Regorafenib dose-optimisation in patients with refractory metastatic colorectal cancer (ReDOS): a randomised, multicentre, open-label, phase 2 study

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Summary

Background Regorafenib confers an overall survival benefit in patients with refractory metastatic colorectal cancer; however, the adverse event profile of regorafenib has limited its use. Despite no supportive evidence, various dosing schedules are used clinically to alleviate toxicities. This study evaluated the safety and activity of two regorafenib dosing schedules.

Methods In this randomised, multicentre, open-label, phase 2 study done in 39 outpatient cancer centres in the USA, adults aged 18 years or older with histologically or cytologically confirmed advanced or metastatic adenocarcinoma of the colon or rectum that was refractory to previous standard therapy, including EGFR inhibitors if *KRAS* wild-type, were enrolled. Eligible patients had an Eastern Cooperative Oncology Group performance status of 0–1 and had no previous treatment with regorafenib. Patients were randomly assigned (1:1:1:1) into four groups with two distinct regorafenib dosing strategies and two clobetasol usage plans, stratified by hospital. Regorafenib dosing strategies were a dose-escalation strategy (starting dose 80 mg/day orally with weekly escalation, per 40 mg increment, to 160 mg/day regorafenib) if no significant drug-related adverse events occurred and a standard-dose strategy (160 mg/day orally) for 21 days of a 28-day cycle. Clobetasol usage plans (0·05% clobetasol cream twice daily applied to palms and soles) were either pre-emptive or reactive. After randomisation to the four preplanned groups, using the Pocock and Simon dynamic allocation procedures stratified by the treating hospitals, we formally tested the interaction between the two interventions, dosing strategy and clobetasol usage. Given the absence of a significant interaction (p=0·74), we decided to pool the data for the pre-emptive and reactive treatment with clobetasol and compared the two dosing strategies (dose escalation *vs* standard dose). The primary endpoint was the proportion of evaluable patients (defined as those who were eligible, consented, and received any protocol treatment) initiating cycle 3 and was analysed per protocol. Superiority for dose escalation was declared if the one-sided p value with Fisher's exact test was less than 0·2. This trial is registered with ClinicalTrials.gov, number NCT02368886. This study is fully accrued but remains active.

Findings Between June 2, 2015, and June 22, 2017, 123 patients were randomly assigned to treatment, of whom 116 (94%) were evaluable. The per-protocol population consisted of 54 patients in the dose-escalation group and 62 in the standard-dose group. At data cutoff on July 24, 2018, median follow-up was 1·18 years (IQR 0·98–1·57). The primary endpoint was met: 23 (43%, 95% CI 29–56) of 54 patients in the dose-escalation group initiated cycle 3 versus 16 (26%, 15–37) of 62 patients in the standard-dose group (one-sided p=0·043). The most common grade 3–4 adverse events were fatigue (seven [13%] patients in the dose-escalation group *vs* 11 [18%] in the standard-dose group), hand-foot skin reaction (eight [15%] patients *vs* ten [16%] patients), abdominal pain (nine [17%] patients *vs* four [6%] patients), and hypertension (four [7%] patients *vs* nine [15%] patients). 14 patients had at least one drug-related serious adverse event: six patients in the dose-escalation group and eight patients in the standard-dose group. There was one probable treatment-related death in the standard-dose group (myocardial infarction).

Interpretation The dose-escalation dosing strategy represents an alternative approach for optimising regorafenib dosing with comparable activity and lower incidence of adverse events and could be implemented in clinical practice on the basis of these data.

Funding Bayer HealthCare Pharmaceuticals.

Introduction

Colorectal cancer is the third most common cancer with more than 1·8 million cases estimated to have occurred worldwide in 2018.[1] Regorafenib is an oral, multitargeted, kinase inhibitor that blocks the activity of various protein kinases, including those involved in angiogenesis

Research in context

Evidence before this study

Regorafenib has proven survival benefits in patients with treatment-refractory metastatic colorectal cancer. However, its use is often limited by the early onset of adverse events, such as hand-foot skin reaction and fatigue. Consequently, various dosing regimens have been used to reduce these adverse events, despite the lack of clinical evidence on the efficacy of these dosing modifications. We searched PubMed from inception to June 30, 2015, for clinical trial reports to identify the various dosing regimens of regorafenib that have been explored and used to mitigate the onset of adverse events. Terms used in this search were "regorafenib", "dosing", "dose", "strategy", "optimization", "diarrhea", "fatigue", "plantar erythrodysesthesia syndrome (PPES)", and "hand-foot skin reaction (HFSR)". There was a paucity of published literature in this area. Only two studies adequately addressed the concept of different dosing schedules and toxicities and patient care. Hence, there remains a need for the evaluation of different dosing and the potential effect on adverse events and their onset.

Added value of this study

A dose-escalation strategy, in which regorafenib is started at a lower daily dose with planned dose-escalation to the standard dose of 160 mg per day, is a viable and potentially preferred option in patients with metastatic colorectal cancer. More patients on this dose-escalation strategy initiated a third cycle of therapy, which was a composite endpoint encompassing both safety and activity parameters. Escalation of the regorafenib dose might also reduce the incidence of several of the higher-grade adverse events. As one of only three studies that have specifically addressed the effect of an alternative regorafenib dosing schedule, these data present valuable clinical evidence supporting the use of a dose-escalation strategy.

Implications of all the available evidence

Using a dose-escalation strategy of regorafenib is a feasible alternative to the current upfront 160 mg dosing regimen in patients who have metastatic colorectal cancer. This regimen could serve as the basis for the use of regorafenib in combination trials.

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(VEGF-1, VEGF-2, VEGF-3, and TIE2), oncogenesis (KIT, RET, RAF-1, and BRAF), and the tumour microenvironment (PDGFR and FGFR).[2] Regorafenib significantly improved survival in patients with refractory metastatic colorectal cancer in the phase 3 CORRECT trial.[3] In this study, median overall survival was 6·4 months (IQR 3·6–11·8) in patients treated with regorafenib, compared with 5·0 months (IQR 2·8–10·4) in the placebo group (hazard ratio [HR] 0·77, 95% CI 0·64–0·94; p=0·0052). An overall survival benefit was also observed in the CONCUR trial,[4] a study of Asian patients. On the basis of the CORRECT study results, regorafenib was approved worldwide for the treatment of patients with metastatic colorectal cancer who had previously received fluoropyrimidine-based, oxaliplatin-based, and irinotecan-based chemotherapy; prior anti-VEGF therapy; and, if patients have a *KRAS* wild-type tumour, previous anti-EGFR therapy.

Despite the observed survival benefits, the emergence of toxicities, such as hand-foot skin reaction and fatigue, has limited the use of regorafenib. Clinical trial data show that regorafenib-related adverse events such as hand-foot skin reaction and fatigue occur early following treatment initiation, usually within the first cycle, and improve rather than worsen over time.[5]

The standard daily dose of regorafenib used in the registration trial was 160 mg/day in a 3-weeks-on, 1-week-off schedule. In clinical practice, however, physicians have commonly adopted various dosing or interval schedules and topical agents to counteract the toxicities, despite the lack of supportive clinical data. There is a need to optimise the dosing strategy of regorafenib in patients with refractory metastatic colorectal cancer to allow maintenance of the observed antitumour benefits while improving the tolerability profile. This study evaluated a dose-escalation strategy that used a lower starting dose of regorafenib with weekly planned dose increases to standard dose on the basis of tolerability and compared this strategy with the standard dose in patients with refractory metastatic colorectal cancer.

Methods

Study design and participants

The regorafenib dose-optimisation study (ReDOS) was a randomised, open-label, phase 2 study conducted through the Academic and Community Cancer Research United research network and enrolled patients at 39 outpatient cancer centres in the USA (appendix pp 1–2). The applicable regulations and guidelines governing clinical study conduct were followed and the study was performed in compliance with the Declaration of Helsinki. The study protocol (appendix) was approved by the institutional review board at each participating center and all patients provided written, informed consent.

