

Regorafenib in combination with FOLFOX or FOLFIRI as first- or second-line treatment of colorectal cancer: results of a multicenter, phase Ib study

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Background: Metastatic colorectal cancer (mCRC) is commonly treated with 5-fluorouracil, folinic acid, and oxaliplatin or irinotecan. The multitargeted kinase inhibitor, regorafenib, was combined with chemotherapy as first- or second-line treatment of mCRC to assess safety and pharmacokinetics (primary objectives) and tumor response (secondary objective).

Patients and methods: Forty-five patients were treated every 2 weeks with 5-fluorouracil 400 mg/m² bolus then 2400 mg/m² over 46 h, folinic acid 400 mg/m², and either oxaliplatin 85 mg/m² or irinotecan 180 mg/m². On days 4–10, patients received regorafenib 160 mg orally once daily.

Results: The median duration of treatment was 108 (range 2–345 days). Treatment was stopped for adverse events or death (17 patients), disease progression (11 patients), and consent withdrawal or investigator decision (11 patients). Six patients remained on regorafenib at data cutoff (two without chemotherapy). Drug-related adverse events occurred in 44 patients [grade ≥ 3 in 32 patients: mostly neutropenia (17 patients) and leukopenia, hand–foot skin reaction, and hypophosphatemia (four patients each)]. Thirty-three patients achieved disease control (partial response or stable disease) for a median of 126 (range 42–281 days).

Conclusion: Regorafenib had acceptable tolerability in combination with chemotherapy, with increased exposure of irinotecan and SN-38 but no significant effect on 5-fluorouracil or oxaliplatin pharmacokinetics.

Key words: chemotherapy, colorectal cancer, combination therapy, regorafenib, tyrosine kinase inhibition

introduction

Colorectal cancer is a major cause of morbidity and mortality globally [1]. Although death rates appear to be declining, 50%–60% of patients can be expected to develop metastatic disease, and most of these patients will require palliative systemic therapy [2, 3].

First-line therapy commonly involves the combination regimens of 5-fluorouracil, folinic acid, and either oxaliplatin (FOLFOX) or irinotecan (FOLFIRI) [2, 3]; with median survival of up to 20 months, but 5-year survival not exceeding 10% [4]. Addition of targeted therapies, such as bevacizumab,

cetuximab, and panitumumab, to FOLFOX or FOLFIRI can improve the results achieved with chemotherapy alone [2, 3, 5–7]. However, there is concern that the combination of chemotherapy with more than one targeted agent can be associated with reduced tolerability and no beneficial impact on efficacy [8, 9]. Hence, there is interest in identifying single-targeted therapies that can be used in association with FOLFOX or FOLFIRI to improve survival without imposing an unacceptable toxicity burden.

Regorafenib (BAY 73-4506; Bayer Pharma AG, Berlin, Germany) is a novel oral multikinase inhibitor that blocks the activity of multiple protein kinases, including kinases involved in the regulation of tumor angiogenesis [vascular endothelial growth factor receptors (VEGFRs) 1, 2, and 3, and angiotensin-1 receptor], oncogenesis [stem cell growth factor receptor, proto-oncogene tyrosine-protein kinase receptor Ret, Raf proto-oncogene serine/threonine protein kinase, and

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serine/threonine kinase protein B-raf (BRAF), including BRAF^{V600E}], and the tumor microenvironment [platelet-derived growth factor receptor (PDGFR)- β and fibroblast growth factor receptor] [10]. Regorafenib has shown antitumor activity in preclinical xenograft models, including models of colorectal cancer [10]. The first study of regorafenib in humans demonstrated an acceptable safety profile and preliminary evidence of antitumor activity in patients with solid tumors [11]. In a phase I extended-cohort clinical trial, single-agent regorafenib was associated with stable disease in 19 of 27 assessable patients with heavily pretreated colorectal cancer [12]. Recently, a phase III trial (CORRECT) reported an increase in overall survival (OS) in regorafenib-treated patients, randomized against best supportive care, after progression on standard therapy (6.4 versus 5.0 months, respectively). This result led to the Food and Drug Administration approval for regorafenib monotherapy in the USA; European approval is pending [13].

