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ORIGINAL REPORT

FOLFIRI Followed by FOLFOX6 or the Reverse Sequence in Advanced Colorectal Cancer: A Randomized GERCOR Study

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ABSTRACT

Purpose
In metastatic colorectal cancer, phase III studies have demonstrated the superiority of fluorouracil (FU) with leucovorin (LV) in combination with irinotecan or oxaliplatin over FU + LV alone. This phase III study investigated two sequences: folinic acid, FU, and irinotecan (FOLFIRI) followed by folinic acid, FU, and oxaliplatin (FOLFOX6; arm A), and FOLFOX6 followed by FOLFIRI (arm B).

Patients and Methods
Previously untreated patients with assessable disease were randomly assigned to receive a 2-hour infusion of *l*-LV 200 mg/m^2 or *dl*-LV 400 mg/m^2 followed by a FU bolus 400 mg/m^2 and 46-hour infusion 2,400 to 3,000 mg/m^2 every 46 hours every 2 weeks, either with irinotecan 180 mg/m^2 or with oxaliplatin 100 mg/m^2 as a 2-hour infusion on day 1. At progression, irinotecan was replaced by oxaliplatin (arm A), or oxaliplatin by irinotecan (arm B).

Results
Median survival was 21.5 months in 109 patients allocated to FOLFIRI then FOLFOX6 versus 20.6 months in 111 patients allocated to FOLFOX6 then FOLFIRI ($P = .99$). Median second progression-free survival (PFS) was 14.2 months in arm A versus 10.9 in arm B ($P = .64$). In first-line therapy, FOLFIRI achieved 56% response rate (RR) and 8.5 months median PFS, versus FOLFOX6 which achieved 54% RR and 8.0 months median PFS ($P = .26$). Second-line FOLFIRI achieved 4% RR and 2.5 months median PFS, versus FOLFOX6 which achieved 15% RR and 4.2 months PFS. In first-line therapy, National Cancer Institute Common Toxicity Criteria grade 3/4 mucositis, nausea/vomiting, and grade 2 alopecia were more frequent with FOLFIRI, and grade 3/4 neutropenia and neurosensory toxicity were more frequent with FOLFOX6.

Conclusion
Both sequences achieved a prolonged survival and similar efficacy. The toxicity profiles were different.

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INTRODUCTION

Colorectal cancer accounts for 10% to 15% of all cancers and is the second leading cause of cancer deaths in western countries. Approximately half of all patients develop metastatic disease [1]. Palliative chemotherapy is more effective than the best supportive care at prolonging survival and improving quality of life [2]. Until recently, the antimetabolite fluorouracil (FU), which has been available for over 40 years, and leucovorin (LV) modulation were the standard of care, despite having no major impact on survival [3]. We showed that a fortnightly (every 2 weeks) regimen (LVFU2) which combined LV + FU bolus and infusion was safer and more active than LV + FU as a bolus [4]. We further developed a simplified fortnightly LVFU2 regimen which combined LV + FU bolus on day 1 only with a high-dose FU infusion [5]. This regimen achieved promising activity without increasing toxicity [6].

Two new drugs, irinotecan and oxaliplatin, have demonstrated survival improvement, when given either alone or in

combination with LV + FU, in first- or second-line therapy [7-12]. Irinotecan inactivates topoisomerase I via its active metabolite SN38. Phase III studies of patients whose disease had progressed after first-line FU have shown that irinotecan as a single agent increased survival compared with best supportive care or LV + FU infusion [7,8]. In two first-line phase III studies, a significant survival advantage was demonstrated for irinotecan combined with LV + FU, compared with LV + FU alone [9,10]. Oxaliplatin, a cytotoxic agent from the diaminocyclohexane family, has a mechanism of action similar to that of other platinum derivatives, but its spectrum of antitumor activity against tumor models differs from those of cisplatin and carboplatin. Its activity against cisplatin-resistant carcinoma and colon carcinoma cell lines has been demonstrated in vitro. In addition, experimental data showed synergistic activity for the oxaliplatin/FU combination [13]. Phase II studies of the combination of FU + LV and oxaliplatin have demonstrated activity in patients previously treated with FU [14-17]. A randomized study has shown that the combination of the LVFU2 schedule with oxaliplatin (FOLFOX4) prolonged progression-free survival (PFS) [11]. Another recent phase III study has shown improved survival for FOLFOX4 over irinotecan in combination with LV + FU as a bolus [12].

The simplified LVFU2 regimen has been combined with irinotecan (FOLFIRI regimen) and with oxaliplatin (FOLFOX6 regimen) and evaluated in second-line therapy [16,18,19].

The present randomized study was designed to evaluate these two improved regimens and to determine the best sequence to treat patients with metastatic colorectal cancer.

