Original Study

ROCKET: Phase II Randomized, Active-controlled, Multicenter Trial to Assess the Safety and Efficacy of RRx-001 + Irinotecan vs. Single-agent Regorafenib in Third/Fourth Line Colorectal Cancer

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Abstract

The purpose of this phase II clinical trial (ROCKET) was to compare the safety and efficacy of RRx-001 + irinotecan (RxI) vs. regorafenib in 34 patients with third/fourth line colorectal cancer that were previously treated with irinotecan. The results demonstrate improved efficacy of RxI compared with Reg. Late-stage clinical development in this indication is planned.

Introduction: RRx-001 is a novel cysteine-targeted alkylating agent that releases nitric oxide (NO). The primary biological activities of this hybrid molecule include macrophage repolarizing and vascular normalization. The purpose of this clinical trial (ROCKET) (NCT02096354) was to compare the safety and efficacy of the combination therapy RRx-001 + irinotecan vs. regorafenib in third/fourth line colorectal cancer that previously received treatment with irinotecan. **Patients and Methods:** A total of 34 patients were randomized (24 to RRx-001 + irinotecan (RxI) and 10 to single-agent regorafenib (RegI)) and were the basis for the intention-to-treat analysis (ITT, comprising all 34 patients). RRx-001 treatment was administered as an up-to-2-month "primer" followed by irinotecan for patients randomized to the RRx-001 arm (24). The efficacy and safety data are presented for the 34 patients in the (ITT) efficacy analysis. Therapy consisted of intravenous administration of RRx-001 at 4 mg once weekly for up to 2 months, at which point RRx-001 was discontinued, followed by intravenous infusion of irinotecan at 180 mg/m^2 on day 1 in a 21-day cycle vs. 160 mg oral regorafenib daily for 3/4 weeks followed at progression, if applicable, by irinotecan 180 mg/m^2 on day 1 in a 21-day cycle. There were 3 patients (3/24 = 12.5%) with prior single agent irinotecan on the RRx-001 randomized arm and 2 (2/10 = 20%) on the regorafenib randomized arm. Numerous patients had irinotecan combination therapies prior to randomized treatment. There were 15 patients on RRx-001 arm that received irinotecan post-RRx-001 in the randomized trial. There were 5 PRs on RRx-001 plus irinotecan leading to an overall response of 20.8% (5/24). There were 37.5% (9/24) of RRx-001 randomized patients with KRAS mutant type while 60% (6/10) regorafenib randomized patients were of KRAS type mutant. There were only 4 patients with available QOL and Edmonton Symptom Assessment System, an insufficient sample size to allow for any meaningful analysis. **Results:** Median patient follow-up was approximately 14.5 months (SD 4.5 months). Median overall survival was 8.6 months for RxI and 4.7 months for RegI. Median progression free survival was 6.1 months for RxI vs. 1.7 months for RegI (a statistically significant result, 2-sided log-rank test, $P = .0030$). The toxicity profile of RxI was substantially improved compared with RegI. **Conclusion:** The results of this trial demonstrate improved efficacy of RxI compared with RegI in patients with metastatic colorectal cancer after previous treatment with

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Submitted: Jul 8, 2022; Revised: Oct 29, 2022; Accepted: Nov 21, 2022

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https://doi.org/10.1016/j.clcc.2022.11.003

Please cite this article as: Tony R. Reid et al, ROCKET: Phase II Randomized, Active-controlled, Multicenter Trial to Assess the Safety and Efficacy of RRx-001 + Irinotecan vs. Single-agent Regorafenib in Third/Fourth Line Colorectal Cancer, Clinical Colorectal Cancer, https://doi.org/10.1016/j.clcc.2022.11.003

irinotecan, and late-stage clinical development in this indication is planned on the strength of the observed "signal" accompanied by a sufficient safety profile.

Clinical Colorectal Cancer, Vol. 000, No.xxx, 1–8 © 2022 The Author(s). Published by Elsevier Inc.

