European Journal of Cancer 177 (2022) 154–163

Available online at www.sciencedirect.com

ScienceDirect

journal homepage: www.ejcancer.com

Original Research

A randomised phase 2 study comparing different dose approaches of induction treatment of regorafenib in previously treated metastatic colorectal cancer patients (REARRANGE trial)

Guillem Argilés [a,r,s,*], Nuria Mulet [a], Manuel Valladares-Ayerbes [b], José M. Viéitez [c], Cristina Grávalos [d], Pilar García-Alfonso [e], Cristina Santos [f], María Tobeña [g], Beatriz García-Paredes [h], Manuel Benavides [i], María T. Cano [j], Fotios Loupakis [k], Mercedes Rodríguez-Garrote [l], Fernando Rivera [m], Richard M. Goldberg [n], Chiara Cremolini [o], Jaafar Bennouna [p], Fortunato Ciardiello [q], Josep M. Tabernero [a], Enrique Aranda [i], on behalf of theSpanish Cooperative Group for the Treatment of Digestive Tumors (TTD) and UNICANCER GI, The, REARRANGE investigators, Principal investigatorGuillem Argilés [a], Josep Tabernero [a], Steering Committee, Investigators

[a] *Vall d'Hebron University Hospital and Institute of Oncology (VHIO), CIBERONC, Barcelona, Spain*
[b] *Virgen del Rocío University Hospital and Institute of Biomedicine (IBIS), Sevilla, Spain*
[c] *Hospital Universitario Central de Asturias, Oviedo, Spain*
[d] *Universitary Hospital 12 de Octubre, Madrid, Spain*
[e] *Gregorio Marañón Hospital, Madrid, Spain*
[f] *Institute Català d'Oncologia (ICO), Duran i Reynals Hospital – ONCOBELL, CIBERONC, Barcelona, Spain*
[g] *Santa Creu i Sant Pau Hospital, Barcelona, Spain*
[h] *Clínico San Carlos Hospital, Instituto de Investigación Hospital Clinico San Carlos (IdISSC) CIBERONC, Madrid, Spain*
[i] *Regional University Hospital, Málaga, Spain*
[j] *IMIBIC, Reina Sofía Hospital, University of Córdoba, CIBERONC, Instituto de Salud Carlos III, Spain*
[k] *Istituto oncologico Veneto, Italy*
[l] *Ramon y Cajal University Hospital-IRYCIS, CIBERONC, Alcalá University, Madrid, Spain*
[m] *University Hospital Marqués de Valdecilla (IDIVAL) Santander, Spain*
[n] *West Virgina University Cancer Institute, Morgantown, USA*
[o] *Department of Translational Research and New Technologies in Medicine and Surgery, University of Pisa, Pisa, Italy*
[p] *University Hospital of Nantes, Digestive Oncology, Nantes, France*
[q] *Università della Campania L. Vanvitelli, Italy*
[r] *Universitat Autònoma de Barcelona, Barcelona, Spain*
[s] *Memorial Sloan Kettering Cancer Center, New York, USA*

* *Corresponding author*. Medical Oncology Department University Hospital Vall d'Hebron, Barcelona, Spain.
E-mail address: argilesg@mskcc.org (G. Argilés).

https://doi.org/10.1016/j.ejca.2022.09.037

Received 15 June 2022; received in revised form 28 September 2022; accepted 30 September 2022
Available online 14 October 2022

KEYWORDS
Colorectal cancer;
Drug administration schedule;
Metastasis;
Regorafenib

Abstract ***Purpose:*** The purpose of this article is to evaluate the safety of two regorafenib dose-escalation approaches in refractory metastatic colorectal cancer (mCRC) patients.
Patients and methods: Patients with mCRC and progression during or within 3 months following their last standard chemotherapy regimen were randomised to receive the approved dose of regorafenib of 160 mg QD (arm A) or 120 mg QD (arm B) administered as 3 weeks of treatment followed by 1 week off, or 160 mg QD 1 week on/1 week off (arm C). The primary end-point was the percentage of patients with G3/G4 treatment-related adverse events (AEs) in each arm.
Results: There were 299 patients randomly assigned to arm A (n = 101), arm B (n = 99), or arm C (n = 99); 297 initiated treatments (arm A n = 100, arm B n = 98, arm C n = 99: population for safety analyses). G3/4 treatment-related AEs occurred in 60%, 55%, and 54% of patients in arms A, B, and C, respectively. The most common G3/4 AEs were hypertension (19, 12, and 20 patients), fatigue (20, 14, and 15 patients), hypokalemia (11, 7, and 10 patients), and hand–foot skin reaction (8, 7, and 3 patients). Median overall survival was 7.4 (IQR 4.0–13.7) months in arm A, 8.6 (IQR 3.8–13.4) in arm B, and 7.1 (IQR 4.4–12.4) in arm C.
Conclusions: The alternative regorafenib dosing schedules were feasible and safe in patients with mCRC who had been previously treated with standard therapy. There was a higher numerical improvement on the most clinically relevant AEs in the intermittent dosing arm, particularly during the relevant first two cycles.
Clinicaltrials.gov identifier: NCT02835924.

