Clinical Trial

Regorafenib plus modified FOLFOX6 as first-line treatment of metastatic colorectal cancer: A phase II trial [☆]

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Abstract Background: The oral multikinase inhibitor regorafenib improves overall survival (OS) in patients with metastatic colorectal cancer (CRC) for which all standard treatments have failed. This study investigated regorafenib plus modified FOLFOX (mFOLFOX6) as first-line treatment of metastatic CRC.

Methods: In this single-arm, open-label, multicentre, phase II study, patients received mFOLFOX6 on days 1 and 15, and regorafenib 160 mg orally once daily on days 4–10 and 18–24 of each 28-day cycle. The primary end-point was centrally assessed objective response rate (ORR). Secondary end-points included disease control rate (DCR), OS, progression-free survival (PFS) and safety.

Results: Median overall treatment duration with any study drug was 9.9 months (range 0.6–19.6); median treatment duration with regorafenib was 7.7 months (range 0.1–19.5); six patients remained on regorafenib for more than 1 year. Fifty-three patients received at least one dose of regorafenib. ORR was 43.9% (all partial responses); DCR was 85.4%; median OS was not reached; median PFS was 8.5 months. Treatment-emergent adverse events were experienced by all patients but were manageable with dose modifications.

Conclusion: Regorafenib + mFOLFOX6 as first-line treatment in patients with metastatic CRC did not improve ORR over historical controls. Regorafenib plus mFOLFOX6 did not appear to be associated with a markedly worse tolerability profile versus mFOLFOX6 alone. ClinicalTrials.gov identifier: NCT01289821.

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1. Introduction

Every year, more than 1.36 million patients worldwide are diagnosed with colorectal cancer (CRC) and nearly 700,000 deaths are attributed to this disease [1]. At the time of diagnosis, up to 25% of patients present with metastatic disease, while 50–60% of patients with CRC will develop metastases at some point [2,3]. Standard treatment for these patients consists of a fluoropyrimidine-based chemotherapy backbone combined with other systemic cytotoxic agents, such as oxaliplatin and irinotecan, together with monoclonal antibodies such as bevacizumab and, in patients with *RAS* wild-type tumours, cetuximab or panitumumab. These therapies have improved overall survival (OS) from six to around 20–24 months [2,4].

Regorafenib is an oral multikinase inhibitor that blocks the activity of a variety of protein kinases involved in the regulation of oncogenesis (KIT, RET, RAF1, BRAF and BRAF^{V600E}), angiogenesis (vascular endothelial growth factor [VEGF] receptors 1–3 and TIE2) and the tumour microenvironment (platelet-derived growth factor receptor and fibroblast growth factor receptor) [5]. The phase III CORRECT trial demonstrated the efficacy and tolerability of regorafenib monotherapy in patients with previously treated metastatic CRC [6]. On the basis of those findings, regorafenib monotherapy has been approved internationally for patients with metastatic CRC previously treated with other available standard therapies.

A phase I study of regorafenib in combination with 5-fluorouracil (5-FU) + folinic acid with either

oxaliplatin (FOLFOX) or irinotecan (FOLFIRI) demonstrated an acceptable tolerability profile in patients with metastatic CRC [7]. Pharmacokinetic data revealed increased exposure to irinotecan, as well as its active metabolite SN-38, when administered in combination with regorafenib; however, regorafenib did not significantly affect the pharmacokinetics of either 5-FU or oxaliplatin [7]. The current study was designed to assess the activity and tolerability of regorafenib in combination with a modified FOLFOX regimen (mFOLFOX6) as first-line therapy for metastatic CRC.

2. Materials and methods

2.1. Study design and participants

The CORDIAL trial (ClinicalTrials.gov identifier: NCT01289821) was an international, multicentre, single-arm, open-label, phase II exploratory study conducted at 16 centres in Australia, Belgium, Spain, Germany, Italy, the United Kingdom (UK) and the United States of America (USA) (investigators at each site are listed in the Supplementary appendix). Ethical approval of the study protocol was provided by each centre's institutional review board or independent ethics committee. The trial followed the principles of the Declaration of Helsinki and good clinical practice, complying with all local laws and regulations. All patients provided written informed consent before enrolment.