Keywords: tumor associated macrophage polarization, chemotherapy resensitization, vascular normalization, MYC

Introduction

Current standard care for patients (pts) with metastatic colorectal cancer (mCRC), which causes nearly 700,000 deaths per year worldwide,[1] involves various active agents, either alone or in combination: fluorouracil plus leucovorin (5-FU/LV), capecitabine, irinotecan, oxaliplatin, panitumumab (PAN) plus mFOLFOX6,[2] regorafenib, and trifluridine–tipiracil (TAS-102). A typical treatment sequence is triplet chemotherapy (FOLFOXIRI) +/- anti-VEGF therapy (bevacizumab, ziv-aflibercept or ramucirumab) based on the randomized phase III TRIBE trial [3]or doublet chemotherapy (FOLFOX or FOLFIRI) +/- anti-VEGF therapy as frontline therapy followed by cetuximab if KRAS mutation is absent, regorafenib and trifluridine–tipiracil. Checkpoint inhibitors are an additional option in the event of high levels of microsatellite instability (MSI-high).[4]

Despite the availability of these different options, patients tend to develop resistance to treatment,[5] and since rechallenge with previously administered therapies such as irinotecan, which has demonstrated superiority to best supportive care and 5-fluorouracil (5-FU) in second line mCRC,[6] is not typically attempted, methods to overcome this resistance are urgently needed.

RRx-001 is a novel cysteine-targeted alkylating agent that, like nitroglycerine, yields nitric oxide upon selective alkylation of cysteine moieties. Nitric oxide has a myriad of effects including vasodilation and relaxation of smooth muscle through cGMP signaling. In tumors, NO has proapoptotic, antiangiogenic and immunomodulatory effects mediated through p53 upregulation, MYC inhibition,[7] CD47 downregulation[8] and macrophage repolarization.[9] In a small phase I pilot trial, the combination of RRx-001 and nivolumab in previously treated, nonimmunogenic, checkpoint inhibitor unresponsive tumor types with no remaining approved therapeutic options, the objective response rate at 12 weeks was 25% and the disease control rate (DCR) consisting of stable disease or better was 67% by Response Evaluation Criteria in Solid Tumors (RECIST) version 1.[10] Based on these findings, our hypothesis is that pretreatment with RRx-001 could sensitize or resensitize tumors to previously administered chemotherapeutic agents such as irinotecan and platinum (cisplatin and carboplatin). Consistent with this hypothesis, enrollment on a randomized phase III trial in third line or beyond small-cell lung cancer (SCLC) for a combination of RRx-001 used primarily as a primer prior to the administration of previously received platinum doublet has started. In addition, a soon-to-start late-stage trial for protection against severe oral mucositis is also planned in first line head and neck cancer based on promising data in a randomized phase II study (PREVLAR) (NCT03515538) with RRx-001 also primarily used as a primer prior to the administration of cisplatin and intensity modulated radiotherapy (IMRT).[11]

Regorafenib is an oral multi-kinase inhibitor that was approved in 2012 by the FDA[12] as a third-line therapy for the treatment of patients with metastatic colorectal cancer (CRC) previously treated with fluoropyrimidine-, oxaliplatin- and irinotecan-based chemotherapy as well as an anti-VEGF therapy or an anti-EGFR therapy if KRAS wild type. The approval was based on the results of the 760-patient randomized multi-center phase III CORRECT (Colorectal Cancer Treated With Regorafenib or Placebo After Failure of Standard Therapy) trial, which showed statistically significant improvement with Regorafenib over placebo in overall survival (OS) of 6.4 months (95% CI: 5.8, 7.3) in the regorafenib arm and 5.0 months (95% CI: 4.4, 5.8) in the placebo arm as well as a statistically significant improvement in progression-free survival (PFS) of 2.0 months (95% CI: 1.9, 2.3) in the regorafenib arm vs. 1.7 months (95% CI: 1.7, 1.8) in the placebo arm.

The current study, ROCKET, was undertaken to compare the efficacy of RRx-001 as a primer prior to the administration of irinotecan (if patients were considered fit enough to receive it) vs. regorafenib followed by irinotecan (if patients were considered fit enough to receive it) in third/fourth line metastatic colorectal cancer that previously received treatment with irinotecan.

Patients and Methods

Patient eligibility. Patients with histologically confirmed metastatic colorectal cancer that previously received at least oxaliplatin-, and irinotecan-based regimens with bevacizumab and with cetuximab or panitumumab if KRAS wildtype were eligible for the study. Other enrollment criteria included Eastern Cooperative Oncology Group (ECOG) performance status of 0 to 1, age >18 years, written informed consent, measurable disease per RECIST v. 1.1, life expectancy of at least 12 weeks, absolute neutrophil count of >1500/mm^3, platelets ≥75,000/ mm^3, hemoglobin > 9.0 g/dL, serum bilirubin level <1.5x upper limit of normal (ULN), serum aspartate aminotransferase and alanine aminotransferase levels <2x ULN or <5x ULN if liver metastases, alkaline phosphatase ≤ 2.5 ULN and serum creatinine level in the normal range. Patients that were excluded included those with clinically significant cardiovascular disease, unresolved toxicity higher than version 4.0 CTCAE grade 2 excluding alopecia, hypothyroidism, oxaliplatin-induced neurotoxicity, and EGFR-targeted therapy skin rash, predisposition to active bleeding, active brain metastases, history of allergy or intolerance to irinotecan, hepatic encephalopathy, cholangitis that required treatment or intervention within 4 weeks of study enrollment, concurrent anticancer therapy or any cytotoxic therapy within 14 days prior to Day 1, with previous exposure

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to regorafenib, severe hypoalbuminemia <3.0 g/dL, pregnancy or lactation.

