Regorafenib plus best supportive care versus placebo plus best supportive care in Asian patients with previously treated metastatic colorectal cancer (CONCUR): a randomised, double-blind, placebo-controlled, phase 3 trial

Jin Li, Shukui Qin*, Ruihua Xu*, Thomas C C Yau, Brigette Ma, Hongming Pan, Jianming Xu, Yuxian Bai, Yihebali Chi, Liwei Wang, Kun-Huei Yeh, Feng Bi, Ying Cheng, Anh Tuan Le, Jen-Kou Lin, Tianshu Liu, Dong Ma, Christian Kappeler, Joachim Kalmus, Tae Won Kim*, on behalf of the CONCUR Investigators†*

Summary

Background In the international randomised phase 3 CORRECT trial (NCT01103323), regorafenib significantly improved overall survival versus placebo in patients with treatment-refractory metastatic colorectal cancer. Of the 760 patients in CORRECT, 111 were Asian (mostly Japanese). This phase 3 trial was done to assess regorafenib in a broader population of Asian patients with refractory metastatic colorectal cancer than was studied in CORRECT.

Methods In this randomised, double-blind, placebo-controlled, parallel-group, phase 3 trial done in 25 hospitals in mainland China, Hong Kong, South Korea, Taiwan, and Vietnam, we recruited Asian patients aged 18 years or older with progressive metastatic colorectal cancer who had received at least two previous treatment lines or were unable to tolerate standard treatments. Patients had to have an Eastern Cooperative Oncology Group performance status of 0 or 1, life expectancy of at least 3 months, and adequate bone marrow, liver, and renal function, without other uncontrolled medical disorders. We randomly allocated patients (2:1; with a computer-generated unicentric randomisation list [prepared by the study funder] and interactive voice response system; block size of six; stratified by metastatic site [single *vs* multiple organs] and time from diagnosis of metastatic disease [<18 months *vs* ≥18 months]) to receive oral regorafenib 160 mg once daily or placebo on days 1–21 of each 28 day cycle; patients in both groups were also to receive best supportive care. Participants, investigators, and the study funder were masked to treatment assignment. The primary endpoint was overall survival, and we analysed data on an intention-to-treat basis. This trial is registered with ClinicalTrials.gov, number NCT01584830.

Findings Between April 29, 2012, and Feb 6, 2013, we screened 243 patients and randomly assigned 204 patients to receive either regorafenib (136 [67%]) or placebo (68 [33%]). After a median follow-up of 7·4 months (IQR 4·3–12·2), overall survival was significantly better with regorafenib than it was with placebo (hazard ratio 0·55, 95% CI 0·40–0·77, one-sided p=0·00016; median overall survival 8·8 months [95% CI 7·3–9·8] in the regorafenib group *vs* 6·3 months [4·8–7·6] in the placebo group). Drug-related adverse events occurred in 132 (97%) of 136 regorafenib recipients and 31 (46%) of 68 placebo recipients. The most frequent grade 3 or higher regorafenib-related adverse events were hand–foot skin reaction (22 [16%] of 136 patients in the regorafenib group *vs* none in the placebo group), hypertension (15 [11%] *vs* two [3%] of 68 patients in the placebo group), hyperbilirubinaemia (nine [7%] *vs* one [1%]), hypophosphataemia (nine [7%] *vs* none), alanine aminotransferase concentration increases (nine [7%] *vs* none), aspartate aminotransferase concentration increases (eight [6%] *vs* none), lipase concentration increases (six [4%] *vs* one [1%]), and maculopapular rash (six [4%] *vs* none). Drug-related serious adverse events occurred in 12 (9%) patients in the regorafenib group and three (4%) in the placebo group.

Interpretation This phase 3 trial is the second to show an overall survival benefit with regorafenib compared with placebo in patients with treatment-refractory metastatic colorectal cancer, substantiating the role of regorafenib as an important treatment option for patients whose disease has progressed after standard treatments. In this trial, preceding standard treatments did not necessarily include targeted treatments. Adverse events were generally consistent with the known safety profile of regorafenib in this setting.

Funding Bayer HealthCare Pharmaceuticals.

Lancet Oncol 2015; 16: 619–29

Published **Online** May 14, 2015 http://dx.doi.org/10.1016/S1470-2045(15)70156-7

See **Comment** page 596

*Contributed equally

†Primary investigators from the participating centres are listed in the appendix

Department of Medical Oncology, Fudan University Shanghai Cancer Center, and Department of Oncology, Shanghai Medical College, Fudan University, Shanghai, China (Prof J Li MD); **Department of Medical Oncology, Chinese People's Liberation Army Cancer Center of Nanjing Bayi Hospital, Nanjing, China** (Prof S Qin MD); **Department of Medical Oncology, Sun Yat-Sen University Cancer Center, Collaborative Innovation Center for Cancer Medicine, Guangzhou, China** (Prof R Xu MD); **Department of Medicine, University of Hong Kong, Queen Mary Hospital, Hong Kong, China** (T C C Yau MD); **Department of Clinical Oncology, Prince of Wales Hospital, Chinese University of Hong Kong, Hong Kong, China** (Prof B Ma MD); **Medical Oncology, Sir Run Run Shaw Hospital Medical School, Zhejiang University, Hangzhou, China** (Prof H Pan MD); **Beijing 307 People's Liberation Army Hospital Cancer Centre, Beijing, China** (Prof J Xu MD); **Third Affiliated Hospital of Harbin Medical University, Harbin, China** (Prof Y Bai MD); **Department of Medical Oncology, Cancer Hospital, Chinese Academy of Medical Sciences, Beijing, China** (Prof Y Chi MD); **Comprehensive Cancer Center, Shanghai First**

Introduction

During the past few decades, the incidence of colorectal cancer has increased around the world, including in Asia.[1–3] Although isolated metastases might be resectable with potentially curative outcomes,[4] around 25% of patients with colorectal cancer have metastatic disease that has a clinically significant detrimental effect on prognosis.[5,6] Consensus guidelines for treatment of Asian patients with metastatic colorectal cancer are mostly similar to other international guidelines, with adaptations to account for differences in clinical practice and local availability of approved drugs.[2,4] Patients with metastatic

People's Hospital, Shanghai Jiaotong University, Shanghai, China (Prof L Wang MD); Department of Oncology, National Taiwan University Hospital, Taipei, Taiwan (Prof K-H Yeh MD); Department of Medical Oncology, West China Hospital, Sichuan University, Chengdu, China (Prof F Bi MD); Jilin Provincial Tumor Hospital, Changchun, China (Prof Y Cheng MD); Department of Oncology, Cho Ray Hospital, Ho Chi Minh City, Vietnam (A T Le MD); Department of Surgery, Taipei Veterans General Hospital, National Yang-Ming University, Taipei, Taiwan (Prof J-K Lin MD); Department of Medical Oncology, Zhong Shan Hospital, Fudan University, Shanghai, China (Prof T Liu MD); Department of Medical Oncology, Guangdong General Hospital, Guangzhou, Guangdong, China (Prof D Ma MD); Bayer Pharma AG, Berlin, Germany (C Kappeler PhD, J Kalmus MD); and Department of Oncology, Asan Medical Center, University of Ulsan College of Medicine, Songpa-gu, South Korea (Prof T W Kim MD)

Correspondence to: Prof Tae Won Kim, Department of Oncology, Asan Medical Center, University of Ulsan College of Medicine, 88, Olympic-ro 43-gil, Songpa-gu, South Korea
twkimmd@amc.seoul.kr

Research in context

Evidence before this study

We searched for articles published up to Jan 31, 2012, reporting on treatment of metastatic colorectal cancer in Asian patients using the search terms "colorectal cancer" AND ("treatment" OR "therapy") AND "Asian", with no language restrictions, retrieving 211 articles. Of these, 11 were clinical studies of treatments for advanced colorectal cancer, consisting of fluoropyrimidines, oxaliplatin, irinotecan, bevacizumab, and panitumumab. More than half of the studies were in the first-line setting, with only one (of panitumumab) focusing exclusively on pretreated patients. Thus, evidence is scarce for continuing treatment of patients with metastatic colorectal cancer that has progressed on standard treatment. At the time of the search, the international, randomised, phase 3 CORRECT trial, which included patients from Asia (mostly Japan), was in progress.