See Online for appendix

Eligible patients were aged 18 years or older, with histological or cytological documentation of advanced or metastatic adenocarcinoma of the colon or rectum, for whom no curative options were available and who had progressed (as defined by the Response Evaluation Criteria in Solid Tumors [RECIST] version 1.1)[6] on standard therapy (irinotecan, oxaliplatin, fluoropyrimidines, and VEGF inhibitor). Patients eligible for EGFR inhibitors had to progress after anti-EGFR therapy before enrolling in the study. Other inclusion criteria were an

Eastern Cooperative Oncology Group (ECOG) performance status of 0 or 1 and adequate organ and bone marrow function. The main exclusion criteria were previous treatment with regorafenib, congestive heart failure (worse than New York Heart Association criteria class II), unstable angina or myocardial infarction less than 6 months prior to randomisation, cardiac arrhythmias requiring therapy or uncontrolled hypertension, arterial or venous thrombotic or embolic events, history of hepatitis B or C virus infection, and symptomatic metastatic brain or meningeal tumours (unless the patient was more than 6 months from definitive therapy, had a negative imaging study within 4 weeks of randomisation, and was clinically stable with respect to the tumour at the time of randomisation). Patients were expected to have a life expectancy of at least 3 months and also were required to have an absolute neutrophil count of more than 1500 cells per mm³, platelet count of more than 100 000 per mm³, haemoglobin greater than 9·0 g/dL, total bilirubin within 1·5×upper limit of normal (ULN), alanine aminotransferase and aspartate aminotransferase within 2·5×ULN (≤5×ULN for patients with liver involvement of their cancer), serum creatine within 1·5×ULN, ratio of international normalised ratio to partial thromboplastin time within 1·5×ULN, and alkaline phosphatase limit within 2·5×ULN (≤5×ULN for patients with liver involvement of their cancer). Full inclusion and exclusion criteria are presented in the appendix (pp 20–24).

Randomisation and masking

Patients were enrolled by treating physicians at the participating hospitals and then randomly assigned (1:1:1:1) to four groups with two distinct regorafenib dosing strategies (standard dose *vs* escalated) and clobetasol usage (pre-emptive *vs* reactive; appendix p 4). Treatment was assigned by computerised central randomisation using the Pocock and Simon dynamic allocation procedure stratified by the treating hospitals; this balances the marginal distributions of the stratification factors between the treatment groups.[7] A random element was incorporated in the minimisation algorithm in which a patient would be randomly assigned to the group that creates more balance 75% of the time. In this open-label study, patients, investigators, and the study team were not masked to study treatment.

Procedures

Patients assigned to the two clobetasol pre-emptive strategy groups received prophylactic 0·05% clobetasol cream twice daily applied to palms and soles starting at cycle 1 day 1 for prevention of hand-foot skin reaction. Patients assigned to the two clobetasol reactive strategy groups had the clobetasol cream applied when hand-foot skin reaction developed.

In both regorafenib dosing strategies, regorafenib was administered orally for 21 consecutive days of a 28-day treatment cycle. In the dose-escalation group, the starting dose of regorafenib was 80 mg/day in week 1, 120 mg/day in week 2, and 160 mg/day in week 3 for cycle 1. Weekly incremental dose escalation occurred up to the maximum of 160 mg/day if no significant drug-related toxicities were observed. In cycle 2 and all subsequent cycles, patients received the highest tolerated dose from cycle 1. In the regorafenib standard dose group, patients received 160 mg/day starting on day 1 until dose modification or discontinuation (appendix p 4). We selected the dose of 160 mg as the standard dose because it is the approved and most commonly used dose and schedule in clinical practice based on the results of randomised trials.

Regorafenib dose was modified during treatment on the basis of the occurrence of adverse events; the criteria for dose modification were the same for both treatment groups (appendix p 2). Dose modifications for toxicities other than hand-foot skin reaction, hypertension, or elevated aspartate aminotransferase, alanine aminotransferase, or bilirubin were included for grades greater than 2. Dose modifications for hand-foot skin reaction and hypertension were included for grades 2 or worse and based on occurrence. Dose modifications for elevated aspartate aminotransferase, alanine aminotransferase, or bilirubin if less than grade 3 included weekly monitoring of liver function until return to less than grade 2, interruption if grade 3, and discontinuation for grades 4. During the first two cycles of treatment, if significant drug-related toxicities were observed, regorafenib dose was reduced in the dose-escalation group to the preceding dose level (appendix p 2). Significant drug-related toxicities were defined as any toxicities thought to be related to regorafenib, including hand-foot skin reaction; hypertension; elevated aspartate aminotransferase, alanine aminotransferase, or bilirubin; and any adverse events of grade 3 or worse that led to dose reduction. If the significant drug-related toxicities resolved (ie, grade <1) after week 8 of treatment, re-escalation of 40 mg every 4 weeks was allowed until 160 mg was reached. In the first two cycles, investigators were asked to precisely adhere to the protocol-specified regorafenib dose modifications to ascertain a patient's treatment tolerance.

Patients received regorafenib until disease progression, unacceptable toxicity, or consent withdrawal from protocol treatment. Patients requiring dose reductions to less than 80 mg or those who had toxicities requiring more than 4 weeks' treatment delay were taken off regorafenib and evaluated for overall survival. If more than two dose-level reductions were required, regorafenib treatment was permanently discontinued. Antiemetics were used at the physician's discretion and growth factors were allowed during the study, according to published guidelines.[8] Patients received full supportive care while participating in the study, including blood products, antibiotic treatment, and treatment of other newly diagnosed or concurrent medical conditions. Adverse events were assessed by the investigator and

