Irinotecan/Fluorouracil/Leucovorin or the Same Regimen Followed by Oxaliplatin/Fluorouracil/ Leucovorin in Metastatic Colorectal Cancer

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Abstract. *Background: This study reports the long-term follow-up of patients with metastatic colorectal cancer (CRC) participating in a randomised phase II study that compared the efficacy and toxicity of the combination of irinotecan (IRI), fluorouracil (FU) with leucovorin (LV) (arm A) versus sequential chemotherapy with IRI plus FU/LV followed by oxaliplatin (OXA) plus FU/LV (arm B) as first line therapy. Materials and Methods: Intent-to-treat analysis was performed on 417 patients (211 in arm A and 206 in arm B). Treatment schedules of weekly IRI 80 mg/m^2 or OXA 45 mg/m^2 plus LV 200 mg/m^2 immediately followed by intravenous bolus FU 450 mg/m^2 for 6 weeks were followed by a 2-week rest period. Treatment continued for 4 cycles. Patients in arm A were treated with IRI/FU/LV for 4 cycles, while patients in arm B were initially treated with IRI/FU/LV for 2 cycles followed by sequential administration of 2 cycles of OXA/FU/LV. Results: No significant difference emerged in overall response rate or overall survival. There was a difference in progression-free survival (median, 7.3 versus 8.2 months, p=0.040) in favour of arm B. Toxicity profiles were similar in both arms. Conclusion: IRI/FU/LV and IRI/FU/LV followed by OXA/FU/LV showed comparable activity with a manageable toxicity profile.*

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Colorectal cancer (CRC) is a worldwide public health problem, accounting for nearly 800,000 new cases diagnosed each year and approximately 500,000 deaths (1). Significant advances have been made in the management options for patients with metastatic disease and a median survival of 21-24 months is now frequently reported.

Over the past 10 years, three new chemotherapeutic agents have been approved for metastatic CRC. These compounds

include the topoisomerase I inhibitor irinotecan (IRI), the third-generation platinum analogue oxaliplatin (OXA), and the oral fluoropyrimidine capecitabine. Since 2004, three novel biological agents have been approved by the FDA, namely the anti-epidermal growth factor receptor (EGFR) antibodies cetuximab and panitumumab and the anti-vascular endothelial growth factor (VEGF) antibody bevacizumab (2).

Several studies have shown a clinical benefit of adding IRI or OXA to fluorouracil (FU) in the first-line setting (3-6). In patients with advanced CRC whose metastases are potentially resectable, immediate treatment with the highest chance for response is desirable. However, in terms of survival, there does not seem to be an optimum sequence of administration of IRI and OXA (7) and the optimum timing and duration of delivery of these agents has not been clearly defined. OXA and IRI have been directly compared in several studies. In a phase III study by Tournigand *et al*. (8), FOLFIRI and FOLFOX6 were compared, in the first-line setting, in patients with metastatic CRC with no differences found in response rates, progression-free survival (PFS) or overall survival (OS). At progression, IRI was replaced by OXA and OXA by IRI. Not only did this study show an equivalent clinical efficacy between IRI and OXA, but it also demonstrated that there does not appear to be an optimal sequence of combination regimens, as the OS at the end of both treatment arms was virtually identical. In recent years, evidence has emerged on the advantageous use of all three cytotoxic drugs during the course of a patient's illness (9), but only 50% to 80% of patients can be exposed to all three drugs in a sequential strategy with doublets. Simultaneous combination chemotherapy can be more effective than single agents if all drugs can be given at adequate dose levels. However, simultaneous combination chemotherapy of several drugs often requires the dose of each agent to be reduced from its optimal single-agent level.

A solid theoretical framework supports the hypothesis that the sequential administration of cytotoxic drugs at adequate doses can maximise cancer cell death and overcome drug resistance. However, an important question remains, namely how the active drugs should be sequenced to provide patients with the maximum duration of disease control and acceptable toxicity. Mathematical models support sequential chemotherapy as being superior to concurrent therapy (10, 11). Indeed, sequential chemotherapy may allow the delivery of a higher number of drugs with the dose of each drug being optimised and toxicity therefore reduced. There is now a growing list of clinical examples in other tumour types in which sequential therapies have outperformed alternating cyclic use of the same programs, when the dose intensity of the two regimens is carefully controlled (12, 13).