Added value of this study

Although CORRECT provided evidence of a significant overall survival benefit of regorafenib versus placebo in patients with pretreated metastatic colorectal cancer, only a low proportion of patients were Asian (mostly Japanese). This trial was designed specifically to assess regorafenib in a broader population of Asian patients with metastatic colorectal cancer than was studied in CORRECT.

Implications of all the available evidence

This phase 3 trial is the second to show an overall survival benefit with regorafenib compared with placebo in patients with treatment-refractory metastatic colorectal cancer, substantiating the additional clinical benefit of regorafenib monotherapy in these patients.

colorectal cancer are typically offered chemotherapy (fluoropyrimidines plus either oxaliplatin or irinotecan) and might also receive biological drugs targeting VEGF (bevacizumab) and, if they have *RAS* wild-type tumours, EGFR (cetuximab or panitumumab).[4,7]

Regorafenib is an orally available, small-molecule multikinase inhibitor that targets signalling pathways implicated in tumour angiogenesis (VEGF receptors 1–3 and TIE2), oncogenesis (KIT, RET, RAF1, and BRAF), and the tumour microenvironment (platelet-derived growth factor receptor and fibroblast growth factor receptor).[8] Evidence of the activity of regorafenib in preclinical models of colorectal cancer[8,9] and a phase 1 trial of patients with advanced colorectal cancer[10] prompted an international, randomised, phase 3 trial (CORRECT, NCT01103323), in which regorafenib monotherapy added to best supportive care improved overall survival versus placebo plus best supportive care in patients with disease progression after standard treatments (hazard ratio [HR] 0·77, 95% CI 0·64–0·94; one-sided p=0·0052).[11]

For any new drug, confirmation that activity and toxicity profiles noted in non-Asian patients are similar in Asian patients is important in view of evidence of differences in treatment effects between populations with some drugs (eg, S-1, which has a different toxicity profile in Japanese populations compared with European or US populations).[12,13] Of the 760 patients enrolled in CORRECT, 111 (15%) were Asian, and, of those, 100 (90%) were Japanese.[11,13] We did this phase 3 CONCUR trial to allow robust assessment of the efficacy and safety of regorafenib in a broader population of Asian patients with metastatic colorectal cancer than that in CORRECT. Although similar to CORRECT in design, our protocol allowed inclusion of patients who had not been given targeted biological drugs because, when CONCUR was initiated, these drugs were not widely available in some Asian countries.

See Online for appendix

Methods

Study design and patients

CONCUR was a randomised, double-blind, placebo-controlled, parallel-group, phase 3 trial done in 25 hospitals in mainland China, Hong Kong, South Korea, Taiwan, and Vietnam. Each centre's institutional review board approved the protocol. The trial adhered to the guiding principles of the Declaration of Helsinki and Good Clinical Practice, and complied with local laws and regulations.

Eligible patients had histologically or cytologically confirmed adenocarcinoma of the colon or rectum, with measurable or non-measurable metastatic disease according to Response Evaluation Criteria in Solid Tumors (RECIST) version 1.1.[14] Patients had to have received at least two previous treatment lines, including a fluoropyrimidine plus oxaliplatin or irinotecan. Previous treatment with bevacizumab, cetuximab, or panitumumab was allowed but not mandatory. Patients had to have evidence of disease progression during or within 3 months after the last standard treatment (or within 6 months of stopping adjuvant oxaliplatin) or have stopped standard treatment because of unacceptable toxic effects. Patients had to be Asian adults (≥18 years of age) with an Eastern Cooperative Oncology Group performance status of 0 or 1, a 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 other uncontrolled medical disorders. Full inclusion and exclusion criteria are shown in the appendix. All participants provided written informed consent before enrolment.

Randomisation and masking

We randomly assigned patients (2:1) to receive either regorafenib or placebo using a computer-generated randomisation list prepared by the trial funder, with a unicentric randomisation scheme. Investigators received the randomisation number for each participant through an interactive voice response system (IVRS). We used a

preallocated block design (block size of six) and stratified randomisation by number of metastatic sites (single *vs* multiple organs) and time from diagnosis of metastatic disease (<18 months *vs* ≥18 months). Patients, investigators, and the funder were masked to treatment allocation. To maintain masking, each bottle of study drug was labelled with a unique number and assigned to patients through the IVRS. All study drugs were labelled according to the requirements of local laws and legislation. The trial funder produced booklet labels containing appropriate label text for each participating country. Packaging, labelling, and distribution was done centrally by Fisher Clinical Services (Basel, Switzerland). We allowed unmasking for individual patients via the IVRS only for emergencies.

Procedures

Patients received regorafenib 160 mg or matching placebo orally once daily on days 1–21 of each 28 day 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. Patients with disease progression could continue treatment at the investigator's discretion. All patients received best supportive care, excluding other investigational anti-tumour drugs or antineoplastic chemotherapy, hormonal treatment, or immunotherapy.

We allowed predefined treatment modifications to manage clinically significant toxic effects (appendix). Patients who needed dose reductions could re-escalate up to 160 mg daily at the investigator's discretion once the toxic effects resolved to baseline. We discontinued treatment permanently if the toxic effects did not resolve after a treatment delay of 28 days or after two consecutive dose reductions (minimum permissible dose 80 mg per day). We followed patients up every 2 weeks for the first six cycles and then monthly while on treatment and after treatment was stopped until death or the analysis cutoff date.

Investigators assessed tumour response and progression every 8 weeks, either radiologically using RECIST version 1.1, or clinically if a patient could not have radiological examination. We measured patient-reported outcomes using the European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire-Core 30 (EORTC QLQ-C30)[15] and the EuroQol-5 dimension (EQ-5D)[16] questionnaires. High EORTC QLQ-C30 functioning-domain scores represent a high level of functioning and health-related quality of life, whereas high symptom-domain scores represent severe symptoms. High EQ-5D scores represent good health status. We deemed differences of at least ten points on the EORTC QLQ-C30 scale, 0·07 points on the EQ-5D index, and seven points on the EQ-5D visual analogue scale (VAS) clinically meaningful.

Patients had safety assessments on the first day of every cycle, including adverse events, laboratory changes (haematology, clinical chemistry, and urinalysis), vital signs, and electrocardiography. We monitored blood pressure every week for the first 6 weeks. We did liver function tests every week for the first two cycles. We measured other laboratory changes on day 15 of each cycle for the first six cycles. We graded adverse events using the National Cancer Institute Common Terminology Criteria for Adverse Events version 4.0.[17]

Outcomes

The primary endpoint was overall survival (time from randomisation to death from any cause). Secondary efficacy endpoints were progression-free survival (time from randomisation to first radiological or clinical finding of disease progression or death from any cause), the proportion of patients who achieved an objective overall response (defined as a complete or partial response), and the proportion of patients who achieved disease control (defined as a complete or partial response, or stable disease recorded ≥6 weeks after randomisation). Tertiary endpoints were duration of response, duration of stable disease, and health-related quality of life.

