Regorafenib pharmacokinetics and its association with real-world treatment outcomes

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Abstract

Purpose Despite the established activity of regorafenib in metastatic colorectal cancer (CRC), gastrointestinal stromal tumor (GIST), and hepatocellular carcinoma (HCC), its toxicity profile has limited clinical use. We aimed to evaluate the pharmacokinetics of regorafenib and its active metabolites M-2/M-5, and to clarify the relationships between total drug-related exposure and clinical outcomes in real-world practice.

Methods Blood samples were obtained at steady state in Cycle 1 in patients treated with regorafenib. Plasma concentrations of regorafenib and its metabolites were measured by liquid chromatography–tandem mass spectrometry. The efficacy and safety endpoints were progression-free survival (PFS) and dose-limiting toxicities (DLTs), respectively. The exposure–response relationships were assessed.

Results Thirty-four Japanese patients with advanced cancers were enrolled (CRC, $n = 26$; GIST and HCC, each $n = 4$). Nine patients started regorafenib treatment at the recommended dose of 160 mg once daily (3 weeks on / 1 week off), while the other patients received a reduced starting dose to minimize toxicities. The median PFS was significantly longer in patients achieving total trough concentrations (C_{trough}) of regorafenib and M-2/M-5 ≥2.9 μg/mL than those who did not (112 vs. 57 days; $p = 0.044$). Furthermore, the cumulative incidence of DLTs during the first 2 cycles was significantly higher in patients with summed C_{trough} levels ≥4.3 μg/mL than in others ($p = 0.0003$).

Conclusions Dose titration of regorafenib to achieve drug-related C_{trough} levels in Cycle 1 between 2.9 and 4.3 μg/mL may improve the efficacy and safety, warranting further investigation in a larger patient population.

Introduction

Regorafenib is an oral multikinase inhibitor that blocks the activity of various protein kinases associated with angiogenesis (vascular endothelial growth factor [VEGF] receptors 1–3 and TIE2), oncogenesis (KIT, RET, RAF-1, and BRAF), and the tumor microenvironment (PDGFR and FGFR) [1]. The survival benefit of regorafenib has been demonstrated in metastatic colorectal cancer (CRC), gastrointestinal stromal tumor (GIST), and hepatocellular carcinoma (HCC) [2–5]. The recommended dosage is 160 mg once daily (3 weeks on / 1 week off). However, this standard dosing schedule is associated with significant adverse events, including hand–foot skin reaction (HFSR), hypertension, and fatigue, which has limited the clinical use of regorafenib. Hence, there is a need to improve its tolerability and develop an individualized dosing strategy for regorafenib.

Previous studies have suggested that a flexible, first-cycle dose-escalation approach may help some patients with metastatic CRC manage toxicity and continue treatment [6]. However, long-term efficacy as measured by progression-free survival (PFS) and overall survival (OS) did not differ significantly between the alternative starting dose group and the standard-dose group [6]. Regarding pharmacokinetics, regorafenib shows large interindividual variability in its plasma exposure, which may result in altered

clinical efficacy and/or safety [7]. It has been shown that increased average exposure to regorafenib during Cycle 1 is significantly associated with prolonged OS in patients with HCC [8]. These data suggest that the titration scheme might benefit from further refinement, including pharmacokinetically guided dosing with therapeutic drug monitoring (TDM) to optimize regorafenib exposure.

Regorafenib is metabolized primarily in the liver by cytochrome P450 (CYP) 3A4 to form two active metabolites, M-2 and M-5 [9]. Moreover, regorafenib and M-2 are biotransformed via uridine diphosphate glucuronosyltransferase (UGT) 1A9 to the inactive glucuronides M-7 and M-8, respectively [9]. Regorafenib, M-2, and M-5 are substrates of breast cancer resistance protein (ABCG2) and P-glycoprotein (ABCB1) [10,11]. However, the associations of *ABCG2* and *ABCB1* genetic variations with the pharmacokinetics of regorafenib, M-2, and M-5 have not been well established [12–14].

In this study, we aimed to (1) evaluate the clinical pharmacokinetics and pharmacogenetics of regorafenib and its metabolites, (2) clarify the relationships between total drug-related exposure and treatment outcomes in real-world practice, and (3) determine a therapeutic window for regorafenib exposure to guide dose titration.

Patients And Methods

Study design and patients

This study was conducted as a part of a single-center, prospective cohort study in routine clinical practice rather than clinical trials, which was called PRecision dOsing of moLecular-targeted agents based On therapeutic drug monitoriNG (PROLONG) (clinical study identifier, UMIN000036158). The study aimed to optimize targeted therapy with multikinase inhibitors through pharmacokinetically guided dosing with TDM in a real-world setting. The protocol was approved by the institutional ethics committee of Asahikawa Medical University (#15018). No inclusion criteria but being treated with regorafenib was applied. We prospectively enrolled all consecutive patients with metastatic CRC, GIST, and HCC who were receiving regorafenib treatment at our institution. Written informed consent was obtained from each patient. The baseline characteristics of the patients are summarized in **Table 1**.

Pharmacokinetic assessment

During hospitalization, the full pharmacokinetic profile at steady state in Cycle 1 (i.e., at least one week after repetitive administration) was assessed by obtaining serial blood samples (before regorafenib dose and at 2, 4, 8, and 24 h post-dose) at the first week of treatment, and, if possible, at the second and/or third weeks to check fluctuations in regorafenib exposure at a given dose. In outpatient settings, remnant blood specimens after laboratory tests at each visit were used for monitoring trough concentrations (C_{trough}). Plasma was separated by centrifugation (1,800 g, 10 min) and stored at –30°C until the analysis. Additionally, first-morning or spot urine samples were obtained to evaluate the urinary excretion of regorafenib and its metabolites. Plasma and urine concentrations of regorafenib and its metabolites were

measured by validated liquid chromatography–tandem mass spectrometry. Methodological details on pharmacokinetic analysis are provided in the **ESM Methods**.

Treatment

Regorafenib was administered orally after breakfast at a starting dose of 160 mg once daily (3 weeks on / 1 week off). In patients with poor liver function or co-morbidities and those with poor Eastern Cooperative Oncology Group performance status, the initial dose was reduced at the discretion of each treating physician. If regorafenib was well tolerated with a reduced starting dose, the dosage was titrated stepwise up to 160 mg/day. The treatment was continued until disease progression or patient refusal. When unacceptable toxicities were present, the dose was reduced or interrupted temporarily, followed by resumption at a reduced dose. Regorafenib treatment was discontinued at the discretion of the treating physicians in cases of severe adverse events.