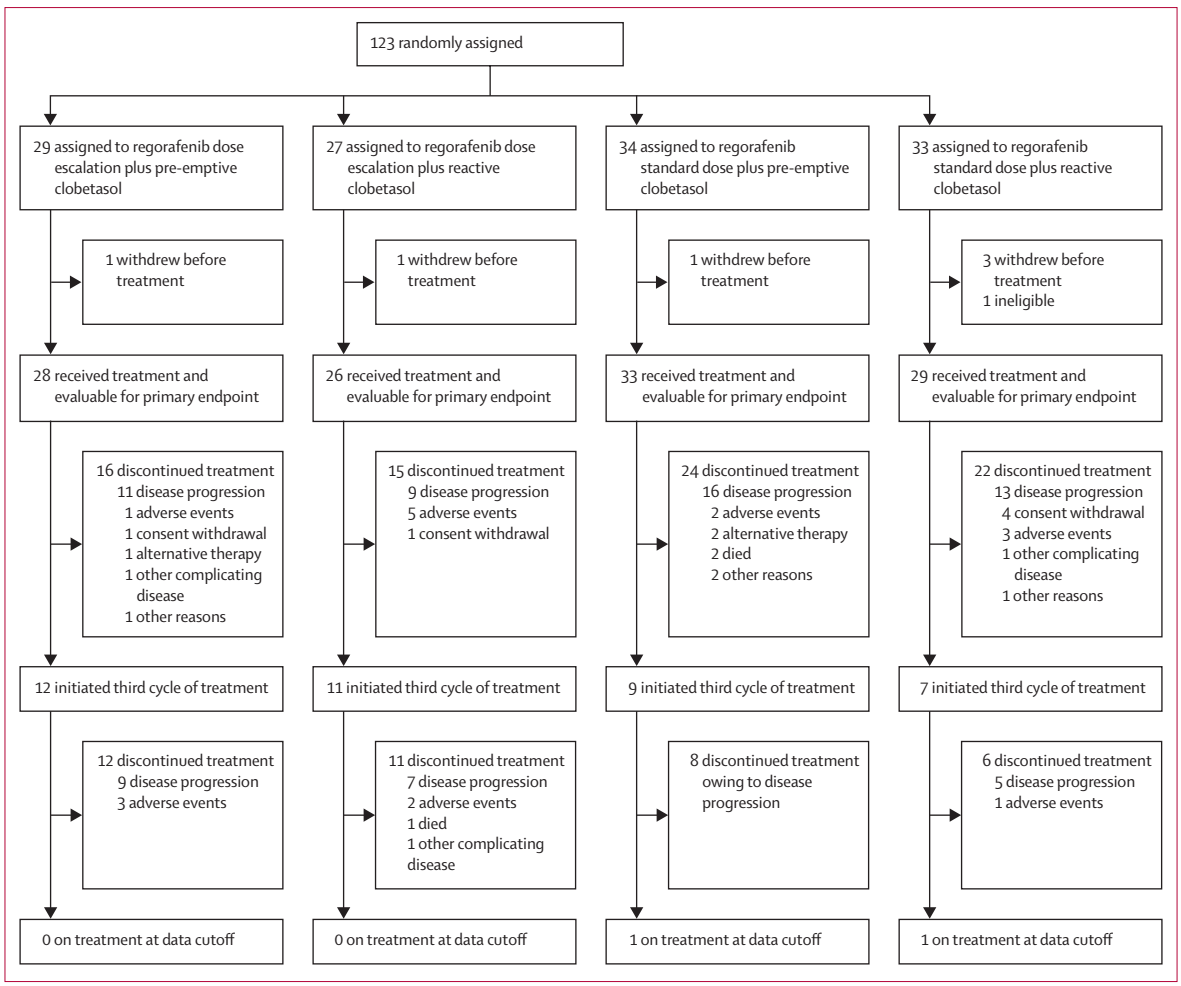

Figure 1: **Trial profile**

reported per the National Cancer Institute Common Terminology Criteria for Adverse Events version 4.0.

Response and progression were evaluated every 8 weeks by the investigator using RECIST 1.1.[6] Blood was collected on days 7, 14, and 21 prior to dosing in cycle 1 and on days 1 and 21 prior to dosing in cycle 2 for pharmacokinetic analysis of regorafenib and metabolites. Quality of life (QOL) measures were assessed at baseline and end of weeks 2, 4, 6, and 8 using the Hand-Foot Syndrome 14 (HFS-14), the Brief Fatigue Inventory (BFI), and Linear Analogue Self-Assessment (LASA) questionnaire. HFS-14 was designed specifically to capture changes in QOL related to hand-foot skin reaction and includes 14 questions with three domains: hand, feet, and social.[9] BFI is a validated nine-item questionnaire that was used to assess the severity of fatigue and fatigue-related impairment in patients with cancer,[10] while the LASA questionnaire was used to measure global QOL.[11] For BFI and LASA, a high score indicates better QOL is reported, whereas for HFS-14, a high score indicates worse QOL is reported.

Outcomes

The primary endpoint was the proportion of patients in each group who completed two cycles of treatment and initiated the third cycle. The secondary endpoints were progression-free survival, overall survival, and time to progression in the dose-escalation group versus the standard-dose group; cumulative dose and dose intensity received within the first two cycles in the two groups; proportion of patients in each group who exhibited grade 3 hand-foot skin reaction or fatigue; and a comparison of QOL, as measured by the HFS-14, BFI, and LASA questionnaires, between treatment groups. Overall survival was defined as time from randomisation to death due to any cause. Progression-free survival was defined as the time from randomisation to the earliest evidence of disease progression (per RECIST 1.1) or death due to any cause. Time to progression was defined as the time from randomisation to disease progression as defined by RECIST 1.1. Patients who were alive and progression free (as assessed by the investigator) were censored at the last disease assessment. Dose intensity

	Dose-escalation group (n=54)	Standard-dose group (n=62)
Age, years		
Median (IQR)	62 (53–68)	61 (53–68)
Range	29–77	32–81
Sex		
Female	18 (33%)	27 (44%)
Male	36 (67%)	35 (56%)
Race		
White	44 (81%)	55 (89%)
Black or African American	5 (9%)	4 (6%)
Asian	3 (6%)	2 (3%)
American Indian or Alaska Native	1 (2%)	0
Not reported or unknown	1 (2%)	1 (2%)
ECOG performance status		
0	20 (37%)	23 (37%)
1	34 (63%)	39 (63%)
Primary tumour status		
Local recurrence	4 (7%)	1 (2%)
Resected	37 (69%)	44 (71%)
Unresected	13 (24%)	17 (27%)
Number of metastatic sites		
1	6 (11%)	2 (3%)
2	12 (22%)	18 (29%)
≥3	36 (67%)	42 (68%)
***BRAF* mutation status**		
Mutated	0	2 (3%)
Wild-type	17 (31%)	20 (32%)
Unknown	37 (69%)	40 (65%)
***KRAS* mutation status**		
Mutated	21 (39%)	34 (55%)
Wild-type	31 (57%)	27 (44%)
Unknown	2 (4%)	1 (2%)

ECOG=Eastern Cooperative Oncology Group.

Table 1: **Patient demographics and baseline characteristics**

was defined as the cumulative (total) dose of regorafenib divided by the expected total dose. Exploratory endpoints included pharmacokinetic analysis of regorafenib and M2 and M5 metabolites in both groups, and correlations with toxicity and activity parameters. These outcomes will be reported at a later date.

Statistical analysis

In the CORRECT study, the median treatment duration for the regorafenib group was 1·7 months;[3] we therefore assumed an 8-week continuation rate of 45% in the standard-dose group. To improve this assumed continuation rate by 18 percentage points to 63% in the dose-escalation group, a one-sided test with $\alpha=0\cdot20$ and power of 80% required a sample size of 110 patients enrolled in the study (approximately 55 patients in each regorafenib treatment group). A one-sided test with $\alpha=0\cdot20$ was chosen because we felt that an absolute improvement of 18 percentage points in the 8-week continuation would be clinically relevant while limiting the sample size to close to 100 patients for feasibility purposes. An additional 13 patients overall were also planned for enrolment to account for ineligibility, withdrawn consent, and drop-outs, leading to a final sample size of 123 patients.

After randomisation to the four preplanned groups, we formally tested the interaction between the two interventions (regorafenib dosing strategy and clobetasol usage) and given the absence of a significant interaction (p=0·74; appendix p 2), we decided to pool the data for the pre-emptive and reactive treatment with clobetasol and instead compared just the two dosing strategies (regorafenib dose-escalation *vs* regorafenib standard dose). Henceforth, these pooled groups will be referred to as the dose-escalation group and the standard-dose group. Results regarding the activity of clobetasol in treating hand-foot skin reaction will be reported separately.

Evaluable patients were defined as those who were eligible, consented, and received any protocol treatment. All endpoints were analysed in this population per protocol. The primary endpoint was chosen because it combines the important aspects of activity (only patients with at least stable disease on the first planned imaging evaluation at 8 weeks would continue therapy) and toxicity (only patients who have no treatment-limiting toxicities would continue therapy). It was hypothesised that the dose-escalation strategy would have fewer patients who go off protocol due to early toxicity but would still delay progression, given a more prolonged exposure to a mainly cytostatic agent, thereby maintaining activity.

