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# Safety and effectiveness of regorafenib in patients with metastatic colorectal cancer in routine clinical practice in the prospective, observational CORRELATE study

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**Abstract** ***Background:*** Regorafenib prolonged overall survival (OS) versus placebo in patients with treatment-refractory metastatic colorectal cancer (mCRC) in phase III trials. We conducted an observational study of regorafenib for patients with mCRC in real-world clinical practice.

***Methods:*** The international, prospective, CORRELATE study recruited patients with mCRC previously treated with approved therapies, for whom the decision to treat with regorafenib

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was made by the treating physician according to the local health authority approved label. The primary objective was safety, assessed by treatment-emergent adverse events (TEAEs; National Cancer Institute Common Terminology Criteria for Adverse Events, version 4.03).

***Results:*** A total of 1037 patients were treated. The median age was 65 years (range: 24–93); 87% of patients had Eastern Cooperative Oncology Group performance status 0–1, 56% of patients had *KRAS,* 7% had *NRAS* and 4% had *BRAF* mutations. The initial regorafenib dose was 160 mg/day in 57% of patients. The most common grade III or IV drug-related TEAEs were fatigue (9%), hand–foot skin reaction (7%) and hypertension (6%). Drug-related grade V (fatal) TEAEs occurred in 1% of patients. Dose reductions for drug-related TEAEs occurred in 24% of patients. Median OS was 7.7 months (95% confidence interval [CI]: 7.2–8.3), and median progression-free survival (PFS) was 2.9 months (95% CI: 2.8–3.0).

***Conclusions:*** In this real-world, observational study of patients with mCRC, the regorafenib toxicity profile was similar to that reported in phase III trials. The starting dose for almost half of patients was less than the approved 160-mg dose, and the median OS and PFS were in the range observed in phase III trials.

Trial registration: NCT02042144.



## 1. Introduction

Regorafenib is a multikinase inhibitor, first approved in 2012 for patients with metastatic colorectal cancer (mCRC) and disease progression after standard therapies [1–4]. Subsequently, it was approved for patients with advanced gastrointestinal stromal tumours and patients with unresectable hepatocellular carcinoma [3–6]. The approved starting dose of regorafenib is 160 mg orally once daily for the first 3 weeks of each 4-week cycle [3,4].

Regorafenib was evaluated in treatment-refractory mCRC in three large, international trials [2,7,8]. In the randomised, phase III CORRECT trial, regorafenib improved overall survival (OS) versus placebo, with a hazard ratio (HR) of 0.77 (95% confidence interval [CI]: 0.64–0.94; one-sided $P = 0.0052$) and a median OS of 6.4 versus 5.0 months [2]. Progression-free survival (PFS) was also significantly improved (HR: 0.49; 95% CI: 0.42–0.58; one-sided $P < 0.0001$); median PFS was 1.9 versus 1.7 months. The most common grade III or higher drug-related treatment-emergent adverse events (TEAEs) in the CORRECT trial were hand–foot skin reaction (HFSR), fatigue, diarrhoea, hypertension and rash or desquamation [2]. The randomised, phase III CONCUR trial confirmed the efficacy and safety of regorafenib in Asian patients with mCRC [7]. The single-arm, phase IIIb CONSIGN trial, carried out in nearly 3000 patients with mCRC, showed that the safety profile and median PFS were consistent with the results of the CORRECT and CONCUR trials [2,7,8].

The selected patient populations and regulated protocols characterising phase III trials may not reflect the real-world contexts in which patients are treated [9,10]. Data from observational studies can help address this gap, complementing the findings of interventional trials [10]. We report the results of CORRELATE, a prospective, observational study designed to characterise the safety and effectiveness of regorafenib in an unselected, real-world population of patients with mCRC treated in routine clinical practice settings.

## 2. Patients and methods

### 2.1. Study design

CORRELATE was a prospective, observational, cohort study conducted in 126 centres in Europe, Asia and Latin America (NCT02042144). The study population comprised patients with mCRC who were previously treated with, or who were not considered candidates for, other approved therapies and for whom a decision was made by the treating physician to treat with regorafenib according to the local health authority approved label. The observation period for each patient was the time from treatment initiation until death, withdrawal of consent, loss to follow-up or the end of the study. The frequency of tumour evaluations was not defined; assessments were conducted according to the treating physician's routine practice. Patients participating in any investigational program with interventions outside routine practice were excluded. All patients provided signed informed consent.

