Regorafenib monotherapy for previously treated metastatic colorectal cancer (CORRECT): an international, multicentre, randomised, placebo-controlled, phase 3 trial

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Summary

Background No treatment options are available for patients with metastatic colorectal cancer that progresses after all approved standard therapies, but many patients maintain a good performance status and could be candidates for further therapy. An international phase 3 trial was done to assess the multikinase inhibitor regorafenib in these patients.

Methods We did this trial at 114 centres in 16 countries. Patients with documented metastatic colorectal cancer and progression during or within 3 months after the last standard therapy were randomised (in a 2:1 ratio; by computer-generated randomisation list and interactive voice response system; preallocated block design (block size six); stratified by previous treatment with VEGF-targeting drugs, time from diagnosis of metastatic disease, and geographical region) to receive best supportive care plus oral regorafenib 160 mg or placebo once daily, for the first 3 weeks of each 4 week cycle. The primary endpoint was overall survival. The study sponsor, participants, and investigators were masked to treatment assignment. Efficacy analyses were by intention to treat. This trial is registered at ClinicalTrials.gov, number NCT01103323.

Findings Between April 30, 2010, and March 22, 2011, 1052 patients were screened, 760 patients were randomised to receive regorafenib (n=505) or placebo (n=255), and 753 patients initiated treatment (regorafenib n=500; placebo n=253; population for safety analyses). The primary endpoint of overall survival was met at a preplanned interim analysis; data cutoff was on July 21, 2011. Median overall survival was 6·4 months in the regorafenib group versus 5·0 months in the placebo group (hazard ratio 0·77; 95% CI 0·64–0·94; one-sided p=0·0052). Treatment-related adverse events occurred in 465 (93%) patients assigned regorafenib and in 154 (61%) of those assigned placebo. The most common adverse events of grade three or higher related to regorafenib were hand-foot skin reaction (83 patients, 17%), fatigue (48, 10%), diarrhoea (36, 7%), hypertension (36, 7%), and rash or desquamation (29, 6%).

Interpretation Regorafenib is the first small-molecule multikinase inhibitor with survival benefits in metastatic colorectal cancer which has progressed after all standard therapies. The present study provides evidence for a continuing role of targeted treatment after disease progression, with regorafenib offering a potential new line of therapy in this treatment-refractory population.

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Introduction

Worldwide, nearly 1·25 million patients are diagnosed with and more than 600 000 patients die from colorectal cancer each year.[1] At least 50% of patients develop metastases,[2] and most of these patients have unresectable tumours.[2,3] Standard treatment for these patients involves chemotherapy based on fluoropyrimidines, oxaliplatin, and irinotecan (used in combination and sequentially); and monoclonal antibodies targeting vascular endothelial growth factor (VEGF; bevacizumab). In patients with *KRAS* wild-type tumours, monoclonal antibodies targeting epidermal growth factor receptor (EGFR; cetuximab and panitumumab) are also used.[2,3] Additional options are needed for patients who have disease progression despite all currently available standard therapies, because many patients maintain good performance status and might be candidates for further therapy.

Various signalling pathways have been implicated in the development and progression of colorectal cancer, involving receptor tyrosine kinases (eg, EGFR, VEGF receptor, platelet-derived growth factor receptor [PDGFR], and fibroblast growth factor receptor [FGFR]) and downstream signalling cascades (RAS-RAF-MEK-ERK and PI3K-PTEN-AKT-mTOR).[4] Regorafenib is a novel oral multikinase inhibitor that blocks the activity of several protein kinases, including kinases involved in the regulation of tumour angiogenesis (VEGFR1 [also known as FLT1], VEGFR2 [KDR], VEGFR3 [FLT4], TIE2 [TEK]), oncogenesis (KIT, RET, RAF1, BRAF, and $BRAF^{V600E}$), and the tumour microenvironment (PDGFR and FGFR).[5] In preclinical studies, regorafenib has shown antitumour activity, including in colorectal cancer models.[5]

In a phase 1b study, oral regorafenib, given at a dose of 160 mg once daily for the first 3 weeks of each 4 week

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See Online for appendix

cycle, showed a tolerable toxicity profile and preliminary evidence of antitumour activity in 38 patients with progressive colorectal cancer who had received previous therapy for metastatic disease (median four lines).[6] The disease control rate (partial response plus stable disease) was 74% (20 of 27 assessable patients). On the basis of these results and the high unmet need in this population of patients, the decision was made to proceed to a randomised phase 3 trial. We did the CORRECT trial (patients with metastatic colorectal cancer treated with regorafenib or placebo after failure of standard therapy) to assess efficacy and safety of regorafenib in patients with metastatic colorectal cancer, progressing after all approved standard therapies.

Methods

Study design and participants

CORRECT was a randomised, placebo-controlled, phase 3 study involving 114 centres in 16 countries in North America, Europe, Asia, and Australia. Patients were eligible to participate when they had histological or cytological documentation of adenocarcinoma of the colon or rectum. They had to have received locally and currently approved standard therapies and to have disease progression during or within 3 months after the last administration of the last standard therapy or to have stopped standard therapy because of unacceptable toxic effects. Because the trial was done in countries throughout the world, available standard therapies varied from country to country but had to include as many of the following as were licensed: a fluoropyrimidine, oxaliplatin, irinotecan, and bevacizumab; and cetuximab or panitumumab for patients who had *KRAS* wild-type tumours.

Patients had to be aged 18 years or older and have an Eastern Cooperative Oncology Group (ECOG) performance status of 0 or 1; life expectancy of at least 3 months; and adequate bone-marrow, liver, and renal function at the start of the trial. Patients could not participate if they had previously received regorafenib or had uncontrolled medical disorders. The appendix shows full inclusion and exclusion criteria.