The proportion of patients in each treatment group who completed two cycles of treatment and initiated cycle 3 was calculated with asymptotic Wald 95% CIs, with a one-sided Fisher's exact test used to detect a difference in proportion between treatment groups. The dose-escalation strategy was declared promising if the p value from the one-sided Fisher's exact test was less than 0·2. Overall survival, progression-free survival, and time to progression were estimated with Kaplan-Meier survival curves and differences between the treatment groups were tested using log-rank tests. These analyses were not powered for non-inferiority assessments. The cumulative dose of regorafenib received by patients and dose intensity in the first two cycles was summarised with descriptive statistics and compared between groups using the Wilcoxon rank sum test. A proportional hazard model was used to do an adjusted post-hoc analysis to determine if patients' *KRAS* status affected overall survival. The time-to-event variable was overall survival and the variables included in the model were the treatment group (dose escalation *vs* standard dose) and *KRAS* mutation status (wild-type *vs* mutant).

The proportion of patients overall and within each group experiencing grade 3 hand-foot skin reaction, fatigue,

hypertension, and diarrhoea (the latter two as part of a post-hoc analysis) was computed and differences between regorafenib dosing strategies tested using Fisher's exact test. Patients were also descriptively compared between treatment groups according to self-reported outcomes on the HFS-14, BFI, and LASA questionnaires. Results from the cycle 1 and 2 questionnaires were summarised descriptively, with prespecified comparisons made between groups using the *t* test or Wilcoxon rank sum test as appropriate. QOL analyses were done using complete-case analysis where missing QOL measures were simply removed from the statistical analysis. A post-hoc sensitivity analysis in which missing data are set to the worst QOL score was carried out. The rationale of this sensitivity analysis is that the second most common reason for stopping treatment in early cycles, which results in missing QOL measures, is adverse events, which potentially imply worse QOL measures. All analyses were done in evaluable patients.

We did a post-hoc analysis using χ^2 tests to explore whether there was a difference in the receipt of non-protocol therapy between the two treatment groups. This analysis was done separately for patients who went into the third cycle of therapy and patients who ended treatment before starting the third cycle.

All analyses were done with SAS (version 9.2). This trial is registered with ClinicalTrials.gov, number NCT02368886.

Role of the funding source

Study sponsor (Academic and Community Cancer Research United) investigators were responsible for the trial design, study conduct, and collection, analysis, and interpretation of the data, as well as the writing, review, and approval of this manuscript. Bayer HealthCare Pharmaceuticals supported this study through an unrestricted grant and supplied regorafenib for this study, but had no role in the trial design, conduct, or collection, analysis, and interpretation of data, nor in the writing, review, or approval of this manuscript. The corresponding author had unrestricted access to all the data in the study and had the final responsibility for the decision to submit for publication.

Results

Between June 2, 2015, and June 22, 2017, 123 patients were enrolled and randomly assigned to one of the four preplanned treatment groups (figure 1). The data cutoff was July 24, 2018. 116 patients (54 in the dose-escalation group and 62 in the standard-dose group) were evaluable for the primary endpoint. The median age was 61·5 years (IQR 53·0–68·0), 73 (63%) of 116 patients had an ECOG performance status of 1, and 55 (47%) patients had *KRAS*-mutant metastatic colorectal cancer (table 1). Overall, demographics and baseline characteristics seemed relatively balanced between groups.

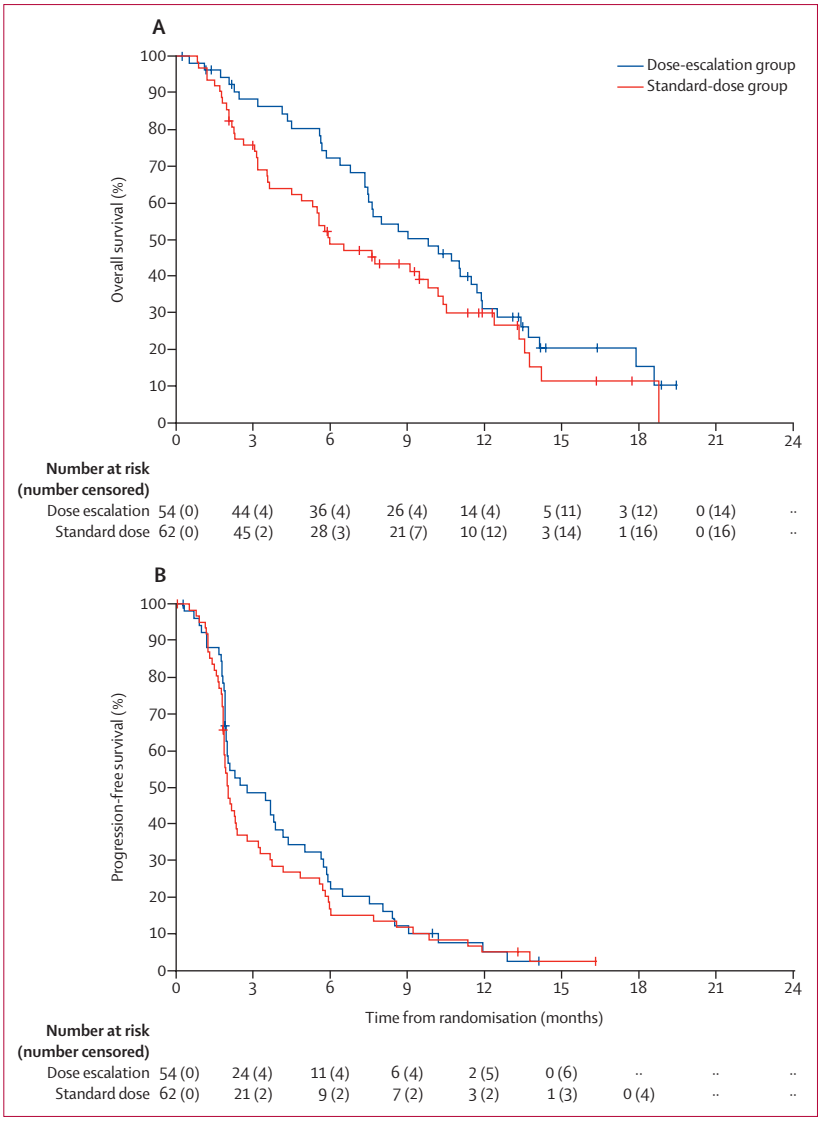

Figure 2: **Overall survival (A) and progression-free survival (B) in the dose-escalation and standard-dose groups**
Censored patients are marked on the curves with a cross.

The proportion of patients who completed two cycles of therapy and initiated cycle 3 was significantly higher in the dose-escalation group than in the standard-dose group (23 [43%, 95% CI 29–56] of 54 patients in the dose-escalation group *vs* 16 [26%, 15–37] of 62 patients in the standard-dose group; one-sided p=0·043; appendix p 4). The primary reason for not initiating a third cycle of treatment was disease progression (20 [37%] in the dose-escalation group *vs* 29 [47%] in the standard-dose group); other reasons were adverse events (six [11%] *vs* five [8%]), withdrawn consent (two [4%] *vs* four [6%]), other complicating disease (one [2%] *vs* one [2%]), alternative therapy (one [2%] *vs* two [3%]), death (no patients *vs* two [3%]), and other reasons (one [2%] *vs* three [5%]; figure 1).

