		1.32 (0.97-1.78)[2]	
Median Duration of Response (months)	9.9	8.8	10.1	8.8
Hazard Ratio (90% CI)	0.91 (0.67-1.24)[2]		0.88 (0.64-1.21)[2]	

Efficacy Analyses

	XELOX (n=155)		FOLFOX (n=149)	
	All Grades	Grades 3/4	All Grades	Grades 3/4
Adverse Event	**No (%)**	**No (%)**	**No (%)**	**No (%)**
Neuropathy	139 (90)	17 (11)	141 (95)	38 (26)
Diarrhoea	95 (61)	22 (14)	85 (57)	10 (7)
Nausea	88 (57)	4 (3)	104 (70)	9 (6)
Asthenia	69 (45)	13 (8)	88 (59)	14 (9)
Vomiting	54 (35)	3 (2)	58 (39)	7 (5)
Hand-Foot Syndrome	31(20)	5 (3)	19 (13)	1 (<1)
Fever	22(14)	3 (2)	23 (15)	4 (3)
Alopecia	12 (8)	0 (0)	39 (26)	1 (<1)
Stomatitis	10(7)	0 (0)	15 (10)	1 (<1)
Neutropenia	41(27)	8 (5)	93 (62)	70 (47)
Thrombocytopenia	41(27)	18 (12)	74 (50)	8 (5)
Anaemia	23(15)	3 (2)	33 (22)	6 (4)
Febrile Neutropenia	0(0)	0(0)	9 (6)	9 (6)

Toxicities

Citation: Falcone A, Ricci S, Brunetti I, Pfanner E et al (2007) Phase III trial of infusional fluorouracil, leucovorin, oxaliplatin and irinotecan (FOLFOXIRI) compared with infusional fluorouracil, leucovorin and irinotecan (FOLFIRI) as first line treatment for metastatic colorectal cance: the GRUPPO Ocologico Nord Ovest *Journal of Clinical Oncology* 25;13

Design: Randomised Phase III Trial

Country: Italy

Setting: Multi-centre

Aim: to compare the simplified FOLFOXIRI regimen to a standard FOLFIRI regimen

Inclusion criteria
Adenocarcinoma of the colon or rectum
Unresectable metastatic disease
Age 18-75 years
ECOG performance status of 2 or lower if aged 70 years or younger
ECOG performance status of 0 is aged 71-75 years
Measurable disease according to WHO criteria
Adequate haematologic parameters
AST, ALT and alkaline phosphatase 2.5 x normal values or less (≤5 if liver metastases)
Previous fluoropyrimidine based chemotherapy to be completed at least 6 months before randomisation

Exclusion criteria
Previous palliative chemotherapy for metastatic disease
Previous chemotherapy including oxaliplatin or irinotecan
Symptomatic cardiac disease
Myocardial infarction in the last 24 months or uncontrolled arrhythmia
Active Infections
Inflammatory bowel disease
Total Colectomy

Sample Size
Assuming a response rate of 40% in the FOLFIRI arm, to demonstrate an improvement of 20% in with FOLFOXIRI (60%), using a two-sided X^2 test with a power of 0.8 and an alpha error of 0.05, and considering approximately 10% of patients non –assessable, the study planned to randomise a total of 240 patients.

Randomisation Method
Patients were stratified according to centre, ECOG performance status and history or adjuvant therapy and were then randomly assigned to either FOLFOXIRI or FOLFIRI (no method or randomisation reported).

Population
N=244

Study Duration
Recruitment Phase: November 2001 to April 2005

Interventions
FOLFIRI: Irinotecan 180mg/m^2, 1 hour I.V. on day 1, Leucovorin 100mg/m^2, 2hours i.v. on days 1 and 2, FU 400mg/m^2 bolus followed by FU 600mg/m^2 22 hour continuous infusion on days 1 and 2.

FOLFOXIRI: Irinotecan 165mg/m^2, 1 hour I.V. on day 1, oxaliplatin 85mg/m^2, 2 hours i.v. on day 1, Leucovorin 200mg/m^2 on day 1 and FU 3,200mg/m^2 48 hours flat continuous infusion i.v. days 1-3.

Each cycle repeated every two weeks until evidence of disease progression, unacceptable toxicity or patient refusal or for a maximum 12 cycles.

Outcomes
Response Rate

Progression Free survival (defined as the length of time from randomisation to disease progression or death resulting from any cause or to last contact)

Overall survival
Postchemotherapy R0 surgical resections
Safety
Quality of Life

Results

Treatment Administration and Safety

All patients received at least one cycle of study treatment and both treatments were relatively well tolerated and associated with manageable toxicities.

Median number of cycles administered was 10 in the FOLFIRI arm and 11 in the FOLFOXIRI arm and the relative dose intensity of administered FU, Irinotecan and Oxaliplatin ranged between 82% and 87% of planned for all agents in both arms.

Treatment interruptions for toxicity were 4% in the FOLFIRI arm and 9% in the FOLFOXIRI arm (p=0.19), there were no toxic deaths and 2 patients in each arm died within 60 days of treatment start due to rapidly progressive disease.

Grade 3/4 toxicities were incommon apart from neutropenia.

Objective Tumour Response

According to intention to treat analysis, all patients were considered assessable for response and response rate (assessed by study investigators) was 66% for FOLFOXIRI and 41% for FOLFIRI (p=0.0002). External assessment response rate was 60% for FOLFOXIRI and 34% for FOLFIRI (p<0.0001).

Rate of progression was significantly lower for patients treated with FOLFOXIRI than FOLFIRI (11% versus 24%, p=0.02).

In multivariate analysis, only treatment with FOLFOXIRI was an independent predictive factor for response: **Hazard Ratio 2.8; 95% CI 1.7 – 4.8, p<0.001**.

Secondary Surgery on Metastases

15% of patients (n=18) in the FOLFOXIRI arm underwent radical (R0) surgery of metastases compared with 6% (n=7) in the FOLFIRI arm (p=0.033).

For patients with metastases confined to the liver, the rate of secondary R0 surgery was 36% for FOLFOXIRI compared with 12% for FOLFIRI (p=0.017).

In multivariate analysis, only treatment with FOLFOXIRI was an independent predictor for achieving R0 resection: **Hazard Ratio 3.1, 95% CI, 1.2-7.9, p=0.018**.

Progression free survival and second line treatment

At the time of analysis, 104 patients in the FOLFOXIRI arm and 112 patients in the FOLFIRI arm had progressed; median progression free survival was 9.8 months for FOLFOXIRI and 6.9 months for FOLFIRI (p=0.0006), **Hazard Ratio 0.63 (95% CI, 0.47-0.81)**.

The rate of early progression (progression within 6 months from treatment onset) was significantly higher on FOLFIRI compared with FOLFOXIRI (18% vs. 45%, p<0.0001).

Independent prognostic factors for reduction of the progression risk were:

- Treatment Arm **Hazard Ratio 0.6, 95% CI, 0.46-0.79, p<0.001**
- Male Sex **Hazard Ratio 0.68, 95% CI, 0.51-0.91, p=0.01**
- Leukocyte count <8,000/mm^3 **Hazard Ratio 0.60, 95% CI, 0.45-0.81, p=0.003**

73% of patients on FOLFIRI and 76% on FOLFOXIRI received second line treatment.

Overall Survival

After median follow up of 18.4 months, 65 patients in the FOLFOXIRI arm and 81 patients in the FOLFIRI arm had died.

Median overall survival was significantly longer for FOLFOXIRI (22.6 vs. 16.7 months, p=0.032) **Hazard Ratio 0.7 (95% CI, 0.5-0.96)**.

Independent prognostic factor for reduction of death risk was liver involvement less than 25% **Hazard Ratio 0.57 (95% CI, 0.39-0.84, p=0.005)**.

Treatment with FOLFOXIRI was significantly associated with prolonged survival on univariate analysis (p=0.032) but not on multivariate analysis (p=0.054).

Quality of Life

36% of patients in the FOLFIRI arm and 37% on the FOLFOXIRI arm were assessable for quality of life and there

were no significant difference between the two arms.

Tables

	FOLFIRI	FOLFOXIRI
	N (%)	N(%)
Sex		
Male	69 (57)	75 (61)
Female	53 (43)	47 (39)
Age (years)		
Median	64	62
Range	21-75	27-75
ECOG Performance Status		
0	74 (61)	74 (61)
1	41 (34)	45 (37)
2	7 (6)	3 (2)
Previous Adjuvant Chemotherapy		
Yes	29 (24)	29 (24)
No	93 (76)	93 (76)
Time from diagnosis to random assignment (months)		
<3	76 (65)	76 (65)
≥3	43 (35)	43 (35)

Table 1: Patient characteristics

	FOLFIRI	FOLFOXIRI
No. of Cycles		
Total	1056	1083
Median	10	11
Range	1-16	1-16
Relative dose intensity with respect to planned		
Oxaliplatin		83
Irinotecan	87%	82
Fluorouracil	86%	82

Table 2: Number of Cycles and relative dose intensities

	FOLFIRI (n=122)	FOLFOXIRI (n=122)	
	N (%)	N (%)	P
Nausea			
Grade 1	48 (39)	49 (40)	NS
Grade 2	20 (16)	34 (28)	
Grade 3	1 (1)	7 (6)	
Grade 4	0 (0)	0 (0)	
Vomiting			
Grade 1	28 (23)	24 (20)	NS
Grade 2	22 (18)	31 (25)	
Grade 3	1 (1)	8 (7)	
Grade 4	1 (1)	0 (0)	
Diarrhoea			
Grade 1	30 (25)	40 (33)	NS
Grade 2	27 (22)	30 (25)	
Grade 3	13 (11)	21 (17)	
Grade 4	1 (1)	4 (3)	
Stomatitis			
Grade 1	28 (23)	32 (26)	NS
Grade 2	7 (6)	17 (14)	
Grade 3	4 (3)	5 (4)	
Grade 4	0 (0)	1 (1)	
Neurotoxicity			
Grade 1	0 (0)	45 (37)	<0.0001 (grade 2-3)
Grade 2	0 (0)	21 (17)	
Grade 3	0 (0)	3 (2)	
Grade 4	0 (0)	0 (0)	
Astenia			
Grade 1	29 (24)	27 (22)	NS
Grade 2	12 (10)	19 (16)	
Grade 3	4 (3)	7 (6)	
Grade 4	0 (0)	0 (0)	

Thrombocytopenia			
Grade 1	5 (4)	22 (18)	NS
Grade 2	3 (2)	7 (6)	
Grade 3	1 (1)	2 (2)	
Grade 4	0 (0)	0 (0)	
Anaemia			
Grade 1	50 (41)	53 (43)	NS
Grade 2	11 (9)	23 (19)	
Grade 3	1 (1)	4 (3)	
Grade 4	0 (0)	0 (0)	
Neutropenia			
Grade 1	22 (18)	16 (13)	0.0006
Grade 2	16 (13)	24 (20)	
Grade 3	21 (17)	40 (33)	
Grade 4	13 (11)	21 (17)	
Febrile Neutropenia	4 (3)	6 (5)	NS

Table 3: Maximum toxicity per patient

	FOLFIRI (n=122)	**FOLFOXIRI (n=122)**	
Investigators Assessment			**P**
Complete	6%	8%	
Partial	35%	58%	
Complete + Partial	41%	66%	0.0002
95 % CI	0.32-0.50	0.56-0.74	
Stable Disease	33%	21%	
Progression	24%	11%	0.002
Not Assessable	2%	2%	
Externally Reviewed			
Complete	6%	7%	
Partial	28%	53%	
Complete + Partial	34%	60%	<0.0001
95 % CI	0.25-0.43	0.51-0.68	
Stable Disease	34%	21%	
Progression	24%	11%	
Not Reviewed	8%	8%	

Table 4: Objective Response

General comments.
Overall the population was relatively selected to exclude elderly and frail patients expected to have and increased risk of toxicity by using combination chemotherapy.

Kaplan Meier curves presented for progression free and overall survival.

Citation: Gennatas C, Papaxoninis G, Michalaki V et al (2006) A prospective randomised study of irinotecan (CPT-11), leucovorin (LV) and 5-fluorouracil (5FU) versus leucovorin and 5-fluorouracil in patients with advanced colorectal carcinoma *Journal of Chemotherapy* 18;5:538-544

Design: Prospective Randomised Trial

Country:

Setting:

Aim: to compare the activity and toxicity of an irinotecan, leucovorin and 5-FU combination with a standard regimen of leucovorin and 5-FU.

Inclusion criteria
Histologically documented colorectal cancer
Patients ≥18 years
ECOG performance status 0-2
Measurable disease
Adequate organ function

Exclusion criteria
Prior therapy for metastatic disease
Previous adjuvant chemotherapy which contained topoisomerase I inhibitors

Sample Size
IT was estimated that 80 patients per arm was required to detect a 40% improvement in median progression free survival (7 months for the experimental group with triple drug therapy and 4.3 months for the reference group) with a power of 0.85.

Randomisation Method
Details not provided

Population
N=160

Study Duration
Recruitment Phase: January 1998-December 2001
Data were collected for an additional 24 months after accrual ended, with data on survival collected through December 2003.

Interventions

Group A	Group B
Leucovorin 20mg/m^2 iv. Bolus	Irinotecan 80 mg/m^2 iv. (over a 30-90 minute period)
5-Fluorouracil 425mg/m^2 iv. bolus	Leucovorin 20mg/m^2 iv. bolus
	5-flourouracil 425mg/m^2 iv. bolus
Given on days 1-5, every 4 weeks	Given on days 1, 8, 15, 22, 29, 36 every 8 weeks

Outcomes
Response Rates
Progression free survival (defined as the time interval from randomisation to progression or death. For patients removed from the study or who died of causes unrelated to colorectal cancer, PFS was conservatively defined as the time from randomisation to the last date on which the patient was known to be progression free)
Overall survival

Results
Median treatment duration was 4.5 months in group A and 5.8 months in group B. The median relative intensity of the dose of 5FU in group B was lower than that in group A (71% vs. 86%) possibly as a result of the weekly reductions in dose permitted in group B.

Most patients with disease progression received second line treatment; 56% of patients in group A received an irinotecan based regimen and patients in group B received an oxaliplatin based regimen (no numbers provided).

No patient received surgical treatment

Efficacy
Progression free survival was significantly higher among patients in group B compared with group A (median; 7.5 months versus 4.5 months, p=0.0335).

Group B patients showed higher response rates compared with group A (47.5% versus 30%, p=0.034). Complete response was seen in 3 (3.8%) patients in group B.
Median duration of confirmed response was approximately 3.5 months in group A and 5.5 months in group B.
Median survival of patients in group A and group B was similar (15 months versus 14 months, p=0.3531).

Adverse Events
Patients in group B had higher rates of grade 3 diarrhoea (35% versus 19%, p=0.032) and mucositis (14% versus 2%; p=0.017).
There was no difference between the groups in the incidence of grade 3 vomiting or neutropenia and there were no grade 4 toxicities or treatment related deaths in either group.

Tables

	5FU+LV (n=80)	CPT-11+5FU+LV (n=80)	P
	N (%)	N (%)	
Gender			
Male	54 (68)	56 (70)	0.733
Female	26 (32)	24 (30)	
Age, years			
Median	63	62	0.832
Range	35-78	32-78	
ECOG Performance Status			
0	23 (29)	22 (28)	0.920
1	43 (54)	42 (52)	
2	14 (17)	16 (20)	
Prior Adjuvant fluorouracil			
Yes	7 (9)	9 (11)	0.598
No	73 (91)	71 (89)	
Prior Radiotherapy			
Yes	21 (26)	16 (20)	0.348
No	59 (74)	64 (80)	

Table 1: Patient Characteristics

	5FU+LV (n=80)	CPT-11+5FU+LV (n=80)	P
Median progression free survival (months)	4.5	7.5	0.0335
Objective Response Rate (%)	30	47.5	0.034
Median duration of response (months)	3.5	5.5	
Median overall survival (months)	14	15	0.3531

Table 2: Efficacy

	5FU+LV	CPT-11+5FU+LV	
	%	%	P
Diarrhoea			
Grade 3	19	35	0.032
Grade 4	0	0	
Vomiting			
Grade 3	3	5	0.681
Grade 4	0	0	
Mucositis			
Grade 3	2	14	0.017
Grade 4	0	0	
Neutropenia			
Grade 3	20	24	0.702
Grade 4	0	0	

Table 3: Adverse Events

Citation: Giacchetti S, Perpoint B, Zidani R, Le B et al (2000) Phase III multicenter randomised trial of oxaliplatin added to chronomodulated fluorouracil-leucovorin as first line treatment of metastatic colorectal cancer *Journal of Clinical Oncology* 18;1:136-147

Design: Phase III Randomised Trial

Country: Multiple

Setting: Multicentre (outpatient)

Aim: To study how adding oxaliplatin

Inclusion criteria
Histologically proven adenoncarcinoma
Bidimensionally measurable metastatic lesions with one diameter of at least 20mm
WHO performance status 0-2
Prior adjuvant chemotherapy completed at least 6 months prior to randomisation
Adequate bone marrow, renal and hepatic function
Clinical, biologic and radiologic assessments to be performed within 30 days of starting treatment

Exclusion criteria
Brain metastases
Age greater than 76 years
Previous Chemotherapy or radiotherapy for metastatic disease
Second malignancy (except in situ carcinoma of the cervix or basal cell skin cancer)
Peripheral sensory neuropathy

Sample Size
A target size of 200 patients was calculated based on the assumption that the objective tumour response would be 30% in the 5-FU-LV arm and 50% in the 5-FU-LV/l-OHP arm. This sample size would show a 20% difference in response rate with a 5% probability of a type 1 error, a power of 80% and two intermediate analyses in the first 30 and 100 patients.

Randomisation Method
A prerandomised list of treatment allocation by blocks of four subjects was computer generated from a hazards table for each of the 15 participating institutions. The study coordinator held the list and assigned each registered patients to the next available study number at the centre where the patient was recruited. The inclusion forms were faxed from each centre to the coordination centre to verify the randomisation checklist before registration.

Population
N=200

Study Duration

Interventions
5-FU-LV (arm A): 5 day course of chronomodulated, intravenous infusion 5-FU (700mg/m^2/d) and LV (300mg/m^2/d) simultaneously infused from 22:15-09:45 hours in an outpatients setting.

5-FU-LV/l-OHP (arm B): 5 day course of chronomodulated, intravenous infusion 5-FU (700mg/m^2/d) and LV (300mg/m^2/d) simultaneously infused from 22:15-09:45 hours in an outpatients setting and l-OHP (125mg/m^2) as a continuous 6-hour intravenous infusion from 10:00 to 16:00 hours on day 1.

Outcomes
Maximum tumour response

Toxicity
Progression Free Survival (defined as time from randomisation to date of disease progression with patients who dropped out for reasons other than disease progression censored at dropout point. Patients for whom response was not evaluated were considered to have progressed on day 1)
Overall Survival

Results

200 patients were enrolled, 2 patients in arm A (5-FU-LV) and 1 patient in arm B (5-FU-LV/l-OHP) were ineligible. One patient in arm B did not receive oxaliplatin.
There were some imbalances in baseline patient's characteristics between the two group; the incidence of rectal cancer was higher in arm B compared to arm A, twice as many patients in arm A had received 5FU based adjuvant chemotherapy compared to arm B (p=0.013) and twice as many patients in arm B had normal CEA levels compared to arm A (p=0.03).

A total of 728 courses were given to patients in arm A and 776 to patients in arm B; the median number of courses per patients was 6 in arm A and 8 in arm B (range 1-15 for both arms).

Follow-up ranged from 35 to 67 months (median follow-up, 47 months).

Toxicity
One patient in arm 2 was not assessed for toxicity as he did not receive oxaliplatin.
2 treatment related deaths were recorded; 1 patient in arm A died of respiratory failure after thrombosis of the central venous line and 1 patient died with grade 4 diarrhoea and sepsis.
12 patients in arm B withdrew from therapy due to toxicity including grade 4 diarrhoea and vomiting in 1 patient.

Antitumour Efficacy
Independent assessment was carried out for 91% of all registered patients; 16 patients in arm A and 53 patients in arm B achieved an objective response for an objective response rate of 16% (95% CI 9-24%) in arm A and 53% (95% CI 42%-63%) in arm B (p<0.0001).
Responses were further confirmed at 9 weeks in 12 patients in arm A and 34 patients in arm B; the objective response rate was 12% (95% CI 6-20%) in arm A and 34% (95% CI 24-44%) in arm B (p<0.001)
Median time to best response was similar in both arms at 6 months (range:4.3-7.4) in arm A and 5 months (range 4.3-5.5) in arm B.

Metastases Surgery
Surgical removal of metastases was attempted in 21 patients in arm A and in 32 patients in arm B. A complete macroscopic resection was performed in 17 patients in arm A and in 21 patients in arm B.