Each centre's institutional review board or independent ethics committee approved the protocol. The trial followed the guiding principles of the Declaration of Helsinki and good clinical practice, and complied with all local laws and regulations. Participants provided written informed consent before enrolment; when a patient was not capable of providing a signature an oral statement of consent could be provided in the presence of a witness.

Randomisation and masking

Patients were randomly assigned in a 2:1 ratio to regorafenib or placebo with a computer-generated randomisation list prepared by the study sponsor. The 2:1 ratio was used to facilitate recruitment into a placebo-controlled trial. Investigators received the randomisation number for each participant through an interactive voice response system, which was also used to manage study drug supply.

Randomisation was on the basis of preallocated block sizes (block size six) and was stratified by previous treatment with VEGF-targeting drugs (yes or no; on the assumption that not all countries would have access to such agents), time from diagnosis of metastatic disease (≥18 months or <18 months), and geographical region (North America, western Europe, Israel, and Australia; Asia; and eastern Europe).

Randomisation was concealed so that neither the patient, nor the investigator, nor the sponsor knew which agent was being administered. To maintain masking, study medication was labelled with a unique drug pack number preprinted on each bottle, which was assigned to the patient through the interactive voice response system. Unmasking for individual patients could occur via the voice response system for emergencies only; serious adverse events did not necessarily precipitate immediate unmasking.

Procedures

All patients received best supportive care, excluding other investigational antitumour agents or antineoplastic chemotherapy, hormonal therapy, or immunotherapy. Patients were randomised to receive oral regorafenib 160 mg or matching placebo once daily for the first 3 weeks of each 4 week cycle until disease progression, death, unacceptable toxic effects, withdrawal of consent by the patient, or decision by the treating physician that discontinuation would be in the patient's best interest. No crossover between treatment groups was allowed. Patients were followed up every 2 weeks while receiving treatment and every month after cessation of treatment until death or trial data cutoff date.

Predefined dose modifications were permitted to manage clinically significant treatment-related toxic effects (appendix). Patients who required dose reductions could re-escalate the dose up to 160 mg daily at the discretion of the investigator once the toxic effect resolved to baseline levels. Treatment was discontinued permanently if the toxic effect did not recover after a 4 week interruption or after dose reduction by two dose levels.

The primary endpoint was overall survival, defined as the time from randomisation to death from any cause. Secondary endpoints were progression-free survival (PFS; defined as time from randomisation to first radiological or clinical observation of disease progression or any-cause death), objective tumour response rate (defined as proportion of patients with complete or partial response), disease control rate (defined as proportion of patients with a best response of complete or partial response or stable disease; assessment of stable disease had to be made at least 6 weeks after randomisation), and safety. Tumour response and progression were assessed by investigators radiologically every 8 weeks with Response

Evaluation Criteria in Solid Tumors (RECIST, version 1.1, or the investigator's clinical assessment if a patient could not have radiological examination, eg, because of deterioration of medical condition).

Duration of response and stable disease was assessed as a tertiary endpoint, as were health-related quality-of-life and health utility values, which were measured with the European Organisation for Research and Treatment of Cancer (EORTC) general health status and quality-of-life questionnaire QLQ-C30 and the EuroQol five dimension (EQ-5D) index questionnaire and visual analogue scale. Plasma and tissue samples were collected for a substudy (with separate written informed consent, or oral consent in the presence of a witness) for biomarker analysis.

Safety assessments were adverse events, laboratory changes (haematology, clinical chemistry, and urinalysis), vital signs, and electrocardiography. Adverse events were graded with the National Cancer Institute Common Terminology Criteria for Adverse Events (version 3.0). Duration, seriousness, and relation to study medication, based on the investigator's clinical assessment, were recorded.

Statistical analysis

The study was designed to have 90% power to detect a 33·3% increase in median overall survival, assuming a 4·5 month median overall survival for the placebo group (ie, a hazard ratio [HR] of 0·75 for regorafenib over placebo). Assuming a one-sided overall α of 0·025, a power of 90%, a randomisation ratio of 2:1 between regorafenib and placebo, and two formal interim analyses of overall survival during the study, with an O'Brien-Fleming-type error spending function, the study required 582 deaths for the final analysis, and we planned to randomise about 690 patients. The first formal interim analysis, when roughly 30% of the expected total number of deaths had occurred, was for futility only. The second interim analysis, at about 70% of expected deaths, was for efficacy and futility. A Lan-Demets alpha spending function determined the monitoring boundary for efficacy so the overall false positive rate (α) was less than or equal to 0·025 (one-sided). The alpha spending function was the O'Brien-Fleming type boundary specified. Boundaries were specified to stop the study for efficacy or futility on the basis of the actual number of events included in the analysis. At the second interim analysis, the study was to be stopped for futility if the HR (regorafenib over placebo) was 0·9006 or greater, and for efficacy if the one-sided p value was less than or equal to 0·009279, roughly corresponding to an HR (regorafenib over placebo) of less than or equal to 0·7864.

We did statistical analyses with SAS (version 9.1 or higher). Overall survival and PFS were compared between treatment groups with a stratified log-rank test; HRs (with 95% CI) were calculated with the Cox model, adjusting for stratification factors; and Kaplan-Meier survival estimates were calculated for each treatment group. Objective response and disease control rates were compared between treatment groups with the Cochran-Mantel-Haenszel test, adjusting for stratification factors. Adverse events and laboratory abnormalities were reported by treatment group, category, and worst grade.

Efficacy analyses were based on the intention-to-treat population. No imputation was made for missing assessments. Safety analyses included all patients who received at least one dose of study drug. This trial is registered with ClinicalTrials.gov, number NCT01103323.