PATIENTS AND METHODS

The eligibility criteria for inclusion onto the study were: adenocarcinoma of the colon or rectum; unresectable metastases; at least one bidimensionally measurable lesion of $\geq$ 2 cm or a residual nonmeasurable lesion; adequate bone marrow, liver (alkaline phosphatases $<$ 3 upper limits of normal [UNL], total bilirubin $<$ 1.5 UNL, AST and ALT $\leq$ 3 UNL) and renal function (creatinine $\leq$ 135 μmol/L); WHO performance status (PS) of 0 to 2; age 18 to 75 years. Previous adjuvant chemotherapy, if given, must have been completed at least 6 months before inclusion. Patients with CNS metastases, second malignancies, bowel obstruction, current diarrhea $\geq$ grade 2, symptomatic angina pectoris, or disease confined to previous radiation fields were excluded. Written informed consent was required and the Ethical Committee approved the study.

Chemotherapy

FOLFIRI (Fig 1) consisted of *l*-LV 200 mg/m^2 or *dl*-LV 400 mg/m^2 as a 2-hour infusion, and irinotecan 180 mg/m^2 given as a 90-minute infusion in 500 mL dextrose 5% via a Y-connector, followed by bolus FU 400 mg/m^2 and a 46-hour infusion FU 2,400 mg/m^2 for two cycles, increased to 3,000 mg/m^2 from cycle 3 in case of no toxicity $>$ grade 1 during the two first cycles, repeated every 2 weeks. FOLFOX6 consisted of the same LV + FU regimen, with the addition of oxaliplatin 100 mg/m^2 on day 1, given as a 2-hour infusion in 500 mL dextrose 5%, concurrent with LV. Antiemetic prophylaxis with a $5HT_3$-receptor antagonist was administered. The use of implantable ports and disposable or electronic pumps allowed chemotherapy to be administered on an outpatient basis.

Patients randomly assigned to arm A received first FOLFIRI until progression or unacceptable toxicity and then FOLFOX6. The opposite sequence was administered in patients randomly assigned to arm B. In case of toxicity imputed to oxaliplatin or irinotecan during first-line therapy and no progressive disease, patients could receive LV and FU alone until progression, and then

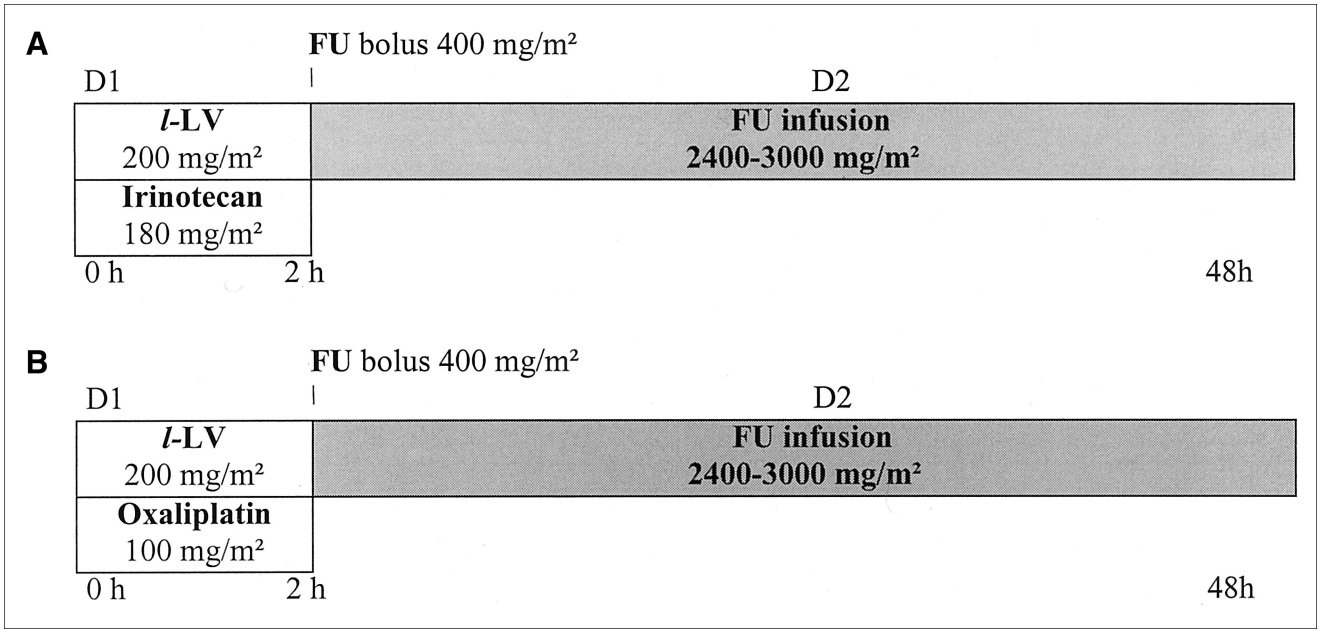

Fig 1. Chemotherapy regimens. (A) Simplified leucovorin (*l*-LV) and fluorouracil (FU) every 2 weeks (LVFU2) plus irinotecan (FOLFIRI); (B) simplified LVFU2 plus oxaliplatin (FOLFOX6).

the other regimen. Treatment was continued until disease progression, unacceptable toxicity, or patient choice.

