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Phase III trial of irinotecan plus infusional 5-fluorouracil/folinic acid versus irinotecan plus oxaliplatin as first-line treatment of advanced colorectal cancer

Ludwig Fischer von Weikersthal [b,s], *Andreas Schalhorn* [a,s], *Martina Stauch* [c], *Detlef Quietzsch* [d], *Peter A. Maubach* [e], *Helmut Lambertz* [f], *Daniel Oruzio* [g], *Rudolf Schlag* [h], *Karin Weigang-Köhler* [i], *Ute Vehling-Kaiser* [j], *Manfred Schulze* [k], *Juergen Truckenbrodt* [l], *Mariele Goebeler* [m], *Johann Mittermüller* [n], *Daniel Bosse* [o], *Borika Szukics* [p], *Marc Grundeis* [q], *Thomas Zwingers* [r], *Clemens Giessen* [a,t], *Volker Heinemann* [a,*,t]

[a] *Klinikum Grosshadern, University of Munich, Germany*
[b] *Klinikum Sankt Marien, Amberg, Germany*
[c] *Oncological Practice, Kronach, Germany*
[d] *Klinikum Chemnitz, Germany*
[e] *Oncological Practice Nussbaumstrasse, Munich, Germany*
[f] *Klinikum Garmisch-Partenkirchen, Germany*
[g] *Klinikum Augsburg, Germany*
[h] *Oncological Practice Wuerzburg, Germany*
[i] *Klinikum Nord, Nuremberg, Germany*
[j] *Oncological Practice, Landshut, Germany*
[k] *Kreiskrankenhaus Zittau, Germany*
[l] *Georgius Agricola Klinikum, Zeitz, Germany*
[m] *Universitätsklinikum Wuerzburg, Germany*
[n] *Oncological Practice, Germering, Germany*
[o] *Oncological Practice, Munich, Germany*
[p] *Klinikum Grosshadern, University of Munich, Med II, Germany*
[q] *Oncological Practice Chemnitz, Germany*
[r] *Fa Estimate GmbH Augsburg, Germany*

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ABSTRACT

Purpose: To determine whether irinotecan plus oxaliplatin (mIROX) is superior to irinotecan plus infusional 5-fluorouracil, leucovorin (FUFIRI) as first-line therapy of patients with metastatic colorectal cancer (mCRC).

Patients and methods: A phase III, randomised, open-label multicentre study compared standard treatment with FUFIRI (irinotecan 80 mg/m^2, 5-fluorouracil 2000 mg/m^2, folinic acid 500 mg/m^2 weekly times 6) to mIROX using an identical schedule of irinotecan plus

* *Corresponding author:* Address: Department of Medical Oncology, Klinikum Grosshadern, University of Munich, Marchioninistr. 15, 81377 Munich, Germany. Tel.: +49 89 7095 2208; fax: +49 89 7095 2257.
E-mail address: Volker.Heinemann@med.uni-muenchen.de (V. Heinemann).
[s] Schalhorn A. and Fischer von Weikersthal L. contributed equally to this work.
[t] Giessen C. and Heinemann V. contributed equally to this work.
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oxaliplatin 85 mg/m^2 applied on days 1, 15 and 29 of a 7-week cycle. The primary end-point was progression-free survival (PFS).

Results: A total of 479 eligible patients were randomly assigned. Progression-free survival was 7.2 months in the mIROX arm and 8.2 months in the FUFIRI arm [hazard ratio = 1.14; 95% confidence interval (CI) 0.94–1.37; $P = 0.178$]. Comparable results were also obtained for overall survival time with 19 months in the mIROX-arm and 22 months in the FUFIRI-arm (hazard ratio = 1.08, $P = 0.276$). Both regimens induced an identical objective response rate (ORR) of 41%, but disease control rate (ORR plus stable disease) was significantly greater in the FUFIRI group (81% versus 68%, $P = 0.001$). Most frequent grades 1–4 side-effects of mIROX and FUFIRI treatment were nausea (80% versus 73%) and delayed diarrhoea (79% versus 68%). Grades 3–4 toxicities were generally below 10%, except for diarrhoea which was more frequent in the mIROX-arm compared to the FUFIRI-arm (19% versus 30%, $P = 0.006$)

Conclusion: mIROX failed to show superior activity compared to high-dose 5-FU/folinic acid plus irinotecan. Due to better tolerability the combination of high-dose 5-FU/folinic acid and irinotecan remains a standard of care in first-line treatment of metastatic colorectal cancer.

1. Introduction

The introduction of irinotecan and oxaliplatin caused a major improvement in the treatment of metastatic colorectal cancer (mCRC). The combined use of 5-fluorouracil (5-FU)/folinic acid (FA) together with irinotecan or oxaliplatin not only increased remission rates but also prolonged progression-free and overall survival compared to 5-FU/FA alone.[1–3]

The combined use of irinotecan and oxaliplatin was based on three assumptions: (1) There is little overlapping toxicity between the two agents with irinotecan mainly causing diarrhoea and haematotoxicity, while neurotoxicity is dose-limiting for oxaliplatin. (2) The technical applicability of the treatment may be improved if infusional 5-FU regimens requiring pump systems can be avoided. (3) Preclinical studies demonstrated that topoisomerase-I inhibitors may potentiate the cytotoxicity of DNA-damaging agents. In this context, it was shown that SN-38, the active metabolite of irinotecan, delayed the reversion of oxaliplatin-induced DNA interstrand crosslinks causing a superadditive tumour growth reduction.[4] The pharmacodynamic potentiation was observed only at the cellular level, while plasmatic pharmacokinetic interactions were not reported.[4,5]

