Sequential versus combination chemotherapy for the treatment of advanced colorectal cancer (FFCD 2000–05): an open-label, randomised, phase 3 trial

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Summary

Background The optimum use of cytotoxic drugs for advanced colorectal cancer has not been defined. Our aim was to investigate whether combination treatment is better than the sequential administration of the same drugs in patients with advanced colorectal cancer.

Methods In this open-label, randomised, phase 3 trial, we randomly assigned patients (1:1 ratio) with advanced, measurable, non-resectable colorectal cancer and WHO performance status 0–2 to receive either first-line treatment with bolus (400 mg/m²) and infusional (2400 mg/m²) fluorouracil plus leucovorin (400 mg/m²) (simplified LV5FU2 regimen), second-line LV5FU2 plus oxaliplatin (100 mg/m²) (FOLFOX6), and third-line LV5FU2 plus irinotecan (180 mg/m²) (FOLFIRI) or first-line FOLFOX6 and second-line FOLFIRI. Chemotherapy was administered every 2 weeks. Randomisation was done centrally using minimisation (minimisation factors were WHO performance status, previous adjuvant chemotherapy, number of disease sites, and centre). The primary endpoint was progression-free survival after two lines of treatment. Analyses were by intention-to-treat. This trial is registered at ClinicalTrials.gov, NCT00126256.

Findings 205 patients were randomly assigned to the sequential group and 205 to the combination group. 161 (79%) patients in the sequential group and 161 (79%) in the combination group died during the study. Median progression-free survival after two lines was 10·5 months (95% CI 9·6–11·5) in the sequential group and 10·3 months (9·0–11·9) in the combination group (hazard ratio 0·95, 95% CI 0·77–1·16; p=0·61). All six deaths caused by toxic effects of treatment occurred in the combination group. During first-line chemotherapy, significantly fewer severe (grade 3–4) haematological adverse events (12 events in 203 patients in sequential group *vs* 83 events in 203 patients in combination group; p<0·0001) and non-haematological adverse events (26 events *vs* 186 events; p<0·0001) occurred in the sequential group than in the combination group.

Interpretation Upfront combination chemotherapy is more toxic and is not more effective than the sequential use of the same cytotoxic drugs in patients with advanced, non-resectable colorectal cancer.

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Introduction

Advanced colorectal cancer causes more than half a million deaths every year worldwide.[1,2] For most patients with advanced disease, the aim of treatment is not to cure but to extend life expectancy and enhance, or at least preserve, quality of life, with as little inconvenience as possible for patients, keeping toxic effects of treatment to a minimum.

Fluorouracil was the only standard of care for patients with advanced colorectal cancer for decades. Efforts to improve the effectiveness of fluorouracil culminated with a regimen of infusional plus bolus fluorouracil and folinic acid (eg, the de Gramont [LV5FU2] regimen) every 2 weeks, which yielded higher response rates and progression-free survival and less toxic effects than did monthly bolus fluorouracil and folinic acid (the Mayo Clinic regimen).[3] However, in the absence of effective salvage treatment, reported median overall survival with fluorouracil (or capecitabine) alone ranged from 11 months to 13 months.[4–7]

With a 3·5 month improvement in median overall survival,[8] frontline combination chemotherapy regimens with fluorouracil and either irinotecan[9,10] or oxaliplatin[11,12] became the standard of care for most patients with advanced colorectal cancer. However, the survival results of randomised studies in which combination treatments were investigated should be interpreted with caution, because salvage treatments—which might have affected the results—were not a prospective part of the study designs, and the availability of irinotecan and especially oxaliplatin was variable when these studies were done.[13] An analysis of 11 phase 3 trials with 5768 patients with advanced colorectal cancer[4,9–11,14–20] showed that the wide variation (14·8–21·5 months) in median overall survival was not attributable to whether or not a doublet was administered during first-line treatment, but only to

patients' access to fluorouracil, irinotecan, and oxaliplatin.[21] Therefore, a strategy of making all active drugs available to patients with advanced colorectal cancer seems more important than the use of combination treatment upfront, or than the overall percentage of patients receiving any second-line treatment. Effective salvage treatments might compensate for less active first-line treatment.

Nevertheless, only 50–60% of patients starting a line of treatment receive a further line of treatment, and phase 3 trials of doublet sequences with mandatory crossover (eg, FOLFOX [folinic acid,tenek fluorouracil, and oxaliplatin] followed by FOLFIRI [folinic acid, fluorouracil, and irinotecan] *vs* FOLFIRI followed by FOLFOX[17]) or first-line chemotherapy triplets (FOLFOXIRI or FOLFIRINOX, both combinations of folinic acid, fluorouracil, oxaliplatin, and irinotecan[22,23]), in which patients had the greatest chances of receiving all three active agents during their treatment, yielded the longest median overall survival times ever reported in the pre-targeted therapy era. Thus, in clinical practice, combination therapy is the most widely accepted standard of care for first-line treatment of patients with advanced colorectal cancer. However, these combinations increase toxicity and cost.

In the Fédération Francophone de Cancérologie Digestive (FFCD) 2000–05 trial, our aim was to establish whether initial combination therapy (FOLFOX followed by FOLFIRI[17]) is better than sequential administration of the same drugs starting with first-line fluorouracil and folinic acid alone (LV5FU2[3] followed by FOLFOX then by FOLFIRI) in terms of progression-free survival after two lines of therapy in patients with advanced, non-resectable colorectal cancer.

Methods

Participants

In this open-label, randomised, phase 3 trial, we enrolled patients with histologically proven, metastatic colorectal cancer not amenable to curative intent surgery. Patients were recruited between Feb 1, 2002, and Feb 1, 2006, from 53 centres in France. Patients were eligible for enrolment if they were older than 18 years and had measurable disease according to WHO criteria;[24] a WHO performance status of 0–2;[24] no history of chemotherapy for metastatic disease; and adequate hepatic, renal, and bone marrow function (ie, haemoglobin concentration >90 g/L, white blood cell count >4×10⁹ cells per L, platelet count >100×10⁹ per L, serum bilirubin concentration <1·5 times the upper limit of normal, alkaline phosphatase concentration less than five times the upper limit of normal, and creatinine concentration less than two times normal). Previous adjuvant chemotherapy without oxaliplatin was allowed provided that the last administration was given at least 6 months before randomisation. Patients were excluded if they had a serious concomitant medical disorder that would prevent the safe administration of chemotherapy or would be likely to interfere with study assessments.

Written informed consent was obtained from all patients before study entry. The study was approved by the Kremlin Bicêtre Hospital ethics committee.

