CLINICAL STUDY PROTOCOL

Protocol No.	RRx001-21-02
Product	RRx-001
Title:	A Phase 2 Randomized, Open-Label Study of RRx-001 vs Regorafenib in Subjects with Metastatic Colorectal Cancer
Development Phase	Phase 2
IND #:	107,674
Version: Original	15 November 2013
Amendment No.	Amendment 08
Date:	09 November 2016
Sponsor:	EpicentRx, Inc. 800 W. El Camino Real, Suite 180 Mountain View, CA 94040
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INVESTIGATOR AGREEMENT PAGE

EpicentRx, Inc.

Protocol No. RRx001-21-02,
A Phase 2 Randomized, Open-Label Study of RRx-001 vs Regorafenib in Subjects with Metastatic Colorectal Cancer
Version: Amendment 08
09 November 2016

I will provide copies of the protocol, any subsequent protocol amendments and access to all information provided by the Sponsor to the study personnel under my supervision. I will discuss this material with them to ensure that they are fully informed about the investigational drug and the study protocol.

I agree to conduct this clinical trial according to the attached protocol, except when mutually agreed to in writing. I also agree to conduct this study in compliance with all federal, state and local regulations, as well as with the requirements of the appropriate Institutional Review Board and any other institutional requirements.

_____ _____

Principal Investigator **Date**

Printed Name: _____

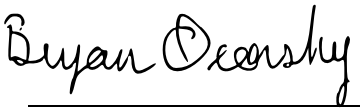
Institution: _____

PROTOCOL APPROVAL PAGE

TITLE: A Phase 2 Randomized, Open-Label Study of RRx-001 vs Regorafenib in Subjects with Metastatic Colorectal Cancer

SPONSOR:

EpicentRx, Inc.
800 W. El Camino Real
Mountain View, CA 94040



09 November 2016

Bryan Oronsky, M.D. Date

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1.0 STUDY SYNOPSIS

Protocol Title:	A Phase 2 Randomized, Open-Label Study of RRx-001 vs Regorafenib in Subjects with Metastatic Colorectal Cancer
Sponsor:	EpicentRx, Inc.
Active Ingredient:	RRx-001
Study Phase:	Phase 2
Number of Study Sites:	Up to 10
Study Design:	This is a two-stage phase 2, open-label, randomized (2:1), two-arm study comparing RRx-001 vs regorafenib in subjects with metastatic colorectal cancer who have been treated with at least oxaliplatin- and irinotecan-based regimens with bevacizumab and cetuximab or panitumumab (if KRAS wildtype). Effective August 15th, 2016, general enrollment for this protocol has been closed to new enrollment. An expansion cohort remains open at Stanford University with the potential to enroll up to 10 patients. The following content is maintained for intent of overall evaluation of previously enrolled and new patients enrolled by Stanford: **Stage 1** • Arm 1 – subjects will receive once-weekly intravenous, by blood mix administration, RRx-001 for up to 4 hours at a dose of 4 mg on Days 1, 8, 15, and 22 of a 4-week cycle. • Arm 2 – subjects will receive regorafenib at 160 mg orally daily on Days 1-21 of a 4-week cycle. To determine progression and entry to Stage 2, CT or MRI response will be evaluated according to immune related response criteria (irRC) (for evaluation of response or progression on irinotecan, RECIST 1.1 criteria will be used, see below). However, for informational purposes, since the presence of treatment-induced inflammation may confound interpretation of radiologic scans, RRx-001 subjects may receive an FDG-PET (see Section 9.1.2). Patients will receive RRx-001 until intolerable toxicity or progression as defined by Immune Related Response Criteria. Note: Continuation of RRx-001 per irRC past the initial scan at Week 12 to the confirmatory scan at Week 16 (no earlier) following the appearance of a new lesion is only permissible provided the following criteria stated below are met: • In order to allow continued administration of RRx-001 (or regorafenib) despite progression of disease based on appearance of a new lesion (per irRC), patients must have absence of symptoms and signs of clinically important morbidity due to disease progression (e.g., requirement for additional medical management to control symptoms or irradiation to prevent morbidity), absence of symptomatic rapid disease progression requiring urgent medical intervention (e.g., spinal cord compression), and no decline in ECOG or Karnofsky performance status. • Patients are re-consented using a written informed consent document at the time of progression of disease.