Statistical analysis

The design of this trial was similar to that of CORRECT, but with a lower predefined significance level and a slightly lower power because of the smaller sample size. With a one-sided significance level of 0·2 and a power of 80%, and with the assumption of an improvement in median overall survival from 4·5 months to 6 months with regorafenib versus placebo (33·3% improvement and an HR of 0·75 favouring regorafenib), 154 events were needed. To complete the trial in a reasonably short time, we planned to randomly allocate 200 patients to treatment groups.

We did statistical analyses with SAS version 9.1. We compared overall survival and progression-free survival using a stratified log-rank test, and calculated HRs (with 95% CIs) using the Cox model, adjusting for baseline stratification factors. We calculated Kaplan-Meier survival estimates for each treatment group. We provide descriptive statistics, HRs, and 95% CIs for overall survival and progression-free survival for prespecified subgroup analyses. We based *KRAS* and *BRAF* mutational status on information given by the investigators in each patient's case report form.

We compared proportions of patients with objective response and disease control using a Cochran-Mantel-Haenszel test, adjusted for stratification factors. We report adverse events and laboratory abnormalities using National Cancer Institute Common Terminology Criteria for Adverse Events category and worst grade. For patient-reported outcomes, we used an analysis-of-covariance model to compare the time-adjusted area under the curve (AUC) between groups, with covariates for baseline score and stratification factors. We estimated the least-squares mean (LSM) with 95% CIs for each treatment group and for treatment group differences.

We based all efficacy analyses on the intention-to-treat population, which included all randomly allocated patients. We made no imputation for missing assessments. We analysed patients as randomly allocated, even if they did not receive the study drug or they received the incorrect treatment. Safety analyses included patients who received at least one dose of study drug.

An independent data monitoring committee, consisting of three oncologists and a statistician, ensured the overall integrity of the trial and safety of the participants.

This trial is registered with ClinicalTrials.gov, number NCT01584830.

Role of the funding source

The funder of the study provided study drugs and funding for writing assistance, and collaborated with the investigators on study design, data collection, data analysis, data interpretation, and writing of the report. All authors had full access to all the data in the study and had final responsibility for the decision to submit for publication.

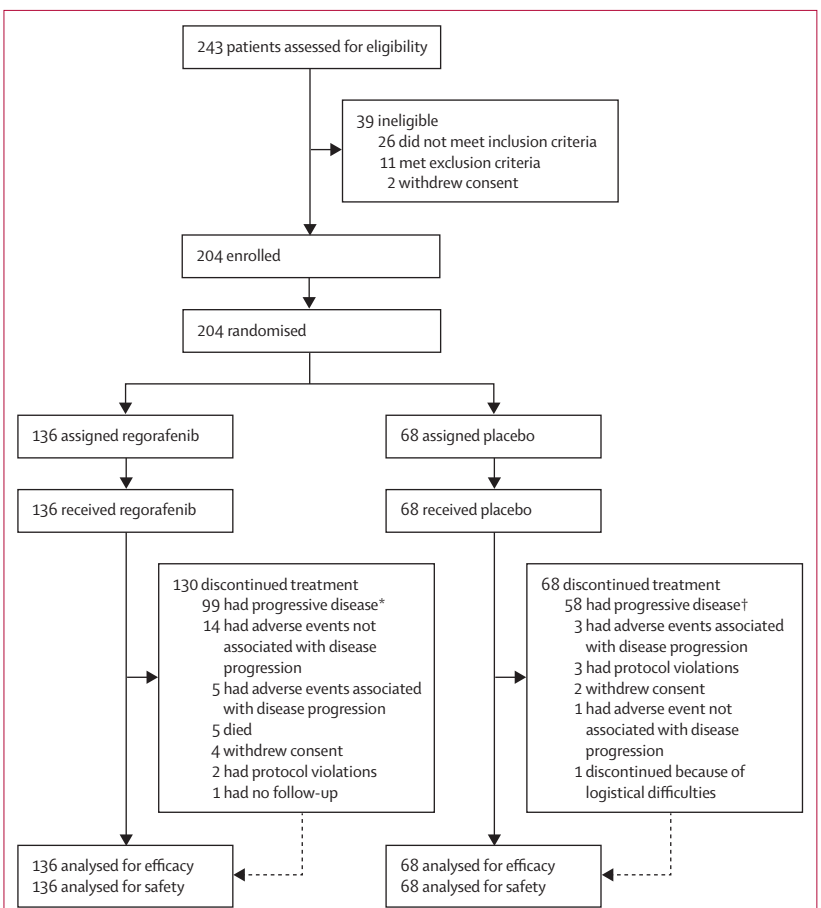

Figure 1: **Trial profile**
*95 patients had radiological disease progression and four had clinical progression. †56 patients had radiological progression and two had clinical progression.

Results

Of the 243 patients screened between April 29, 2012, and Jan 19, 2013, we randomly allocated 204 (84%) patients to receive either regorafenib (136 [67%]) or placebo (68 [33%]; figure 1); we randomly allocated and began treating the last patient on Feb 6, 2013. At the cutoff date for analysis of the primary endpoint (Nov 29, 2013), 155 (76%) deaths had occurred (95 [70%] in the regorafenib group and 60 [88%] in the placebo group). Median follow-up for the overall survival analysis was 7·4 months (IQR 4·3–12·2).

In general, baseline characteristics of treatment groups were balanced (table 1). Overall, 82 (40%) of the 204 participants in the trial had not previously received any targeted biological treatment before randomisation, and 128 (63%) had received three or more lines of treatment for metastatic colorectal cancer.

Patients in the regorafenib group were on the study drug longer than were those in the placebo group, with a median treatment duration of 2·4 months (IQR 1·6–5·3) for those in the regorafenib group versus 1·6 months (1·1–1·6) for those in the placebo group, and a mean duration of 4·0 months (SD 3·7) for those in the regorafenib group versus 1·6 months (1·3) for those in the placebo group. Patients given regorafenib received a median daily dose of 153·5 mg (IQR 134·8–160·0) and a mean daily dose of 145·4 mg (SD 18·1). The mean and median daily dose of placebo was 160 mg. We modified treatment (treatment interruption or delay, dose reduction, or rechallenge at either protocol dose or lower than the protocol dose) in 102 (75%) of the 136 patients in the regorafenib group and 15 (22%) of the 68 patients in the placebo group; patients could have had more than one treatment modification (appendix). The most frequent reasons for treatment discontinuation were radiological disease progression and adverse events (figure 1). After progression, 71 (35%) patients received further systemic treatment (42 [31%] of 136 in the regorafenib group; 29 [43%] of 68 in the placebo group), including cytotoxic anticancer treatments, monoclonal antibodies, and kinase inhibitors (appendix).