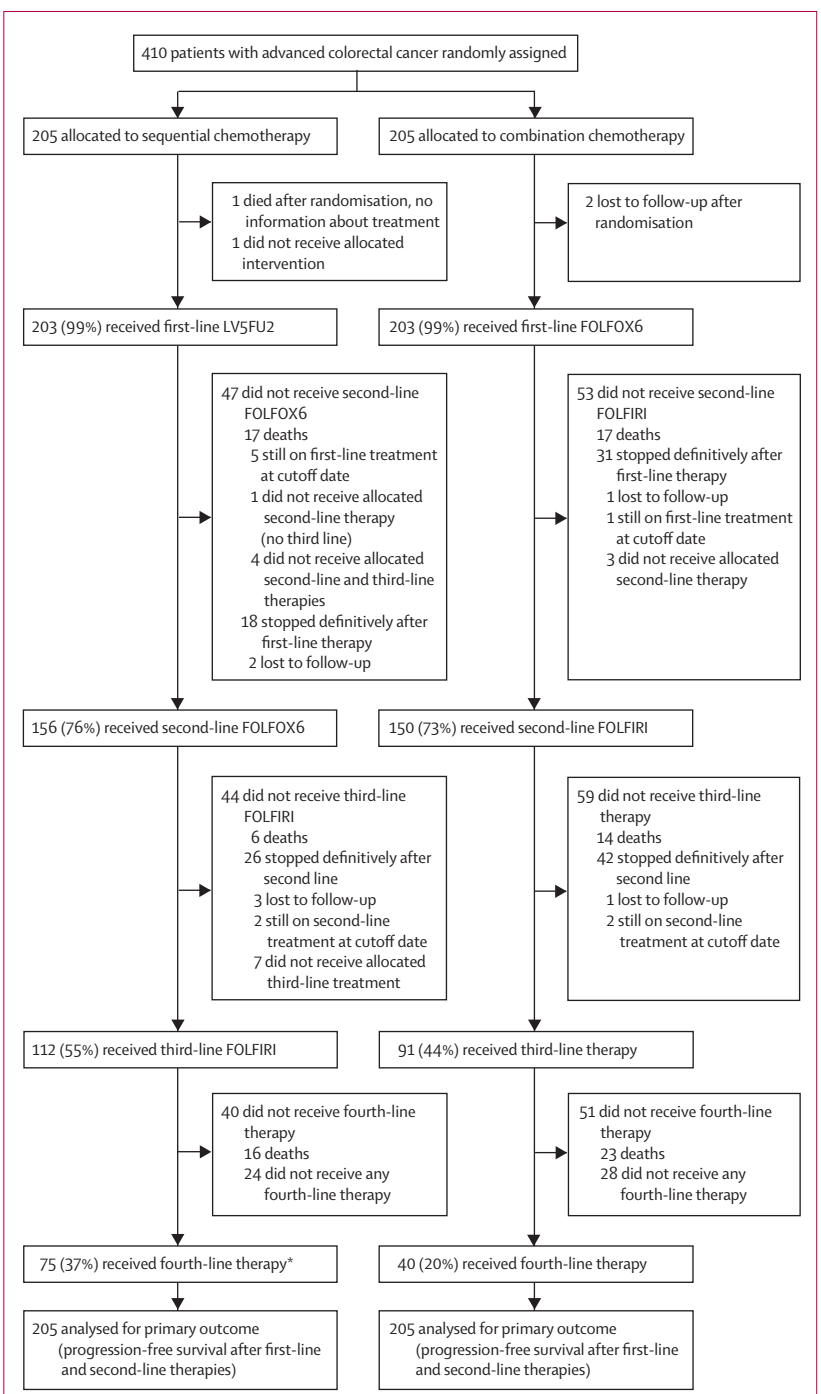

Figure 1: **Trial profile**
*Including three patients who received a fourth-line therapy other than the one planned.

Randomisation and masking

For the **Tenalea program** see http://www.tenalea.com

Eligible patients were randomly assigned to either sequential or combination treatment in a one-to-one ratio. Randomisation was done centrally with a minimisation technique that ensured equal distribution of patients on the basis of WHO performance status (0–1 *vs* 2), previous adjuvant chemotherapy (yes *vs* no), number of disease sites (one *vs* more than one), and treatment centre. Investigators or research assistants sent the randomisation form by fax to the biostatistics department of the Institut Gustave-Roussy. After checking the inclusion criteria, the study data manager did the randomisation with the Tenalea program, an online, central randomisation service, and sent the allocated treatment back to the investigator by fax. Investigators who assessed the response to the treatment were not masked to group assignment.

See Online for webappendix

	Sequential treatment (n=205)	Combination treatment (n=205)
Sex		
Male	123 (60%)	130 (63%)
Female	82 (40%)	75 (37%)
Age		
Median age at randomisation (years [IQR])	66 (56–72)	68 (57–73)
<50 years	17 (8%)	14 (7%)
50–69 years	116 (57%)	104 (51%)
≥70 years	72 (35%)	87 (42%)
WHO performance status*		
0	96 (47%)	91 (44%)
1	77 (38%)	81 (40%)
2	32 (16%)	33 (16%)
Previous surgery		
Primary†	132 (65%)	120 (59%)
Metastases‡	7 (3%)	8 (4%)
Previous adjuvant treatment		
Chemotherapy*	23 (11%)	23 (11%)
Radiotherapy	20 (10%)	14 (7%)
Site of primary tumour§		
Colon	154 (76%)	159 (79%)
Rectum	49 (24%)	41 (21%)
Number of disease sites*		
1	107 (52%)	107 (52%)
>1	98 (48%)	98 (48%)
Main metastatic sites		
Liver	177 (86%)	187 (91%)
Lung	83 (40%)	74 (36%)
Abdominal lymph nodes	36 (18%)	46 (22%)
Extra-abdominal lymph nodes	21 (10%)	22 (11%)
Peritoneum	23 (11%)	40 (20%)
Köhne score¶		
1	36 (18%)	36 (18%)
2	70 (34%)	71 (35%)
3	95 (46%)	92 (45%)

Data are n (%) unless otherwise stated. *Stratification factor. †Three patients with missing data (one in the sequential group and two in the combination group). ‡Six patients with missing data (two in the sequential group and four in the combination group). §Seven patients with missing data (four in the sequential group and five in the combination group). ¶Ten patients with missing data (four in the sequential group and six in the combination group); Köhne score was calculated with an algorithm that used WHO performance status, white blood-cell count, number of metastatic sites, and alkaline phosphatase concentration.[29]

Table 1: **Baseline characteristics**

Procedures

All treatment cycles were administered at 2-week intervals. Treatment was started within 7 days of randomisation. Two treatment strategies were compared. In the sequential treatment group, first-line treatment was with fluorouracil (a simplified LV5FU2 regimen, described in the webappendix p 2) and continued until treatment failure (ie, disease progression or unacceptable toxic effects). Thereafter, in patients fit enough for second-line treatment, oxaliplatin was added (FOLFOX6 regimen;[17] webappendix p 2) until treatment failure. In patients fit enough for third-line treatment, oxaliplatin was replaced by irinotecan (FOLFIRI regimen;[25] webappendix p 2). In the combination group, patients received FOLFOX6 from the outset until treatment failure. In patients fit enough for second-line treatment, FOLFIRI was given (webappendix p 2). Third-line treatment in the combination group and further lines of treatment in either group were at the investigator's discretion. Chemotherapy-free intervals were not allowed during the first 6 months, but were allowed at the investigator's discretion thereafter in patients with responding or stable disease. The same treatment was resumed after such breaks, provided disease did not progress within 12 weeks.

Tumour response was assessed every 8 weeks with CT scans or MRI. Treatment response was assessed by the investigators with WHO criteria.[24] Responses were not systematically confirmed by repeat scans. An external radiological review was not undertaken. Toxic effects were scored with the US National Cancer Institute Common Toxicity Criteria (version 2.0[26]) until 4 weeks after the end of study treatments. At every visit, patients underwent a history and physical examination, haematological tests, and biochemical tests. Drug dose reductions and delays in cases of haematological or non-haematological toxic effects were done as specified per protocol. Patients receiving oxaliplatin were carefully monitored for sensory neuropathy, and oxaliplatin was discontinued if grade 2 or worse symptoms persisted between cycles. In case of progressive disease, oxaliplatin was resumed provided neuropathy had resolved to grade 1 or below. The reintroduction of oxaliplatin was regarded as the continuation of the treatment line (first or second) and not as treatment of progression. An independent data monitoring committee reviewed safety data on a regular basis.

We used the QLQ-C questionnaire of the European Organisation for Research and Treatment of Cancer (EORTC) to assess wellbeing of patients during the study. Of the 15 dimensions, we regarded three as being

especially relevant for the trial: global, physical, and emotional dimensions; we did not analyse the other dimensions. Questionnaires were completed during the week before randomisation and every 8 weeks thereafter until progression during second-line treatment or after 6 months of study treatment, whichever came first.