We designed the present study (ClinicalTrials.gov identifier: NCT00934882) to explore whether addition of regorafenib to FOLFOX or FOLFIRI could be feasible as a treatment of metastatic colorectal cancer (mCRC), in terms of safety and pharmacokinetic interactions of the various drug components of the regimen. Preliminary data from this study were presented at the American Society of Clinical Oncology Annual Meeting, June 2011, in Chicago, IL, USA [14].

materials and methods

This multicenter study was undertaken at seven specialist oncology departments in Germany. The protocol and all amendments were reviewed and approved by each study site's independent ethics committee or institutional review board, and the study was conducted in accordance with the principles of the Declaration of Helsinki and International Conference on Harmonization Guidance on Good Clinical Practice, as well as local and European legislation.

patients

Men or women with metastatic, histologically or cytologically confirmed colorectal cancer, for which FOLFOX or FOLFIRI was considered appropriate as first- or second-line treatment, were able to enter the study.

Participants had to have at least one measurable lesion according to Response Evaluation Criteria in Solid Tumors (RECIST) version 1.0, with progressive disease (based on radiological assessment or clinical evaluation) evaluated within 4 weeks before the pre-study examination. Additional inclusion criteria included Eastern Cooperative Oncology Group (ECOG) performance status of 0 or 1, anticipated life expectancy of at least 12 weeks, and adequate bone marrow, liver, and renal function.

Exclusion criteria included more than one previous line of chemotherapy; FOLFOX or FOLFIRI treatment of patients who were scheduled to receive that regimen in the present study; radiotherapy, major surgery, or treatment with another investigational agent within 4 weeks before the study; major organ dysfunction or bleeding risks, such as therapeutic anticoagulation; significant traumatic injuries; or thromboembolic events before study entry.

treatments

The choice of the cytotoxic chemotherapy (FOLFOX or FOLFIRI) was at the investigators' discretion. However, to ensure that pharmacokinetics and

safety data were available from at least 12 patients receiving each regimen, we aimed to recruit a minimum of 20 participants for each combination. When 20 patients had been allocated to one regimen, all subsequent patients were allocated to the other regimen.

The treatment schedule was as follows: starting on days 1 and 15 of each 28-day cycle, all patients received D/L-folinic acid 400 mg/m² as a 2-h intravenous (IV) infusion before an IV bolus injection of 5-fluorouracil 400 mg/m² followed by a 46-h infusion of 5-fluorouracil 2400 mg/m². Patients in the FOLFOX group received oxaliplatin 85 mg/m² as a 2-h IV infusion at the same time as the folinic acid infusion. Patients in the FOLFIRI group received irinotecan 180 mg/m² as a 1.5-h infusion starting 30 min after the start of the folinic acid infusion. On days 4–10 and 18–24 of each cycle, all patients received regorafenib 160 mg orally once daily. Treatment continued for at least six cycles or until tumor progression, unacceptable toxicity, consent withdrawal, or withdrawal from the study at the discretion of the investigator. Prespecified dose adjustments for each agent could be made to manage adverse events. If a patient required more than two dose reductions, treatment was discontinued.

assessments

The primary objectives of the study were to define the safety profile of regorafenib in combination with FOLFOX or FOLFIRI and to determine the effect of regorafenib on the pharmacokinetics of the FOLFOX and FOLFIRI components.

All patients who had taken at least one dose of study drug (regorafenib and/or oxaliplatin or irinotecan and/or 5-fluorouracil) and had post-treatment data were assessable for safety. Adverse events were evaluated using National Cancer Institute Common Terminology Criteria for Adverse Events (NCI CTCAE) version 3.0.