Progression Free Survival and Overall Survival
Median progression free survival was 6.1 months (range 4-7.4) for arm A and 8.7 months (range 7.4-9.2) for arm B (p=0.048).
When treatment failed for 57 patients in arm 1, oxaliplatin was added to the 5-FU-LV regimen.

Median overall survival was 19.9 months (range 14-25.7) in arm A and 19.4 (range 15.4-23.4) in arm B. The estimated survival rates at 2 and 3 years were 45% and 30% respectively in arm A and 37% and 23.5% respectively in arm B.

Prognostic Factors for Response and Survival
On multivariate analysis, number of involved organs was the only factor to influence both response and survival. Treatment arm and age were joint prognostic factors for response and performance status and percentage of liver involvement were jointly predictive for survival.

Tables

	Arm A: 5-FU-LV (n=100)	Arm B: l-OHP+5-FU-LV (n=100)	P
Age, years			
Median	61	61	
Range	29-74	31-75	
Sex			
Female	36	34	
Male	64	66	
WHO Performance Status			
0	66	69	
1	27	20	
2	7	11	
Previous Adjuvant Treatment			
Chemotherapy	28	10	0.013
Radiotherapy	8	12	
Previous surgery to remove metastases	8	6	

Table 1: Patient Characteristics

	Arm A: 5-FU-LV (n=100)	Arm B: l-OHP+5-FU-LV (n=100)	P
Hospital Admission for severe toxic event, (n)	3	11	<0.1
Withdrawal for toxic effects, no of patients			
Total no. of patients	1	13	0.01
Grade 4 gastrointestinal	1	1	
Senosry Neuropathy	0	10	
Other	0	2	
Grade 3-4 Diarrhoea			
% patients	5	43	0.001
No. of courses	5	73	
% of courses	0.7	10	
Grade 3-4 nausea/vomiting			
% patients	2	25	0.001
No. of courses	2	34	
% of courses	0.2	5	
Grade 3-4 mucositis			
% patients	4	10	0.09
No. of courses	6	13	
% of courses	1	2	
Grade 3-4 hand-foot syndrome			
% patients	1	0	0.319
No. of courses	2	0	
% of courses	0.2		
Grade 3-4 anaemia			
% patients	3	1	0.254
No. of courses	4	1	
% of courses	1	0.1	
Grade 3-4 Neutropenia			
% patients	1	2	0.555
No. of courses	1	2	
% of courses	0.1	0.2	
Grade 3-4 Thrombocytopenia			
% patients	0	1	0.314
No. of courses	0	1	
% of courses		0.1	

Table 2: Incidence of severe toxicity per patient and per course

	Arm A: 5-FU-LV (n=100)		Arm B: l-OHP+5-FU-LV (n=100)			
	5-FU		5-FU		l-OHP	
	Dose Intensity ($mg/m^2/wk$)	No. of patients	Dose Intensity ($mg/m^2/wk$)	No. of patients	Dose Intensity ($mg/m^2/wk$)	No. of patients
No. of courses given						
3	1092 ±84	97	1017±104.3	99	34.6±5	99
6	1088±66.5	62	1018±104	82	34.5±4.7	82
9	1083±61.3	39	1016±95.6	44	34.3±4.6	44

Table 3: Dose Intensities of 5-FU and l-OHP over 3, 6 and 9 courses

	Arm A: 5-FU-LV (n=100)	Arm B: l-OHP+5-FU-LV (n=100)
Total no. of patients	100	100
Not evaluated	8	12
Progressive Disease	31	11
Stable Disease	45	24
No. of Objective Responses		
Partial	16	50
Complete	0	3
Total	16	53
Objective Response Rate, %	16*	53*
95% CI	9-24	42-63
Rate of confirmed response at 9 weeks, %	12	34
95% CI	6-20	24-44

*p<0.0001

Table 4: Resposne Rates (Intent-to-treat analysis)

	Response (p)	Survival (p)
No. of organs involved	0.003	0.0017
Treatment group	0.0002	NS

Age	0.126	NS
Performance Status	NS	0.0001
Percentage of liver involved	NS	0.0013

Table 5: Results from multivariate analysis of prognostic factors for tumour response and survival

General comments

Kaplan Meier Curves for progression free survival and overall survival

Citation: Goldberg, RM, Sargent DJ, Morton RF, Fuchs CS et al (2006) Randomised controlled trial of reduced dose bolus fluorouracil plus leucovorin and irinotecan or infused fluorouracil plus leucovorin and oxaliplatin in patients with previously untreated metastatic colorectal cancer: A North American intergroup trial *Journal of Clinical Oncology* 24;21:3347-3353

Design: Randomised Trial

Country: USA

Setting:

Aim:

Inclusion criteria
Histologically proven unresectable adenocarcinoma
Biopsy required if Dukes A or B primary or ≥5 years since surgery
Age ≥18 years
Life expectancy >12 weeks
ECOG performance status 0-2
Effective contraception if child bearing potential
Neutrophils ≥1.5x10^9/l
Platelets ≥100x10^9/l
Haemoglobin ≥9.0g/dl
Creatinine and total bilirubin ≤1.5x institutional normal upper limit
AST and alkaline phosphatase ≤5x institutional normal upper limit
Signed informed consent
Institutional review board approval

Exclusion criteria
Adjuvant fluorouracil within the previous 12 months
Prior treatment for advanced disease
Prior radiation to ≥15% of bone marrow
Radiotherapy of major surgery within 4 weeks
Minor surgery within 2 weeks
Uncontrolled infection
Symptomatic peripheral neuropathy
Known brain or meningeal metastases
Interstitial pneumonia
Grade ≥ 2 dyspnea
≥3 loose stools per day
Comorbid condition that could confound outcome
Active or prior malignancy in the past 3 years (exceptions: nonmelanoma skin cancer, cervical carcinoma in situ and other malignancy with <10% chance of relapse within 3 years).

Sample Size
275 patients per arm to afford 80% power to detect a hazard ratio of 1.33 between the treatment arms using a 2 sided log rank test at p=0.025.

Interim analysis demonstrated that the outcomes of patients treated on FOLFOX4 were superior to the outcomes of patients treated with the full dose IFL in the earlier component of the trial with, based on the crossing of prespecified boundaries for superiority of one regimen over the other as a result the trial was closed with 305 patients enrolled.

Randomisation Method
Dynamic allocation designed to balance random assignment for performance status score (0 vs. 1 or 2), prior adjuvant chemotherapy (yes vs no), prior immunotherapy (yes vs. no), age (<65 vs. ≥65) and treating location.

Population
N=305

Study Duration
Recruitment phase: April 25th, 2001 – April 23rd, 2002

Interventions
rIFL: Irinotecan 100mg/m^2 and bolus FU 400 mg/m^2 plus leucovorin 20mg/m^2 on days 1, 8, 15 and 22 every 6 weeks

FOLFOX4: Oxaliplatin 85mg/m^2 on day 1 and bolus FU 400mg/m^2 plus leucovorin 200mg/m^2 followed by FU 600mg/m^2 as 22 hour infusion on days 1 and 2 every 2 weeks.

Outcomes
Time to progression (calculated from study entry to disease progression regardless of patients treatment status. In post hoc sensitivity analysis, patients were censored for TTP when they discontinued initial treatment)

Response Rate
Overall Survival
Toxicity

Results
Efficacy
Median follow up time was 40 months by which time 87.5% of patients had experienced disease progression. Time to disease progression was significantly different between patients receiving rIFL and patients receiving FOLFOX4 (median 5.5 months versus 9.7 months, p<0.0001; hazard ratio=0.55; 95% CI 0.43-0.7).

In sensitivity analysis in which patients whose initial treatment ceased without progression were censored at the completion of protocol-specified therapy, these results remained significant (median time to disease progression, 5.6 and 10.1 months on rIFL and FOLFOX4 respectively; hazard ratio=0.42; p<0.0001).

Median survival time for patients receiving rIFL was 16.4 months versus 19 months for patients receiving FOLFOX4 (p=0.26 hazard ratio=0.76, 95% CI 0.6-0.97).

The response rate of patients receiving FOLFOX4 was higher than in patients receiving rIFL (48% versus 32%, p=0.006).

Time to treatment discontinuation was not significantly different between the two treatment groups though the reasons for discontinuation of treatment were different in each arm; 71.8% of patients in the rIFL group discontinued due to disease progression or death compared with 36.2% of patients receiving FOLFOX4 (p<0.0001).

Adverse Events
The death rates within the first 60 days of treatment were 3.3% (95% CI, 1.1-7.7%) in the IFL group and 2% (95% CI, 0.4-5.7%) in the FOLFOX4 group.
Rates of paresthesis and neutropenia were significantly lower in the IFL group compared with the FOLFOX4 group.

Second Line Therapy
A high proportion of patients in each arm received second line therapy (74% on rIFL and 75% on FOLFOX4). The proportion of patients receiving second line therapy before progression was 40% on IFL and 29% on FOLFOX4. 58% of patients initially treated with rIFL received an oxaliplatin based regimen second line while 55% of patients intitially treated with FOLFOX4 received an irinotecan based regimen second line.

Dose-Intensity of rIFL compared with IFL
In the prior stage of N9741, the full dose IFL regimen was used and comparing the dose intensity of irinotecan in patients treated with rIFL and patients treated with IFL showed that many patients required a dose reduction of full dose IFL with 85.5% of the intended dose delivered during the first cycle compared with 93.8% of the planned dose of rIFL (p=0.012).
The absolute doses of irinotecan also differed in cycle 2, with a median delivered dose of 375mg/m^2 of rIFL versus 425mg/m^2 of full dose IFL (p<0.001).
At cycles 3 and 6, there was no significant difference observed between the absolute doses of the drugs administered in IFL and iIFL due to the fact that the IFL dose had been reduced to a dose similar to that of the rIFL protocol.

Tables

	rIFL (N=151)	FOLFOX4 (N=154)
	N (%)	N (%)
Age, years		
Median	60	58
Range	27-83	19-83
ECOG Performance Status		
0-1	147 (97)	131 (86)
2	4 (3)	21 (14)
Sex		
female	54 (36)	64 (42)
Male	97 (64)	90 (58)
Prior Adjuvant Chemotherapy		
Yes	21 (14)	21 (14)
No	130 (86)	131 (85)
Unknown		2 (1)

Table 1: Patient Characteristics

	rIFL (n=146)	FOLFOX4 (n=146)	
	n (%)	n (%)	P
Nausea	15 (10.3)	10 (6.9)	0.296
Vomiting	12 (8.2)	9 (6.2)	0.497
Diarrhoea	24 (16.4)	18 (12.3)	0.317
Febrile Neutropenia	10 (6.9)	18 (12.3)	0.112
Dehydration	8 (5.5)	6 (4.1)	0.584
Parathesias	1 (0.7)	21 (14.4)	≤0.0001
Neutropenia	39 (26.7)	86 (58.9)	≤0.0001

Table 2: Toxicity Grade ≥3

	rIFL (n=149)	FOLFOX4 (n=149)	
	n (%)	n (%)	P
Any second line therapy			
Overall	110 (74)	112 (75)	0.79
Before Progression	44 (40)	32 (29)	0.07
Irinotecan			
Overall	37 (24.8)	82 (55)	<0.001
Before progression	15 (10)	32 (21.5)	0.71
Oxaliplatin			
Overall	86 (57.7)	31 (20.8)	<0.001
Before Progression	45 (30.2)	15 (10)	0.71
Fluorouracil			
Overall	85 (57)	69 (46.3)	0.011
Before Progression	36 (24.2)	21 (14.1)	

Table 3: Second line therapy

		Absolute dose delivered of Irinotecan (mg/m^3)		% targeted dose delivered of Irinotecan	
Cycle	**No. of Patients**	**Median (Range)**	**P**	**Median (Range)**	**P**
[1] iIFL	145	375 (97.8-461.2)	<0.001	93.8 (24.5-115.3)	0.12
IFL	274	427.6 (122.2-623.9)		85.5 (24.4-124.8)	
[3] rIFL	88	373.1 (148.6-500.9)	0.57	93.3 (37.1-125.2)	0.002
IFL	179	392.9 (59.9-523.4)		78.6 (12-104.7)	
[6] rIFL	35	373.1 (148.6-500.9)	0.62	100 (18.7-125.1)	0.006
IFL	86	75-520.9		76.9 (15-104.2)	

Table 4: Dose Intensity of rIFL compared with IFL

General comments
Kaplan Meier curves presented for time to tumour progression, overall survival and time to treatment discontinuation.

Citation: Goldberg R, Sargent D, Morton R, Fuchs C et al (2004) A randomised controlled trial of fluourouracil plus leucovorin, irinotecan and oxaliplation combinations in patients with previously untreated metastatic colorectal cancer *Journal of Clinical Oncology* 22;1:23-30

Design: Randomised Trial

Country: USA

Setting:

Aim: to compare the activity and toxicity of three different two-drug combinations in patients with metastatic colorectal cancer who had not been previously treated for advanced disease.

Inclusion criteria
Histologically proven unresectable adenocarcinoma
Biopsy required if Dukes A or B primary or ≥5 years since surgery
Age ≥18 years
Life expectancy >12 weeks
ECOG performance status 0-2
Effective contraception if child bearing potential
Neutrophils ≥1.5x10^9/l
Platelets ≥100x10^9/l
Haemoglobin ≥9.0g/dl
Creatinine and total bilirubin ≤1.5x institutional normal upper limit
AST and alkaline phosphatase ≤5x institutional normal upper limit
Signed informed consent
Institutional review board approval

Exclusion criteria
Adjuvant fluorouracil within the previous 12 months
Prior treatment for advanced disease
Prior radiation to ≥15% of bone marrow
Radiotherapy of major surgery within 4 weeks
Minor surgery within 2 weeks
Uncontrolled infection
Symptomatic peripheral neuropathy
Known brain or meningeal metastases
Interstitial pneumonia
Grade ≥ 2 dyspnea
≥3 loose stools per day
Comorbid condition that could confound outcome
Active or prior malignancy in the past 3 years (exceptions: nonmelanoma skin cancer, cervical carcinoma in situ and other malignancy with <10% chance of relapse within 3 years).

Sample Size
The protocol specified 375 patients per arm to give 90% power to detect a hazard ratio of 0.75 between each experimental regimen and control, using a two sided log-rank test at level 0.025 for each comparison.

Randomisation Method
Dynamic allocation to balance random assignment for performance status, prior adjuvant chemotherapy, prior immunotherapy, age and randomising location.

Population
N=795

Study Duration
Enrolment and randomisation: May 1999-April 2001

Interventions
IFL: Irinotecan 125 mg/m^2 and bolus FU 500mg/m^2 + LV 20 mg/m^2 on days 1, 8, 15 and 22 every 6 weeks

FOLFOX: Oxaliplatin 85 mg/m^2 on day 1 and bolus FU 400 mg/m^2 plus LV 200 mg/m^2 followed by FU 600 mg/m^2

in 22 hour infusions on days 1 an 2 every 2 weeks.

IROX: Oxaliplatin 85 mg/m^2 and Irinotecan 200 mg/m^2 every 3 weeks.

Outcomes
Time to progression (calculated from study entry to disease progression regardless of treatment status. In post-hoc sensitivity analysis, patients were censored for TTP when they discontinued initial treatment and deaths occurring within 30 days of treatment discontinuation were considered progression in both analyses)

Overall Survival
Tumour response rate (complete and partial response in measurable patients, regression in evaluable patients, confirmed at second evaluation)
Time to treatment discontinuation (time from randomisation to treatment cessation on assigned treatment)

Results
Treatment continued until disease progression, unacceptable toxicity or withdrawal of consent

The arms were balanced in relation to stratification factors and other baseline characteristics.

Median follow up was 20.4 months at which point 85% of patients had disease progression.

Time to progression differed significantly between patients receiving IFL and patients receiving FOLFOX (median time to progression: 6.9 months versus 8.7 months; hazard ratio, 0.74; 95% CI 0.61 – 0.89; p=0.0014). In the sensitivity analysis, the results remained significant (median time to progression: 7 months versus 9.3 months, p=0.0015).
For patients receiving IROX, median time to progression was 6.5 months which, when compared to IFL was not significantly different (Hazard Ratio; 1.02; 95% CI, 0.85-1.23; p>0.5) and when compared to FOLFOX was significantly lower (Hazard Ratio; 0.72; 95% CI 0.6-0.87; p=0.001).

Median survival for patients receiving IFL was 15 months, 19.5 months for patients receiving FOLFOX and 17.4 months for patients receiving IROX.

Experimental	Control	Hazard Ratio (95% CI)	P
FOLFOX	IFL	0.66 (0.54-0.82)	0.0001
IROX	IFL	0.81 (0.66-1.00)	0.04
IROX	FOLFOX	0.83 (0.67-1.03)	0.09

Table: Pairwise comparison for Survival

The response rate for patients receiving FOLFOX was higher than for patients receiving IFL or IROX while response rates of patients receiving IROX and IFL did not differ significantly.

Comparison	Response Rates	P
FOLFOX versus IFL	45% versus 31%	0.002
IROX versus IFL	31% versus 35%	0.34
FOLFOX versus IROX	45% versus 35%	0.03

Table: Pairwise Comparison of response rates

Time to treatment discontinuation did not differ significantly for any pairwise comparison however reason for treatment discontinuation did differ significantly between the treatment arms.

Comparison	Rate of treatment discontinuation	P
FOLFOX versus IFL	42% versus 67%	0.0001
IROX versus IFL	55% versus 67%	0.004
FOLFOX versus IROX	42% versus 55%	

Table: Pairwise comparison for treatment discontinuation

Patients treated with IFL had significantly higher rates of diarrhoea, vomiting, nausea, febrile neutropenia and dehydration when compared with patients treated with FOLFOX. Patients in the IFL group had significantly lower rates of paresthesias and neutropenia.
Onset of grade 3 paresthesias in FOLFOX patients occurred after a median of twelve 2-week treatment cycles.
The rates of grade 3 or higher toxicity for patients receiving IROX were similar to those for patients receiving IFL.

The death rates within the first 60 days of treatment were 4.5% (95% CI, 2.4% to 7.8%) for patients receiving IFL, 2.6% (95% CI, 1.1% to 5.3%) for patients receiving FOLFOX and 2.7% (95% CI, 1.1% to 5.4%) for patients receiving IROX.

The proportion of patients receiving 2nd line treatment before progression was similar across the three arms (26% to 32%).
A high proportion of patients treated with FOLFOX received second line irinotecan; fewer patients receiving IFL were treated with oxaliplatin regimens as second line therapy due the limited availability of the agent at the time the study was underway.

Toxicity Grade ≥3	**IFL** (n=255)	**FOLFOX** (n=258)	**IROX** (n=256)	**p** (IFL versus FOLFOX)	**p** (IFL versus IROX)	**p** (FOLFOX versus IROX)
	%	**%**	**%**			
Nausea	16	6	19	0.001	0.43	0.001
Vomiting	14	3	22	0.001	0.02	0.001
Diarrhoea	28	12	24	0.001	0.35	0.001
Febrile Neutropenia	15	4	11	0.001	0.23	0.002
Dehydration	9	4	6	0.03	0.17	0.41
Paresthesias	3	18	7	0.001	0.04	0.001
Neutropenia	40	50	36	0.04	0.35	0.002

Table: Toxicity Grade ≥3

Second line therapy	**IFL (n=251)**	**FOLFOX (n=259)**	**IROX (n=262)**
Any			
Overall	67	75	70
Before Progression	32	26	26
Irinotecan			
Overall	25	60	32
Before Progression	9	25	10
Oxaliplatin			
Overall	24	8	9
Before Progression	17	3	3
Fluorouracil			
Overall	41	40	50
Before Progression	18	14	21

Table: Second line therapy

General comments

An imbalance between the arms in the number of deaths within the first 60 days of treatment was detected; a higher number of deaths in the IFL was observed and on the recommendation of the External data monitoring committee, doses of irinotecan and FU were reduced in that arm. The results of the current study report on the comparative efficacy and toxicity for the 795 patients that were randomised to full dose IFL or to FOLFOX or IROX.

Citation: de Gramont A, Figer A, Seymour M, Homerin M, et al (2000) Leucovorin and Flourouracil with or without oxaliplatin as first line treatment in advanced colorectal cancer *Journal of Clinical Oncology* 18;2938-2947

Design: Randomised Trial

Country:

Setting: Multicentre

Aim: to investigate the effect of combining oxaliplatin with LV5FU2.