Statistical analysis

The primary endpoint was progression-free survival for first-line and second-line treatment (PFS2), and was calculated from the date of randomisation to the first report of disease progression or death from any cause after the start of second-line treatment (FOLFOX6 regimen for the sequential group, FOLFIRI regimen for the combination group), or, if a patient did not start second-line treatment, the date of the first sign of progression reported after randomisation or death or the date when the patient was last known to be alive. Secondary objectives were to assess the objective response rate and progression-free survival for first-line treatment (PFS1), and, for first-line, second-line, and third-line treatment (PFS3), overall survival, toxic effects, and quality of life. PFS1 was calculated from the date of randomisation to the first report of disease progression or death from any cause. PFS3 was defined as the time from randomisation until the first sign of progression, death, or the date when the patient was last known to be alive after the start of third-line treatment. PFS2 was used when the patients did not start third-line treatment. Likewise, PFS1 was used when the patients did not start second-line treatment.[17] The first progression occurring during a treatment line was used in PFS1, PFS2, and PFS3 without taking into account treatment breaks. Overall survival was calculated as the interval from the date of randomisation until death from any cause or until the date of the last follow-up. Patients were regarded as assessable for toxic effects of treatment if they had started treatment and for response to treatment if they had completed at least two cycles of treatment. We did pharmacogenetic analyses during this trial, the results of which are reported elsewhere.[27] We also assessed temporal variation in the proportion of patients with a low quality-of-life score (≤75%, on a scale between 0 and 100%).

We needed 570 patients (450 events) to show an absolute improvement in median PFS2 of 3 months, from 10 months in the sequential group to 13 months in the combination group, with 90% power and a 5%, two-sided, type I error rate.

All analyses, except safety analyses of toxicity, were by intention to treat. We estimated median follow-up with the reverse Kaplan-Meier method.[28] The cutoff date for the analysis was Jan 1, 2007. We estimated overall and progression-free survival curves with the Kaplan-Meier method and compared with the log-rank test, stratified by centre. Analysis with the Cox model, stratified by centre and adjusted for age, sex, and the Köhne score,[29] gave much the same results and is not reported here. The occurrence of grade 3–4 adverse events was compared with the χ^2 test. Patients who completed the quality-of-life questionnaire at baseline and at least once during treatment were included in the analysis of quality of life. Repeated measurements of quality of life were analysed with a generalised estimating equation model for multinomial data with initial score and treatment as covariates. To take into account missing quality-of-life data, mainly because of disease progression, a dummy variable (to indicate whether each measurement was the last) was included in the model.[30] We used Fisher's exact test to compare deaths caused by study treatment between groups. All tests were two-sided and p values of less than 0·05 were regarded as significant. Data were analysed with SAS statistical software (version 9.01). This study is registered at ClinicalTrials.gov, number NCT00126256.

	Sequential treatment	Combination treatment	p value
Relative dose intensity			
First-line treatment			
Fluorouracil (bolus)	91% (17–115)	80% (0–114)	<0·0001
Fluorouracil (infusion)	90% (25–118)	82% (27–113)	<0·0001
Oxaliplatin	..	69% (0–114)	..
Second-line treatment			
Fluorouracil (bolus)	81% (0–105)	77% (0–176)	0·21
Fluorouracil (infusion)	81% (0–104)	81% (28–115)	0·81
Oxaliplatin	77% (3–104)	..	..
Irinotecan	..	81% (38–113)	..
Third-line treatment			
Fluorouracil (bolus)	78% (0–108)	..	..
Fluorouracil (infusion)	78% (28–108)	..	..
Irinotecan	82% (23–107)	..	..
Total cumulative dose			
First-line treatment			
Fluorouracil (bolus)	4000 (390–20 213)	4314 (0–20 720)	..
Fluorouracil (infusion)	25 635 (1200–120 250)	28 370 (1289–126 120)	..
Oxaliplatin	..	916 (0–2232)	..
Second-line treatment			
Fluorouracil (bolus)	3030 (0–14 204)	1868 (0–28 400)	..
Fluorouracil (infusion)	19 265 (0–84 980]	12 379 (1349–170 400)	..
Oxaliplatin	768 (5–1616)	..	..
Irinotecan	..	915 (159–12 600)	..
Third-line treatment			
Fluorouracil (bolus)	1772 (0–15 047)	..	..
Fluorouracil (infusion)	12 239 (2105–90 295)	..	..
Irinotecan	941 (84–6811)	..	..

Data are % (range) or mg/m² (range).

Table 2: **Relative dose intensity and total dose**

Role of the funding source

The sponsor of the study had no role in study design, data collection, data analysis, data interpretation, or writing of the report. The corresponding author and study statistician had full access to all the data in the study and had final responsibility for the decision to submit for publication.

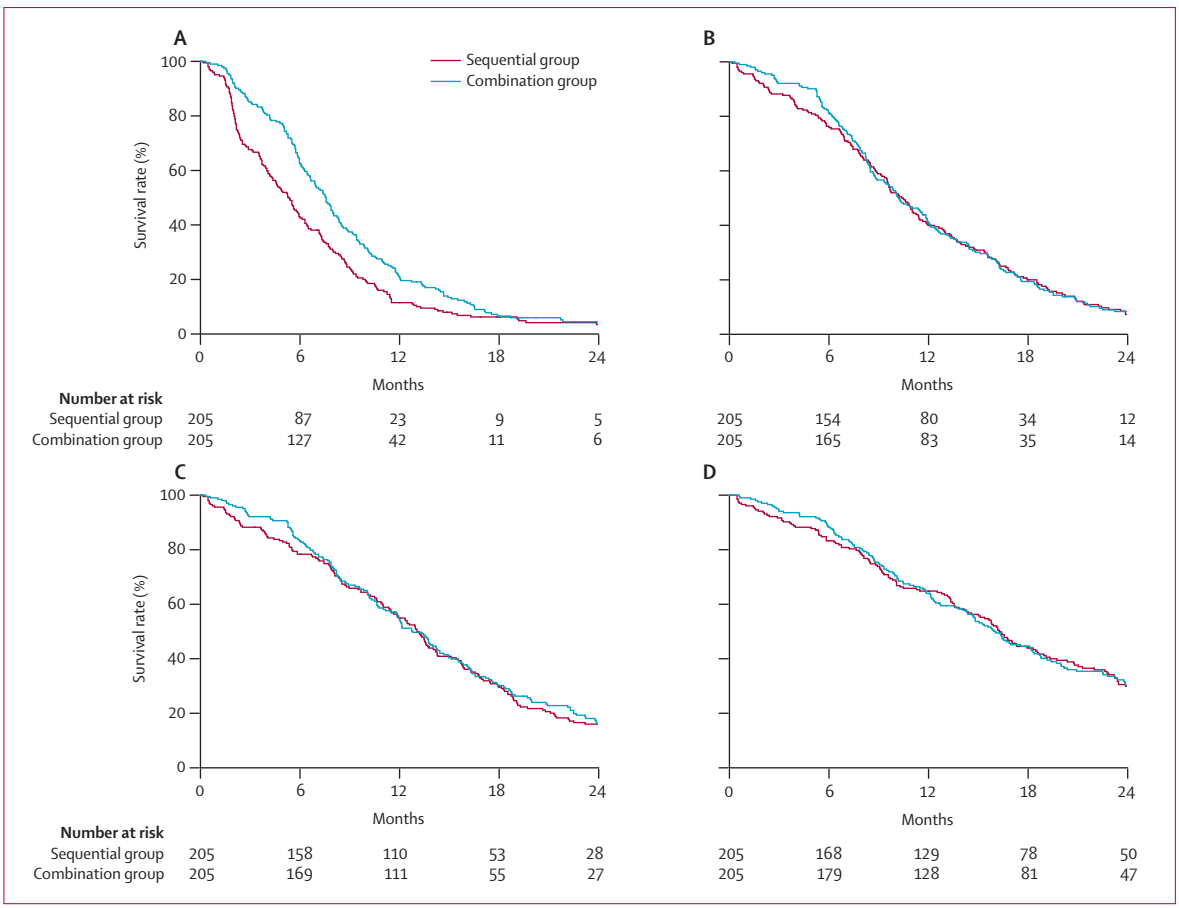

Figure 2: **Progression-free and overall survival by treatment group**
(A) Progression-free survival after first-line treatment. (B) Progression-free survival after two lines of treatment. (C) Progression-free survival after three lines of treatment. (D) Overall survival. LV5FU2 corresponds to the sequential group and FOLFOX to the combination group. The p values correspond to a logrank test.