Pharmacokinetics were assessed before (cycle 1) and after (cycle 2) regorafenib treatment of irinotecan and its metabolite, SN-38, platinum (unbound and total), and 5-fluorouracil. Blood samples for pharmacokinetics were collected on day 1 of cycles 1 and 2 according to the following schedule: irinotecan and SN-38, before the dose and at 1, 2, 2.25, 2.5, 2.75, 3, 4, 6, 8, 24, and 48 h after onset of infusion; free and total platinum, before the dose and at 1, 2, 2.25, 2.5, 2.75, 3, 4, 6, 8, 24, 48, and 72 h after onset of oxaliplatin infusion; 5-fluorouracil, before the dose and at 5 min, 24 h, and 46 h (end of infusion), and 20 min, 30 min, 45 min, 1 h, 2 h, and 3 h after the end of infusion. Analysis of irinotecan and SN-38 was carried out using high-performance liquid chromatography–tandem mass spectrometry. Platinum was assayed using inductively coupled plasma mass spectrometry. 5-Fluorouracil was assayed using liquid chromatography–tandem mass spectrometry. All methods were validated according to US Food and Drug Administration guidelines [15].

Tumor response, evaluated using RECIST version 1.0, was assessed at the end of every second treatment cycle, starting at the end of cycle 2. A documented tumor response was confirmed at a minimum of 4 weeks after the response had first been recorded.

results

In total, 48 patients were enrolled between August 2009 and August 2010, with data cutoff in December 2010. Forty-five patients completed screening and received at least one dose of study medication (FOLFOX: $n = 25$ and FOLFIRI: $n = 20$). Baseline patient characteristics are tabulated in Table 1. At the data cutoff, six patients were still receiving regorafenib treatment. In the other 39 patients, reasons for treatment discontinuation were adverse events ($n = 16$), disease progression, recurrence, or relapse ($n = 11$), consent withdrawal

Table 1. Baseline patient characteristics

	Regorafenib + FOLFOX (<i>n</i> = 25)	Regorafenib + FOLFIRI (<i>n</i> = 20)
Sex, <i>n</i> (%)		
Male	14 (56)	13 (65)
Female	11 (44)	7 (35)
Median age, years (range)	63 (42–80)	68 (18–77)
Eastern Cooperative Oncology Group performance status, <i>n</i> (%) ^a		
0	11 (44)	16 (80)
1	12 (48)	4 (20)
Histology, <i>n</i> (%)		
Mucinous (colloid) adenocarcinoma	3 (12)	1 (5)
Adenocarcinoma not otherwise specified	22 (88)	19 (95)
Clinical/radiographic tumor status at entry, <i>n</i> (%)		
Progressive disease	22 (88)	15 (75)
Stable disease	3 (12)	1 (5)
Missing	0	4 (20)
Number of metastatic sites at screening, <i>n</i> (%)		
1	9 (36)	4 (20)
2	7 (28)	10 (50)
3	3 (12)	5 (25)
4	4 (16)	1 (5)
5	2 (8)	0
Treatment line, <i>n</i> (%)		
First	16 (64)	15 (70)
Second	9 (36)	5 (30)

^aPerformance status data were missing from two patients in the FOLFOX group.

(*n* = 6), investigator decision (*n* = 5; mostly for planned tumor surgery, *n* = 3), and death (*n* = 1). The median duration of treatment was 108 (FOLFOX: 107, range 10–273 days and FOLFIRI: 112, range 2–345 days).

safety and tolerability

All 45 patients reported one or more adverse events, which were deemed to be related to at least one of the study drugs in 44 (98%) patients. Table 2 presents the incidence of drug-related adverse events by treatment and grade. Overall, the incidence of drug-related adverse events of any grade was similar between FOLFOX and FOLFIRI groups.

Thirty-two (71%) patients had drug-related adverse events of CTCAE grade 3 or higher (Table 2).