Patients had to be at least 18 years old, with histological or cytological documentation of

adenocarcinoma of the colon or rectum, and had to be suitable to receive first-line treatment with mFOLFOX6 for metastatic disease. Patients had to have at least one measurable lesion according to Response Evaluation Criteria in Solid Tumors (RECIST) version 1.1 [8], an Eastern Cooperative Oncology Group performance status of 0 or 1, adequate bone-marrow, liver and renal function and an anticipated life expectancy of at least 3 months. Exclusion criteria included previous systemic anticancer therapy for metastatic CRC (although adjuvant chemotherapy for stages I–III CRC was permitted provided that therapy had ceased >6 months before screening and disease recurrence was documented), previous treatment with anti-VEGF therapies or signal transduction inhibitors or uncontrolled hypertension (systolic >150 mm/Hg or diastolic >90 mm/Hg) despite optimal management.

Patient recruitment commenced in February 2011 and was stopped in July 2011 when the target number of patients was reached. The data cut-off date for the present analyses was 15th November 2012. The last end-of-survival follow-up visit took place in June 2014.

2.2. Procedures

Patients were treated with a combination of mFOLFOX6 plus regorafenib. The mFOLFOX6 regimen was administered according to normal clinical practice starting on days 1 and 15 of each 28-day cycle and consisted of oxaliplatin 85 mg/m² and folinic acid 400 mg/m², both as 2-h intravenous (IV) infusions, and 5-FU 400 mg/m² as an IV bolus immediately followed by a 2400 mg/m² IV infusion over 46 h. Regorafenib was given orally as a single morning dose of 160 mg on days 4–10 and 18–24 of each 28-day cycle. The treatment schedule is summarised in Fig. 1.

Treatment continued until death, tumour progression (defined by RECIST), unacceptable toxicity, withdrawal of consent or investigator's decision to stop. If an individual drug had to be withdrawn because of toxicity, the patient could continue to receive the remaining components until one of the above criteria was met. Dose modifications were implemented for any individual component of the combination therapy to manage toxicities related to that drug. If patients stopped all components

of mFOLFOX6 and continued on single-agent regorafenib, the treatment regimen for regorafenib was modified to 160 mg once daily in repeating cycles of 3 weeks on/1 week off treatment according to the schedule used for regorafenib when given as monotherapy.

2.3. Study end-points

The primary end-point was objective response rate (ORR) based on blinded central radiological review. ORR was defined as the proportion of patients with a best overall tumour response of partial or complete response. Secondary end-points included disease control rate (DCR; sum of complete response + partial response + stable disease), progression-free survival (PFS), OS, duration of response and duration of stable disease. In addition, the safety and tolerability of the regimen were evaluated using adverse events and changes in laboratory measures (haematology, chemistry and urinalysis), vital signs (blood pressure, heart rate and temperature) and electrocardiogram. Although not a prespecified end-point, investigator-reported duration of treatment was also assessed.

2.4. Assessments

Tumour assessment by CT or MRI was performed at screening and every two cycles throughout the study until disease progression was documented, using identical techniques at each assessment. Unless consent to follow up was specifically withdrawn, survival assessments were made every 2 months until death, via review of medical records and regular contact. Safety was monitored continuously until 30 ± 4 days after discontinuation of treatment.

2.5. Statistical analysis

Statistical evaluation and estimation, using SAS version 9.1 or higher (SAS Institute Inc., Cary, NC, USA), were based on a one-sided type I error level of 10% and a two-sided confidence level of 80%, respectively.

The primary end-point (ORR) was analysed based on a one-sample exact binomial test. The aim was to assess whether regorafenib plus mFOLFOX6 significantly

Fig. 1. Treatment schedule (28-day cycle). mFOLFOX6, modified regimen of folinic acid + 5-fluorouracil + oxaliplatin 6; od, once-daily.