Results

410 patients were randomly assigned, 205 in each study group (figure 1). The trial was stopped before the planned interim analysis, when the approval of bevacizumab for treatment of advanced colorectal cancer resulted in a pronounced decrease in accrual of patients. Nine patients (2%) were lost to follow-up. Baseline characteristics of patients were much the same between the two groups (table 1). Overall, median age was 67 years (IQR 34–83); 159 patients [39%] were aged 70 or over, 65 patients (16%) had a performance status of 2, and almost half (196 patients [48%]) had at least two metastatic sites.

Almost all patients received at least one cycle of the planned first-line treatment, whilst around three-quarters received at least one cycle of the planned second-line treatment (figure 1). Significantly more patients received third-line treatment in the sequential group than in the combination group (p=0·03; figure 1). The proportion of patients who received any fourth-line treatment was significantly higher in the sequential group than in the combination group (p=0·0001).

In the sequential group, the median number of cycles was 12 (IQR 4–16) during first-line, eight (6–12) during second-line, and six (4–9) during third-line treatment. In the combination group, the median number of cycles was 12 (8–18) during first-line, six (4–10) during second-line, and four (2–6) during third-line treatment. During first-line treatment, the proportions of patients who received 12 cycles or less was 64% in the sequential group (131 of 205 patients), and 56% in the combination group (114 of 205 patients). Third-line cetuximab was administered to 41 (45%) of 91 patients in the combination group (with irinotecan in all but one patient). Overall, the median number of cycles (all lines) was 22 (IQR 12–30) in the sequential group and 20 (12–30) in the combination group (p=0·48). Of 4660 cycles administered in the sequential group, 2414 (52%) were during first-line, 1462 (31%) were during second-line, and 784 (17%) were during third-line treatment; whereas of 4548 cycles given in the combination group, 2838 (63%) were during first-line, 1286 (28%) were during second-line, and 424 (9%) were during third-line treatment (p<0·0001). The median time that patients received treatment (ie, interval between the start of

protocol treatment and a patient leaving the study) was 285 days (IQR 172–458) in the sequential treatment group and 278 (180–461) in the combination group.

The relative dose intensity of fluorouracil (both bolus and infusional) was higher in the sequential group than it was in the combination group during first-line (p<0·0001), but not during second-line treatment (table 2). The relative dose intensity of oxaliplatin was higher during second-line treatment in the sequential group than it was during first-line treatment in the combination group (p=0·0005). Oxaliplatin was included in 1322 (90%) of 1462 cycles in the sequential group and in 2094 (74%) of 2838 cycles in the combination group. In the remaining cycles, fluorouracil was given alone after the development of persistent neuropathy. The relative dose intensity of irinotecan was much the same during second-line treatment in the combination group and third-line treatment in the sequential group (p=0·41).

Treatment discontinuation because of unacceptable toxic effects during first-line treatment occurred more often in the combination group (31 [15%] of 205 patients) than in the sequential group (two [1%] of 205 patients, p<0·0001), whereas during second-line treatment it occurred more often in the sequential group (25 [16%] of 159 patients) than in the combination group (three [2%] of 147 patients, p<0·0001).

There was no significant difference in median PFS2 between the two groups (378 events—188 in the sequential group and 190 in the combination group; HR 0·95, 95% CI 0·77–1·16; log-rank p=0·61; figure 2 and table 3). Likewise, PFS3 was not significantly different between the two groups (HR 0·95, 0·77–1·16; p=0·62; figure 2 and table 3). Progression-free survival was significantly longer in the combination group than it was in the sequential group during first-line treatment (HR 0·70, 0·57–0·85; p=0·0004; figure 2 and table 3).

At the time of the analysis, 322 (79%) of the 410 randomly assigned patients had died (161 in each group). Median follow-up was 36 months (IQR 26–44). Overall survival did not differ significantly between the two groups (HR 1·02, 95% CI 0·82–1·27; p=0·85; figure 2 and table 3). Figure 3 shows the effect of treatment on overall survival according to baseline covariates. Patients with two or more disease sites or with poor-prognosis disease, as predicted by a Köhne prognostic score of 1–2,[29] seemed to benefit more from the combination treatment, whereas those with one disease site or good-prognosis disease (ie, a Köhne prognostic score of 3[29]) seemed to benefit more from the sequential treatment (interaction test for number of disease sites, p=0·05 and trend test for Köhne prognostic score, p=0·04).

Of all participants, the objective response rate (ie, complete plus partial responses) during first-line treatment was significantly better in the combination group than it was in the sequential group (p<0·0001; table 3). The disease control rate (ie, complete response plus partial response plus stable disease) was significantly better in the combination group than in the sequential group (table 3). Of 306 patients who received at least one cycle of the planned second-line treatment, the objective response rate was significantly better in the sequential group than it was in the combination group (p=0·02; table 3), as was the disease control rate (table 3). Of the 203 patients who received at least one cycle of third-line treatment, the objective response rate was not significantly different between the two groups (p=0·85), but the disease control rate was significantly higher in the sequential group (p=0·0007; table 3). The curative resection rates during all treatment lines did not differ between groups (table 3).

During first-line treatment, grade 3–4 neutropenia occurred significantly more in the combination group than in the sequential group (p<0·0001), as did nausea and vomiting (p=0·006) and grade 2–4 neurological toxicity (p<0·0001; table 4). Table 5 shows adverse events that occurred during all lines of treatment. Neutropenia and neurological toxicity (p<0·0001)

	Sequential treatment (n=205)	Combination treatment (n=205)	p value
Survival outcomes			
First-line PFS (PFS1)	5·3 (4·4–6·0)	7·6 (6·7–8·3)	0·0004
1-year survival	12% (7–16)	21% (15–27)	
2-year survival	3% (1–6)	5% (1–8)	
3-year survival	1% (0–3)	2% (0–5)	
Second-line PFS (PFS2)	10·5 (9·6–11·5)	10·3 (9·0–11·9)	0·61
1-year survival	40% (33–47)	41% (35–48)	
2-year survival	7% (3–11)	8% (4–12)	
3-year survival	2% (0–4)	3% (1–6)	
Third-line PFS (PFS3)	13·2 (11·7–14·3)	12·9 (11·9–14·4)	0·62
1-year survival	55% (48–62)	55% (48–62)	
2-year survival	16% (11–21)	16% (11–22)	
3-year survival	5% (2–8)	8% (4–12)	
Overall survival	16·4 (14·5–18·6)	16·2 (14·4–18·4)	0·85
1-year survival	65% (58–71)	64% (57–71)	
2-year survival	30% (23–37)	30% (24–37)	
3-year survival	16% (10–22)	13% (7–18)	
Objective response rate (CR and PR)			
First-line*	24% (18–30)	58% (51–65)	<0·0001
Second-line†‡	21% (15–28)	11% (6–18)	0·02
Third-line†§	8% (3–13)	9% (3–15)	0·85
Disease control rate (CR, PR, and SD)			
First-line¶	68% (61–74)	83% (78–88)	0·0004
Second-line†‖	77% (70–83)	50% (42–58)	<0·0001
Third-line†**	47% (38–56)	24% (15–33)	0·0007
Curative resection rate (during all lines)††	2% (0–4)	4% (1–7)	0·24

Data are median number of months (95% CI) or % (95% CI). CR=complete tumour response. PR=partial tumour response. SD=stable disease. *50 of 205 patients *vs* 118 of 205 patients. †In patients receiving at least one dose of chemotherapy. ‡31 of 148 patients *vs* 14 of 131 patients. §10 of 124 patients *vs* eight of 91 patients. ¶139 of 205 patients *vs* 170 of 205 patients. ‖114 of 148 patients *vs* 66 of 131 patients. **58 of 124 patients *vs* 22 of 91 patients. ††Four of 205 patients *vs* eight of 205 patients.