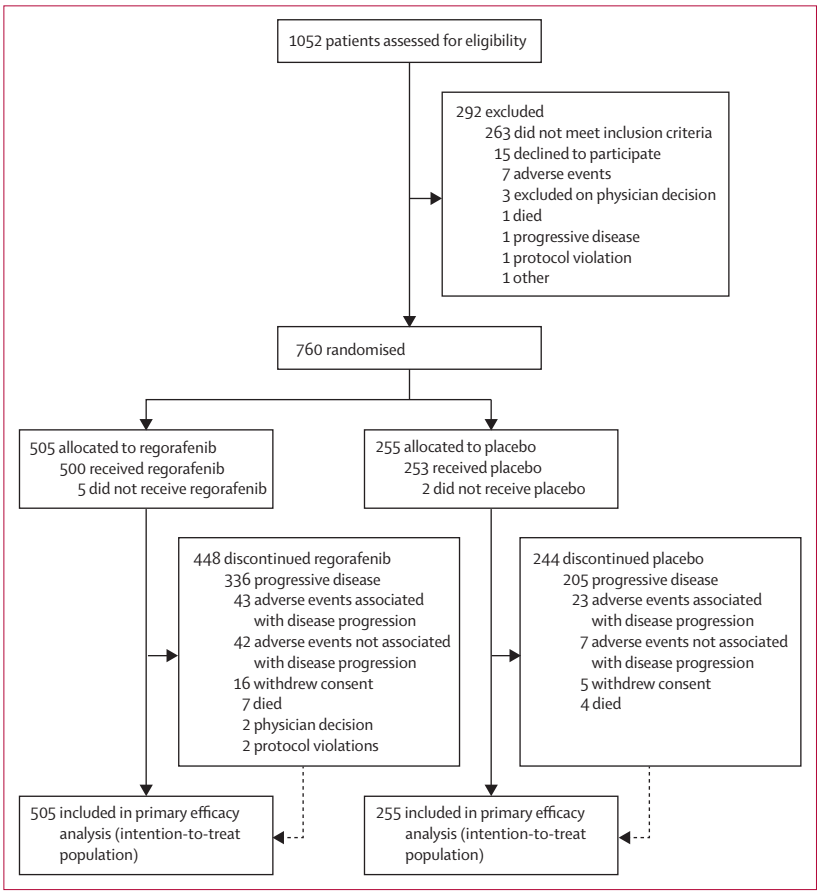

Figure 1: **Trial profile**

Role of the funding source

The study sponsor provided the study drug and collaborated with the investigators on protocol design, data collection and interpretation, and preparation of this report. An independent data monitoring committee, of three oncologists and a statistician, ensured the overall integrity of the trial and safety of participants. The two principal investigators (AG and EVC) had final responsibility for the content of the report and for the decision to submit for publication. All authors had access to the study data and reviewed this report. The sponsors funded writing assistance.

Results

Between April 30, 2010, and March 22, 2011, 1052 patients were screened and 760 patients were randomised to receive regorafenib (n=505) or placebo (n=255; population for efficacy analyses; figure 1). 753 patients initiated treatment (regorafenib n=500, placebo n=253; population for safety analyses; four patients, two in each group, did not receive treatment because of an adverse event associated with clinical disease progression; additionally in the regorafenib group, one patient had an adverse event not associated with clinical disease progression, one patient was found to have ECOG performance status >1 after randomisation, and one patient withdrew consent. The target sample size of 690 patients was exceeded because of the rapid accrual rate. The second interim analysis by the data monitoring committee was done on Oct 22, 2011, and the database cutoff date used for the analysis was July 21, 2011.

Most baseline characteristics were similar in regorafenib and placebo groups (table 1). However, a lower proportion of patients in the regorafenib group (273 of 505, 54%) had a *KRAS* mutation compared with the placebo group (157 of 255, 62%). The low frequency of *BRAF* mutations (table 1) was expected in these patients who had received several lines of therapy while maintaining a good performance status. All patients had received previous anti-VEGF treatment (even though we had assumed that some countries, such as China, would not have access to such treatments and anti-VEGF therapy had therefore been included in the protocol as a stratification factor). A higher proportion of patients in the placebo group had progressed on bevacizumab, irinotecan, and oxaliplatin than in the regorafenib group (table 1).

Mean duration of treatment was 2·8 months (SD 2·3; median 1·7, IQR 1·4–3·7) for the regorafenib group and 1·8 months (SD 1·2; median 1·6, IQR 1·3–1·7) for the placebo group. Patients assigned regorafenib received 78·9% of the planned dose during the course of the study (mean daily dose 147·1 mg, SD 18·6), compared with 90·1% for the placebo group (mean 159·2 mg, SD 4·9). Dose modifications were required in 378 (76%) of

	Regorafenib (N=505)	Placebo (N=255)
Median age (years [IQR])	61 (54·0–67·0)	61 (54·0–68·0)
Sex		
Men	311 (62%)	153 (60%)
Women	194 (38%)	102 (40%)
Race		
White	392 (78%)	201 (79%)
Black	6 (1%)	8 (3%)
Asian	76 (15%)	35 (14%)
Other or not specified	31 (6%)	11 (4%)
Region		
North America, western Europe, Israel, Australia	420 (83%)	212 (83%)
Asia	69 (14%)	35 (14%)
Eastern Europe	16 (3%)	8 (3%)
ECOG performance status		
0	265 (52%)	146 (57%)
1	240 (48%)	109 (43%)
Primary site of disease*		
Colon	323 (64%)	172 (68%)
Rectum	151 (30%)	69 (27%)
Colon and rectum	30 (6%)	14 (5%)
KRAS mutation†		
No	205 (41%)	94 (37%)
Yes	273 (54%)	157 (62%)
Unknown	27 (5%)	4 (2%)
BRAF mutation‡		
No	322/336 (96%)	163/166 (98%)
Yes	14/336 (4%)	3/166 (2%)
Histology		
Adenocarcinoma	493 (98%)	245 (96%)
Adenocarcinoma in situ	2 (<1%)	3 (1%)
Adenosquamous carcinoma	1 (<1%)	1 (<1%)
Carcinoma, not otherwise specified	4 (1%)	1 (<1%)
Mucinous carcinoma	5 (1%)	4 (2%)
Undifferentiated carcinoma	0	1 (<1%)
(Continues in next column)		
(Continued from previous column)		
Number of previous systemic anticancer therapies (on or after diagnosis of metastatic disease)		
1–2§	135 (27%)	63 (25%)
3	125 (25%)	72 (28%)
≥4	245 (49%)	120 (47%)
Previous anti-VEGF treatment		
Bevacizumab	505 (100%)	255 (100%)
Patients stopping previous treatment because of progression		
Fluoropyrimidine	421 (83%)	221 (87%)
Bevacizumab	403 (80%)	214 (84%)
Irinotecan	405 (80%)	229 (90%)
Oxaliplatin	278 (55%)	160 (63%)
Panitumumab or cetuximab, or both	219 (43%)	107 (42%)
Time from diagnosis of metastases		
Median (months, [IQR])	31·0 (20·6–43·3)	29·9 (20·2–46·4)
<18 months	91 (18%)	49 (19%)
≥18 months	414 (82%)	206 (81%)