Toxicity was assessed before starting each 2-week cycle using the National Cancer Institute-Common Toxicity Criteria [20]. A specific scale was used for sensory neurotoxicity: grade 1 is short-lasting paresthesia with complete regression before the next cycle, grade 2 is persistent paresthesia or dysesthesia without functional impairment, and grade 3 is persistent functional impairment.

Chemotherapy was delayed until recovery if neutrophils $< 1.5 \times 10^9$/L, platelets $< 100 \times 10^9$/L, or for significant persisting nonhematologic toxicity. FU infusion dose was reduced to the previous level or 2,000 mg/m^2 if related $\geq$ grade 3 toxicity occurred at 2,400 mg/m^2. Irinotecan dose was reduced to 150 mg/m^2 for grade 2 to 4 neutropenia, thrombocytopenia, and diarrhea. Oxaliplatin dose was reduced to 75 mg/m^2 in case of grade 4 neutropenia, grade 3/4 thrombocytopenia, or grade 4 diarrhea. In the case of grade 2 paresthesia, oxaliplatin was first reduced to 75 mg/m^2, and if persistent, to 50 mg/m^2. In cases of persistent painful paresthesia or grade 3 neurotoxicity, oxaliplatin was omitted from the regimen.

Evaluation Criteria

Physical examinations and blood counts were performed every cycle. Hepatic, renal function tests, and computed-tomography (CT) scans of measurable lesions were assessed at baseline and repeated every four cycles. WHO criteria were used to assess tumor response [21]. Complete response (CR) was defined as complete disappearance of all clinically assessable disease for at least 4 weeks, and partial response as a decrease of at least 50% of the sum of the products of the diameters of measurable lesions for at least 4 weeks. CT scans were done 4 weeks later to confirm a response. Stable disease was defined as a decrease of less than 50% or an increase of less than 25% of measurable lesions, and progressive disease as an increase of at least 25% of measurable lesions or the appearance of new malignant lesion(s). All CT scans were subjected to external review by at least two radiologists.

The primary objective of the study was the second PFS; time duration from randomization until progression after the second-line of chemotherapy. If the patient could not receive the second-line for medical reason or refusal, the PFS on first-line therapy was used. Secondary objectives of the study were PFS, overall survival (OS), response rates (RRs), and safety.

Statistical Considerations

Randomization was performed using a minimization technique [22], stratifying patients by center and by presence or absence of measurable disease. 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%) [23]. Using Freedman's formulas, 109 patients and 49 events per arm were required. The analysis was made on an intent-to-treat basis. The Kaplan-Meier method was used to estimate survival and PFS curves, and the log-rank test was used to compare the curves [24]. The Mantel-Haenszel test was used to compare proportions (RR and toxicities) [25]. The Cox regression model was used for multivariate analysis of prognostic factors for survival and PFS, using a backward selection approach [26].

RESULTS

Patient Characteristics

From December 1997 to September 1999, 226 patients were randomly assigned at 42 institutions, 113 in each arm. Six patients were not analyzed as a result of being ineligible and not treated (four in arm A and two in arm B). Characteristics of 220 eligible patients are reported in Table 1. Characteristics of the patients were well-balanced between arms, except for sex-ratio, where the percentage of males was higher in arm B, and age $>$ 65 years, where the percentage was slightly greater in arm B.

The cutoff dates were March 31, 2001 for PFS, when the number of events required for analysis was reached, and

Table 1. Patient Characteristics

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	49	45	52	47
1	42	39	52	47
2	18	17	7	6
Primary site				
Colon	73	67	80	72
Rectum	36	33	29	26
Multiple	0	0	2	2
Metastases				
Synchronous	83	76	85	77
Metachronous	26	24	26	23
Metastatic site				
Liver	95	87	89	80
Lung	34	31	33	30
Other	43	39	55	50
No. of sites				
1	64	59	66	59
$\geq$ 2	45	41	45	41
CEA				
$<$10 ng/ml	28	26	37	33
$\geq$10 ng/ml	76	70	66	59
Unknown	5	5	8	7
Alkaline phosphatase				
Normal	48	44	59	51
Increased	52	49	33	40
Unknown	9	8	9	9
Adjuvant chemotherapy				
Yes	19	17	23	21
No	90	83	88	79

Abbreviations: FOLFIRI, folinic acid, fluorouracil, and irinotecan; FOLFOX6, folinic acid, fluorouracil, and oxaliplatin; CEA, carcinoembryonic antigen.