The primary objective was to characterise the safety of regorafenib for mCRC in real-world practice, assessed by TEAEs during treatment through 30 days after treatment, using the National Cancer Institute Common Terminology Criteria for Adverse Events (NCI-CTCAE), version 4.03. The secondary objective was to assess effectiveness, as measured by OS—the time from treatment start until death; PFS—the time from treatment start until radiological or clinical progression

or death; and the disease control rate (DCR)—the percentage of patients with complete response, partial response or stable disease lasting at least 6 weeks.

For each patient, the treating physician documented an initial visit, when regorafenib was started, follow-up visits and a final visit. There was no fixed visit schedule; visits followed local routine clinical practice. The physician collected data (demographic and baseline disease characteristics) from medical records or by interview at the initial visit. Treatment-related data, including adverse events and tumour status, were collected during follow-up visits. After treatment discontinuation, physicians were encouraged to contact patients every 2 months to assess survival. They were encouraged to make at least three efforts, 1 month apart, via visits, telephone calls, emails or contacting other physicians. Information on survival status obtained from public records could also be used. A final visit was documented at death, withdrawal of consent, loss to follow-up or the end of the study.

### 2.2. Statistical analysis

Using a sample size of 1000 patients, a previously unreported adverse event with a true incidence of 1 per 1000 would have a 63% probability of being observed. To avoid potential selection bias and increase representativeness, patients were selected only based on inclusion and exclusion criteria, and investigators were encouraged to enrol consecutive patients.

Statistical analyses were exploratory and descriptive. Categorical variables were analysed by frequency tables, and continuous variables were analysed by sample statistics. All patients who received at least one dose of regorafenib were included in the safety and effectiveness analyses. OS and PFS were estimated using the Kaplan-Meier method. Patients without calculable OS were censored at day 1, and patients with an unknown date of death were censored at the last date they were known to be alive. Patients without calculable PFS were censored at day 1, and patients with an unknown date of progression were censored at the last date they were known not to have progressed or at day 1 if no tumour assessment existed. An interim analysis was performed after 500 patients had been observed for at least 3 months [11]. The final analysis was performed after all patients were enrolled and followed up until 6 months after regorafenib discontinuation or until death, withdrawal of consent or loss to follow-up, whichever came first.

Exploratory analyses of OS and PFS were performed in subgroups defined by primary tumour location: left-sided (splenic flexure, descending colon, sigmoid/rectosigmoid colon or rectum) versus right-sided (caecum, appendix, ascending colon or hepatic flexure). Patients with primary tumours in the transverse colon and patients with both left-sided and right-sided primary tumours were excluded. An exploratory analysis of OS was performed in subgroups of patients with a resected versus unresected primary tumour.

## 3. Results

Between 8 April 2014 and 18 January 2017, 1048 patients were enrolled. Of those, 11 patients were not treated and were excluded from the analysis. A total of 1037 patients were treated between 9 April 2014 and 21 July 2017, and all patients were analysed for safety and effectiveness (Fig. 1). The final analysis cut-off date was 15 December 2017.

Patients were enrolled from Europe (n = 883), Asia (n = 133) and Latin America (n = 21), including 242 from France, 193 from Italy, 143 from Spain, 136 from Austria and 128 from Taiwan. Approximately half the patients were 65 years or older (Table 1). The primary tumour site was the colon in 70% (n = 721) of patients, the rectum in 28% (n = 294) and the colon and rectum in 2% (n = 21); the primary tumour site was missing for one patient. Most patients (87%) had an Eastern Cooperative Oncology Group (ECOG) performance status of 0 or 1. Thirty-nine percent of patients had received at least four prior systemic anti-cancer therapies.

The median duration of treatment was 2.5 months (range: 0.03–29.5; Table 2). Fifty-seven percent of patients (n = 591) started regorafenib at the approved daily dose of 160 mg, 30% of patients (n = 315) started at 120 mg daily and 12% of patients (n = 127) started at 80 mg daily. Patients starting at 80 mg tended to be older, were more likely to be Asian and had a worse ECOG performance status than patients starting at 120 mg or 160 mg (Appendix Table 1). In approximately 60% of patients, the initial dose was the same as the last dose (Table 2). Forty-eight percent of patients had at least one treatment interruption, and 40% had at least one dose reduction (Table 2). The median time to the first dose modification was 21 days. Most dose modifications (66%; 1187/1809 events) were due to adverse events.