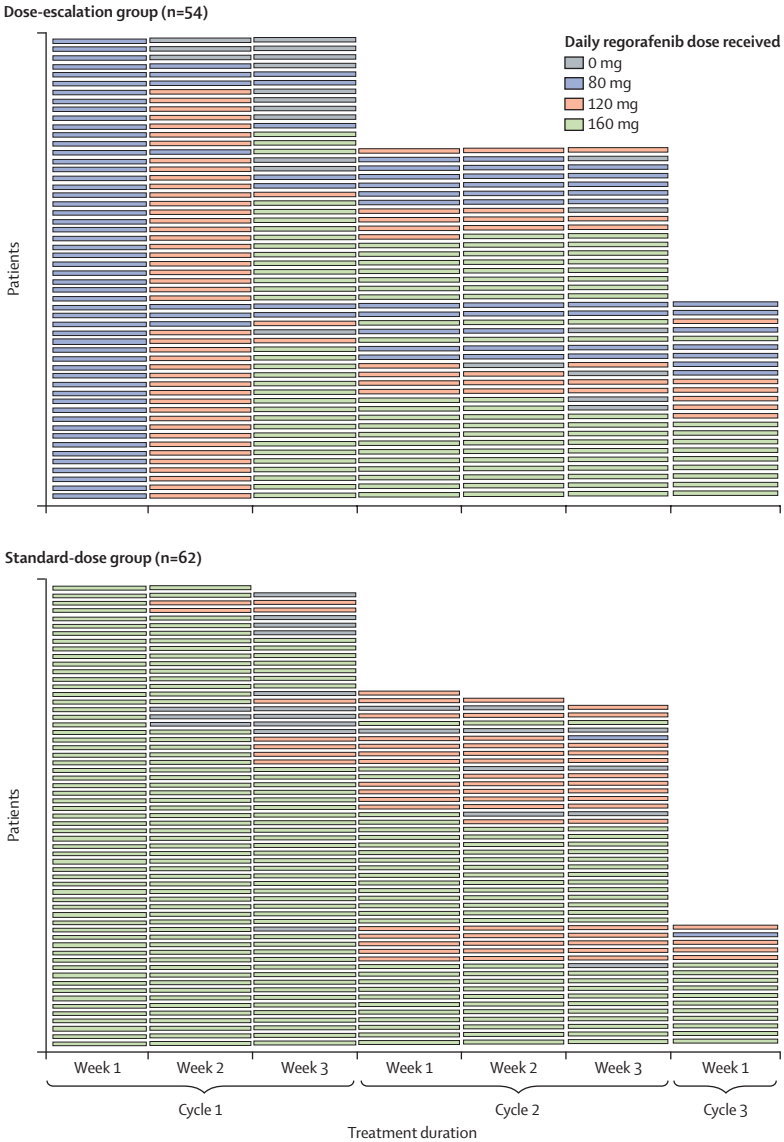

***Figure 3*: Swimmer plot presenting dosing history up to week 1 of cycle 3**
Individual patients are represented throughout the different weeks and cycles by a horizontal series of bars.

Subsequent treatment information was available for 44 (81%) patients in the dose-escalation group and 49 (79%) in the standard-dose group. Among patients who did not continue to cycle 3, 18 (69%) of 26 patients in the dose-escalation group and 14 (33%) of 42 in the standard-dose group received subsequent treatment (p=0·0040). Among patients who continued to cycle 3, 11 (61%) of 18 patients in the dose-escalation group and five (71%) of seven in the standard-dose group received subsequent treatment (p=0·63). Patients with unknown information on subsequent treatment were excluded from this analysis.

At data cutoff on July 24, 2018, median follow-up was 1·18 years (IQR 0·98–1·57). The median overall survival for the dose-escalation group was 9·8 months (95% CI 7·5–11·9) compared with 6·0 months (4·9–10·2) for the standard-dose group (HR 0·72, 95% CI 0·47–1·10; log-rank p=0·12; figure 2A). 40 (74%) of 54 patients in the dose-escalation group and 46 (74%) of 62 in the standard-dose group had died by data cutoff. In a post-hoc analysis in patients who initiated cycle 3, we observed no significant difference in overall survival (17 events in 23 patients in the dose-escalation group *vs* five events in 16 patients in the standard-dose group; appendix p 5).

Progression-free survival was similar in the dose-escalation group (median 2·8 months, 95% CI 2·0–5·0) and the standard-dose group (2·0 months, 1·8–2·8; HR 0·84, 95% CI 0·57–1·24; log-rank p=0·38; figure 2B) with 48 progression-free survival events in the dose-escalation group versus 58 events in the standard-dose group reported by data cutoff.

Weekly dosing history for patients by treatment group up to week 1 of cycle 3 is summarised in figure 3 and the appendix (p 2). In cycle 1, patients in the dose-escalation group received a mean percentage of planned dose of 77% (SD 28) whereas patients in the standard-dose group received 83% (22). Dose modifications occurred in 13 (24%) of 54 patients in the dose-escalation group and in 13 (21%) of 62 patients in the standard-dose group. Dose omissions (ie, interruptions) occurred in 22 (41%) patients in the dose-escalation group and 26 (42%) patients in the standard-dose group. Dose delays occurred in five (9%) patients in the dose-escalation group and one (2%) patient in the standard-dose group.

41 (76%) of 54 patients in the dose-escalation group and 47 (76%) of 62 patients in the standard-dose group continued to cycle 2. In cycle 2, patients received a mean percentage of planned dose of 93% (SD 15) in the dose-escalation group and 73% (31) in the standard-dose group. Nine (22%) patients in the dose-escalation group and 15 (32%) in the standard-dose group had dose modifications and a dose was omitted in 14 (34%) patients in the dose-escalation group and in 15 (32%) patients in the standard-dose group. There was no delay in dosing for any patient in the dose-escalation group whereas a delay occurred in seven (15%) patients in the standard-dose group.

In cycle 1, patients in the dose-escalation group received a lower mean total dose compared with patients in the standard-dose group (appendix p 2), which was expected per study design.

The incidence of grade 3 adverse events commonly associated with regorafenib treatment, such as fatigue, hand-foot skin reaction, hypertension, and diarrhoea (the latter two were analysed post hoc), was generally lower in the dose-escalation group compared with the standard-dose group in both cycles of treatment (appendix p 3).

Most patients responded to HFS-14, LASA, and BFI questionnaires and we observed no difference in compliance between the two patient groups (appendix p 8). LASA and BFI QOL scores at baseline were similar