Inclusion criteria
Adenocarcinoma of the colon or rectum
Unresectable metastases
At least one bidemensionally measurable lesion of ≥ 2cm
Adequate bone marrow, liver and renal function
WHO performance status of 0-2
Age 18-75 years
Ability of complete QoL questionnaires
Previous adjuvant chemotherapy completed at least 6 months prior to inclusion

Exclusion criteria
Patients with CNS metastases, second malignancies of disease confined to previous radiation fields

Sample Size
The study was designed to have the power to detect a 3 months prolongation of progression free survival using a two sided log-rank test with an alpha risk of 0.05 and a beta risk of 0.2

Randomisation Method
Minimisation technique with stratification for performance status, number of metastatic sites and institution.

Population
N=420 (210 in each arm)

Study Duration
Recruitment Phase: August 1995 to July 1997
Cut-off date for follow-up: December 1st 1998

Interventions
LV5FU2: leucovorin 200mg/m^2, 5FU bolus 400mg/m^2, 5FU infusion 600 mg/m^2 repeated for 2 consecutive days every 2 weeks.

LV5FU2+oxaliplatin (FOLFOX4): LV 200mg/m^2, 5FU bolus 400mg/m^2, 5FU infusion 600mg/m^2 repeated for 2 consecutive days every two weeks with Oxaliplatin 85mg/m^2 given on day 1 of each cycle.

Outcomes
Progression Free Survival (defined as the time interval from randomisation to disease progression or death for patients who died without evidence of progression)

Response Rate
Overall Survival
Tolerability
Quality of Life

Results
Seven patients were unassessable for treatment efficacy; four on Arm A and three on Arm B, all 7 were retained for intent to treat analysis.

Potential median follow-up for the entire cohort was 27.7 months

Objective Tumour Response
An external panel of radiologists reviewed CT scans of 380 patients (90.5%); response rates for assessable patients were 22.3% in Arm A and 50.7% in Arm B.

The intent to treat response rates were 21.9% (95% CI 17.9-25.9%) in Arm A and 50% (95% CI, 46.1-54.9%) in Arm B (p=0.0001).
Median time to response in arm A was 12 weeks and in arm B was 9 weeks and the median duration of response was 46.1 weeks and 45.1 weeks respectively.
Secondary surgery to remove metastases could be performed in 7 patients in Arm A and in 14 patients in Arm B.

Treatment allocation to oxaliplatin and synchronous metastases were the only independent prognostic factors for response on multivariate analysis.

Progression Free Survival
On external review, median progression free survival was 6 months in arm A and 8.2 months in arm B (p=0.0003). Treatment allocation to oxaliplatin, low LDH level and good performance status were significant predictors for improved progression free survival.

Survival
Median overall survival was not significantly different between the arms 14.7 months in arm A versus 16.2 months in arm B; log rank p =0.12; Wilcoxin p=0.05). 69% of patients receiving oxaliplatin were alive at 1 year compared with 61% of patients not receiving oxaliplatin.

Post study chemotherapy was administered to 127 patients on Arm A (60.5%) and 122 patients on arm B (58.1%). Among those 78 patients on Arm A and 62 patients on Arm B received oxaliplatin post study and/or irinotecan. For patients that did not receive second line post-study oxaliplatin or irinotecan, median overall survival was 12.2 months for arm A (132 patients) and 14.8 months for arm B (148 patients); p=0.04) and median time from progression to death was 8.2 months in arm A and 7.2 months in arm B.
Independent prognostic factors for improved overall survival were allocation to oxaliplatin, low LDH level, good performance status, low alkaline phosphatase level and a limited number of involved sites.

Toxicity
Median of number of on study cycles was 11for arm A and 12 for arm B.
There was one therapy related death in arm B, resulting from gastrointestinal and haematologic toxicities. Grade 3/4 neutropenia, diarrhoea, musositis and neuropathy were more frequent on arm B than arm A.
Grade 3/4 neutropenia was more frequent in women than in men (52% versus 35%, p=0.015).
1.9% of patients on arm B had severe allergic reactions.

Dose Intensity
The 5FU dose intentsity was 92% of the scheduled dose for the first four cycles and 89% for all cycles in arm A and in arm B the 5FU dose intensity was 84% and oxaliplatin dose intensity was 86% during the first four cycles and 76% for 5FU and 73% for oxaliplatin during all cycles.

Quality of Life
83.6% of patients participated in the QoL assessment; age and sex influenced baseline QoL scores.
At cycle 4, emotional functioning improved and insomnia was attenuated on both arms, general condition improved and pain decreased on arm A and nausea and vomiting were worse on arm B.
At cycle 8, emotional functioning improved on both arms, role functioning and general condition improved and insomnia diminished on arm A and nausea and vomiting worsened on arm B.
Overall median QoL scores were comparable for the two arms and neither response to treatment nor occurrence of side effects significantly influenced the changes in patients QoL.
Time to deterioration of the global health status of 20%(p=0.0039) or 40% (p=0.0004) was significantly prolonged on arm B.
Performance status improved in 59/108 patients on arm A and in 71/119 patients on arm B.

Tables

	Arm A: LV5FU2 (n=210)	**Arm B LV5FU2+Oxaliplatin (n=210)**
	N (%)	**N (%)**
Sex		
Male	122 (58.1)	127 (60.5)
Female	88 (41.9)	83 (39.5)
Age, years		
Median	63	63

Range	22-76	20-76
WHO Performance Status		
0	102 (48.6)	91 (43.3)
1	88 (41.9)	97 (46.2)
2	20 (9.5)	22 (10.5)
Adjuvant Chemotherapy		
Yes	43 (20.5)	72 (20)
No	167 (79.5)	168 (80)

Table 1: Patient Characteristics

	Arm A: LV5FU2			Arm B: LV5FU2+Oxaliplatin		
	No. of Patients	**No. of Responses**	**%**	**No. of Patients**	**No. of Responses**	**%**
Overall						
Intent to Treat	210	46	21.9	210	105	50
Assessable	206	46	22.3	207	105	50
Complete Response	210	1	0.5	210	3	1.4
Partial Response	210	45	21.4	210	102	48.6
Stable Disease	210	107	51	210	67	31.9
Disease Progression	210	34	16.2	210	21	10
Not reviewed/not assessable	210	23	10.9	210	17	8.1
Response (CR/PR) by age						
≤65 years	126	28	22.2	134	67	50
>65 years	84	18	21.4	76	38	50
Response (CR/PR) by disease						
Synchronous	139	32	23	135	76	56.3
Metachronous	70	14	20	70	29	41.4
Liver only	68	16	23.6	79	43	54.4
Liver + other sites	105	23	21.9	103	54	52.4
Other sites	37	7	18.9	28	8	28.6
Response (CR/PR) by prior adjuvant chemotherapy						
Yes	43	6	14	42	16	38.1
No	167	40	23.9	168	89	53

Table 2: Objective tumour response rates after external review

	Response		Progression Free Survival		Overall Survival	
	P	**Odds Ratio**	**P**	**Risk Ratio**	**P**	**Risk Ratio**
WHO Performance Status	0.5938		0.0049	1.24	0.0001	1.52
Synchronous/metachronous metastases	0.0423	1.58	0.2458		0.1548	
No. of metastatic sites, continuous	0.1040		0.0008	1.21	0.0001	1.34
Alkaline Phosphatase, NCI grade	0.5887		0.0031	1.25	0.0001	1.59
LDH, ≤upper limit versus >upper limit	0.4944		0.0001	1.57	0.0001	2.17
Assigned oxaliplatin	0.0001	3.43	0.0001	0.81	0.1171	
Treatment Centre	0.504		0.6637		0.0079	
Sex	0.8903		0.793		0.4079	
Age, Continuous	0.7390		0.3976		0.5753	
Liver involved, yes versus no	0.2439		0.2773		0.8469	
Prior Chemotherapy	0.04	0.57	0.5632		0.2163	
Prior radiotherapy	0.5958		0.2253		0.0374	0.65
Primary Site, colon versus rectum	0.3026		0.6282		0.3798	
ALT, NCI grade	0.6829		0.1070		0.0012	1.38
AST, NCI grade	0.8721		0.6455		0.5086	
Creatinine, NCI grade	0.5684		0.5019		0.5960	
CEA, ≤5ng/ml, 5050ng/ml, >50ng/ml	0.5406		0.0015	1.251	0.0001	1.48

Table 3: Prognostic Factors in Univariate Analysis

	Response		Progression Free Survival		Overall Survival	
	Odds ratio	**P**	**Risk Ratio**	**P**	**Risk Ratio**	**P**
WHO Performance Status		NS	1.30	0.0023	1.5	0.0001
Synchronous/metachronous metastases	1.57	0.0306		NS		NS
No. of metastatic sites		NS		NS	1.17	0.0029
Alkaline phosphatase		NS		NS	1.34	0.0062
LDH		NS	1.60	0.0001	1.94	0.0001
Assigned Oxaliplatin	1.84	0.0001	1.71	0.0001	0.80	0.0001

Table 4: Prognostic Factors in Multivariate Analysis

	Arm A: LV5FU2				Arm B: LV5FU2+Oxaliplatin				
	1	**2**	**3**	**4**	**1**	**2**	**3**	**4**	**P (grade 3/4)**
Neutropenia	16.3	8.6	3.8	1.5	14.3	14.3	29.7	12.0	<0.001
Thrombocytopenia	26.5	2.4	0.5	0.0	62.2	11.5	2.0	0.5	NS

Anaemia	57.7	21.2	1.5	1.0	59.8	23.5	3.3	0.0	NS
Infection	15.9	5.8	1.0	0.5	17.7	6.7	1.5	0.0	NS
Nausea	40.4	11.1	2.0	NA	44.0	22.5	5.7	NA	0.043
Vomiting	18.3	9.1	1.5	0.5	24.0	24.4	4.3	1.5	0.043
Diarrhoea	27.9	10.6	3.8	1.5	30.6	16.3	8.6	3.3	0.015
Mucositis	25	9.1	1.5	0.0	24.9	12.9	5.3	0.5	0.019
Cutaneous	20.2	10.6	0.0	0.5	19.6	9.1	0.0	0.0	NS
Alopecia	15.4	3.4	NA	NA	15.8	1.9	NA	NA	NS
Neurological Toxicity	9.1	2.9	0.0	NA	20.6	29.2	18.2	NA	<0.001

Table 5: Maximum Toxicity per patient (%)

General comments

Kaplan-Meier Curves for Progression Free Survival, Overall Survival, Time to Global Health Status Deterioration of 40%.

Citation: Hochester HS, Hart LL, Ramanathan RK et al (2008) Safety and efficacy of oxaliplatin and fluoropyrimidine regimens with or without bevacizumab as first line treatment of metastatic colorectal cancer: results of the TREE study *Journal of Clinical Oncology* 26;21: 3523-3529

Comparison: FOLFOX versus bFOL versus XELOX

Design: Open label Randomised Trial

Country: USA

Setting:

Aim: To evaluate the safety and efficacy of three oxaliplatin and fluorourpyrimidine regimens with or without bevacizumab as first line treatment for metastatic colorectal cancer.

Inclusion criteria
Histologically documented mCRC or recurrent CRC
No prior therapy for metastatic or recurrent disease
Adjuvant treatment completed ≥6 months prior to study registration
Age ≥18 years
≥1 unidimensionally measurable lesion
ECOG performance status 0-1
Adequate haematologic and hepatic parameters

Exclusion criteria
Myocardial infarction within 6 months
Current congestive heart disease
Nonstable coronary artery disease
Peripheral neuropathy
Interstitial pneumonia or extensive lung fibrosis
Uncontrolled infection
Malabsorption syndrome
Dihyropyrimidine fehydrogenase deficiency
Therapeutic warfarin
Uncontrolled hypertension

Sample Size
Accrual of 70 patients per arm was deemed to be sufficient to detect a 15% increase in the overall incidence of grade 3/4 adverse events for the experimental treatments compared with historical controls based on a one group X^2 test with a normal one sided 0.05 significance level and 80% power within the 50% t0 70% Adverse Event rate of historical controls.

Randomisation Method
Central Registry to randomly assign patients in a 1:1:1 ratio

Population
TREE 1 – 150 patients

mFOLFOX6 – 50 patients
bFOL – 50 patients
CapeOx – 50 patients

Study Duration
Recruitment Stage: November 2002 to November 2003

Interventions
mFOLFOX-6: oxaliplatin 85mg/m^2 IV with leucovorin 350mg/m^2 IV over 2 hours plus FU 400mg/m^2 IV bolus and 2,400mg/m^2 continuous infusion over 46 hours every 2 weeks

bFOL: oxaliplatin 85mg/m^2 IV on days 1 and 15 and leucovorin 20mg/m^2 IV over 10 to 20 minutes followed by FU 500mg/m^2 IV push on days 1, 8 and 15 every 4 weeks

CapeOx: oxaliplatin 130mg/m^2 IV on day 1 and caecitabine 1,000mg/m^2 orally twice daily on days 1-15 every 3

weeks

Outcomes
Overall incidence of grade 3/4 adverse events possibly or probably related to study drug within the first 12 weeks of treatment in each of the TREE-2 groups

Adverse events in TREE-1 during the first 12 weeks of treatment
All adverse events occurring within 30 days of treatment
Overall response rate
Time to treatment failure (defined as time from randomisation to first documentation of tumour progression, discontinuation of study treatment or death from any cause)
Time to Progression (defined as time from randomisation to first documented progression or death from any cause in the absence of documented tumour progression)
Overall Survival

Results
Baseline characteristics were similar across groups except for prior adjuvant chemotherapy, male:female ratio and primary site of diagnosis.

147/150 patients were treated (1 ineligible due to prior chemotherapy and 2 did not start treatment).

Discontinuation of treatment was primarily attributable to adverse events (mFOLFOX6 29%, bFOL 46% and CapeOx 52%) or disease progression (mFOLFOX6 43%, bFOL 42% and CapeOx 25%).

Treatment delays were most common with mFOLFOX6 (81%) although the number of cycles administered was highest in this arm. The most common cause of treatment delay was neutropenia and thrombocytopenia in the mFOLFOX6 and bFOL arms and diarrhoea, nausea and dehydration with CapeOx.
Oxaliplatin dose reductions were more common with mFOLFOX6 (50%) reflecting the longest time on study.
Median dose intensity was ≥82% for all arms.

69% of patients received subsequent therapy including biologic agent (bevacizumab, n=31, cetuximab, n=28, other biologic agents, n=3) or oxaliplatin (n=36).

Safety and Tolerability
59%, 36% and 67% of patients in the mFOLFOX6, bFOL and CapeOx arms respectively had at least one grade 3/4 toxicity during the first 12 weeks of treatment.
Four patients had adverse events leading to death within 30 days of last treatment, 1 patient in the CapeOx arm died due to grade 4 dehydration and diarrhoea considered treatment related. No treatment related deaths were reported in the FOLFOX arm.
Overall 60 day mortality was 3.4%

Efficacy
The highest confirmed overall response rate occurred with mFOLFOX6 (41%) but there was no statistically significant difference between the arms.
Median time to failure was longer for mFOLFOX6 (6.5 months, 95% CI 5.4 – 8.3).
Median survival was 18.2 months (95% CI 14.5-21.6) and at the time of follow-up 70% of patients had died.

Tables

	mFOLFOX6	bFOL	CapeOx
No. of Patients	49	50	48
Age, years			
Median	62	62	62.5
Range	35-79	31-84	32-84
Sex			
Female	43%	38%	35%
Male	57%	62%	65%
ECOG Performance Status			
0	61%	58%	52%
1	39%	42%	48%
Prior Adjuvant Chemotherapy			
Primary Site	45	16	27
Colon	55	74	75

Colon/Rectum	27	14	19
Rectum	18	12	6
OTher	0	0	0

Table 1: Demographic and baseline characteristics

	mFOLFOX6	bFOL	CapeOx
No. of Patients	49	50	48
Duration of therapy (weeks)			
Median	24	22	18
Range	2-52	4-60	3-83
No. of cycles	490	275	282
Patients receiving >1 cycle (%)	98	88	83
Patients with ≥1 delay (%)	81	64	63
Patients with oxaliplatin dose reduction (%)	50	32	20
Median RDI			
Oxaliplatin	82	88	94
FU/Capecitabine	81	86	80

Table 2: Treatment Administration

	mFOLFOX6	bFOL	CapeOx
No. of Events	49	50	48
Events occurring during the first 12 weeks of treatment			
Related to treatment	55	36	67
95% CI	44-73	23-51	52-80
Regardless of casualty	76	44	73
95% CI	61-87	30-59	58-85
Selected events occurring during or within 30 days of treatment			
Anaemia	8	2	6
Leukopenia	4	2	2
Neutropenia	53	18	15
Thrombocytopenia	6	8	10
Abdominal Pain	2	4	13
Diarrhoea	31	26	31
Nausea or vomiting	31	24	38
Fatigue	8	14	6
PT	NR	NR	NR
Dehydration	8	12	27
Paresthesia	18	10	21
Hand-foot syndrome	8	2	19
Deep vein thrombosis	6	2	0
Hypertension	0	0	2

Table 3: Incidence of Grade 3 and Grade 4 Adverse Events

	mFOLFOX6	bFOL	CapeOx
No. of Patients	49	50	48
Response			
Complete Response	0	0	2
Partial Response	41	20	25
Stable Disease	24	42	40
Progressive Disease	27	26	10
Overall Response Rate	41	20	27
95% CI	27-56	10-34	15-42
Median time to treatment failure, months	6.5	4.9	4.4
95% CI	5.4-8.3	3.5-6.1	3.0-5.8
Median time to progression, months	8.7	6.9	5.9
95% CI	6.5-9.8	4.2-8	5.1-7.4
Median OS, months	19.2	17.9	17.2
95% CI	14.2-24.9	11.5-24.6	12.5-22.3
1 year survival	77.2	60	

Table 4: Efficacy

General comments

This study had two different populations with later patients randomised to receive XELOX, FOLFOX or bFOL + bevacizumab. Only the results from the population without bevacizumab are presented here as these are the only relevant comparisons for the topic.

Kaplan Meier curves presented for survival time (months).

Citation: Kohne CH, De Greve J, Hartmann JT, Lang I et al (2008) Irinotecan combined with infusional 5-fluorouracil/folinic acid or Capecitabine plus celecoxib or placebo in the first line treatment of patients with metastatic colorectal cancer. EORTC study 40015 *Annals of Oncology* 19;920-926

Comparison: CAPIRI versus FOLFIRI

Design: Prospective 2x2 factorial Phase III Randomised Trial

Country: Belgium

Setting:

Aim: to demonstrate the non-inferiority of Capecitabine to 5-fluorouracil (5-FU)/folinic acid (FA) in relation to progression free survival after first line treatment of metastatic colorectal cancer (i.e. that Capecitabine could replace 5FU/FA as the fluorourpyrimidine component of an irinotecan combination without compromising progression free survival).

Inclusion criteria
Aged ≥18 years with previously untreated metastatic, histologically verified adenocarcinoma of the colon or rectum.
WHO performance status ≤2
Measurable disease according to RECIST
Located outside the field of any radiotherapy
Radiotherapy to have been completed at least 4 weeks prior to randomisation
Prior adjuvant chemotherapy to have been completed at least 6 months prior to randomisation
Adequate renal, hepatic and haematological function

Exclusion criteria
Central Nervous system metastases
Second Malignancies
Severe Cardiac Disease
Active Crohns disease
Any uncontrolled severe medical condition

Sample Size
Unacceptable inferiority of Capecitabine over 5-FU/FA in relation to progression free survival was defined by a hazard ratio ≥1.25. Given a one sided alpha level of 2.5% it was estimated that 632 events were needed to exclude a difference of this magnitude with 80% probability. This number of events would also allow the detection of a 2 month difference between the celecoxib and placebo arms with a power of 89% and a two sided 5% significance level test. It was determined that 692 patients should be randomised (1:1).

Randomisation Method
Minimisation technique with stratification for institution, previous adjuvant therapy and risk groups (low risk: performance status of 1 or 0 and only 1 tumour site, intermediate risk: patients with performance status <1 but with more than one tumour site plus alkaline phosphatase level of <300U/l, or those with a poor PS, a low white blood cell count and only one tumour site; high risk: patients with good PS but more than one tumour site and a high ALP level, or a poor PS plus high WBC count or a poor PS, low WBC count and more than two tumour sites)

Population
N=85

Study Duration
May 2003 – January 2005

Interventions
FOLFIRI: Irinotecan 180mg/m^2 as a 30 to 90 minute i.v. infusion on days 1, 15 and 22; FA 200mg/m^2 as a 2-hr infusion on days 1, 2, 15, 16, 29 and 30 (1hour after irinotecan on days 1, 15 and 29); 5-FU as a 400mg/m^2 bolus given after FA followed by 22hour continuous infusion, 600mg/m^2 given after the bolus (days 1, 1, 15, 16, 29 and 30).