For patients with advanced CRC, in the CAIRO study (14), 820 patients were randomised to receive either first-line treatment with capecitabine, second-line IRI, and third-line capecitabine plus OXA or first-line treatment with capecitabine plus IRI and second-line capecitabine plus OXA. The authors concluded that the combination treatment does not significantly improve overall survival compared with the sequential use of cytotoxic drugs in advanced CRC. However, in the FOCUS study (15), over 2000 patients were randomised to one of five groups: initial FU followed by single-agent IRI, initial FU followed by FU with either IRI or OXA, or initial combinations that consisted of FU with either IRI or OXA. The sequential single-agent strategy gave the poorest survival and the authors recommended that this approach should not be advocated. Thus, data are conflicting regarding the use of combination or sequential chemotherapy in patients with advanced CRC.

A phase II study comparing the efficacy and toxicity of the combination of IRI plus FU with leucovorin (LV) *versus* sequential chemotherapy with IRI plus FU/LV followed by OXA plus FU/LV as first-line therapy in patients with metastatic CRC was run by the Hellenic Cooperative Oncology Group. Results were presented at the 42th ASCO meeting in 2006 (16). In the present study, the long-term follow-up of these patients is reported.

Patients and Methods

In this phase II trial, patients were required to have histologically or cytologically confirmed, advanced, recurrent or metastatic adenocarcinoma of the colon or rectum, previously untreated, or bi-dimensionally measurable disease located outside of a previously irradiated field. Previous palliative radiation therapy was permitted, provided that <20% of the bone marrow was involved and a target lesion outside the radiation port was present.

Patients were permitted to have received adjuvant cytotoxic chemotherapy, provided it was completed ≥6 months before study entry. Eligible patients had to be aged ≥18 years, and have a World Health Organization (WHO) performance status (PS) ≤2; no other malignancy, except adequately treated *in situ* carcinoma of the cervix uteri and basal or squamous cell carcinoma of the skin; no other serious illness; and adequate bone marrow reserve (neutrophil count ≥1500/ml and platelet count ≥100000/ml), renal function [creatinine ≤1.5 × the upper limit of normal (ULN)] and liver function (serum transaminases ≤5 × ULN, serum bilirubin <1.5 mg/dl and alkaline phosphatase ≤5 × ULN). Exclusion criteria included the presence of central nervous system lesions, as well as bone metastases or pleural effusions, as the sole indication of tumour; pregnant or lactating women; and a high risk of poor outcome due to concomitant non-malignant disease, peripheral neuropathy, active uncontrolled infection or chronic enteropathy.

The clinical protocol and collateral translational research studies were approved by the Hellenic Cooperative Oncology Group (HeCOG) Protocol Review Committee, by the Institutional Review Board of Hygeia Hospital and by the Bioethics Committee of Aristotle University of Thessaloniki School of Medicine. The trial was registered at the Australian New Zealand Clinical Trials Registry (No: ACTRN12609000585224). Before randomisation, all patients gave written informed consent according to institutional guidelines and eligibility was confirmed by a protocol-specific checklist.

All eligible patients had to provide complete medical history and undergo a physical examination that included assessment of weight, height and WHO PS. In addition, assessment of tumour size, carcino-embryonic antigen (CEA) and carbohydrate antigen 19–9 levels, abdominal pelvic computed tomography (CT), chest X-ray, complete blood count, biochemistry profile and electrocardiography were also performed. Patients were stratified according to WHO PS (0 *versus* 1 and 2), presence of hepatic metastases and previous adjuvant chemotherapy. Patients were then randomly assigned to one of the two treatment regimens by the HeCOG central office in Athens, Greece.

During treatment, clinical examination, body weight, WHO PS, subjective symptoms and all adverse reactions were recorded before each treatment. A biochemistry profile and complete blood count were repeated every 2 weeks and target lesions were re-assessed every two cycles of chemotherapy by CT, X-ray and/or magnetic resonance imaging, enabling retrospective evaluation. An independent review of response was performed in all patients.