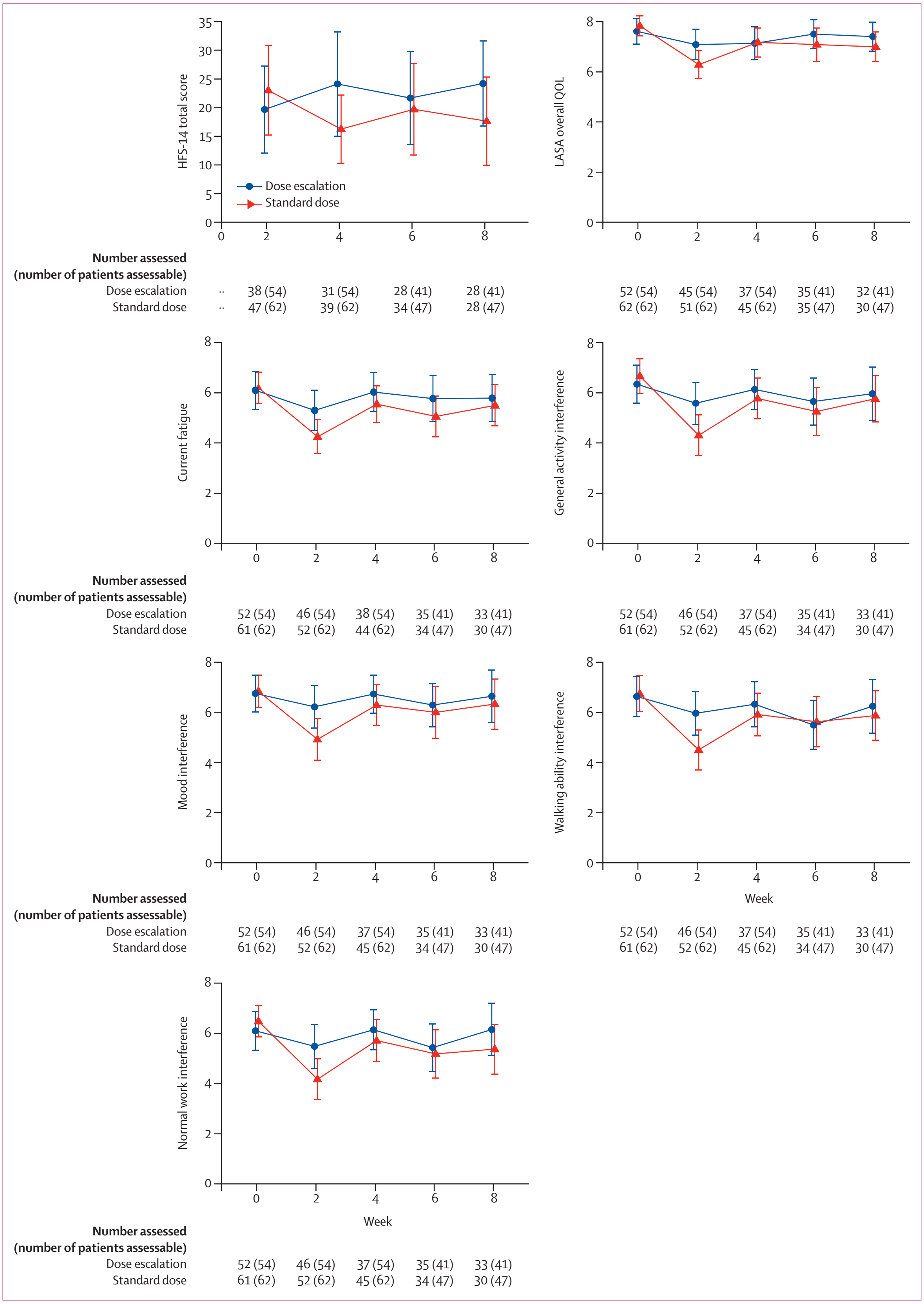

Figure 4: **Effect of treatment strategies on QOL parameters**
Data shown are mean (95% CI). The range of scores is 0–10 for all graphs except for HFS-14, which has range 2–100. A higher score indicates better QOL except for LASA, where a higher score indicates worse QOL. HFS and LASA are indicated as such on the graphs; all other data are from the BFI. BFI=Brief Fatigue Inventory. HFS=Hand-Foot Syndrome. LASA=Linear Analogue Self-Assessment. QOL=quality of life.

	Dose-escalation group (n=54)				Standard-dose group (n=62)			
	Grade 1–2	Grade 3	Grade 4	Grade 5	Grade 1–2	Grade 3	Grade 4	Grade 5
Fatigue	42 (78%)	7 (13%)	0	0	44 (71%)	11 (18%)	0	0
Hand-foot skin reaction	27 (50%)	8 (15%)	0	0	33 (53%)	10 (16%)	0	0
Hypertension	34 (63%)	4 (7%)	0	0	29 (47%)	9 (15%)	0	0
Nausea	23 (43%)	0	0	0	31 (50%)	0	0	0
Diarrhoea	23 (43%)	1 (2%)	0	0	25 (40%)	2 (3%)	0	0
Anorexia	14 (26%)	1 (2%)	0	0	16 (26%)	2 (3%)	0	0
Rash maculopapular	10 (19%)	0	0	0	16 (26%)	3 (5%)	0	0
Vomiting	13 (24%)	0	0	0	14 (23%)	1 (2%)	0	0
Blood bilirubin increased	7 (13%)	2 (4%)	0	0	13 (21%)	5 (8%)	0	0
Anaemia	12 (22%)	1 (2%)	0	0	12 (19%)	1 (2%)	0	0
Aspartate aminotransferase increased	8 (15%)	1 (2%)	0	0	12 (19%)	4 (6%)	0	0
Alkaline phosphatase increased	6 (11%)	3 (6%)	0	0	10 (16%)	1 (2%)	1 (2%)	0
Abdominal pain	1 (2%)	9 (17%)	0	0	5 (8%)	4 (6%)	0	0
Dyspnoea	5 (9%)	1 (2%)	1 (2%)	0	8 (13%)	4 (6%)	0	0
Alanine aminotransferase increased	8 (15%)	0	0	0	8 (13%)	1 (2%)	0	0
Hoarseness	8 (15%)	0	0	0	8 (13%)	0	0	0
Weight loss	4 (7%)	1 (2%)	0	0	10 (16%)	1 (2%)	0	0
Hyponatremia	0	2 (4%)	1 (2%)	0	7 (11%)	4 (6%)	1 (2%)	0
Platelet count decreased	7 (13%)	0	0	0	8 (13%)	0	0	0
Mucositis oral	4 (7%)	1 (2%)	0	0	8 (13%)	1 (2%)	0	0
Hypoalbuminemia	5 (9%)	1 (2%)	0	0	7 (11%)	0	0	0
Peripheral sensory neuropathy	6 (11%)	0	0	0	6 (10%)	0	0	0
Lymphocyte count decreased	1 (2%)	4 (7%)	0	0	6 (10%)	0	0	0
Hypocalcaemia	6 (11%)	0	0	0	3 (5%)	1 (2%)	0	0
Hypokalaemia	3 (6%)	1 (2%)	0	0	5 (8%)	0	1 (2%)	0
Generalised muscle weakness	5 (9%)	1 (2%)	0	0	2 (3%)	1 (2%)	0	0
Myalgia	0	1 (2%)	0	0	6 (10%)	2 (3%)	0	0
Pain	5 (9%)	0	0	0	3 (5%)	1 (2%)	0	0
Dehydration	1 (2%)	0	0	0	2 (3%)	5 (8%)	0	0
Investigations, other (specified)	3 (6%)	0	0	0	4 (6%)	1 (2%)	0	0
Back pain	1 (2%)	1 (2%)	0	0	5 (8%)	0	0	0
Dry skin	1 (2%)	1 (2%)	0	0	3 (5%)	0	0	0
Neoplasms: benign, malignant, unspecified, other (specified)	0	0	0	2 (4%)	0	0	0	2 (3%)
Colonic obstruction	0	3 (6%)	0	0	0	0	0	0
Hyperglycaemia	1 (2%)	1 (2%)	0	0	0	1 (2%)	0	0
Hyperkalaemia	1 (2%)	0	0	0	1 (2%)	1 (2%)	0	0
Sinus tachycardia	0	1 (2%)	0	0	1 (2%)	1 (2%)	0	0
Ascites	1 (2%)	1 (2%)	0	0	0	0	0	0
Chest wall pain	0	1 (2%)	0	0	1 (2%)	0	0	0
Death not otherwise specified	0	0	0	1 (2%)	0	0	0	1 (2%)
Encephalopathy	0	0	0	0	0	2 (3%)	0	0
Respiratory failure	0	0	1 (2%)	0	0	0	0	1 (2%)
Sepsis	0	0	1 (2%)	0	0	0	1 (2%)	0
Thromboembolic event	1 (2%)	1 (2%)	0	0	0	0	0	0
Abdominal infection	0	1 (2%)	0	0	0	0	0	0
Adult respiratory distress syndrome	0	0	1 (2%)	0	0	0	0	0
Atelectasis	0	0	0	0	0	1 (2%)	0	0
Colitis	0	1 (2%)	0	0	0	0	0	0
Confusion	0	0	0	0	0	1 (2%)	0	0
Hepatic failure	0	0	0	0	0	0	1 (2%)	0

(Table 2 continues on next page)

	Dose-escalation group (n=54)				Standard-dose group (n=62)			
	Grade 1–2	Grade 3	Grade 4	Grade 5	Grade 1–2	Grade 3	Grade 4	Grade 5
(Continued from previous page)								
Hepatobiliary disorders, other (specified)	0	1 (2%)	0	0	0	0	0	0
Hypoxia	0	0	0	0	0	1 (2%)	0	0
Infections and infestations, other (specified)	0	0	0	0	0	1 (2%)	0	0
Increased international normalised ratio	0	0	0	0	0	1 (2%)	0	0
Lower gastrointestinal haemorrhage	0	0	0	0	0	1 (2%)	0	0
Lung infection	0	0	1 (2%)	0	0	0	0	0
Myocardial infarction	0	0	0	0	0	0	0	1 (2%)
Rectal fistula	0	1 (2%)	0	0	0	0	0	0
Rectal obstruction	0	1 (2%)	0	0	0	0	0	0
Syncope	0	1 (2%)	0	0	0	0	0	0
Urinary retention	0	1 (2%)	0	0	0	0	0	0

Events are listed in order of overall frequency. All grade 3, 4, and 5 events are shown as well as grade 1 and 2 occurrence of these events. For other grade 1–2 events, only events occurring in at least 10% of patients are included.