1. Introduction

While <25% of patients with CRC have metastatic disease at diagnosis, up to 70% of patients eventually develop metastases [1]. For decades, the backbone of therapy for patients with metastatic colorectal cancer (mCRC) was 5-fluorouracil (5-FU) with leucovorin. In the late 1990s, oxaliplatin and irinotecan were added to the therapeutic arsenal, and when administered with 5-FU improved median overall survival (OS) to nearly 24 months [2–4]. In the last two decades, the development of targeted biologic agents, improvements in surgical techniques, and a better understanding of the molecular biology of cancer have improved median OS to nearly 30 months [5–7]. However, a large majority of patients who develop disease progression despite standard therapies maintain a good performance status, creating a demand for active antineoplastic drugs in the refractory setting.

Regorafenib is a multityrosine kinase inhibitor (TKI) with a broad biological spectrum of action. In two randomised, controlled, phase III trials (the CORRECT and the CONCUR studies), regorafenib treatment increased the overall survival of patients with mCRC after disease progression on multiple drug regimens [8,9]. Unfortunately, in both studies, many patients experienced toxicity that required dose modifications and interruptions, leading to lower dose intensity than planned and adversely affecting the incorporation of the drug into clinical practice.

In the CORRECT, the highest incidence of treatment-related adverse events (AEs) occurred during the first two cycles of treatment [8]. Moreover, regorafenib's recommended dose and schedule that was used in the study and incorporated to drug labelling was determined in a small phase 1 trial that recommended a dose of 160 mg QD administered for 3 weeks followed by 1 week off treatment in 4-week cycles. Of note, with this dose and schedule, 2 of the total 12 patients (16.7%) had a dose limiting toxicity (DLT), while at the next lower tested dose of 120 mg QD 3 weeks on 1 week off, among 7 patients treated, none experienced any DLT [10]. Additional studies tested other dose and schedule strategies similar to those used in the development of other multi-TKIs [11,12]. One alternative intermittent dose approach used regorafenib at 160 mg administered once daily (QD) for 1 week on 1 week off. This strategy was tested in a population receiving first-line therapy for

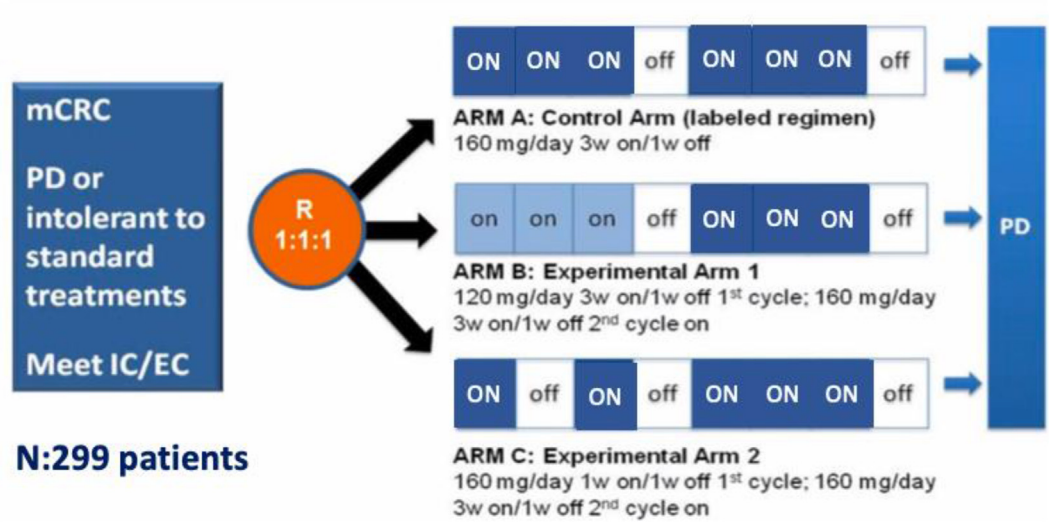

Fig. 1. Trial design.

mCRC in combination with modified FOLFOX6 in the CORDIAL trial [13], demonstrating a favourable safety profile.

Integrating the data resulting from the CORRECT, CONCUR, and CORDIAL trials, with the observations on the phase 1 study, we designed the REARRANGE trial to evaluate the feasibility, tolerability, and potential impact on efficacy of two different dose-escalation approaches of regorafenib in refractory mCRC patients on a European practice environment.

2. Patients and methods

2.1. Trial design

This multinational randomised, three-arm, open-label, phase 2 trial, carried out by the Spanish Cooperative Group for the Treatment of Digestive Tumors (TTD) Group, was conducted in accordance with the Declaration of Helsinki and Good Clinical Practice Guidelines. Prerandomisation written informed consent was