Study Design

Thirty-four patients were randomized (2:1 in favor of RRx-001 arm) in a parallel group design and received 1 of 2 treatments: Priming with RRx-001 for 2 months, then followed by irinotecan administration if patients were deemed fit enough to receive it or regorafenib followed by irinotecan administration if patients were deemed fit enough to receive it. Patients randomized to the RRx-001 arm (n = 24) received either 4 mg of RRx-001 as an up-to-2-month "primer", then followed, if deemed clinically applicable, by irinotecan 180 mg/m^2 administered every 2 weeks ± 5 mg/kg bevacizumab (although only 5 patients received bevacizumab) until disease progression or unacceptable toxicity or 160 mg regorafenib once daily for 21 of 28 days until progression or unacceptable toxicity followed, if deemed clinically applicable, by irinotecan 180 mg/m^2 administered every 2 weeks ± 5 mg/kg bevacizumab until disease progression or unacceptable toxicity.

Toxicity and response assessment. Toxicity was graded by using the Common Terminology Criteria for Adverse Events, version 4.03 (CTCAE). Dose adjustments for RRx-001, regorafenib, irinotecan and bevacizumab were made depending on the toxicity observed with each treatment cycle. Within 28 days before treatment, patients were required to undergo a complete history and physical examination, including date and stage of CRC and of metastases, prior cancer therapy, site(s) of metastases, performance status, and review of symptoms. Patients also underwent the following tests: complete blood count, renal and hepatic function tests, pregnancy test for premenopausal women, and electrolytes. Tumor assessments with computerized tomography, or magnetic resonance imaging were required within 1 month before the start of treatment as well as all other tests. The overall response rate (ORR) was defined as the percentage of patients with complete or partial responses documented and subsequently confirmed (and using the ITT denominator of 24 and 10 patients in RxI and RegI arms, respectively. Missing responses were imputed as "nonresponders"). During treatment, history and physical examination, concomitant medications, hepatic and renal function tests, electrolytes, and toxicity assessment were performed at each clinic visit, once weekly for RRx-001, once monthly for regorafenib and once every 2 weeks for irinotecan. At each visit assessments of complete blood count and complete metabolic profile were collected. Assessment of response, including radiographic assessment, was performed approximately every 8 weeks.

Dose modifications. The doses of RRx-001, regorafenib and irinotecan were reduced in case of toxicity. Treatment was interrupted in the case of grade 2 or higher toxicity and was not resumed until the toxicity resolved or had improved to grade 0 or 1. The dose of RRx-001 was able to be reduced by 50% to 2 mg in case of intolerance, but no dose reductions occurred. The dose of regorafenib was reduced successively to 120 mg and 80 mg based on the package insert eg, in case of occurrence or re-occurrence of hand-foot skin reaction, after recovery of any grade 3 or grade 4 adverse reaction at 160 mg or 120 mg, and for grade 3 AST/ALT transaminitis. Regorafenib was discontinued in case of failure to tolerate the 80mg dose. In case of toxicity per the package insert 3 dose reductions of irinotecan were allowed: 140 to 150 mg/m^2, 110 to 120 mg/m^2 and 100 mg/m^2. No dose increases were allowed. Treatment was discontinued if, despite the dose reduction, the same toxicity occurred for a fourth time at grade 2, a third time at grade 3, or a second time at grade 4. In addition, if the toxicity had not improved to grade 0 or 1 after 3 weeks to allow the continuation of treatment, the patient was removed from the study.