Fig. 2. Flow of patients through the study.

improved the ORR compared with that seen in a similar population of historical cohorts. With a total planned sample size of 41 evaluable patients in the primary analysis set (i.e. all patients who were evaluated for objective response), the null hypothesis was to be rejected if at least 21 patients (51%) were classified as responders. The estimated response rate and its two-sided 80% confidence interval (CI) were given.

Variables measured on interval scales were summarised using descriptive statistics, while frequency tables were provided for variables measured on nominal scales. Time-to-event data were displayed using Kaplan–Meier estimates for survival functions.

3. Results

3.1. Patient demographics and characteristics

In total, 66 patients were screened for inclusion in CORDIAL; 54 patients started the study and were included in the full analysis set (FAS; Fig. 2). Patient demographic and baseline tumour characteristics are presented in Table 1.

At the time of data cut-off, five patients were still receiving regorafenib treatment (regorafenib + 5-FU, $n = 2$; regorafenib + 5-FU infusion only, $n = 2$; regorafenib monotherapy, $n = 1$). In November 2013, one patient was still receiving regorafenib monotherapy. Treatment duration and reasons for discontinuations are summarised in Table 2.

3.2. Efficacy

In the primary analysis set ($n = 41$), a confirmed ORR was observed in 43.9% of patients ($n = 18$; all partial responses), while DCR (complete response + partial response + stable disease) was observed in 85.4% of

Table 1

Patient demographic and baseline tumour characteristics (full analysis set, $N = 54$).

Characteristic	<i>n</i>	%
Male:female ratio	28:26	51.9:48.1
Age (years)		
Median (range)	61 (32–80)	61.1
<65	33	33.3
65–75	18	5.6
≥75	3	
ECOG performance status		
0	35	64.8
1	19	35.2
Primary disease site		
Colon	35	64.8
Rectum	15	27.8
Colon and rectum	4	7.4
TNM stage at diagnosis		
I	1	1.9
IIa	5	9.3
IIb/c	7	13.0
IV	41	75.9
Number of target lesions		
0	2	3.7
1	3	5.6
2–3	42	77.8
4–5	7	13.0

ECOG, Eastern Cooperative Oncology Group; TNM, tumour, node, metastasis.

Table 2

Treatment duration and reasons for discontinuation (full analysis set, $N = 54$).

	Any study treatment ^a	Regorafenib ^b
Treatment duration		
Months (median [range])	9.9 (0.6–19.6)	7.7 (0.1–19.5)
Cycles (median [range])	8 (1–21)	7 (1–21)
Patients on treatment	26 (48.1)	29 (53.7)
>6 months (n [%])		
Patients on treatment >1 year (n [%]) ^c	6 (11.1)	6 (11)
Reasons for treatment discontinuation (n [%])		
Disease progression	39 (72.2)	
Adverse events	4 (7.4)	
Investigator's decision	3 (5.6)	
Patient withdrawal	1 (1.9)	

^a Regorafenib, oxaliplatin, folinic acid and/or 5-fluorouracil (5-FU).

^b As combination therapy or monotherapy.

^c Regorafenib + mFOLFOX6, $n = 1$; regorafenib + 5-FU, $n = 2$; regorafenib + 5-FU infusion only, $n = 2$; regorafenib monotherapy, $n = 1$.

patients ($n = 35$); no patients achieved a complete response (Table 3). The findings were similar in the per-protocol analysis ($n = 48$; see Table 3).

Kaplan–Meier estimates of OS and PFS in the FAS are presented in Fig. 3. The median duration of clinical

Table 3
Centrally assessed response using RECIST version 1.1.

		Primary analysis set (<i>N</i> = 41)		Per-protocol set (<i>N</i> = 48)	
		<i>n</i> (%)	80% CI	<i>n</i> (%)	80% CI
Best overall response	Complete response	0	0.0–3.9	0	0.0–3.3
	Partial response	18 (43.9)	33.2–55.1	20 (41.7)	31.9–52.0
	Stable disease	17 (41.5)	30.9–52.7	22 (45.8)	35.9–56.1
	Progressive disease	5 (12.2)	6.1–21.5	5 (10.4)	5.2–18.5
	Missing	1 (2.4)	0.3–9.2	1 (2.1)	0.22–7.9
DCR ^a		35 (85.4)	75.7–92.1	42 (87.5)	79.1–93.3
ORR ^b		18 (43.9)	33.2–55.1	20 (41.7)	31.9–52.0

CI, confidence interval; DCR, disease control rate; ORR, objective response rate; RECIST, Response Evaluation Criteria in Solid Tumors.