Table 3: **Efficacy results**

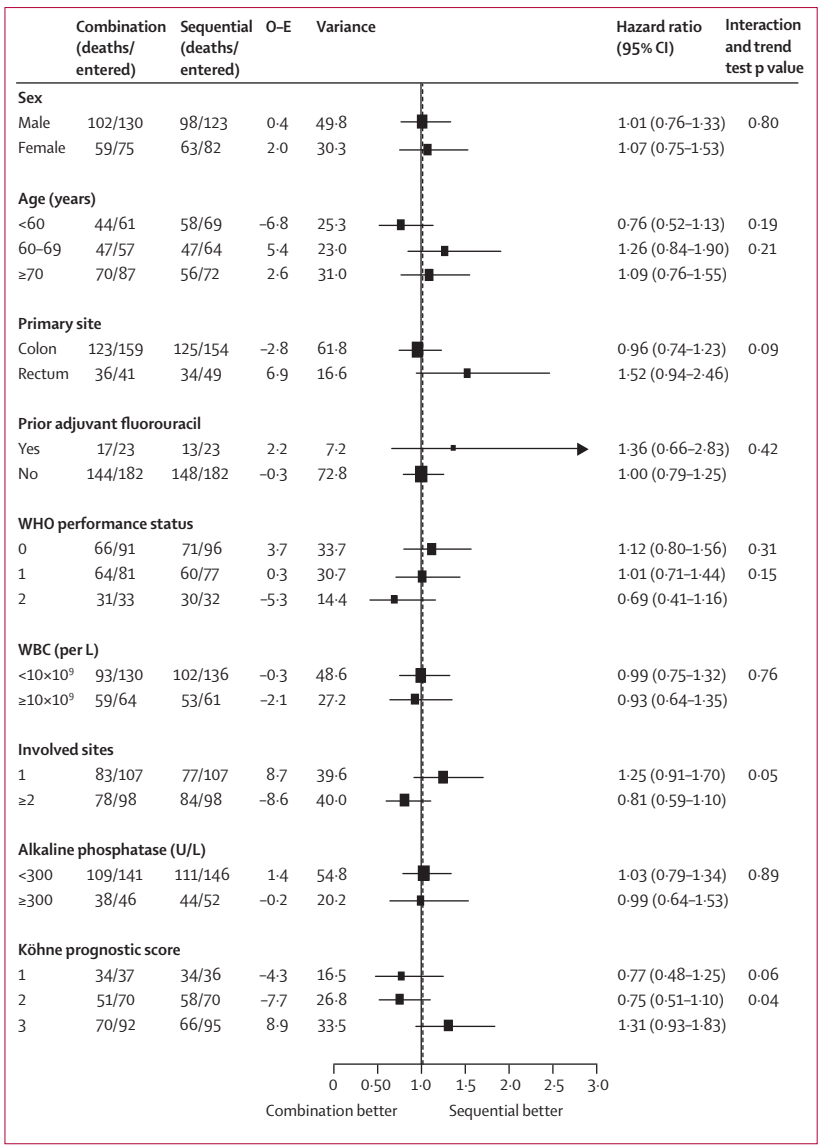

Figure 3: **Interaction between covariates and the treatment effect on overall survival**
O–E=observed minus expected results. WBC=white blood-cell count.

occurred more often in the combination group than in the sequential group.

The webappendix shows adverse events associated with FOLFOX (first-line *vs* second-line; p 3), FOLFIRI (second-line *vs* third-line; p 4), and during second-line treatment (FOLFIRI *vs* FOLFOX; p 5). Overall, the FOLFOX regimen was slightly more toxic during first-line than during second-line treatment (grade 3–4 toxicity, 173 [85%] of 203 patients *vs* 115 [74%] of 156 patients; p=0·007). This finding was because severe neuropathy occurred less often when FOLFOX6 was given in second line instead of first line—the lower rate of neuropathy is explained by the shorter duration of FOLFOX (grade 2–4 neuropathy, 129 [64%] of 203 patients in the combination group *vs* 75 [48%] of 156 in sequential group; p=0·003). During second-line treatment, thrombocytopenia occurred more often with the FOLFOX regimen than with FOLFIRI (all grades of thrombocytopenia, 87 [56%] of 156 patients *vs* 41 [27%] of 150 patients; p<0·0001). Side-effects did not differ significantly for the FOLFIRI regimen when it was given as second-line or a third-line treatment.

Overall, severe toxicity (grade 3–4) occurred more often in the combination group than it did in the sequential group during first-line treatment (p<0·0001) and all lines of treatment together (p<0·0001), but not during second-line treatment (p=0·27; table 5).

Six non-cancer deaths (1·5% of patients) reported as definitely or probably caused or precipitated by study treatment occurred in the combination group (four with first-line treatment and two with second-line treatment) and none were reported in the sequential group (Fisher's exact test, p=0·03). The causes of death were sepsis (three patients), and colonic ischaemia, myocardiopathy, stroke, and anaphylactic shock during oxaliplatin infusion (one patient in each case; one patient died from two contributing factors—myocardiopathy and stroke).

Of 281 patients (140 in the sequential group and 141 in the combination group) for whom at least two completed quality-of-life questionnaires were available, we recorded no significant difference between groups in the global and physical dimensions. The only significant difference was in the emotional dimension; the proportion of patients with a score on the emotional scale of 75% or below decreased significantly more in the combination group than in the sequential group (p=0·009; webappendix p 6).

Discussion

Our results show that frontline combination chemotherapy was not better than deferred combination chemotherapy for the treatment of patients with advanced colorectal cancer. The response rate and progression-free survival were higher with first-line treatment in the combination group than they were in the sequential group. However, combination chemotherapy was associated with more toxic effects during first-line treatment than with fluorouracil alone. Progression-free survival during subsequent lines of treatment and overall survival were not significantly different between the study groups. Our findings suggest that the survival benefit recorded with combination chemotherapy in previous phase 3 studies[13] might have been overestimated because of the insufficient use of salvage treatments in the control group.