Chemotherapy regimens. In arm A, IRI was administered at a dose of 80 mg/m^2 in 250 ml normal saline as a 90-min intravenous (*i.v.*) infusion, followed by LV 200 mg/m^2 in 500 ml normal saline as a 2-h *i.v.* infusion and 5-FU 450 mg/m^2 as an *i.v.* bolus at the end of the LV infusion. Treatment was administered weekly for 6 weeks, followed by a 2-week rest period. A single cycle represented six weekly infusions over 8 weeks. In arm B, initially 2 cycles of the same regimen as in arm A were administered followed by 2 cycles of OXA/FU/LV. OXA was administered at a dose of 45 mg/m^2 in 250 ml 5% dextrose as a 90-min *i.v.* infusion, followed by LV 200 mg/m^2 in 500 ml normal saline as a 2-h *i.v.* infusion and FU 450 mg/m^2 as an *i.v.* bolus at the end of the LV infusion. Treatment was administered weekly for 6 weeks, followed by a 2-week rest period. In both arms, chemotherapy was administered for up to four cycles or until disease progression, unacceptable toxicity or patient refusal. Concomitant medication, routinely given before chemotherapy, included ondasetron 8 mg according to the conventional anti-emetic protocol.

Dose adjustments of all study drugs or treatment delays were calculated according to toxicity grade, as previously described (17, 18).

Response criteria. Response was assessed in accordance with the WHO criteria. Measurements were obtained at baseline, week 16, at the completion of the treatment, and every 12 weeks until disease progression. Measurement of bone metastases was not used as a parameter of tumour response. Patients with tumours not meeting the criteria for response or progressive disease (PD) were considered stable (SD). All patients entered in the study were analysed on an intent-to-treat basis.

Statistical considerations. The primary endpoint of the study was the objective response rate (ORR). Secondary endpoints were OS and PFS. A sample of 304 patients was required for the study, to ensure an 80% power at the 5% level of significance, for a two-sided test of the hypothesis that a difference of ±15% in response rate exists to a baseline response rate of 25%. Considering a 3% withdrawal rate, 314 patients needed to enter the study. Accrual was better than originally anticipated and a total of 417 eligible patients entered the study, ensuring a 90% power for the difference of interest (±15%). Pearson's chi-square tests and Fisher's exact tests were applied to compare patient characteristics, response and toxicity. Exact confidence intervals (CI) were used to determine the 95% upper and lower confidence limits of the response rates. PFS was calculated from the randomisation date to the first progression of the disease. However, patients who died due to disease-related factors without previously having documentation of disease progression were considered as an event for the estimation of PFS. Survival time was calculated from the date of randomisation to the date of death or day of last follow-up. The Kaplan-Meier method was used to estimate the PFS, median follow-up, and OS distributions, while the log-rank test was used to compare these distributions. Prognostic factor analyses for the duration of response, PFS and OS were performed using the Cox proportional hazards model. A backward selection procedure identified a subclass of significant variables among the following: age (<65 *versus* ≥65), PS (0 *versus* 1 or 2), sex (men *versus* women), treatment arm (A *versus* B), haemoglobin (Hgb) level (<12 g/dl *versus* ≥12 g/dl), SGOT (normal *versus* abnormal), SGPT (normal *versus* abnormal), CEA (<10 *versus* ≥10), number of metastatic sites (single *versus* multiple), adjuvant chemotherapy (no *versus* yes) and weight loss (no *versus* yes). The significant factors were kept in the model if the maximum likelihood ratio criterion had a *p*-value <0.10. The analysis of ORR, OS and PFS was made on an 'intent-to-treat' basis. In the safety analysis and the description of treatment characteristics only the treated population was included. Data were analysed using SPSS for Windows version 15 (SPSS Inc., Chicago, IL, USA).

Results

From November 2001 until October 2004, 443 patients entered the study. A flow chart of the study is shown in Figure 1. Twenty-six patients were ineligible. In addition, eight patients (two in arm A and six in arm B) never started chemotherapy; these patients were included in the efficacy analysis according to the intent-to-treat, but were excluded from the analyses of toxicity and treatment characteristics. Five patients were randomised to arm A, but were then switched to OXA treatment after the first two IRI containing treatment cycles, while 18 patients who were randomised to arm B, continued receiving the IRI containing treatment.