Overall survival was significantly better with regorafenib than it was with placebo (HR 0·55, 95% CI 0·40–0·77; one-sided p=0·00016; figure 2). Median overall survival was 8·8 months (95% CI 7·3–9·8) in the regorafenib group and 6·3 months (4·8–7·6) in the placebo group. Progression-free survival was also significantly better with regorafenib than it was with placebo (HR 0·31; 95% CI 0·22–0·44; one-sided p<0·0001; figure 3), with a median progression-free survival of 3·2 months (95% CI 2·0–3·7) in the regorafenib group and 1·7 months (1·6–1·8) in the placebo group. Prespecified subgroup analyses of overall survival and progression-free survival showed a consistent effect of regorafenib in almost all subgroups examined (figures 2 and 3). In an exploratory analysis of the effect of previous targeted biological treatment, the HR for overall survival was 0·31 (95% CI 0·19–0·53) in favour of regorafenib in the 82 patients who had not previously received targeted treatment

	Regorafenib group (n=136)	Placebo group (n=68)
Age (years)		
Median	57·5 (50·0–66·0)	55·5 (48·5–62·0)
<65	95 (70%)	58 (85%)
≥65	41 (30%)	10 (15%)
Sex		
Men	85 (63%)	33 (49%)
Women	51 (38%)	35 (51%)
Region		
China (mainland China, Taiwan, and Hong Kong)	112 (82%)	60 (88%)
Asia other than China	24 (18%)	8 (12%)
Body-mass index (kg/m²)	23·1 (20·8–25·5)	22·8 (20·0–25·0)
ECOG performance status		
0	35 (26%)	15 (22%)
1	101 (74%)	53 (78%)
Main site of disease		
Colon	79 (58%)	48 (71%)
Rectum	53 (39%)	19 (28%)
Colon and rectum	4 (3%)	1 (1%)
KRAS mutation		
No	50 (37%)	29 (43%)
Yes	46 (34%)	18 (26%)
Unknown	40 (29%)	21 (31%)
BRAF mutation		
No	28 (21%)	14 (21%)
Yes	0	1 (1%)
Unknown	108 (79%)	53 (78%)
Histology		
Adenocarcinoma	130 (96%)	66 (97%)
Mucinous carcinoma	6 (4%)	2 (3%)
Time from diagnosis of metastatic disease (months)		
Median	20·3 (13·8–28·8)	19·9 (13·3–27·7)
<18 months	53 (39%)	32 (47%)
≥18 months	83 (61%)	36 (53%)
(Table 1 continues in next column)		
(Continued from previous column)		
Number of metastatic sites		
Single	28 (21%)	15 (22%)
Multiple	108 (79%)	53 (78%)
Previous targeted biological treatment		
None	56 (41%)	26 (38%)
Any (anti-VEGF* or anti-EGFR†,or both)	80 (59%)	42 (62%)
Anti-VEGF but not anti-EGFR	32 (24%)	13 (19%)
Anti-EGFR but not anti-VEGF	24 (18%)	17 (25%)
Anti-VEGF and anti-EGFR	24 (18%)	12 (18%)
Previous systemic anticancer treatment lines		
Any intention		
2	31 (23%)	14 (21%)
3	32 (24%)	19 (28%)
≥4	73 (54%)	35 (51%)
On or after diagnosis of metastatic disease‡		
1–2	48 (35%)	24 (35%)
3	32 (24%)	17 (25%)
≥4	52 (38%)	27 (40%)

Data are median (IQR) or n (%). ECOG=Eastern Cooperative Oncology Group. *Bevacizumab. †Cetuximab or panitumumab. ‡Four patients (3%) in the regorafenib group had not previously received any treatment for metastatic disease.

Table 1: **Baseline characteristics (intention-to-treat population)**

and 0·78 (0·51–1·19) in the 122 who had received at least one targeted biological drug (figure 2 and appendix). However, outcomes in some of the previous targeted treatment subgroups were confounded by the small number of patients (<45) and imbalances in the proportion of patients receiving post-study treatments (eg, six [19%] of the 32 patients in the regorafenib group who had previously received only anti-VEGF-targeted treatment went on to receive systemic anticancer treatment during follow-up compared with seven [54%] of the 13 patients in the placebo group). Exploratory subgroup analyses of overall survival with censoring at the start of post-study treatment showed an HR of 0·57 (95% CI 0·32–1·02) in patients who had received previous targeted treatment and 0·27 (0·15–0·49) in those who had not (appendix).

In the regorafenib group, six (4%) of the 136 patients achieved an objective overall response (all partial responses; no complete response). No patients in the placebo group had a complete or partial response (difference between groups one-sided p=0·045). The proportion of patients who achieved disease control was higher in the regorafenib group than it was in the placebo group (70 [51%] *vs* five [7%]; one-sided p<0·0001). The median duration of response in the six patients with a partial response to regorafenib was 4·8 months (IQR 3·8–14·4). The median duration of stable disease was 3·0 months (IQR 1·8–5·6) in the regorafenib group and 1·7 months (1·4–1·9) in the placebo group.

All 136 (100%) patients in the regorafenib group and 60 (88%) of 68 patients in the placebo group had an adverse event during treatment (or up to 30 days after stopping of treatment; appendix); these events were deemed drug-related in 132 (97%) patients in the regorafenib group and 31 (46%) in the placebo group (table 2). Drug-related grade 3 or higher adverse events occurred in 74 (54%) patients receiving regorafenib and ten (15%) receiving placebo. The most frequent drug-related adverse events of grade 3 or worse associated with regorafenib were hand–foot skin reaction (22 [16%]), hypertension (15 [11%]), hyperbilirubinaemia, hypophosphataemia, and alanine aminotransferase concentration