Our results are in line with those of two randomised trials[16,31] that investigated whether patients with advanced colorectal cancer should be treated initially with combination chemotherapy, or whether fluoropyrimidine alone, followed at disease progression by different drug combinations or a second drug on its own (irinotecan),

	Sequential treatment (n=203)	Combination treatment (n=203)	p value
Overall toxicity			
All grades	194 (96%)	202 (>99%)	0·01
Grade 3–4	57 (28%)	173 (85%)	<0·0001
Non-haematological adverse events			
Diarrhoea			
All grades	76 (37%)	94 (46%)	0·08
Grade 3–4	10 (5%)	10 (5%)	0·99
Nausea			
All grades	98 (48%)	126 (62%)	0·006
Grade 3–4	3 (1%)	17 (8%)	0·001
Vomiting			
All grades	98 (48%)	126 (62%)	0·006
Grade 3–4	3 (1%)	17 (8%)	0·001
Stomatitis			
All grades	54 (27%)	70 (34%)	0·09
Grade 3–4	3 (1%)	7 (3%)	0·34
Sensory neuropathy			
All grades	22 (11%)	181 (89%)	<0·0001
Grade 2–4	2 (1%)	129 (64%)	<0·0001
Alopecia			
All grades	28 (14%)	33 (16%)	0·50
Grade 3	0 (0%)	2 (1%)	0·50
Cutaneous			
All grades	39 (19%)	50 (25%)	0·20
Grade 3–4	2 (1%)	1 (<1%)	0·62
Cardiac toxicity			
All grades	5 (2%)	5 (2%)	0·99
Grade 3–4	3 (1%)	3 (1%)	1·00
Haematological adverse events			
Anaemia			
All grades	125 (62%)	137 (67%)	0·24
Grade 3–4	5 (2%)	11 (5%)	0·13
Neutropenia			
All grades	32 (16%)	134 (66%)	<0·0001
Grade 3–4	4 (2%)	62 (31%)	<0·0001
Thrombocytopenia			
All grades	20 (10%)	130 (64%)	<0·0001
Grade 3–4	3 (1%)	10 (5%)	0·05

Data are n (%). Adverse-event data are for 203 of 205 patients in each group because one patient died after randomisation with no information about treatment received (sequential group), one did not receive the allocated treatment (sequential group), and two were lost to follow-up after randomisation (combination group).

Table 4: **Adverse events associated with sequential versus combination treatment during first-line treatment**

	Sequential treatment (n=203)	Combination treatment (n=203)	p value
Overall toxicity			
All grades	202 (>99%)	203 (100%)	1·00
Grade 3–4	161 (79%)	190 (94%)	<0·0001
Non-haematological adverse events			
Diarrhoea			
All grades	123 (61%)	134 (66%)	0·26
Grade 3–4	17 (8%)	22 (11%)	0·40
Nausea or vomiting			
All grades	143 (70%)	145 (71%)	0·83
Grade 3–4	13 (6%)	23 (11%)	0·08
Stomatitis			
All grades	81 (40%)	88 (43%)	0·48
Grade 3–4	6 (3%)	12 (6%)	0·15
Sensory neuropathy			
All grades	141 (69%)	184 (91%)	<0·0001
Grade 2–4	83 (41%)	134 (66%)	<0·0001
Alopecia			
All grades	59 (29%)	56 (28%)	0·74
Grade 3	3 (1%)	9 (4%)	0·08
Cutaneous			
All grades	60 (30%)	83 (41%)	0·02
Grade 3–4	7 (3%)	5 (2%)	0·56
Cardiac toxicity			
All grades	7 (3%)	9 (4%)	0·61
Grade 3–4	4 (2%)	5 (2%)	1·00
Haematological adverse events			
Anaemia			
All grades	161 (79%)	163 (80%)	0·80
Grade 3–4	17 (8%)	13 (6%)	0·45
Neutropenia			
All grade	122 (60%)	159 (78%)	<0·0001
Grade 3–4	51 (25%)	80 (39%)	0·002
Thrombocytopenia			
All grades	105 (52%)	135 (67%)	0·003
Grade 3–4	16 (8%)	13 (6%)	0·56

Data are n (%). Adverse-event data are for 203 of 205 patients in each group because one patient died after randomisation with no information about treatment received (sequential group), one did not receive the allocated treatment (sequential group), and two were lost to follow-up after randomisation (combination group).

Table 5: **Adverse events associated with sequential versus combination treatment during all lines of treatment**

might give similar results (panel). In the FOCUS study,[16] the comparison of initial fluorouracil followed by fluorouracil with either irinotecan or oxaliplatin and initial combinations of fluorouracil with either irinotecan or oxaliplatin, an initially unplanned analysis before participant accrual was closed, showed similar survival results. All three drugs were included exclusively in a small subset of patients at a later stage (table 6). In the CAIRO study,[31] a non-significant difference in overall survival was recorded with initial capecitabine and irinotecan followed by capecitabine and oxaliplatin (combination strategy) as compared with initial capecitabine followed by irinotecan and then capecitabine and oxaliplatin (sequential strategy). A third randomised trial[32] assessed the overall survival of patients receiving

continuous infusion of fluorouracil, LV5FU2, or the same fluoropyrimidine regimen plus oxaliplatin followed by an irinotecan-based regimen after progression. No difference was recorded in overall survival between the two groups of patients. However, this trial had a different design, with no crossover in the sequential group and the percentage of patients receiving second-line treatment was much lower than in our trial (54% in the combination group and 41% in the sequential group).

We acknowledge that with our study design, patients in the sequential group who were not fit enough for second-line treatment did not truly receive sequential treatment. However, because patients in the sequential group who received a second-line treatment and had treatment failure were able to receive additional treatment, assessment of only this subgroup of patients, who might not be representative of the initial group that was randomly allocated to one of the two treatment groups, might yield a potentially biased group comparison. Indeed, our analysis was by intention-to-treat rather than per protocol.

A concern before starting our trial with respect to first-line fluorouracil monotherapy—and one of the most important reasons for doing the study—was that it would result in a higher dropout rate (in patients not able to receive second-line treatment at the time of disease progression because of a lower tumour control rate) compared with frontline combination treatment. Collectively, the results of our study and those from the FOCUS and CAIRO trials—which were also designed on an intention-to-treat basis—provide firm evidence that such higher dropout does not occur. Finally, we believe that the design of our study allows comparison of its results with those of the CAIRO and FOCUS studies and those of other studies[17,22] in terms of, for example, PFS1, PFS2 (when calculated), percentages of patients starting second-line therapy, and overall survival.

Our study was designed to test if FOLFOX6 followed by FOLFIRI followed by a third line of treatment at the investigator's discretion is better than the LV5FU2 regimen followed by FOLFOX6 followed by FOLFIRI. The combination strategy used consisted of two doublet chemotherapy regimens widely accepted as standard regimens. This combination strategy was the same as in a previous randomised trial,[17] which showed similar survival results of 20·6 months with FOLFOX6 followed by FOLRIRI and 21·5 months for the reverse sequence—the longest ever reported in the pre-targeted treatment era, other than those yielded by first-line triplet chemotherapy regimens.[22,23] With no difference in terms of progression-free survival and overall survival, our study suggests that treatment intensification can be planned safely after failure of frontline fluoropyrimidine on its own.

Although progression-free survival after two lines of treatment in the combination group was much the same as that reported by Tournigand and colleagues,[17] overall survival in our trial was lower (table 6) compared with that reported in subsequent randomised trials that showed the superiority of frontline triplet treatment regimens in either the pre-targeted[22,23] or post-targeted[15,33,34] therapy era. In fact, patients in our study had somewhat poorer prognostic features than in other studies. Patients with potentially resectable metastases were excluded from our study, as was the case in FOCUS, and were under-represented in CAIRO. Consequently, the findings of these trials cannot be applied to this subgroup of patients with potentially resectable metastases. Accordingly, secondary resection rates were low in all three trials compared, for instance, with those recorded in the trial done by Tournigand and colleagues.[17] The proportion of patients with liver-only metastases is lower than is usually reported in other phase 3 trials in this setting, which could have resulted in a study population with a worse prognosis on average, and thus in a lower proportion of patients who were able to receive subsequent treatment lines. Our study included patients who were older than those in other studies (median age, 67 years), with almost two-fifths aged 70 years or older. Additionally, a substantial proportion of our patients had a performance status of 2 (higher than in

***Panel:* Research in context**

Systematic review

Frontline combination chemotherapy regimens with fluorouracil and either irinotecan or oxaliplatin became the mainstay of treatment of advanced colorectal cancer more than a decade ago. However, these combinations increase toxicity and cost compared with treatment regimens with fluoropyrimidine alone. We searched Medline for published studies and ClinicalTrials.gov for any additional open or closed trials of combination versus sequential chemotherapy in advanced colorectal cancer, with the search term "strategy and metastatic colorectal neoplasms" up to March, 2000, and retrieved only one (ongoing) trial comparing these approaches (MRC FOCUS[16]). One additional trial (CAIRO[31]) was launched about 1 year after the initiation of our study.