Substantial clinical activity of irinotecan plus oxaliplatin in the treatment of advanced colorectal cancer was supported by numerous phase I–II studies.[5–11] In patients pretreated with fluoropyrimidine-based chemotherapy, this combination induced objective response rates of 15–64% and overall survival times of 11–16 months which appeared promising compared to those previously reported.[12–14]

These results led us to combine these two active agents and to investigate mIROX as a fluoropyrimidine-free combination for first-line chemotherapy of metastatic colorectal cancer. The FUFIRI-regimen was chosen as a comparator. This regimen applies infusional 5-FU given as a weekly 24-hour infusion which appeared to be associated with better tolerability and efficacy compared to bolus-5-FU regimens such as IFL. To minimise the effects of heterogeneous second line treatment on survival and to obtain data on consecutive treatment, crossover between the two study protocols was advised in case of failure of first-line therapy.

2. Patients and methods

2.1. Study design

This study was a randomised, multicentre phase III trial to investigate the efficacy of FUFIRI versus mIROX as first-line chemotherapy in patients with metastatic colorectal cancer. The study was conducted according to the Declaration of Helsinki and was approved by the local ethics committee. Regular site visits were performed. The study was funded by Aventis and Pfizer.

2.2. Patient evaluation

Patients between 18 and 75 years were eligible if they had histologically proven metastatic adenocarcinoma of the colon or rectum without prior chemotherapy for metastatic disease. Prior adjuvant chemotherapy was allowed with a treatment-free interval $\geqslant 6$ months and did not include topoisomerase I inhibitors or platinum compounds. A Karnofsky performance status $\geqslant 70\%$, adequate liver- and bone marrow function parameters and bidimensionally measurable tumour lesions were mandatory. Written informed consent was obtained from each patient. Patients were excluded in the presence of symptomatic peritoneal carcinomatosís or brain metastasis, chronic inflammatory bowel disease or bowel obstruction, intolerability of 5-fluorouracil or folinic acid, secondary malignancies (except for basal cell skin cancer or in situ carcinoma of the cervix) or known Gilbert's syndrome. Further exclusion criteria were administration of other

antineoplastic drugs, pregnancy and/or lactation and radiation treatment within 6 weeks prior to study entry.

2.3. Random assignment and stratification

Patients were assigned to treatment arms by central randomisation via fax. Stratification was performed according to the following factors: Karnofsky performance status (100% versus 70–90%), lactate dehydrogenase (⩽240 U/L versus >240 U/L), adjuvant pretreatment (yes versus no).

2.4. Treatment plan

The trial compared the standard treatment with FUFIRI to the experimental treatment with mIROX using an identical regimen of irinotecan application in both arms. In the standard arm, patients received FUFIRI: irinotecan 80 mg/m^2 as a 0.5-hour infusion followed by folinic acid 500 mg/m^2 applied over 2 hours and 5-fluorouracil 2000 mg/m^2 given as a 24-hour infusion. In the experimental arm, patients received a modified IROX regimen (mIROX): irinotecan 80 mg/m^2 as a 0.5-hour infusion weekly times 6 plus oxaliplatin 85 mg/m^2 as 2-hour infusion on days 15 and 29 of each cycle. In both arms, treatment was repeated every 49 d. In case of isolated resectable liver metastases, resection was recommended after completion of two treatment cycles.

Patients achieving complete remissions (CR) received one further cycle of therapy, and treatment was stopped only after confirmation of CR. Patients achieving partial remission or stable disease continued therapy until progression or toxicity. At the time of disease progression or treatment intolerability, crossover from FOLFIRI to mIROX and vice versa was recommended.

Toxicity-related dose adjustments were predefined, e.g. occurrence of NCI-CTC toxicities grade ⩾1 for diarrhoea, mucositis/stomatitis and thrombocytes or grade ⩾2 for leucocytes and every other toxicity >2 on the day of planned therapy resulted in postponement of treatment until normalisation. Dose reduction of oxaliplatin by 25% was performed at the occurrence of persistent paresthesia or painful paresthesia lasting >7 d, a 50% reduction was performed in case of paresthesia with functional impairment for >7 d, while treatment was stopped at the occurrence of persistent painful paresthesia or persistent functional impairment.

2.5. Patient assessment and follow-up

Prestudy evaluation included full medical examination, vital signs, CBC and blood chemistry tests. Tumour assessments were performed preferably by computed tomography scans, but also included magnetic resonance imaging, X-ray and ultrasound. During therapy, tumour assessments were carried out after the first and the second cycle, thereafter every two cycles. Response was evaluated by World Health Organisation (WHO) criteria. For evaluation of progression-free survival, overall survival and efficacy of 2nd-line treatment, patients were followed up at 3-months intervals. National Cancer Institute Common Toxicity Criteria (NCI-CTC) version 2.0 were used to assess toxicity.

2.6. Statistical considerations

The primary objective of the study was progression-free survival (PFS) comparing FUFIRI with mIROX. Secondary end-points were response rate, overall survival, resectability of liver metastases and toxicity. Both study arms were compared within a group-sequential design. Assuming a median PFS of 6.7 months in the control group (FUFIRI) it was sought to reach a presumed hazard ratio of 0.787 in favour of the experimental regimen (mIROX). With a power of 80% and a two-sided type-one error of $\alpha = 0.05$ an average number of 365 events were expected. This led to the assumption that with a probability of 90% the sample size would not exceed 569 patients. There were 495 patients assigned when the Data Safety and Monitoring Board decided to close the study based on a PFS analysis indicating that the primary end-point could not be reached.