Statistical Methods

This phase II trial was approved by local research Ethics Committees and patient enrollment began in June 2014. The primary endpoint was OS. Secondary endpoints included safety, PFS, and clinical benefit rate (ie, stable disease or better). The responses were assessed every 6 weeks, and complete and partial responses required subsequent confirmation. Survival endpoints (OS and PFS) were analyzed using the Kaplan-Meier method and median survival estimates were derived along with their corresponding 95% confidence intervals (Brookmeyer-Crowley 1982). OS was defined as the time from randomization to death from any cause. PFS was defined as the time from initiation of treatment to documented disease progression (ie, tumor volume > 20%) on irinotecan if the patient was fit enough to receive irinotecan after either RRx-001 or regorafenib, or documented disease progression on RRx-001 or regorafenib if the patient was not fit to receive irinotecan afterward. ORR was defined as the proportion of patients with a confirmed complete response (CR) or confirmed partial response (PR) per RECIST 1.1 criteria, based upon the best response, and was determined based on investigator assessment (according to RECIST 1.1 criteria). Clopper-Pearson 95% confidence intervals were derived for response rates. Clinical benefit was defined as CR, PR, or SD. There was only 1 missing response (RRx-001 plus irinotecan, 4.2% (1/24)) which was imputed as a nonresponse.

Efficacy Analyses

Analysis of efficacy data used the intention-to-treat population (all randomized patients). A total sample size of 34 subjects was determined based on prior clinical experiences with RRx-001 in various cancer types and published results of regorafenib studies in colorectal cancer. The planned (2-to-1) randomization was carried out for 34 patients (24 were primed with RRx-001 for 2 months, then received irinotecan and 10 were received regorafenib but none were deemed fit enough to receive subsequent irinotecan), and was motivated by generating sufficient data to allow for an estimation of the efficacy endpoints activity in irinotecan pretreated colorectal patients. Time-to-event survival curves were estimated using Kaplan Meier method and Brookmeyer-Crowley 95% CI for the medians were derived. Inferential comparisons of the survival curves (for OS and PFS) were compared using a two-sided log-rank test and Cox's proportional hazards model used to derive an estimate of the hazard ratio and its 95% CI (with RegI as a reference group). Fisher's exact test was used to compare the overall objective response (ORR) between the 2 arms.

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Table 1 Patients Baseline Characteristics

Age (in years)							
	Treatment	n	Mean	Median	SD	Min	Max
	regorafenib+irinotecan	10	53.6	49.5	11.2	43	79
	RRx-001+irinotecan	24	57.1	57.0	11.2	30	74
Sex (Male/Female)							
	Arm	M/F	n	%			
	regorafenib+irinotecan	F	7	70.0			
		M	3	30.0			
	RRx-001+irinotecan	F	12	50.0			
		M	12	50.0			
Race							
	Arm	Race	n	%			
	regorafenib+irinotecan	Asian	1	10.0			
		Missing	2	20.0			
		Native Hawaiian	1	10.0			
		White	6	60.0			
	RRx-001+irinotecan	Asian	4	16.7			
		Missing	7	29.1			
		Native Hawaiian	1	4.2			
		White	12	50.0			
ECOG							
	Arm	ECOG	n	%			
	regorafenib+irinotecan	0	7	70.0			
		1	3	30.0			
	RRx-001+irinotecan	0	12	50.0			
		1	11	45.8			
		Missing	1	4.2			

Safety Analysis

Safety data, including adverse events (AEs), serious adverse events (SAEs), ECOG performance status, clinical laboratory tests, vital signs and physical examination results were listed and summarized descriptively by treatment group. Adverse events were coded by system organ class (SOC) and preferred term using MedDRA (Version 18.1). Severity was based on NCI CTCAE Grade criterion (Version 5.0). Descriptive statistics (sample size, mean, median, standard deviation, quartiles, and range) and graphical methods (longitudinal plots) were used to present change from pretreatment values in laboratory parameters during the treatment period.

Results

Patients

The clinical features of all heavily pretreated 34 patients with a median number of 4 therapies enrolled in this study are listed in Table 1. All 34 eligible patients received at least 1 course of treatment. Fifteen patients that received RRx-001 were treated subsequently with irinotecan and no patients that received regorafenib were subsequently treated with irinotecan due to deteriorated performance statuses. Five patients treated with RRx-001 then followed with irinotecan in the randomized period also received bevacizumab.

Median age was 57.1 and 53.6 years for RxI and RegI, respectively. Females were 50% on RxI and and 70% on RegI. Whites were 50% and 60% on RxI and RegI, respectively. Median number of prior therapies was 4 for each arm. Fifty percent of RxI patients were ECOG 0 and 45.8% were ECOG 1 (and with 1 missing value, 4.2%). 70% of RegI patients were ECOG 0 and 30% were ECOG 1

Efficacy

The median follow-up was approximately 14.5 months (stand. dev 4.5 months). Of 24 patients on the RRx-001 arm, 13 experienced death or progression and out of the 10 patients on the regorafenib arm 6 experienced death or progression (see Table 2, below). An improvement in OS in favor of RxI over RegI was observed. Kaplan-Meier median OS for RxI and RegI were 8.6 and 4.7 months, respectively (see Figure 1A, below). The difference in OS curves was statistically insignificant (2-sided log-rank test $P = .4940$, see Table 3, below). The hazard ratio estimate was approximately 0.71 but statistically insignificant ($P = .4940$).