Data are n (%) unless otherwise specified. ECOG=Eastern Cooperative Oncology Group. VEGF=vascular endothelial growth factor. *Information missing from one patient in the regorafenib group. †*KRAS* mutation status was based on historical patient record. ‡*BRAF* mutation status was determined with plasma DNA samples collected from 502 patients (regorafenib 336, placebo 166) with BEAMing technology. §Five patients on placebo (2%) and 16 patients on regorafenib (3%) had received only one previous line of treatment for metastatic disease.

Table 1: **Baseline characteristics (efficacy population)**

500 patients assigned regorafenib (100 patients [20%] required ≥1 dose reduction; 352 [70%] required ≥1 dose interruption) and 97 (38%) of 253 patients assigned placebo (eight [3%] required dose reduction; 95 [38%] required dose interruption; appendix). Adverse events were the most common reason for dose modification.

The appendix shows information about treatment after progression. After completion of the present data analysis, the study was unblinded, at which point four patients in the placebo group crossed over to receive regorafenib.

At the second planned interim analysis, after 432 deaths, the HR for overall survival was 0·77 for regorafenib versus placebo (95% CI 0·64–0·94; p=0·0052; figure 2A), which crossed the prespecified overall survival efficacy boundary. Median overall survival was 6·4 months (IQR 3·6–11·8) in the regorafenib group and 5·0 months (2·8–10·4) in the placebo group. The overall survival rate was 80·3% in the regorafenib group and 72·7% in the placebo group at 3 months; 52·5% and 43·5%, respectively, at 6 months; 38·2% and 30·8%, respectively, at 9 months; and 24·3% and 24·0%, respectively, at 12 months. The HR for PFS was 0·49 for regorafenib versus placebo (95% CI 0·42–0·58; p<0·0001; figure 3A). Median PFS was 1·9 months (IQR 1·6–3·9) in the regorafenib group and 1·7 months (1·4–1·9) in the placebo group.

For overall survival, regorafenib showed an apparent benefit in 24 of 25 subgroups, the exception being the group of patients with primary disease in colon and rectum, which was based on only a few events. Compared with placebo, regorafenib had a greater effect on overall survival in the subgroup of patients with colon cancer (HR 0·70, 95% CI 0·56–0·89) than in those with rectal cancer (0·95, 0·63–1·43). For PFS, all subgroup analyses significantly favoured regorafenib compared with placebo, except for patients from eastern Europe, for whom the difference was not significant (figure 3B). Regorafenib had much the same effect on PFS in patients with colon cancer (HR 0·55, 95% CI 0·45–0·67) and those with rectal cancer (0·45, 95% CI 0·33–0·62).

No patients had a complete response; five patients assigned regorafenib and one patient assigned placebo had a partial response, giving objective response rates of 1·0% and 0·4%, respectively (p=0·19). Disease control (partial response plus stable disease assessed at least 6 weeks after randomisation) was achieved in 207 (41%) of 505 patients assigned regorafenib and 38 (15%) patients assigned placebo (p<0·0001). Median duration of stable disease was 2·0 months (IQR 1·7–4·0) in the regorafenib group and 1·7 months (1·4–1·9) in the placebo group.

Overall, 498 (of 500) patients in the regorafenib group and 245 (of 253) patients in the placebo group had adverse events (appendix), which were deemed to be treatment-related in 465 (93%) patients assigned regorafenib and in 154 (61%) of those assigned placebo. Table 2 shows treatment-related adverse events that occurred in at least 5% of patients in either group during the study. The most frequent adverse events of any grade in the regorafenib group were fatigue and hand-foot skin reaction, and in the placebo group were fatigue and anorexia (table 2). Most adverse events occurred early in the course of treatment (during cycles 1–2, data not shown).

Grade 3 or 4 treatment-related adverse events occurred in 270 (54%) patients assigned regorafenib and 35 patients assigned placebo (14%; table 2). The most frequent regorafenib-related adverse events of grade 3 or higher (affecting ≥5% of patients) were hand-foot skin reaction, fatigue, diarrhoea, hypertension, and rash or desquamation. Serious adverse events were reported in 219 (44%) of 500 patients in the regorafenib group and 100 (40%) of 253 patients in the placebo group. Of the 110 deaths reported during the study (regorafenib n=69, 14%; placebo n=41, 16%), most were due to progression of underlying disease (regorafenib n=58, 12%; placebo n=35, 14%), and only 11 (regorafenib n=8, 2%; placebo n=3, 1%) were attributed to adverse events not associated with disease progression. In the regorafenib group, these adverse events were pneumonia (n=2), gastrointestinal bleeding (n=2), intestinal obstruction (n=1), pulmonary haemorrhage (n=1), seizure (n=1), and sudden death (n=1). In the placebo group, these adverse events were pneumonia (n=2) and sudden death (n=1). Occurrence of thromboembolism did not differ between groups (12 [2%] patients assigned regorafenib; four [2%] patients assigned placebo).