The duration of PFS, remission duration and overall survival (OS) were estimated using the Kaplan–Meier technique. Cox proportional hazards modelling was used to calculate hazard ratios and confidence intervals (CI). Fisher's exact test and the Chi-square test were applied to compare tumour response rates and toxicities. All P values were calculated as two-sided, and $P < 0.05$ was considered as statistically significant.

3. Results

3.1. Patients

The study enrolled 495 patients from 48 German centres between July 2000 and October 2004. Sixteen patients were ineligible (1 hyperbilirubinaemia, 15 documentation failure) and 479 patients were randomly assigned to treatment with either FUFIRI (n = 238) or with mIROX (n = 241). All analyses were performed as intent-to treat analyses based on the full analysis set of patients. Overall, the treatment arms were well balanced with regard to stratification factors and other patient- or tumour characteristics (Table 1). With a median age of 63 years, approximately 50% of patients were in excellent general condition with a Karnofsky index of 100%, 60% suffered from metastatic cancer of the colon, and lactate dehydrogenase (LDH) was elevated in 42%. Twenty-nine percent of patients had received prior adjuvant therapy which mainly consisted of 5-FU/folinic acid (14.4%) or chemoradiotherapy (9.2%). Median follow-up time in the FUFIRI arm was 20.7 months (95% CI, 17.9–23.6 months) and in the mIROX arm it was 17.2 months (95%, CI 15.4–19.0 months) (see Figs. 1 and 2).

3.2. Treatment administration and safety

In the FUFIRI arm 238 patients received a total of 841 cycles, while in the mIROX arm 716 cycles were applied in 241 patients. Duration of 1st-line therapy was 5.2 months (range 0–18.2 months) in the FUFIRI-arm and was 4.7 months (range 0–19.0 months) in the mIROX-arm during which a median of 2 cycles was applied per patient (range 1–10 cycles). Dose reductions in the FUFIRI versus mIROX arm

Table 1 – Patient characteristics.

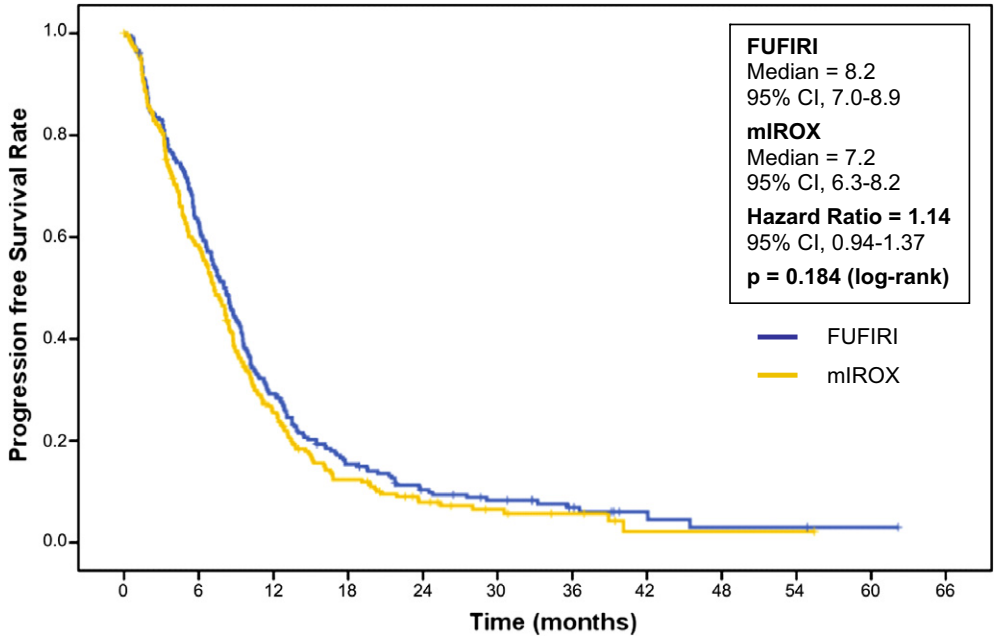
Characteristics	FUFIRI (*n* = 238)		mIROX (*n* = 241)	
	No. of patients	%	No. of Patients	%
Sex				
Male	158	66	177	73
Female	80	34	64	27
Age (years)				
Median	63		63	
Range	32–79		21–79	
Karnofsky performance status				
100%	118	50	118	49
70–90%	120	50	123	51
Primary tumour				
Colon	138	58	149	62
Rectum	100	42	92	38
Previous adjuvant treatment				
Yes	70	29	67	28
No	168	71	174	72
Time from diagnosis to randomisation				
<3 months	132	55.5	128	53.1
⩾3 months	106	44.5	113	46.9
No. of metastatic sites				
1	135	57	151	63
⩾2	101	42	87	36
NA	2	1	3	1
Metastatic site				
Liver	200	84	204	85
Liver only	114	49	134	56
LDH				
⩽240 U/l	137	58	139	58
>240 U/L	101	42	102	42
CEA				
⩽ULN	49	21	44	18
>ULN	157	66	170	71
NA	32	13	27	11
Alkaline phosphatase				
⩽ULN	127	53	129	53
>ULN	89	37	95	39
NA	22	9	17	7
White blood cells				
<8000	128	54	143	59
⩾8000	102	43	94	39
NA	8	3	4	2