PFS Kaplan-Meier medians for RxI and RegI were 6.1 and 1.7 months, respectively (see Table 4 and Figure 2 C, below). The difference was statistically significant in favor of RxI (2-sided log-rank test $P = .0014$), see Table 5, below).

Overall Objective Response (ORR) was estimated as the percentage of patients experiencing CR or PR among the ITT patients (n = 34), and patients with missing response values were imputed as "nonresponders". ORR was approximately 20.8% (RxI) and 0% (RegI) (see Table 5, Table 6 and Figure 3, below).

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Table 2 Overall Survival Kaplan-Meier Median Estimates With Brookmeyer-Crowley 95% CI

Treatment	N at start	# Events	Median OS	Lower CI	Upper CI
Regorafenib+irinotecan	10	6	4.7	2.2	NA
RRx-001+irinotecan	24	13	8.6	4.8	NA

Figure 1 ROCKET treatment schema.

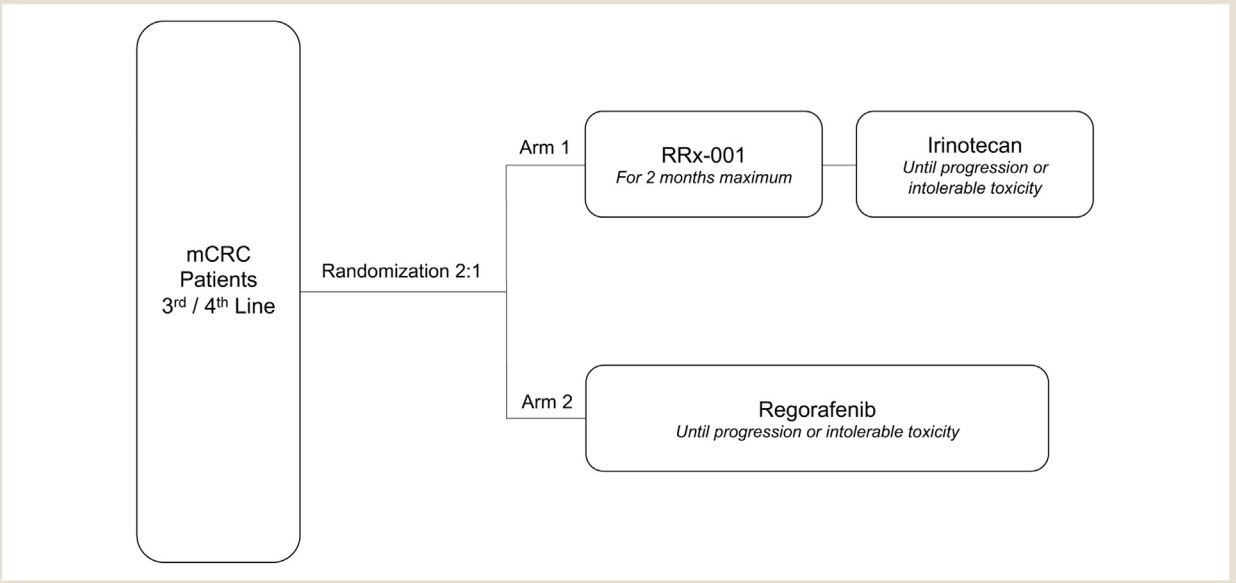

Table 3 Overall Survival Cox Proportional Hazards Model Results

Treatment	HR Lower CI	HR	HR Upper CI	*P*-value
RRx-001+irinotecan vs. Regorafenib+irinotecan	0.27	0.71	1.9	.494

Table 4 Progression Free Survival Kaplan-Meier Curves Estimates With Brookmeyer-Crowley 95% CI

Treatment	N at start	# Events	Median OS	Lower CI	Upper CI
Regorafenib+irinotecan	10	8	1.7	0.7	NA
RRx-001+irinotecan	24	12	6.1	3.7	NA

Table 5 Progression Free Survival Cox Proportional Hazards Model Results

Treatment	HR Lower CI	HR	HR Upper CI	*P*-value
RRx-001+irinotecan vs. Regorafenib+irinotecan	0.09	0.24	0.61	.003