Twelve (27%) patients reported at least one drug-related serious adverse event, including three patients with thrombosis or embolism, two patients with diarrhea, and one patient each with allergic reaction, brain ischemia, empyema, hypertension, leukocytopenia, liver dysfunction, neutropenia, oral mucositis, pneumonia and raised alanine aminotransferase (ALT). Of the three (7%) patients who died during the study or within 30 days after the last dose of study treatment, only one death was

attributed to an adverse event (hepatic toxicity), whereas the other two were due to disease progression. The most frequent drug-related adverse events leading to dose modification were neutropenia (*n* = 12; 27%), mucositis (*n* = 8; 18%), hand–foot skin reaction (*n* = 8; 18%), and leukopenia (*n* = 5; 11%).

Drug-related adverse events resulted in dose modification, dose interruption, or permanent discontinuation of study treatment in 31 (69%) patients overall (18 [72%] FOLFOX and 13 [65%] FOLFIRI). Dose reduction or dose interruption of at least one of the chemotherapy components was observed in 52% of patients treated with FOLFOX and 65% of patients receiving FOLFIRI. A dose reduction of 5-fluorouracil due to adverse events was necessary in 18% of administered cycles. 5-Fluorouracil administration was interrupted (omitted) in 8% of cycles. Oxaliplatin and irinotecan doses were reduced in 11% and 12% and interrupted in 11% and 5% of administered cycles, respectively.

pharmacokinetics

The primary pharmacokinetic parameters of irinotecan, SN-38, total and unbound platinum, and 5-fluorouracil are presented in Table 3. For irinotecan, area under the curve (AUC) was significantly higher in cycle 2 (following regorafenib dosing) than in cycle 1 (before regorafenib dosing); the ratio of AUC values (cycle 2:cycle 1) was 1.28 (90% confidence interval [CI] 1.06–1.54). C_{max} for irinotecan was only slightly increased, and $t_{1/2}$ was unchanged. For SN-38, AUC was significantly higher in cycle 2 than in cycle 1 (ratio 1.44, 90% CI 1.12–1.85), while C_{max} was unchanged.

efficacy

Thirty-eight patients were evaluable for tumor response (a secondary objective of this study) and were included in the efficacy analysis. Seven patients achieved a partial response (FOLFOX: *n* = 4 and FOLFIRI: *n* = 3). Twenty-six patients had stable disease as best response (FOLFOX: *n* = 14 and FOLFIRI: *n* = 12). Overall, disease control (i.e. partial response or stable disease) was achieved in 33 (87%) patients. In these patients, the median time without progression was 126 (range 42–281 days) in the whole population, 122.5 (range 42–188 days) for the FOLFOX group, and 126 (range 67–281 days) for the FOLFIRI group.

Median time to progression was 119 (range 45–340 days) overall, 116 (range 45–278 days) in the FOLFOX group, and 186.5 (range 64–340 days) in the FOLFIRI group. Figure 1 shows the time to progression for each patient.

discussion

The results of this study indicate that regorafenib given sequentially after cytotoxic chemotherapy (FOLFOX or FOLFIRI) has acceptable tolerability, with relatively little impact on the pharmacokinetics of the chemotherapy components.

Combination therapy did not appear to result in substantially worse toxicity than would be expected from each component individually. As expected, more than half of the patients experienced diarrhea (*n* = 25; 56%) and almost half of

Table 2. Incidence of drug-related, treatment-emergent adverse events occurring in at least 5% of patients overall