FUFIRI, 5-fluorouracil plus folinic acid plus irinotecan; mIROX, modified irinotecan plus oxaliplatin; CEA, carcinoembryonic antigen.

were observed in 19.4 versus 20.8% of patients, while dose delays occurred in 18.4% versus 17.6% of patients, respectively. In the FUFIRI versus mIROX arm, ⩾80% of the scheduled irinotecan doses were applied in 87% versus 85% of cycles, respectively; ⩾80% of the scheduled 5-FU doses were applied in 83% of FUFIRI cycles, and ⩾80% of the scheduled oxaliplatin doses were applied in 83% of the mIROX cycles.

The most frequent side-effects were nausea, diarrhoea, anaemia, vomiting and leucocytopenia (Table 2). With regard to all-grade toxicities (CTC-NCI grades 1–4), mIROX induced significantly more delayed diarrhoea (79% versus 68%, $P = 0.01$), sensory neuropathy (48% versus 13%, $P < 0.001$), leucocytopenia (60% versus 48%, $P = 0.01$) and thrombocytopenia (32% versus 12%, $P < 0.001$) than FUFIRI.

Grade 3–4 delayed diarrhoea was significantly more frequent in the mIROX arm (29.9% versus 18.9%, $P = 0.006$). As expected, grade 3–4 neurosensory toxicity did not occur in the FUFIRI arm, but was only 2.1% in the IROX arm. Otherwise, haematological and non-haematological grade 3–4 toxicities occurred in <10% of patients and did not show significant differences between treatment arms.



No at risk	0	6	12	24	36	48	60
FUFIRI	237	148	69	21	9	2	1
mIROX	240	138	58	14	5	1	1

Fig. 1 – Progression-free survival. FUFIRI, 5-FU/folinic acid plus irinotecan; mIROX, irinotecan plus oxaliplatin.

3.3. *Sixty-day mortality*

The overall 60-day mortality rate was 5.5% in the FUFIRI arm and 4.6% in the mIROX-arm ($P = 0.680$). The rate of deaths possibly related to treatment was 1.3% versus 1.7% ($P = 0.695$), while deaths related to other causes occurred in 4.2% versus 2.9% of patients respectively (Table 3).

3.4. *Efficacy*

Median PFS was evaluated as a primary end-point of the study. At the time of analysis, 81.4% and 85.0% of patients had experienced progressive disease, respectively. First-line treatment in the FUFIRI-arm resulted in a PFS of 8.2 months (95% CI, 7.0–8.9), while it was 7.2 months (95% CI, 6.3–8.2) in the mIROX-arm (hazard ratio 1.14, 95% CI, 0.94–1.37, log rank $P = 0.184$). A multivariate analysis defined baseline carcinoembryonic antigen (CEA) ($P = 0.014$) and LDH ($P = 0.032$) as independent prognostic factors for PFS.

Also overall survival times were not significantly different between treatment arms (hazard ratio 1.08, 95% CI, 0.88–1.33, log rank $P = 0.472$) and reached medians of 21.8 months (95% CI, 19.2–25.6) versus 18.9 months (95% CI, 16.4–22.8) in the FUFIRI- and mIROX-arm, respectively. In a multivariate analysis, baseline CEA ($P = 0.005$), LDH ($P < 0.001$), haemoglobin ($P < 0.001$) and leucocytes ($P = 0.001$) were identified as independent prognostic factors for overall survival.

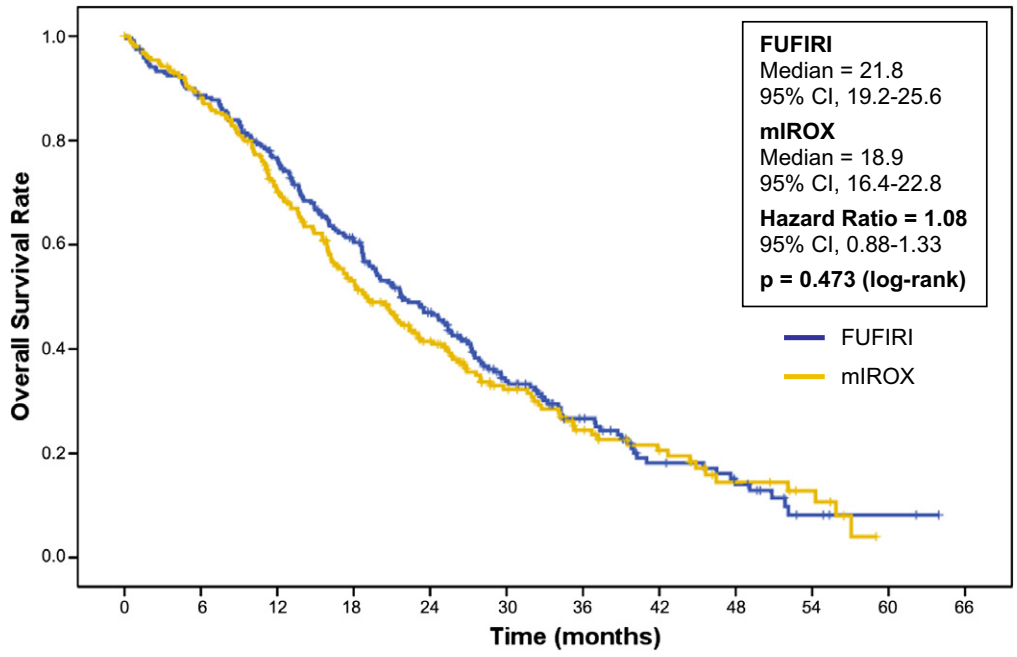
Tumour response rates were identical for FUFIRI and mIROX (41% versus 41%) (Table 4). However, evaluation of disease control rate (DCR), which included complete response, partial response and stable disease, showed a significant superiority of the FUFIRI regimen (DCR 81%, 95% CI, 75–85%) compared to the mIROX-regimen (DCR 68%, 95% CI, 61–73%). A trend for a longer remission duration was observed in the FUFIRI – compared to the mIROX-group (9.5 months versus 7.7 months, $P = 0.310$).