	Stage 2 On progression, provided ECOG performance status is 0 or 1, and if clinically appropriate i.e. there are no absolute or relative contraindications in the opinion of the Investigator, all subjects will receive irinotecan plus bevacizumab: (irinotecan 180 mg/m^2 iv on day 1 of each 2 week cycle) see Section 6.1.3. Prior to entering stage 2, *all* study patients will need to meet Inclusion Criterion #10 regarding required laboratory parameters (a-e) (Inclusion Criteria). This two-stage study is designed to compare the safety and activity between RRx-001 against regorafenib followed by irinotecan-based therapies in a parallel comparative study. Subjects with confirmed progression from their last treatment will be randomized 2:1 to receive either RRx-001 or regorafenib in 4-week cycles until confirmed radiologic progressive disease per irRC and clinical deterioration or intolerable toxicity (Section 9.1.2). The study is also designed to investigate potential resenitization to irinotecan therapies post RRx-001 or regorafenib. Subjects will undergo long term follow up for their response to subsequent therapy and for overall survival. See Appendix 9 for Study Schema
Objectives:	• Primary Objective: • To assess and compare the overall survival (OS) in the RRx-001 vs regorafenib treatment arms. • Secondary Objectives: • To assess and compare Progression Free Survival 2 (PFS2) as a surrogate for overall survival (OS) in the RRx-001 vs regorafenib treatment arms. • To assess and compare the safety and tolerability in the RRx-001 vs regorafenib treatment arms. • To assess and compare objective response rate (ORR) in the RRx-001 vs regorafenib treatment arms. • To assess and compare the clinical benefit rate (CBR = CR+PR + SD≥4 months) in the RRx-001 vs regorafenib treatment arms. • To assess and compare the progression free survival (PFS) in the RRx-001 vs regorafenib treatment arms. • To assess and compare the duration of response (DOR) in the RRx-001 vs regorafenib treatment arms. • To assess and compare the duration of clinical benefit (DCB) in the RRx-001 vs regorafenib treatment arms. • To assess and compare the response and clinical benefit to subsequent therapies in the RRx-001 vs regorafenib treatment arms. • To assess and compare the quality of life (QOL) in the RRx-001 vs regorafenib treatment arms using the EORTC QLQ-C30 questionnaire. • Exploratory Objectives: o To assess the impact of RRx-001 on tumor blood flow by Contrast Enhanced Ultrasound (CEUS)
Subject Population and Sample Size:	Subjects with metastatic colorectal cancer who have been treated with oxaliplatin- and irinotecan-based regimens with bevacizumab and cetuximab or panitumumab (if KRAS wildtype) and that are refractory to irinotecan and do not have a history

	of an allergic reaction or intolerance to irinotecan will be enrolled in this study. Approximately 190 subjects will be randomized (127 RRx-001 and 63 regorafenib). The study has been powered based upon observing 123 deaths in total. The number of subjects randomized may increase or decrease depending upon the observed OS rates. Due to the changes in Amendment 01 onward, particularly with respect to inclusion/exclusion criteria and study design, subjects that were enrolled prior to Amendment 01 will be analyzed for safety only. Due to the changes in Amendment 08 onward, up to 10 additional patients will be enrolled by Stanford only at which point data will be analyzed.
Inclusion Criteria:	Eligible subjects must meet **all** of the following Inclusion Criteria: 1. Subject is capable of understanding the purpose and risks of the study and is able to provide written Informed Consent; 2. Subject is male or female, aged at least 18 years; 3. Histological or cytological documentation of adenocarcinoma of the colon or rectum; 4. Subject must have received at least oxaliplatin-, and irinotecan-based regimens with bevacizumab and with, cetuximab or panitumumab if KRAS wildtype and are refractory to irinotecan; 5. Subject has measurable disease per RECIST v1.1 by radiographic techniques (computerized tomography [CT] or magnetic resonance imaging [MRI]); 6. Subjects with a history of brain metastasis are eligible for the study as long as they meet all the following criteria: their brain metastases have been treated, they have no evidence of progression or hemorrhage after treatment, have been off dexamethasone for 4 weeks prior to first study drug administration, and have no ongoing requirement for dexamethasone or anti-epileptic drugs; 7. Ability to evaluate p53 status, via archival slides or fresh biopsy. Patients without archival slides or who are not candidates for fresh biopsy may continue on study and will be excluded from this evaluation. 8. Life expectancy of at least 12 weeks 9. Subject's Eastern Cooperative Group (ECOG) performance status is 0 or 1; 10. Laboratory parameters as follows: a. Absolute neutrophil count (ANC) $\geq$1,500/mm$^{3;}$ b. Platelets $\geq$75,000/mm^3; c. Hemoglobin $\geq$9.0 g/dL; d. Normal serum creatinine or a measured or calculated creatinine clearance > 50 mL/min (based on the Cockroft-Gault formula); e. AST and ALT $\leq$2 x ULN ($\leq$5.0 × ULN for subjects with liver involvement of their cancer); f. Bilirubin $\leq$1.5 X ULN; g. Alkaline phosphatase $\leq$2.5 x ULN ($\leq$5 x ULN with liver involvement of their cancer); 11. Subject must provide consent to the access, review and analysis of previous medical and cancer history, including archival tissue and imaging data by the Sponsor or a Third Party nominated by the sponsor. 12. Fertile subjects must use effective contraception during the course of the study and for 30 days following withdrawal from the study; 13. Subject is willing and able to comply with all protocol procedures, evaluations and rescue measures 14. Measurable Lesions in the Liver suitable for CEUS imaging