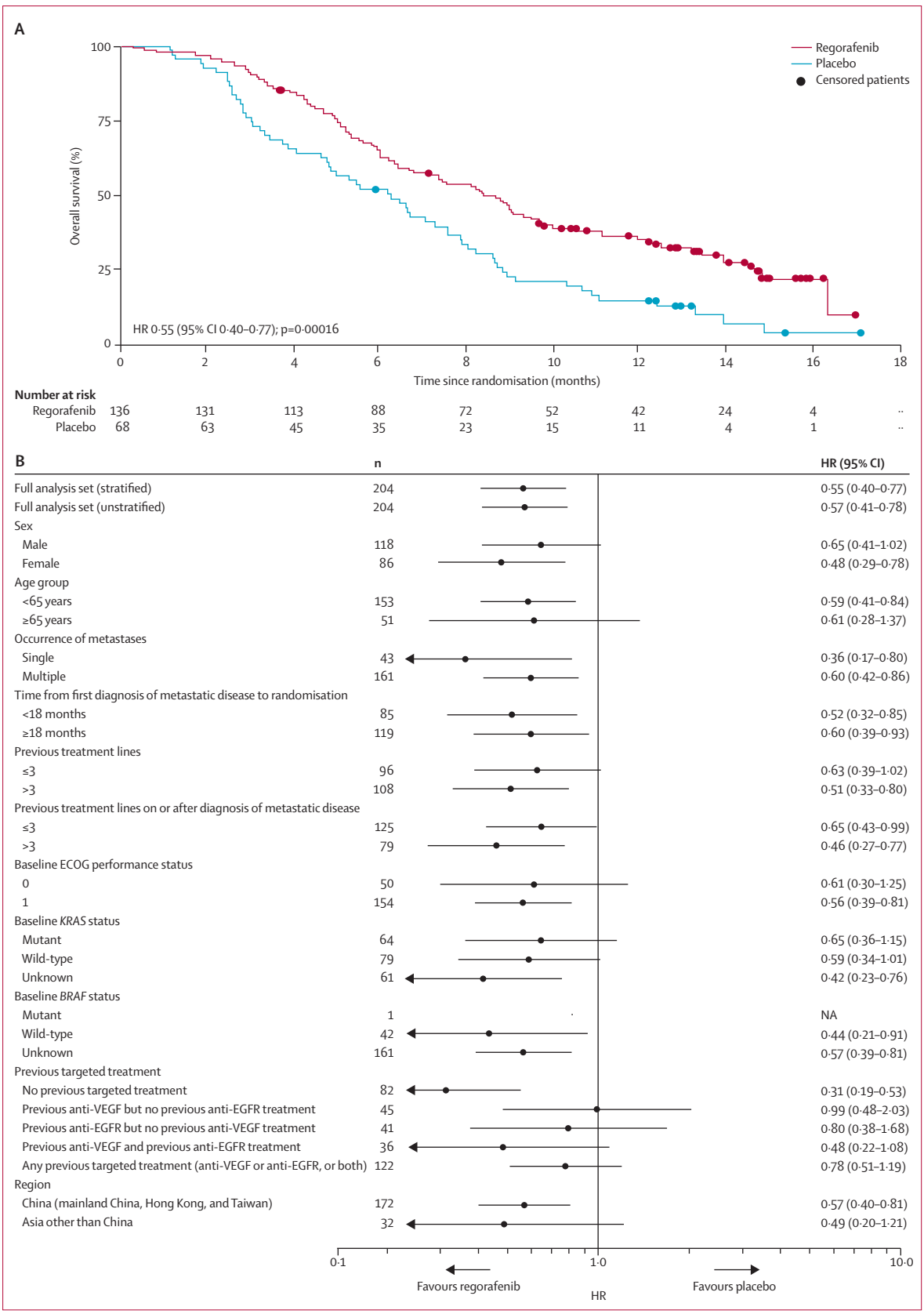

Figure 2: **Overall survival**
(A) Kaplan-Meier analysis (full analysis set). (B) Subgroup analysis. We calculated HRs and CIs using the unstratified Cox regression model for the subgroup analysis. Error bars are 95% CIs. HR=hazard ratio. NA=not applicable.

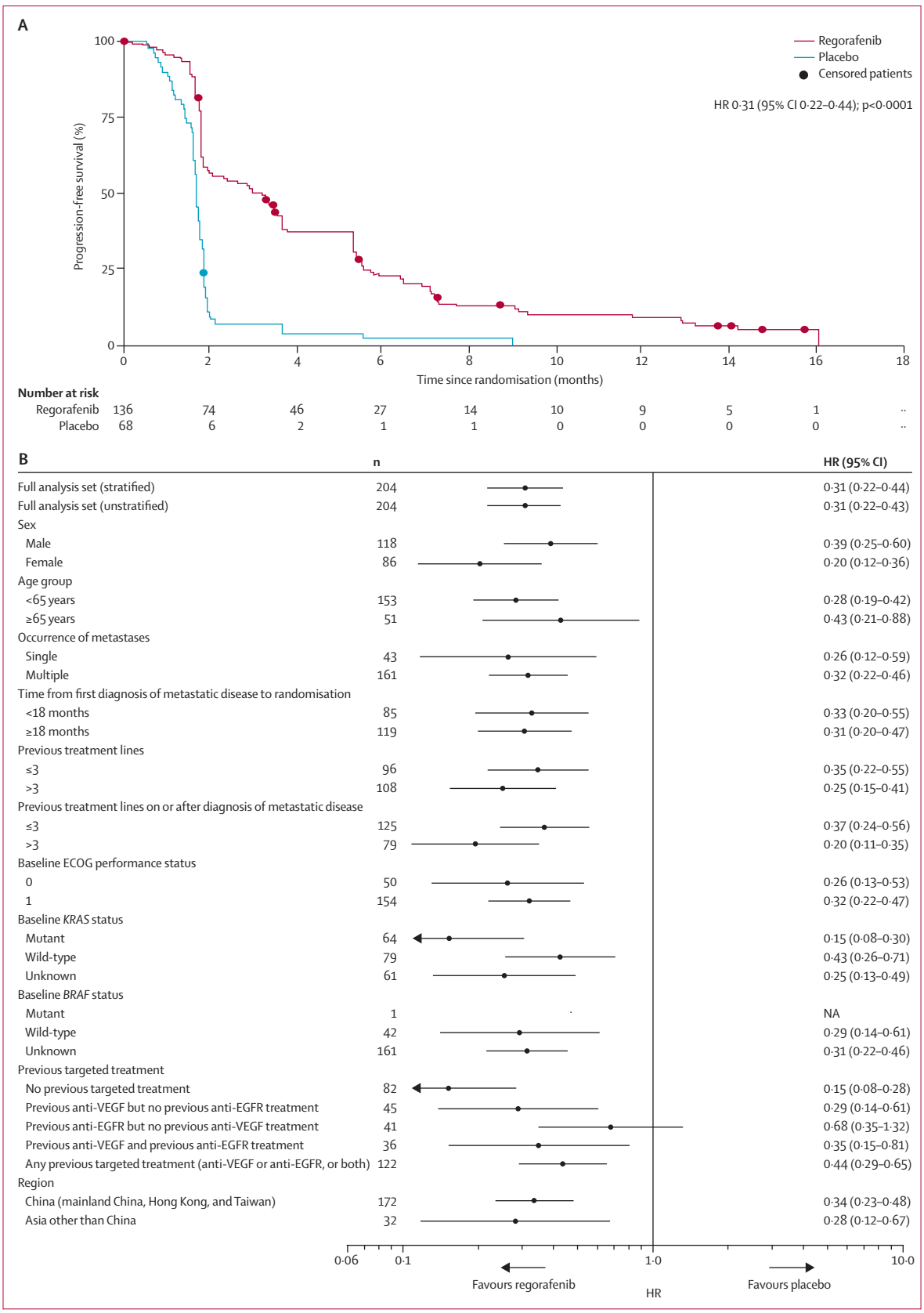

***Figure 3*: Progression-free survival**
(A) Kaplan–Meier analysis (full analysis set). (B) Subgroup analysis. We calculated HRs and CIs using the unstratified Cox regression model for the subgroup analysis. Error bars are 95% CIs. ECOG=Eastern Cooperative Oncology Group. HR=hazard ratio. NA=not applicable.