3.5. *Secondary resection of liver metastases*

The analysis of the intent-to-treat population indicated that 38 patients (7.9%) underwent surgical resection of liver metastases, 10% (23/238) in the FUFIRI-arm and 6% (15/241) in the mIROX-arm. When those 248 patients were evaluated who suffered from liver metastasis only, the resection rate was 20% (23/114) in the FUFIRI arm compared to 11% (15/134) in the mIROX arm. R0-resections were achieved in 16% versus 8% of patients.

3.6. *Second-line therapy*

Second-line chemotherapy after FUFIRI versus mIROX was documented in 70% (167/238) versus 68% (164/241) of patients. According to the study protocol, centres were encouraged to switch patients after failure of first-line therapy to the respective other treatment arm. A cross-over from the FUFIRI-arm to mIROX was performed in 39%, and from the mIROX-arm to FUFIRI in 35% of patients. All three agents (5-fluorouracil, irinotecan and oxaliplatin) were applied in 53% versus 56% of patients, respectively. In assessable patients crossed over to



No at risk	0	12	24	36	48	60
FUFIRI	238	177	97	36	13	2
mIROX	241	163	77	28	10	0

Fig. 2 – Overall survival. FUFIRI, 5-FU/folinic acid plus irinotecan; mIROX, irinotecan plus oxaliplatin.

Table 2 – Analysis of CTC grades 1–4 toxicities (per patient analysis).

Toxicity	FUFIRI (*n* = 238)				mIROX (*n* = 241)				P*	P**
	Grades 1–2		Grades 3–4		Grades 1–2		Grades 3–4		(G3–4)	(G1–4)
	No.	%	No.	%	No.	%	No.	%		
Nausea	162	68.1	11	4.6	172	71.4	20	8.3	0.137	0.086
Vomiting	126	52.9	7	2.9	133	55.2	9	3.7	0.800	0.519
Diarrhoea early	79	33.2	10	4.2	95	39.4	17	7.1	0.234	0.052
Diarrhoea delayed	117	49.2	45	18.9	118	49.0	72	29.9	0.006	0.010
Mucositis	58	24.4	2	0.8	70	29.0	3	1.2	1.316	0.222
Constipation	46	19.3	5	2.1	41	17.0	2	0.8	0.283	0.358
Alopecia	68	28.6	–	–	80	33.2	–	–	–	0.279
Skin	41	17.2	1	0.4	37	15.4	1	0.4	1.501	0.625
Pain	91	38.2	5	2.1	101	41.9	10	4.1	0.294	0.231
Cholinergic syndrome	21	8.8	–	–	28	11.6	2	0.8	0.499	0.236
Neuropathy sensory	32	13.4	–	–	110	45.6	5	2.1	0.061	<0.001
Leucopenia	105	44.1	10	4.2	124	51.5	21	8.7	0.062	0.010
Anaemia	153	64.3	7	2.9	167	69.3	8	3.3	1.200	0.232
Thrombocytopenia	27	11.3	1	0.4	73	30.3	5	2.1	0.216	<0.001
Neutropenic fever	6	2.5	5	2.1	5	2.1	7	2.9	0.772	1.000
Fever	38	16.0	4	1.7	46	19.1	6	2.5	0.751	0.302

FUFIRI, 5-FU/folinic acid plus irinotecan; mIROX, irinotecan plus oxaliplatin.
P* comparison of grade 3–4 toxicities; P** comparison of grades 1–4 toxicities.

mIROX versus FUFIRI, the overall response rate was 14% versus 26% ($P = 0.047$), and the disease control rate was 58% versus 74%, respectively ($P = 0.046$) indicating greater 2nd-line activity of FUFIRI (Table 4). Median post-progression survival was nearly identical between treatment arms (10.9 versus 10.6 months).

Table 3 – Sixty-day mortality.

	FUFIRI		mIROX		Total		P-value
	No.	%	No.	%	No.	%	
All	13	5.5	11	4.6	24	5	0.68
Death possibly related to treatment	3	1.3	4	1.7	7	1.5	0.695
GI-syndrome	0		1		1		
Sepsis	1		1		2		
GI-syndrome + sepsis	2		2		4		
Death related to other causes	10	4.2	7	2.9	17	3.5	0.659
Tumour progression	5		7		12		
Thromboembolism	2		0		2		
Others	3		0		3		

FUFIRI, 5-FU/folinic acid plus irinotecan; mIROX, irinotecan plus oxaliplatin.

Table 4 – Best response to first- and second-line therapy.