Exclusion Criteria:	Subjects will be ineligible for study participation if they meet **any** of the following Exclusion Criteria: 1. Clinically significant cardiovascular disease; 2. Unresolved toxicity higher than CTCAE (v. 4.03) Grade 2 attributed to any prior therapy/procedure excluding alopecia, hypothyroidism, oxaliplatin-induced neurotoxicity and EGFR-targeted therapy induced skin rash for at least 14 days; 3. Evidence or history of tendency or predisposition to active bleeding. Any hemorrhage or bleeding event of CTCAE grade 3 or higher within 4 weeks of start of study medication; 4. Symptoms or signs of active brain metastases; 5. History of an allergic reaction or intolerance to irinotecan 6. Hepatic encephalopathy 7. Cholangitis that required treatment or intervention within 4 weeks of study enrollment 8. Concurrent anticancer therapy or any cytotoxic therapy within 14 days prior to Day 1. Corticosteroid therapy is not allowed except on dosing days; 9. Subject has previously received regorafenib; 10. Clear contraindication for systemic corticosteroids (diabetes mellitus is not per se a clear contraindication); 11. Subjects with a serious co-morbid medical condition, or a clinically significant laboratory finding(s) or any finding(s) on history and/or examination that, in the opinion of the Investigator, could interfere with the conduct of the study or could put the subject at unacceptable risk; 12. Severe hypoalbuminemia (albumin < 3.0 g/dL); 13. Previous exposure to etirinotecan pegol (NKTR-102) 14. Subjects who are pregnant or lactating or who are planning to become pregnant during the course of the study are excluded.
RRx-001, Dose, Dose Schedule and Mode of Administration:	**RRx-001 Drug Product and Diluent Product:** RRx-001 Drug Product is supplied as a sterile solution in PEG-400. Prior to administration, DMA will be added to RRx-001 Drug Product to yield a solution containing 66% PEG-400 and 33% DMA. This solution will then be diluted to 2.0 mg/mL with Water for Injection (WFI). Each dose of RRx-001 will be administered via an intravenous infusion. A list of preferred infusion sets is listed in the Pharmacy Manual and in Appendix 8. All doses of RRx-001 will be administered on an open-label basis. Full details for preparation of the RRx-001 infusion can be found in the Pharmacy Manual. **Dose and Dose Schedule:** The dose in this trial will be 4 mg based on ongoing evidence of activity. The dose of 4 mg translates to 2 mL, which will be mixed with an aliquot of autologous blood and anticoagulant ACDA and re-infused into the subject once a week over an expected time period of less than an hour and, for safety, this must not to exceed four (4) hours of blood collection. The procedure is outlined in detail in the latest version of the *Blood Administration Best Practices & Guidelines for IV Infusion of RRx-001 + Blood Mix.* The dosing schedule window may vary ± 1 day for subject convenience or clinic schedules. **Dose and Dosage Modifications:** Dose interruptions are permitted.