August 30, 2002 for OS, with a median potential follow-up time for the entire cohort of 43.9 months.

Progression-Free Survival

First-line therapy. According to the external review, median PFS was 8.5 months (95% CI, 7.0 to 9.5) for arm A (FOLFIRI) versus 8.0 months (95% CI, 6.2 to 9.4) for arm B (FOLFOX6; $P = .26$; Fig 2). According to the investigators' assessments, these values were 8.4 months (95% CI, 6.9 to 9.5) for arm A versus 8.0 months (95% CI, 6.2 to 9.5) for arm B.

Second-line therapy. According to the external review, median PFS was 4.2 months (95% CI, 3.7 to 5.2) for arm A (FOLFOX6) versus 2.5 months (95% CI, 2.1 to 3.3) for arm B (FOLFIRI; $P = .003$; Fig 2). According to the investigators' assessments, these values were 4.9 months (95% CI, 3.8 to 5.7) for arm A versus 2.3 months (95% CI, 2.1 to 3.5) for arm B.

The median delay between progression on first-line therapy and the first cycle of second-line therapy was 21 days in arm A and 15 days in arm B ($P = .27$).

As of March 31, 2001, 81 patients (74%) had received per protocol FOLFOX6, second-line therapy in arm A and 69 patients (62%) FOLFIRI second-line therapy in arm B, including one patient who received FOLFOX6 instead of FOLFIRI.

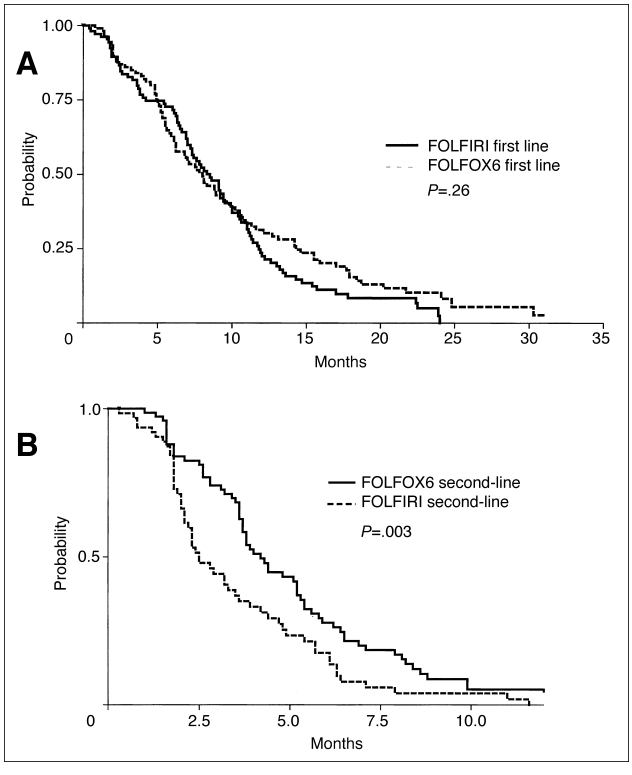

Fig 2. Progression-free survival in (A) first-line therapy and (B) second-line therapy. FOLFIRI, folinic acid, fluorouracil, and irinotecan; FOLFOX6, folinic acid, fluorouracil, and oxaliplatin.

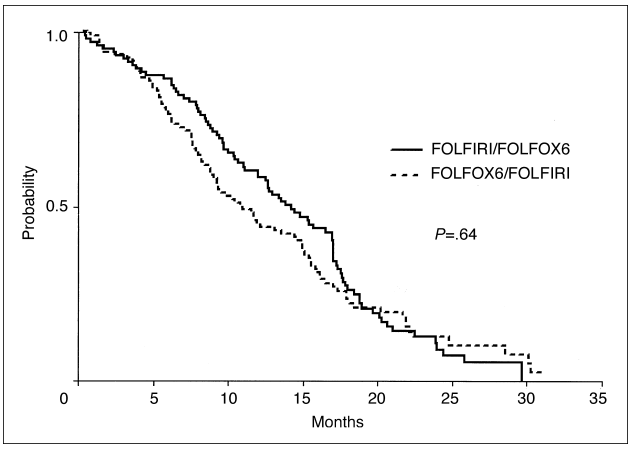

Fig 3. Time to second progression. FOLFIRI, folinic acid, fluorouracil, and irinotecan; FOLFOX6, folinic acid, fluorouracil, and oxaliplatin.