### 3.1. Safety

Most patients (95%) had at least one TEAE, and 80% had a TEAE judged regorafenib-related (Table 3). Regorafenib-related grade III or IV TEAEs were reported in 35% of patients. Grade V (fatal) TEAEs were reported in 17% of patients and were judged regorafenib-related in 1% (n = 10; Appendix Table 2). The most common regorafenib-related grade III or IV TEAEs were fatigue (9%), HFSR (7%) and hypertension (6%) (Table 3).

Approximately one-quarter of patients (24%; n = 251) had a dose reduction due to a regorafenib-

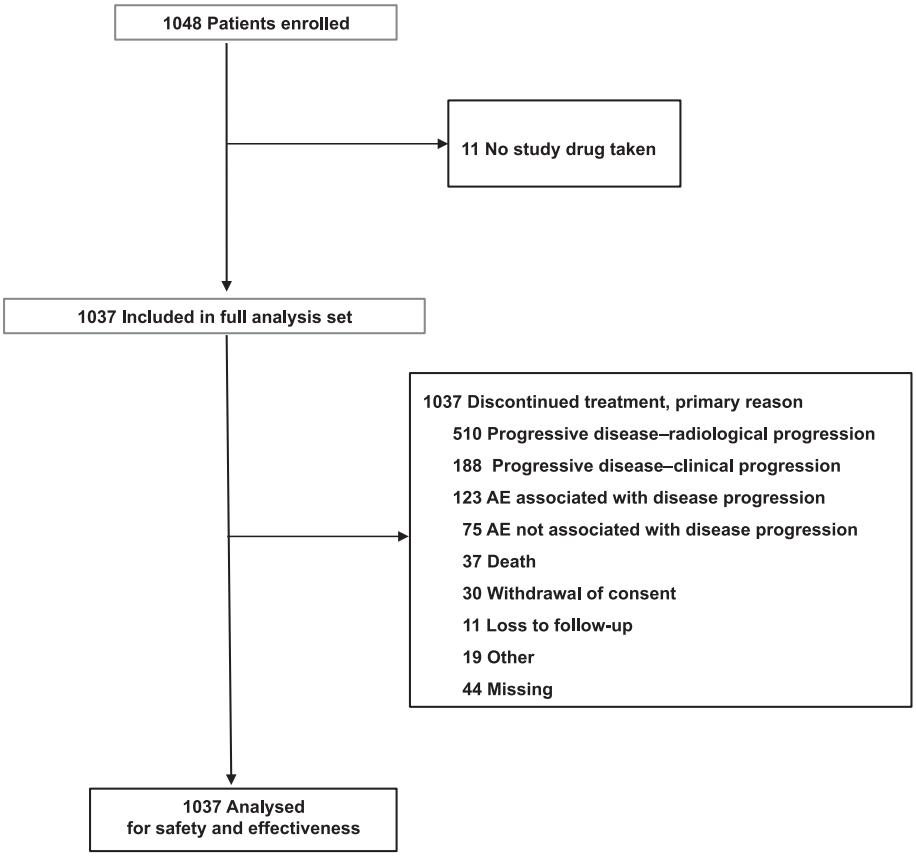


Fig. 1. Patients enrolled and treated. AE, adverse effect.

related TEAE and 31% (n = 319) had a treatment interruption due to a regorafenib-related TEAE (Appendix Table 2). Treatment was permanently discontinued because of a regorafenib-related TEAE in 16% of patients (n = 163).

### 3.2. Effectiveness

The median OS was 7.7 months (95% CI: 7.2–8.3; interquartile range [IQR]: 3.9–15.2; Fig. 2A). The 3-month, 6-month and 1-year estimates for OS were 83%, 60% and 34%, respectively. The median PFS was 2.9 months (95% CI: 2.8–3.0; IQR: 1.9–5.0) (Fig. 2B).

In patients with left-sided primary tumours (n = 761), the median OS was 7.5 months (95% CI: 6.8–8.1; IQR: 4.0–15.1) and the median PFS was 2.9 months (95% CI: 2.8–3.1; IQR: 1.9–5.1) (Appendix Fig. 1A and B). In patients with right-sided primary tumours (n = 206), the median OS was 8.2 months (95% CI: 6.6–9.4; IQR: 3.6–15.0) and the median PFS was 2.8 months (95% CI: 2.6–3.3; IQR: 1.8–5.0). Patients whose primary tumour was resected (n = 806) had a median OS of 8.2 months (95% CI: 7.6–8.8), compared with 5.8 months (95% CI: 4.7–7.1) in patients with unresected primary tumours (n = 229).