	Regorafenib group (n=136)				Placebo group (n=68)			
	Grade 1–2	Grade 3	Grade 4	Grade 5	Grade 1–2	Grade 3	Grade 4	Grade 5
Any event*	58 (43%)	67 (49%)	5 (4%)	2 (1%)	21 (31%)	9 (13%)	1 (1%)	0
Hand–foot skin reaction	78 (57%)	22 (16%)	NA	NA	3 (4%)	0	NA	NA
Hyperbilirubinaemia	41 (30%)	6 (4%)	3 (2%)	NA	4 (6%)	1 (1%)	0	NA
Alanine aminotransferase concentration increased	23 (17%)	9 (7%)	0	NA	5 (7%)	0	0	NA
Aspartate aminotransferase concentration increased	24 (18%)	7 (5%)	1 (1%)	NA	6 (9%)	0	0	NA
Hypertension	16 (12%)	15 (11%)	0	0	1 (1%)	2 (3%)	0	0
Hoarseness	27 (20%)	1 (1%)	NA	NA	0	0	NA	NA
Diarrhoea	23 (17%)	1 (1%)	0	0	1 (1%)	1 (1%)	0	0
Fatigue	19 (14%)	4 (3%)	NA	NA	4 (6%)	1 (1%)	NA	NA
Thrombocytopenia	9 (7%)	3 (2%)	1 (1%)	NA	1 (1%)	0	0	NA
Hypophosphataemia	4 (3%)	9 (7%)	0	0	0	0	0	0
Proteinuria	11 (8%)	2 (1%)	NA	NA	0	1 (1%)	NA	NA
Maculopapular rash	6 (4%)	6 (4%)	NA	NA	1 (1%)	0	NA	NA
Leucopenia	8 (6%)	3 (2%)	0	NA	0	0	0	NA
Anorexia	9 (7%)	1 (1%)	0	0	3 (4%)	0	0	0
Lipase concentration increased	3 (2%)	6 (4%)	0	NA	3 (4%)	1 (1%)	0	NA
Neutropenia	4 (3%)	3 (2%)	0	NA	0	0	0	NA
Myalgia	6 (4%)	1 (1%)	NA	NA	0	0	NA	NA
Abdominal pain	5 (4%)	1 (1%)	NA	NA	3 (4%)	0	NA	NA
Anaemia	3 (2%)	1 (1%)	1 (1%)	0	0	0	0	0
Other investigations†	3 (2%)	1 (1%)	0	0	0	0	0	0
Other skin and subcutaneous tissue disorders	3 (2%)	1 (1%)	0	0	1 (1%)	0	0	0
Alkaline phosphatase concentration increased	3 (2%)	0	0	NA	0	1 (1%)	0	NA
Hypoalbuminaemia	2 (1%)	1 (1%)	0	0	0	0	0	0
Hypokalaemia	2 (1%)	1 (1%)	0	0	0	0	0	0
Visceral arterial ischaemia	0	1 (1%)	0	0	0	0	0	0
γ glutamyl transferase concentration increased	1 (1%)	1 (1%)	0	NA	0	0	0	NA
Pharyngitis	1 (1%)	1 (1%)	0	0	0	0	0	0
Atrial fibrillation	1 (1%)	0	0	0	0	0	1 (1%)	0
Cardiac arrest	NA	NA	0	1 (1%)	NA	NA	0	0
Oesophageal varices haemorrhage	0	1 (1%)	0	0	0	0	0	0
Death not otherwise specified	NA	NA	NA	1 (1%)	NA	NA	NA	0
Serum amylase concentration increased	1 (1%)	0	0	NA	0	1 (1%)	0	NA
Wound infection	0	1 (1%)	0	0	0	0	0	0
Flank pain	0	1 (1%)	NA	NA	0	0	NA	NA
Vaginal fistula	0	1 (1%)	0	0	0	0	0	0
Conduction disorder	0	0	0	0	0	1 (1%)	0	0
Heart failure	0	0	0	0	0	0	1 (1%)	0
Acute kidney injury	0	0	0	0	0	0	1 (1%)	0
Other vascular disorders	0	0	0	0	0	1 (1%)	0	0

Data are n (%). Data in each column show the number of patients experiencing that grade as their worst severity of the relevant adverse event. NA=not applicable. *For patients with more than one adverse event, only the highest grade of the most severe event is shown. †Laboratory or diagnostic tests or clinical assessments.

***Table 2*: Drug-related adverse events occurring at any grade in at least 10% of patients, or at grade 3 or higher in any patients in either group, from the start of treatment to 30 days after the end of treatment (safety population)**

increases (nine [7%] each), aspartate aminotransferase concentration increase (eight [6%]), and lipase concentration increase and maculopapular rash (six [4%] each). Frequencies of adverse events leading to death irrespective of relation to study drug were similar, at 12 (9%) in the regorafenib group (one [1%] cardiac arrest; two [1%] deaths not otherwise specified; two [1%] multiorgan failures; two [1%] lung infections; two [1%] other neoplasms; one [1%] dyspnoea; two [1%] respiratory failures) and seven (10%) in the placebo group (one [1%] death not otherwise specified; three [4%] multiorgan failures; one [1%] general disorder or administration-site condition; two [3%] other neoplasms). Two (1%) patients in the regorafenib group had deaths deemed to be

drug-related within 30 days after the last dose. One patient was a 65-year-old woman who stopped regorafenib treatment during her first cycle as a result of a non-serious grade 2 increase in bilirubin. 1 week after stopping treatment, she collapsed at home with coffee-ground vomiting and had a cardiac arrest in the ambulance 20 min later. The investigator reported the patient's underlying disease as the cause of death, but he deemed the death to be related to the study drug. The second patient was a 67-year-old man who received regorafenib for 2 days. On the next day, he had a grade 4 cardiac arrest, resulting in admission to hospital and death. According to the investigator, the main cause of death was unknown. No autopsy was done. The event was assessed by the investigator as related to the study drug.

Serious adverse events occurred in 43 (32%) of the 136 patients receiving regorafenib and 18 (26%) of the 68 patients receiving placebo, which were deemed to be drug-related in 12 (9%) patients in the regorafenib group and three (4%) in the placebo group (appendix). We noted hepatobiliary serious adverse events in one (1%) patient receiving regorafenib and one (1%) receiving placebo; we deemed both drug-related. We noted no hepatic failure, hepatic necrosis, or death due to hepatobiliary adverse events.

Adverse events resulted in discontinuation of the study drug in 19 (14%) of the 136 patients receiving regorafenib and four (6%) of 68 patients receiving placebo. The most common adverse events leading to discontinuation were laboratory events; only one (1%) patient stopped treatment because of hand–foot skin reaction (appendix). Adverse events led to treatment modification (treatment interruption, dose reduction, or both) in 97 (71%) patients receiving regorafenib and 11 (16%) receiving placebo. Treatment was interrupted because of adverse events in 85 (63%) patients in the regorafenib group and 11 (16%) in the placebo group, with grade 3 events accounting for most interruptions (appendix). The dose of study drug was decreased because of adverse events in 54 (40%) patients in the regorafenib group and none in the placebo group, with most dose reductions being due to grade 1 or 2 events (appendix). The most common events needing treatment modifications (treatment interruptions or dose reductions) were hand–foot skin reaction and laboratory events (appendix).

According to the changes in mean scores from baseline to end of treatment in the EORTC QLQ-C30 general health status or quality-of-life domain, and the EQ-5D index and VAS, patients' quality of life and health status deteriorated to a similar extent in both treatment groups. For the EORTC QLQ-C30 general health status or quality-of-life domain, mean scores were 66·7 (SD 18·4) in the regorafenib group and 58·0 (23·0) in the placebo group at baseline, and 51·1 (22·3) in the regorafenib group and 52·2 (25·9) in the placebo group at the end of treatment; the LSM difference in time-adjusted AUC of the overall treatment effect between groups was –0·40 (95% CI –3·5 to 2·7). Mean EQ-5D index scores were 0·84 (SD 0·19) for the regorafenib group and 0·75 (0·23) for the placebo group at baseline, and 0·57 (0·40) for the regorafenib group and 0·57 (0·39) for the placebo group at the end of treatment; the LSM difference in AUC was –0·0 (95% CI –0·1 to 0·0). Mean EQ-5D VAS scores were 73·4 (SD 17·3) in the regorafenib group and 71·4 (17·4) in the placebo group at baseline, and 61·5 (21·4) in the regorafenib group and 62·6 (22·3) in the placebo group at the end of treatment; the LSM difference in AUC was –1·2 (95% CI –4·0 to 1·7).

Discussion

This study is the second phase 3 trial to show an overall survival benefit from the addition of regorafenib to best supportive care in patients with metastatic colorectal cancer in whom standard treatments have failed. Few treatment options exist for this population of patients. Although this trial had a smaller number of patients than the international CORRECT trial did, the sample size calculation and statistical power were appropriate for a confirmatory trial of this type, and the benefit of regorafenib in an Asian population noted here is consistent with findings from both the mostly non-Asian overall population and the Japanese subpopulation in CORRECT.[11,13] The superiority of regorafenib to placebo was also noted in analyses of progression-free survival and disease control, and in prespecified subgroup analyses of overall survival and progression-free survival.