Eight patients in both arms received a second line of treatment out of study. Three patients in arm A and five in arm B received the second line after the cut-off date. Five patients in arm A and eight in arm B had no tumor progression after first-line therapy. Twelve patients (11%) in arm A and 17 (15%) in arm B could not receive a second-line therapy as a consequence of death, poor PS, or refusal.

Second progression-free survival. According to the external review, median second PFS was 14.2 months (95% CI, 12.0 to 16.9) for arm A versus 10.9 months for arm B (95% CI, 9.0 to 14.6; $P = .64$; Fig 3). According to the investigators' assessments, median second PFS was 14.2 months (95% CI, 12.2 to 15.4) for arm A versus 11.8 months (95% CI, 9.2 to 14.6) for arm B. At 15 months, PFS was 47.2% in arm A versus 37.3% in arm B.

Independent prognostic factors for improved second PFS were: good PS ($P = .001$), no prior adjuvant chemotherapy ($P = .001$), low lactate dehydrogenase ($P = .011$), and female sex ($P = .043$).

Overall Survival

Median OS was 21.5 months (range, 16.9 to 25.2) for arm A versus 20.6 months for arm B (range, 17.7 to 24.6; $P = .99$; Fig 4).

Independent prognostic factors for improved OS were: good PS ($P < .0001$), low lactate dehydrogenase ($P < .001$), no prior adjuvant chemotherapy ($P = .001$), low alkaline phosphatase ($P = .012$), metastasis confined to the liver ($P = .016$), carcinoembryonic antigen ($P = .016$), and female sex ($P = .048$).

Objective Tumor Responses

First-line therapy. In first-line therapy, three CRs were observed with FOLFIRI (2.8%) versus five with FOLFOX6 (4.5%). The RRs were 56% with FOLFIRI (95% CI, 47% to 65%) versus 54% with FOLFOX6 (95% CI, 45% to 63%; P was not significant). Median time to

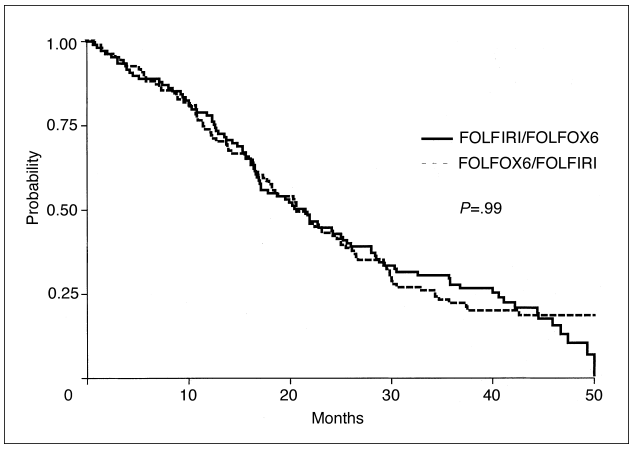

Fig 4. Overall survival curves. FOLFIRI, folinic acid, fluorouracil, and irinotecan; FOLFOX6, folinic acid, fluorouracil, and oxaliplatin.

response in arm A was 2.1 months versus 1.8 months in arm B ($P = .02$). The response lasted a median of 11 months for arm A versus 10.6 months for arm B. The investigators' assessments of objective response for FOLFIRI and FOLFOX6 were 54% and 51%, respectively. The RRs are reported in Table 2.

Only two independent prognostic factors were found to be significant for first-line response: good PS ($P = .001$) and liver-only metastases ($P = .004$).

Secondary surgery to remove metastases was performed in 10 patients (9%) in arm A versus 24 patients (22%) in arm B ($P = .02$). All patients undergoing secondary surgery had liver metastases except one who had a lumbar aortic lymph node metastasis. Thirty patients had a single metastatic site, three had two sites, and one 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, eight patients (7%) had a R0 resection in arm A versus 14 in arm B (13%; $P = .26$). In addition, two patients underwent a second or third surgical resection. Median OS in patients who had surgery was 47 months in the FOLFIRI first-line arm, and was not reached in the FOLFOX6 arm ($P = .96$).