Based on historical data of regorafenib pharmacokinetics after multiple doses of 160 mg once daily (area under the concentration–time curve from 0 to 24 h [AUC_{0-24}] 33,042.8 μg*h/L) [15], the average concentration within a 24-h dosing interval (C_{av}) was estimated to be approximately 1.4 μg/mL. Thus, we utilized regorafenib concentrations higher than this threshold as provisional target concentrations in the present study. Patients' pharmacokinetic profiles at steady state and individual C_{trough} measurements at outpatient visits were provided to physicians (i.e., to indicate whether or not the provisional target was reached) to support the clinical decision regarding the need for dose escalation at the next visit. Finally, physicians decided on regorafenib dose adjustments based on patients' pharmacokinetic assessments in addition to individual tolerability and clinical and laboratory findings.

Genotyping

Genomic DNA was extracted from the peripheral blood of patients using NucleoSpin Blood QuickPure (Takara Bio, Kusatsu, Japan). Based on previous findings regarding pharmacogenetic determinants associated with metabolism and disposition of regorafenib and its analogue sorafenib, we examined the *CYP3A4*22*, *CYP3A5*3*, *UGT1A9*3*, and *ABCG2* 421C>A polymorphisms [12-14,16,17]. Genotyping was performed using TaqMan SNP genotyping assays (Thermo Fisher Scientific, Tokyo, Japan).

Outcomes

Efficacy endpoints were PFS and best overall response per Response Evaluation Criteria in Solid Tumors (RECIST) 1.1. For safety assessment, all adverse events were graded according to the Common Terminology Criteria for Adverse Events (CTCAE) version 4.03. The cumulative incidence of dose-limiting toxicities (DLTs), including grade 3/4 adverse events leading to treatment discontinuation and grade 2 HFSR requiring dose interruption, was estimated by adjusting for competing risks (e.g., death or treatment discontinuation due to disease progression) with the Fine and Gray model [18].

Statistical analysis

The statistical significance of differences in non-parametric values between 2 groups was analyzed with the Mann–Whitney *U* test. A receiver operating characteristic (ROC) curve was constructed to calculate an area under the ROC curve (AUC_{ROC}) and estimate an optimal cutoff value of total drug-related exposure for predicting development of grade ³2 HFSR. The median PFS was estimated using the Kaplan–Meier method, and the difference between groups was examined using the log-rank test. A 2-sided $p < 0.05$ was considered statistically significant. All statistical analyses were performed using STATA software, version 16 (StataCorp LLC, Texas, USA).

Results

Patients and treatment duration

Between October 2013 and February 2020, 34 Japanese patients with advanced cancers were enrolled (CRC, *n* = 26; GIST and HCC, each *n* = 4) (**Table 1**). Regorafenib treatment was discontinued because of disease progression (*n* = 26), adverse events (*n* = 6), or patient refusal (*n* = 1). Adverse events leading to discontinuation included fatigue (*n* = 2), HFSR, fistula, hyperbilirubinemia, and pruritus (each *n* = 1). As of the data cutoff date (March 31, 2020), regorafenib therapy was still ongoing in one patient. The median (range) follow-up period was 140 (22–713) days. No pharmacokinetic or pharmacogenetic data were obtained in 8 patients; however, these patients were included in efficacy and safety analyses.

Nine patients started regorafenib treatment at the recommended dose of 160 mg once daily, while 20 patients received a lower starting dose (80 mg, *n* = 18; 120 mg, *n* = 2); the lowest starting dose of 40 mg was used in 5 patients to minimize toxicities. The median (range) duration of treatment was 83 (8–520) days in all patients (**Fig. 1a**). Patients starting at 80 mg tended to continue regorafenib therapy for a longer period than those in the other starting dose groups. In approximately 60% of patients in each starting dose group, the last dose was the same as the initial dose (**Fig. 1b**); the exception was the 120-mg dose group, in which both patients maintained the original dose. Among patients starting at 40 mg, dose escalation only reached 80 mg. Among those who initially received 80 mg, the dose was finally increased to 120 mg and 160 mg in 22% and 6% of patients, respectively.

Pharmacokinetic profile

Plasma levels of M-8 were negligible. Full pharmacokinetic profiles and parameters of regorafenib and its metabolites at steady state in Cycle 1 are shown in **Fig. 2a** and summarized in **Table 2**, respectively. These results were generally comparable with those in previous reports [15]. The sum of the areas under the concentration–time curves (AUCs) of regorafenib and M-2/M-5 within a 24-h dosing interval, which reflects the total pharmacological activity of regorafenib and its two active metabolites, was not correlated with C_{trough} level of regorafenib alone but significantly correlated with the sum of their corresponding C_{trough} levels ($r^2 = 0.90$; $p < 0.0001$) (**ESM Fig. S1**). Accordingly, we used the sum of the C_{trough} levels as a surrogate therapeutic marker for subsequent analyses including exposure–response relationships. Throughout the course of treatment, there was large variability in plasma exposures to regorafenib as well

as its metabolites (total no. of observations, 204 each), with a median value of 1,511 ng/mL for regorafenib (**Fig. 2b**), which was above the provisional target of 1.4 μg/mL.

No *CYP3A4*22* or *UGT1A9*3* alleles were found in our patients. Genetic polymorphisms of *CYP3A5*3* (**1/*1* and **1/*3* [*n* = 15] vs. **3/*3* [*n* = 11]) and *ABCG2* 421C>A (C/C [*n* = 19] vs. C/A and A/A [*n* = 7]) did not influence the sum of the dose-adjusted C_{trough} levels of regorafenib and M-2/M-5 at steady state in Cycle 1 (**ESM Fig. S2**). When patients were categorized into 2 groups according to the median value of the M-7/regorafenib metabolic ratio (i.e., 0.52), it was evident that the sum of the dose-adjusted C_{trough} levels was significantly lower in the high-ratio group than in the low-ratio group (median 21.2 ng/mL/mg [*n* = 13] vs. 42.2 ng/mL/mg [*n* = 13]; *p* = 0.012).

In urine, regorafenib and M-2/M-5 were hardly detectable, as shown in **ESM Fig. S3**, whereas M-7 and M-8 were detected in significant amounts (M-7 > M-8; total no. of observations, 31 each) (**Fig. 2c**). Furthermore, M-5 was also detected after treatment with b-glucuronidase, suggesting the presence of a previously unidentified glucuronide metabolite of M-5 in urine.

Dose/exposure–response

Overall, only one patient with CRC who started regorafenib treatment at 120 mg/day achieved a partial response (3%; 4% in CRC), whereas 6 had stable disease (18%), 26 had progressive disease (76%), and one was not evaluated for tumor response. As shown in **Figure 3a**, the median PFS was numerically shorter in the lowest-dose group compared with the other starting dose groups, although the difference was not statistically significant (log-rank *p* = 0.62). When patients were divided into 2 groups according to the median value of the sum of the C_{trough} levels of regorafenib and M-2/M-5 at steady state in Cycle 1, patients with higher exposure (³2.9 μg/mL) demonstrated significantly longer PFS than those with a level <2.9 μg/mL (112 vs. 57 days; log-rank *p* = 0.044) (**Fig. 3b**).