Response parameter	FUFIRI (*n* = 238)		mIROX (*n* = 241)		P
	n	%	*n*	%	
Complete response (CR)	18	8	19	8	1.135
Partial response (PR)	79	33	79	33	1.077
Overall response rate (CR + PR)	97	41	98	41	1.074
Stable disease	95	40	65	27	0.004
Disease control rate (CR + PR + SD)	192	81	163	68	0.001
Progressive disease	19	8	37	15	0.015
Not assessable	27	11	41	17	0.089
Patients receiving 2nd-line therapy	167	70.2	164	68.0	
Patients with 2nd-line cross-over	92	38.7	85	35.3	
Cross-over patients assessable for response	2nd-linemIROX (88)		2nd-lineFUFIRI (72)		P
	n	%	*n*	%	
Complete response (CR)	2	2.3	3	4.2	0.658
Partial response (PR)	10	11.4	16	22.2	0.085
Overall response rate (CR + PR)	12	13.6	19	26.4	0.047
Stable disease	39	44.3	34	47.2	0.751
Disease control rate (CR + PR + SD)	51	58.0	53	73.6	0.046
Progressive disease	37	42.0	19	26.4	0.046

FUFIRI, 5-FU/folinic acid plus irinotecan; mIROX, irinotecan plus oxaliplatin.

4. Discussion

This study was designed to compare the combination of irinotecan plus oxaliplatin (mIROX) with the standard first-line combination of irinotecan plus infusional 5-FU/folinic acid. The rationale of this combination was based on the preclinical observation of synergistic drug interaction and on impressive results obtained in second-line treatment of patients after failure of fluoropyrimidines. Goldberg and colleagues were among the first to investigate the IROX combination in a randomised first-line study. They used a regimen where irinotecan (200 mg/m^2) and oxaliplatin (85 mg/m^2) were applied at 3-week intervals. The mIROX regimen of the present study employed a different regimen with a higher initial dose intensity and weekly drug application. Irinotecan (80 mg/m^2) was given weekly six times and oxaliplatin (85 mg/m^2) was given every 2 weeks in a 7-week treatment cycle. Within two cycles of the mIROX regimen (14 weeks) patients received comparable cumulative doses of irinotecan and a 20% greater dose of oxaliplatin compared to IROX-regimen used in the Goldberg trial.

As a comparator, irinotecan plus high-dose infusional FU/FA according to the standard AIO FU/FA regimen was selected in the present trial. Both treatment arms were defined by identical dose intensities for irinotecan and thus set the basis for a comparison of oxaliplatin versus infusional high-dose FU/FA.

The present trial did not meet its primary end-point in that the PFS time in the mIROX-arm was not superior compared to irinotecan plus infusional 5-FU/folinic acid (HR = 1.14, P = 0.178). Moreover, no significant difference was observed with regard to median overall survival time and objective response rate. This trial therefore clearly indicates that replacement of the fluoropyrimidine by oxaliplatin in the

mIROX regimen did not improve clinical efficacy. Accordingly, the use of a fluoropyrimidine remains a standard of care in the first-line treatment of metastatic colorectal cancer.

It should, however, be pointed out that mIROX clearly demonstrated clinically relevant antitumour activity. With an ORR of 41%, a median PFS of 7.2 months and an overall survival time of 19 months this regimen compares well with other chemotherapy combinations such as FOLFIRI or FOLFOX.[1,15–17] In the unselected patient population, the rate of liver resections (8%) and R0-resections (6%) was comparably high and closely matched the linear correlation of ORR and resection rate established by Folprecht and colleagues.[18] In accordance with an identical response rate in mIROX- and FUFIRI-treated patients, there was no significant difference in resection rates between treatment arms.

The efficacy data of this trial may be discussed in relation to the study by Goldberg and colleagues who compared the 3-weekly IROX regimen to FOLFOX4 and IFL. Compared to IROX, FOLFOX was superior with regard to response rate, time to progression and overall survival. IROX, however, induced a significantly longer survival time than IFL (17.4 versus 15 months, $P = 0.04$).[16,19] Becouarn and colleagues performed a randomised phase II trial which investigated a biweekly regimen of irinotecan plus oxaliplatin and compared it to standard chemotherapy with LV5-FU2 plus either irinotecan or oxaliplatin.[20] Comparable efficacy was reported with regard to ORR (52.5% versus 55%), PFS (8.4 versus 8.1 months) and OS (19 versus 20.4 months).

Based on the available data, the present trial provides strong arguments to apply mIROX in patients with contraindications and/or intolerance against 5-FU. Candidates for mIROX are patients with proven or suspected cardiac toxicity of 5-FU and are patients with reduced 5-FU catabolism caused by defects in the rate-limiting enzyme dihydropyrimidine dehydrogenase.

Both, the present trial and the EORTC trial 40986 investigated the FUFIRI regimen.[17] The latter reported a median PFS time of 8.5 months and a median overall survival time of 20.1 months. These results closely match with those obtained in the present trial (PFS = 8.2 months, OS = 21.8 months) and thus support the consistently high activity of irinotecan plus infusional high-dose 5-FU/folinic acid.