Table 6 Overall Objective Response (ORR) Estimates Bar Plot, ITT Population

(RECIST) Response	Regorafenib+irinotecan n (%)	RRx-001+irinotecan n (%)
Sample size	10	24
PR	0 (00.0)	5 (20.8)
PD	6 (60.0)	6 (25.0)
SD	4 (40.0)	12 (50.0)
Nonevaluable	0 (00.0)	1 (4.2)
Clinical Benefit Rate	4 (40.0)	17 (70.8)
ORR Fisher's exact test *P*-value	.2980	

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Figure 2 (A) Overall survival Kaplan-Meier curves estimates. (B) Overall survival swimmer plot (C) Progression free survival Kaplan-Meier curves estimates. (D) Progression free survival swimmer plot.

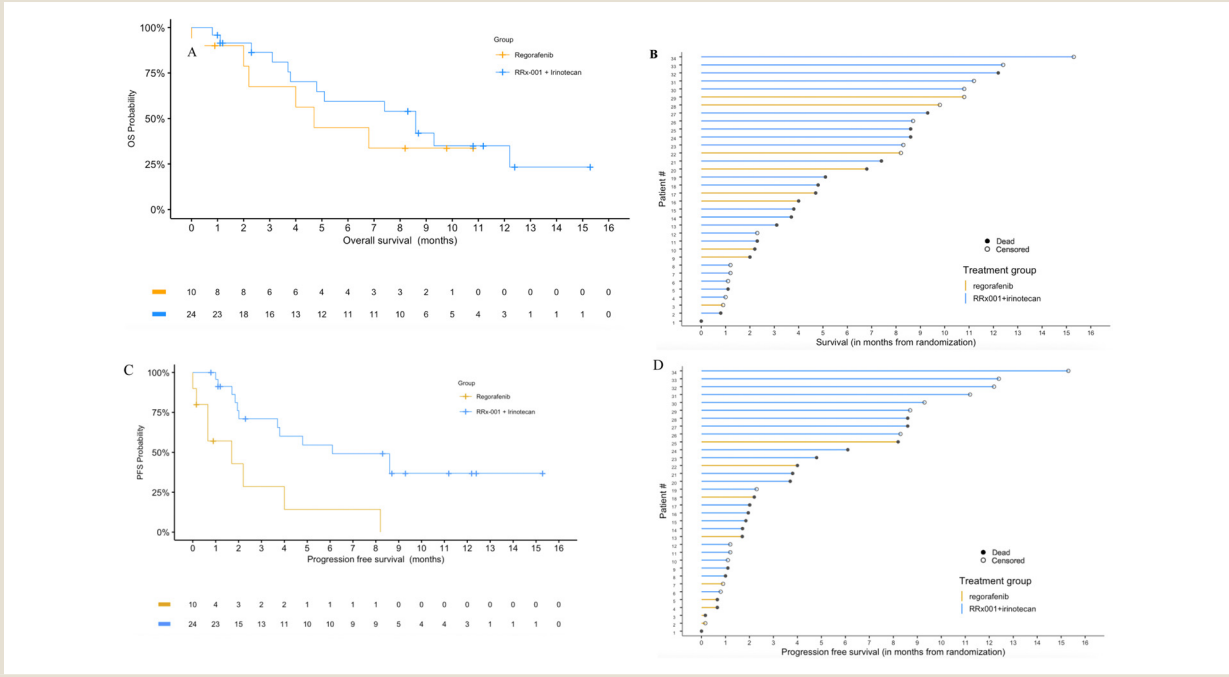
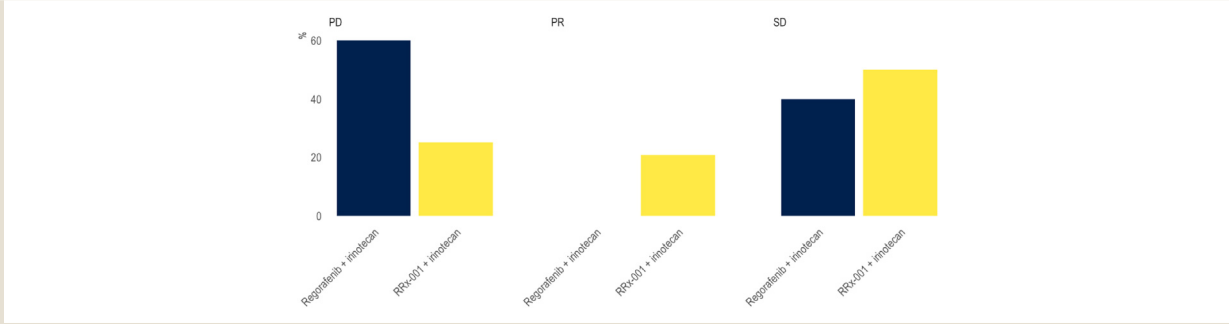


Figure 3 Overall Objective Response (ORR) estimates bar plot, ITT Population.