In this observational study, in which intervals for tumour assessments were not defined, a total of 758 patients (73%) had at least one tumour assessment (radiological or clinical) and 279 (27%) had no tumour assessment. Of the 758 patients with at least one assessment, 68% of patients (513/758) had one assessment and 21% of patients (159/758) had two assessments. Based on patients with at least one assessment, no patient (0/758) had a complete response, 4% of patients (31/758) had a partial response and 22% of patients (164/758) had stable disease lasting at least 6 weeks. Six patients had stable disease documented earlier than 6 weeks after treatment start. The DCR was 26% (195/758).

## 4. Discussion

This prospective, observational study of more than 1000 patients characterised the safety and effectiveness of regorafenib in mCRC in real-life practice settings. The safety profile of regorafenib was consistent with reports from the phase III trials, with lower rates of some TEAEs, possibly because of more effective management of adverse events [2,7,8]. Although many patients initiated regorafenib at doses lower than the approved label dose, the median OS and PFS were in the range of what was reported in prior trials [2,7,8].

The patient population in CORRELATE was typical of patients with mCRC and generally similar to

Table 1
Demographics and baseline characteristics.

| | Regorafenib (N = 1037) |
|---|---|
| Age (years), median (range) | 65 (24–93) |
| Age ≥65 years, n (%) | 544 (52) |
| Male, n (%) | 629 (61) |
| Race, n (%)[a] | |
| White | 643 (62) |
| Asian | 133 (13) |
| Black | 2 (<1) |
| American Indian or Alaska native | 2 (<1) |
| Not reported | 259 (25) |
| ECOG PS, n (%) | |
| 0 | 426 (41) |
| 1 | 477 (46) |
| 2–4 | 66 (6) |
| Missing | 68 (7) |
| Body mass index (kg/m$^2$), median (IQR)[b] | 24 (22–28) |
| Body weight (kg), median (IQR)[c] | 70 (59–80) |
| Primary tumour site, n (%)[a] | |
| Appendix | 9 (1) |
| Caecum | 75 (7) |
| Ascending colon | 127 (12) |
| Hepatic flexure | 18 (2) |
| Transverse colon | 63 (6) |
| Splenic flexure | 17 (2) |
| Descending colon | 112 (11) |
| Sigmoid colon | 281 (27) |
| Rectosigmoid colon | 85 (8) |
| Rectum | 315 (30) |
| Missing | 1 (<1) |
| Primary tumour classification by location, n (%)[d] | |
| Right-sided | 206 (20) |
| Left-sided | 761 (73) |
| Left- and right-sided | 6 (1) |
| Not assessable | 64 (6) |
| *KRAS* mutation status, n (%) | |
| Wild-type | 387 (37) |
| Mutant | 581 (56) |
| Unknown | 69 (7) |
| *NRAS* mutation status, n (%) | |
| Wild-type | 495 (48) |
| Mutant | 73 (7) |
| Unknown | 469 (45) |
| *BRAF* mutation status, n (%) | |
| Wild-type | 518 (50) |
| Mutant | 46 (4) |
| Unknown | 473 (46) |
| Main metastatic sites at study entry, n (%)[e] | |
| Liver | 747 (72) |
| Lung | 592 (57) |
| Lymph node | 169 (16) |
| Peritoneum | 134 (13) |
| Bone[f] | 118 (11) |
| Status of primary tumour at treatment start, n (%) | |
| Resected | 806 (78) |
| Unresected | 229 (22) |
| Missing | 2 (<1) |
| Time from diagnosis of metastatic disease at study start, months[g] | |
| Median (range) | 26 (<1–169) |
| <18 months, n (%) | 314 (30) |
| ≥18 months, n (%) | 714 (69) |
| Prior systemic anti-cancer therapy, n (%) | |
| Any | 1025 (99) |
| Anti-VEGF | 896 (86) |
| Anti-EGFR | 408 (39) |
| Number of prior systemic anti-cancer therapies | |
| Median (IQR) | 3 (2–4) |
| 0, n (%) | 12 (1) |
| 1–2, n (%) | 316 (30) |
| 3, n (%) | 307 (30) |
| ≥4, n (%) | 402 (39) |

ECOG PS, Eastern Cooperative Oncology Group performance status; EGFR, epidermal growth factor receptor; IQR, interquartile range; VEGF, vascular endothelial growth factor.