The most frequently observed adverse event of any grade was HFSR (68%) (**ESM Fig. S4**). No grade 5 toxicity was reported in this study. The most common grade 3/4 adverse events were elevated gamma-glutamyltransferase levels (12%), followed by HFSR, hypertension, and anorexia (9% each), proteinuria, fatigue, and elevated total bilirubin levels (6% each), and decreased platelet counts and elevated alanine aminotransferase levels (3% each). As shown in **Figure 4**, the sum of the C_{trough} levels among patients who experienced grade 2/3 HFSR was significantly higher than that in patients with grade 0/1 HFSR (median 5.2 vs. 2.2 μg/mL; *p* = 0.021). Furthermore, the optimal cutoff value for the sum of the C_{trough} levels to predict development of grade ³2 HFSR was 4.3 μg/mL, with an AUC_{ROC} of 0.78 (95% confidence interval [CI] 0.57–0.98).

Starting regorafenib treatment at a reduced dose was associated with a lower cumulative incidence of DLTs during the first 2 cycles, although the difference was not statistically significant (*p* = 0.87) (**Fig. 5a**). Notably, the cumulative incidence of DLTs was significantly higher in patients in whom the sum of the C_{trough} levels was greater than or equal to the aforementioned cutoff of 4.3 μg/mL, as compared with others (sub-hazard ratio 8.84; 95% CI 2.71–28.8; *p* = 0.0003) (**Fig. 5b**).

Discussion

In this real-world study that included all patients who were consecutively treated with regorafenib at our institution, the safety profile was generally consistent with that reported in phase 3 trials, except for proteinuria, which was more common in the current study [2–5]. Overall, in approximately 60% of patients, the initial dose was the same as the dose in the last cycle of treatment or at last follow-up, a finding comparable to that of a previous study under routine clinical practice (CORRELATE) [19]. Although the present study was limited by a small sample size, lack of randomization, and patient heterogeneity (i.e., tumor types and prior systemic therapies), we observed clear relationships of efficacy and safety with early exposure to regorafenib and its active metabolites M-2 and M-5, but not with the starting dose itself (**Figs. 3** and **5**).

To our best knowledge, this study provides the first evidence regarding a potential therapeutic window of regorafenib exposure, which might range from 2.9 to 4.3 μg/mL in terms of the sum of the C_{trough} levels at steady state in Cycle 1. Recently, Keunecke et al. reported a population pharmacokinetic model for regorafenib and M-2/M-5, incorporating enterohepatic circulation [20]. The model-informed precision dosing with Bayesian estimation to optimize regorafenib therapy could be used to rapidly achieve the target therapeutic exposure in individual patients. Further investigation is warranted to determine the benefit of this approach in routine clinical practice.

This study identified no genetic determinants of interindividual variability regarding total exposure to regorafenib and M-2/M-5, a result that is comparable with the findings of previous studies [12,13]. Recently, we demonstrated that poor absorption of axitinib, a multikinase inhibitor used to treat patients with metastatic renal cell carcinoma, was linked to higher glucuronidation of the drug, primarily by UGT1A1 in the liver [21]. The present study revealed that like axitinib, greater glucuronidation activity of UGT1A9 toward regorafenib (i.e., higher M-7/regorafenib metabolic ratio) was associated with decrease in the sum of the dose-adjusted C_{trough} levels of regorafenib and M-2/M-5, probably due to a reduction in the relative contribution of CYP3A4-mediated regorafenib metabolism into M-2 (**ESM Fig. S2c**). Therefore, rapid dose titration should be considered in patients with increased glucuronidation activity toward regorafenib to prevent subtherapeutic exposure to regorafenib and M-2/M-5.

Interestingly, M-8 was not detectable in plasma but was observed in urine (**Fig. 2**). Furthermore, M-7 was more abundant in urine than in plasma. These findings suggest that renal UGT1A9 plays an important role in the glucuronidation of regorafenib, M-2, and possibly M-5, thus facilitating the urinary excretion of their metabolites [22]. Further investigation is necessary to clarify whether the interindividual variability in urinary concentrations of M-7 and M-8 is associated with the clinical outcomes of regorafenib.

In a randomized, open-label, phase 2 study in patients with refractory metastatic CRC (ReDOS), a weekly dose-escalation strategy starting from 80 mg to 160 mg based on individual tolerability has been demonstrated as an alternative approach for optimizing regorafenib dosing, allowing more patients to initiate Cycle 3 [23]. Although this dose titration schedule is not included in the labeling, the National Comprehensive Cancer Network Colon Cancer Guidelines recently included it as an option to treat patients

with metastatic CRC. Furthermore, a similar randomized phase 2 trial (REARRANGE) showed that flexible initial dosing (i.e., 120 mg/day 3 weeks on / 1 week off [reduced dose] or 160 mg/day 1 week on / 1 week off [intermittent dose] in Cycle 1) alleviated toxicities without compromising efficacy [24]. Despite the improved outcomes of regorafenib with these modified dosing approaches, there was no long-term survival benefit [23,24]. In outpatient settings, even if TDM is applied, initiating regorafenib at the standard dose might lead to early termination due to intolerable toxicity before dose is modified based on drug overexposure detected at next clinical visit. Taking our findings on regorafenib dose/exposure–response relationships into consideration, a dose titration strategy starting from a reduced dose (e.g., 80 mg or 120 mg) might be beneficial to prevent severe toxicities in certain patients, such as those with poor performance status, and patients may be able to continue regorafenib treatment while maintaining disease control. In particular, the “start low and go slow” approach integrating pharmacokinetically guided dosing may define a safer, individualized regorafenib regimen for each patient and thus prolong survival. In future clinical studies, toxicity-based, pharmacokinetically guided dose titration of regorafenib should be validated for monotherapy as well as for combination treatment with immunotherapy such as nivolumab (REGONIVO) [25]. This should be done in selected groups of patients with various types of cancer to develop a more refined dosing approach for regorafenib.

Conclusions

The present study suggests that the potential therapeutic window for the sum of the C_{trough} levels of regorafenib and M-2/M-5 at steady state in Cycle 1 is between 2.9 and 4.3 μg/mL. In addition to individual tolerability, TDM of regorafenib that evaluates total drug-related exposure will help guide dose titration and improve treatment outcomes in routine clinical practice. Larger, randomized studies are warranted to confirm this approach.

Declarations

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Conflicts of interest: None to declare.