<table>
<tr><td></td><td>Dose modifications arising from subject intolerance of the infusion reaction and/or physician preference are permitted as follows:
<table>
<tr><th>Sequential Dose Modification</th><th>RRx-001 Dose</th><th>Infusion Time</th><th>Frequency</th><th>Interval</th></tr>
<tr><td>Initial</td><td>4 mg</td><td>Up to 4 h from time of blood extraction</td><td>1 x week</td><td>Separated by 7 days ± 1 day</td></tr>
<tr><td>Dose reduction option</td><td>2 mg</td><td>Up to 4 h from time of blood extraction</td><td>1 x week</td><td>Separated by 7 days ± 1 day</td></tr>
</table></td></tr>
<tr><td>Regorafenib:</td><td>Regorafenib:
<u>Effective August 15th, 2016, general enrollment for this protocol has been closed to new enrollment. An expansion cohort remains open at Stanford University with the potential to enroll up to 10 additional RRx-001 patients.</u>

For patients previously randomized and enrolled to the Regorafenib arm:

Regorafenib will be commercially supplied and prescribed as described in the package insert and paid for by insurance. It is supplied as light pink oval shaped tablets containing 40 mg of regorafenib in the anhydrous state, which corresponds to 41.49 mg of regorafenib monohydrate.

Dose and Dose Schedule:
The recommended dose of regorafenib is 160 mg (four 40 mg tablets) taken orally once daily for the first 21 days of each 28 day cycle. Regorafenib is to be administered as described in the package insert.

Dose Modifications:
Dose modifications of regorafenib due to adverse events are to be adjusted based on the package insert per standard clinical practice.</td></tr>
<tr><td>Irinotecan</td><td>Irinotecan:
The recommended dose for irinotecan will be 180 mg/m^2 every two (2) weeks. Recommended dose alterations for toxicity from the FDA approved irinotecan product information are shown below (Camptosar (irinotecan hydrochloride injection). US FDA-approved product information):</td></tr>
</table>

Table 11. Recommended Dose Modifications for CAMPTOSAR/5-Fluorouracil (5-FU)/Leucovorin (LV) Combination Schedules

Patients should return to pre-treatment bowel function without requiring antidiarrhea medications for at least 24 hours before the next chemotherapy administration. A new cycle of therapy should not begin until the granulocyte count has recovered to ≥1500/mm³, and the platelet count has recovered to ≥100,000/mm³, and treatment-related diarrhea is fully resolved. Treatment should be delayed 1 to 2 weeks to allow for recovery from treatment-related toxicities. If the patient has not recovered after a 2-week delay, consideration should be given to discontinuing therapy

Toxicity NCI CTC Grade[a] (Value)	During a Cycle of Therapy	At the Start of Subsequent Cycles of Therapy[b]
No toxicity	Maintain dose level	Maintain dose level
Neutropenia		
1 (1500 to 1999/mm³)	Maintain dose level	Maintain dose level
2 (1000 to 1499/mm³)	↓ 1 dose level	Maintain dose level
3 (500 to 999/mm³)	Omit dose until resolved to ≤ grade 2, then ↓ 1 dose level	↓ 1 dose level
4 (<500/mm³)	Omit dose until resolved to ≤ grade 2, then ↓ 2 dose levels	↓ 2 dose levels
Neutropenic fever	Omit dose until resolved, then ↓ 2 dose levels	
Other hematologic toxicities	Dose modifications for leukopenia or thrombocytopenia during a cycle of therapy and at the start of subsequent cycles of therapy are also based on NCI toxicity criteria and are the same as recommended for neutropenia above.	
Diarrhea		
1 (2-3 stools/day > pretx[c])	Delay dose until resolved to baseline, then give same dose	Maintain dose level
2 (4-6 stools/day > pretx)	Omit dose until resolved to baseline, then ↓ 1 dose level	Maintain dose level
3 (7-9 stools/day > pretx)	Omit dose until resolved to baseline, then ↓ 1 dose level	↓ 1 dose level
4 (≥ 10 stools/day > pretx)	Omit dose until resolved to baseline, then ↓ 2 dose levels	↓ 2 dose levels
Other nonhematologic toxicities[d]		
1	Maintain dose level	Maintain dose level
2	Omit dose until resolved to ≤ grade 1, then ↓ 1 dose level	Maintain dose level
3	Omit dose until resolved to ≤ grade 2, then ↓ 1 dose level	↓ 1 dose level
4	Omit dose until resolved to ≤ grade 2, then ↓ 2 dose levels	↓ 2 dose levels
	For mucositis/stomatitis decrease only 5-FU, not CAMPTOSAR	*For mucositis/stomatitis decrease only 5-FU, not CAMPTOSAR.*

[a] National Cancer Institute Common Toxicity Criteria (version 1.0)
[b] Relative to the starting dose used in the previous cycle
[c] Pretreatment
[d] Excludes alopecia, anorexia, asthenia

Recommended dose reductions for irinotecan.