Occurrence of increased liver transaminases and bilirubin was higher in the regorafenib group than in the placebo group (appendix). The difference was mainly attributable to grade 1 and 2 events. One fatal case compatible with regorafenib-related, drug-induced liver injury was reported: 43 days after first regorafenib administration, a 62 year-old Asian man with liver metastases had progressive liver dysfunction from which he died 6 weeks later.

Overall, 333 (67%) of 500 patients in the regorafenib group and 57 (23%) of 253 patients in the placebo group had an adverse event leading to dose modification (dose reductions in 188 [38%] patients assigned regorafenib and eight [3%] patients assigned placebo; dose interruption in 304 [61%] patients assigned regorafenib and 55 [22%] patients assigned placebo). The most frequent adverse events necessitating dose modification were dermatological, gastrointestinal, constitutional, and metabolic or laboratory events.

Patients' health-related quality-of-life and health utility values were measured with the EORTC QLQ-C30 and EQ-5D, respectively. For the EORTC QLQ-C30, the possible score could range from 0 to 100, with higher scores representing a higher level of functioning and better health-related quality of life. A change of at least 10 points on the EORTC QLQ-C30 scale is deemed to be clinically meaningful.[7,8] For the EQ-5D, higher scores represent better health status. A change of 0·06 to 0·12 points on the EQ-5D index and a change of 7 to

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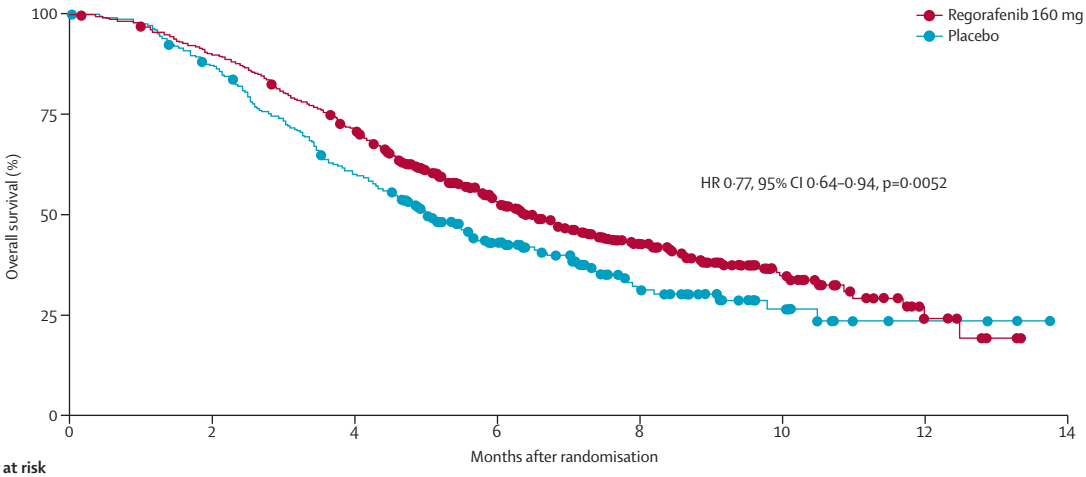

Number at risk

Regorafenib	452	352	187	93	33	7
Placebo	221	150	75	32	9	3

B

	N	HR (95% CI)
All patients	760	0·77 (0·64–0·94)
Race		
White	593	0·76 (0·61–0·94)
Asian	111	0·79 (0·44–1·45)
Sex		
Men	464	0·77 (0·60–1·00)
Women	296	0·75 (0·55–1·02)
Age group		
<65 years	475	0·72 (0·56–0·91)
≥65 years	285	0·86 (0·61–1·19)
Region		
North America, western Europe, Israel, and Australia	632	0·77 (0·62–0·95)
Asia	104	0·79 (0·43–1·46)
Eastern Europe	24	0·69 (0·20–2·47)
Time from first diagnosis of metastatic disease to randomisation		
<18 months	140	0·82 (0·53–1·25)
≥18 months	620	0·76 (0·61–0·95)
Previous anticancer treatment		
With VEGF-targeted drugs	760	0·77 (0·63–0·93)
Fluoropyrimidine, oxaliplatin, irinotecan, bevacizumab	375	0·83 (0·63–1·09)
Fluoropyrimidine, oxaliplatin, irinotecan, bevacizumab, anti-EGFR agent	385	0·71 (0·54–0·94)
Previous treatment lines		
≤3	301	0·71 (0·52–0·97)
>3	459	0·80 (0·62–1·04)
Previous treatment lines for metastatic disease		
≤3	395	0·79 (0·60–1·04)
>3	365	0·75 (0·56–0·99)
***KRAS* mutation at study entry**		
No	299	0·65 (0·48–0·90)
Yes	430	0·87 (0·67–1·12)
Baseline ECOG score		
0	411	0·70 (0·53–0·93)
1	349	0·77 (0·59–1·02)
Primary site of disease		
Colon	495	0·70 (0·56–0·89)
Rectum	220	0·95 (0·63–1·44)
Colon and rectum	44	1·09 (0·44–2·70)

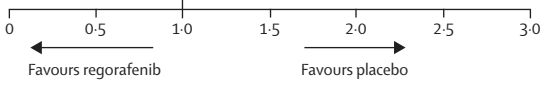

Figure 2: **Overall survival**
(A) Kaplan-Meier analysis, intention-to-treat population. (B) Subgroup analysis. HR=hazard ratio. ECOG=Eastern Cooperative Oncology Group.