Second-line therapy. The RRs were 15% with FOLFOX6 second-line (95% CI, 7% to 23%) versus 4% with FOLFIRI second-line (95% CI, 0% to 9%; $P = .05$; Table 3). In second-line therapy, the investigators' assessments of objective response for FOLFOX6 and FOLFIRI 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. During first-line therapy, arm A patients received a median of 13 cycles (range, 1 to 43) of FOLFIRI and those in arm B a median of 12 cycles (range, 1 to 38) of FOLFOX6. There was one therapy-related death in arm B as a result of hematologic toxicity. In addition to grade 3 sensory neurotoxicity, grade 3/4 neutropenia 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. Table 3 summarizes the frequency of toxicity during first- and second-line treatment in each arm. Thirty-four percent of patients developed grade 3 sensory neurotoxicity in arm B. Among these patients, five (13%) recovered from grade 3 toxicity within 1 month and 12 (31%) within 3 months. Overall, more patients experienced grade 3/4 toxicities with FOLFOX6 than FOLFIRI (74 *v* 53%; $P = .001$) but more patients had serious adverse events with FOLFIRI than with FOLFOX6 (14% *v* 5%; $P = .03$). Six patients (6%) had to stop FOLFIRI first-line as a result of toxicity compared with 12 patients (11%) on first-line FOLFOX6. During the first 60 days in first-line therapy, four patients (4%) died in arm A and three patients (3%) died in arm B.

Elderly patients (> 65 years; n = 90) did not experience

Table 2. Objective Tumor Response Rates After External Review

	First-Line				Second-Line			
	Arm A: FOLFIRI (n = 109)		Arm B: FOLFOX6 (n = 111)		Arm A: FOLFOX6 (n = 81)		Arm B: 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

Abbreviations: FOLFIRI, folinic acid, fluorouracil, and irinotecan; FOLFOX6, folinic acid, fluorouracil, and oxaliplatin.

Table 3. Frequency of Common Toxicities (percentage)*

	First-Line									Second-Line								
	Arm A: FOLFIRI (n = 110)†				Arm B: FOLFOX6 (n = 110)†					Arm A: FOLFOX6 (n = 82)				Arm B: FOLFIRI (n = 68)				
Toxicity	Grade 1	Grade 2	Grade 3	Grade 4	Grade 1	Grade 2	Grade 3	Grade 4	*P* (grade 3/4)	Grade 1	Grade 2	Grade 3	Grade 4	Grade 1	Grade 2	Grade 3	Grade 4	*P* (grade 3/4)
Neutropenia	19	33	15	9	18	20	31	13	.003	17	24	15	2	21	18	21	0	NS
Thrombocytopenia	15	1	0	0	57	21	5	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	.007	0	0	0	0	0	0	1	0	NS
Nausea	29	30	13	0	39	25	3	0	.005	37	21	6	0	26	21	0	0	.03
Vomiting	17	23	8	2	22	17	3	0	.027	17	17	4	1	16	16	3	0	NS
Diarrhea	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	.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	NA	NA	19	9	NA	NA	.003‡	13	9	NA	NA	26	13	NA	NA	NS
Neurological	10	0	0	NA	26	37	34	NA	< .001	45	29	20	0	1	0	1	0	< .001
Fatigue	15	27	4	0	17	15	3	0	.028§	9	22	5	0	12	21	1	0	NS

Abbreviations: FOLFIRI, folinic acid, fluorouracil, and irinotecan; FOLFOX6, folinic acid, fluorouracil, and oxaliplatin; NS, not significant; NA, not applicable.
*Maximum toxicity per patient.
†One patient randomized in arm B received FOLFIRI as first-line.
‡Comparison grade 2.
§Comparison grade 2–3.

increased toxicity in first-line therapy as compared with younger subjects.

Second-line therapy. During second-line therapy, arm A patients received a median of eight cycles (range, 2 to 23) of FOLFOX6, and those in arm B received a median of six cycles (range, 1 to 33) of FOLFIRI. There were no therapy-related deaths. The toxicity profile in each regimen showed minor differences compared with first-line therapy (Table 3). Grade 3/4 neutropenia and thrombocytopenia and neurotoxicity were less frequent with FOLFOX6, while gastrointestinal toxicities were less frequent with FOLFIRI. Of note, only 19% of the patients who developed grade 3 neurotoxictiy on first-line oxaliplatin still had a grade 3 neurotoxicity when they began second-line FOLFIRI.

Overall, 49% of the patients experienced grade 3/4 toxicities with FOLFOX6 second-line versus 44% with FOLFIRI (*P* was not significant). Serious related adverse events occurred in 6% of the patients with FOLFIRI and in 4% of patients with FOLFOX6. Ten (12%) of the patients with FOLFOX6 second-line and one patient (1%) with FOLFIRI had to stop for toxicity. Elderly patients (> 65 years; n = 59) did not experience increased toxicity, as compared with younger subjects. During the first 60 days in second-line therapy, six patients died (three in each arm; arm A, 4%; arm B, 3%).