Table 2: **Adverse events**

between the two dosing strategies (figure 4). At week 2 of treatment, mean QOL scores were significantly better in the dose-escalation group compared with the standard-dose group for current fatigue (5·30, 95% CI 4·48–6·12 *vs* 4·25, 3·55–4·95; p=0·046), general activity interference (5·59, 4·73–6·45 *vs* 4·31, 3·48–5·14; p=0·032), mood interference (6·22, 5·35–7·09 *vs* 4·92, 4·07–5·77; p=0·038), walking ability interference (5·96, 5·07–6·85 *vs* 4·50, 3·68–5·32; p=0·019), and normal work interference (5·48, 4·58–6·38 *vs* 4·17, 3·34–5·00; p=0·039) as measured by the BFI questionnaire (figure 4). At weeks 4, 6, and 8, no significant differences were found in QOL scores between the two dosing strategies (figure 4; appendix pp 9–13). Overall, patients in the dose-escalation group had slightly higher QOL score in terms of HFS-14 and LASA questionnaires than did those in the standard-dose group, although the difference was not significant (appendix p 7). The post-hoc sensitivity analysis supported these QOL results (appendix p 6).

Overall, the safety profile was consistent with previous experience with regorafenib, with no substantial differences noted between the two dosing strategies (table 2). However, in a prespecified analysis of cycle 1, fewer patients had grade 2–3 hand-foot skin reaction in the dose-escalation group than in the standard-dose group (appendix p 3). The most common grade 3–4 adverse events were fatigue (seven [13%] patients in the dose-escalation group *vs* 11 [18%] in the standard-dose group), hand-foot skin reaction (eight [15%] patients *vs* ten [16%] patients), abdominal pain (nine [17%] patients *vs* four [6%] patients), and hypertension (four [7%] patients *vs* nine [15%] patients). 14 (26%) patients in the dose-escalation group and 21 (34%) patients in the standard-dose group reported at least one serious adverse event. Abdominal pain was the most frequent serious adverse event for both groups (seven [13%] patients in the dose-escalation group and four [6%] patients in the standard-dose group). 14 patients had at least one drug-related serious adverse event: six patients in the dose-escalation group and eight patients in the standard-dose group. In the dose-escalation group, the most frequent drug-related serious adverse events reported, each occurring in one (2%) patient were fatigue, increased alanine aminotransferase, increased alkaline phosphatase, increased aspartate aminotransferase, increased blood bilirubin, colitis, colonic obstruction, respiratory failure, and hand-foot skin reaction. In the standard-dose group, the most frequent drug-related serious adverse event was fatigue (two [3%] patients).

Three patients died on study: two patients died from disease-related causes (one in each treatment group), both of which were not considered study-drug related. One patient in the standard-dose group died from myocardial infarction, which was considered to be probably related to study drug. At the time of analysis, two patients, both in the standard-dose group, remained on treatment. Reasons for treatment discontinuation were mainly related to disease progression and adverse events (figure 1).

We noted that the proportion of patients with a *KRAS*-mutant tumour was lower in the dose-escalation group than in the standard-dose group (table 1), which raised the concern that the difference might have affected overall survival. In a post-hoc analysis, the adjusted hazard ratio of overall survival for the regorafenib dose escalation group compared with the regorafenib standard dose group was 0·742 (95% CI 0·478–1·151; p=0·18). The *KRAS* variable was found not to be a significant covariate in this adjusted model (p=0·95; data not shown). Additionally, the two patients with *BRAF*-mutated cancers (both in the standard-dose group) had individual survival outcomes that were above the median for the standard-dose group (7·0 and 11·5 months, respectively).

Discussion

Our study shows that a dose-escalation strategy for regorafenib is a feasible alternative to the standard regorafenib dosing strategy of 160 mg/day. The data presented herein show that the dose-escalation strategy does not negatively affect activity and is well tolerated. Additionally, patients in the dose-escalation group had slightly higher QOL scores overall in terms of HFS-14 and LASA questionnaires than did those in the standard-dose group, although the difference was not significant.

Optimising treatment outcomes in metastatic colorectal cancer with a personalised regorafenib dose and schedule adjustments is common in clinical practice and many physicians have adopted an empirical titration approach to manage toxicities. Dose-adjustment guidelines are largely based on the results from phase 3 studies.[12] A recent observational cohort study[13] suggested that individualised regorafenib dosing strategies in patients with metastatic colorectal cancer might lead to improved clinical outcomes. However, as shown in the CORRELATE observational study,[14] various dosing strategies are being adopted in the community without prospective evidence from randomised trials to support these approaches.

Our phase 2 randomised trial compared a strategy with a lower starting dose of regorafenib and planned weekly dose escalation to standard dose with the standard regorafenib dosing in patients with metastatic colorectal cancer. This study provides the clinical data to potentially establish a new approach for optimising regorafenib dosing through a dose-escalation strategy. The study met its prespecified primary endpoint. The results suggest that an increase of the dose of regorafenib from 80 to 160 mg/day via 40 mg increments over 3 weeks is a viable regimen, compared with the standard starting dose of 160 mg/day, with a significantly higher proportion of patients from the dose-escalation group initiating cycle 3 of treatment compared with the standard-dose group (43% *vs* 26%; one-sided p=0·043). Numerically higher overall survival was observed in the dose-escalation group, although this was not significantly different. With 86 deaths observed (74% of the analysis population), the survival results have reached maturity. This observation is secondary to a more predictable dosing during the first cycle in the dose-escalation group as well as having fewer patients with progressive disease after two cycles of therapy. Sensitivity analyses showed that the slight difference between groups in the proportion of patients with a *KRAS* mutation did not appear to affect overall survival. *BRAF* mutations were also found to be unlikely to have influenced survival outcomes, although this is based on two patients in the standard-dose group. It is interesting to note that patients in both groups who were able to initiate cycle 3 had relatively similar survival, which was close to 1 year. Additionally, although more patients in the dose-escalation group received subsequent therapy overall, a similar proportion of patients who continued onto cycle 3 received subsequent therapy in both groups. These findings suggest that a dose-escalation strategy that allows more patients to initiate cycle 3 might lead to improved outcomes.

Safety data were consistent with previous experience with regorafenib and were found to be similar between both groups. Overall, mild (grade 1–2) hand-foot skin reaction was reported in 50% of patients and severe (grade 3) hand-foot skin reaction in 16% of patients. Around 75% of all patients experienced mild fatigue whereas 13–18% experienced severe fatigue. Adverse events of severe hypertension occurred more frequently in the standard-dose group (15%) than in the dose-escalation group (7%). Although adverse events were similar between the two groups, severity of hand-foot skin reaction, fatigue, and hypertension might be slightly lower in the dose-escalation group than in the standard-dose group during cycles 1 and 2. This is not surprising given that these toxicities are both time and dose dependent and differences would be primarily expected in the first 2 cycles. Fatigue and various QOL scores, including general activity interference, mood interference, walking ability interference, and normal work interference, were better in the dose-escalation group compared with the standard-dose group at week 2 of treatment, suggesting that the dose-escalation strategy is beneficial at the time when the standard-dose administration seems to compromise QOL.