Of the 417 eligible patients, 269 were men and 148 were women. Patient characteristics are shown in Table I. Demographics and baseline clinical characteristics were balanced between the two groups of patients.

Treatment administration. Two hundred and three patients did not complete treatment as planned. The most common reason for treatment discontinuation was PD (58 patients in arm A *versus* 34 in arm B). Additional reasons for treatment discontinuation were voluntary withdrawal (16 patients in each arm), death (6 *versus* 8), toxicity (15 *versus* 9) and others (15 *versus* 26). In all, 88 patients (42%) in arm A and 97 (47%) in arm B completed the treatment in the allocated arm. There were no significant differences between the two arms regarding discontinuation.

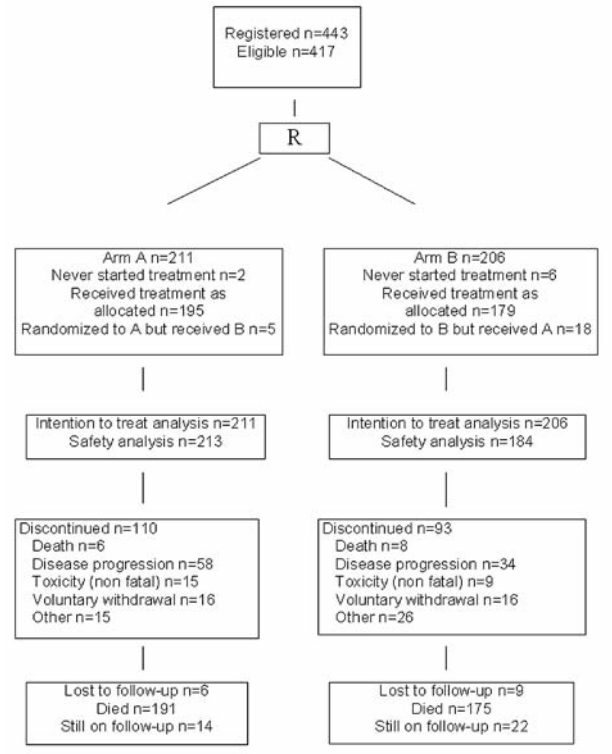

Figure 1. *Study flow chart. R: Randomisation.*

The median relative dose intensity for FU was 0.75 (range 0.2-1.00) in arm A and 0.78 (range 0.2-1.00) in arm B. The median relative dose intensity for IRI in both arms A and B was 0.72 (range 0.2-1.00). The median relative dose intensity for OXA in arm B was 0.72 (range 0.3-0.9) (Table II). The median number of treatment cycles was 3 (range 1-4) in arm A and 4 (range 1-4) in arm B.

Efficacy. There were no significant differences between arms A and B in overall ORR. In the intent-to-treat analysis, the overall ORR was 25% (95% CI 19%-31%) in arm A and 27% (95% CI 21%-33%) in arm B. The objective tumour responses in arms A and B are listed in Table III. It should be noted that 14 patients (7%) in arm A and 12 patients (6%) in arm B were not assessed for response because of unknown reasons (12 *versus* 11), no measurable disease at study entry (one in each arm) and the absence of a comparable CT scan in one patient in arm A.

Long-term follow-up. Reporting the results with data updated 4 years after the last patient entered the study, a median follow-up of 54.6 (range 0.1-84.5) months was reached, with PD demonstrated in 388 patients (93%) (200 in arm A and 188 in arm B) and 366 (88%) deaths observed (191 and 175, respectively). Median PFS values were 7.3 months (range 0.4-41.3 months; 95% CI 6.8-7.9) in arm A and 8.2 months (range 0.1-35.6 months; 95% CI 7.4-9.1) in arm B (p=0.04; Figure 2). Median OS values were 16 months (range 0.4-72.3 months; 95% CI 13.2-18.8) in arm A and 15.4 months (range 0.1-78.8 months; 95% CI 13.1-17.6) in arm B (p=0.484; Figure 3). In multivariate Cox analysis, WHO PS, number of metastatic sites and serum CEA were identified as significant predictors of PFS (Table IV). In the presence of these independent prognostic factors a trend was detected in favour of arm B (hazard ratio [HR]=0.81, p=0.068). For OS, the significant factors were WHO PS, sex, CEA level, Hgb level, and number of metastatic sites (Table IV). No treatment arm was clearly superior in terms of OS.