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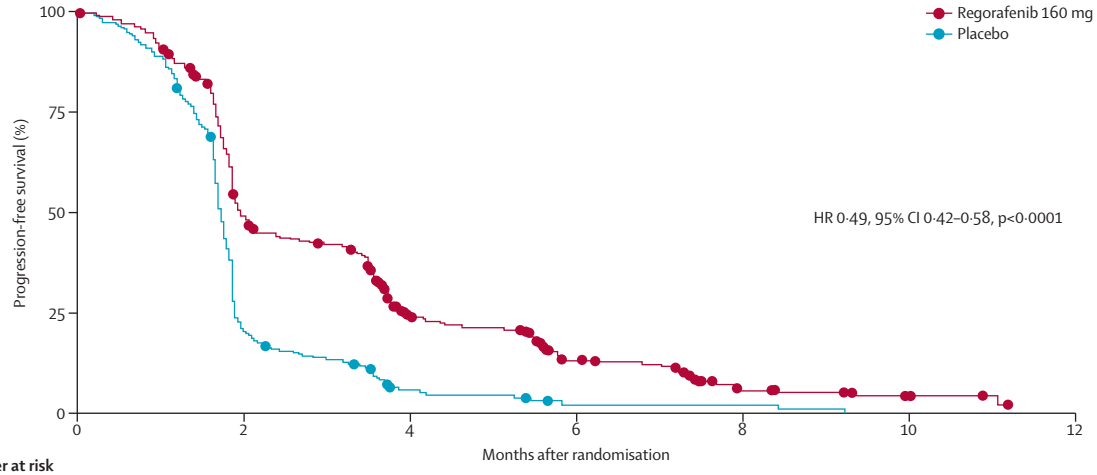

Number at risk

Regorafenib	238	98	42	12	3
Placebo	51	9	2	2	0

B

	N	HR (95% CI)
All patients	760	0·49 (0·42–0·58)
Race		
White	593	0·50 (0·42–0·61)
Asian	111	0·44 (0·29–0·69)
Sex		
Men	464	0·54 (0·43–0·66)
Women	296	0·44 (0·34–0·57)
Age group		
<65 years	475	0·42 (0·34–0·51)
≥65 years	285	0·65 (0·50–0·86)
Region		
North America, western Europe, Israel, and Australia	632	0·50 (0·42–0·60)
Asia	104	0·43 (0·28–0·68)
Eastern Europe	24	0·58 (0·20–1·66)
Time from first diagnosis of metastatic disease to randomisation		
<18 months	140	0·58 (0·41–0·84)
≥18 months	620	0·48 (0·40–0·58)
Previous anticancer treatment		
Previous treatment with VEGF-targeted drugs	760	0·50 (0·43–0·59)
Fluoropyrimidine, oxaliplatin, irinotecan, bevacizumab	375	0·51 (0·41–0·65)
Fluoropyrimidine, oxaliplatin, irinotecan, bevacizumab, anti-EGFR agent	385	0·50 (0·39–0·63)
Previous treatment lines		
≤3	301	0·52 (0·40–0·68)
>3	459	0·48 (0·39–0·59)
Previous treatment lines for metastatic disease		
≤3	395	0·53 (0·43–0·67)
>3	365	0·47 (0·37–0·59)
***KRAS* mutation at study entry**		
No	299	0·48 (0·36–0·62)
Yes	430	0·53 (0·43–0·65)
Baseline ECOG score		
0	411	0·44 (0·36–0·56)
1	349	0·57 (0·45–0·72)
Primary site of disease		
Colon	495	0·55 (0·45–0·67)
Rectum	220	0·45 (0·33–0·62)
Colon and rectum	44	0·35 (0·16–0·75)

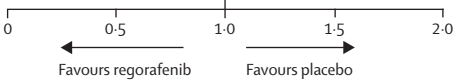

Figure 3: **Progression-free survival**
(A) Kaplan–Meier analysis, intention-to-treat population. (B) Subgroup analysis. HR=hazard ratio. ECOG=Eastern Cooperative Oncology Group.

12 points on the visual analogue scale are judged to be clinically meaningful.[9] Mean EORTC QLQ-C30 scores at baseline were 62·6 (SD 21·7) in the regorafenib group and 64·7 (22·4) in the placebo group. Mean scores at the end of treatment were 48·9 (21·6) in the regorafenib group and 51·9 (23·9) in the placebo group. Mean EQ-5D index scores were 0·73 (0·25) in the regorafenib group and 0·74 (0·27) in the placebo group at baseline, and 0·59 (SD 0·31 for regorfenib, SD 0·34 for placebo) in each group at the end of treatment. The mean EQ-5D visual analogue scale scores were 65·4 (19·6) in the regorafenib group and 65·8 (20·5) in the placebo group at baseline and 55·5 (20·4) and 57·3 (21·6), respectively, at the end of treatment. These results suggest that deterioration in patients' quality of life and health status was much the same in both the regorafenib and placebo groups.