The inherent nature of a randomised phase 2 study with a small sample size confers a limitation for data interpretation. p values tend to be variable and if the probabilities of response differ significantly from those hypothesised, the result could be due to an underpowered study.[15] This analysis was not done by comparing across the four preplanned groups into which the patients were randomised but, rather, pooling the data for the pre-emptive and reactive treatment with clobetasol, which potentially increases the overall variability. Furthermore, the migration of estimates of median survival from phase 2 to phase 3 should be approached with extreme caution, as numerical differences might not necessarily become or remain significant with larger sample sizes.[16] We assessed QOL with complete-case analysis, which might introduce bias to the results. However, a randomised phase 2 trial does have advantages over a single-arm trial that uses historical data as a control, and if the limitations are properly understood, phase 2 data can be clinically meaningful. Although no significant difference in overall survival was observed, it is worth noting that survival data can be confounded by multiple factors, including exposure to further therapy following progression and potentially other unidentified influences. That said, the data reported in this study are similar to those reported in the phase 3 CORRECT trial,[3] in which a median overall survival of 6·4 months was observed in patients with metastatic colorectal cancer treated with standard-dose regorafenib. The subjective nature of patient-reported adherence to treatment in our study

might also limit data interpretation. There are mixed reports about the reliability of self-reported adherence,[17,18] with such methodology criticised for poor distributional properties (eg, restricted range and skewness) and a potential for measurement bias surrounding recall and response.[19] Despite this, at least one report[20] suggests that self-reported questionnaires have high or moderate concordance with adherence measured by medical monitoring devices.

Given that the cumulative dose of regorafenib received was similar in both treatment groups, the clear implication is that the dosing strategy, and potentially the predictability of exposure in the first two cycles, is important, rather than the dose itself. Additionally, we plan to separately report the final pharmacokinetic analysis for regorafenib and active M2 and M5 metabolites and correlate these with the clinical outcomes, including treatment exposure. Two ongoing phase 2 trials, REGOCC[21] and RE-ARRANGE (NCT02835924), are comparing different dose-escalation and scheduling approaches of regorafenib in metastatic colorectal cancer and will provide valuable information for further optimisation of dosing strategies. The data from ReDOS clearly show that starting treatment with a lower dose of regorafenib with a planned dose escalation during the first cycle of therapy does not compromise activity compared with the standard, higher starting dose that was established in the pivotal CORRECT trial.

In summary, our data support the use of a dose-escalation strategy in patients with metastatic colorectal cancer during the first cycle of regorafenib treatment.[22] With the increased number of patients initiating a third cycle of treatment, and corresponding potential improvement in overall survival, physicians might view this strategy as a welcome alternative approach for optimising regorafenib dosing in the management of patients with refractory metastatic colorectal cancer.

Contributors

TSB-S and AG conceived the study. TSB-S, EGC, H-JL, and AG contributed to the study design. TSB-S, KP, RJD, and AG participated in patient recruitment. KKC participated in patient enrolment. KP participated in patient treatment. TSB-S, F-SO, DHA, PMB, KKC, NLJ, JMC, RJD, JPM, KP, EGC, JS, MEL, H-JL, and AG participated in data collection. TSB-S, F-SO, DHA, KKC, ENH, TJD, JMC, JPM, JSM, AB, EGC, JS, MEL, H-JL, and AG participated in data analysis. TSB-S, F-SO, DHA, PMB, KKC, TJD, JPM, JSM, KP, AB, EGC, JS, MEL, H-JL, and AG participated in data interpretation. ENH developed the figures and tables. TSB-S, F-SO, DHA, PMB, KKC, ENH, TJD, NLJ, BCP, JMC, RJD, JPM, JSM, KP, AB, EGC, JS, MEL, H-JL, and AG participated in manuscript writing, review, and final approval. BCP was the responsible co-author for the Wake Forest Baptist Comprehensive Cancer Center.

Declaration of interests

TSB-S received travel expenses from Bayer to attend advisory board meetings; served as a paid consultant for AbbVie, Immunneering, Imugene, and Glenmark; and served on the data and safety monitoring boards of Exelixis, Silajen, and Armo during the conduct of the study. His institution has received honoraria from Bayer, Pfizer, Celgene, Ipsen, Amgen, Array, Bristol-Myers Squibb, and Incyte for consultant services, outside of the submitted work. DHA served as a consultant for Eisai and Astellas during the conduct of the study. PMB has received research funding from Merck, Boehringer Ingelheim, Ipsen, Merrimack, Advaxis, Theradiag, Athenex, Boston Biomedical, MedImmune, Bristol-Myers Squibb, Novartis, Incyte, Amgen, Sanofi, Array Biopharma, Daiichi Sankyo, and Nucano; and honoraria from Sirtex and Boston Biomedical, outside of the submitted work. KKC has been a consultant for Bayer, Foundation Medicine, Research to Practice and Taiho; she has received research funding to her institution from Incyte, Pfizer, Boston Biomedical, MedImmune, Onyx, Bayer, Boehringer Ingelheim, Bristol-Myers Squibb, Merck, Novartis, Amgen, Sanofi, Array, Daiichi Sankyo, and Nucana, outside of the submitted work. JMC has received research funding from Merck and Tesaro; has been a consultant for Bristol-Myers Squibb; and has received travel expenses from Bristol-Myers Squibb, Roche and Agios, outside of the submitted work RJD is currently an employee of Bristol-Myers Squibb. KP reports personal fees from Bayer during the conduct of the study; and travel expenses from Beigene and Array Pharmaceuticals and grants from Mayo Foundation for Medical Education and Research and BiolineRx, outside of the submitted work. EGC has received research funding from Boehringer Ingelheim, Celgene, Stemline, Ignyta, Incyte, Eli Lilly, and Merck; and has received honoraria from Halozyme, Vicus, Ipsen, Five Prime, Exelixis, AstraZeneca, and Seattle Genetics, outside of the submitted work. She received research funding from Boehringer Ingelheim, Celgene, Stemline, Ignyta, Incyte, Eli Lilly; and honoraria from Halozyme, Vicus, Ipsen and Five Prime during the conduct of the study. MEL has received royalties from Legacy Healthcare Services, Adgero Bio Pharmaceuticals, Amryt Pharmaceuticals, Celldex Therapeutics, Debiopharm, Galderma Research and Development, Johnson and Johnson, Novocure, Lindi, Merck Sharp & Dohme, Helsinn Healthcare, Janssen Research & Development, Menlo Therapeutics, Novartis, F Hoffman-La Roche, AbbVie, Boehringer Ingelheim, Allergen, Amgen, ER Squibb & Sons, EMD Serono, AstraZeneca, Genentech, Leo Pharma, Seattle Genetics, Bayer, Manner, Lutris, Pierre Fabre, Paxman Coolers, Adjucare, Dignitana, Biotechspert, Teva Mexico, Parexel, OnQuality Pharmaceuticals, and Our Brain Bank; and has received research funding from Veloce, US Biotest, Berg, Bristol-Myers Squibb, Lutris, Paxman, and Novocure, outside of the submitted work. H-JL received honoraria from Bristol-Myers Squibb, Bayer, Merck, Isofol, and Genentech; and travel expenses from Merck KGA and Bayer during the conduct of the study. He also has a patent pending. AG received travel expenses from Bayer to attend advisory board meetings during the conduct of the study.His previous institution received honoraria from Genentech, Merck, Boston Biomedicals, Taiho, and Array for consulting activities outside of the submitted work. F-SO, ENH, TJD, NLJ, BCP, JPM, JSM, AB, and JS declare no competing interests.

Data sharing

Data collected for this study, including individual patient data, will not be made available.

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