Ethics approval and consent to participate: The protocol of this study was approved by the institutional ethics committee of Asahikawa Medical University (#15018). The study was performed in accordance with the Declaration of Helsinki and its amendments. All patients provided written informed consent to participate in the study.

Consent for publication: All authors approved the final version of the manuscript.

Availability of data and material: The data supporting the findings of this study are available on request from the corresponding author. The data are not publicly available because of privacy or ethical restrictions.

Author contributions: Study concept and design: M.F.; acquisition, analysis, or interpretation of data: all authors; drafting of the manuscript: M.F.; critical revision of the manuscript for important intellectual content: all authors; statistical analysis: M.F.; obtained funding: M.F.; administrative, technical, or material support: K.A., C.T., M.M., K.A., and N.U; supervision: M.F.

Compliance with Ethical Standards

Disclosure of potential conflicts of interest: All authors have no conflicts of interest to declare.

Research involving human participants: The protocol of this study was approved by the institutional ethics committee of Asahikawa Medical University (#15018). The study was performed in accordance with the Declaration of Helsinki and its amendments.

Informed consent: Written informed consent was obtained from each patient prior to enrollment.

References

1. Wilhelm SM, Dumas J, Adnane L, Lynch M, Carter CA, Schütz G, Thierauch KH, Zopf D (2011) 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 129:245–255
2. Grothey A, Van Cutsem E, Sobrero A, Siena S, Falcone A, Ychou M, Humblet Y, Bouché O, Mineur L, Barone C, Adenis A, Tabernero J, Yoshino T, Lenz HJ, Goldberg RM, Sargent DJ, Cihon F, Cupit L, Wagner A, Laurent D; CORRECT Study Group (2013) Regorafenib monotherapy for previously treated metastatic colorectal cancer (CORRECT): an international, multicentre, randomised, placebo-controlled, phase 3 trial. Lancet 381:303–312
3. Li J, Qin S, Xu R, Yau TC, Ma B, Pan H, Xu J, Bai Y, Chi Y, Wang L, Yeh KH, Bi F, Cheng Y, Le AT, Lin JK, Liu T, Ma D, Kappeler C, Kalmus J, Kim TW; CONCUR Investigators (2015) 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. Lancet Oncol 16:619–629
4. Demetri GD, Reichardt P, Kang YK, Blay JY, Rutkowski P, Gelderblom H, Hohenberger P, Leahy M, von Mehren M, Joensuu H, Badalamenti G, Blackstein M, Le Cesne A, Schöffski P, Maki RG, Bauer S, Nguyen BB, Xu J, Nishida T, Chung J, Kappeler C, Kuss I, Laurent D, Casali PG; GRID study investigators (2013) 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 381:295–302
5. Bruix J, Qin S, Merle P, Granito A, Huang YH, Bodoky G, Pracht M, Yokosuka O, Rosmorduc O, Breder V, Gerolami R, Masi G, Ross PJ, Song T, Bronowicki JP, Ollivier-Hourmand I, Kudo M, Cheng AL, Llovet JM, Finn RS, LeBerre MA, Baumhauer A, Meinhardt G, Han G; RESORCE Investigators (2017) Regorafenib for patients with hepatocellular carcinoma who progressed on sorafenib treatment (RESORCE): a randomised, double-blind, placebo-controlled, phase 3 trial. Lancet 389:56–66

6. Grothey A, Blay JY, Pavlakis N, Yoshino T, Bruix J (2020) Evolving role of regorafenib for the treatment of advanced cancers. Cancer Treat Rev 86:101993
7. Yoshino T, Komatsu Y, Yamada Y, Yamazaki K, Tsuji A, Ura T, Grothey A, Van Cutsem E, Wagner A, Cihon F, Hamada Y, Ohtsu A (2015) Randomized phase III trial of regorafenib in metastatic colorectal cancer: analysis of the CORRECT Japanese and non-Japanese subpopulations. Invest New Drugs 33:740–750
8. Solms A, Reinecke I, Fiala-Buskies S, Keunecke A, Drenth HJ, Bruix J, Meinhardt G, Cleton A, Ploeger B (2017) Exposure-response relationship of regorafenib efficacy in patients with hepatocellular carcinoma. Eur J Pharm Sci 109S:S149–S153
9. Gerisch M, Hafner FT, Lang D, Radtke M, Diefenbach K, Cleton A, Lettieri J (2018) Mass balance, metabolic disposition, and pharmacokinetics of a single oral dose of regorafenib in healthy human subjects. Cancer Chemother Pharmacol 81:195–206
10. Kort A, Durmus S, Sparidans RW, Wagenaar E, Beijnen JH, Schinkel AH (2015) Brain and testis accumulation of regorafenib is restricted by breast cancer resistance protein (BCRP/ABCG2) and P-glycoprotein (P-GP/ABCB1). Pharm Res 32:2205–2216
11. Fujita KI, Masuo Y, Yamazaki E, Shibutani T, Kubota Y, Nakamichi N, Sasaki Y, Kato Y (2017) Involvement of the transporters P-glycoprotein and breast cancer resistance protein in dermal distribution of the multikinase inhibitor regorafenib and its active metabolites. J Pharm Sci 106:2632–2641
12. Maeda A, Irie K, Ando H, Hasegawa A, Taniguchi H, Kadowaki S, Muro K, Tajika M, Aoki M, Inaguma K, Kajita M, Fujimura A, Fukushima S (2019) Associations among regorafenib concentrations, severe adverse reactions, and ABCG2 and OATP1B1 polymorphisms. Cancer Chemother Pharmacol 83:107–113
13. Taguchi D, Inoue M, Fukuda K, Yoshida T, Shimazu K, Fujita K, Okuyama H, Matsuhashi N, Tsuji A, Yoshida K, Miura M, Shibata H (2020) Therapeutic drug monitoring of regorafenib and its metabolite M5 can predict treatment efficacy and the occurrence of skin toxicities. Int J Clin Oncol 25:531–540
14. Kubota Y, Fujita KI, Takahashi T, Sunakawa Y, Ishida H, Hamada K, Ichikawa W, Tsunoda T, Shimada K, Masuo Y, Kato Y, Sasaki Y (2020) Higher systemic exposure to unbound active metabolites of regorafenib is associated with short progression-free survival in colorectal cancer patients. Clin Pharmacol Ther 108:586–595
15. Sunakawa Y, Furuse J, Okusaka T, Ikeda M, Nagashima F, Ueno H, Mitsunaga S, Hashizume K, Ito Y, Sasaki Y (2014) Regorafenib in Japanese patients with solid tumors: phase I study of safety, efficacy, and pharmacokinetics. Invest New Drugs 32:104–112
16. Jain L, Woo S, Gardner ER, Dahut WL, Kohn EC, Kummar S, Mould DR, Giaccone G, Yarchoan R, Venitz J, Figg WD (2011) Population pharmacokinetic analysis of sorafenib in patients with solid tumours. Br J Clin Pharmacol 72:294–305
17. Boudou-Rouquette P, Narjoz C, Golmard JL, Thomas-Schoemann A, Mir O, Taieb F, Durand JP, Coriat R, Dauphin A, Vidal M, Tod M, Loriot MA, Goldwasser F, Blanchet B (2012) Early sorafenib-induced toxicity

is associated with drug exposure and UGTIA9 genetic polymorphism in patients with solid tumors: a preliminary study. PLoS One 7:e42875