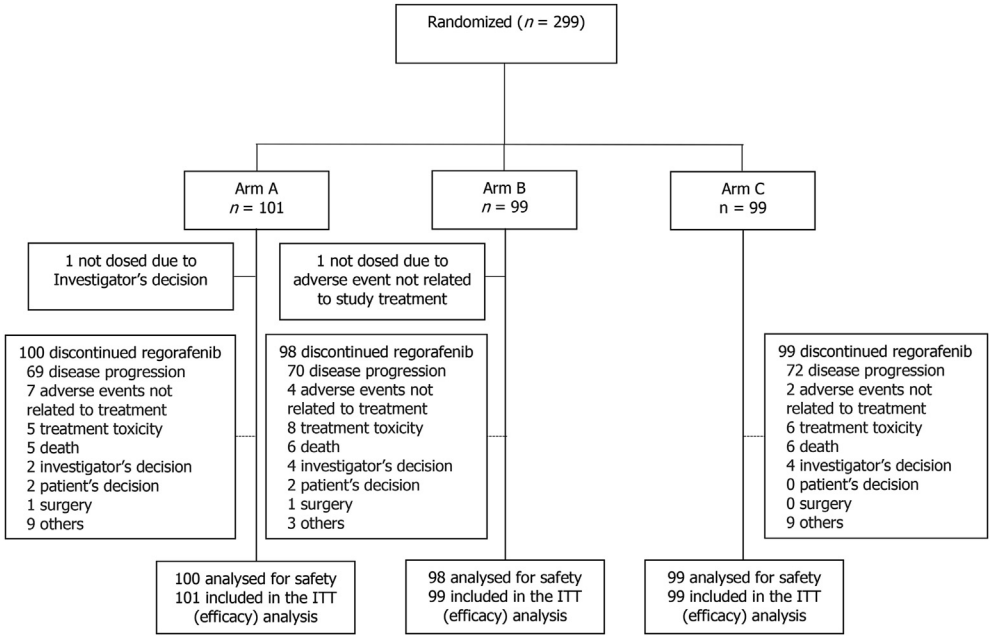

Fig. 2. CONSORT diagram.

Table 1
Baseline characteristics: intention-to-treat population (n = 299).

	Arm A (*n = 101*)	Arm B (*n = 99*)	Arm C (*n = 99*)
Median age (years, Q1-Q3)[a]	65 (56–70)	63 (56–70)	63 (56–69)
Sex			
Men	59 (58%)	53 (54%)	52 (53%)
Women	42 (42%)	46 (46%)	47 (47%)
ECOG[a]			
0	36 (36%)	33 (33%)	35 (35%)
1	65 (64%)	66 (67%)	64 (65%)
Primary site of disease			
Colon	53 (52%)	59 (60%)	49 (50%)
Right	22 (22%)	13 (13%)	15 (15%)
Transverse	9 (9%)	6 (6%)	5 (5%)
Left	22 (22%)	40 (41%)	29 (29%)
Rectum	31 (31%)	22 (22%)	39 (39%)
Both	17 (17%)	18 (18%)	11 (11%)
KRAS mutation			
No	29 (29%)	40 (40%)	39 (39%)
Yes	72 (71%)	59 (60%)	60 (61%)
BRAF mutation			
No	32 (32%)	31 (31%)	31 (31%)
Yes	2 (2%)	3 (3%)	3 (3%)
Unknown	67 (66%)	65 (66%)	65 (66%)
Prior surgery	83 (82%)	81 (82%)	79 (80%)
Prior radiotherapy			
Yes	28 (28%)	22 (22%)	27 (27%)
No	73 (72%)	77 (78%)	72 (73%)
Number of previous systemic anticancer lines after diagnosis of metastatic disease (median, Q1-Q3)	4 (3–5)	4 (3–5)	3 (3–5)
Previous systemic anticancer drugs with palliative intention			
Fluoropyrimidines	101 (100%)	98 (99%)	98 (99%)
Oxaliplatin	85 (84%)	83 (84%)	86 (87%)
Irinotecan	101 (100%)	99 (100%)	99 (100%)
Bevacizumab/Aflibercept	99 (98%)	96 (97%)	99 (100%)
Cetuximab/Panitumumab	31 (31%)	40 (40%)	40 (40%)
Others	26 (26%)	41 (41%)	26 (26%)

[a] Stratification factor.

obtained from all patients. The Institutional Ethics Review Board of all participating centres approved the protocol.

2.2. Patient selection

Eligibility criteria were identical to the CORRECT and CONCUR trials (see Supplementary file S1).

2.3. Randomisation and dose modification

Randomisation was centralised, using permuted blocks with stratification by ECOG performance status (0 vs.1) and age (70 years or less vs. > 70 years), with a block size of six patients who were randomly assigned in an 1:1:1 ratio to arm A (the approved regorafenib regimen of 160 mg/d for 3 weeks followed by 1 week off therapy), arm B (120 mg/d for 3 weeks followed by 1 week off therapy during the first cycle), or arm C (160 mg/d 1 week on/1 week off during the first cycle) (Fig. 1). In patients allocated to arms B or C, doses were escalated to 160 mg QD for 3 weeks followed by 1 week off from cycle 2 onwards, unless they experienced relevant toxicity (Supplementary file S2 details the prespecified toxicities that preclude dose escalation and Supplementary file S3 the administered dose levels to patients enrolled on each of the study's arms).

At the discretion of the investigator, once toxicities resolved, patients could have their doses escalated to the standard dose. Treatment was discontinued permanently if the patient did not recover from the toxicities after a 4-week delay or after dose reduction by two dose levels. The protocol called for treatment to continue until disease progression, intolerance, withdrawal of consent by the patient, or at physician

Table 2
Treatment compliance (safety population).