Starting Dose of Irinotecan (mg/m^2)	Dose level -1 (mg/m^2)	Dose level -2 (mg/m^2)	Dose level -3 (mg/m^2)
180	140-150	110-120	100

Duration of Treatment:

In the absence of unacceptable treatment-related toxicity or disease progression as defined by the protocol, subjects may receive treatment to which they have been randomized (Arm 1, RRx-001 or Arm 2, regorafenib) for up to 1 year at the discretion of the Investigator and beyond 1 year with the agreement of the Investigator and the Sponsor. Subjects will remain on study as long as they continue to receive RRx-001, regorafenib or irinotecan plus bevacizumab.

Subjects randomized to regorafenib are not permitted to crossover to receive RRx-001.

Methodology:

Effective August 15th, 2016, general enrollment for this protocol has been closed to new enrollment. An expansion cohort remains open at Stanford University with the potential to enroll up to 10 patients.

- Subjects will now be enrolled to RRx-001 only
- Subjects receiving RRx-001 will receive RRx-001 as described in RRx-001 dose section above
- Subjects receiving regorafenib will receive regorafenib daily as described in

	the regorafenib package insert • Subjects receiving irinotecan will receive these agents as described in the irinotecan and bevacizumab (Section 6.1.3) • After progression on either arm, subjects will receive irinotecan-based therapies until progression. **General procedures:** • Subjects will be screened for eligibility within the twenty-eight (28) days prior to enrollment according to the Schedule of Assessments. • Tumor assessment (see below) will be performed at Screening unless a CT or MRI was performed within 28 days of Cycle 1, Day 1. • Diagnostic CT with contrast (see Section 9.1.2) will be carried out for RRx-001 randomized subjects at Baseline. . • A diagnostic CT scan with contrast for RRx-001 subjects that are at Stage 2 (i.e. receiving irinotecan/bevacizumab therapies) will be carried out at the first scheduled imaging visit after starting irinotecan. • In addition to safety labs as indicated in the Schedule of Assessments, blood may be drawn for the biomarker assays at Screening, Cycle 2, Day 1 and Progression. • Tumor biopsies may be performed following discussion and concurrence with the Medical Monitor. • Determination of p53, PDI and beta glucoronidase (RRx-001 subjects): Documentation of p53 status can occur via the following: 1) Prior genetic testing/profiling results; 2) Submission of archival tissue to local laboratory if site has the required capabilities; or 3) Submission of archival tissue to central laboratory. Only in the event that p53 status is unknown and there is not sufficient archival tissue to be submitted, the patient should undergo a research biopsy of the primary tumor if deemed clinically appropriate. • Subjects will undergo a full physical exam at Screening. • Subjects will undergo all assessments including laboratory evaluations, vital signs and symptom-directed physical exam every 2 weeks during Cycles 1-2, then every 4 weeks from Cycle 3+. • Subjects will be imaged by contrast-enhanced chest/abdomen/pelvic CT (or non-contrast chest CT + abdomen/pelvic MRI if iodinated contrast is contraindicated) every 8 weeks per institutional standard of care. MRI is permitted if the subject in intolerant of CT contrast agent or if MRI is the best imaging modality for a given tumor site. The same imaging modality for tumor assessments for each subject should be performed throughout the study. • At progression, subjects may have blood drawn for biomarker assays. • Subjects will complete the QOL questionnaire every 2 weeks at a clinical visit. • Females of child-bearing potential will receive a serum pregnancy test at screening. • Adverse events (AEs) and concomitant medications will be collected throughout the study at clinical visits. • CEUS will be performed in patients, at the discretion of the Principal Investigator and Radiologist, with liver metastases before and after RRx-001 treatment and also be used to assess tumor response with irinotecan post-RRx-001 in accordance with the schedule outlined in the Schedule of Assessments. (Subjects enrolled at Stanford University only, see Appendix 6). • The physician will complete the ESASr Assessment at Screening and the first week of every cycle. Questionnaire is not required at Cycle 1 Day 1 if screening ESASr Assessments completed within 48 hours prior. An increase of 2 or more points is classified as deteriorated, a change of 0 or ±1 as stable, and a decrease of 2 or more as improved. If the ESAS increases by two or more