^a DCR defined as complete response + partial response + stable disease (stable disease had to be maintained for ≥ 7 weeks).

^b ORR defined as complete response + partial response.

Fig. 3. Kaplan–Meier estimates of (A) overall survival (median not reached because >50% of patients were still alive at the cut-off date; 38 censored [70.4%]) and (B) progression-free survival (median 8.5 months, 95% confidence interval 7.4–11.3 months; median time to treatment failure 7.8 months, 95% confidence interval 6.2–11.2 months). Full analysis set, *N* = 54.

response in patients with an objective response (*n* = 20) was 9.0 months (95% CI 6.6 months to not reached), while the median duration of stable disease in patients with stable disease as the best response (*n* = 22) was 7.6 months (95% CI 5.5–8.5 months). Change in target lesion volume from baseline is shown in Fig. 4.

Fig. 4. Best change in target lesion size from baseline (full analysis set, *N* = 54). Best change could not be determined in two patients. Six patients (11.1%) had increases in tumour size, while 46 patients (85.2%) had tumour shrinkage. Maximum tumour reductions of $\geq 30\%$ were recorded in 29 patients (53.7%).

3.3. Safety

In total, 52 patients (98.1%) received greater than 90% of the planned regorafenib dose, with 51 patients (96.2%) requiring regorafenib dose modifications (reductions or interruptions) as a result of adverse events (Table 4).

All 53 patients who received study medication experienced at least one treatment-emergent adverse event (TEAE) during the study. TEAEs affecting more than 20% of patients are presented in Table 5. No grade 5 TEAEs were reported. Serious TEAEs occurred in 21 patients (39.6%), with drug-related serious TEAEs reported in 13 patients (24.5%). Overall, TEAEs led to dose modifications in 51 patients (96.2%), with discontinuation of a component of study treatment required by 19 patients (35.8%) and discontinuation of full study treatment in four patients (8%). The most frequent

Table 4
Dose modifications (safety population, $N = 53$).

	Regorafenib	Oxaliplatin	5-FU bolus	5-FU infusion
Patients requiring dose interruptions or delays (n [%])				
Any	50 (94.3)	48 (90.6)	46 (86.8)	47 (88.7)
1–3	27 (50.9)	21 (39.6)	19 (35.8)	18 (33.9)
>3	23 (43.4)	27 (50.9)	27 (50.9)	29 (54.7)
Patients requiring dose reductions (n [%])				
Any	25 (47.2)	37 (69.8)	29 (54.7)	30 (56.6)
1	15 (28.3)	25 (47.2)	28 (52.8)	22 (41.5)
2	10 (18.9)	11 (20.8)	3 (5.7)	9 (17.0)

5-FU, 5-fluorouracil.

adverse events leading to regorafenib dose reductions were diarrhoea and hand–foot skin reaction. The most frequent adverse events leading to oxaliplatin dose reduction were neurotoxicity, paraesthesia and diarrhoea, while the most frequent adverse events resulting in 5-FU dose reduction were neutropenia, diarrhoea and decreased platelets.

4. Discussion

The CORDIAL study failed to reach its primary end-point, with the ORR in patients receiving regorafenib and mFOLFOX6 showing little difference from that seen with standard therapy alone. The combination of regorafenib and mFOLFOX6 was associated with a comparable median PFS (8.5 months) to FOLFOX and FOLFIRI chemotherapy alone (8.0 and 8.5 months, respectively) [9]. Median PFS in the current study appeared to be longer than that in most trials investigating chemotherapy and kinase inhibitor combinations (Supplementary Table 1) [10,11].