Safety. Serious adverse events associated with each treatment regimen are listed in Table V. Regarding toxicity, patients were analysed according to treatment arm. The most frequently recorded grade 3/4 toxicity was diarrhoea in both treatment arms, followed by bone marrow toxicity in both arms and peripheral neuropathy in arm B. There were no significant differences in toxicities between the two arms. No treatment induced deaths occurred with either regimen.

In arm A, there were 18 cases of grade 3/4 neutropenia (8%), while there were 4 cases of febrile neutropenia (2%). In arm B, there were 25 cases of grade 3/4 neutropenia (13%), while there were 3 cases of febrile neutropenia (1.5%). Grade 3/4 diarrhoea was noted in 26 patients (12%) in arm A, while in arm B it was noted in 26 patients (14.5%). Two patients in arm B developed grade 3 peripheral neuropathy (1%).

Second-line therapy. One hundred and twenty-eight patients in arm A and one hundred and seven patients in arm B received second-line chemotherapy as depicted in Table VI.

Discussion

The present phase II study was designed to compare the efficacy of IRI plus FU/LV *versus* sequential treatment of IRI/FU/LV followed by OXA/FU/LV as first-line chemotherapy in patients with advanced CRC. The rationale was that sequential treatment can maximise cell death and overcome resistance. Additionally, the administration of the most active drugs early in the course of the disease could possibly increase response rates by eliminating resistant clones.

The study did not demonstrate the protocol-specified 15% difference in response rate, which was the primary endpoint of the study. In the current update at 4 years after the last patient entered the study, regarding the secondary efficacy endpoints of PFS and OS, there was a trend detected favouring the sequential arm for PFS, but no such indication was detected for OS. The ORRs were 25% in the IRI/FU/LV arm and 27% in the sequential arm, which

Table I. *Patient characteristics*.

	Arm A IRI-LV-FU	Arm B IRI-LV-FU followed by OXA-LV-FU
	211	206
Age (years)		
Median	67	66
Range	36-88	29-91
	N (%)	N (%)
Gender		
Female	68 (32)	80 (39)
Male	143 (68)	126 (61)
Family history of neoplasia		
Yes	46 (22)	32 (15)
No	154 (73)	164 (80)
Unknown	11 (5)	10 (5)
Previous surgery		
Yes	184 (87)	186 (90)
No	18 (8)	12 (6)
Unknown	9 (4)	8 (4)
Primary site		
Caecum	23 (11)	24 (12)
Ascending	21 (10)	21 (10)
Transverse	10 (5)	11 (5)
Descending	9 (4)	3 (2)
Sigmoid	70 (33)	74 (36)
Rectum	61 (29)	62 (30)
Unknown	17 (8)	11 (5)
Stage at diagnosis		
B_1	2 (1)	5 (2)
B_2	23 (11)	19 (9)
C_1	17 (8)	11 (5)
C_2	21 (10)	21 (10)
D	131 (62)	130 (63)
Unknown	17 (8)	20 (10)
Nerve invasion		
Yes	25 (12)	16 (8)
No	140 (66)	147 (71)
Non-applicable	7 (3)	5 (2)
Unknown	39 (19)	38 (18)
Blood vessel invasion		
Yes	24 (11)	33 (16)
No	141 (67)	130 (63)
Non-applicable	7 (3)	5 (2)
Unknown	39 (18)	38 (18)
Lymphatic vessel invasion		
Yes	29 (14)	33 (16)
No	136 (65)	130 (63)
Non-applicable	7 (3)	5 (2)
Unknown	39 (19)	38 (18)
Performance status		
0	126 (60)	132 (64)
1	74 (35)	64 (31)
2	7 (3)	5 (2)
Unknown	4 (2)	5 (2)
Symptoms		
Pain	58 (25)	61 (28)
Bloody stools	51 (23)	38 (18)
Diarrhea	18 (8)	12 (6)
Constipation	32 (14)	35 (16)
Weight loss		
<10%	17 (8)	10 (5)
≥10%	8 (4)	6 (3)
Fever	14 (6)	9 (4)
Other	81 (37)	65 (30)
Sites of metastasis		
Ascites	4 (2)	7 (3)
Pleural effusion	2 (1)	7 (3)
Liver	151 (72)	142 (69)
Abdomen	11 (5)	16 (8)
Pelvis	21 (10)	18 (9)
Lung	62 (29)	58 (28)
Nodes	36 (17)	24 (12)
Bone	8 (4)	4 (2)
Locoregional	6 (3)	4 (2)
Other	13 (6)	9 (4)
Pattern of liver metastasis		
Single	26 (17)	25 (18)
Multiple	116 (77)	106 (75)
Unknown	9 (6)	11 (8)
Involvement of liver parenchyma		
<30%	85 (56)	89 (63)
>30%	61 (40)	48 (34)
Unknown	5 (3)	5 (3)
Number of metastatic sites		
Single	130 (62)	132 (64)
Multiple	78 (37)	69 (34)
Unknown	3 (1)	5 (2)
Adjuvant chemotherapy		
Yes	36 (17)	39 (19)
No	163 (77)	159 (77)
Unknown	3 (1)	8 (4)