	Arm A (*n* = *100*)	Arm B (*n* = *98*)	Arm C (*n* = *99*)	*p-value*
Treatment duration (months): **mean (SD)**	3.2 (2.4)	3.8 (3.4)	3.8 (3.3)	0.39
RDI cycles 1 and 2: **mean (SD)**	71.2 (25.9)	70.2 (26.6)	79.7 (24.7)	*0.006*
At least one dose delay: **n (%)**	35 (35.0)	33 (33.7)	29 (29.3)	0.49
At least one dose reduction: **n (%)**	39 (39.0)	38 (38.8)	25 (25.3)	0.09
At least one dose interruption: **n (%)**	81 (81.0)	77 (78.6)	69 (69.7)	0.11

RDI, relative dose intensity; SD, standard deviation.

Table 3
Summary of type of adverse events per patient (safety population).

	Arm A (*n* = *100*)	Arm B (*n* = *98*)	Arm C (*n* = *99*)	*p-value*
At least one TRAE: **n (%)**	97 (97.0)	96 (98.0)	98 (99.0)	0.79
At least one grade 3/4 AE	74 (74.0)	66 (67.4)	67 (67.7)	0.52
At least one grade 3/4 TRAE	60 (60.0)	55 (56.1)	54 (54.5)	0.73
Discontinued due to AEs	28 (28.0)	29 (29.6)	20 (20.2)	0.27
Grade 5 TRAE	1 (1.0)	0 (0.00)	1 (1.0)	1.00
At least one SAE	29 (29.0)	29 (29.6)	24 (24.2)	0.65
At least one TR-SAE	9 (9.0)	10 (10.2)	9 (9.1)	0.95

AE, adverse event; SAE, serious adverse event; TRAE, treatment-related adverse event; TR-SAE, treatment-related serious adverse event.

discretion. After treatment discontinuation, patients were monitored at least once every 3 months via clinic visit or telephone.

2.4. Evaluations during the study

Baseline and follow-up evaluations included a complete medical history, physical examination, haematological and biochemical blood analyses, thyroidal hormones, urinalysis, carcinoembryonic antigen, electrocardiogram, and abdominal-pelvic and thoracic computerised axial tomography or magnetic resonance imaging (see supplementary file S4 for study's flow chart). Toxicities were graded using the National Cancer Institute Common Toxicity Criteria for Adverse Events (NCI-CTCAE) version 4.03 and recorded from randomisation to the final study visit.

2.5. Statistical analysis

Based on the safety data from the CORRECT trial [8], we assumed that 54% of patients in arm A would develop G3/G4 treatment-related AEs. A sample size of 93 patients per treatment group would provide at least 80% of power to detect a 20%-point difference in the percentage of patients with G3/G4 treatment-related

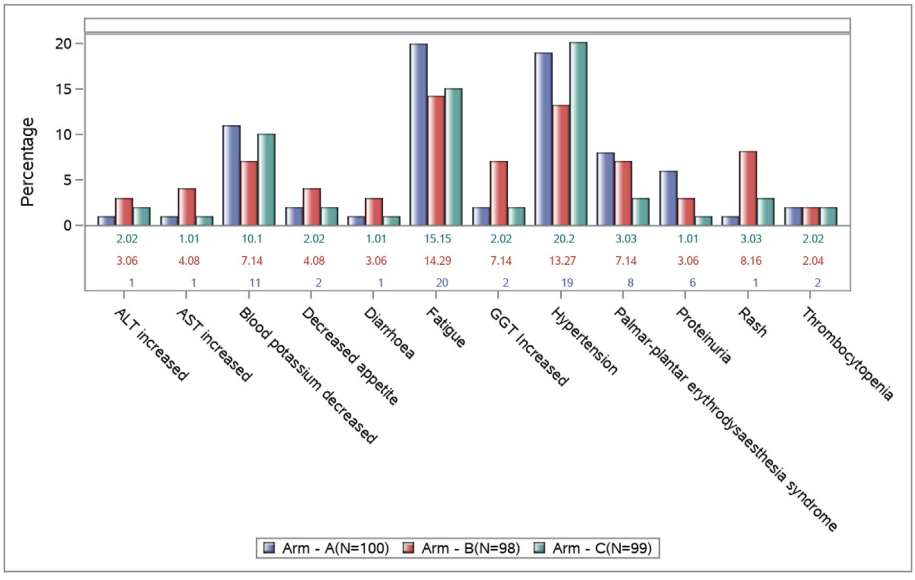

Fig. 3. Treatment-related grade 3-4 adverse events occurring in >2% of patients.

Table 4
Comparison of ≥G3 adverse events (occurring in ≥5% of patients) in cycles 1 and 2 versus subsequent cycles.

	Arm A (*n = 100*)		Arm B (*n = 98*)		Arm C (*n = 99*)	
	Cycles 1 + 2	Cycles 3+	Cycles 1 + 2	Cycles 3+	Cycles 1 + 2	Cycles 3+
Total ≥ G3 AEs	55%	15%	55%	8%	45%	14%
Asthenia + fatigue	16%	4%	14%	1%	11%	4%
Hypertension	17%	4%	12%	0%	18%	2%
Hypokalemia	10%	4%	7%	1%	7%	6%
HFSR	6%	2%	4%	3%	3%	0%
GGT increased	2%	0%	7%	0%	2%	0%
Proteinuria	6%	0%	3%	0%	1%	0%
Rash	1%	0%	3%	1%	2%	0%
AST increased	0%	1%	4%	0%	1%	0%
Decreased appetite	2%	0%	4%	0%	2%	0%

AE, adverse event; HFSR, hand–foot skin reaction.