Safety

Safety was assessed in 34 patients consisting of the randomized 34 (24 RxI and 10 RegI.). For RxI the most common treatment emergent adverse event (see Table 7, below) was grade 1-2 infusion-related reaction, referring to localized transient pain or discomfort during the infusion, at 91.7% (22/24). For regorafenib the most common treatment emergent adverse events were fatigue (40%), hypertension at 20%, hyperbilirubinemia at 20%, decreased appetite at 50%, headache at 40%, and increased aspartate aminotransferase at 40%. No regorafenib patients received subsequent irinotecan due to degraded performance status.

Neutrophil count decrease (grade 3) was observed in 4.2% of the RxI patients (1/24), anemia was observed in 8.3% of the RxI patients and in 20% of RegI patients, with 10% grade 3 toxicity (1/10, RegI patient). Nonhematologic toxic effects were usually mild (mostly grade 1/2) and manageable. The most common nonhematologic toxic effects were anorexia, neuropathy, nausea, asthenia, and hyperbilirubinemia.

One SAE in a patient with a fatal GI bleed and an elevated INR due to near complete metastatic infiltration of the liver was attributed to RxI; however, it was later discovered that prodromal GI bleeding was present prior to this incident. Other than this SAE no other >grade 3 adverse events were attributed to RxI treatment.

Diarrhea was observed in 16.7% of RxI patients (4/24) where only 1 diarrhea event was deemed related to study drug. Among the 4 diarrhea events, 3 were of grade 1 and one was of grade 2. Figure 4,

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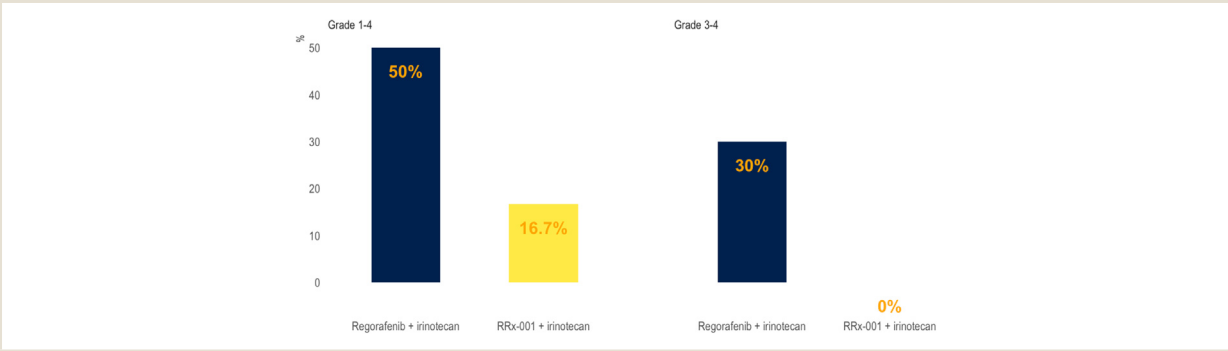
Table 7 Adverse Events With the Highest Frequency of Occurrence, Safety Population

Preferred Term	RRx-001 priming → Irinotecan	Regorafenib + Irinotecan	Total
Stomatitis	0 (0.0)	4 (40)	4 (11.8)
Vomiting	6 (25)	3 (30)	9 (26.5)
Fatigue	10 (41.7)	4 (40)	14 (41.2)
Hyperbilirubinaemia	0 (0.0)	2 (20)	2 (5.9)
Infusion related reaction	22 (91.7)	0 (0.0)	22 (64.7)
Aspartate aminotransferase increased	0 (0.0)	4 (40)	4 (11.8)
Weight decreased	1 (4.2)	3 (30)	4 (11.8)
Decreased appetite	4 (16.7)	5 (50)	9 (26.5)
Headache	3 (12.5)	4 (40)	7 (20.6)
Hypertension	2 (8.3)	2 (20)	4 (11.8)

Figure 4 Diarrhea incidence rate in ROCKET and per Irinotecan approval label.



below, depicts diarrhea incidence on ROCKET as contrasted to Irinotecan (per approval label) diarrhea incidence. A meaningful reduction of the diarrhea incidence is apparent on RxI with 0% grade 3-4 as opposed to irinotecan 30% rate.