The two arms were well balanced with respect to patient and tumour characteristics (chi-square test).

are lower than those reported with the FOLFIRI, FOLFOX or XELOX regimens (8,19). This could be attributed to the use of bolus administration of FU in the current study, which was designed before it had clearly been demonstrated that the infusional administration of FU is more active than the bolus administration of FU (20). In another study, the combination of IRI with bolus FU/LV was compared directly with OXA followed by bolus FU/LV as first-line treatment in metastatic CRC, with comparable ORRs (33% *versus* 32%), and no difference between PFS or OS (17).

Nevertheless, the observed trend for PFS in favour of the sequential arm should be discounted in the light of no difference found either in ORR or in OS.

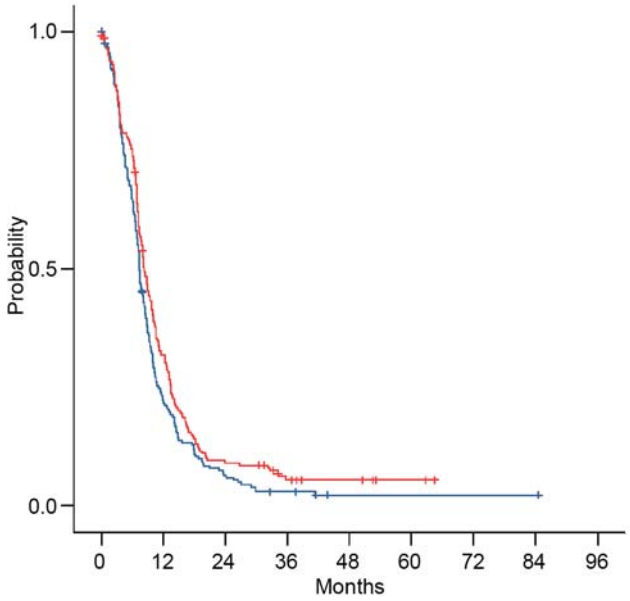

Figure 2. *Progression-free survival distributions in arm A (blue line) and arm B (red line).*