18. Fine JP, Gray RJ (1999) A proportional hazards model for the subdistribution of a competing risk. J Am Stat Assoc 94:496–509
19. Ducreux M, Petersen LN, Öhler L, Bergamo F, Metges JP, de Groot JW, Wang JY, García Paredes B, Dochy E, Fiala-Buskies S, Cervantes A, O'Connor JM, Falcone A; CORRELATE Investigators (2019) Safety and effectiveness of regorafenib in patients with metastatic colorectal cancer in routine clinical practice in the prospective, observational CORRELATE study. Eur J Cancer 123:146–154
20. Keunecke A, Hoefman S, Drenth HJ, Zisowsky J, Cleton A, Ploeger BA (2020) Population pharmacokinetics of regorafenib in solid tumours: exposure in clinical practice considering enterohepatic circulation and food intake. Br J Clin Pharmacol 86:2362–2376
21. Fukudo M, Tamaki G, Azumi M, Kakizaki H, Matsumoto S, Tasaki Y (2020) Absorption of the orally active multikinase inhibitor axitinib as a therapeutic index to guide dose titration in metastatic renal cell carcinoma. Invest New Drugs https://doi.org/10.1007/s10637-020-01023-z
22. Margaillan G, Rouleau M, Fallon JK, Caron P, Villeneuve L, Turcotte V, Smith PC, Joy MS, Guillemette C (2015) Quantitative profiling of human renal UDP-glucuronosyltransferases and glucuronidation activity: a comparison of normal and tumoral kidney tissues. Drug Metab Dispos 43:611–619
23. Bekaii-Saab TS, Ou FS, Ahn DH, Boland PM, Ciombor KK, Heying EN, Dockter TJ, Jacobs NL, Pasche BC, Cleary JM, Meyers JP, Desnoyers RJ, McCune JS, Pedersen K, Barzi A, Chiorean EG, Sloan J, Lacouture ME, Lenz HJ, Grothey A (2019) Regorafenib dose-optimisation in patients with refractory metastatic colorectal cancer (ReDOS): a randomised, multicentre, open-label, phase 2 study. Lancet Oncol 20:1070–1082
24. Argiles G, Margalef NM, Valladares-Ayerbes M, de Prado JV, Grávalos C, Alfonso PG, Santos C, Tobeña M, Sastre J, Benavides M, Cano T, Loupakis F, Garrote MR, Rivera F, Goldberg R, Falcone A, Bennouna J, Ciardiello F, Tabernero J, Aranda E (2019) Results of REARRANGE trial: a randomized phase 2 study comparing different dosing approaches for regorafenib (REG) during the first cycle of treatment in patients (pts) with metastatic colorectal cancer (mCRC). Ann Oncol 30:Abstract O-026
25. Fukuoka S, Hara H, Takahashi N, Kojima T, Kawazoe A, Asayama M, Yoshii T, Kotani D, Tamura H, Mikamoto Y, Hirano N, Wakabayashi M, Nomura S, Sato A, Kuwata T, Togashi Y, Nishikawa H, Shitara K (2020) Regorafenib plus nivolumab in patients with advanced gastric or colorectal cancer: an open-label, dose-escalation, and dose-expansion phase Ib trial (REGONIVO, EPOC1603). J Clin Oncol 38:2053–2061

Tables

Table 1 Baseline characteristics of the patients by starting dose

Characteristic	Lowest-dose group (n = 5)	Lower-dose group (n = 20)	Standard-dose group (n = 9)	Total (N = 34)
Age, median (range), years	64 (34–69)	65 (44–82)	56 (49–74)	63 (34–82)
Sex, male/female, n (%)	3/2 (60/40)	15/5 (75/25)	5/4 (56/44)	23/11 (68/32)
Body weight, median (range), kg	43 (36–78)	60 (38–79)	65 (42–72)	60 (36–79)
ECOG performance status, n (%)				
0/1	3 (60)	19 (95)	9 (100)	31 (91)
2	2 (40)	1 (5)	0	3 (9)
Tumor type, n (%)				
CRC	2 (40)	16 (80)	8 (89)	26 (76)
GIST	1 (20)	2 (10)	1 (11)	4 (12)
HCC	2 (40)	2 (10)	0	4 (12)
Previous lines of systemic therapy, n (%)				
2/≥3 in CRC	1/1 (50/50)	5/11 (31/69)	1/7 (13/88)	7/19 (27/73)
2/≥3 in GIST	1/0 (100/0)	1/1 (50/50)	0/1 (0/100)	2/2 (50/50)
1/≥2 in HCC	2/0 (100/0)	2/0 (100/0)	—	4/0 (100/0)
Number of metastatic sites, n (%)				
1	2 (40)	3 (15)	2 (22)	7 (21)
2	2 (40)	9 (45)	3 (33)	14 (41)
≥3	1 (20)	8 (40)	4 (44)	13 (38)
Sites of metastases, n (%)				
Liver	2 (40)	14 (70)	8 (89)	24 (71)
Lung	2 (40)	13 (65)	8 (89)	23 (68)
Peritoneum	1 (20)	7 (35)	2 (22)	10 (29)
Bone	3 (60)	3 (15)	2 (22)	8 (24)
Lymph nodes	2 (40)	5 (25)	0	7 (21)
Brain	0	1 (5)	0	1 (3)
Other	0	5 (25)	1 (11)	6 (18)
Starting dose, n (%)				
160 mg/day	0	0	9 (100)	9 (26)
120 mg/day	0	2 (10)	0	2 (6)
80 mg/day	0	18 (90)	0	18 (53)
40 mg/day	5 (100)	0	0	5 (15)

CRC colorectal cancer, *ECOG* Eastern Cooperative Oncology Group, *GIST* gastrointestinal stromal tumor, *HCC* hepatocellular carcinoma

Table 2 Plasma pharmacokinetics of regorafenib and its metabolites at steady state in Cycle 1[a]