	points, compared to baseline, indicating deterioration, then the patient should be scanned for progression. • Other tests and evaluations that are to be performed during Screening and at each visit to the study center are detailed in Table 1, Schedule of Assessments.
Criteria for Evaluation	**Safety:** All available data will be provided to an independent Data Monitoring Committee (DMC) at the interim and final efficacy analyses to also review safety. There will be 2 planned analyses; an interim analysis once 61 (50%) OS events have occurred, and a final analysis once enrollment has been completed and 123 OS events have occurred. Safety will be assessed by periodic physical examinations, clinical laboratory assessments, and monitoring of adverse events (AEs). Adverse events will be graded using NCI CTCAE version 4.03. **Efficacy:** Radiographic and/or physical assessments of the malignancy will be made at Screening/Baseline (within 28 days prior to the first study drug administration) and every 2 cycles (8 weeks ±7 days) thereafter. Objective response (complete response [CR] and partial response [PR]) as determined by the subject's best tumor response, duration of response, and time to progression will be assessed by the Investigator radiologic review using immune related response criteria (irRC) for RRx-001 response and Response Evaluation Criteria in Solid Tumors Criteria (RECIST) version 1.1 for irinotecan response. A confirmatory CT/MRI scan should be performed at approximately 4 weeks from the previous scan for all patients with an objective response of ≥ PR. The Clinical Benefit Rate (CBR = CR + PR + stable disease [SD] of ≥4 months duration) will also be determined. Tumor markers will also be assessed on a monthly basis, but will not be used as a basis for disease progression or response in the absence of radiologic findings consistent with disease or progression or response.
Exploratory Assessments:	**Tumor Biopsy:** Tumor biopsies may be performed as needed following discussion and approval by the Medical Monitor. **Biomarker Assays:** Determination of p53, PDI and beta glucoronidase (RRx-001 subjects only): Documentation of p53 status can occur via the following: 1) Prior genetic testing/profiling results; 2) Submission of archival tissue to local laboratory if site has the required capabilities; or 3) Submission of archival tissue to central laboratory. Only in the event that p53 status or level of PDI expression is unknown and there is not sufficient archival tissue to be submitted, the patient should undergo a research biopsy of the primary tumor if deemed clinically appropriate. Soluble PD-L1, epigenetic markers and Serum glutamine levels and RRx-001 transporter effects including Transferrin receptor-1 (TfR1), ASC amino-acid transporter 2 (ASCT2), and the cystine/glutamate antiporter (system xc) and glutamine transporter blockade will be studied.
Statistical Methods:	**Determination of Sample Size:** Effective August 15th, 2016, general enrollment for this protocol has been closed to new enrollment. An expansion cohort remains open at Stanford University with the potential to enroll up to 10 patients. The following content is maintained for intent of overall evaluation of previously enrolled and new patients enrolled by Stanford: We hypothesize that the administration of RRx-001 as a single agent for relapsed metastatic colorectal cancer that have failed 2 prior lines of systemic therapy,