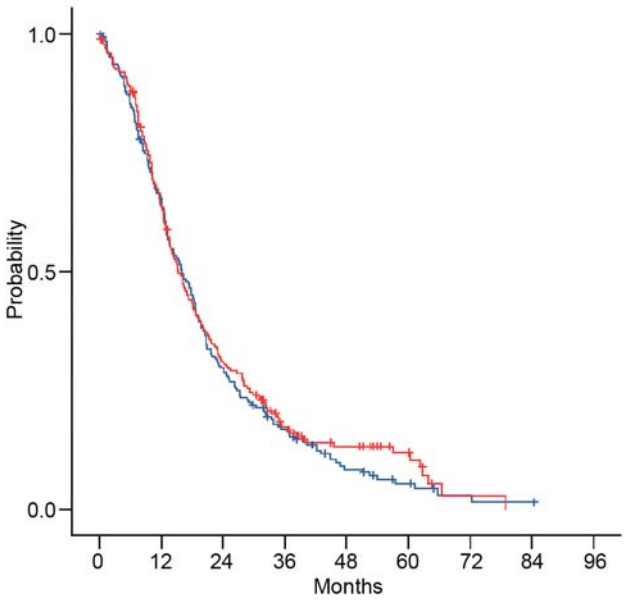

Figure 3. *Overall survival distributions in arm A (blue line) and arm B (red line).*

Table II. *Selected treatment characteristics (as treated).*

	Arm A IRI-LV-FU			Arm B IRI-LV-FU followed by OXA-LV-FU			
Number of patients	213			184			
Number of complete cycles delivered	572			521			
DI	LV	FU	IRI	LV	FU	IRI	OXA
Median delivered	114	252	43	118	262	43	24
Range	25-159	56-333	10-58	23-123	53-339	10-61	11-31
Median relative DI							
Median delivered	0.76	0.75	0.72	0.78	0.78	0.72	0.72
Range	0.2-1.0	0.2-1.0	0.2-1.0	0.2-1.1	0.2-1.0	0.2-1.0	0.3-0.9

FU, 5-Fluorouracil; IRI: irrinotecan; OXA, oxaliplatin; LV, leucovorin; DI, dose intensity (mg/m^2/week).

In the current study, in addition to the lack of a difference in OS between the two arms, OS was shorter than that seen with newer treatments incorporating targeted therapies and continuously infused FU. Emerging data suggest that the distinction between lines of therapy may not be absolute and that patients may move on to a different treatment regimen prior to disease progression and/or return to a previously used drug or regimen later (21). As currently it is not possible to accurately predict the patients that will respond to IRI- or OXA-based chemotherapy, current evidence supports the use of IRI- or OXA-based combination chemotherapy as first-line treatment followed by the other in the second-line setting. However, patients with cancer-induced poor PS may be a group in which it may be preferable to use first-line sequential combination chemotherapy, as without rapid tumour response, they are at high-risk of being unable to proceed to second-line options. Another way of exposing patients to all three active drugs in the first-line setting is to combine them as a triplet instead of using them sequentially. Two studies that have used all three active drugs as first-line treatment have been reported. In the first study by Falcone *et al.* (22), patients were randomised to receive FOLFOXIRI or FOLFIRI. Response rates were 60% *versus* 34% for FOLFOXIRI and

Table III. *Best response to treatment in the two arms.*

	Arm A N=211			Arm B N=206			
Response	N	%	95% CI	N	%	95% CI	χ^2 *p*-Value
CR	8	4	2-7	12	6	3-10	
PR	45	21	16-27	43	21	15-27	
ORR	53	25	19-31	55	27	21-33	0.71
SD	64	30	24-37	59	28	22-34	
PD	54	25	20-32	53	25	19-31	
Early death	4	2	0.5-5	4	2	(0.5-5)	
Treatment discontinuation prior to evaluation	22	10	7-15	23	11	7-16	
NE*	14	7	4-11	12	6	3-10	

Percentages are rounded up. *NE, non-evaluable; Arm A: 12 unknown, 1 no measurable disease at study entry, 1 no comparable CT; Arm B: 11 unknown, 1 no measurable disease at study entry. CR, complete response; PR, partial response; ORR, objective response rate; SD, stable disease; PD, progressive disease; CI, confidence interval.

FOLFIRI, respectively ($p<0.0001$), while PFS and OS were both significantly improved in the FOLFOXIRI arm. However, in the second study (23), patients were randomised to FOLFOXIRI *versus* FOLFIRI, with no differences in terms of OS, PFS and ORR. Additionally, patients treated with FOLFOXIRI had a higher incidence of toxicity, including alopecia, diarrhoea and neurosensory toxicity, which probably restricts considerably the administration of 3 drug regimens in patients with metastatic CRC.