The apparent lack of improvement in tumour shrinkage following the addition of regorafenib to mFOLFOX6 versus historical data for chemotherapy alone (ORR of 43.9% versus an expected 35–55% for mFOLFOX6 alone [9,12–16]) together with the slowing of tumour growth observed in CORDIAL (as suggested by the higher than expected PFS) are consistent with results from the phase III CORRECT trial [6]. In CORRECT, regorafenib monotherapy significantly increased OS and PFS compared with placebo, despite a negligible ORR of 1.4% in a refractory population that had received multiple prior lines of therapy. The observations from CORDIAL and CORRECT could support a cytostatic rather than a cytotoxic effect of regorafenib on metastatic CRC. It may be possible to determine whether this theorised effect translates into prolonged OS once data are available from longer-term follow up of patients in CORDIAL.

The limitations of the CORDIAL study are its single-arm design and relatively small population. Despite the small sample size and exploratory nature of the trial, the PFS and ORR results are consistent with those reported with regimens containing other small-molecule kinase inhibitors (such as cediranib, vatalanib and sunitinib), while the duration of treatment in CORDIAL appears to be prolonged compared with those agents (Supplementary Table 1) [10,11,17].

The design of the CORDIAL study allowed modification of any component of the study treatment to manage adverse events. As a result of this tailored approach, the study showed that this combination regimen had a manageable tolerability profile in the first-line treatment of patients with metastatic CRC. Overall, the adverse event profile of the regorafenib plus mFOLFOX6

Table 5
Treatment-emergent adverse events occurring in $\geq 20\%$ of patients (safety population, $N = 53$).

Adverse event (n [%])	Any grade	Grade 1	Grade 2	Grade 3	Grade 4
Diarrhoea	37 (69.8)	16 (30.2)	9 (17.0)	12 (22.6)	0
Neutropenia	34 (64.2)	2 (3.8)	11 (20.8)	13 (24.5)	8 (15.1)
Fatigue	34 (64.2)	20 (37.7)	12 (22.6)	2 (3.8)	0
Hypertension	29 (54.7)	4 (7.4)	10 (18.9)	13 (24.5)	2 (3.8)
Paraesthesia	28 (52.8)	14 (26.4)	9 (17.0)	5 (9.4)	0
Abdominal pain	27 (50.9)	14 (26.4)	11 (20.8)	2 (3.8)	0
Nausea	26 (49.1)	23 (43.4)	2 (3.8)	1 (1.9)	0
Thrombocytopenia	25 (47.2)	10 (18.9)	11 (20.8)	4 (7.5)	0
Oral mucositis	24 (45.3)	15 (28.3)	8 (15.1)	1 (1.9)	0
Peripheral neuropathy	24 (45.3)	13 (24.5)	4 (7.5)	7 (13.2)	0
Anorexia	19 (35.8)	15 (28.3)	3 (5.7)	1 (1.9)	0
Hand–foot skin reaction	19 (35.8)	7 (13.2)	10 (18.9)	2 (3.8)	0
Constipation	16 (30.2)	13 (24.5)	2 (3.8)	1 (1.9)	0
Dysgeusia	16 (30.2)	14 (26.4)	2 (3.8)	0	0
Vomiting	16 (30.2)	12 (22.6)	2 (3.8)	2 (3.8)	0
Alopecia	15 (28.3)	13 (24.5)	2 (3.8)	0	0
Increased lipase	14 (26.4)	4 (7.5)	0	9 (17.0)	1 (1.9)
Anaemia	12 (22.6)	4 (7.5)	6 (11.3)	2 (3.8)	0
Voice alteration	12 (22.6)	11 (20.8)	1 (1.9)	0	0
Increased aspartate aminotransferase	12 (22.6)	8 (15.1)	1 (1.9)	3 (5.7)	0
Hypophosphataemia	11 (20.8)	0	4 (7.5)	7 (13.2)	0

combination appeared to be generally consistent with that of chemotherapy alone, although some regorafenib-related TEAEs, such as hand–foot skin reaction, were reported in addition to chemotherapy-related TEAEs. Of note, discontinuation of all study treatment (chemotherapy and regorafenib) as a result of TEAEs only occurred in four patients, with most patients continuing at least one component of study treatment [9,12–16].