AEs in arm B and arm C, assuming a 0.05 one-sided significance level and after adjusting for multiple comparisons using the Bonferroni method. Considering a 5.5% drop-out rate, a total of 295 patients should be included. The protocol did not plan for nor was it powered for comparisons between arm B versus arm C.

Patients who received at least one dose of study treatment comprised the safety population. The intention-to-treat population was defined as all randomised patients, irrespective of whether they receive study medication.

The primary end-point was the percentage of patients with G3/G4 treatment-related AEs in each arm using CTCAE v4.03 criteria. The safety population was used to analyse the primary and secondary objectives related to safety and tolerability. AEs and laboratory abnormalities were reported by treatment group, category, and worst grade (see Supplementary file S5 for the complete statistical assumptions).

3. Results

Between July 2016 and September 2017, 299 patients from 19 (13 Spanish, 2 Italian and 4 French) hospitals were randomised to arm A (n = 101), B (n = 99), or C (n = 99) and 297 received at least one dose of study treatment (arm A n = 100, arm B n = 98, arm C n = 99: population for safety analyses) (Fig. 2). Baseline patient characteristics, which were stratified according ECOG (0 versus 1) and age (70 years or less versus > 70 years), were well balanced between groups (Table 1).

3.1. Treatment compliance and safety

The mean duration of treatment was 3.0, 3.7, and 3.8 months for arms A, B, and C, respectively, with no statistically significant differences (Table 2). After the first cycle, 45% of patients in arm B and 64% in arm C escalated to the full dose (160 mg QD for 3 weeks followed by 1 week off). The relative dose intensity in cycles 1 and 2 was significantly higher in arm C than in the other two arms although the number of patients requiring dose delay, reduction, and interruption was similar in all three study arms (Supplementary file S6). AEs, mainly hand–foot skin reaction (HFSR) and hypertension, were the most common reasons for dose modification (Supplementary file S7).

All subjects (100%) reported at least one AE. Table 3 summarises the incidence and type of AEs by treatment arm. One-hundred and sixty-nine subjects (57%) presented at least one grade 3/4 treatment-related AE: 60% arm A, 56% arm B, and 55% arm C. These differences between arms were not statistically significant (p = 0.7262). The most frequently reported AEs (occurring in ≥30% of subjects) were fatigue (67%), hypertension (46%), dysphonia (46%), HFSR (45%), decreased appetite (43%), and diarrhoea (41%). Fig. 3 and Supplementary file S8 show treatment-related grade 3–4 AEs that occurred in ≥2% of patients. There were two deaths (arm A n = 1, 1%; arm C n = 1, 1%) attributed to AEs unassociated with disease progression.

A detailed analysis of G3 or higher AEs occurred during C1 and C2 in different arms showed a numerical decrease of G3 or higher overall AE (45 versus 55%), fatigue (11 versus 16%), HFSR (3 versus 6%), and proteinuria (1 versus 6%) in the intermittent versus standard dosing arm comparison, not being this trend as pronounced on the reduced-dose schedule (Table 4).

3.2. Treatment efficacy

As of November 26, 2018, there were 80, 78, and 83 patients that had died in arm A, arm B, and arm C, respectively. Those deaths were attributed to disease progression in 87% of cases. Median OS was 7.39 (IQR 3.96–13.70) months in arm A, 8.58 (IQR 3.78–13.38) months in arm B, and 7.13 (IQR 4.37–12.43) months in arm C (Fig. 4a), with no statistically significant difference (p = 0.7222) between the arms. At 1 year, 32.41%,