	Regorafenib + FOLFOX (<i>n</i> = 25)		Regorafenib + FOLFIRI (<i>n</i> = 20)		Total (<i>n</i> = 45)	
	All grades	Grade ≥3	All grades	Grade ≥3	All grades	Grade ≥3
Any event, <i>n</i> (%)	25 (100)	19 (76)	19 (95)	13 (65)	44 (98)	32 (71)
Hematological, <i>n</i> (%)						
Neutropenia ^a	11 (44)	8 (32)	11 (55)	9 (45)	22 (49)	17 (38)
Leukopenia	10 (40)	2 (8)	7 (35)	2 (10)	17 (38)	4 (9)
Thrombocytopenia	5 (20)	1 (4)	4 (20)	1 (5)	9 (20)	2 (4)
Anemia	1 (4)	0	4 (20)	0	5 (11)	0
Gastrointestinal, <i>n</i> (%)						
Diarrhea	13 (52)	1 (4)	12 (60)	2 (10)	25 (56)	3 (7)
Mucositis	10 (40)	2 (8)	7 (35)	0	17 (38)	2 (4)
Nausea	10 (40)	1 (4)	5 (25)	0	15 (33)	1 (2)
Abdominal pain	4 (16)	0	5 (25)	1 (5)	9 (20)	1 (2)
Vomiting	4 (16)	0	4 (20)	0	8 (18)	0
Anorexia	4 (16)	1 (4)	3 (15)	0	7 (16)	1 (2)
ALT elevation	3 (12)	1 (4)	1 (5)	1 (5)	4 (9)	2 (4)
Weight loss	1 (4)	0	3 (15)	0	4 (9)	0
Lipase elevation	2 (8)	2 (8)	1 (5)	1 (5)	3 (7)	3 (7)
AST elevation	2 (8)	0	1 (5)	0	3 (7)	0
Flatulence	1 (4)	0	2 (10)	0	3 (7)	0
Heartburn	0	0	3 (15)	0	3 (7)	0
Dermatological, <i>n</i> (%)						
Hand-foot skin reaction	9 (36)	1 (4)	7 (35)	3 (15)	16 (36)	4 (9)
Alopecia	2 (8)	0	8 (40)	0	10 (22)	0
Rash or desquamation	5 (20)	0	2 (10)	0	7 (16)	0
Other events, <i>n</i> (%)						
Fatigue	7 (28)	0	9 (45)	0	16 (36)	0
Sensory neuropathy	11 (44)	1 (4)	4 (20)	0	15 (33)	1 (2)
Voice changes	7 (28)	0	5 (25)	0	12 (27)	0
Headache	8 (32)	0	1 (5)	0	9 (20)	0
Nose bleed	3 (12)	0	4 (20)	0	7 (16)	0
Allergic reaction	5 (20)	1 (4)	1 (5)	0	6 (13)	1 (2)
Hypertension	2 (8)	2 (8)	4 (20)	1 (5)	6 (13)	3 (7)
Hypophosphatemia	4 (16)	3 (12)	1 (5)	1 (5)	5 (11)	4 (9)
Thrombosis, embolism	2 (8)	2 (8)	1 (5)	1 (5)	3 (7)	3 (7)
Musculoskeletal/soft-tissue disorder	2 (8)	0	1 (5)	0	3 (7)	0
Dizziness	2 (8)	0	1 (5)	0	3 (7)	0
Hypokalemia	1 (4)	0	2 (10)	1 (5)	3 (7)	1 (2)
Cough	1 (4)	0	2 (10)	0	3 (7)	0

^aOnly one patient had febrile neutropenia (grade 3); this patient was receiving FOLFIRI.

ALT: alanine aminotransferase; AST: aspartate aminotransferase.

Table 3. Pharmacokinetics of irinotecan, SN-38, total and unbound platinum, and 5-fluorouracil before (cycle 1) and after (cycle 2) dosing with regorafenib