Parameter[b]	40 mg (n = 5)	80 mg (n = 10)	120 mg (n = 3)	160 mg (n = 8)
Regorafenib				
$AUC_{0\text{-}24}$, µg*h/mL	28.6 (76.7)	41.1 (72.0)	40.2 (31.7)	53.6 (68.5)
C_{max}, ng/mL	1,599 (78.6)	2,278 (78.0)	2,313 (45.1)	3,030 (57.2)
C_{trough}, ng/mL	1,136 (84.9)	1,869 (82.6)	1,382 (64.6)	2,452 (74.1)
C_{av}, ng/mL	1,191 (76.7)	1,711 (72.0)	1,674 (31.7)	2,233 (68.5)
T_{max}, h	4 (2–8)	8 (0–24)	8 (0–8)	4 (0–24)
CL/F, L/h	1.40 (76.7)	1.95 (72.0)	2.99 (31.7)	2.99 (68.5)
M-2				
$AUC_{0\text{-}24}$, µg*h/mL	5.56 (102)	12.4 (116)	8.32 (15.8)	22.5 (114)
C_{max}, ng/mL	283 (109)	701 (115)	525 (48.6)	1,319 (93.2)
C_{trough}, ng/mL	243 (104)	594 (125)	302 (60.9)	1,154 (119)
C_{av}, ng/mL	232 (102)	515 (116)	347 (15.8)	938 (114)
T_{max}, h	8 (4–24)	4 (0–24)	8 (0–8)	24 (0–24)
M-5				
$AUC_{0\text{-}24}$, µg*h/mL	1.54 (287)	3.53 (249)	3.38 (114)	14.8 (231)
C_{max}, ng/mL	87 (290)	223 (261)	174 (141)	911 (199)
C_{trough}, ng/mL	81 (288)	196 (240)	133 (166)	827 (233)
C_{av}, ng/mL	64 (287)	147 (249)	141 (114)	615 (231)
T_{max}, h	8 (0–24)	3 (0–24)	4 (0–8)	24 (0–24)
M-7				
$AUC_{0\text{-}24}$, µg*h/mL	28.8 (171)	20.7 (74.7)	32.2 (130)	11.5 (121)
C_{max}, ng/mL	1,468 (170)	1,016 (79.9)	1,797 (104)	611 (113)
C_{trough}, ng/mL	1,149 (181)	819 (59.7)	1,233 (92.1)	435 (139)
C_{av}, ng/mL	1,199 (171)	862 (74.7)	1,343 (130)	478 (121)
T_{max}, h	4 (2–24)	4 (0–24)	0 (0–8)	4 (0–24)

$AUC_{0\text{–}24}$ area under the concentration–time curve from 0 to 24 h, *C_{av}* average concentration within a 24-h dosing interval (= $AUC_{0\text{-}24}$/24), *CL/F* apparent oral clearance, *C_{max}* maximum concentration, *C_{trough}* trough concentration, *T_{max}* time to C_{max}

[a] Serial blood samples were obtained at the following time points: Week 1 (n = 5) for 40 mg Weeks 1, 2, and 3 (n = 5, 3, and 2, respectively) for 80 mg; Weeks 1 and 3 (n = 1 and 2 respectively) for 120 mg; and Weeks 1 and 2 (n = 5 and 3, respectively) for 160 mg

[b] Data are expressed as geometric mean (geometric CV%) or median (range)

Figures

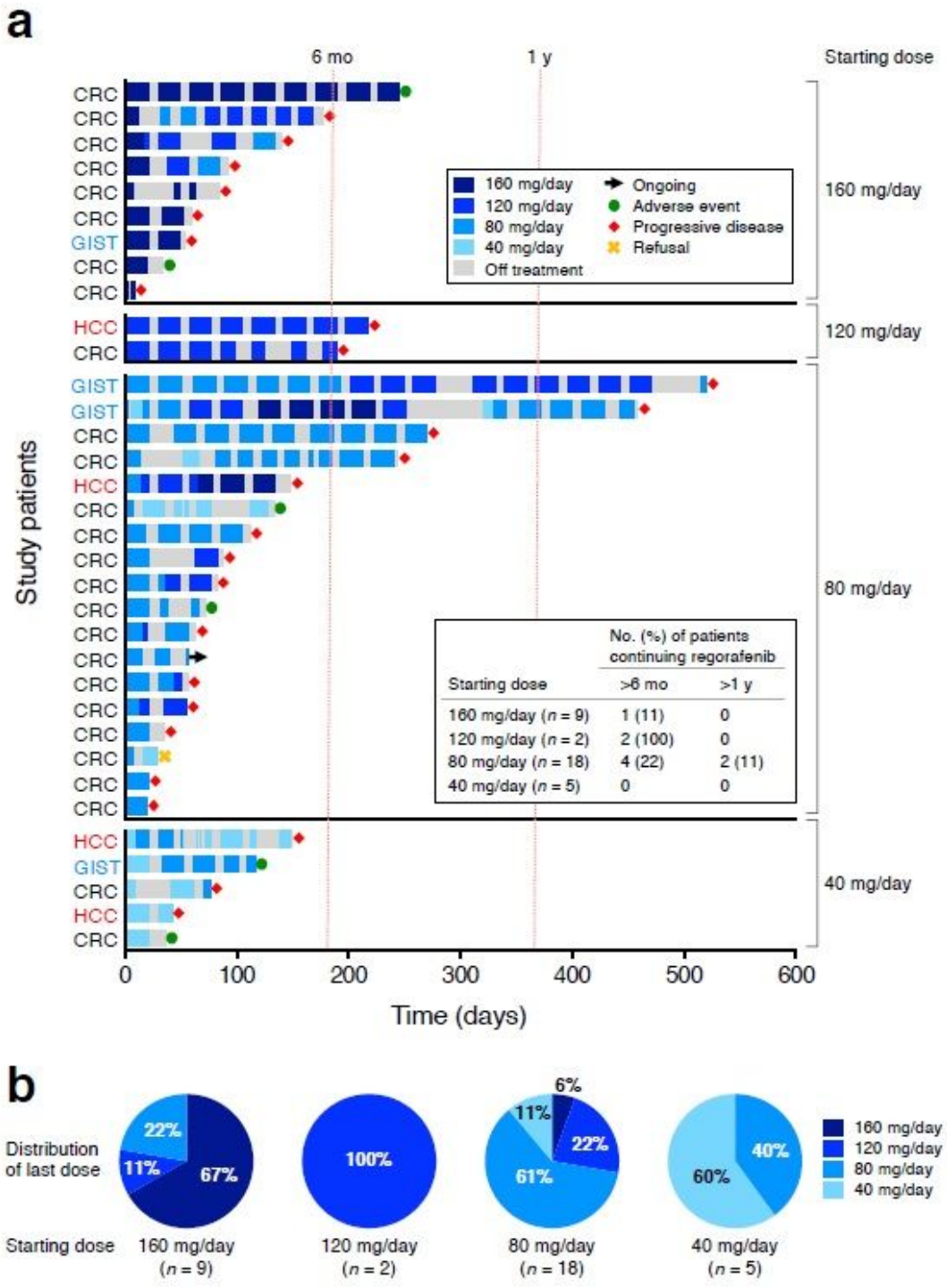

Figure 1

a Duration of regorafenib treatment and b distribution of final regorafenib dose according to starting dose