Vascular events were reported in three 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. Twenty-two percent of the patients on FOLFIRI first-line received FU 3,000 mg/m^2 for at least one cycle, and 34% received FU 3,000 mg/m^2 on FOLFOX6. The corresponding figures in second-line were 11% with FOLFIRI and 10% with FOLFOX6. Relative dose-intensity for irinotecan was 85.9% in first-line and 87.3% in second-line. For oxaliplatin, the respective figures were 84.7% first-line and 90.1% second-line.

Weight and Performance Status

A weight increase of at least 5% was recorded for 38 patients on first-line FOLFIRI (35%) versus 25 patients on FOLFOX6 (23%; $P = .05$). PS improved in 18 patients among 52 assessable patients with PS > 0 (35%) on FOLFIRI, versus 19 among 57 assessable patients (33%) on FOLFOX6 ($P = .99$).

A weight increase of at least 5% was recorded for four patients receiving second-line therapy FOLFIRI (6%) versus seven patients on FOLFOX6 (9%; $P = .55$). PS improved in 12 patients among 34 assessable patients with PS > 0 (35%) on FOLFIRI, versus nine among 35 assessable patients (26%) on FOLFOX6 ($P = .44$).

DISCUSSION

Our study is the first randomized study of two sequential regimens incorporating oxaliplatin and irinotecan in the treatment of advanced colorectal cancer.

Table 4. Results and Prognostic Factors in First-Line Randomized Studies of LV and FU With Irinotecan or Oxaliplatin

	LVFU and Irinotecan				LVFU and Oxaliplatin		
	IFL (Saltz et al [8])	IFL (Goldberg [18])	LVFU2/Irinotecan (Douillard [10])	FOLFIRI (present study)	FOLFOX4 (de Gramont [11])	FOLFOX4 (Goldberg [12])	FOLFOX6 (present study)
No. of patients	231	264	198	109	210	267	111
RR, %	39	31	41	56	51	45	54
PFS, months	7.0	6.9	6.7	8.5	9.0	8.7	8.1
OS, months	14.8	14.8	17.4	21.5	16.2	19.5	20.6
PS, %							
0	39	NA	51	49	43	NA	45
1	46	NA	42	42	46	NA	39
2	15	5	7	18	11	6	17
One site, %	64	NA	NA	64	43	NA	59
Alkaline phosphatases increased, CEA	NA	NA	45	52	50	NA	53
CEA, %							
> 10 ng/mL	NA	NA	73	76	85	NA	73
> 100 ng/mL	40	NA	NA	NA	36	NA	NA
Adjuvant chemotherapy, %	11	15	26	19	20	16	23

Abbreviations: LV, leucovorin; FU, fluorouracil; IFL, leucovorin, FU bolus, and irinotecan; LVFU2, leucovorin and fluorouracil every 2 weeks; FOLFIRI, folinic acid, fluorouracil, and irinotecan; FOLFOX, folinic acid, fluorouracil, and oxaliplatin; RR, response rate; PFS, progression-free survival; OS, overall survival; PS, performance status; CEA, carcinoembryonic antigen; NA, not available.

The first and most impressive result of this study is an OS in excess of 20 months in both arms, which has not been previously reached in any randomized study of metastatic colorectal cancer therapy. We could not identify better prognostic factors in our population compared with other studies (Table 4).

Previous studies have shown that in first-line therapy, the addition of irinotecan or oxaliplatin to the LVFU2 fortnightly regimen has an impact on survival of patients with metastatic colorectal cancer [9-11]. However, survival in the trials with the combination of LV + FU, and irinotecan or oxaliplatin was in the range of 15 to 17 months, a benefit of 1.5 to 3.5 months over LV + FU alone, although crossovers from LV + FU alone to the more active treatment tended to decrease the relative size of the benefit.

Second-line studies have also shown an impact on survival. In the two randomized second-line studies using irinotecan as single agent, the benefit on survival ranged between 1.5 to 3 months [7,8]. Oxaliplatin alone has a limited efficacy as single-agent in second-line therapy, but FOLFOX regimens have given 20% to more than 40% RRs and median survivals between 10 and 17 months [14-17]. Of note, in the present study, 82% of the patients in one arm and 74% in the other arm received second-line chemotherapy. However, the low RR of FOLFIRI in second-line suggests that FU may not be necessary in this setting.

The new simplified LVFU2 fortnightly regimen could also have an impact on survival. Three phase III studies combined the first LVFU2 regimen with irinotecan (LVFU2/irinotecan) and oxaliplatin (LVFU2/oxaliplatin or FOLFOX4) [10-12]. In our study, the new simplified LVFU2 regimen was combined with irinotecan at the same dose as the previous study (FOLFIRI) and oxaliplatin at higher dose (FOLFOX6). The results of FOLFIRI first-line compared favorably to LVFU2/irinotecan. However, the results of FOLFOX6 and FOLFOX4 first-line were similar despite the higher dose of oxaliplatin in FOLFOX6 (Table 4). In second line therapy, after irinotecan based-chemotherapy, FOLFOX6 and FOLFOX4 also achieved similar results [27].