Parameter	Unit	Cycle 1			Cycle 2			Ratio (90% CI) Cycle 2/Cycle 1
		Geometric mean	% CV	Range	Geometric mean	% CV	Range	
Irinotecan (n = 11)								
AUC	mg × h/l	10.7	24.2	7.4–15.6	13.8	35.6	8.5–28.7	1.28 (1.07–1.54)
C _{max}	mg/l	1.9	33.2	1.3–3.4	2.3	70.0	1.4–13.2	1.22 (0.80–1.85)
t _{1/2}	h	8.5	27.3	5.2–11.9	7.8	26.2	4.7–10.9	n.c.
SN-38 (n = 10)								
AUC	mg × h/l	0.4	42.7	0.2–0.7	0.5	57.8	0.2–0.9	1.44 (1.12–1.84)
C _{max} *	mg/l	33.6	104.7	11.8–239.9	30.4	47.8	14.1–60.6	0.91 (0.55–1.50)
t _{1/2}	h	16.8	39.1	9.4–34.1	19.3	66.6	7.7–55.9	n.c.
Total platinum (n = 12)								
AUC	mg × h/l	81.0	22.2	44.8–109.8	112.9	11.4	89.9–134.5	1.39 (1.23–1.58)
C _{max}	mg/l	2.2	22.8	1.2–2.7	2.4	17.5	1.7–3.2	1.09 (0.98–1.22)
t _{1/2}	h	46.4	17.6	36.9–60.2	52.0	23.6	36.9–72.9	n.c.
Unbound platinum (n = 10)								
AUC	mg × h/l	4.2	39.0	1.6–5.3	4.9	15.2	4.2–6.6	1.17 (0.96–1.43)
C _{max}	mg/l	0.8	32.7	0.4–1.3	1.0	19.5	0.7–1.3	1.19 (0.96–1.47)
t _{1/2}	h	17.2	18.2	10.8–22.1	19.0	17.7	15.0–29.0	n.c.
5-fluorouracil (FOLFOX regimen) (n = 9)								
AUC	mg × h/l	123.2	73.1	31.5–287.8	139.9	106.1	35.1–418.5	1.06 (0.69–1.64)
C _{max} [†]	mg/l	19.1	163.7	1.9–71.3	19.2	413.8	0.2–79.5	0.89 (0.50–1.61)
t _{1/2}	H	0.4	513.0	0.1–9.3	2.4	1813.8	0.09–149.2	
5-fluorouracil (FOLFIRI regimen) (n = 4)								
AUC	mg × h/l	258.6	79.4	112.6–569.8				n.c.
C _{max}	mg/l	23.6	92.1	11.1–66.0	21.6	1275.9	1.2–222.8	0.92 (0.06–13.9)
t _{1/2}	H	0.2	135.7	0.0–0.4				n.c.

*n = 11; †n = 12 for cycle 1 and 11 for cycle 2.

CV: coefficient of variance; AUC: area under the concentration–time curve; C_{max}: maximum concentration; t_{1/2}: elimination half-life; n.c.: not calculated.

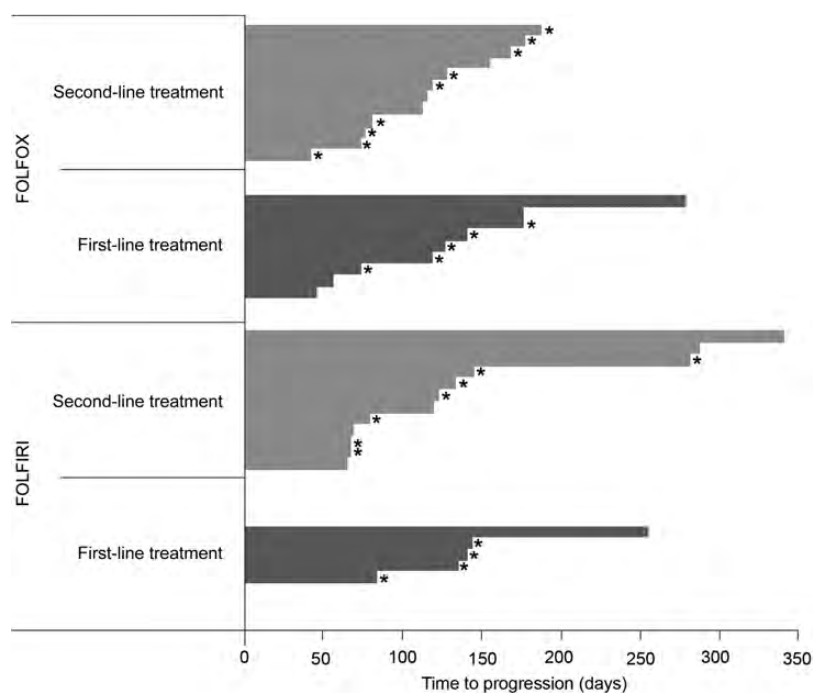


Figure 1. Time to progression in patients with disease progression or “censored at last contact”.

the patients ($n = 22$; 49%) had neutropenia, although only one patient had febrile neutropenia (in the FOLFIRI group). Relatively few drug-related adverse events were grade 3 or higher, most commonly neutropenia ($n = 17$; 38%) and hand-foot skin reaction, leukopenia, and hypophosphatemia (each $n = 4$; 9%).