	Regorafenib (N=500)			Placebo (N=253)		
	Any grade	Grade 3	Grade 4	Any grade	Grade 3	Grade 4
Any event	465 (93%)	253 (51%)	17 (3%)	154 (61%)	31 (12%)	4 (2%)
Clinical adverse event						
Fatigue	237 (47%)	46 (9%)	2 (<1%)	71 (28%)	12 (5%)	1 (<1%)
Hand-foot skin reaction	233 (47%)	83 (17%)	0	19 (8%)	1 (<1%)	0
Diarrhoea	169 (34%)	35 (7%)	1 (<1%)	21 (8%)	2 (1%)	0
Anorexia	152 (30%)	16 (3%)	0	39 (15%)	7 (3%)	0
Voice changes	147 (29%)	1 (<1%)	0	14 (6%)	0	0
Hypertension	139 (28%)	36 (7%)	0	15 (6%)	2 (1%)	0
Oral mucositis	136 (27%)	15 (3%)	0	9 (4%)	0	0
Rash or desquamation	130 (26%)	29 (6%)	0	10 (4%)	0	0
Nausea	72 (14%)	2 (<1%)	0	28 (11%)	0	0
Weight loss	69 (14%)	0	0	6 (2%)	0	0
Fever	52 (10%)	4 (1%)	0	7 (3%)	0	0
Constipation	42 (8%)	0	0	12 (5%)	0	0
Dry skin	39 (8%)	0	0	7 (3%)	0	0
Alopecia	36 (7%)	0	0	1 (<1%)	0	0
Taste alteration	35 (7%)	0	0	5 (2%)	0	0
Vomiting	38 (8%)	3 (1%)	0	13 (5%)	0	0
Sensory neuropathy	34 (7%)	2 (<1%)	0	9 (4%)	0	0
Nose bleed	36 (7%)	0	0	5 (2%)	0	0
Dyspnoea	28 (6%)	1 (<1%)	0	4 (2%)	0	0
Muscle pain	28 (6%)	2 (<1%)	0	7 (3%)	1 (<1%)	0
Headache	26 (5%)	3 (1%)	0	8 (3%)	0	0
Pain, abdomen	25 (5%)	1 (<1%)	0	10 (4%)	0	0
Laboratory abnormalities						
Thrombocytopenia	63 (13%)	13 (3%)	1 (<1%)	5 (2%)	1 (<1%)	0
Hyperbilirubinaemia	45 (9%)	10 (2%)	0	4 (2%)	2 (1%)	0
Proteinuria	35 (7%)	7 (1%)	0	4 (2%)	1 (<1%)	0
Anaemia	33 (7%)	12 (2%)	2 (<1%)	6 (2%)	0	0
Hypophosphataemia	25 (5%)	19 (4%)	0	1 (<1%)	1 (<1%)	0

Data are n (%). *The appendix provides a detailed breakdown of all adverse events by National Cancer Institute Common Terminology Criteria for Adverse Events (version 3.0) category or term and worst grade.

Table 2: **Treatment-related adverse events occurring in ≥5% of patients in either group from start of treatment to 30 days after end of treatment (safety population)***

Discussion

We showed that the addition of regorafenib to best supportive care increases overall survival, compared with best supportive care only, in patients with metastatic colorectal cancer who have received all currently approved standard therapies. The trial met its primary endpoint of overall survival at the second planned interim analysis. Although the recorded difference in median overall survival was modest at 1·4 months, the HR of 0·77 translates into a 23% reduction in risk of death during the course of the study in this population of patients with very poor prognosis and a high unmet clinical need. Other efficacy measures such as PFS and disease control rate were also improved in the regorafenib group, and these results support the robustness of the efficacy data. The main effect of regorafenib on metastatic colorectal cancer seems to be disease stabilisation, rather than tumour shrinkage, because few patients who received regorafenib achieved an objective tumour response, yet 207 patients (41%) had stable disease as their best response.

Overall survival in the rectal subgroup showed a higher, HR of 0·95 as compared with that recorded in the colon subgroup (0·70) in favour of regorafenib. However, patients with rectal cancer and those with colon carcinoma derived much the same clinical benefit from treatment with regorafenib, with HRs for PFS of 0·45 and 0·55, respectively. The apparent lack of overall survival benefit in patients with rectal cancer might be explained by the fact that, in this subgroup, more patients in the placebo group and fewer patients in the regorafenib group received post-study anticancer therapies compared with the overall population (placebo 36% [25 of 69] for rectal cancer patients *vs* 30% [76 of 255] in the overall population; regorafenib 23% [35 of 151] for rectal patients *vs* 26% [131 of 505] in the overall population).

The safety profile of regorafenib in the CORRECT trial is consistent with early-phase clinical experience[6] and typical of the small-molecule tyrosine-kinase inhibitor class. The most frequent adverse events of grade 3 or higher related to regorafenib were hand-foot skin reaction, fatigue, diarrhoea, hypertension, and rash or desquamation. Although the occurrence of these adverse events was substantially higher than in the placebo group, most events occurred early in the course of treatment (within 1–2 cycles) and were readily manageable with dose reduction or interruption.

In this population of patients with progressive, treatment-refractory metastatic colorectal cancer, any negative effect of treatment on quality of life could quickly outweigh the potential benefits of treatment. The CORRECT trial used standard, validated measures of quality of life in patients with cancer to assess the effect of regorafenib on patients and confirmed that the agent had no worse effect than placebo. Although the EORTC QLQ-30 and EQ-5D do not address some of the adverse events typically associated with regorafenib (eg, hand-foot skin

Panel: Research in context

Systematic review

We searched PubMed and the abstracts of major oncology congresses (American Society of Clinical Oncology [ASCO] and ASCO gastrointestinal symposium, European Society for Medical Oncology World Congress on Gastrointestinal Cancer, International Society of Gastrointestinal Oncology Conference, American Association for Cancer Research–National Cancer Institute–European Organisation for Research and Treatment of Cancer Congress, ESMO annual meeting, and European Multidisciplinary Cancer Congress). We used MeSH and full-text search terms for metastatic colorectal cancer and molecular targeted therapies, limiting our results to English language articles and abstracts published or presented in the past 2 years. For PubMed, the search was: ("molecular targeted therapy" OR ("molecular" AND "targeted") AND ("therapy" OR "therapies") AND ("colorectal neoplasms" OR "colorectal cancer") OR ("colorectal" AND "cancer") AND ("2010/01/01" : "2012/12/31") AND English[lang]). For conferences, the search was: "metastatic colorectal cancer" or "advanced colorectal cancer", manually limited to abstracts on targeted therapies. The last search was done on Aug 23, 2012. We identified several potential targeted agents (either monoclonal antibodies or small-molecule tyrosine-kinase inhibitors) that are being investigated either in synergy with, or in place of, established treatments, including inhibitors of growth factors and their receptors (VEGF, EGFR, IGF, PGF), histone-deacetylase inhibitors, MEK inhibitors, and agents targeting hedgehog and aurora kinases. We used information from the abstracts and ClinicalTrials.gov to identify the latest stage of clinical development of these agents in colorectal cancer. We have limited our discussion to the agents that we believe are most promising, on the basis of clinical trial efficacy.