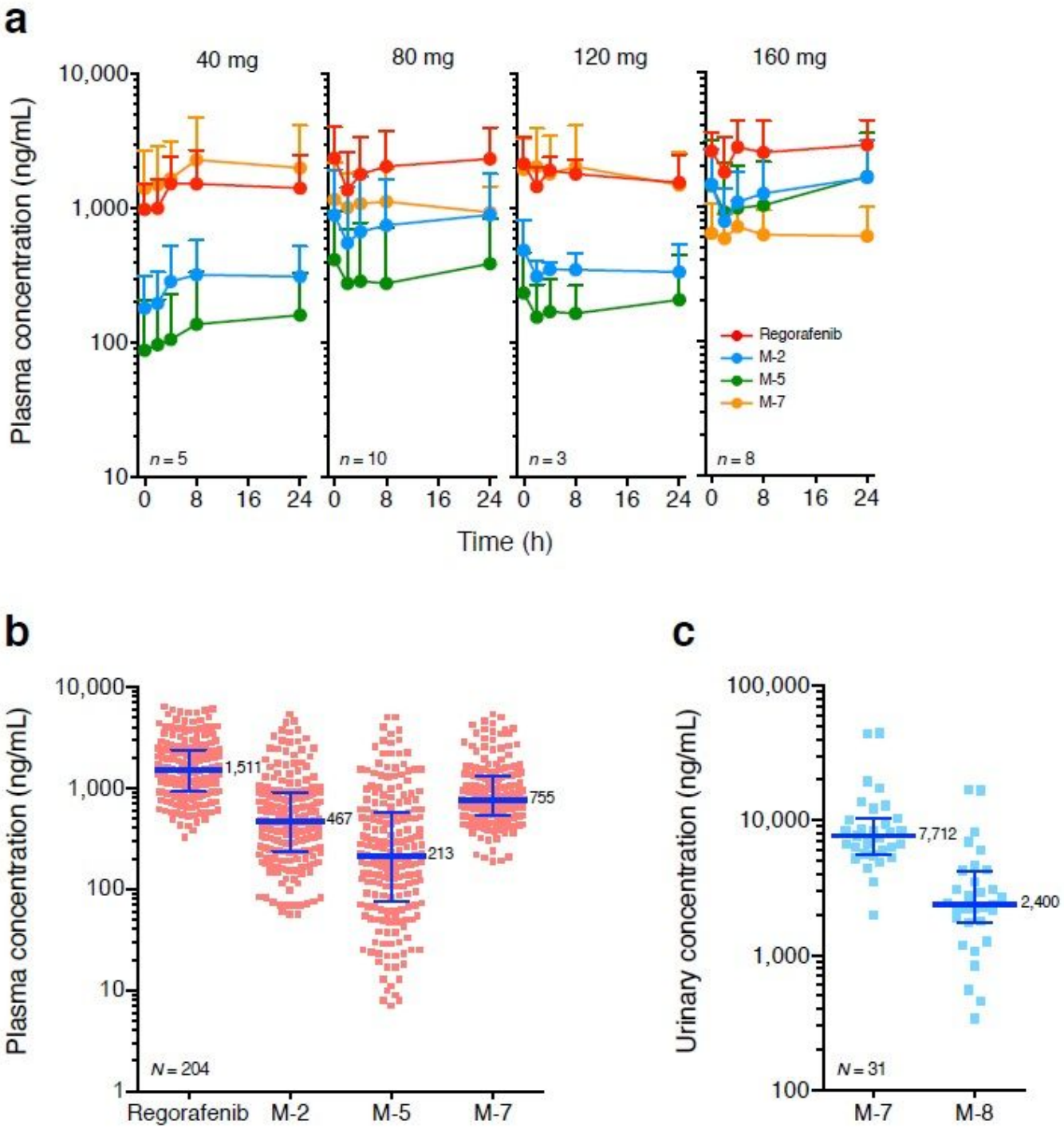

Figure 2

a Time course of mean plasma concentrations of regorafenib and its metabolites M-2/M-5/M-7 at steady state in Cycle 1 in patients receiving 40–160 mg/day. Error bars represent standard deviation. b Distribution of plasma concentrations of regorafenib and its metabolites M-2/M-5/M-7 throughout the course of treatment. Data are presented with the median and interquartile range and include individual data points (N = 204). c Distribution of urinary concentrations of M-7 and M-8 in 11 patients from whom urine samples

were available. Data are presented with the median and interquartile range and include individual data points (N = 31)

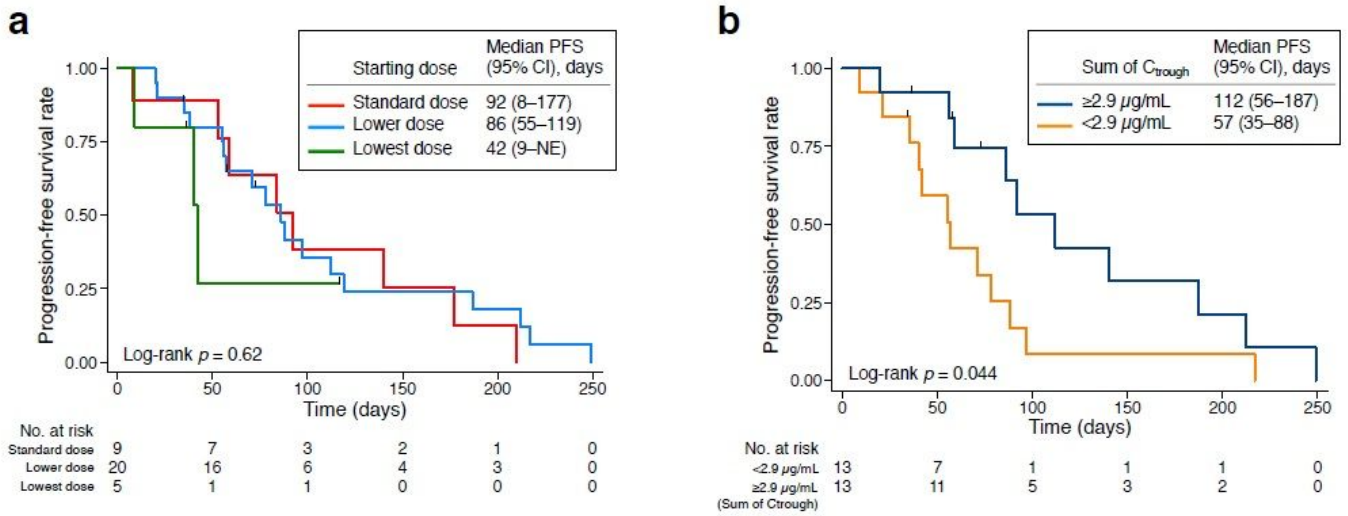

Figure 3

Progression-free survival (PFS) rates according to a starting dose and b sum of the trough concentrations (Ctrough) of regorafenib and M-2/M-5 at steady state in Cycle 1. CI confidence interval, NE not estimable