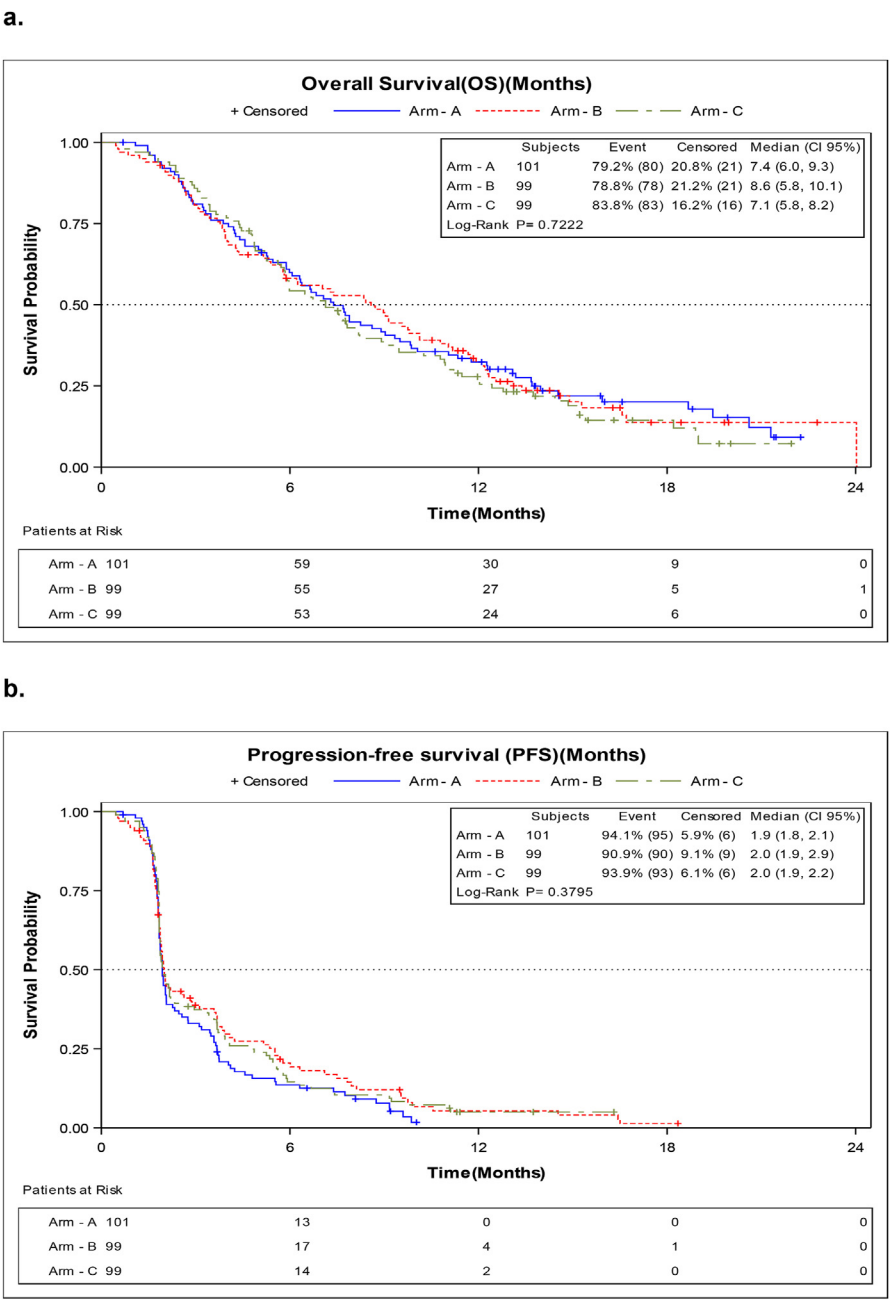

Fig. 4. a: Overall survival Kaplan–Meier curve. b: Progression-free survival Kaplan–Meier curve.

32.3%, and 27.8% of the patients in arms A, B, and C were alive.

Median progression-free survival (PFS) was 1.94 (IQR 1.78–3.68) in arm A, 2.00 (IQR 1.78–5.52) months in arm B, and 2.00 (IQR 1.81–4.80) months in arm C, with no statistically significant difference ($p = 0.3795$) between the three arms (Fig. 4b).

Median time to treatment failure (TTF) was 1.87 (IQR 1.71–3.48) months in arm A, 1.94 (IQR 1.68–4.24) months in arm B, and 1.94 (IQR 1.74–3.93) months in arm C, with no statistically significant difference ($p = 0.2114$) between the three arms (Supplementary file S9). No patients had a complete response. Two patients assigned to arm A, two in arm B, and three in arm C had a partial response. The overall disease control rate was 33% (95% CI 23.67–42.72) in arm A, 36% (95% CI 26.93–46.64) in arm B, and 35% (95% CI 26.01–45.60) in arm C ($p = 0.8515$).

When the classical prognostic factors used in COR-RECT trial [8] were applied to PFS and OS analysis, we saw a trend towards a more favourable PFS on the two experimental arms taken as a whole and a neutrality in OS (Supplementary file S10). The post hoc nature of this analysis, though precluding the establishment of any conclusion per se, reinforces the lack of any detrimental effect in efficacy derived from the initial dose-reduction.

4. Discussion

The REARRANGE trial showed a modest numerical improvement in patient overall tolerability profiles, failing to meet its primary end-point of significantly decreasing the percentage of patients presenting G3/4 AEs during the entire course of regorafenib treatment. We attribute this observation to (1) stringency of the primary end-point, (2) duration of the initial dose deintensification in relation to median TTF, and (3) the high proportion of patients escalating to full dose beyond C1 in both experimental arms. However, the particularities of the European regulatory and practice environments requested pursuing simplified alternative dose schedules while keeping up as much as possible with the labelling of the drug, since the incorporation to normal clinical practice of our alternative schedules was pursued.

Nevertheless, a detailed analysis revealed some relevant qualitative toxicity improvements in both REARRANGE experimental arms that should be taken into consideration. The incidence of grade 3 HFSR was half as lower in the intermittent dosing arm than in the control arm. We do believe this is of clinical relevance since to patients HFSR is one of the most bothersome AEs resulting from regorafenib treatment. Remarkably, while some authors have reported that mCRC patients treated with regorafenib who experienced severe HFSR showed better OS, we did not observe this trend in our study [16]. Fatigue is another AE typical form TKIs with impact on patient's quality of life. Reported grade 3 fatigue figures were numerically lower in arms B (14%) and C (15%) than in the standard dose arm (20%). In contrast, the most frequent regorafenib-related AE of grade $\geq$3 was hypertension with 20% of patients affected in arms A and C, almost doubling the rate reported in CORRECT, CONCUR, or REBECCA. However, this AE tends to be manageable and rarely interfered with patients quality of life in other regorafenib trials [17]. Moreover, hypertension is a pharmacodynamic effect of multi-TKIs and might be in relation with the high proportion of patients starting C2 at full dose on arms A and C in our trial [18]. The initial intermittent dosing was the explored alternative schedule that showed a trend towards a greater reduction on rates of G3/4 fatigue, HFSR and proteinuria versus normal dose during the first two cycles, an observation of relevance since this period corresponds to regorafenib's median PFS.