Tolerability of mIROX and FUFIRI was generally acceptable with grade 3–4 toxicities mostly below 10%. The most frequent all-grade toxicities in both arms were nausea and delayed diarrhoea. Grade 3–4 delayed diarrhoea was significantly more frequent in the mIROX arm (30% versus 19%, $P = 0.006$) which is well in keeping with previous reports on the IROX-regimen and reflects overlapping gastrointestinal toxicity of both agents.[16,21]

Sensory neuropathy was expectedly more pronounced in the mIROX- compared to the FUFIRI-arm (48% versus 13%), but grade 3–4 neuropathy in the mIROX-arm was only 2%. This observation is supported by previous phase II and III studies where grade 3–4 neuropathy in the IROX regimen was 0–8%[6,9–11,16,21] and thus contrasts with higher rates reported for the FOLFOX regimen (18–34%).[3,16,22]

Patients clearly benefit from second- and further-line treatment.[23] In the present trial, 69% of patients received second line therapy and 37% performed the recommended cross over from mIROX to FUFIRI and vice versa. The high rate of 2nd-line treatment and the high percentage of patients receiving all three drugs (54%) may explain the survival time observed in the trial (22 versus 19 months). The comparable rates of 2nd-line therapy and the nearly identical post-progression survival time in both arms (10.9 versus 10.6 months) indicate that treatment-associated toxicity did not induce an imbalance with regard to further treatment. By comparison, the rate of 2nd-line treatment was 56% in the EORTC 40986 trial.[17]

At the time this trial was performed, neither anti-EGFR- nor antiangiogenic agents were part of treatment recommendations. Monoclonal antibodies such as cetuximab or bevacizumab were generally not applied in 2nd-line therapy and therefore had no effect on treatment outcome. Accordingly, the survival results obtained with combination chemotherapy in this as well as in the EORTC 40986 trial may serve as an evidence-based benchmark against which new regimens involving targeted therapy need to be compared.[24–26]

In conclusion, the mIROX-regimen failed to show superior activity compared to high-dose 5-FU/folinic acid plus irinotecan. While both regimens appeared to have comparable clinical activity with regard to ORR, PFS and OS, the more unfavourable toxicity profile of mIROX favours the combination of irinotecan plus infusional high-dose 5-FU/folinic acid. Accordingly, the inclusion of a fluoropyrimidine into first- line treatment of mCRC remains a standard of care, while the mIROX-regimen may be reserved for patients who do not tolerate infusional regimens or who have contraindications against fluoropyrimidines.

Authors' contributions

Fischer von Weikersthal – provision of study material or patients; collection and assembly of data; final approval of manuscript; Schalhorn – provision of study material or patients; collection and assembly of data; final approval of manuscript; Stauch – nothing; Quietzsch – nothing; Maubach – nothing; Lambertz – collection and assembly of data; final approval of manuscript; Oruzio – nothing; Schlag – provision of study material or patients; collection and assembly of data; final approval of manuscript; Weigang-Koehler – provision of study material or patients; collection and assembly of data; final approval of manuscript; Vehling-Kaiser – collection and assembly of data; final approval of manuscript; Schulze – nothing; Truckenbrodt – nothing; Goebeler – collection and assembly of data; data analysis and interpretation; final approval of manuscript; Mittermueller – provision of study material or patients; collection and assembly of data; final approval of manuscript; Bosse – nothing; Szukiczs – provision of study material or patients; collection and assembly of data; final approval of manuscript; Grundeis – nothing; Zwingers – conception and design; collection and assembly of data; data analysis and interpretation; final approval of manuscript; Giessen – collection and assembly of data; data analysis and interpretation; final approval of manuscript; equal contribution with last author: Prof. Dr. V. Heinemann; Heinemann – conception and design; provision of study material or patients; collection and assembly of data; data analysis and interpretation; manuscript writing; final approval of manuscript.

Conflict of interest statement

All authors except A. Schalhorn and V. Heinemann have no conflict of interest. A.S. and V.H. are funded by Pfizer Germany GmbH.