The active metabolite of irinotecan, SN-38, is predominantly converted to an inactive metabolite by glucuronidation. As regorafenib is a strong inhibitor of the glucuronosyltransferases, UGT1A1 and UGT1A9, there was a potential for pharmacokinetic interaction. In anticipation of such an interaction, dosing of irinotecan was separated from regorafenib by 4 days. The present study indicated that irinotecan and SN-38 exposure was increased significantly following regorafenib dosing, even with a 4-day interval between irinotecan and regorafenib dosing. In line with the known elimination pathways of platinum and 5-fluorouracil, no pharmacokinetic interaction with regorafenib was expected, and this was largely corroborated by the results of the study. The slight increase in total platinum AUC at cycle 2 may be at least partially due to the long terminal elimination phase of platinum [16].

The regorafenib dosing regimen in this study was selected to reduce the risk of toxic effects and drug interactions by moderating the total monthly regorafenib dose and avoiding simultaneous dosing of regorafenib and chemotherapy, especially since regorafenib has two active metabolites (M2 and M5) with half-lives of 25 (regorafenib), 26–28 (M2), and 51–64 h (M5) [12]. This regorafenib schedule resulted in a total monthly dose of 2240 mg, which is lower than the 3360-mg total monthly dose in trials of single-agent regorafenib (which use a treatment schedule of 160 mg once daily for the first 21 days of each 28-day cycle). Patients could also have dose modifications of regorafenib or chemotherapy if deemed appropriate to manage toxic effects. The regimen may have achieved its aim of reducing the risk of toxic effects and drug interactions, but we acknowledge that the schedule can be difficult for patients to remember and requires careful instructions to achieve optimal adherence.

The median duration of disease control reported in this trial was similar in the FOLFOX and FOLFIRI groups (122.5 and 126 days, respectively). No clear difference was seen in progression-free survival (PFS) between patients receiving the first- or second-line treatment. In contrast, Tournigand et al. [17] reported median PFS of 8.5 and 2.5 months for first-line FOLFIRI and second-line FOLFIRI treatments, respectively, whereas for FOLFOX the median PFS was 8.0 and 4.2 months in first- and second-line treatments, respectively. For the present trial, it should be borne in mind that time to progression was not a primary end point, and patients were therefore not followed up long term: most observations were censored (13 of the 21 patients in the FOLFOX group and 11 of the 17 patients in the FOLFIRI group), making the interpretation of PFS data in this trial difficult.

Two additional factors may explain the rather low clinical efficacy observed in this trial. (i) The addition of regorafenib to standard treatment with FOLFOX or FOLFIRI may have resulted in a higher frequency of dose reductions and interruptions, resulting in reduced dose intensity. More than 50% of patients required a reduction of chemotherapy dose

due to adverse events observed in this trial. This is higher than what has been reported with FOLFIRI (20.9%) and FOLFOX (14%) without the addition of targeted therapy [18, 19]. (ii) Normalization of the tumor vasculature through antiangiogenic treatment might improve tumor perfusion and, consequently, delivery of systemic chemotherapy [20]. However, significantly reduced tumor vascularity might result in inefficient uptake of cytotoxic agent in the tumor [21, 22]. In this regard, the scheduling of a targeted compound in relation to chemotherapy may influence the efficacy of the combination treatment. *In vivo* data demonstrate that the impact of scheduling and dosing sequence on antiangiogenic agents with chemotherapy may depend on the combined drugs and models used. When axitinib was combined with gemcitabine in a pancreatic xenograft model and with paclitaxel plus carboplatin in a xenograft model of non-small-cell lung cancer (NSCLC), tumor growth inhibition was highest with concurrent dosing of antiangiogenic and chemotherapy [23]. Similar data were obtained with vandetanib in combination with irinotecan in a colon cancer xenograft model [24]. On the other hand, docetaxel immediately followed by sunitinib in a human NSCLC xenograft model resulted in superior tumor growth inhibition compared with concurrent administration of these compounds [25]. We cannot exclude the possibility that a different dosing schedule of regorafenib and FOLFOX or FOLFIRI would have altered the efficacy profile of the combination treatments. Despite the clinical doses being extrapolated from preclinical pharmacokinetic studies, the human metabolism data suggest that dose reductions might be more suitable for further clinical testing in order to avoid extensive toxic effects.