[a] Multiple answers possible.
[b] n = 780.
[c] n = 833.
[d] Left-sided primary tumours were those in the splenic flexure, descending colon, sigmoid/rectosigmoid colon or rectum; right-sided primary tumours were those in the caecum, appendix, ascending colon or hepatic flexure; patients with primary tumours in the transverse colon were not assessable.
[e] Patients may have had >1 metastatic site.
[f] Includes spine.
[g] n = 1028.

populations in phase III trials in mCRC. The median age was 65 years, slightly older than that in the CORRECT (61 years, regorafenib arm) and CONSIGN (62 years) trials and considerably older than the median age in the CONCUR (58 years, regorafenib arm) and IMblaze370 (58 years) trials [2,7,8,12]. Fifty-two percent of patients in CORRELATE were 65 years or older, compared with 40% in CONSIGN [8]. Most patients in CORRELATE (86%) had received prior anti-VEGF treatment, similar to patients in other studies [2,8,13], and 39% of patients had received at least four prior systemic anti-cancer therapies. Approximately half of patients had *KRAS*-mutant tumours, similar to the proportions in other studies [2,13], and *BRAF* mutations were found in 46 patients (4%), similar to the proportion in CORRECT (4%, regorafenib arm) [2]. Thirty percent of patients had been diagnosed with metastatic disease for less than 18 months, a higher proportion than those in the CORRECT (18%, regorafenib arm), CONSIGN (18%) and RECOURSE (21%, TAS-102 arm) trials, and a lower proportion than that in the CONCUR trial (39%, regorafenib arm) [2,7,8,13]. Unlike many phase III trials in mCRC, CORRELATE enrolled patients with an ECOG performance status of 2–4, who constituted 6% of the study population [2,7,13].

The incidence and severity of TEAEs in CORRELATE were generally consistent with the known safety profile of regorafenib. The most frequently reported regorafenib-related TEAEs were fatigue, HFSR, diarrhoea, oral mucositis and hypertension, which were also among the most frequently reported regorafenib-related TEAEs in the CORRECT, CONCUR and CONSIGN trials [2,7,8]. No new safety signals were observed. The incidence rates of some regorafenib-related TEAEs were lower in CORRELATE than in CORRECT, including HFSR (26% vs 47%), diarrhoea (19% vs 34%), anorexia

Table 2
Treatment duration and modifications by initial daily dose.

| | 160 mg (n = 591) | 120 mg (n = 315) | 80 mg (n = 127) | All patients[a] (N = 1037) |
|---|---|---|---|---|
| Duration of treatment, months | | | | |
| Median (range) | 2.6 (0.03–29.5) | 2.4 (0.03–20.6) | 2.3 (0.16–15.4) | 2.5 (0.03–29.5) |
| Mean (SD) | 3.2 (2.9) | 3.3 (3.3) | 3.2 (3.0) | 3.3 (3.0) |
| Any dose modification, n (%)[b] | 386 (65) | 200 (63) | 89 (70) | 678 (65) |
| Dose reduction | 278 (47) | 107 (34) | 28 (22) | 415 (40) |
| Dose interruption/delay | 293 (50) | 149 (47) | 58 (46) | 501 (48) |
| Re-escalation[c] | 40 (7) | 59 (19) | 61 (48) | 163 (16) |
| Escalation[d] | 0 | 47 (15) | 61 (48) | 111 (11) |
| No treatment modification | 205 (35) | 115 (37) | 38 (30) | 359 (35) |
| Time (days) to first dose modification, median (range) | 21 (1–403) | 26 (1–242) | 19 (3–133) | 21 (1–403) |
| Last daily dose, n (%)[e] | | | | |
| 160 mg | 326 (55) | 35 (11) | 10 (8) | 373 (36) |
| 120 mg | 166 (28) | 196 (62) | 30 (24) | 393 (38) |
| 80 mg | 94 (16) | 79 (25) | 82 (65) | 255 (25) |
| 40 mg | 4 (1) | 4 (1) | 4 (3) | 13 (1) |

SD, standard deviation.
[a] Four patients who initiated treatment at 40 mg daily are included in the analysis of all patients but are not shown separately.
[b] Modifications include reductions, interruptions/delays, re-escalations and escalations.
[c] Dose higher than the last non-zero dose.
[d] Dose higher than initial dose.
[e] Three patients are not shown: one in the 80-mg group whose last daily dose was 20 mg, and two (one in the 120-mg group; one in the 160-mg group) whose last daily dose was 100 mg.