Although the study was not powered to find differences on efficacy, numbers show that dose deintensification during the first treatment cycle had no significant numerical impact on OS, PFS, TTF, or disease control rate, being confidence intervals for these parameters in each of the arms almost overlapping, and in the ranges reported by other regorafenib studies conducted in the setting [8,9,14,15].

Furthermore, the overall tolerability and efficacy figures were consistent with those reported by the American postmarketing Phase II study ReDOS, which explored an alternative starting dose of 80 mg and specified 40 mg weekly regorafenib dose scalations during the first cycle dependent on observed toxicities [8,9,14,15]. However, relevant differences are seen when the percentage of patients starting C3 –primary end-point of REDOS study – is compared. While similar proportion of patients started C3 in the experimental arms of both trials (43% REDOS versus 45% and 46% REARRANGE B and C), a higher percentage of patients initiated C3 in the control arm of our study 39% versus 26%. Differences may be explained due to different practice environments and patient populations.

5. Conclusions

REARRANGE is the largest study reported so far showing the feasibility and efficacy of alternative regorafenib dose-escalation schedules in patients with chemorefractory mCRC, with a trend towards a better safety profile compared with the current recommended dosing schedule of this drug, particularly for the clinically relevant AEs of fatigue and HFSR. Out of the two alternatives explored, intermittent dosing seems to favour a better tolerability during C1 and C2. However, the lack of double-blinding and the limited sample size in this randomised Phase II study, while informative, lack the power inherent in a Phase III randomised clinical trial, and such a study is unlikely to be completed. Therefore, the outcome of this trial has to be interpreted as one more piece of data that supports the implementation of alternative regorafenib starting schedules in normal clinical practice on a European practice environment.

Author contributions

Guillem Argilés and Josep M. Tabernero: Conceptualisation, Methodology, Project administration, Writing – Original draft preparation. **Guillem Argilés:** Supervision and Visualisation **All authors:** Investigation, Writing – reviewing and editing.

Role of the funding source

Financial support for this research was provided by Bayer HealthCare Pharmaceuticals Inc., which has no role in the design of the study; collection, analysis, and interpretation of data; and in writing the manuscript.

The results reported in this manuscript are originals and were presented in part as oral presentation at the ESMO World Congress on Gastrointestinal Cancers 2019.

Conflict of interest statement

The authors declare the following financial interests/personal relationships which may be considered as potential competing interests: G. Argilés received advisory honoraria, from Gadetta BV. Amgen, Bayer and Servier; M. Valladares-Ayerbes received honoraria, travel grants, and research grants from Hoffman La Roche, Bristol-Myers Squibb, Bayer, Servier, Amgen, Merck Serono and Sanofi. N. Mulet received grants and non-financial support from Merck Serono, Amgen and Roche, outside the submitted work; M. Tobeña received personal fees from Amgen, Kyowa Kirin and Grunenthal, non-financial support from Merck, Roche and Rovi, outside the submitted work; B. García received personal fees from Advanced Accelerator Applications (a Novartis company), Amgen, Bayer Hispania, Eisai, Lilly, MSD and Roche Farma, personal fees and non-financial support from Ipsen, Merck, Novartis, Sanofi-Aventis and Servier, outside the submitted work; E. Aranda received honoraria for advisory role from Amgen, Bayer, Celgene, Merck, Roche and Sanofi; C. Cremolini received honoraria for Advisory Board/Speaker from Amgen, Bayer, Merck, MSD, Roche, Servier and Research, grants from Bayer, Roche and Servier. The other authors have stated that they have no conflicts of interest.

Acknowledgements

The authors thank the medical and nursing staff from all the participating institutions, the patients, and their families for participating in the study, and the study investigators for their cooperation and support.

The REARRANGE investigators are as follows:

Principal investigator: Guillem Argilés and Josep Tabernero.

Steering Committee: Josep Tabernero, Guillem Argilés, Alfredo Falcone, Fortunato Ciardiello, Richard Goldberg, and Jaafar Bennouna. Investigators:

Argilés and J. Tabernero and N. Mulet, H. Universitari Vall d'Hebron, Barcelona, Spain; M. L. Limón and M. Valladares. H. Virgen del Rocío, Sevilla, Spain; P. Jiménez and J. M[a] Vieitez, H. Universitario Central de Asturias, Spain; C. Grávalos. H. 12 de Octubre, Madrid, Spain; P. García-Alfonso, H. Gregorio Marañón, Madrid, Spain; C. Santos, ICO.