Other trials have been undertaken to assess the impact of combining standard chemotherapy with antiangiogenic kinase inhibitors. In a phase I trial, Starling et al. [26] found that, in combination with FOLFIRI, continuous dosing of sunitinib was not feasible because of toxicity, while only the 37.5-mg/day sunitinib dose (and not the standard 50-mg/day dose) was tolerated using a schedule of 4 weeks on–2 weeks off treatment. A phase II trial of sunitinib plus FOLFIRI showed promising efficacy, although toxicity continued to be a concern [27], while a phase III trial combining sunitinib with FOLFIRI was discontinued prematurely for futility on the advice of the independent data monitoring committee [28]. For sorafenib, combination with either oxaliplatin, irinotecan, or cisplatin with gemcitabine has proven to be feasible in a phase I trial [29–31]. Data from randomized phase III trials in colorectal cancer are available for the combination of vatalanib with FOLFOX-4 [32, 33], semaxanib with 5-FU and leucovorin [34], brivanib with cetuximab [35], and cediranib with FOLFOX-6 [36] or with FOLFOX or capecitabine plus oxaliplatin [37]. Unfortunately, the addition of antiangiogenic treatment to standard chemotherapy did not result in an improvement in OS in any of these trials.

The present study was designed to explore the potential role of regorafenib given sequentially with cytotoxic chemotherapy for mCRC. The results indicate that the combination has acceptable tolerability. Further exploration of such regimens in larger clinical trials is ongoing. (ClinicalTrials.gov identifiers: NCT01289821, NCT01298570).

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disclosure

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A randomized phase II study of PEP02 (MM-398), irinotecan or docetaxel as a second-line therapy in patients with locally advanced or metastatic gastric or gastro-oesophageal junction adenocarcinoma[†]

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Background: PEP02 is a novel highly stable liposomal nanocarrier formulation of irinotecan. This randomized phase II study evaluated the efficacy and safety of single agent PEP02 compared with irinotecan or docetaxel in the second-line treatment of advanced oesophago-gastric (OG) cancer.

Patients and methods: Patients with locally advanced/metastatic disease who had failed one prior chemotherapy regimen were randomly assigned to PEP02 120 mg/m², irinotecan 300 mg/m² or docetaxel (Taxotere) 75 mg/m² every 3 weeks. The primary end point was objective response rate (ORR). Simon's two-stage design was used and the ORR of interest was 20% ($\alpha = 0.05$, type II error $\beta = 0.10$, null hypothesis of ORR was 5%).

Results: Forty-four patients per arm received treatment, and 124 were assessable for response. The ORR statistical threshold for the first stage was reached in all arms. In the intent-to-treat (ITT) population, ORRs were 13.6% (6/44), 6.8% (3/44) and 15.9% (7/44) in the PEP02, irinotecan and docetaxel arms, respectively. The median progression-free survival (PFS) and overall survival were similar between the trial arms. Commonest grade 3–4 adverse event reported was diarrhoea in the PEP02 and irinotecan groups (27.3% versus 18.2%).

Conclusion: The ORR associated with PEP02 was comparable with docetaxel and numerically greater than that of irinotecan. PEP02 warrants further evaluation in the advanced gastric cancer setting.

Key words: docetaxel, irinotecan, liposomal irinotecan, oesophago-gastric cancer, phase II, second line

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