CAPIRI: Irinotecan 250mg/m^2 as a 30 to 90 minute iv infusion on days 1 and 22 and Capecitabine p.o. 1000mg/m^2, twice daily on days 1-15 and 22-36.

Within these arms patients were randomly assigned to either celecoxib or placebo (800mg as 2x200mg twice daily, before irinotecan when administered)

Outcomes
Progression free survival (calculated as time from randomisation until first report of progression or death; patients with no evidence of progression at the time of their last visit were censored at that point)

Safety
Response Rate
Time to treatment failure
Overall Survival

Results
Recruitment was suspended as a consequence of 7 deaths not due to disease progression; there was one further death following suspension (6 in CAPIRI and 2 in FOLFIRI). Following review of the individual hospital files, it was determined that 7/8 deaths were deemed to be treatment related with no underlying risk factors identified as a likely explanation.

The results are based on the data available from 85 eligible patients recruited before trial closure.

Median follow-up time was 14.6 months (95% CI 13.1-16.8)
Patient characteristics were similar in both groups
Dose reductions were more common in the CAPIRI arms and were primarily the result of gastrointestinal toxicity with 53% of CAPIRI versus 33% of FOLFIRI patients experiencing at least one cycle with dose reduction.
Treatment delays were more common in the FOLFIRI arm; 54% of patients on FOLFIRI versus 30% on CAPIRI experiencing at least one cycle with delay.
Relative dose intensity for Capecitabine and 5-FU did not differ (82.4% versus 84.8%) (placebo arms)

Adverse Events
4% (n=3) of patients were not included in the analysis as they did not receive study treatment.
62% of patients experienced at least one grade 3/4 adverse event, the most common of which were diarrhoea and WBC toxicity.

Efficacy
Response rates were 48% for CAPIRI + placebo and 46% for FOLFIRI + placebo (higher than for either treatment + celecoxib).

Tables

	CAPIRI + Placebo	FOLFIRI + Placebo
No. of patients	**21**	**22**
Sex		
Male n(%)	12 (57)	14 (64)
Female n(%)	9 (43)	8 (36)
Age, years		
Median	65	60.5
Range	43-78	45-75
≤65 years n(%)	11 (52)	14 (64)
>65 years n(%)	10 (58)	8 (36)
Risk Group		
Good n(%)	10 (48)	11 (50)
Intermediate n(%)	6 (29)	8 (36)
Poor n(%)	5 (24)	3 (14)
WHO Performance Status		
0 n(%)	12 (57)	14 (64)
1 n(%)	8 (38)	8 (36)
2 n(%)	1 (5)	0 (0)
Patients who started chemotherapy	20	21
Dose reductions in at least one cycle n(%)	10 (50)	10 (48)
Delays in at least one cycle n(%)	5 (25)	13 (62)
Median relative dose intensities % (range)		
Capecitabine	82.4 (47.5-119.6)	
5-FU		92.1 (21.2-107.4)
Irinotecan	83.6 (47.5-101.7)	88.4 (20.9-98.6)
Celecoxib/Placebo	98.3 (59.5-101.2)	96.2 (37.6-100.0)

Table 1: Patient Characteristics

Treatment	Total number of cycles	Time since last treatment (days)	Relatedness	Agreed Classification
CAPIRI + Placebo	1	6	Exacerbated	Pulmonary Embolism
CAPIRI + Placebo	1	75	Related	Diarrhoea/neutropenia/septic shock
CAPIRI + Placebo	2	9	Related	Diarrhoea/myocardial infarction
CAPIRI + Placebo	1	5	Related	Diarrhoea/suspected pulmonary embolism

Table 2: Early death and relationship to study treatment (classified by panel of experts)

	CAPIRI + Placebo	FOLFIRI + Placebo
Best overall response n(%)	21	22
Complete Response	1 (5)	0
Partial Response	9 (43)	10 (45)
Stable Disease	5 (24)	9 (41)
Progressive Disease	2 (10)	3 (14)
Early death	3 (14)	0
Not assessable	1 (5)	0
Response Rate (CR+PR)	10 (48)	10 (45)
Disease Control Rate (CR+PR+SD)	15 (71)	19 (86)
Adverse Event n(%)	n=20	n=21
Diarrhoea	7 (35)	2 (10)
Vomiting	1 (5)	1 (5)
Nausea	1 (5)	2 (10)
Gastrointestinal	0	1 (5)
Cardiovascular	1 (5)	0
Febrile Neutropenia	2 (10)	0
Hepatic Toxicity	1 (5)	1 (5)
White Blood Cells	3 (15)	4 (19)
Haemoglobin	0	0
Renal Toxicity	0	0
All grade 3/4 events	13 (65)	11 (52)

Table 3: Best overall response to treatment and grade 3/4 adverse events reported for 2 or more patients who started treatment

	CAPIRI (n=44)	FOLFIRI (n=41)
Progression Free Survival		
Median, months (95% CI)	5.9 (4.4-8.9)	9.6 (6.9-10.9)
1 year, % (95% CI)	22.6 (11.4-36.2)	29.3 (16.4-43.4)
Hazard Ratio (95% CI)	1.00	0.76 (0.48-1.21)
Overall Survival		
Median, months (95% CI)	14.75 (10.7-18.3)	19.9 (18.9-NR)
1 year, % (95% CI)	53.5 (36-68.2)	84.9 (69.4-92.9)
Hazard Ratio (95% CI)	1.00	0.31 (0.14-0.71)

Table 4: Progression Free and overall survival

General comments

The data from the arms with Celecoxib are not relevant to this topic, therefore only the data from the results of the arms with placebo are recorded here.

Kaplan Meier curves are included for available data

Citation: Kohne CH, van Cutsem E, Wils J, Bokemeyer C et al (2005) Phase III study of weekly high dose infusional fluorouracil plus folinic acid with or without irinotecan in patients with metastatic colorectal cancer: European organisation for research and treatment of cancer gastrointestinal group study 40986

Design: Randomised Phase III Trial

Country:

Setting:

Aim: to demonstrate that adding irinotecan to a standard weekly schedule of high dose, infusional fluorouracil and leucovorin can prolong progression free survival

Inclusion criteria
Aged >18 years
Histologically verified adenocarcinoma of the colon or rectum
WHO performance status 0-2
Measurable or assessable disease outside of the irradiation field in patients who had recently received radiotherapy
Previous adjuvant chemotherapy that did not contain topoisomerase I inhibitors and had been completed at least 6 months prior to randomisation.
Adequate haematological, renal and hepatic function

Exclusion criteria
Therapeutic drugs within 4 weeks of trial entry
Second malignancies except for in situ carcinoma of the cervix or nonmelanoma skin cancer
Bowel obstruction or subobsruction
Crohn's disease, ulcerative colitis or history of chronic diarrhea
Pregnant or breast feeding women
Fertile patients (male or female) not using adequate contraception

Sample Size
A total of 350 progressions or deaths (events) were required to provide an at least 80% power to be able to detect a shift in the median progression free survival from 7 months to 9.5 months thus is was estimated that 430 patients were needed (215 per arm).

Randomisation Method
Minimisation technique with stratification for institution, prior adjuvant treatment, WHO performance status and serum alkaline phosphatase

Population
N=430 recruited

Study Duration
Recruitment Phase: August 1999-July 2001

Interventions
Reference Group: AIO schedule of FA 500mg/m^2 administered by intravenous infusion over 2 hours followed by FU 2.6g/m^2 administered by infusion over 24 hours. Both drugs administered on days 1, 8, 15, 22, 29 and 36 followed by a two week rest. Each treatment cycle consisted of 49 days.

Experimental group: The same schedule but with FU 2.3g/m^2, subsequently reduced to 2.0g/m^2 because of toxicity. Treatment preceded by irinotecan 80mg/m^2 administered intravenously over 30 minutes.

Outcomes
Progression Free survival (defined as the time interval from randomisation to progression or death. Patients were censored at date of last visit)
Overall Survival
Tumour Response
Toxicity

Results
Toxicity and dose amendment

Of the first 89 patients assigned to irinotecan and HDFU/FA with the FU dose of 2.3g/m^2, 18 serious adverse events were reported in 16 patients which were thought to be treatment related compared with 7 serious adverse events in 7 patients in the standard arm.
There were 3 toxic deaths in the irinotecan arm and one toxic death in the HDFU/FA arms respectively.

37% of patients in the Irinotecan arm and 18% of patients in the reference arm showed toxicity necessitating FU dose reduction. In the 2nd cycle, dose reduction was in 17% in the reference arm and 14% in the irinotecan arm and in cycle 3, dose reduction was in 6% and 7% respectively. Thereafter dose reductions occurred in no more than 2% of patients.

Of the 89 patients in the irinotecan arm that received the initial dose of FU, 40.4% needed a dose reduction during the first chemotherapy cycle compared with 33.9% of the 124 irinotecan patients exposed to the amended FU dose.

Overall, relative dose intensities for FU and FA were similar in both groups with a median of approximately 80% of the intended dose being administered.

Treatment Response
Median follow-up duration was 2.3 years (95% CI, 2.1-2.4 years).

Median progression free survival in the irinotecan group was 8.5 months (95% CI 7.6-9.9 months) versus 6.4 months (95% CI 5.3-7.2) in the reference group (p<0.0001) **Hazard Ratio 0.71 (95% CI 0.55 to 0.91)**
At 1 year, 27.6% (95% CI, 21.5%-33.7%) and 14.8% (95% CI, 10%-19.5%) of patients were free from progression in the irinotecan arm and reference arm respectively.

Improvement in progression free survival was not associated with enhanced overall survival. Median overall survival was 20.1 months (95% CI 18.0-21.9) in the irinotecan arm and 16.9 months (95% CI 15.3-19 months) in the reference group.
A transient benefit of irinotecan was observed in the short term (Wilcoxin P=0.0509) with a 1 year survival rate of 74.5% (95% CI, 69.6%-81.3%) in the irinotecan group compared with 66.4% (95% CI 60-72.8%) in the reference group.

The survival curves cross at around 24 months of the trial, reflecting a greater benefit of salvage treatment in the reference arm.

Overall the trial shows no statistically significant benefit of immediate intensive treatment in terms of overall survival (log rank p=0.2779).
The observed survival difference corresponded to a hazard rate of 0.88 (95% CI, 0.7-1.11) for the whole cohort.
For patients entering the trial after the FU dose reduction the **hazard ratio was 0.87 (95% CI 0.63-1.20)**.

The response to treatment in patients with measurable disease was 62.2% (95% CI, 55%-69.5%) in the irinotecan group and 34.4% (95% CI, 27.5%-41.3%) in the reference group (p<0.0001).
Median response duration was 10.1 months (95% CI, 8.7-11.2) in the irinotecan group and 9.2 months (95% CI, 8.2 to 10.4 months) in the reference group (log rank p=0.11).

Secondary resection of metastases was possible in 6 patients in the irinotecan group and in 14 patients in the reference group.

Treatment Discontinuation and Second line Therapy
A higher proportion of patients in the reference group discontinued treatment because of disease progression or relapse (61.5% versus 43.7% in the irinotecan group.
No difference was observed between patients receiving FU 2.3g/m^2 and patients receiving FU 2.0g/m^2.
A lower proportion of patients in the irinotecan group (55.6%) received additional second line treatment than in the reference group (65.3%).
A higher proportion of patients in the irinotecan group received oxaliplatin as second line therapy compared with reference group patients (34% versus 52% respectively).

Tables

	Reference Group	Irinotecan Group

	N (%)	N (%)
Age, years		
Range	24-80	32-78
Median	60.5	61
>70 years	(14.3)	(15.4)
Sex		
Male	(61.1)	(63.6)
Female	(38.9)	(36.4)
Performance Status		
0	126 (58.3)	120 (56.1)
1	81 (37.5)	84 (39.3)
2	9 (4.2)	10 (4.7)
Adjuvant treatment for primary disease		
No	167 (77.3)	166 (77.6)
Yes	49 (22.7)	48 (22.4)
Radiotherapy		
No	204 (94.4)	196 (91.6)
Yes	12 (5.6)	18 (8.4)

Table 1: Patient Characteristics (other factors reported include Alkaline phosphatase, primary tumour site, differentiation grade of primary tumour, adjuvant treatment for primary disease and number of disease sites)

	Reference Group	**Irinotecan group**		
Grade 3 and 4 Toxicity	**Total (n=213)**	**Total (n=213)**	**2.3g/m^2 (n=89)**	**2.0 g/m^2 (n=124)**
Leukopenia	3	7	8	6
Febrile Neutropenia	1	3	5	2
Diarrhoea	21	29	36	24
Stomatitis	1	3	2	3
Nausea	7	8	8	8
Vomiting	5	7	5	9
Alopecia, grade 2	2	8	12	5
Hand-foot syndrome	2	1	1	1
Cardiovascular (any grade)	9	8	11	5
Cardiovascular (grade 3/4)	4	2	3	1

Table 2: Toxic Side Effects Experienced

	Treatment Group	
Dose-Intensity	**Reference Group**	**Irinotecan Group**
No of Cycles		
Median	3	3
Range	1-9	1-9
Relative Dose Intensity, FU		
Median (%)	83.4	80.8
Range (%)	11.8-103.7	15.9-114.2
No. of patients	213	213
Relative Dose Intensity, FA		
Median (%)	80.7	80.3
Range (%)	11.8-105.6	7.9-101.0
No of Patients	213	212
Relative Dose Intensity, Irinotecan)		
Median (%)		78.7
Range (%)		15.4-104.2
No of patients		212*

*One patient received FU but did not receive FA or Irinotecan

Table 3: Relative Dose Intensities or Different Drugs for Reference and Experimental Drugs

	Reference Group (n=189)	**Irinotecan Group (n=180)**
Treatment Outcome	**N (%)**	**N (%)**
Complete Response	7 (3.7)	5 (2.8)
Partial Response	58 (30.7)	107 (59.4)
No Change	78 (41.3)	30 (16.7)
Progressive Disease	31 (16.4)	14 (7.8)
Early Death as a result of malignant disease	1 (0.5)	1 (0.6)
Early death as a result of toxicity	4 (2.1)	2 (1.1)
Early death as a result of other cause	3 (1.6)	0 (0)
Not Assessable	7 (3.7)	21 (11.7)
Responders, CR+PR	65 (34.4)	112 (62.9)

Table 4: Treatment Outcomes and Response Rates

	Reference Group (n=141)	Irinotecan Group (n=119)
Treatment	**N (%)**	**N (%)**
FU/FA + Irinotecan	44 (31)	23 (19.3)
Irinotecan + Oxaliplatin	16 (11.3)	7 (5.9)
Irinotecan + Other	24 (17)	12 (10)
Oxaliplatin + Other	32 (22.7)	55 (46)
Other	25 (17.7)	22 (18.5)

Table 5: First second line treatment administered

General comments

Kaplan Meier Curves for progression free survival and overall survival

Citation: Koopman M, Antonini NF, Douma J, Wals J et al (2007) Sequential versus combination chemotherapy with Capecitabine, irinotecan, and oxaliplatin in advanced colorectal cancer (CAIRO): a phase III randomised controlled trial *Lancet* 370;9582:135-142

Design: Open Label Randomised Trial

Country: The Netherlands

Setting: Multicentre

Aim: To determine whether first line combination treatment is better than sequential administration of the same drugs in terms of overall survival in patients with advanced colorectal cancer

Inclusion criteria
Aged ≥18 years
Histologically proven advanced colorectal cancer not amenable to curative surgery
Measurable of assessable disease parameters
No previous systemic treatment for advanced disease
Previous adjuvant chemotherapy completed 6 months before randomisation
WHO performance score 0-2
Adequate hepatic, bone marrow and renal function

Exclusion criteria
Serious concomitant disease preventing the safe administration of chemotherapy or likely to interfere with the study assessments
Other malignancies in the past 5 years with the exception of adequately treated carcinoma in situ of the cervix and squamous or basal cell carcinoma of the skin
Pregnancy or lactation
Patients with reproductive potential not implementing adequate contraceptive measures (both male and female)
Central nervous system metastases
Serious active infections
Inflammatory bowel disease or other diseases associated with chronic diarrhea
Previous extensive irradiation of the pelvis or abdomen (excluding 5x5 Gy irradiation for rectal carcinoma)
Concomitant (or within 4 weeks before randomization) administration of any other experimental drug
Concurrent treatment with any other anti cancer therapy

Sample Size
Anticipated median overall survival sequential treatment of 14 months and assuming a median overall survival for combination treatment of 17.5 months it was calculated that to have 80% power to detect a 20% reduction in the hazard of death at a significance level of 5% a sample size of 800 patients was required.

Randomisation Method
Minimisation technique with stratification according to WHO performance status (0-1 vs. 2), serum lactate dehydrogenase concentration (normal vs. abnormal), previous adjuvant treatment (yes vs. no), predominant location of metastases (liver vs. extrahepatic) and treatment centre

Population
N=820 randomised (803 eligible)

Study Duration
Randomisation Phase: January 2003-December 2004

Interventions
Sequential treatment group: first line treatment consisted of Capecitabine, 1250mg/m^2 twice daily for 14 days; second line treatment of Irinotecan, 350mg/m^2 on day 1 and third line treatment of Capecitabine, 1000mg/m^2 twice daily for 14 days plus oxaliplatin, 130mg/m^2 on day 1.

Combination treatment group: Capecitabine, 1000mg/m^2 twice daily for 14 days plus irinotecan, 250mg/m^2 on day 1 as first line treatment and Capecitabine, 1000mg/m^2 twice daily for 14 days plus oxaliplatin, 130mg/m^2 on day 1 as second line treatment.

Outcomes
Overall survival (calculated as the interval from the date of randomization until death from any further cause or

until date of last follow-up)

Progression free survival*
Tumour Response
Toxicity Profile
Quality of life

*Progression free survival for first line treatment was calculated from the date of randomization to the first observation of disease progression or death from any cause and was also calculated for the first line and second line treatment (PFS2) and for first line, second line and third line treatment (PFS3).

Results
795 patients received at least one cycle of treatment; in the sequential group median number of cycles was 6 (range 1-45) in first line; 6 (range 1-35) in second line and 4 (range 1-14) in third line treatment and in combination group, the median number of cycles was 7 (range 1-42) in first line treatment and 4 (range 1-23) in second line.

Median time (interval between start of protocol treatment and a patient being off study) on treatment was 10.7 (range 0.1-45.1) months in the sequential group and 7.4 months (range 0.1-43.2) in the combination group (p=0.002).

At the time of analysis 84% (675/803) patients had died; 336 in the sequential group and 339 in the combination group. Median follow-up for the 128 patients still alive was 31.5 months (range 14-49months).

Median overall survival was 16.3 months (95% CI 14.3-18.1) for the sequential group and 17.4 months (95% CI 15.2-19.2) for the combination group.
Hazards Ratio for combination versus sequential treatment was 0.92 (95% CI 0.79-1.08) though the difference was not significant (p=0.3281). Multivariate analysis taking account of the stratification factors and age over 70 years; performance status 2 **(HR 1.44, 95% CI 1.02-2.06; p=0.04)** and abnormal serum LDH **(HR 1.9, 95% CI 1.68-2.33; p<0.0001)** were associated with worse survival.

In first line treatment, progression free survival was significantly longer in the combination treatment group than it was in the sequential treatment group (p=0.0002); **Hazard Ratio 0.77, 95% CI 0.67-0.89, p=0.0002**. Progression free survival was not affected when calculated to disease progression upon which the previous line of treatment was definitely discontinued and treatment free intervals after which the previous treatment was resumed, were ignored; 6.0, 95% CI 5.4-6.5 months in the sequential group versus 8.0, 95% CI 7.3-8.4 months in the combination group.
PFS2 was not significantly different between the two groups (p=0.15); likewise the difference between PFS3 in sequential treatment and PFS2 in combination treatment was not significant (p=0.19).

719 patients were assessable for response in first line treatment; 379 in the sequential group and 340 in the combination group.
Overall response rate in the first line was significantly better in the combination group than in the sequential group (p<0.0001).
Disease control rate was significantly better in the combination treatment group than in the sequential treatment group (p<0.001).
In second line treatment, the response rate and disease control rates were not significantly different between the two groups.

Results of the interim safety analysis in the first 400 patients that were enrolled were published separately. In the total patient cohort there was no significant difference in the frequency of grade 3-4 toxicity over all lines of treatment in either group (p=0.61).
Grade 3 hand-foot syndrome occurred more frequently with sequential treatment than with combination treatment (p=0.004). The frequency of thrombosis or embolism and of cardiac ischaemia did not differ significantly between the two treatment groups.

Grade 3-4 diarrhoea occurred significantly more frequently in the combination group than in the sequential group than in the sequential group (p<0.0001) as did grade 3-4 nausea (p=0.004), grade 3-4 vomiting (p=0.0002), febrile neutropenia (p<0.0001) and grade 3-4 neutropenia including febrile neutropenia (p<0.0001).
Grade 3 hand-foot syndrome occurred significantly more frequently in the sequential treatment group than in the combination treatment group (p=0.002).