With regard to treatment tolerance, no unexpected adverse events or toxic deaths were observed in this study. Treatment-related grade 3/4 toxicities were acceptable and corresponded to the known toxicities of IRI/FU/LV and OXA/FU/LV, as recorded in previous trials. The incidence of severe (grade 3/4) toxicities was similar between treatment regimens, including neurotoxicity, with only two cases of grade 3 neurotoxicity in arm B, due to OXA. Also, neutropenia was similar in both arms as well as grade 3/4 diarrhoea, which was recorded in 12% of patients in the IRI only arm and in 14% in the sequential arm.

In conclusion, the current trial, comparing the combination of IRI/FU/LV *versus* the sequential use of this regimen followed by OXA/FU/LV as first-line treatment for advanced CRC, showed equal activity in terms of ORR, PFS and OS with manageable toxicity. In the secondary endpoint of PFS, a trend favouring the sequential arm was noted, probably warranting further study of this approach. However, with the availability of targeted agents, the treatment options and outcome of patients with advanced CRC have since been changed considerably. New studies are needed to integrate new effective agents in the management of CRC and define which specific treatment should be used and when, in order to maximise the benefit in individual patients.

Table IV. *Multivariate Cox regression analysis for PFS and OS.*

	PFS		
	HR	95% CI	*p*-Value
Arm			
A	1	-	-
B	0.81	0.65-1.02	0.068
PS			
0	1	-	-
1-2	1.50	1.19-1.90	0.001
CEA			
<10	1	-	-
≥10	1.63	1.28-2.08	<0.001
Metastatic site			
Single	1	-	-
Multiple	1.36	1.08-1.73	0.010
	OS		
	HR	95% CI	*p*-Value
Arm			
A	1	-	-
B	1.00	0.79-1.27	0.999
PS			
0	1	-	-
1-2	2.02	1.56-2.61	<0.001
Gender			
Female	1	-	-
Male	1.45	1.12-1.88	0.005
CEA			
<10	1	-	-
≥10	1.79	1.39-2.32	<0.001
Hgb			
<12	1	-	-
≥12	0.73	0.58-0.93	0.010
Metastatic site			
Single	1	-	-
Multiple	1.46	1.14-1.87	0.003

Table V. *Incidence n (%) of grade 3-4 toxicities (treatment as administered).*

	Arm A (N=213) IRI-LV-FU		Arm B (N=184) IRI-LV-FU followed by OXA-LV-FU	
	Grade 3	Grade 4	Grade 3	Grade 4
Anaemia	3 (1)	-	4 (2)	-
Leucopenia	8 (4)	1 (0.5)	14 (8)	-
Neutropenia	10 (4)	8 (4)	19 (10)	6 (3)
Febrile neutropenia	-	4 (2)	2 (1)	1 (0.5)
Thrombocytopenia	2 (1)	-	-	-
Nausea/Vomiting	3 (1)	-	6 (3)	1 (0.5)
Mucositis	-	-	1 (0.5)	-
Diarrhoea	20 (9)	6 (3)	25 (14)	1 (0.5)
Alopecia	4 (2)	-	2 (1)	-
Infection	1 (0.5)	-	-	1 (0.5)
Peripheral neuropathy	-	-	2 (1)	-
Fatigue	2 (1)	-	1 (0.5)	-
DVT	-	-	1 (0.5)	-
Pain	-	-	1 (0.5)	-
Hepatotoxicity	-	1 (0.5)	-	-

No significant differences in the rates of toxicity were observed (Fisher's exact test); Percentages are rounded-up.

Table VI. *Second-line chemotherapy.*

	Arm A IRI-LV-FU	Arm B IRI-LV-5FU followed by OXA-LV-5FU
	N (%)	N (%)
2nd line chemotherapy		
Yes	128 (61)	107 (52)
No	64 (30)	87 (42)
Unknown	19 (9)	12 (6)
	N=128	N=107
FOLFIRI	8 (6)	13 (12)
FOLFOX	56 (44)	23 (22)
XELIRI	45 (35)	16 (15)
XELOX	15 (12)	48 (45)
Other	3 (2)	5 (5)
Unknown	1 (1)	2 (2)

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