(13% vs 30%) and hypertension (14% vs 28%) [2]. The lower rates could be due to better adverse event management, the proportion of patients starting treatment at doses lower than 160 mg or underreporting.

The starting dose of regorafenib for almost half the patients was less than the approved 160-mg daily dose. Physicians previously described starting regorafenib at doses less than 160 mg and increasing the dose as tolerated [14,15]. A recent randomised phase II trial (ReDOS) reported that weekly dose escalation from 80 mg to 160 mg during the first cycle allowed more patients to complete two cycles of treatment and initiate a third compared with starting at the approved 160-mg dose [16]. In CORRELATE, patients starting regorafenib at 80 mg daily tended to be older, were more likely to be Asian and had a worse performance status, a lower body weight and a lower body mass index than those starting at 160 mg or 120 mg daily. The rates of dose reductions due to TEAEs and dose interruptions due to TEAEs in CORRELATE were lower than those in CORRECT, CONCUR and CONSIGN, likely due to many patients starting treatment at doses lower than 160 mg [2,7,8].

Despite the different dosing schedules reported in CORRELATE, regorafenib effectiveness was consistent with previous reports [2,7,8]. The results of ReDOS support this flexible dosing approach, showing that a dose-escalation schedule can be used in clinical practice [16]. Exploratory analyses of effectiveness in CORRELATE showed that OS and PFS were similar for patients with left- and right-sided tumours, suggesting that although tumour sidedness has been found to be

Table 3
Treatment-emergent adverse events and drug-related treatment-emergent adverse events.[a]

| | Regorafenib (N = 1037) | | | | | |
|---|---|---|---|---|---|---|
| | Treatment-emergent adverse events | | | Drug-related treatment-emergent adverse events | | |
| n (%) | All-grade | Grade III | Grade IV | All-grade | Grade III | Grade IV |
| Any event | 990 (95) | 426 (41) | 41 (4) | 830 (80) | 338 (33) | 22 (2) |
| Fatigue | 545 (53) | 106 (10) | NA | 425 (41) | 89 (9) | NA |
| HFSR | 281 (27) | 77 (7) | NA | 273 (26) | 77 (7) | NA |
| Diarrhoea | 261 (25) | 38 (4) | 2 (<1) | 196 (19) | 31 (3) | 1 (<1) |
| Anorexia | 228 (22) | 22 (2) | 0 | 137 (13) | 16 (2) | 0 |
| Mucositis oral | 185 (18) | 23 (2) | 0 | 159 (15) | 21 (2) | 0 |
| Hypertension | 174 (17) | 78 (8) | 1 (<1) | 144 (14) | 65 (6) | 1 (<1) |
| Abdominal pain | 168 (16) | 36 (3) | NA | 29 (3) | 4 (<1) | NA |
| Nausea | 130 (13) | 6 (1) | NA | 74 (7) | 3 (<1) | NA |
| Fever | 126 (12) | 2 (<1) | 0 | 26 (3) | 2 (<1) | 0 |

HFSR, hand–foot skin reaction; NA, not applicable.
National Cancer Institute Common Terminology Criteria for Adverse Events (NCI-CTCAE), version 4.03.
[a] Events listed are treatment-emergent adverse events occurring in at least 10% of patients.