H. Duran i Reynals, Barcelona, Spain; D. Páez and M. Tobeña, H. Santa Creu i Sant Pau, Barcelona, Spain; J. Sastre and B. García Paredes, H. Universitario Clínico San Carlos, Madrid, Spain; M. Benavides, Hospital Universitario Regional y Virgen de la Victoria, Málaga, Spain; E. Aranda and M.T. Cano, H. Universitario Reina Sofía, Córdoba, Spain.

F. Loupakis, IOV (Istituto oncologico Veneto), Italy; M. Rguez Garrote and C. Guillén, H. Ramón y Cajal, Madrid, Spain; F. Rivera, H. Marqués de Valdecilla, Santander, Spain.

J. Safont, H. General Universitario, Valencia, Spain; S. Hiret, Institut de Cancérologie de l'Ouest, France; J. Bennouna, CHU-Nante, France; D. Pannier, Centre Oscar Lambret, France; D. Malka, Gustave Roussy , France; A. Falcone and C. Cremolini, A. O. Universitaria Pisana, Italy.

TTD Data Center: Inmaculada Ruiz de Mena and Susana Rodriguez Statistics and Data Management: Pivotal.

Support for third-party writing assistance for this manuscript was provided by Pivotal.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.ejca.2022.09.037.

References

[1] Shah MA, Renfro LA, Allegra CJ, et al. Impact of patient factors on recurrence risk and Time dependency of oxaliplatin benefit in patients with colon cancer: analysis from modern-era adjuvant studies in the adjuvant colon cancer end points (ACCENT) database. J Clin Oncol 2016;34:843–53.

[2] Colucci G, Gebbia V, Paoletti G, et al. Phase III randomized trial of FOLFIRI versus FOLFOX4 in the treatment of advanced colorectal cancer: a multicenter study of the Gruppo Oncologico Dell'Italia Meridionale. J Clin Oncol 2005;23:4866–75.

[3] Goldberg RM, Sargent DJ, Morton RF, et al. A randomized controlled trial of fluorouracil plus leucovorin, irinotecan, and oxaliplatin combinations in patients with previously untreated metastatic colorectal cancer. J Clin Oncol 2004;22:23–30.

[4] Tournigand C, Andre T, Achille E, et al. FOLFIRI followed by FOLFOX6 or the reverse sequence in advanced colorectal cancer: a randomized GERCOR study. J Clin Oncol 2004;22:229–37.

[5] Grothey A, Marshall JL. Optimizing palliative treatment of metastatic colorectal cancer in the era of biologic therapy. Oncology (Williston Park) 2007;21:553–64. 566; discussion 566-558, 577-558.

[6] Loree JM, Kopetz S, Raghav KP. Current companion diagnostics in advanced colorectal cancer; getting a bigger and better piece of the pie. J Gastrointest Oncol 2017;8:199–212.

[7] Van Cutsem E, Cervantes A, Adam R, et al. ESMO consensus guidelines for the management of patients with metastatic colorectal cancer. Ann Oncol 2016;27:1386–422.

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

[9] Li J, Qin S, Xu R, et al. 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 2015;16:619–29.

[10] Mross K, Frost A, Steinbild S, et al. A phase I dose-escalation study of regorafenib (BAY 73-4506), an inhibitor of oncogenic, angiogenic, and stromal kinases, in patients with advanced solid tumors. Clin Cancer Res 2012;18:2658–67.
[11] Kondo T, Takagi T, Kobayashi H, et al. Superior tolerability of altered dosing schedule of sunitinib with 2-weeks-on and 1-week-off in patients with metastatic renal cell carcinoma–comparison to standard dosing schedule of 4- weeks-on and 2-weeks-off. Jpn J Clin Oncol 2014;44:270–7.
[12] Strumberg D, Clark JW, Awada A, et al. Safety, pharmacokinetics, and preliminary antitumor activity of sorafenib: a review of four phase I trials in patients with advanced refractory solid tumors. Oncol 2007;12:426–37.
[13] Argiles G, Saunders MP, Rivera F, et al. Regorafenib plus modified FOLFOX6 as first-line treatment of metastatic colorectal cancer: a phase II trial. Eur J Cancer 2015;51:942–9.
[14] Van Cutsem E, Martinelli E, Cascinu S, et al. Regorafenib for patients with metastatic colorectal cancer who progressed after standard therapy: results of the large, single-arm, open-label phase IIIb CONSIGN study. Oncol 2019;24:185–92.
[15] Bekaii-Saab TS, Ou FS, Ahn DH, et al. Regorafenib dose-optimisation in patients with refractory metastatic colorectal cancer (ReDOS): a randomised, multicentre, open-label, phase 2 study. Lancet Oncol 2019;20:1070–82.
[16] Kobayashi K, Kawakami K, Yokokawa T, et al. Association of hand-foot skin reaction with regorafenib efficacy in the treatment of metastatic colorectal cancer. Oncology 2019;96:200–6.
[17] Sastre J, Argiles G, Benavides M, et al. Clinical management of regorafenib in the treatment of patients with advanced colorectal cancer. Clin Transl Oncol 2014;16:942–53.
[18] Jesus-Gonzalez de N, Robinson E, Penchev R, et al. Regorafenib induces rapid and reversible changes in plasma nitric oxide and endothelin-1. Am J Hypertens 2012;25:1118–23.