The overall survival benefit noted in our trial was apparently larger than that in CORRECT[11] (HR 0·55 *vs* 0·77), although the reasons for this difference are unclear. Although caution is needed with cross-trial comparisons, we speculate that the most likely reason is the difference in previous exposure to targeted treatments. 122 (60%) of the 204 patients in our trial had been previously given VEGF-targeted or EGFR-targeted biological drugs, or both, whereas, in CORRECT, 100% of patients had received at least one previous targeted biological drug (all had received bevacizumab).[11] A planned subgroup analysis of overall survival showed that patients who were not exposed to a targeted biological treatment before the trial seemed to derive a greater benefit from regorafenib than did those who had received at least one previous targeted drug; nonetheless, the benefit in those receiving previous targeted treatment was similar to that seen in CORRECT (HR 0·77 [95% CI 0·64–0·94]), suggesting that the effect of regorafenib is independent of ethnic origin but might be affected by previous treatments. However, these findings need to be interpreted with caution for several reasons. First, although these analyses were planned, they should be deemed exploratory only. Additionally, the sample size in each previous-treatment subgroup was small, and previous targeted treatment was not a stratification factor,

therefore imbalances might exist in prognostic factors between the regorafenib and placebo groups. Finally, in an exploratory analysis of overall survival with censoring at the start of post-study treatment, the favourable effect of regorafenib seemed to be more pronounced in patients who had received previous targeted treatment than it was in the uncensored analysis, suggesting an effect of post-study treatment in all subgroups of patients who had received previous targeted treatment (appendix). In the VELOUR trial of the VEGF inhibitor aflibercept,[18] patients had similar outcomes irrespective of whether or not they received previous bevacizumab, but that trial was done in the second-line setting in less heavily pretreated patients than were those in our study.

In general, baseline demographic and disease characteristics were broadly similar between the two regorafenib trials, with a few apparent differences. Although patients in our trial had a similar body-mass index (BMI) to the Japanese patients in CORRECT, the BMI was slightly lower than that of the non-Japanese CORRECT participants; however, the Japanese subpopulation in CORRECT achieved a similar treatment benefit to the non-Japanese population, suggesting that efficacy is not affected by BMI.[13] In our trial, the proportion of patients randomly allocated within 18 months of diagnosis of metastatic disease was higher than it was in CORRECT (85 [42%] of 204 in our trial *vs* 140 [18%] of 760 in CORRECT), which might be related to the low availability of previous targeted treatments for patients participating in our trial. Duration of treatment and frequency of treatment modifications (treatment interruption or dose reduction) in the regorafenib groups were similar between the two trials.

The adverse events reported here are consistent with the known safety profile of regorafenib in other clinical trials,[10,11,19–24] including in Asian patients.[13,25,26] As has been reported elsewhere with regorafenib[13,27–29] and other multikinase inhibitors (eg, sorafenib[30,31] and sunitinib[32,33]), occurrence of drug-related hand–foot skin reaction was more frequent in the Asian patients in our trial (100 [74%] of 136) than it was in the predominantly non-Asian population in CORRECT (233 [47%] of 500).[11] However, the frequency of grade 3 hand–foot skin reaction was similar between the two trials (22 [16%] of 136 *vs* 83 [17%] of 500) and consistent with that in Japanese patients in CORRECT (all grades: 52 [80%] of 65; grade 3: 18 [28%] of 65).[11,13] The reason for any differences in hand–foot skin reaction frequency between populations receiving regorafenib is unclear. In CORRECT, no clear relation was noted between the incidence of regorafenib-associated adverse events and BMI or body surface area in the Japanese and non-Japanese subpopulations.[13] Symptoms were generally manageable, with only one patient stopping treatment because of hand–foot skin reaction in our trial. Hepatotoxicity was also more frequent in Japanese than in non-Japanese patients in CORRECT.[11,13] In our trial, although the proportion of patients with increased aminotransferases was higher than that in CORRECT, few patients had hepatobiliary events, with only one drug-related event in the regorafenib group (grade 1 hepatic pain).

Despite a higher proportion of adverse events in the regorafenib group than in the placebo group, the number of patients discontinuing treatment because of toxic effects was small, and patients taking regorafenib were able to stay on treatment longer than were those taking placebo. Early and proactive prophylaxis, and management of adverse events, especially hand–foot skin reaction and liver function test abnormalities (which were the most common adverse events needing treatment modifications), are important to ensure that patients are able to remain on treatment. In view of evidence that adverse events such as hand–foot skin reaction, rash, and fatigue are most likely to occur during the first one or two treatment cycles,[34] some clinicians have explored initiation of regorafenib at a reduced dose as a means of avoiding early toxic effects.[35,36] However, this method has not been assessed in a controlled clinical trial, and the median daily dose noted during our trial was close to the 160 mg recommended starting dose. The difference in adverse events did not seem to affect quality of life because we noted no clinically relevant differences in validated measures of health-related quality of life between the regorafenib and placebo groups.

In summary, we have shown a significant and clinically meaningful benefit of regorafenib compared with placebo in Asian patients in terms of overall survival, progression-free survival, tumour response, and disease control, with no unexpected toxic effects. The results are consistent with those of the international phase 3 CORRECT trial,[11] substantiating the clinical benefit of regorafenib monotherapy for patients with metastatic colorectal cancer.

Contributors

JL, SQ, RX, TCCY, HP, JX, YB, YChi, LW, K-HY, FB, J-KL, TL, DM, CK, JK, and TWK conceived and designed the trial. JL, SQ, RX, TCCY, BM, HP, JX, YB, YChi, LW, K-HY, FB, YChe, ATL, J-KL, TL, DM, JK, and TWK collected the data. JL, SQ, RX, TCCY, HP, JX, YB, YChi, LW, K-HY, FB, J-KL, TL, DM, CK, JK, and TWK analysed and interpreted the data. All authors drafted, reviewed, and approved the manuscript.

Declaration of interests

BM has received consulting fees or honoraria for advisory board participation from Bayer, Novartis, and Boehringer Ingelheim, and grants to her institution (Chinese University of Hong Kong) from Novartis and Boehringer Ingelheim. JL's institution (Fudan University) has received grants from Merck. CK and JK are employees of Bayer and have stocks in the company. TWK has received funding from Lilly for board membership and payment for lectures from Bayer, and has received grants to his institution (University of Ulsan) from Bayer, Sanofi, Taiho, and Roche. All other authors declare no competing interests.

Acknowledgments

This trial was supported by Bayer HealthCare Pharmaceuticals. Editorial assistance in preparation of this manuscript was provided by Sara Black from Succinct Medical Communications, with financial support from Bayer HealthCare Pharmaceuticals; the authors retained editorial control over the content. We thank participating patients and staff at each of the trial centres.

References

1 Center MM, Jemal A, Ward E. International trends in colorectal cancer incidence rates. *Cancer Epidemiol Biomarkers Prev* 2009; **18:** 1688–94.

2 Cheng AL, Li J, Vaid AK, et al. Adaptation of international guidelines for metastatic colorectal cancer: an Asian consensus. *Clin Colorectal Cancer* 2014; **13:** 145–55.

3 WHO International Agency for Research on Cancer. GLOBOCAN 2012. Colorectal cancer: estimated incidence, mortality and prevalence worldwide in 2012. http://globocan.iarc.fr/Pages/fact_sheets_cancer.aspx?cancer=colorectal (accessed Feb 9, 2015).

4 Ku G, Tan IB, Yau T, et al. Management of colon cancer: resource-stratified guidelines from the Asian Oncology Summit 2012. *Lancet Oncol* 2012; **13:** e470–81.

5 Lemmens V, van Steenbergen L, Janssen-Heijnen M, et al. Trends in colorectal cancer in the south of the Netherlands 1975–2007: rectal cancer survival levels with colon cancer survival. *Acta Oncol* 2010; **49:** 784–96.