Our study failed to demonstrate that a sequence of first-line irinotecan followed by second-line oxaliplatin, or the reverse sequence beginning with first-line oxaliplatin, was better than the other. RRs, PFS first-line, second PFS, and OS did not differ between the two arms with statistical significance. However, our first objective, second PFS, did not provide a good evaluation of two lines of treatment. The effect of chemotherapy could not be properly evaluated in patients having surgery, a therapeutic break, or delayed second-line therapy. Furthermore, in our study there was an imbalance between the numbers of patients in the two study arms who had received the second-line therapy at the time of analysis. For future trials using a multiline strategy, we will use the concept of time of disease control (TDC) which could be a new tool to assess the duration of the therapeutic effect [28]. To perform TDC, PFS for each line is added. But, in case of progression at the first tumor assessment on any therapy line, PFS for this line is null. Intervals between the therapeutic lines are also not considered in the TDC. The Kaplan-Meier method is then used to perform TDC curves. In this study, median TDC was 10.5 months in arm A and 8.7 months in arm B ($P =$

.64), 3.7 months and 2.2 months less than the median second PFS, respectively.

Over 15% of the patients underwent curative surgery in our study—22% with FOLFOX6 first-line and 9% with FOLFIRI. However, inoperability criteria were not provided, which could explain in part this high resection rate and the difference between two regimens that achieved the same RR. Surgery of metastases after chemotherapy could be another breakthrough in the therapy of patients with advanced colorectal cancer.

As expected, the toxicity profile of both regimens showed some differences. Gastrointestinal toxicities, except diarrhea, were more frequent with FOLFIRI and hematologic toxicity was more frequent with FOLFOX6 in first-line therapy. Alopecia and fatigue were more frequent with FOLFIRI. We observed an unexpectedly high rate of oxaliplatin neurotoxicity, with 34% of first-line patients developing grade 3 toxicity. This could be because of the higher dose of oxaliplatin in the FOLFOX6 regimen than in the FOLFOX4. However, it may also reflect the difficulty of assessing sensory neurotoxicity. The specific scale which rates grade 3 as a persistent functional impairment could overestimate the incidence of severe neurotoxicity when cycles are repeated at short intervals. This is supported by the observation that only 19% of the patients remained with grade 3 neuropathy at the beginning of FOLFIRI after FOLFOX6, despite a median time between the regimens of less than 1 month.

The final conclusion of the study is that both sequences are similar and achieve an impressive survival. However, the fact that a substantial proportion of patients did not get second-line therapy makes the choice in first-line therapy particularly important. Future developments should focus on the two limitations shown in this study, namely neurotoxicity that forces many patients to stop oxaliplatin before tumor resistance develops, and the relatively poor efficacy of FOLFIRI as second-line therapy. The ongoing GERCOR studies are designed to overcome these limitations. These are OPTIMOX [29], which evaluates a limited number of cycles of the new FOLFOX7 regimen with reintroduction of oxaliplatin after LV/FU maintenance therapy, and the FOLFIRI3 study [30] which evaluates a new second-line regimen. Preliminary results of this study have been presented previously by others based on earlier data, and with different conclusions about the results [31]. With the full data, we believe our conclusions about the roles of oxaliplatin and irinotecan in first- and second-line therapy are correct.

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Appendix

The appendix is included in the full-text version of this article, available on-line at www.jco.org. It is not included in the PDF (via Adobe® Acrobat Reader®) version.

Authors' Disclosures of Potential Conflicts of Interest

The following authors or their immediate family members have indicated a financial interest. No conflict exists for drugs or devices used in a study if they are not being evaluated as part of the investigation. Acted as a consultant within the last 2 years: Aimery de Gramont, Aventis, Sanofi; Gerard Lledo, Aventis, Sanofi; Christophe Louvet, Aventis, Sanofi. Performed contract work within the last 2 years: Emmanuel Quinaux, Aventis; Marc Buyse, Aventis. Served as an officer or member of the Board of a company: Dominique Mery-Mignard, Aventis; Corinne Couteau, Aventis; Gerard Lledo, Sanofi. Received more than $2,000 a year from a company for either of the last 2 years: Aimery de Gramont, Aventis, Sanofi; Dominique Mery-Mignard, Aventis; Corinne Couteau, Aventis; Christophe Louvet, Sanofi.

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