Interpretation

Various signalling processes have been implicated in the development and progression of colorectal cancer, and experience with the monoclonal antibodies bevacizumab, cetuximab, and panitumumab show that these pathways are valid targets for therapy. The present study shows that, in patients with progressive colorectal cancer after standard cytotoxic and targeted treatments, regorafenib can significantly prolong survival compared with placebo, providing further evidence for the role of targeted therapies and offering hope for a new standard of care in this treatment-refractory population.

reaction), in the absence of more specific, validated instruments we believe that the overall results are relevant.

The rapid accrual of the CORRECT trial (760 patients in 10 months) was indicative of the unmet need for this group of patients, and also dispelled potential concern about the feasibility of a randomised trial in colorectal cancer with best supportive care as the comparator.

In our study, where overall suvival was the primary endpoint, investigator assessment using RECIST (version 1.1) was adopted for tumour scan assessments. We judged this approach appropriate for a setting of secondary endpoints such as PFS and other tumor-related variables and do not believe that the absence of independent review had any negative effect on the validity of the overall conclusion of the study. Although measurement variability might be a concern of potential bias introduced when using investigator assessment as opposed to using independent review, in this setting, where a significant overall survival benefit was identified along with a significant overall treatment effect for PFS (ie, HR=0·49), such bias was probably minimal and the outcome of the trial would remain unchanged. Masking of investigators should have further minimised bias.

Previous efforts to develop small-molecule kinase inhibitors for the treatment of metastatic colorectal cancer have been unsuccessful.[10–16] In such trials, kinase inhibitors were often combined with chemotherapy in early lines of treatment. As far as we are aware, CORRECT is the first randomised phase 3 study in which a small-molecule kinase inhibitor has shown significant overall survival benefit in patients with treatment-refractory metastatic colorectal cancer (panel). The study's success shows that a monotherapy design in a last-line-of-treatment setting and the use of placebo as the comparator can be an effective approach for the development of new drugs for the treatment of cancer.

In view of these findings, regorafenib could be a new standard of care in late-stage metastatic colorectal cancer. Nonetheless, several questions remain to be answered. First, although some preclinical data are available in colorectal cancer models,[17,18] the mechanism of action of regorafenib in human colorectal cancer remains to be elucidated. Second, the Kaplan-Meier curves for PFS suggest that different subgroups of patients might have differential responses to regorafenib treatment. Future research should aim to identify these subgroups, probably through the identification and validation of biomarkers, to refine the population of patients likely to obtain benefit from regorafenib. Analyses of relevant biomarkers in specimens collected in the CORRECT trial are currently underway.

Contributors

AG, EVC, AW, and DL conceived and designed the study. AG, EVC, AS, SS, AF, MY, YH, OB, LM, CB, AA, JT, TY, H-JL, and LC collected the data. AG, EVC, AS, H-JL, RMG, DJS, FC, AW, and DL analysed and interpreted the data. All authors were involved in the drafting, review, and approval of the manuscript and the decision to submit for publication.

Conflicts of interest

The Mayo Foundation has received research funding for clinical studies done by AG from Genentech, Sanofi, Bayer, Daiichi, and Imclone and has received honoraria for consulting activities of AG for Genentech, Roche, Onyx, Bayer, Imclone, Bristol-Myers Squibb, and Sanofi. EVC has received research funding from Bayer. AS has been an advisory board member and has spoken at symposia for Roche, Merck, Bayer, Amgen, and Sanofi. SS has been an advisory board member for Amgen, AstraZeneca, Bayer, Genentech, Merck Serono, Roche, and Sanofi. AF

has received honoraria from Amgen, Bayer, Merck Serono, Roche, and Sanofi for speaking, consultancy, and advisory board membership, and has received research support from Amgen, Bayer, Merck Serono, Roche, and Sanofi. MY has received honoraria from Bayer for advisory board membership. YH has received honoraria from Bayer to act as a consultant and has received research funding from Bayer. OB has received honoraria from Roche, Merck Serono, and Amgen. LM declares that he has no conflicts of interest. CB has received honoraria for lecturing and advisory board membership from Bayer, Merck, Roche, and Novartis, and has received honoraria for lecturing from GlaxoSmithKline and Amgen. AA has received honoraria from Bayer (conference and research funding). JT has been a consultant and advisory board member for Amgen, Bristol-Myers Squibb, Genentech, Merck KGaA, Millennium, Novartis, Onyx, Pfizer, Roche, Sanofi, and Bayer and has received honoraria from Amgen, Merck KGaA, Novartis, Roche, and Sanofi. TY has received consulting fees from Takeda, honoraria from Chugai, Takeda, Yakult, Bristol-Myers Squibb, and Merck Serono, and research funding from Daiichi Sankyo, Taiho, Bayer, and Imclone. H-JL has been an advisory board member for Bayer. RMG has received research support to Ohio State University from Sanofi, Bayer, Myriad, and Jennerex, has provided unpaid consultancy for Bayer and Sanofi, and has received payment from Lilly for participation in a data safety monitoring board. DJS has received consulting fees from the CORRECT steering committee (less than $5000/year). FC, LC, AW, and DL are employees of Bayer. FC and DL have Bayer stock ownership.

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