Death, probably related to treatment, occurred in 11 patients (8 after sequential treatment and 3 after combination treatment; p=0.13). Causes of death included sepsis, diarrhoea and neutropenic fever.
Protocol violations were identified in 9/11 patients with violations including administration or irinotecan in patients with hyperbilirubinaemia, non-adherence to guidelines for dose reductions or delays of chemotherapy in case of diarrhoea.
6 patients (1 during sequential treatment and 5 during combination treatment) died suddenly (p=0.1); 4 of these patients had cardiopulmonary risk factors.

All cause 60 day mortality was not significantly different between the two groups (3% in the sequential group versus 4.5% in the combination group; p=0.27).

403 patients were assessable for quality of life (203 in the sequential treatment group and 200 in the combination treatment group). Change in financial problems and global health status were similar between the two groups.
The decrease in functioning was on average higher for combination treatment on average higher for combination treatment on all scales (cognitive, emotional, physical, role, and social).
The largest decrease was seen for role functioning, a decrease of 20 points for sequential treatment versus 24 points for combination treatment.
For symptomatic scales, changes were on average greater in the combination treatment except for pain and dyspnoea. The only significant difference in change was seen for diarrhoea: 20 points for sequential versus 28 points for combination treatment (p=0.002).

Tables

	Sequential Treatment (n=401)	Combination Treatment (n=402)	Total (n=803)
Age at randomisation (years)	64 (27-84)	63 (31-81)	63 (27-84)
>70 years	93 (23%)	81 (20%)	174 (22%)
Sex			
Male	252 (63%)	255 (63%)	507 (63%)
Female	149 (37%)	147 (37%)	296 (37%)
Performance Status			
0	257 (64%)	244 (61%)	501 (62%)
1	126 (31%)	142 (35%)	268 (33%)
2	18 (5%)	16 (4%)	34 (4%)
Previous Adjuvant Therapy			
Yes	55 (14%)	56 (14%)	111 (14%)
No	346 (86%)	346 (86%)	692 (86%)

Table 1: Patient characteristics (other factors reported include localisation of metastases, LDH at randomisation and site of primary tumour)

	Sequential Treatment (n=401)	Combination Treatment (n=402)	p value
Overall survival (months)	16.3 (14.3-18.1)	17.4 (15.2-19.2)	0.3281
1 year survival rate (%)	64% (59-69)	67% (62-72)	0.38
Progression free survival first line (months)	5.8 (5.1-6.2)	7.8 (7-8.3)	0.0002
PFS2 (months)	8.7 (8.2-9.6)	10.3 (9.3-10.8)	0.15
PFS3 (months)	10.3 (9-11.1)	NA	0.19*
Overall response rate (CR + PR)			
First line	77 (20%; 17-26%)	139 (41%; 36-46%)	<0.0001
Second line	23 (10%; 6-15%)	24 (12%, 7-17%)	0.46
Third line	5 (4%; 1-9%)		
Disease Control (CR+PR+SD)			
First line	280 (74%; 69-79%)	297 (87%; 82-90%)	<0.0001
Second line	162 (71%; 65-77%)	121 (63%; 56-70%)	0.06
Third line	72 (57%; 48-66%)		

*PFS3 in the sequential group versus PFS2 in the combination group

Table 2: Efficacy

	Sequential treatment (n=397)	Combination Treatment (n=398)	Total (n=795)	p value
Non haematological adverse events				
Overall grade 3-4 toxicity	271 (68%)	265 (67%)	536 (67%)	0.61
Hypersensitivity (total)	25 (6%)	18 (5%)	43 (5%)	0.27
Cardiac ischaemia/infarction (total)	14 (4%)	14 (4%)	28 (4%)	0.99
Thrombosis/embolism	35 (9%)	41 (10%)	76 (10%)	0.48
Grade 3 hand-foot skin	50 (13%)	26 (7%)	76 (10%)	0.004

reaction				
Diarrhoea				
Grade 3	83 (21%)	90 (23%)	173 (22%)	0.23
Grade 4	9 (2%)	17 (4%)	26 (3%)	
Nausea				
Grade 3	31 (8%)	39 (9%)	67 (8%)	0.45
Grade 4	0	1 (<1%)	1 (<1%)	
Stomatitis				
Grade 3	12 (3%)	5 (1%)	17 (2%)	0.15
Grade 4	0	1 (<1%)	1 (<1%)	
Vomiting				
Grade 3	24 (6%)	37 (9%)	61 (8%)	0.16
Grade 4	4 (1%)	2 (<1%)	6 (<1%)	
Neuropathy				
Grade 3	8 (2%)	12 (3%)	20 (3%)	0.18
Grade 4	1 (<1%)	0	1 (<1%)	
Non haematological adverse events				
Anaemia				
Grade 3	2 (<1%)	1 (<1%)	3 (<1%)	0.18
Grade 4	1 (<1%)	2 (<1%)	3 (<1%)	
Neutropenia				
Grade 3	17 (4%)	25 (6%)	42 (5%)	0.19
Grade 4	3 (1%)	4 (1%)	7 (1%)	
Febrile Neutropenia				
Grade 3	16 (4%)	24 (6%)	40 (5%)	0.18
Grade 4	3 (1%)	4 (1%)	7 (1%)	
Thrombocytopenia				
Grade 3	3 (1%)	3 (1%)	6 (1%)	0.99
Grade 4	1 (<1%)	1 (<1%)	2 (<1%)	

Table 3: Adverse events associated with sequential versus combination treatment (p values for grade 3 and 4 toxicities combined)

	Sequential Treatment (n=397)	**Combination treatment (n=398)**	**Total (n=795)**	**p value**
Hypersensitivity reaction (total)	7 (2%)	7 (2%)	14 (2%)	0.99
Cardiac ischaemia/infarction (total)	11 (3%)	13 (3%)	24 (3%)	0.68
Thrombosis/embolism (total)	28 (7%)	38 (10%)	66 (8%)	0.2.
Grade 3 hand-foot skin reaction	48 (12%)	23 (6%)	71 (9%)	0.002
Diarrhoea				
Grade 3	38 (10%)	87 (22%)	125 (16%)	<0.0001
Grade 4	5 (1%)	15 (4%)	20 (3%)	
Nausea				
Grade 3	14 (4%)	33 (8%)	47 (6%)	0.004
Grade 4	2 (<1%)	5 (1%)	7 (<1%)	
Stomatitis				
Grade 3	2 (<1%)	5 (1%)	7 (<1%)	0.16
Grade 4	0	1 (<1%)	1 (<1%)	
Vomiting				
Grade 3	9 (2%)	33 (8%)	42 (5%)	0.0002
Grade 4	1 (<1%)	1 (<1%)	2 (<1%)	
Haematological Adverse Events				
Anaemia				
Grade 3	1 (<1%)	0	1 (<1%)	0.56
Grade 4	1 (<1%)	1 (<1%)	2 (<1%)	
Neutropenia				
Grade 3	2 (<1%)	23 (6%)	25 (3%)	<0.0001
Grade 4	0	4 (1%)	4 (1%)	
Febrile Neutropenia				
Grade 3	2 (<1%)	22 (6%)	24 (3%)	<0.0001
Grade 4	0	4 (1%)	4 (1%)	
Thrombocytopenia				
Grade 3	0	0	0	0.32
Grade 4	0	1 (<1%)	1 (<1%)	

Table 4: Adverse events associated with sequential versus combination treatment first line (p values presented for grade 3 and 4 toxicities combined)

General comments

Kaplan Meier curve presented for overall survival by treatment arm

Citation: Martoni AA, Pinto C, Di Fabio F Lelli G et al (2006) Capecitabine plus oxaliplatin (XELOX) versus protracted 5-fluorouracil venous infusion plus oxaliplatin (PVIFOX) as first line treatment in advanced colorectal cancer: A GOAM phase II randomised study (FOCA trial)

Design: Phase II randomised trial

Country: Italy

Setting:

Aim: to compare pviFOX with XELOX in the first line treatment of advanced colorectal cancer

Inclusion criteria
Histological diagnosis of colorectal carcinoma
Measurable tumour lesions
Karnofsky performance status ≥70
Age < 18 years
Life expectancy >3 months
No prior chemotherapy for metastatic disease
Adjuvant therapy terminated >6 months before
Haemoglobin levels >10g/dl
Neutrophil count ≥2000/mm^3
Platelet count ≥100,000/mm^3
Serum creatinine ≤1.2mg/dl
Creatinine clearance according to Cockcrof-Gault formul >55ml/min
Bilirubin and serum transaminase levels ≤3 times the normal values
Staging examinations carried out within 30 days of the beginning of treatment
Written informed consent

Exclusion criteria
Patients with potentially resectable lesions
Unresolved internal obstruction
Previous malignant neoplasia (except for non-melanoma skin carcinoma and adequately treated *in situ* carcinomas of the uterine cervix)
Dementia or alterations in mental status

Sample Size
The study was designed to test the null hypothesis that the objective remission rate was less than 0.2 a rate which would indicate insufficient benefits; the smallest response probability suggesting that one regimen warranted further studies was 0.35 with a two-sided alpha of 0.05 and a power of 80% (beta=0.2). On these grounds, the number of patients to be treated per arm was 56.

Randomisation Method
Not reported

Population
N=122 patients randomised, patients were subsequently determined ineligible.

N=118 analysed

Study Duration
Recruitment stage: December 2001 to March 2005

Interventions
Arm A: on day 1, dexamethasone 20mg in 100 cc of saline by the intravenous route in 15 min, granisetron 3mg in 100cc of saline i.v. in 15 min, Oxaliplatin 130mg/m^2 in 500cc of 5% glucose solution i.v. in 2hours and at the end 5-FU 250mg/m^2/day in c.i. from the 1st to the 21st day. Before starting therapy, a central venous catheter (CVC) implant was requested for the administration of 5-FU by elastomeric pump to allow for a protracted 7 day long infusion.

Arm B: Oxaliplatin on day 1 (as arm A) and oral Capecitabine 1000mg/sm bid from the 1st to the 14th day. Every patient in arm B was given a diary to help in the administration of Capecitabine and the monitoring of side-effects at home.

Outcomes
Tumour Response Rate

Time to Progression (defined as the time interval between start of treatment and evidence of progression independent of objective response)
Toxicity

Results
Treatment Delivery
A total of 739 therapy cycles were administered: patients in Arm A received a higher number of cycles (424 versus 315).
Median dose intensity was 100% for all three cytotoxic drugs
There was a higher rate of treatment suspension before completion of 6 cycles in Arm A (37.7%) compared with Arm B (27.8%) due to higher suspension resulting from disease progression and toxicity.

48.2% (n=27) of patients in arm A received full doses of 5-FU and OXA and 43.5% (n=27) of patients in arm B received full doses of Capecitabine and oxaliplatin.

Dose reduction was required for pviFU alone in 42.8% (n=27) in arm A, for Capecitabine in 37% (n=23) in arm B and oxaliplatin alone in 17.8% (n=10) in arm A and in 40.3% (n=25) in arm B.

Safety
There were statistically significantly higher rates of stomatitis observed in arm A compared with arm B (25.9% versus 13.1%, p=0.028).

The system of protracted venous infusion of 5-FU in arm A was generally well accepted by patients with minor limitations to daily activities and social life; 8 patients had venous line problems, including infection, thrombosis, bad compliance, dislodged, unthreading of the needle from CV port or sepsis, resulting in temporary suspension (n=6) or to stop 5-FU infusion (n=2).

Grade 3 toxicity resulted in the suspension of treatment in 5 patients (4 in arm A (diarrhoea (3) and stomatitis (1)) and 1 in arm B (diarrhoea and vomiting)).
3 patients died early on during treatment, 1 in arm A due to rapid general deterioration in conditions following the first treatment cycle and 2 in arm B, one due to G4 diarrhoea, dehydration and acute renal failure during the first cycle and one died suddenly following first cycle so no information could be collected.

Efficacy
8 patients (3 in Arm A and 5 in Arm B) were not evaluable as they had received only one cycle or had metastatic lesions documents only by PET.
Median response duration of CR+PR was 8 months (1-14 months) in Arm A and 9 months (4-25 months) in arm B and the median duration of stable disease was 8.5 months (4-13 months) in arm A and 6 months (3-13 months) in arm B.

There was no significant difference between the arms regarding the number of patients that experienced improvement in performance status or disease related symptoms.

Time to Progression
Timing of clinical and imaging test re-evaluation was equally distributed between the two arms: 68.6% of patients in arm A and 69% in arm B had a first re-evaluation before the fourth cycle.
Median time to progression was 7 months (95% CI 8-10 months): at the time of reporting 11 patients in arm A and 15 patients in arm B had not shown disease progression.
At the time of reporting, 92 patients had progressed, 45 in arm A and 47 in arm B while 60 patients had received second line chemotherapy (25 in arm A and 35 in arm B).
Second line chemotherapy consisted primarily of FOLFIRI (n=41), 6 patients received other Irinotecan based regimens and the remaining patients received other regimens (not detailed).
7.6% (n=9) patients underwent surgical resection for liver metastases after first line chemotherapy (5 in arm A and 4 in arm B).

Tables

	Arm A pviFOX	Arm B XELOX	Total
	N (%)	N (%)	N (%)
No of eligible patients	56	62	118
Gender			
M	28 (50)	33 (53.2)	61 (51.7)
F	28 (50)	29 (46.8)	57 (48.3)
Age			
Median	64	67	67
Range	41-79	25-79	25-79
Karnofsky performance status			
Median	90	90	90
Range	70-100	70-100	70-100
Adjuvant Chemotherapy			
Yes n (%)	13 (23.2)	18 (29.9)	31 (26.3)
No n (%)	43 (76.8)	44 (71)	87 (73.3)

Table 1: Patient Characteristics (other factors reported include primary tumour site, primary tumour surgical resection, stage at treatment start, matastases localisation, no. of metastatic sites, CEA plasma levels)

	pviFOX	XELOX	Total
Total no. of delivered cycles	315	424	739
Complete cycles (2 drugs)	307	363	670
Oxaliplatin only	7	5	12
5-FU only	1	-	1
Capecitabine only	-	56	56
Complete Cycles (2 drugs)			
Median (range)	6 (1-10)	6 (1-10)	6 (1-10)
Dose Intensity: Median (Range)			
Oxaliplatin	100% (82-100)	100% (15-100)	100% (15-100)
5-FU	100% (13-100)	-	100% (13-100)
Capecitabine	-	100% (14-100)	100% (14-100)

Table 2: Delivered Treatment

	pviFOX	XELOX	Total
	N (%)	N (%)	N (%)
Total No. of treatment suspension reasons	20 (38)	16 (27)	36 (32)
Progression	12 (23)	10 (17%)	22 (19%)
Refusal	1 (2)	1 (2%)	2 (2%)
Death	1 (2)	2 (3%)	3 (3%)
Toxicity	4 (7.5%)	1 (2%)	5 (4%)
Other	2 (4%)	2 (3%)	4 (3.5%)

Table 3: Treatment suspension before 6 cycles

	pviFOX N (%)				
Grade	**0**	**1**	**2**	**3**	**4**
No of evaluable patients	64				
Neutropenia	43 (79.6)	7 (13)	4 (7.4)		
Anaemia	29 (53.7)	20 (37)	4 (7.4)	1 (1.9)	
Thrombocytopenia	38 (70.4)	14 (25.9)	1 (1.9)	1 (1.9)	
Diarrhoea	18 (33.3)	14 (25.9)	15 (27.8)	6 (11.1)	1 (1.9)
Stomatitis	40 (74.1)	6 (11.1)	6 (11.1)	2 (3.7)	
Epigastralgia	50 (92.6)	2 (3.7)	2 (3.7)		
Hyperbilirubinemia	44 (81.5)	7 (13)	2 (3.7)	1 (1.9)	
SGOT, SGPT increase	38 (70.4)	10 (18.5)	6 (11.1)		
Hand-Foot Syndrome	51 (94.4)	2 (3.7)		1 (1.9)	
Neurotoxicity (chronic)	12 (22.2)	23 (43.6)	9 (16.7)	10 (18.5)	
Acute Neurotoxicity	**Yes**	**No**			

(pharyngo-laryngospasm)					
	13 (24.1)	41 (75.9)			
	XELOX N (%)				
Grade	**0**	**1**	**2**	**3**	**4**
No of evaluable patients	61				
Neutropenia	46 (75.4)	9 (14.8)	6 (9.8)		
Anaemia	35 (57.4)	24 (39.3)	2 (3.3)		
Thrombocytopenia	30 (49.2)	24 (39.3)	5 (8.2)	2 (3.3)	
Diarrhoea	33 (54.1)	15 (24.6)	8 (13.1)	4 (6.6)	1 (1.6)
Stomatitis	53 (86.9)	8 (13.1)			
Epigastralgia	53 (86.9)	7 (11.5)		1 (1.6)	
Hyperbilirubinemia	45 (73.8)	9 (14.8)	6 (9.8)	1 (1.6)	
SGOT, SGPT increase	45 (73.8)	14 (23)	1 (1.6)	1(1.6)	
Hand-Foot Syndrome	57 (93.4)	1 (1.6)	3 (4.9)		
Neurotoxicity (chronic)	13 (21.3)	15 (24.6)	18 (29.5)	15 (24.6)	
Acute Neurotoxicity (pharyngo-laryngospasm)	**Yes**	**No**			
	15 (24.2)	47 (75.8)			
	Total N (%)				
Grade	**0**	**1**	**2**	**3**	**4**
No of evaluable patients	115				
Neutropenia	89 (77.4)	16 (13.9)	10 (8.7)		
Anaemia	64 (55.7)	44 (38.3)	6 (5.2)	1 (0.9)	
Thrombocytopenia	68 (59.1)	38 (33)	6 (5.2)	3 (2.6)	
Diarrhoea	51 (44.3)	29 (25.2)	23 (20)	10 (8.7)	2 (1.7)
Stomatitis	93 (80.9)	14 (12.2)	6 (5.2)	2 (1.7)	
Epigastralgia	103 (89.6)	9 (7.8)	2 (1.7)	1 (0.9)	
Hyperbilirubinemia	89 (77.4)	16 (13.9)	8 (7)	2 (1.7)	
SGOT, SGPT increase	83 (72.2)	24 (20.9)	7 (6.1)	1 (0.9)	
Hand-Foot Syndrome	108 (93.9)	3 (2.6)	3 (2.6)	1 (0.9)	
Neurotoxicity (chronic)	25 (21.7)	38 (33)	27 (23.5)	25 (21.7)	
Acute Neurotoxicity (pharyngo-laryngospasm)	**Yes**	**No**			
	28 (24.1)	88 (75.9)			

Table 4: Side Effects

	pviFOX	**XELOX**	**Total**
	N (%)	**N (%)**	**N (%)**
Total no. of patients	56	62	118

Complete Response (CR)	1 (1.7)	3 (4.8)	4 (3.3)
Partial Response (PR)	26 (46.4)	24 (38.7)	50 (42.4)
CR +PR	27 (48.2)	27 (43.5)	54 (45.8)
95% CI	34.6 – 61.9	31 – 56.7	36 – 54.4
Stable Disease	13 (23.2)	20 (32.3)	33 (27.9)
Progressive Disease	13 (23.2)	10 (16.1)	23 (19.5)
Not evaluable	3 (5.4)	5 (8.1)	8 (6.8)

Table 5: Objective Response

	pviFOX	**XELOX**	**Total**
	N (%)	**N (%)**	**N (%)**
Asthenia	15/27 (56)	11/26 (42)	26/53 (49)
Anorexia	9/15 (60)	4/10 (40)	13/25 (52)
Pain	16/24 (67)	15/23 (65)	31/47 (66)
Karnofsky performance Status	8/16 (50)	8/17 (47)	16/33 (48)

Table 6: Symptomatic Improvement

General comments

Kaplan Meier curves for time to progression

Objective response and toxicity were evaluated according to RECIST criteria and CTC criteria respectively with the exception of neurotoxicity that was evaluated according to the LEVI scale.

Time to progression (TTP) was considered as the time interval between the start of therapy and the evidence of progression independently of the objective response.