	including adjuvant therapy, will increase median OS by 3 months (i.e., from 6 to 9 months) when compared to the control therapy of regorafenib. Such an increase in median OS corresponds to a 33% reduction in the risk of death (i.e., target hazard ratio of 0.667). As this is a proof of concept study, the comparison between the two arms will be made at a 10% (one-sided) significance level. Based on a log-rank test and 2:1 randomization ratio between treatment arms, a total of 123 death events from the 2 treatment arms are required to detect such an improvement in the RRx-001 treatment arm compared to control with 80% power. As part of these calculations, it has been assumed that there will be uniform enrollment over a 12-month period, there will be a minimum 6 months follow-up per subject and survival data will be obtained for all but an insignificant number of subjects. It is expected that 190 subjects will be randomized with 2:1 randomization to achieve 123 events. Study follow-up will continue until it is projected that there will be approximately 123 events. The primary inferential comparison between treatment groups will use the log-rank test using the full analysis population defined as randomized subjects receiving at least one dose of study treatment and not violating the following inclusion/exclusion criteria: Exclusion Criteria: 4. Symptoms or signs of active brain metastases; 6. Cholangitis that required treatment or intervention within 4 weeks of study enrollment **Safety Analyses:** Safety data analysis will be conducted on all subjects receiving at least 1 dose of RRx-001 or regorafenib. Analyses will consist of data summaries for clinical and laboratory parameters, and for AEs. The safety data will be summarized by treatment arm. The number and percentage of subjects experiencing 1 or more AEs will be summarized by the relationship to study drug and severity. Adverse events will be coded using Medical Dictionary for Regulatory Activities (MedDRA) terminology. Laboratory parameters will be summarized using descriptive statistics, by post-dosing shifts relative to baseline, and data listings of clinically significant abnormalities. Vital signs will be summarized by changes from baseline values using descriptive statistics. **Efficacy Analyses:** All available data will be provided to an independent Data Monitoring Committee (DMC) at the interim and final efficacy analyses. The primary efficacy endpoint is OS, defined as the number of months from randomization to death due to any cause. OS will be summarized descriptively using the Kaplan-Meier method. Median OS will be estimated for each treatment group from the 50th percentile of the corresponding Kaplan-Meier estimates. The primary inferential comparison between treatment groups will use the log-rank test using the full analysis population defined as randomized subjects receiving at least on dose of study treatment. The hazard ratio will be estimated using a Cox proportional hazards model. Similar analyses will be performed for progression free survival. A summary of anticancer therapies received after ending protocol therapy will be provided. Efficacy outcomes based upon response will be assessed using irRC for RRx-001 and RECIST (version 1.1) for irinotecan. Such outcomes will be determined by the local Investigator and will serve as the data source for these analyses. Objective response rate and clinical benefit rate will be compared using the chi-square test.

	For all estimates, 95% 2-sided confidence intervals will be calculated. The duration of objective response and clinical benefit response will be described descriptively using the Kaplan-Meier method. We also prospectively plan to conduct exploratory subgroup analyses on the following populations: 1. Subjects with KRAS, BRAF or P53 mutations 2. Subjects with prior bevacizumab or cetuximab therapy 3. Subjects with prior oxaliplatin therapy 4. Subjects with prior irinotecan therapy 5. Subjects with prior 5-FU based therapy A single interim analysis for futility is planned at the time that 50% of the total death events are expected. The objective of the futility analysis is to stop randomization to the study if there is sufficient evidence that such therapy is not improving outcomes relative to the control therapy. As the intent of the interim analysis is for futility only, no adjustment to the type I error at the final analysis is proposed. An independent statistical service provider will perform the interim efficacy analysis. On further review, given the lack of systemic toxicity observed to date, a data monitoring committee will only be convened to review significant serious adverse events and unacceptably frequent adverse events. **Exploratory Analyses:** CEUS results will be summarized descriptively for the RRx-001 treatment arm. **Considerations for Amendment 01:** Due to the changes in Amendment 01 onward, particularly with respect to inclusion/exclusion criteria and study design, subjects that were enrolled prior to Amendment 01 will be analyzed for safety only.

1.1 Schedule of Assessments

Table 1: Schedule of Assessments

	Screening /Baseline Within 28 Days[1]	Cycle 1 (all ±1 day)				Cycle 2 (all ±1 day)				Cycle 3 (all ±1 day)				Cycle 4 (all ±1 day)						
Procedures and Cycles		W1	W2	W3	W4	W1	W2	W3	W4	W1	W2	W3	W4	W1	W2	W3	W4	At PD[13]	Stage 2 Post PD[14]	Survival[15]
Informed consent	X[1]																	X		
Selection criteria assessment	X[1]																	X[1]		
Medical History/Demographics	X[1]																			
Enrollment[2]	X[1]																			
Clinic Visit: Includes Full PE, ECOG, Vitals, Weight, Height[3]	X[1,3]	X		X		X		X		X				X				X		
Tumor Assessment[4]	X[1]												X				X			
CT imaging (RRx-001 subjects only)[5]	X[1,5]																	(X)	X[5]	
Laboratory Assessments[6]	X[1,6]	X		X		X		X		X				X					X	
Urinalysis	X[1]																			
Pregnancy test (WOCBP subjects only)[7]	X[1]	X																X		
Tumor sample submission[8]	X[1]																			
QOL questionnaire[9]	X[1]	X		X		X		X		X				X					X	
Concomitant Medications/procedures[10]	X[1]	X		X		X		X		X		X		X		X		X	X	
Adverse events[10]		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
RRx-001 administration[11]		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X			
Regorafenib administration[12]		X	X	X		X	X	X		X	X	X		X	X	X				
Irinotecan-based therapies[14]																			X	
Overall survival																				X
CEUS Imaging[15]		X	X		X				X										X	
Optional biopsy[16]	X				X															
Edmonton Scale Assessment System (ESAS)[17]	X	X				X				X				X						