Interpretation

Upfront combination chemotherapy is not more effective and is more toxic than the sequential use of the same cytotoxic drugs in patients with advanced, non-resectable colorectal cancer, as in previously reported strategic trials (figure 4). With the advent of biological agents (eg, bevacizumab, cetuximab, panitumumab) for the treatment of advanced colorectal cancer, and given their cost and toxicity, similar trials should be done to test targeted treatment plus either sequential chemotherapy or combination chemotherapy. For patients with advanced, non-resectable colorectal cancer, this study suggests that decreasing the intensity of first-line chemotherapy is associated with no loss of survival and is therefore an option that clinicians should discuss with patients.

	Patients (n)	Median age (years [% ≥70 years])	WHO performance status of 2 (%)	Treatment	Access to all drugs* (%)	Objective response rate after first-line treatment (%)	Resection (%)	PFS1 (months)	PFS2 (months)	Overall survival (months)
Tournigand et al[17]	220	63 (NA%)†	11%	Combination‡	71%§	54–56%¶	17%	8·1–8·5¶	10·9–14·2¶	20·6–21·5¶
				Sequential	..	..	..	..	..	..
FOCUS[16]	1425	64 (~25%‖)	8%	Combination**	33%	49–57%††,‡‡	NA	8·5–8·7††,‡‡	NA	15·9
				Sequential§§	19%	28%	NA	6·3¶¶	NA	15·1
CAIRO[31]	803	63 (22%)	4%	Combination‖‖‖	53%	41%***	1·7%	7·8†††	10·3	17·4
				Sequential‡‡‡	36%	20%	0·5%	5·8	8·7	16·3
LIFE[32]	725	62 (<36%§§§)	55%	Combination¶¶¶	41%	55%***	NA	7·9***	NA	15·9
				Sequential‖‖‖‖‖	NA****	30%	NA	5·9	NA	15·2
FFCD 2000–05	410	67 (39%)	16%	Combination††††	73%	58%***	4%	7·6***	10·2	16·0
				Sequential‡‡‡‡	55%	24%	2%	5·3	10·4	16·3

NA=not available. PFS1=progression-free survival after first-line treatment. PFS2=progression-free survival after first-line and second-line treatment. *Fluoropyrimidine, oxaliplatin, and irinotecan. †Patients older than 75 years were ineligible. ‡FOLFOX6 then FOLFIRI or FOLFOX6 then FOLFIRI. §Including eight patients who received planned second-line treatment after the cut-off date. ¶In the FOLFOX6-FOLFIRI and FOLFIRI-FOLFOX6 groups, respectively. ‖Estimated from the IQR. **Fluorouracil and irinotecan or fluorouracil and oxaliplatin followed by salvage chemotherapy. ††In the fluorouracil plus irinotecan and fluorouracil plus oxaliplatin groups, respectively. ‡‡p<0·001 (combination *vs* sequential treatment). §§Fluorouracil followed by irinotecan plus fluorouracil or oxaliplatin plus fluorouracil. ¶¶Includes 710 additional patients treated with fluorouracil then irinotecan. ‖‖‖Capecitabine-irinotecan then capecitabine-oxaliplatin. ***p<0·0001 (combination *vs* sequential treatment). †††p=0·0002 (combination *vs* sequential treatment). ‡‡‡Capecitabine then irinotecan then capecitabine-oxaliplatin. §§§Percentage available only for patients older than 65 years. ¶¶¶Fluorouracil continuous infusion plus oxaliplatin or FOFOX4 regimen then irinotecan-based regimen. ‖‖‖‖‖Fluorouracil continuous infusion or LV5FU2 then irinotecan-based regimen. ****49% of the patients received second-line treatment with an irinotecan-based regimen, the number of these patients who then received oxaliplatin is not available. †††† FOLFOX6 then FOLFIRI. ‡‡‡‡LV5FU2 then FOLFOX6 then FOLFIRI.

Table 6: **Results of the main strategic randomised trials in advanced colorectal cancer**

frontline phase 3 trials[15,33,34]). In an analysis of the interaction between covariates and the treatment effect on overall survival, two or more involved sites was associated with better overall survival with the combination strategy than with sequential strategy. Accordingly, patients with poor-prognosis disease as assessed by the Köhne prognostic score seemed to benefit more from the combination strategy than the sequential strategy (figure 3). Although FOCUS and CAIRO did not record results in line with previously published prognostic models, FOCUS showed that patients with two of the known poor-prognosis characteristics (performance status of 2, high leucocyte count) might benefit from the upfront combination approach. Our pooled analysis of data from our trial and data from three other similar trials,[16,31,32] showed no significant differences in overall survival (figure 4). However, these findings need to be confirmed in a meta-analysis of individual patient data. The differential overall survival benefit according to prognostic parameters (number of disease sites, Köhne score) suggests that overall survival could be significantly increased by tailoring the treatment strategy according to such baseline parameters. In other words, patients with good-prognosis disease might be better candidates for a step-up, sequential strategy than would patients with poor-prognosis disease, in whom frontline combination regimens might be preferable to control their disease. However, no randomised trial has assigned treatment to patients with advanced colorectal cancer according to their baseline characteristics. Assessment of the benefit of combined treatment versus sequential treatment with a composite score (overall treatment utility [OTU]) proposed in the FOCUS 2 trial[37] would have been useful. However, this score was not already established when the trial began and no strategic trial has used it.

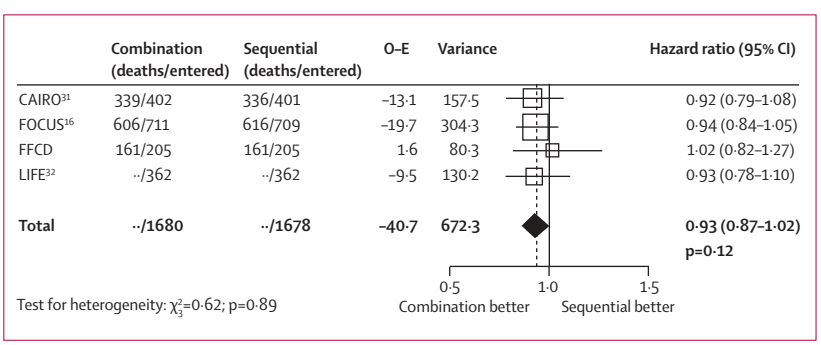

Figure 4: **Pooled analysis of summary data on overall survival in trials comparing combination versus sequential chemotherapy in advanced colorectal cancer**
Number of deaths not available for the LIFE trial.[32]

The lower-than-expected survival noted in our trial could have been because of the small overall proportion of patients treated initially with fluoropyrimidine alone who eventually received all three drugs (fluoropyrimidine, irinotecan, and oxaliplatin) compared with in the combination groups of other clinical trials that used frontline combination chemotherapy.[9–11] Indeed, for patients in FOCUS who received initial monotherapy followed by the irinotecan or oxaliplatin combination, and those in the sequential group in CAIRO, only 19% (in FOCUS) and 36% (in CAIRO) received all three drugs during the entire course of treatment. The same applied to the upfront combination groups in FOCUS (33%) and CAIRO (55%). The proportion of patients receiving all three drugs is strongly associated with median survival in all large published phase 3 trials done in the past decade.[8] Furthermore, overall survival in patients receiving all three drugs in CAIRO and FOCUS matched closely such survival predicted in the other trials.[8] The chance of a patient receiving all three drugs is largely

determined by the use of an initial combination. Only 19–55% of patients in the CAIRO and FOCUS studies received all three drugs; the poor overall survival could be explained by the fact that patients who were selected for these two studies had a rapidly deteriorating clinical status and were therefore only rarely able to receive the three drugs

By contrast, trials of initial triplet treatment, even for only 6 months followed by a break, resulted in a median overall survival of about 23 months, which was better than with initial doublet treatment and than the overall survival recorded in FOCUS or CAIRO.[22,23] This improved efficacy might partly be because of results from patients with poor-prognosis disease and rapid tumour growth—such patients are at high risk of not receiving active salvage treatment. However, in our trial, 55% of patients in the sequential group and 73% of patients in the combination group received all three active chemotherapeutic drugs (table 6)—much higher than in FOCUS and CAIRO, and close to the proportion in the study by Tournigand and colleagues.[17] Our study adds to the growing body of trials (eg CAIRO, FOCUS, and LIFE) in which sequence randomisations have led to wide differences in the proportions of patients who receive all three drugs, but without any benefit in survival. This occurrence is yet more evidence to refute the often repeated but unsubstantiated assertion that the number of drugs administered has a causative (rather than consequent) relation with overall survival.