Citation: Porschen R, Arkenau HT, Kubica S, Greil R et al (2007) Phase III study of Capecitabine plus oxaliplatin compared with fluorouracil and leucovorin plus oxaliplatin in metastatic colorectal cancer: A final report of the AIO colorectal study group *Journal of Clinical Oncology* 25;27:4217-4223

Comparison: CAPOX versus FUFOX (1st line)

Design: Phase III randomised Trial

Country: Germany (68 institutes) and Austria (1 institute)

Setting:

Aim: To evaluate the efficacy and toxicity of CAPOX compared with infusional FU/FA plus oxaliplatin (FUFOX)

Inclusion criteria
≥18 years
ECOG performace status ≤2
Life expectancy of >3 months
Histologically confirmed colorectal cancer
Adjuvant/neoadjuvant treatment completed more than 6 months prior to the start of treatment
Measurable tumlur parameters according to the Response Evaluation Criteria in Solid Tumours

Exclusion criteria
Prior treatment for metastatic colorectal cancer
Previous malignancy within 5 years (apart from basal cell skin cancer or in situ carcinoma of the cervix)
Central nervous system metastasis
Heart disease grade New York Heart Association classification III/IV
Myocardial infarction within 6 months
Renal Impairment
Abnormal liver function tests
White blood cell count <3000/µl or platelets <100000/µl
Pregnant or lactating women

Sample Size
The study was designed to show non-inferiority of the Capecitabine based arm with respect to progression free survival. The sample size was based on the assumption of equal efficacy of both arms, a hypothetical inferiority of CAPOX in median progression free survival of two months or more (7 vs. 9 months, corresponding to a hazard ration of 1.29 or an absolute different of 9% in the progression free survival rate after 9 months) had to be excluded with a 95% CI and a power of 80%.

Randomisation Method
Computer based randomisation performed centrally by fax with stratification for ECOG performance status (0-1 vs. 2), WBC count (<8,000 Vs. ≥8,000/µl, alkaline phosphatase (AP <300 vs. ≥300/µl) and number of metastatic sites (1 vs. >1 site).

Population
N=476 randomised, 2 patients excluded (one due to double randomisation and one due to neuroendocrine tumour histology.

CAPOX N=241
FUFOX N=233

Study Duration
Recruitment Phase: August 2002 to August 2004
Cut off date for analysis was January 31st, 2007.

Interventions
Arm A: Oxaliplatin 50mg/m^2 2-hour infusion; Folinic acid 500mg/m^2 2-hour infusion and FU 2,000 mg/m^2 22-hour infusion on days 1, 8, 15 and 22. After the 4th cycles, oxaliplatin was administered only on days 1 and 15 of each cycles to reduce the risk of oxaliplatin related cumulative peripherally neuropathy.

Arm B: Oxaliplatin 70mg/m^2 2-hour infusion days 1 and 8 every 3 weeks; Capecitabine 1,000mg/m^2 bid orally days 1-14 every three weeks. After the 6th cycle, oxaliplatin was administered only on day 1 of each cycle to reduce the

risk of oxaliplatin related cumulative peripheral neuropathy.

Outcomes
Progression free survival (defined as the interval between random assignment and first recording of progression or death)

Response Rates
Overall Toxicity
Time to Treatment failure

Results
Patient and tumour characteristics were well balanced between the arms with respect to stratification factors and baseline characteristics.

Toxicity
A total of 235 patients in the CAPOX arm received a total of 1,562 cycles (median, 6 cycles/patient; range 1-28 cycles) and 231 patients in the FUFOX arm received a total of 1,073 cycles (median 5 cycles/patient, range 1-17 cycles).
Mean treatment duration in the CAPOX arm was 20.6 weeks (SD ±13.5) and in the FUFOX arm was 21.7 weeks (SD±13.2)

The most frequent nonhaematologic grade 3/4 toxicity was neuropathy (25% in the CAPOX arm verus 27% in the FUFOX arm) while grade 3/4 haematologic toxicities were infrequent and manageable in both arms. Other grade 3/4 toxicities (e.g. nausea, vomiting and diarrhoea) were similar in both arms.
Grade 2/3 hand-foot syndrome occurred more often in the CAPOX arm (10% versus 4%; p=0.028).
Dose reductions due to toxicity were necessary in 39% of patients in the CAPOX arm and in 45% of patients in the FUFOX arm.
The oxaliplatin dose intensity was 94.2% (SD±24.8%) in the CAPOX arm and 95% (SD±38.3% in the FUFOX arm.
The calculated mean dose per cycle for FU was 7,127.2mg (SD±1,237.2) and for Capecitabine 26.801.5mg (SD±3232.2).
Reasons for discontinuation of treatment included tumour progression (46% in CAPOX versus 37% in FUFOX), death as a result of tumour (7% in CAPOX versus 5% in FUFOX), death from other causes (in both arms), severe adverse events (21% in CAPOX versus 24% in FUFOX), patient refusal (8% in CAPOX versus 14% in FUFOX), protocol violation (1% in CAPOX versus 3% in FUFOX) and other reasons (14% in both arms).

Objective Tumour Response and Progression Free Survival
Median follow-up was 17.3 months in both arms.
A total of 395 patients showed sign of tumour progression and objective tumour response rates were as follows: CAPOX 48% (95% CI, 41% to 54%; complete response, 2%, partial response 46%, stable disease 28%) and FUFOX, 54% (95% CI, 47% to 60%; complete response 6%, partial response 48%, stable disease 23%) (p=0.7).
Secondary surgery was performed in 4 patients in the CAPOX arm and in 10 patients in the FUFOX arm.

Median progression free survival was 7.6 months (CAPOX, 7.1 months, FUFOX 8 months) **Hazard Ratio 1.17, 95% CI 0.96 to 1.43, p=0.117)**.
On multivariate analysis more than one metastatic site, higher WBC count and increase AP levels were the only independent prognostic factors.

Time to treatment failure was 5.1 months in the CAPOX arm and 6 months in the FUFOX arm; **Hazard Ratio 1.14; 95% CI 0.94 to 1.39, p=0.19)**.

Overall Survival
At the time of publication, there were 370 deaths of 470 assessable patients and median overall survival was 17.3 months (16.8 months in the CAPOX arm and 18.8 months in the FUFOX arm); **Hazard Ratio 1.12, 95% CI 0.92 to 1.38; p=0.26)**.
Independent prognostic factors for improved overall survival were age <70 years, performance status 0-1, WBC less than 8,000/µl and AP levels less than 300 U/L.

The 60 day mortality was 4.1% in the CAPOX arm and 4.3% in the FUFOX arm.

Second line therapy
66% of patients in both arms went on to receive second line therapy with the majority receiving Irinotecan based

chemotherapy (81% in both arms).
Additional treatments included reintroduction with oxaliplatin (CAPOX 13%; FUFOX 21%), cetuximab (CAPOX 22%; FUFOX 21%) or mitomycin (CAPOX 9%; FUFOX 9%).
On subsequent treatment lines, patients in the CAPOX arm 43% changed to FU and 29% continued with Capecitabine. In the FUFOX arm, 56% continued with FU and 30% received Capecitabine.
56% of the study population received all three drugs; FU, oxaliplatin and irinotecan (CAPOX 57% andFUFOX 55%).

Tables

	CAPOX (n=241)	**FUFOX (n=233)**
	N (%)	**N (%)**
Sex		
Male	150 (62)	146 (63)
Female	91 (38	87 (37)
Age, years		
Median	66	64
Range	32-81	34-86
Previous Adjuvant Treatment		
Chemotherapy	75 (31)	67 (29)
No Chemotherapy	164 (69)	164 (71)
Radiotherapy	35 (15)	30 (13)
No Radiotherapy	205 (85)	201(87)
ECOG Performance Status		
0-1	219 (91)	216 (93)
2	22 (9)	17 (7)

Table 1: Patient Characteristics (other factors reported include Alkaline phosphatase levels, WBC counts and number of metastatic sites)

General comments
Progression free survival was defined as the interval between random assignment and the first recording of disease progression or death.

Efficacy analysis was based on the intent to treat population

Kaplan Meier curves are presented for progression free survival and overall survival

Citation: Seymour MT, Maughan TS, Ledermann JA, Topham C et al (2007) Different strategies of sequential and combination chemotherapuy for patients with poor prognosis advanced colorectal cancer (MRC FOCUS): a randomised controlled trial *Lancet* 370;9582:143-152

Comparison: FOLFOX versus FOLFIRI versus Irinotecan (1st and 2nd line)

Design: Randomised phase III trial

Country: UK (59 centres), Cyprus (1 centre)

Setting:

Aim: To establish the best sequence of the first two cytotoxic drugs, fluorouacil and either irinotecan or oxaliplatin when treating patients with poor prognosis advanced colorectal cancer

Inclusion criteria
Histologically confirmed colorectal adenocarcinoma with inoperable metastatic or locoregional disease.
Disease measurable by RECIST
WHO performance status 0-2
No previous chemotherapy for metastatic disease
White blood count >$4x10^9$/L
Platelet count >$150x10^9$/L
Serum bilirubin concentration <1.25xupper limit of normal
Alkaline phosphatase concentration <5xupper limit of normal
Calculated glomerular filtration rate or ADTA clearance of >50ml/mon
Older than 18 years

Exclusion criteria
Uncontrolled medical co-morbidity likely to compromise treatment

Sample Size
The planned sample size was 2100 patients; 700 in each treatment arm (A, B and C) with 350 in each subgroup of arms B and C. An anticipated 2-year survival of 15% in the control group would detect an improvement of 7.5% (to 22.5%) in any pair wise comparison of control versus an individual novel group (1050 patients, one-sided log rank, 80% power, 1% significance to correct for multiple comparisons).

Randomisation Method
Minimisation procedure with stratification for clinician, performance status, primary tumour resected or in situ and distant metastases (present or absent)

Population
N=2135 patients randomised
Arm A N=710
Arm B_{IR} N=356 and Arm B_{OX} N=356
Arm C_{IR} N=356 and Arm C_{OX} N=357

Study Duration
Recruitment Phase: May 1st 200-December 31st 2003

Interventions
Arm A (FU regimen 1st line and Ir regimen 2nd line)): First line treatment with fluorouracil, continuing until treatment failure and in patients fit enough for second line, single agent Irinotecan was given.

Arm B (FU regimen 1st line and either IrFU or OxFU 2nd line): Deferred combination chemotherapy, fluorouracil first line and combination chemotherapy second line in patients that were fit enough. Arm B was subdivided into two groups in a 1:1 ratio at randomisation. B_{ir} received irinotecan + fluorouracil second line and B_{ox} received oxaliplatin + fluorouracil second line.

Arm C (IrFU or OxFU 1st line): First line combination treatment which continued until treatment failure. Arm C was also subdivided in a 1:1 ratio with patients in C_{ir} receiving irinotecan + fluorouracil first line and C_{ox} receiving oxaliplatin + fluorouracil first line.

	Fluorouracil	Irinotecan	Irinotecan/Fluorouracil	Oxaliplatin/Fluorouracil

Regimen	FU	Ir	IrFU	OxFU
Intravenous drug schedules	Levofolinate 175mg (2h) then FU 400mg/m^2 (bolus) FU 2800mg/m^2 (46hr)	Irinotecan 350mg/m^2 (30-90 mins) (300mg/m^2 if aged >70 years or performance status 2)	Irinotecan 180mg/m^2 (30 mins) then levofolinate 175mg (2hr) then FU 400 mg/m^2 (bolus) FU 2400mg/m^2 (46hr)	Oxaliplatin 85mg/m^2 plus levofolinate 175mg (concurrent, 2hr) then FU 400 mg/m^2 (46hr)
Dexamethasone	8 mg intravenously bolus day 1 Oral days 2-4 (decreasing course)	8mg intravenously bolus day 1 Oral days 2-4 (decreasing course	8mg intravenously bolus day 1 Oral days 2-4 (decreasing course	8mg intravenously bolus day 1 Oral days 2-4 (decreasing course)
Cycle Repeat	14 days	21 days	14 days	14 days

Table 1: Treatment Regimens

Outcomes

Unclear what the primary outcome of the study is

Outcomes appear to include response rates, progression free survival, overall survival and quality of life.

Results

Treatment began as soon as possible after randomisation and breaks in treatment (e.g. for holidays) were not allowed within the first 3 months and were restricted to 4 weeks during the second 3 months. Thereafter patients with responding or stable disease were allowed to pause treatment, resuming the same treatment provided progression did not take place within 12 weeks of last treatment.

Second line treatment in Arm A and B were started provided the patient met the fitness criteria of the regimen, at the first evidence of progression during – or within 12 weeks if pausing – first line fluorouracil.

Patients in Arm A and B received a median of 11 cycles (range 1-51) of the allocated 1st line fluorouracil regimen and patients in arm C received a median of 12 cycles (1-36). Patients in Arm C_{OX} received a median of 12 cycles (1-58) of which oxaliplatin was included for 94% of cycles (3506/3740), median 11 cycles (1-58) per patient) the remainder were given FU alone after persistent neuropathy.

Of the 1348 patients in whom FU treatment failed at the time of analysis, 56% (n=750) had received the planned 2nd line regimen and 10% (n=131) received an alternative 2nd line regimen; 35% of patients had moved to terminal care or died without receiving further treatment.
Median amount of time spent on 2nd line combination therapy was similar in all groups. Patients in arm A received a median of 4 cycles (1-24) of irinotecan every 3 weeks, patients in group B_{IR} received a median of 6 cycles (1-23) of irinotecan + fluorouracil every 2 weeks and patients in group B_{OX} received a median of 6 cycles (1-24) of which oxaliplatin was included fro 1582/1688 (94%) of cycles (median 6 (1-21) per patient).

49% of patients (669/1368) in who allocated treatment failed had received salvage chemotherapy at the time of publishing. The proportion was higher for those in arm C (358/649, 55%) for whom treatment comprised a single line of treatment compared with arms A and B (311/719, 43%) who had already received two lines of therapy at the time of failure.
Changes to salvage chemotherapy recommendations in December 2002 meant that patients could receive all three drugs at some point, however at the time of analysis only 23% (n=482) of patients had done so with the proportion who had received all three higher in arm C (33%) than in arms A (16%) or arm B (19%). The proportions were similar for patients allocated to irinotecan in arms B and C (25%) and patients allocated to oxaliplatin (27%).

All regimens were well tolerated and sage with treatment delays or modification in less than 40% of patients at any point for all treatment regimens with one exception; 1st line oxaliplatin was delayed or modified in 50% of patients, usually for neurosensory of haematological toxic effects after several cycles.
29% (n=610) of patients had serious adverse events likely caused by the trial drugs and a further 12% (n=262) had serious adverse events related to venous access.
24 deaths were reported as definitely or probably precipitated by trial treatment with no significant difference between the regimens.
18/2093 patients receiving first line treatment and 6/755 patients receiving second line treatment died. Death occurred within 30 days of the final dose of the first line treatment in a further 130 patients and within 30 days of last second line chemotherapy in a further 42 patients. There was no imbalance in all cause mortality at day 60.

At the time of publication, 86% (n=1839) of patients had died and median follow up was 26.5 months for survivors. Survival in arms A and B was similar and was slightly better compared with arm A.

2-year survival was 22% in arm A, 25% in arm B and 28% in arm C. In pairwise log rank tests overall comparison of arm C with control (Arm A) reached p=0.02 but did not satisfy the level of p<0.01 required to confirm superiority in the context of multiple setting.

Survival was better in all subgroups of arms B and C when compared with that of arm A but only irinotecan used in first line combination was significantly better.
There was no significant difference between irinotecan and oxaliplatin whether used in the first line combination setting, second line combination or at any time.

An additional non-inferiority analysis was added to compare deferred combination treatment (arm B) with first line combination (arm C) as a result of changes to standard practice. **Hazards Ratio, 1.06 (90% CI 0.97-1.17)**. These data exclude and inferiority margin of HR 1.18 or more, corresponding to a reduction of more than 5% in 2 year survival or a difference in median survival of more than 2.3 months.
Results for the individual drugs are similar but the individual comparisons are not sufficiently powered to conclude non-inferiority.

Response rates and progression free survival for first line IrFU and OxFU regimens were significantly better than for fluorouracil alone. For patients in arm A or B that went on to receive their allotted second line treatment, the combination therapies gave higher response rates than Irinotecan alone though the rates of progression free survival were not significantly improved.

During the first 18 months from randomisation, the WHO performance status fell from 0.7 to 1.1 but no differences were observered between the groups. Mean overall quality of life score varied very little over time or across regimens with no advantage or disadvantage detected at 3 and 6 months associated with first line combination treatment (arm C).

There was no evidence that the effect of treatment on survival was different in any of the subgroups of patients defined by baseline characteristics.

Tables

	Arm A	**Arm B**		**Arm C**	
	FU followed by Irinotecan single agent	**FU followed by Irinotecan combination**	**FU followed by Oxaliplatin combination**	**Irinotecan combination**	**Oxaliplatin Combination**
Total	710	356	356	356	357
Male	494 (70%)	244 (69%)	235 (66%)	240 (67%)	247 (69%)
Age (years)	63 (56-69)	64 (57-70)	64 (56-69)	64 (57-69)	64 (56-69)
Prior Adjuvant Chemotherapy	163 (23%)	96 (27%)	89 (25%)	94 (26%)	94 (26%)
WHO performance status					
0	294 (41%)	147 (41%)	147 (41%)	147 (41%)	148 (41%)
1	355 (50%)	181 (51%)	178 (50%)	179 (50%)	179 (50%)
2	61 (9%)	28 (8%)	31 (9%)	30 (8%)	30 (8%)

Table 2: Patient Characteristics (other factors reported include primary tumour site, baseline WBC count, distant metastases, number of disease sites, disease sites)

	First line treatment			**Second line treatment**		
	FU	**IrFU**	**OxFU**	**Ir**	**IrFU**	**OxFU**
Study groups	**A, B_{IR}, B_{OX}**	**C_{IR}**	**C_{ox}**	**A**	**B_{IR}**	**B_{ox}**
Patients Assessed	1305	337	339	349	180	199
Neutropenia	118 (9%)	65 (19%)	94 (28%)	43 (12%)	32 (18%)	50 (25%)
Nausea or vomiting	55 (4%)	32 (10%)	31 (9%)	31 (9%)	9 (5%)	14 (7%)
Stomatitis	25 (2%)	6 (2%)	6 (2%)	3 (1%)	2 (1%)	6 (3%)
Diarrhoea	74 (6%)	38 (12%)	34 (10%)	58 (17%)	14 (8%)	16 (8%)
Hand/Foot Syndrome	22 (2%)	4 (1%)	4 (1%)	2 (1%)	2 (1%)	6 (1%)
Sensory Neuropathy	11 (1%)	5 (2%)	34 (10%)	3 (1%)	2 (1%)	6 (3%)
Alopecia	3 (<1%)	8 (2%)	3 (1%)	34 (10%)	5(3%)	0 (0%)
Lethargy	174 (13%)	66 (20%)	73 (21%)	59 (17%)	37 (21%)	41 (20%)
Pain	176 (14%)	73 (22%)	60 (18%)	79 (23%)	26 (14%)	39 (20%)
Treatment related death	11 (1%)	3 (1%)	4 (1%)	3 (1%)	1 (1%)	2 (1%)
60 day all cause mortality	52 (4%)	17 (5%)	14 (4%)	31 (9%)	13 (7%)	12 (6%)

Table 3: Grade 3 or 4 adverse events reported

Log Rank test Comparison	Hazard Ratio (95% CI)	p-value (two-sided test)	Median Survival in Reference Group (group A)[1]	Difference (95% CI) between reference group and comparator[2]
Are any of the novel plans better than the control				
A vs. B	0.94 (0.84-1.05)	0.24	13.9	0.9 (-0.7-2.6)
A vs. B_{IR}	0.91 (0.79-1.03)	0.16	13.9	1.4 (-0.4-3.7)
A vs. B_{OX}	0.97 (0.85-1.11)	0.65	13.9	0.4 (-1.4-2.5)
A vs. C	0.88 (0.79-0.98)	0.02	13.9	1.9 (0.3-3.7)
A vs. C_{IR}	0.84 (0.73-0.96)	0.01	13.9	2.6 (0.6-5.1)
A vs. C_{OX}	0.93 (0.81-1.06)	0.26	13.9	1.1 (0.8-3.3)
Does the choice of Irinotecan or Oxaliplatin affect survival				
[B_{IR} + C_{IR}] vs. [B_{OX} + C_{OX}]	1.09 (0.97-1.21)	0.14	15.8	-1.3 (-2.7-0.5)
B_{IR} vs. B_{OX}	1.06 (0.91-1.24)	0.46	15	-0.8 (-2.9-1.5)
C_{IR} vs. C_{OX}	1.12 (0.95-1.31)	0.18	16.7	-1.8 (-4.0-0.9)

[1]Group A is the reference group for whether any of the novel plans are better than control and irinotecan is the reference group for whether the choice of irinotecan or oxaliplatin should affect survival
[2]Difference calculated by application of log rank HR to median survival in control group