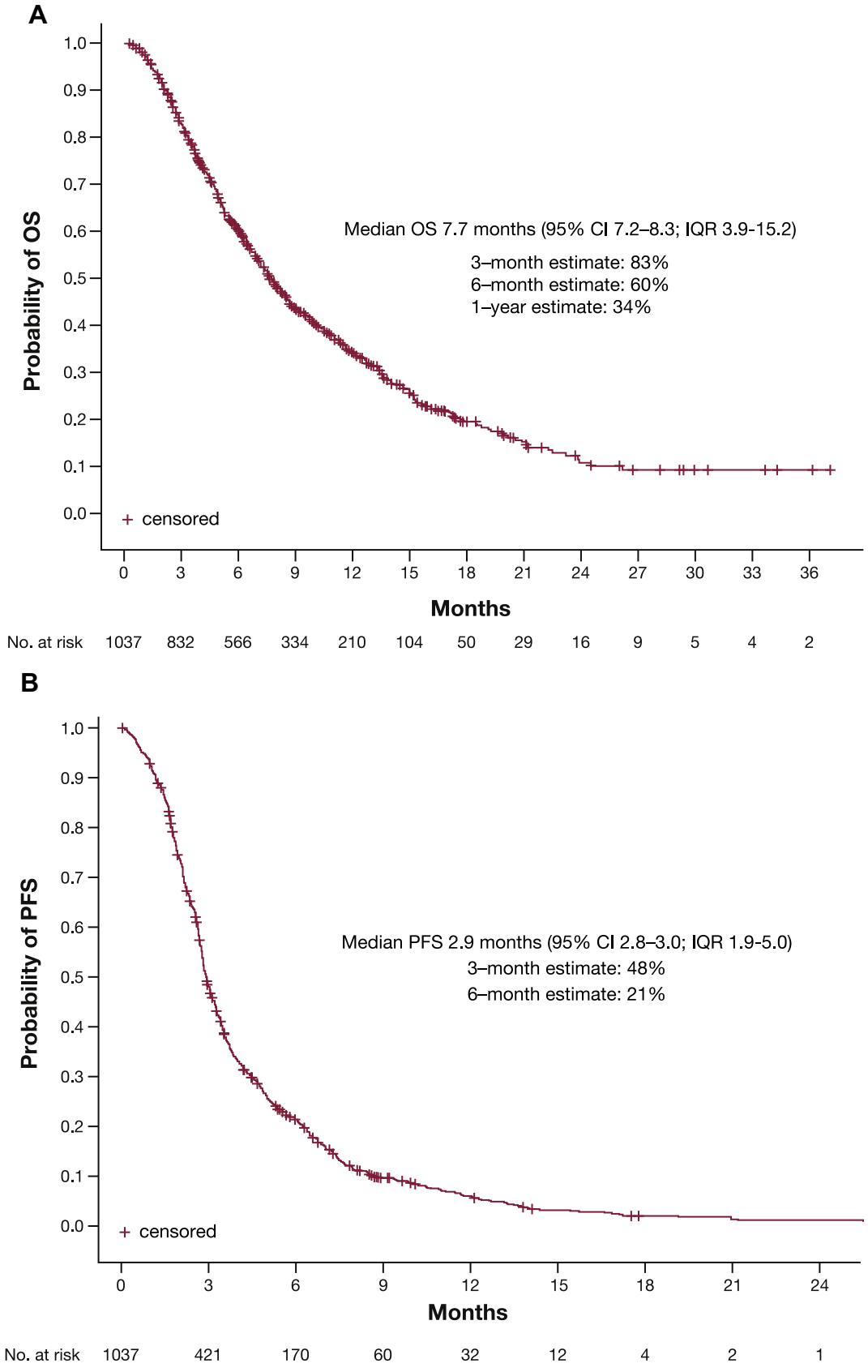


Fig. 2. Kaplan-Meier curves of overall survival (A) and progression-free survival (B). CI, confidence interval; IQR, interquartile range; PFS, progression-free survival; OS, overall survival.

prognostic, and even predictive, in the first-line setting [17,18], this effect may not be observed in later lines.

A limitation of this observational study is the lack of defined intervals for patient visits and tumour evaluations. This could have impacted the results, for example, leading to a longer documented PFS or a lower documented DCR than would have been observed with more frequent tumour evaluations, or to underreporting of adverse events. We found that many patients in CORRELATE had only one tumour assessment and that the observed DCR was lower than that reported in prior studies [2,7].

## 5. Conclusion

The safety profile of regorafenib in patients with mCRC in real-world practice settings is consistent with the safety profile demonstrated in phase III trials. Rates of some common regorafenib-related TEAEs were lower in CORRELATE than previously reported, possibly due to underreporting or proactive management of adverse events, including starting patients on doses lower than the approved 160-mg/day dose. Despite the flexible dosing observed in CORRELATE, the effectiveness of regorafenib was similar to reports from the phase III trials.

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## Conflict of interest statement

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## Appendix A Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.ejca.2019.09.015.

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