6 Van Cutsem E, Borras JM, Castells A, et al. Improving outcomes in colorectal cancer: where do we go from here? *Eur J Cancer* 2013; **49:** 2476–85.

7 Hyodo I, Suzuki H, Takahashi K, et al. Present status and perspectives of colorectal cancer in Asia: Colorectal Cancer Working Group report in 30th Asia-Pacific Cancer Conference. *Jpn J Clin Oncol* 2010; **40** (suppl 1)**:** i38–43.

8 Wilhelm SM, Dumas J, Adnane L, et al. Regorafenib (BAY 73-4506): a new oral multikinase inhibitor of angiogenic, stromal and oncogenic receptor tyrosine kinases with potent preclinical antitumor activity. *Int J Cancer* 2011; **129:** 245–55.

9 Schmieder R, Hoffmann J, Becker M, et al. Regorafenib (BAY 73-4506): antitumor and antimetastatic activities in preclinical models of colorectal cancer. *Int J Cancer* 2014; **135:** 1487–96.

10 Strumberg D, Scheulen ME, Schultheis B, et al. Regorafenib (BAY 73-4506) in advanced colorectal cancer: a phase I study. *Br J Cancer* 2012; **106:** 1722–27.

11 Grothey A, Van Cutsem E, Sobrero A, et al. Regorafenib monotherapy for previously treated metastatic colorectal cancer (CORRECT): an international, multicentre, randomised, placebo-controlled, phase 3 trial. *Lancet* 2013; **381:** 303–12.

12 Ma B, Hui EP, Mok TS. Population-based differences in treatment outcome following anticancer drug therapies. *Lancet Oncol* 2010; **11:** 75–84.

13 Yoshino T, Komatsu Y, Yamada Y, et al. Randomized phase III trial of regorafenib in metastatic colorectal cancer: analysis of the CORRECT Japanese and non-Japanese subpopulations. *Invest New Drugs* 2014; published online Sept 12. DOI:10.1007/s10637-014-0154-x.

14 Eisenhauer EA, Therasse P, Bogaerts J, et al. New response evaluation criteria in solid tumours: revised RECIST guideline (version 1.1). *Eur J Cancer* 2009; **45:** 228–47.

15 European Organisation for Research and Treatment of Cancer. EORTC QLQ-C30 scoring manual, 3rd edn. Brussels: European Organisation for Research and Treatment of Cancer, 2001.

16 Oppe M, Rabin R, deCharro F. EuroQol EQ-5D user guide, version 1. Rotterdam: EuroQoL Group, 2007.

17 US Department of Health and Human Services. Common Terminology Criteria for Adverse Events (CTCAE). Version 4.0. Washington, DC: US Department of Health and Human Services, 2010.

18 Tabernero J, Van Cutsem E, Lakomý R, et al. Aflibercept versus placebo in combination with fluorouracil, leucovorin and irinotecan in the treatment of previously treated metastatic colorectal cancer: prespecified subgroup analyses from the VELOUR trial. *Eur J Cancer* 2014; **50:** 320–31.

19 Mross K, Frost A, Steinbild S, et al. A phase I dose-escalation study of regorafenib (BAY 73-4506), an inhibitor of oncogenic, angiogenic, and stromal kinases, in patients with advanced solid tumors. *Clin Cancer Res* 2012; **18:** 2658–67.

20 Schultheis B, Folprecht G, Kuhlmann J, et al. Regorafenib in combination with FOLFOX or FOLFIRI as first- or second-line treatment of colorectal cancer: results of a multicenter, phase Ib study. *Ann Oncol* 2013; **24:** 1560–67.

21 Bruix J, Tak WY, Gasbarrini A, et al. Regorafenib as second-line therapy for intermediate or advanced hepatocellular carcinoma: multicentre, open-label, phase II safety study. *Eur J Cancer* 2013; **49:** 3412–19.

22 Eisen T, Joensuu H, Nathan PD, et al. Regorafenib for patients with previously untreated metastatic or unresectable renal-cell carcinoma: a single-group phase 2 trial. *Lancet Oncol* 2012; **13:** 1055–62.

23 George S, Wang Q, Heinrich MC, et al. Efficacy and safety of regorafenib in patients with metastatic and/or unresectable GI stromal tumor after failure of imatinib and sunitinib: a multicenter phase II trial. *J Clin Oncol* 2012; **30:** 2401–47.

24 Demetri GD, Reichardt P, Kang YK, et al. Efficacy and safety of regorafenib for advanced gastrointestinal stromal tumours after failure of imatinib and sunitinib (GRID): an international, multicentre, randomised, placebo-controlled, phase 3 trial. *Lancet* 2013; **381:** 295–302.

25 Sunakawa Y, Furuse J, Okusaka T, et al. Regorafenib in Japanese patients with solid tumors: phase I study of safety, efficacy, and pharmacokinetics. *Invest New Drugs* 2013; **32:** 104–12.

26 Tanaka A, Sadahiro S, Suzuki T, Okada K, Saito G. Tolerability and efficacy of regorafenib in patients with unresectable metastatic colorectal cancer. *Gan To Kagaku Ryoho* 2014; **41:** 1231–36.

27 Sugihara K, Ohtsu A, Shimada Y, et al. Safety analysis of FOLFOX4 treatment in colorectal cancer patients: a comparison between two Asian studies and four western studies. *Clin Colorectal Cancer* 2012; **11:** 127–37.

28 Guan ZZ, Xu JM, Luo RC, et al. Efficacy and safety of bevacizumab plus chemotherapy in Chinese patients with metastatic colorectal cancer: a randomized phase III ARTIST trial. *Chin J Cancer* 2011; **30:** 682–89.

29 Kang YK, Xu J, Komatsu Y, et al. Subgroup analysis of Asian patients in the phase III trial (GRID) of regorafenib in pretreated metastatic GIST. *Ann Oncol* 2013; **24** (suppl 9)**:** ix6 (abstr PLS-3).

30 Ueda T, Uemura H, Tomita Y, et al. Efficacy and safety of axitinib versus sorafenib in metastatic renal cell carcinoma: subgroup analysis of Japanese patients from the global randomized phase 3 AXIS trial. *Jpn J Clin Oncol* 2013; **43:** 616–28.

31 Cheng AL, Kang YK, Chen Z, et al. Efficacy and safety of sorafenib in patients in the Asia-Pacific region with advanced hepatocellular carcinoma: a phase III randomised, double-blind, placebo-controlled trial. *Lancet Oncol* 2009; **10:** 25–34.

32 Yoo C, Kim JE, Lee JL, et al. The efficacy and safety of sunitinib in Korean patients with advanced renal cell carcinoma: high incidence of toxicity leads to frequent dose reduction. *Jpn J Clin Oncol* 2010; **40:** 980–85.

33 Zhou A. Management of sunitinib adverse events in renal cell carcinoma patients: the Asian experience. *Asia Pac J Clin Oncol* 2012; **8:** 132–44.

34 Grothey A, Sobrero AF, Siena S, et al. Time profile of adverse events (AEs) from regorafenib (REG) treatment for metastatic colorectal cancer (mCRC) in the phase III CORRECT study. *Proc Am Soc Clin Oncol* 2013; **31** (suppl)**:** abstr 3637.

35 DeSimone PA, Overley C, Long KE. Nightly dosing of regorafenib. *Proc Am Soc Clin Oncol* 2015; **33** (suppl 3): abstr 549.

36 Tabchi S, Ghosn M. Regorafenib: start low and go slow. *Target Oncol* 2014; published online Dec 30, 2014. DOI:10.1007/s11523-014-0352-7.