Table 4: Overall survival log rank comparison

Log Rank test comparison	HR (90% CI)	Median survival (months)		Confidently excludes detriment with strategy B larger than:[1]
		Arm C (reference)	Arm B	
C vs. B	1.06 (0.97-1.17)	15.9	15.1	2.3 months
C_{IR} vs. B_{IR}	1.08 (0.94-1.24)	16.7	15	3.2 months
C_{OX} vs. B_{OX}	1.04 (0.92-1.19)	15.4	15.2	2.5 months

[1]Estimation of the largest detriment to the comparator group that cannot be reliably excluded. It is calculated by u sing the upper end of the 90% CI in the following way: comparator median-([1/upper end of 90% CI]xcomparator median)

Table 5: Is deferred combination (arm B) non-inferior to first line combination (arm C)

	First line treatment			Second line treatment		
	Fluorouracil	Irinotecan + Fluourouracil	Oxaliplatin + Fluorouracil	Irinotecan	Irinotecan + Fluorouracil	Oxapliplatin + Fluorouracil
Study Groups	**A, B_{IR}, B_{OX}**	**C_{IR}**	**C_{OX}**	**A**	**B_{IR}**	**B_{OX}**
Total Number Treated (receiving ≥1 dose)	1393	342	344	364	185	201
Complete Response	57	19	29	8	1	3
Partial Reponse	335	147	166	31	29	43
Stable Disease (≥12 weeks)	487	89	72	107	68	74
Progressive Disease	249	40	40	149	52	50
Not Assessed[1]	265	47	37	69	35	31
Response Rate (CR+PR)[2]	28%	49% (p<0.001)[3]	57% (p<0.001)[3]	11%	16% (p=0.07)[4]	23% (p<0.001)[4]
Disease Control ≥12 weeks (CR+PR+SD)[2]	63%	75% (p<0.001)[3]	78% (p<0.001)[3]	40%	53% p=0.004)[4]	60% (p<0.001)[4]
Median Progression Free Survival (months)	6.3	8.5% (p<0.001)[3]	8.7 (p<0.001)[3]	4.3	4.4 (p=0.75)[4]	4.8 (p=0.74)[4]

[1]Includes any reason for failure to assess radiologically
[2]Denominator includes all patients who received one or more dose, whether or not subsequently assessed
[3]Compared with fluorouracil (X^2 test for response rate and disease control; log rank test for PFS
[4] Compared with Irinotecan (X^2 test for response rates and disease control; log rank test for PFS
[5]Responses did not need to be confirmed by a second scan

Table 6: RECIST[5] response and progression free survival

	Arm B	Arm C	O-E	Variance	Hazard Ratio (95% CI)
	No. events/No. entered	**No. events/No.entered**			
Sex					
Male	405/480	423/488	3.11	206.14	1.02 (0.89-1.16), p=0.828)
Female	211/231	183/225	16.54	97.89	1.18 (0.97-1.44), p=0.095
					Interaction p=0.21
Age (Years)					
<60	203/230	201/252	19.07	99.65	1.21 (1.00-1.47), p=0.056
60-69	258/304	257/290	-9.48	127.99	0.93 (0.78-1.10), p=0.402
70+	155/178	148/171	8.64	74.94	1.12 (0.89-1.41), p=0.318
					Interaction p=0.51

Primary Site					
Colon	412/467	392/452	3.27	200.09	1.02 (0.88-1.17), p=0.817
Rectum	200/237	206/253	14.21	100	1.15 (0.95-1.40), p=0.155
					Interaction p=0.31
Prior Adjuvant Fluorouracil					
Yes	155/185	159/189	-1.61	77.97	0.98 (0.78-1.22), p=0.855
No	460/523	447/523	20.51	225.33	1.10 (0.96-1.25) p=0.172
					Interaction p=0.40
WHO Performance Status					
0	243/293	240/295	7.34	120.3	1.06 (0.89-1.27), p=0.503
1	318/358	310/358	5.93	156.18	1.04 (0.89-1.22), p=0.635
2	55/59	56/60	9.52	26.13	1.44 (0.98-2.11), p=0.063
					Interaction p=0.38
WBC					
<10x10^9/L	444/526	438/526	4.48	219.78	1.02 (0.89-1.16), p=0.763
≥10x10^9/L	169/181	166/184	19.16	80.84	1.27 (1.02-1.58), p=0.033
					Interaction p=0.1
Number of Disease Sites					
1	195/242	157/205	5.84	86.91	1.07 (0.87-1.32), p=0.14
2	252/285	281/322	18.66	130.36	1.15 (0.97-1.37) p=0.102
>2	169/185	168/186	6.03	83.69	1.07 (0.87-1.33) p=0.51
					Interaction p=0.97
Type of Disease					
Measurable	594/684	583/687	25.26	292.98	1.09 (0.97-1.22), p=0.14
Unmeasurable	21/25	20/22	-3.46	9.81	0.7 (0.38-1.31), p=0.27
					Interaction p=0.18
Total	616/709	606/711	19.68	304.32	1.07 (0.95-1.19), p=0.259

Table 7: Overall Survival arm B or Arm C according to subgroups (forest plot is presented in the article)

General comments
Kaplan-Meier curves were produced for overall survival

Citation: Saltz L,Cox, J, Blanke C, Rosen L, Fehrenbacher L et al (2000) Irinotecan plus fluorouracil and leucovorin for metastatic colorectal cancer *New England Journal of Medicine* 343;13:905-915

Design: Randomised Trial

Country: Multiple

Setting: Multicentre

Aim: to compare a combination of irinotecan, fluorouracil and leucovorin with bolus doses of fluorouracil and leucovorin as first line therapy for metastatic colorectal cancer.

Inclusion criteria
Histologically documented colorectal cancer and measurable metastatic disease
ECOG performance status 0-2
Adequate organ function
Patients receiving adjuvant fluorouracil based therapy if they remained free of disease for at least one year after completion of therapy

Exclusion criteria
Prior therapy for metastatic disease
Pelvic irradiation

Sample Size
Based on a median progression free survival with fluorouracil and leucovorin of 5 months, it was estimated that 220 patients would be needed in each group in order to detect a 40% improvement in median progression free survival, to seven months with triple drug therapy with a power of 0.85.

Randomisation Method
Patients were stratified according to age (<65 years versus ≥65 years), ECOG performance status (0 versus 1-2), interval from diagnosis to enrolment (<6 months versus ≥6 months) and history of adjuvant therapy with fluorouracil (yes versus no) and then randomly assigned to one of three treatment arms.

Population
N=683

Intent to treat population:
Arm A (Irinotecan+5FU+LV): 231
Arm B (5FU+LV): 226
Arm C (Irinotecan): 226

Treated Population
Arm A (Irinotecan+5FU+LV): 225
Arm B (5FU+LV): 219
Arm C (Irinotecan): 223

Study Duration
Recruitment Phase: May 1996-May 1998
Data were collected for 19 months after accrual ended, with survival data collected through December 199

Interventions
Arm A: Irinotecan 125mg/m^2 of body surface area intravenously over 90 minutes, leucovorin 20mg/m^2 as an IV bolus and fluorouracil 500mg/m^2 as an IV bolus; each given weekly for 4 weeks every 6 weeks.

Arm B: leucovorin 20mg/m^2 as an IV bolus and fluorouracil 425mg/m^2 as an IV bolus; each given daily for 5 days (on days 1-5) every 4 weeks.

Arm C: Irinotecan 125mg/m^2 intravenously over 90 minutes; given weekly for 4 weeks every 6 weeks

Outcomes
Progression free survival (defined as length of time from randomization to disease progression or to death from disease progression or unknown causes).

Results
The arms were balanced for all baseline characteristics apart from the proportion of men which was greater in arm A compared with arm B (65% versus 54%, p=0.02).

Median duration of treatment was 5.5 months in arm A, 4.1 months in arm B and 3.9 months in arm C.
Median relative dose intensity of irinotecan was 72% in arm A and 75% in arm C; median relative dose intensity of fluorouracil was 71% in arm A and 86% in arm B.

Efficacy
Progression free survival was significantly longer in arm A compared to arm B (median 7.0 versus 4.3 months, p=0.004); median progression free survival in arm C was 4.2 months.

Objective response rate was 50% in arm A and 28% in arm B (p<0.001); the rates of objective response that were confirmed by imaging 4-6 weeks later were also significantly higher among patients in arm A compared with arm B (39 versus 21%, p<0.001).
The rates of objective and confirmed response in arm C were 29% and 18% respectively.
A complete response was seen in 6 patients in arm A, 2 patients in arm B and 4 patients in arm C.
Median duration of confirmed response was approximately 9 months for all arms.

The median survival of patients in arm A was 14.8 months as compared with 12.6 months among patients in arm B (p=0.04); median survival of patients in arm C was 12 months.

Mutiple regression modelling of the rates of objective response revealed no interactions between treatment and the stratification factors or other potentially prognostic factors.

Factors predictive of improved progression free survival and overall survival were a normal lactate dehydrogenase level and a performance status of 0.
Haemoglobin levels of at least 11g/dL and a normal white cell count were predictive of better progression free survival and overall survival respectively.
An age of 65 years or older was associated with better progression free survival.
Treatment with Irinotecan, fluorouracil and leucovorin was a significant independent predictor of longer progression free survival (p<0.001) and overall survival (p=0.03) when other significant baseline characteristics were taken into account.
Treatment with irinotecan, fluorouracil and leucovorin was associated with a 36% reduction in the risk of progression and a 22% reduction in the risk of death relative to treatment with fluorouracil an leucovorin alone.
In the comparison of irinotecan, fluorouracil and leucovorin with fluorouracil and leucovorin, the reduction in the risk of death among patients with a normal lactate dehydrogenase level was 43% as compared with a reduction of 12% among those with elevated levels, suggesting a possible interaction of the lactate dehydrogenase level with treatment with respect to survival (p=0.07).

Adverse Effects
22.7% of patients in arm A hadgrade 3/4 diarrhoea as compared with 13.2% of patients in arm A and 31% of patients in arm C.

Quality of Life
No significant differences between arm A and arm B were observed in relation to quality of life. In univariate analysis comparing the greatest worsening in the QoL from base line, the mean increases in the severity of symptoms were smaller in arm A compared with arm B in respect to fatigue, anorexia and pain.
As indicated by the measurement of the greatest declies from base line in role functioning (the ability to perform the activities of daily living), arm A had a smaller decrease in function compared with arm B.

Tables

	Irinotecan, fluorouracil and leucovorin (n=231)	**Fluorouracil and leucovorin (n=226)**	**Irinotecan Alone (n=226)**
	N (%)	**N (%)**	**N (%)**
Sex			
Male	151 (65)	123 (54)	145 (64)
Female	79 (34)	101 (45)	80 (35)
Not Available	1 (<1)	2 (1)	1 (<1)

Age, years			
Median	62	61	61
Range	25-85	19-85	30-87
<65	139 (60)	136 (60)	135 (60)
≥65	91 (39)	88 (39)2 (1)	90 (40)
not available	1 (<1)		1 (<1)
ECOG Performance Status			
0	89 (39)	93 (41)	104 (46)
1	106 (46)	102 (45)	103 (46)
2	35 (15)	29 (13)	18 (8)
Not available	1 (<1)	2 (1)	1 (<1)
Time from Diagnosis to randomisation, months			
Median	1.9	1.7	1.8
Range	0.1-161	0.1-203	0.1-185
Prior adjuvant fluorouracil			
Yes	25 (11)	18 (8)	23 (10)
No	206 (89)	208 (92)	203 (90)
Prior radiotherapy			
Any	7 (3)	5 (2)	3 (1)
Pelvis or abdomen	4 (2)	2 (1)	3 (1)
Other sites	3 (1)	3 (1)	0

Table 1: Baseline patient characteristics

	Irinotecan, fluorouracil and leucovorin (n=231)	**Fluorouracil and leucovorin (n=226)**	**p**	**Irinotecan Alone (n=226)**
Median Progression Free Survival	7.0	4.3	0.004	4.2
Objective Response Rate	50	28	<0.001	29
Confirned Objective Response Rate	39	21	<0.001	18
Median Duration of Confirmed Response	9.2	8.7	0.37	9.0
Median Overall Survival	14.8	12.6	0.04	12.0

Table 2: Intention to treat analysis of efficacy

	Progression Free Survival		**Overall Survival**	
	Hazard Ratio (95% CI)	**P**	**Hazard Ratio (95% CI)**	**P**
Serum lactate dehydrogenase (≤UNL vs. >UNL)	0.60 (0.47-0.76)	<0.001	0.47 (0.36-0.60)	<0.001
No. of involved organs (1 vs. ≥2)	0.63 (0.50-0.80)	<0.001	0.67 (0.54-0.83)	<0.001
Performance Status (0 vs. 1 or 2)	0.74 (0.59-0.93)	0.009	0.56 (0.44-0.70)	<0.001
Bilirubin Level (≤UNL vs. >UNL)	0.56 (0.35-0.89)	0.01	0.53 (0.33-0.83)	0.005
White Blood Cell count (<8x10^3/mm^3 vs. 8x10^3/mm^3)			0.65 (0.52-0.82)	<0.001
Haemoglobin level (≥11g/dl vs. <11g/dl)	0.74 (0.58-0.95)	0.02		
Age (≥65 yr vs. <65 yr)	0.78 (0.63-0.98)	0.03	0.82 (0.65-1.02)	0.08
Treatment (Irinotecan+FU+ LV vs. FU+LV)	0.64 (0.51-0.79)	<0.001	0.78 (0.63-0.97)	0.03

Table 3: Results of Cox regression Analysis

	Irinotecan, fluorouracil and leucovorin (n=225)	**Fluorouracil and leucovorin (n=219)**	**Irinotecan Alone (n=223)**
Diarrhoea			
Grade 3 or 4	22.7	13.2	31
Grade 3	15.1	5.9	18.4
Grade 4	7.6	7.3	12.6
Vomiting			
Grade 3 or 4	9.7	4.1	12.1
Grade 3	5.3	2.7	5.8
Grade 4	4.4	1.4	6.3
Mucositis			
Grade 3 or 4	2.2	16.9	2.2
Grade 3	2.2	14.6	1.8
Grade 4	0	2.3	0.4
Neutropenia			
Grade 3 or 4	53.8	66.2	31.4
Grade 3	29.8	23.7	19.3
Grade 4	24	42.5	12.1
Neutropenic Complications			

Fever	7.1	14.6	5.8
Infection	1.8	0.0	2.2
Discontinuation due to adverse events	7.6	6.4	11.7
Drug related deaths	0.9	1.4	0.9

Table 5: Adverse Events

General comments

Kaplan Meier Curves for Progression free survival and overall survival

Citation: Souglakos J, Androulakis N, Sygrigos K, Polysos A (2006) FOFLFOXIRI (folinic acid, 5 fluorouracil, oxaliplatin and irinotecan) versus (folinic acid, 5 fluorouracil and irinotecan) as first line treatment in metastatic colorectal cancer (MCC): a multicentre randomised phase III trial from the Hellenic Oncology Research Group (HORG) *British Journal of Cancer* 94;6:798-805

Design: Randomised Trial

Country:

Setting:

Aim: to evaluate the efficacy and safety of the FOLFOXIRI regimen in comparison with the standard combination of FOLFIRI regimen as first line treatment in patients with advanced colorectal cancer.

Inclusion criteria
Histologically documented and measurable adenocarcinoma of the colon or rectum
Prior adjuvant chemotherapy if patients had remained disease free for at least 6 months after completion
ECOG performance status 0-2
At least one bidemensionally measurable lesion of ≥2cm
Life expectancy of at least 3 months
Adequate haematological parameters
Creatinine and total bilirubin ≤1.25 times the upper limit of normal
Aspartate and alanine aminotransferases ≤3.0 times the upper limit of normal
Measurable metastatic disease outside of irradiation fields for patients receiving palliative radiotherapy

Exclusion criteria
Previous chemotherapy for metastatic disease
Patients with operable metastatic disease
Active infection of malnutrition (loss of more than 10% of body weight)
Severe cardiac dysfunction
Liver metastases involving more than 50% of the liver parenchyma
Chronic diarrhea
Prior radiation affecting more than 30% of the active bone marrow

Sample Size
Using Freedman's formula, 136 patients per arm were required with the assumption that the accrual period would last 48 months. The study was designed to detect a 25% improvement in survival for the experimental arm, based on the assumption that overall survival would be 17 months in the standard arm (FOLFIRI) and 22.5 months for the experimental arm (FOLFOXIRI) (type 1 error 5%, type II error 20%).

Randomisation Method
Minimisation method with stratification for centre, prior adjuvant chemotherapy (yes or no), and ECOG performance status (0-1 vs. 2)

Population
N=285 (147 in Arm A and 138 in Arm B)

Study Duration
Recruitment Phase: October 2000 – December 2004

Interventions
FOLFIRI: Irinotecan 180mg/m^2 as a 30 minute i.v. infusion on day 1, LV 200mg/m^2 as a 2hour i.v. infusion followed by 5-FU 400mg/m^2 as i.v. bolus and then 600mg/m^2 as a 22hour continuous i.v. infusion on days 1 and 2.

FOLFOXIRI: Irinotecan 150mg/m^2 as a 30 min infusion on day 1, LV 200mg/m^2 as a 2 hour i.v. infusion, followed by 5-FU 400mg/m^2 as i.v. bolus and then 600mg/m^2 as a 22 hour continuous i.v. infusion on days 2 and 3. Oxaliplatin 65mg/m^2 on day 2 as 2 hour i.v. infusion in parallel with LV but using different lines.

Treatment was administered every two weeks until disease progression or unacceptable toxicity or until patient declined further treatment.

Outcomes
Overall Survival

Time to progression (defined as the interval between start of treatment and date of first documented progression or death from any cause)
Response Rate
Tolerance

Results

Efficacy
Median follow up was 26 months (range 1-62 months) after which 85% of patients had disease progression and 62% of patients had died.

Overall survival was not significantly different between the two arms; 19.5 months (range 1-55.7) in the FOLFIRI arm and 21.5 months (range 1-62.3) in the FOLFOXIRI arm.
The probability of 1 and 2 year survival was 64% and 34% in the FOLFIRI arm and 67% and 43% in the FOLFOXIRI arm.
Independent prognostic factors for decreased survival were performance status of 2 and non response to treatment with **Hazard Ratio 2.5 (95% CI; 1.701-3.703, p=0.0001)** and **2.102 (95% CI; 1.598-2.765, p=0.0001)** respectively.
Age, treatment arm and prior adjuvant chemotherapy were not significant factors for patient outcome.

Overall survival in the FOLFIRI group was 20 months for patients with performance status 0-1 and 6.4 months for patients with performance status 2 (p=0.03) and in the FOLFOXIRI group overall survival was 24 months for patients with performance status 0-1 and 6.6 months for patients with performance status 2 (p=0.0001). There was no statistical difference in terms of overall survival in the young or aged patients irrespective of the treatment regimen:
FOLFIRI: <65 years overall survival = 19.9 months and ≥65 years overall survival = 16.9 months (p=0.452)
FOLFOXIRI: <65 years overall survival = 22.1 months and ≥65 years overall survival = 19.9 months (p=0.263)

Patients in the FOLFIRI arm that went on to receive second line treatment had a significantly better overall survival when compared with patients that did not (median overall survival 21 months (range: 15.9-55.7) versus 12.2 months (range; 7.82-16.64); p=0.016).

Median time to disease progression was 6.9 months (95% CI 6.0-7.7 months; range 1.0-39.3) for patients receiving FOLFIRI and 8.4 months (95% CI 7-1.02 months; range 1.0-32.3) for patients receiving FOLFOXIRI; **Hazard Ratio=0.83 (95% CI; 0.64-1.08; p=0.17)**.

In the FOLFIRI arm, time to progression was 7.1 months (range 1-39.3) for patients with performance status of 0-1 and 2 months (range 1-10.7) for patients with performance status of 2 (p=0.0001).
In the FOLFOXIRI arm, time to progression was 9.7 months (range 1-32.3) and 4.1 months (range 1-15.9) for patients with performance status 0-1 and 2 respectively (p=0.0047).
On Cox multivariate analysis performance status of 2, **(Hazard Ratio 1.857, 95% CI; 1.217-2.834, p=0.004)** and no response to treatment **(Hazard Ratio 2.166, 95% CI; 1.553-3.020, p=0.0001)** were independent prognostic factors for time to progression.

Response to Treatment
In the FOLFIRI arm there were 5 (3.4%) complete response and 9 (6.5%) in the FOLFOXIRI arm; in addition 44 (30.2%) and 50 (36.5%) patients in the enrolled in the FOLFIRI and FOLFOXIRI arm respectively experienced a partial response for an overall response rate of 33.6% for FOLFIRI and 43% for FOLFOXIRI (p=0.168).
39 (26.7%) patients treated with FOLFIRI and 43 (31.3%) patients treated with FOLFOXIRI had disease stabilisation while 58 (39.7%) and 35 (25.5%) respectively patients progressed under treatment.
Median time of response duration was 9 months (range: 1-27) in the FOLFIRI arm and 9.7 months (range: 1-34.6) in the FOLFOXIRI arm (p=0.44).