Discussion

This study showed that priming with RRx-001 followed by irinotecan administration could be an effective regimen for third or fourth-line treatment of advanced colorectal cancer and that this combination was more active and significantly less toxic than regorafenib. Although the reliability of conclusions that can be drawn are very limited due to the small size of the study and require confirmation in a larger setting, these data may suggest that priming with RRx-001 prior to the administration of irinotecan may lead to better ORR, significant amelioration of PFS and better OS outcomes than regorafenib.

This improvement in ORR, PFS, and OS may be attributable to the use of irinotecan after RRx-001. While all patients enrolled on the study had previously progressed on an irinotecan-based regimen, RRx-001 may have "primed" tumors to re-respond to irinotecan. Retreatment of tumors with chemotherapy to which the tumor has become resistant is recognized in certain malignancies. For example, ovarian cancer with platinum-based chemotherapy can result in therapeutic benefit in certain patients. However, requirements for retreatment include tumors that were initially platinum sensitive, a platinum-free interval of greater than six months and several intervening nonplatinum-based therapies.[13] We restricted the RRx-001 pretreatment interval to 8 weeks, which would not be expected to be sufficient time to allow for spontaneous resensitization of tumor that had progressed on the same therapy. The mechanism of the "priming" effect is being investigated and current research efforts are focused on the capacity of RRx-001 to inhibit MYC, downregulate CD47 and repolarize tumor resident macrophages. Notably, 63% (15/24) of the RRx-001-treated patients were systemically well enough to receive irinotecan after 8 weeks of priming with RRx-001. In contrast, the median time to progression of patients on regorafenib was 7 weeks and none of the patients (0/10) on the regorafenib arm received subsequent irinotecan-based therapy due to death or deteriorating performance status. This finding suggests a favorable risk/benefit ratio and the potential for an improved quality of life with RRx-001. However, a true head-to-head comparison was not possible due to the rapid deterioration of the patients who received treatment with regorafenib.

The main adverse event associated with irinotecan is severe diarrhea and it is noteworthy that none of the irinotecan-treated patients on study experienced it, which may be secondary to RRx-001 mediated chemoprotective effects since potential evidence of chemoprotection has been seen in other RRx-001 trials as well as preclinical studies.[14]

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The primary objectives, which were to show at least a 3-month improvement of PFS and OS, were achieved.

We intend to carry out further late-stage clinical trials to better understand the results of this trial comparing the combination of priming with RRx-001 followed by irinotecan vs. regorafenib including in a large randomized controlled phase III confirmatory setting.(Table 6)

Clinical Practice Points

- Colorectal cancer (CRC) is the second most lethal cancer worldwide. Despite the availability of several cytotoxic and targeted therapy options for patients with metastatic CRC, the median OS is only 30 months, representing a high unmet clinical need. In third or later lines, therapeutic options for metastatic colorectal patients are limited to regorafenib or trifluridine/ tipiracil (Lonsurf), both of which are associated with only minimally improved clinical outcomes, as PFS is approximately 2.0 months and objective response rates are not usually seen.
- The hypothesis of the ROCKET trial was that RRx-001 would resensitize colorectal patients to irinotecan, thereby improving OS, PFS, and ORR. The objectives of the study were met. Median OS was 8.6 months for RRx-001 + irinotecan vs. 4.7 months for regorafenib. Median PFS was 6.1 months for RRx-001 + irinotecan vs. 1.7 months for regorafenib, a statistically significant result, two-sided log-rank test, $P = .0030$. The ORR was 20.8% for RRx-001 + irinotecan vs. 0% for regorafenib. In addition, the toxicity profile of RRx-001 + irinotecan was substantially improved compared with regorafenib. These results for regorafenib generally accorded with the OS, PFS, ORR, and toxicity profile from the phase III CORRECT trial, which led to the approval of regorafenib.

Disclosure

The authors have stated that they have no conflicts of interest.

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Please cite this article as: Tony R. Reid et al, ROCKET: Phase II Randomized, Active-controlled, Multicenter Trial to Assess the Safety and Efficacy of RRx-001 + Irinotecan vs. Single-agent Regorafenib in Third/Fourth Line Colorectal Cancer, Clinical Colorectal Cancer, https://doi.org/10.1016/j.clcc.2022.11.003