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REFERENCES

1. Douillard JY, Cunningham D, Roth AD, et al. Irinotecan combined with fluorouracil compared with fluorouracil alone as first-line treatment for metastatic colorectal cancer: a multicentre randomised trial. *Lancet* 2000;**355**:1041–7.
2. Saltz LB, Cox JV, Blanke C, et al. Irinotecan plus fluorouracil and leucovorin for metastatic colorectal cancer. Irinotecan Study Group. *N Engl J Med* 2000;**343**:905–14.
3. De Gramont A, Figer A, Seymour M, et al. Leucovorin and fluorouracil with or without oxaliplatin as first-line treatment in advanced colorectal cancer. *J Clin Oncol* 2000;**18**:2938–47.
4. Zeghari-Squalli N, Raymond E, Cvitkovic E, et al. Cellular pharmacology of the combination of the DNA topoisomerase I inhibitor SN-38 and the diaminocyclohexane platinum derivative oxaliplatin. *Clin Cancer Res* 1999;**5**:1189–96.
5. Wasserman E, Cuvier C, Lokiec F, et al. Combination of oxaliplatin plus irinotecan in patients with gastrointestinal tumors: results of two independent phase I studies with pharmacokinetics. *J Clin Oncol* 1999;**17**:1751–9.
6. Scheithauer W, Kornek GV, Raderer M, et al. Combined irinotecan and oxaliplatin plus granulocyte colony-stimulating factor in patients with advanced fluoropyrimidine/leucovorin-pretreated colorectal cancer. *J Clin Oncol* 1999;**17**:902–6.
7. Goldwasser F, Gross-Goupil M, Tigaud JM, et al. Dose escalation of CPT-11 in combination with oxaliplatin using an every two weeks schedule: a phase I study in advanced gastrointestinal cancer patients. *Ann Oncol* 2000;**11**:1463–70.
8. Kemeny N, Tong W, Gonen M, et al. Phase I study of weekly oxaliplatin plus irinotecan in previously treated patients with metastatic colorectal cancer. *Ann Oncol* 2002;**13**:1490–6.
9. Rougier P, Lepille D, Bennouna J, et al. Antitumour activity of three second-line treatment combinations in patients with metastatic colorectal cancer after optimal 5-FU regimen failure: a randomised, multicentre phase II study. *Ann Oncol* 2002;**13**:1558–67.
10. Bajetta E, Beretta E, Di Bartolomeo M, et al. Efficacy of treatment with irinotecan and oxaliplatin combination in FU-resistant metastatic colorectal cancer patients. *Oncology* 2004;**66**:132–7.
11. Timotheadou E, Papakostas P, Tsavdaridis D, et al. Irinotecan and oxaliplatin combination, as second-line treatment, in fluoropyrimidine-pretreated advanced colorectal cancer. A phase II study by the Hellenic Cooperative Oncology Group (HeCOG). *Tumori* 2005;**91**:309–13.
12. Cunningham D, Pyrhonen S, James RD, et al. Randomised trial of irinotecan plus supportive care versus supportive care alone after fluorouracil failure for patients with metastatic colorectal cancer. *Lancet* 1998;**352**:1413–8.
13. Rougier P, Van Cutsem E, Bajetta E, et al. Randomised trial of irinotecan versus fluorouracil by continuous infusion after fluorouracil failure in patients with metastatic colorectal cancer. *Lancet* 1998;**352**:1407–12.
14. Rothenberg ML, Oza AM, Bigelow RH, et al. Superiority of oxaliplatin and fluorouracil-leucovorin compared with either therapy alone in patients with progressive colorectal cancer after irinotecan and fluorouracil-leucovorin: interim results of a phase III trial. *J Clin Oncol* 2003;**21**:2059–69.
15. Colucci G, Gebbia V, Paoletti G, et al. Phase III randomized trial of FOLFIRI versus FOLFOX4 in the treatment of advanced colorectal cancer: a multicenter study of the Gruppo Oncologico Dell'Italia Meridionale. *J Clin Oncol* 2005;**23**:4866–75.
16. Goldberg RM, Sargent DJ, Morton RF, et al. A randomized controlled trial of fluorouracil plus leucovorin, irinotecan, and oxaliplatin combinations in patients with previously untreated metastatic colorectal cancer. *J Clin Oncol* 2004;**22**:23–30.
17. Koehne CH, van Cutsem E, Wils J, et al. Phase III study of weekly high-dose infusional fluorouracil plus folinic acid with or without irinotecan in patients with metastatic colorectal cancer: European Organisation for Research and Treatment of Cancer Gastrointestinal Group Study 40986. *J Clin Oncol* 2005;**23**:4856–65.
18. Folprecht G, Grothey A, Alberts S, et al. Neoadjuvant treatment of unresectable colorectal liver metastases: correlation between tumour response and resection rates. *Ann Oncol* 2005;**16**:1311–9.
19. Ashley AC, Sargent DJ, Alberts SR, et al. Updated efficacy and toxicity analysis of irinotecan and oxaliplatin (IROX) : intergroup trial N9741 in first-line treatment of metastatic colorectal cancer. *Cancer* 2007;**110**:670–7.
20. Becouarn Y, Senesse P, Thezenas S, et al. A randomized phase II trial evaluating safety and efficacy of an experimental chemotherapy regimen (irinotecan + oxaliplatin, IRINOX) and two standard arms (LV5 FU2 + irinotecan or LV5 FU2 + oxaliplatin) in first-line metastatic colorectal cancer: a study of the Digestive Group of the Federation Nationale des Centres de Lutte Contre le Cancer. *Ann Oncol* 2007;**18**:2000–5.
21. Haller DG, Rothenberg ML, Wong AO, et al. Oxaliplatin plus irinotecan compared with irinotecan alone as second-line treatment after single-agent fluoropyrimidine therapy for metastatic colorectal carcinoma. *J Clin Oncol* 2008;**26**:4544–50.
22. Tournigand C, Andre T, Achille E, et al. FOLFIRI followed by FOLFOX6 or the reverse sequence in advanced colorectal cancer: a randomized GERCOR study. *J Clin Oncol* 2004;**22**:229–37.
23. Grothey A, Sargent D, Goldberg RM, et al. Survival of patients with advanced colorectal cancer improves with the availability of fluorouracil-leucovorin, irinotecan, and oxaliplatin in the course of treatment. *J Clin Oncol* 2004;**22**:1209–14.
24. Hurwitz H, Fehrenbacher L, Novotny W, et al. Bevacizumab plus irinotecan, fluorouracil, and leucovorin for metastatic colorectal cancer. *N Engl J Med* 2004;**350**:2335–42.
25. Saltz LB, Clarke S, Diaz-Rubio E, et al. Bevacizumab in combination with oxaliplatin-based chemotherapy as first-line therapy in metastatic colorectal cancer: a randomized phase III study. *J Clin Oncol* 2008;**26**:2013–9.
26. Van Cutsem E, Kohne CH, Hitre E, et al. Cetuximab and chemotherapy as initial treatment for metastatic colorectal cancer. *N Engl J Med* 2009;**360**:1408–17.