Secondary metastasectomy was performed in six (4%) patients in the FOLFIRI arm and 14 (10%) patients in the FOLFOXIRI arm (p=0.08). 6 patients (3 in each arm) underwent resection of lung metastases and 14 patients (3 in FOLFIRI and 11 in FOLFOXIRI) underwent resection of liver metastases.
R0 resection could be achieved in all patients with lung lesions and 11 patients with liver metastases.

Compliance with treatment

A total of 1212 treatment cycles were administered in the FOLFIRI arm and 1179 in the FOLFOXIRI arm; median number of cycles was 9 (range 1-22) and 10 (range 1-20) per patient treated with FOLFIRI and FOLFOXIRI respectively.

A total of 101 (8.3%) chemotherapy courses in the FOLFIRI and 166 (14%) in the FOLFOXIRI arm were delayed (p=0.04); median duration of the delay was 4 days (range 1-14) in each arm.
Reasons for delay included haematologic and/or nonhaematologic toxicity and 54 (4%) courses in the FOLFIRI arm and 55 (5%) in the FOLFOXIRI arm were delayed for reasons unrelated to disease or treatment.
Median interval between cycles was 16 days in both treatment arms.
Dose reduction was required in 40 (3%) cycles in the FOLFIRI arm and in 87 (7%) cycles in the FOLFOXIRI arm (p=0.001).
In the FOLFIRI arm 10 (7%) patients discontinued treatment while 16 (12%) discontinued treatment in the the FOLFOXIRI arm (p=0.296); reasons included haemotologic and non haematologic toxicity.
Delivered relative dose intensity was 85% for Irinotecan, 84% for oxaliplatin and 88% for 5FU/LV of the protocol planned dose for FOLFOXIRI and 90% for Irinotecan and 92% for 5FU/LV in the FOLFIRI arm.

Toxicity
There was significantly higher incidence of severe alopecia (p=0.0001), diarrhoea (p=0.001) and neurosensory disorders (p=0.001) in the FOLFOXIRI arm compared with the FOLFIRI arm.
There was no significant difference in the incidence of severe (grade 3/4) haematological toxicity.
There were 2 treatment related deaths in each arm, all related to febrile neutropenia and diarrhoea.
Death rates within the first 60 days of treatment were 2.7% (95% CI, 1.1-4.6%) for patients treated with FOLFIRI and 2.9% (95% CI, 1.3-5.3%) for patients treated with FOLFOXIRI.
Patients with performance status of 2 had significantly higher incidence of grade 3/4 diarrhoea (p=0.001), neutropenia (p=0.001), fatigue (p=0.0001) and febrile neutropenia (p=0.02) when compared to patients with performance status of 0-1 in both treatment arms.
Patients older than 65 years showed significantly higher incidence of grade 3/4 diarrhoea when compared with younger patients in both treatment groups (p=0.005 for FOLFIRI and p=0.017 for FOLFOXIRI).
There was no difference in toxicity for patients who had previously received adjuvant chemotherapy or radiotherapy.

Second line treatment
Second line treatments were not protocol specified though there was a requirement to report them. A higher proportion of patients treated with FOLFIRI received second line treatment (70%), the majority of whom were treated with oxaliplatin based therapy (XELOX or FOLFOX).
58% of patients in the FOLFOXIRI arm received second line treatment compared with the 70% in the FOLFIRI arm (p=0.041) with a small proportion receiving Irinotecan and cetuximab.

Tables

	FOLFIRI (n=146)	**FOLFOXIRI (n=137)**
	N (%)	**N (%)**
Age		
Median (range	66 (39-84)	66 (25-82)
≥65 years	82 (56)	75 (55)
Sex		
Male	82 (58)	76 (55)
Female	61 (42)	61 (45)
ECOG Performance Status		
0	55 (38)	49 (36)
1	74 (51)	73 (53)
2	17 (11)	15 (11)
Kohne Prognostic Index		
Low Risk	54 (37)	44 (32)
Intermediate Risk	57 (39)	56 (41)
High Risk	35 (24)	37 (27)
Prior Therapy		
Adjuvant Chemotherapy	48 (33)	49 (36)
Adjuvant Chemoradiotherapy	18 (12)	17 (12)

Table 1: Patient Characteristics (other reported factors include location, number of metastatic sites, metastases)

	FOLFIRI (146)	**FOLFOXIRI (130)**		**FOLFIRI (146)**	**FOLFOXIRI (130)**	

	Any (%)		P	Grade 3/4 (%)		P
Neutropenia	60	73	NS	28	35	0.192
Febrile Neutropenia	6	9	NS	4	7	0.186
Thrombocytopenia	20	31	NS	4	2	0.4
Anaemia	59	60	NS	1	4	0.072
Nausea/Vomiting	45	52	NS	4.8	4.6	0.944
Diarrhoea	51	69	NS	10.9	27.7	0.0001
Mucositis	18	21	NS	4	5	0.748
Neurological	11	59	0.001	0	5.8	0.001
Cutaneous	15	21	NS	3	4	0.133
Alopecia	56	74	NS	12	32	0.0001
Fatigue	36	41	NS	5	5.6	0.944

Table 2: Incidence of common toxicities

	FOLFIRI	FOLFOXIRI	
Second line treatment	**N (%)**	**N (%)**	**P**
Any	102 (70)	80 (58)	0.041
Oxaliplatin Based	92 (63)	39 (28)	0.029
Irinotecan Based	10 (6)	14 (10)	NS
Fluoropyrimidines	44 (30)	29 (21)	NS
Cetuximab	10 (7)	7 (5)	NS

Table 3: Second Line Therapies

General comments

Kaplan Meier Curves presented for overall survival and time to tumour progression.

Citation: Tournigand C, Andre T, Achille R, Lledo G, Flesh M et al. (2004) FOLFIRI followed by FOLFOX6 or the reverse sequence in advanced colorectal cancer: A randomised GERCOR study *Journal of Clinical Oncology* 22;15:229-237

Comparison FOLFIRI → FOLFOX versus FOLFOX → FOLFIRI (Sequence)

Design: Randomised Trial

Country: France

Setting: Hospital Outpatients

Aim: To evaluate FOLFIRI and FOLFOX6 and determine the best sequence to treat patients with metastatic colorectal cancer

Inclusion criteria
Adenocarcinoma of the colon or rectum
Unresectable metastases
At least one bidimensionally measurable lesion of ≥2cm or a residual non measurable lesion
Adequate bone marrow, liver and renal function
WHO Performance Status of 0-2
Age 18-75 years
Previous chemotherapy to be completed at least 6 months prior to inclusion

Exclusion criteria
Patients with CNS metastases
Patients with second malignancies
Patients with bowel obstruction
Current diarrhea ≥ grade 2
Symptomatic angina pectoris
Disease confined to previous radiation fields

Sample Size
The study was designed for the two-sided log rank test to have 80% power to detect a 20% difference in the proportion of patients without progression at 15 months (60% in Arm A, 40% in Arm B, type I error of 5%, type II error of 20%).
Using Freedmans formulas, 109 patients and 49 events per arm were required.

Randomisation Method
Minimisation technique, stratifying patients by centre and by presence or absence of measurable disease

Population
N=226 randomly assigned with 6 patients ineligible (4 in Arm A and 2 in Arm B)

N=220 analysed

Study Duration
Recruitment Stage: Dec 1997-Sept 1999

Cutoff date for progression free survival was March 31st 2001 and for overall survival was August 30, 2002 with a median potential follow up for the entire cohort of 43.9 months.

Interventions
FOLFIRI consisted of *l*-LV 200mg/m^2 or *dl*-LV 400mg/m^2 as a 2 hour infusion and irinotecan given as a 90 minute infusion in 500ml dextrose 5% via a Y connector, followed by bolus FU 400mg/m^2 and a 46 hour infusion FU 2,400mg/m^2 for two cycles increased to 3,000mg/m^2 from cycle 3 in case of no toxicity > grade 1 during the first two cycles, repeated every 2 weeks.
FOLFOX6 consisted of the same LV+FU regimen with the addition of oxaliplatin 100mg/m^2 on day 1, given as a 2 hour infusion in 500ml dextrose 5%, concurrent with LV.
Antiemetic prophylaxis with a $5HT_3$-receptor antagonist was administered.

Arm A: FOLFIRI until progression or unacceptable toxicity then FOLFOX6
Arm B: FOLFOX6 until progression or unacceptable toxicity then FOLFIRI

In case of toxicity imputed to oxaliplatin or irinotecan during first line therapy and no progressive disease patients could receive LV+FU alone until progression and then the second regimen.

Treatment continued until disease progression, unacceptable toxicity or patient choice.

Outcomes
Primary Outcome: second progression free survival (time duration from randomisation to progression after 2nd line chemotherapy). If a patient could not receive 2nd line treatment or refused 2nd line, progression free survival on the first line was used instead.

Secondary outcomes: Progression free survival (no details), overall survival, response rates and safety

Results
Characteristics of the patients were well balanced between the groups apart from sex ratio with the percentage of males in Arm A lower than in Arm B (57% versus 72%) and age >65 with a slightly lower percentage in Arm A.

Progression Free Survival
First line therapy
According to external review, median progression free survival was 8.5months (95% CI, 7-9.5) for Arm A and 8 months (95% CI, 6.2-9.4) for Arm B (p=0.26). Note: these are the figures used in the Kaplan Meier plots.

Second line therapy
According to external review, median progression free survival was 4.2 months (95% CI, 3.7 to 5.2) for Arm A versus 2.5 months (95% CI, 2.1-3.3) for Arm B (p=0.003). Note: these are the figures used in the Kaplan Meier plots.

Median delay between progression on first line and first cycle of second line was 21 days in Arm A versus 15 days in Arm B (p=0.27).

As of March 31, 2001, 74% (n=81) of patients had received per protocol FOLFOX6, second line therapy in Arm A and 62% (n=69) of patients had received FOLFIRI second line in Arm B, including one patient who received FOLFOX6 instead on FOLFIRI.
Eight patients in both arms received a second line of treatment out of study; 3 in Arm A and 5 in Arm B received the second line after the cut-off date.

Five patients in Arm A and 8 in Arm B had no tumour progression after first line treatment.
11% (n=12) of patients in arm A and 15% (n=17) of patients in Arm B could not receive second line treatment due to death, poor performance status or refusal.

Second progression free survival: According to external review, median second progression free survival was 14.2 months (95% CI12-16.9) for Arm A and 10.9 months (95% CI, 9-14.6) for Arm B (p=0.64).
At 15 months, progression free survival was 47.2% in Arm A and 37.3% in Arm B.

Independent prognostic factors for improved second progression free survival were: good performance status (p=0.001), low lactate dehydrogenase (p=0.011), no prior adjuvant chemotherapy (p=0.001) and female sex (p=0.043).

Overall Survival
Median overall survival was 21.5 months (range, 16.9 – 25.2) for Arm A versus 20.6 months for Arm B (range 17.7 to 24.6 months) (p=0.99).
Independent prognostic factors for improved OS were: good performance status (p<0.0001), low lactate dehydrogenase (p<0.001), no prior adjuvant chemotherapy (p=0.001), low alkaline phosphatise (p=0.012), metastasis confined to the liver (p=0.016), carcinoembryonic antigen (p=0.016) and female sex (p=0.048).

Objective Tumour Responses
First line Therapy
Three (2.8%) complete responses were observed with FOLFIRI versus 5 (4.5%) with FOLFOX6.
The response rates were 56% (95% CI, 47% - 65%) with FOLFIRI and 54% (95% CI, 45%-63%) with FOLFOX6.
Median time to response in Arm A was 2.1 months and in Arm B was 1.8 months (p=0.02). Response lasted a median of 11 months for Arm A and 10.6 months for Arm B.

Good performance status (p=0.001) and liver only metastasis (p=0.004) were significant independent prognostic factors.

9% (n=10) of patients in Arm A and 22% (n=24) underwent secondary surgery to remove metastases (p=0.02); 30 patients had a single metastatic site, 3 had two sites and 1 had three sites.
The mean number of cycles given before surgery was 12 cycles of FOLFIRI and 10 cycles of FOLFOX6.
According to expert review, 7% (n=8) of patients in Arm A and 13% (n=14) of patients in Arm B had a R0 resection (p=.26). In addition, 2 patients underwent a second or third surgical resection.

Median overall survival in patients who had surgery was 47 months in Arm A and was not reached in Arm B (p=0.96).

Second line therapy
The response rates were 15% (95% CI, 7% - 23%) with FOLFOX6 second line and 4% (95% CI, 0% - 9%) with FOLFIRI second line (p=0.05).
In second line therapy, the investigators assessments of objective response were 21% and 6% respectively.
Secondary surgery to remove metastases after second line therapy could be performed in two patients in Arm A and one in Arm B.

Toxicity
First line therapy
Patients in Arm A received a median of 13 cycles (1-43) of FOLFIRI and patients in Arm B received a median of 12 cycles (range 1-38) of FOLFOX6.
There was one therapy related death in Arm B as a result of haematological toxicity.
Grade 3 sensory neurotoxicity, grade 3/4 neutropenial and thrombocytopenia were significantly more frequent with FOLFOX6 than with FOLFIRI.
Grade 3/4 febrile neutropenia, nausea/vomiting, mucositis and fatigue were significantly more frequent with FOLFIRI than with FOLFOX6.
More grade 2 alopecia was observed with FOLFIRI than with FOLFOX6.

34% of patients in Arm B developed grade 3 sensory neurotoxicity , 13% (n=5) recovered within 1 month and 31% (n=12) recovered within 3 months.

More patients experienced grade 3/4 toxicities with FOLOX6 than with FOLFIRI (74% versus 53%, p=0.001) but more patients had serious adverse events with FOLFIRI than with FOLFOX6 (14% versus 5%, p=0.03).

6% (n=6) patients had to stop FOLFIRI first line as a result of toxicity compared with 11% (n=12) patients on FOLFOX first line. 4% (n=4) of patients in Arm A and 3% (n=3) patients in Arm B died during the first 60 days in first line therapy.

Elderly patients (>65 years; n=90) did not experience increased toxicity in the first line therapy as compared with younger subjects.

Second line therapy
Patients in Arm A received a median of 8 cycles (range, 2-23) of FOLFOX6 and patients in Arm B received a median of 6 cycles (range, 1-33) of FOLFIRI.
There were no therapy related deaths and the toxicity profile in each regimen showed minor differences compared with first line therapy.
Grade 3/4 neutropenia and thrombocytopenia and neurotoxicity were more frequent with FOLFIRI while gastrointestinal toxicities were more frequent with FOLFOX6.
19% of patients that developed Grade 3 neurotoxicity on first line oxaliplatin still had grade 3 neurotoxicity when starting second line FOLFIRI.

49% of patients in Arm A and 44% of patients in Arm B experienced grade 3/4 toxicities. Serious adverse events occurred in 4% of patients in Arm B and in 6% of patients in Arm A.
12% (n=10) of patients in Arm A and 1% (n=1) of patients in Arm B had to stop treatment due to toxicity.
Elderly patients (>65 years; n=59) did not experience increased toxicity as compared with younger subjects.
4% (n=3) of patients in Arm A and 3% (n=3) of patients in Arm B died during the first 60 days in second line therapy.

Vascular events were reported in 3 cases; pulmonary embolism in one FOLFIRI first line patient and one FOLFOX6 second line patient and a third patient who developed congestive heart failure on first line FOLFOX6.

Dose Intensity

On FOLFIRI first line, the FU dose could be increased for 615 cycles (39%) versus 406 cycles (29%) on FOLFOX6.

22% of patients in FOLFIRI first line and 34% of patients on FOLFOX6 first line received FU 3,000mg/m^2 for at least one cycle.

In second line, 11% of patients in FOLFIRI first line and 10% of patients in FOLFOX6 first line received FU 3,000mg/m^2 for at least one cycle.

Relative dose intensity for Irinotecan was 85.9% in first line and 87.3% in second line and for oxaliplatin relative dose intensity was 84.7% in first line and 90.1% in second line.

Weight and Performance Status

35% (n=38) of patients in Arm A and 23% (n=25) in Arm B recorded a weight increase of at least 5% (p=0.05).

Performance status (PS) improved with 18/52 assessable patients with PS>0 (35%) on FOLFIRI and 19/57 assessable patients with PS>0 (33%) on FOLFOX6 (p=0.99).

6% (n=4) of patients receiving second line FOLFIRI and 9% (n=7) of patients on FOLFOX6 recorded a weight increase of at least 5% (p=0.55).

Performance status improved with 12/24 assessable patients with PS>0 (35%) on FOLFIRI and 9/35 assessable patients with PS>0 (26%) on FOLFOX6 (p=0.44).

Tables

Parameter	Arm A: FOLFIRI/FOLFOX6	Arm B: FOLFOX6/FOLFIRI
	No. of Patients (%)	**No. of Patients (%)**
Demographic Characteristics		
No. of Patients	109 (100)	111 (100)
Male	62 (57)	80 (72)
Female	47 (43)	31 (28)
Age, years		
Median	61	65
Range	29-75	40-75
WHO Performance Status		
0	48 (45	52 (47)
1	42 (39)	52 (47)
2	18 (17)	7 (6)
Adjuvant Chemotherapy		
Yes	19 (17)	23 (21)
No	90 (83)	88 (79)

Table 1: Patient Characteristics (other details recorded in the study include primary tumour site, metastases, metastatic site, no. of sites, CEA and alkaline phosphatise)

	First Line		Second Line	
	Arm A: FOLFIRI/FOLFOX6 (n=109)	**Arm B: FOLFOX/FOLFIRI (n=111)**	**Arm A: FOLFIRI/FOLFOX6 (n=81)**	**Arm B: FOLFOX/FOLFIRI (n=69)**
Event Rate	**No. of patients (%)**	**No. of patients (%)**	**No. of patients (%)**	**No. of patients (%)**
Overall Response Rate	61 (56)	59 (54)	12 (15)	3 (4)
Complete Response	3 (3)	5 (5)	0 (0)	0 (0)
Partial Response	58 (53)	54 (49)	12 (15)	3 (4)
Stable Disease	25 (23)	30 (27)	39 (48)	21 (30)
Progression	15 (14)	14 (13)	15 (19)	35 (51)
Not Assessable	8 (7)	8 (7)	15 (19)	10 (14)

Table 2: Objective Tumour Response after external review

	First Line									Second Line								
	Arm A: FOLFIRI (n=110)[1]				**Arm B: FOLFOX6 (n=110)[1]**					**Arm A: FOLFOX6 (n=82)**				**Arm B FOLFIRI (n=68)**				
Toxicity	**1**	**2**	**3**	**4**	**1**	**2**	**3**	**4**	**P (Grade 3/4)**	**1**	**2**	**3**	**4**	**1**	**2**	**3**	**4**	**P (Grade 3/4)**
Neutropenia	19	33	15	9	18	20	31	13	0.003	17	24	15	2	21	18	21	0	NS
Thrombocytopenia	15	1	0	0	57	21	5	0	0.01	59	9	0	1	34	4	0	0	NS

Anemia	27	12	2	1	39	12	3	0	NS	35	9	2	1	49	13	3	0	NS
Febrile Neutropenia		0	4	3		1	0	0	0.007	0	0	0	0	0	0	1	0	NS
Nausea	29	30	13	0	39	25	3	0	0.005	37	21	6	0	26	21	0	0	0.03
Vomiting	17	23	8	2	22	17	3	0	0.027	17	17	4	1	16	16	3	0	NS
Diarrhoea	26	23	9	5	28	13	9	2	NS	22	7	4	1	29	16	7	1	NS
Mucositis	26	15	10	0	35	10	1	0	0.003	24	10	4	0	15	7	3	0	NS
Cutaneous	18	5	2	0	17	5	2	0	NS	21	2	1	0	12	1	0	0	NS
Alopecia	36	24	N/A	N/A	19	9	N/A	N/A	0.003[2]	13	9	N/A	N/A	26	13	N/A	N/A	NS
Neurological	10	0	0	N/A	26	37	34	N/A	<0.001	45	29	20	0	1	0	1	0	<0.001
Fatigue	15	27	4	0	17	15	3	0	0.028[3]	9	22	5	0	12	21	1	0	NS

[1]*One patient randomised in Arm B received FOLFIRI as first line*
[2]*Comparison grade 2*
[3]*Comparison grade 2-3*

Table 3: Percentage frequency of Common Toxicities

General comments

Kaplan-Meier curves for progression free survival in first line and second line therapy, time to second progression and overall survival are presented.