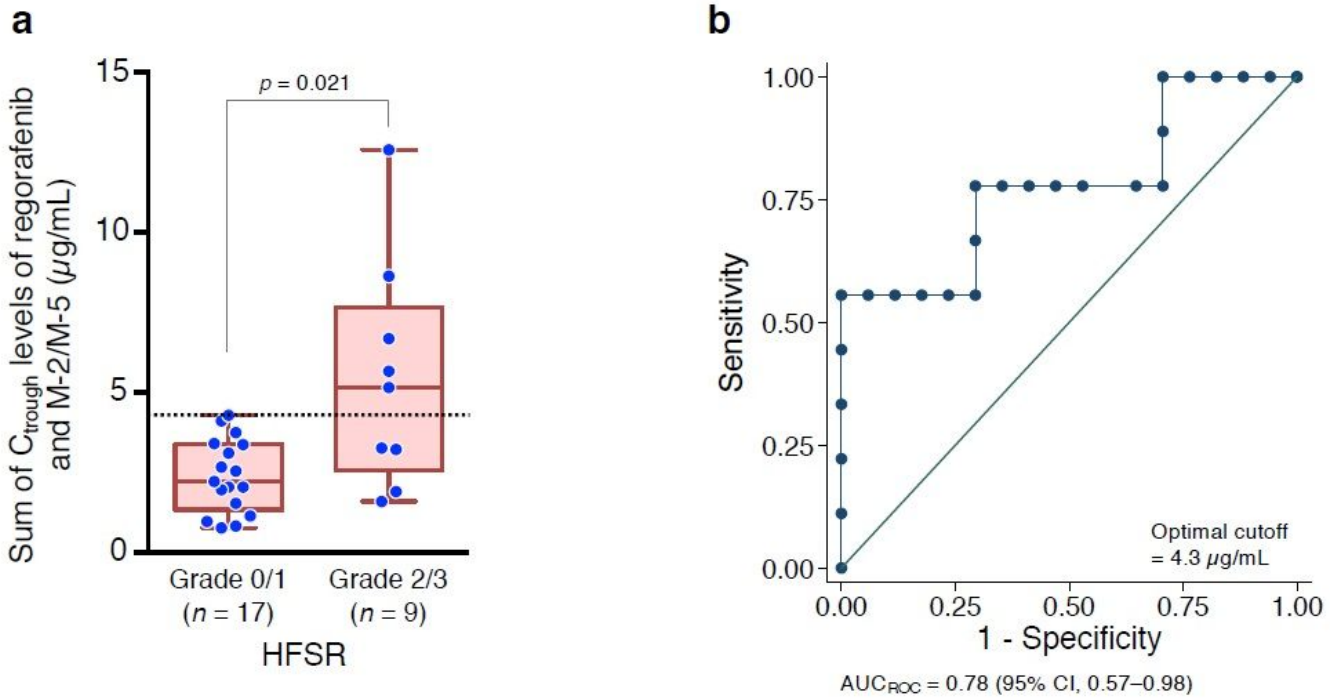

Figure 4

a Association between grade of hand–foot skin reaction (HFSR) and sum of the trough concentrations (Ctrough) of regorafenib and M-2/M-5 at steady state in Cycle 1. The boxes indicate the median and the interquartile range of the data; the whiskers represent the minimum and maximum values. b Receiver operating characteristic (ROC) curve for predicting the development of grade >2 HFSR by the sum of the Ctrough levels. The optimal cutoff value was 4.3 μg/mL, which is shown as the horizontal dotted line in panel a. AUCROC area under the ROC curve, CI confidence interval

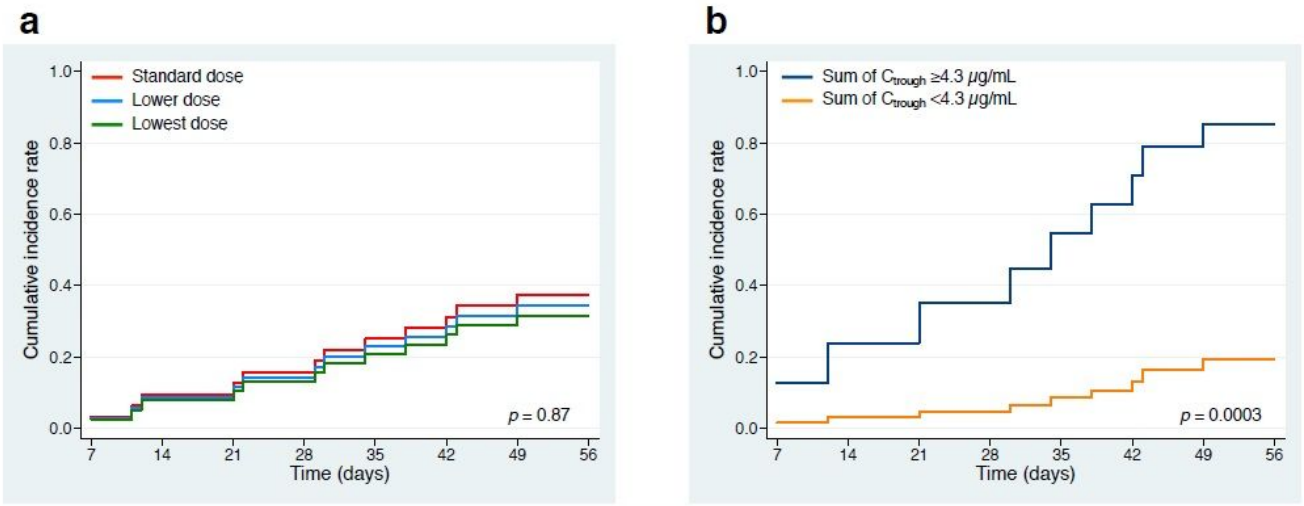

Figure 5

Cumulative incidence rates of dose-limiting toxicities, including grade 3/4 adverse events leading to treatment discontinuation and grade 2 HFSR requiring dose interruption, according to a starting dose and b sum of the trough concentrations (Ctrough) of regorafenib and M-2/M-5 at steady state in Cycle 1