In other studies of tyrosine kinase inhibitors in combination with chemotherapy, a decreased dose intensity of the chemotherapy components has been implicated in the apparent lack of efficacy. In CORDIAL, the intermittent dosing schedule could possibly underlie both the tolerability profile of regorafenib in combination with chemotherapy and the apparent antitumour activity, by avoiding any negative interaction between the impact of regorafenib on cell replication and the efficacy of the chemotherapy components. This hypothesis was first proposed in a serial imaging study of the VEGF receptor inhibitor axitinib; that study showed marked inhibition of fluorothymidine uptake during continuous treatment for 7 days, suggesting inhibition of cancer cell proliferation, which might protect against the cytotoxic effects of chemotherapy. The authors of that study hypothesised that this effect could explain the failure of VEGF receptor inhibitors in combination with chemotherapy regimens to improve outcomes [18].

Although duration of treatment was not a prespecified end-point, it is interesting to note that six patients received at least one component of study medication for 1 year or longer, with an overall median treatment duration for any component of study treatment of 9.9 months and five patients still receiving regorafenib therapy more than 6 months after data cut-off (regorafenib + 5-FU, $n = 2$; regorafenib + 5-FU infusion only, $n = 2$; regorafenib monotherapy, $n = 1$). The relatively long duration of treatment observed, albeit from a phase II study, contrasts with data from phase III studies of other first-line therapies for metastatic CRC, in which the duration of treatment rarely exceeds 6 months (Supplementary Table 2) [9,12–16].

The study did not meet its primary end-point, with no increase in the response rate compared with historical data from patients treated with mFOLFOX6 alone. Thus, the combination of regorafenib and mFOLFOX6 given in this schedule cannot be considered to be synergistic. However, given the median duration of treatment (9.9 months), together with some patients receiving at least one component of study therapy for more than 1 year, it would be interesting to explore the hypothesis that the addition of regorafenib to standard treatment might help patients to continue on treatment, and thus maintain tumour control for longer than might be achieved with chemotherapy alone.

Characterisation of patients who could derive the most long-term benefit, and the impact of dose modifications on tolerability and treatment duration, might provide the groundwork for investigation of the use of regorafenib as maintenance therapy in patients with metastatic CRC who have achieved a clinical response to cytotoxic chemotherapy.

5. Author contributions

J.T., F.C., A.B. III, C.-H.K., J.Z., A.W., V.L.G. and J.G. designed the trial, developed the protocol, coordinated the study and were responsible for management, analysis and interpretation of the data. G.A., M.P.S., F.R., A.S., A.B. III, C.G.-P., S.C., E.V.C., I.R.M., D.S., C.-H.K. J.Z., J.T. and F.C. enrolled patients. G.A., J.T., and F.C. were responsible for drafting the manuscript, with writing support from Succinct Medical Communications, funded by Bayer. All authors were responsible for review and revision of the manuscript, and approval of the submitted version.

Conflict of interest statement

Guillem Argilés: Bayer consultant for the development of regorafenib; Merck Serono consultant.

Mark P. Saunders: Bayer consultant.

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Dirk Strumberg: Bayer consultant.

Claus-Henning Köhne: Honoraria from Bayer; Bayer consultant.

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Andrea Wagner: Employee of Bayer Pharma AG, Berlin, Germany.

Vittorio Luigi Garosi: Employee of Bayer S.p.A., Milan, Italy.

Julia Grunert: Employee of Bayer Pharma AG, Wuppertal, Germany.

Josep Tabernero: Advisory role for Amgen, Bayer, Boehringer, Bristol-Myers Squibb, Genentech, Imclone, Lilly, Merck KGaA, Millennium, Novartis, Onyx, Pfizer, Roche and Sanofi.

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Appendix A. Supplementary data

Supplementary data associated with this article can be found, in the online version, at <http://dx.doi.org/10.1016/j.ejca.2015.02.013>.

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