As expected, the objective response rate was significantly higher in the combination group than it was in the sequential group. Our findings (58% in the combination group and 24% in the sequential group) were consistent with previous trials.[11,12,14,17] However, objective response rates during second-line and third-line treatment were significantly higher in the sequential group than in the combination group. Overall, in this population of elderly patients with mostly never-resectable metastatic disease, curative resection rates—previously shown to have a linear relation with the objective response rate[38]—were much the same and low. Thus, for patients with advanced colorectal cancer in whom the baseline workup ruled out resectability, sequential treatment strategies do not seem to result in lost chances of cure compared with more aggressive approaches. Additionally, our trial confirms the low objective response rates with second-line chemotherapy recorded elsewhere.[16,31,39]

In our trial, although initial combination treatment resulted in higher objective responses and PFS1, which did not translate into higher resection rates, it also resulted in significantly higher toxicity and non-cancer deaths compared with frontline fluorouracil on its own. Therefore, treating all patients with advanced colorectal cancer with upfront combination chemotherapy might expose them to a higher risk of life-threatening adverse events and alter their quality of life, with no clear advantage in terms of chances of cure or even extended survival. By contrast, treatment with a sequential strategy might be suboptimum for many patients and might result in a lower control of tumour symptoms, hence affecting a patient's quality of life. In our study, however, combination treatment had a positive and significant effect exclusively on the emotional scale as compared with the sequential treatment, but no significant effect on global and physical scales. Overall, quality of life (besides the emotional dimension) was not significantly different between the two groups. These results are consistent with those reported in FOCUS.[16] In CAIRO, on average, decreased functioning was higher on all scales (cognitive, emotional, physical, role, and social) for combination treatment as were changes for the symptom scales (except for pain and dyspnoea). However, the only significant difference was seen for diarrhoea, which was significantly greater with combination treatment ($p=0\cdot002$).[31]

A limitation of our study was that it had to be stopped prematurely after the inclusion of only 410 patients because of a decrease in accrual after the approval of bevacizumab for the treatment of advanced colorectal cancer. However, even with the reduced number of events, with a 5% type I error rate, this study had 66% power to detect a PFS2 benefit of 3 months, and we recorded no advantage in the combination group. Furthermore, WHO responses and median progression-free survival for all treatment phases should be interpreted in view of the fact that scans were not reviewed externally. No primary endpoint is without difficulties in a sequencing trial, especially if different numbers of lines of treatment are being compared. PFS2 was used as the main endpoint because it avoids the key drawback of different timings between treatment groups for the assessment of time to events (ie, comparison of PFS2 *vs* PFS3). PFS2 was also the endpoint in Tournigand and colleagues' trial[17] (and a secondary endpoint in other studies that compared sequential and combined treatment regimens). Third-line treatment, whether specified in the study protocol or not, is not relevant for PFS2. However, at the time of initiation of our trial, we regarded the provision of third-line FOLFIRI to patients in the sequential group to be ethically correct, in accordance with the practice and knowledge at this time, although FOLFIRI has been shown in the interim period to give no more than a 7% objective response rate when given as second-line treatment,[17] and has probably an even weaker effect when given as third-line treatment after failure of LV5FU2 and FOLFOX. The number of lines received and the treatments received are, however, relevant for the analysis of overall survival. An alternative study design would have been to use overall survival, our secondary endpoint, as the main endpoint, as done in the CAIRO trial.[31] Since this trial was designed and initiated, first-line combination treatment has become standard in many countries. On the basis of a post-hoc non-inferiority analysis, the maximum disadvantages of sequential

treatment that can be reliably excluded are 25% for PFS2 and 18% for overall survival (data not shown).

In patients with potentially resectable disease, maximally aggressive treatment is needed for tumour shrinkage and to potentially allow curative resection.[38] Additionally, in patients with aggressive disease with tumour-related symptoms or a poor performance status, immediate treatment seems necessary for the greatest chance of response, as suggested by the stronger effect of the upfront combination strategy in patients with poor-prognosis disease in FOCUS and in our trial. However, findings from FOCUS, CAIRO, and our trial lend support to the use of first-line fluoropyrimidine alone for the remaining (and largest) group of patients with less aggressive, never-resectable disease and a good performance status. A molecular marker substudy done in FOCUS showed that patients with low tumour protein expression (topoisomerase-1 and thymidylate synthase) had good outcomes when given fluorouracil alone, but gained little additional benefit from irinotecan or oxaliplatin. Conversely, patients in whom these proteins were highly expressed had poor outcomes with fluorouracil alone, but a major benefit from receiving first-line irinotecan or oxaliplatin.[40] In a comprehensive pharmacogenetic substudy in our trial,[27] the benefit of first-line FOLFOX for progression-free survival was restricted to patients with *2R/2R* (HR 0·39, 95% CI 0·23–0·68) or *2R/3R* (0·59, 0·42–0·82) thymidylate synthase 5′ UTR alleles. Conversely, patients with the *3R/3R* genotype did not seem to benefit from the adjunction of oxaliplatin (0·96, 0·66–1·40; p=0·006 for trend between the three HRs). These data need to be validated in other trial populations, but hold promise for the molecular selection of the best treatment strategy for individual patients.[27,41]

In the present age of targeted treatment, our results provide a basis from which similar strategic trials can be designed. Bevacizumab or anti-EGFR agents were not used as part of first-line or planned salvage treatment in our trial or in FOCUS and CAIRO. The addition of bevacizumab to treatment with fluoropyrimidine alone is safe and effective during first-line treatment[42] but is usually reserved for patients deemed unfit for combination treatment. Findings from FOCUS, CAIRO, and our trial lend support to the extension of this approach to a wider range of patients, and the design of studies in which novel drugs are added to frontline fluoropyrimidine chemotherapy instead of combination chemotherapy, thus reducing the burden of toxic effects on patients. In view of the cost of targeted therapies, such trials would have important public health consequences.

Contributors

MD was the chief investigator of this trial. MD, OB, PR, BP, LB, and J-PP designed the trial and wrote the protocol. All authors except JM, J-PP, MA, and MC recruited patients into the trial. MD, JM, and J-PP contributed to the management, analysis, statistical analysis, and interpretation, and drafting of the report. MC contributed to the data management and statistical analysis. DM contributed to data interpretation and drafting of the report. MA was the main data manager of the trial. All authors took part in data collection. All authors reviewed and helped revise the report, and approved the final version of the paper.

Conflicts of interest

During the trial MD, OB, PR, DM, and LB participated in other trials funded or part-funded by the manufacturers of irinotecan (Aventis at the beginning of the trial, then Pfizer), oxaliplatin (Sanofi and then Sanofi-Aventis), or both, and received educational support in the form of travel bursaries or departmental research support from the manufacturers of these two drugs. All other authors declare no conflicts of interest.

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