1. Screening Assessment: Must be performed within 28 days prior to randomization and Cycle 1 Day 1. Assessments can be performed in one or more visits, so long as they are completed within the time frame. If screening clinic visit is performed within 7 days prior to Cycle 1 Day 1, it does not need to be repeated. If screening labs (hematology, complete metabolic panel, and CEA) are completed within 48 hours prior to Cycle 1 Day 1, these do not need to be repeated. On progression, study patients will need to meet eligibility criteria #10 regarding required laboratory parameters (a-e) before moving to Stage 2 of the protocol (see Inclusion Criteria). In addition, the following criteria need to be met:

- In order to allow continued administration of RRx-001 (or regorafenib) despite progression of disease based on appearance of a new lesion (per irRC), patients must have absence of symptoms and signs of clinically important morbidity due to disease progression (e.g., requirement for additional medical management to control symptoms or irradiation to prevent morbidity), absence of symptomatic rapid disease progression requiring urgent medical intervention (e.g., spinal cord compression), and no decline in ECOG or Karnofsky performance status.
- Patients are re-consented using a written informed consent document at the time of progression of disease.

2. Enrollment: To be performed up to 7 days prior to Cycle 1 Day 1.
3. Subject Assessments: Subjects will undergo all assessments including vital signs, height (screening only), weight, ECOG performance status, and symptom-directed physical exam every 2 weeks for the first 8 weeks on study (Cycles 1 and 2), then every 4 weeks (Cycle 3+) during Stage 1. A full physical exam needs to be conducted at Screening, prior to starting Stage 2, and at the Study Termination Visit (STV). If screening physical exam is performed within seven (7) days prior to Cycle 1 Day 1, it does not need to be repeated.
4. Tumor Assessment: Tumor CT/MRI assessments during the screening period must be performed within 28 days prior to enrollment and no more than 35 days prior to start of treatment. Tumor assessments will be performed every 12 weeks (or more frequently, if clinically indicated), until disease progression per irRC (See Section 9.1.2). Although the use of contrast agent is preferred, for subjects allergic to the iodinated contrast agent, either a non-iodinated CT contrast agent or an MRI is permitted. MRI is also permitted if it is the best imaging modality for a given tumor site. The same imaging modality for tumor assessments for each subject should be performed throughout the study. Per irRC, a confirmatory scan will be carried out at 16 weeks.
5. Subjects randomized to RRx-001 will undergo diagnostic CT imaging (with contrast) at Baseline (Screening). A diagnostic CT scan (with contrast) for RRx-001 randomized subjects that are at Stage 2 (i.e. receiving irinotecan and bevacizumab) will be carried out at the first scheduled imaging visit after starting these therapies. See Section 8.1 and 9.1.2.
6. Laboratory Assessments: All laboratory testing will be performed by institution's local laboratory. Laboratory evaluations are not required at Cycle 1 Day 1 if screening evaluations are performed within 48 hours prior. Hematology includes: red blood cells, hematocrit, hemoglobin, platelets, and white blood cells with differential (neutrophil, lymphocyte, monocyte, basophil, and eosinophil). Complete Metabolic Panel includes: sodium, potassium, chloride, bicarbonate, BUN, creatinine, glucose, calcium, total protein, albumin, AST, ALT, total bilirubin, alkaline phosphatase, and LDH. Laboratory evaluations will be performed every 2 weeks for the first 8 weeks on study (Cycles 1 and 2), then every 4 weeks (Cycles 3+). CEA tumor marker will be assessed at screening, on Day 1 of each cycle, and every two weeks during Stage 2.
7. Pregnancy test: A serum pregnancy test will be performed on women of child-bearing potential (WOCBP) at Screening, and prior to starting Stage 2 (irinotecan).
8. Tissue Submission: Archived tumor tissue will be collected during Screening. Archived tissue will be collected for subjects who consent to the collection and use of archived biopsy material for biomarker analyses. It is preferred that tumor biopsies be submitted for biomarker analysis as a formalin fixed paraffin-embedded (FFPE) blocks; however unstained slides are also acceptable (at least 10 slides, if possible).
9. Quality of Life Questionnaires: QOL Questionnaires should be completed at the beginning of the visit, prior to any other assessments and prior to the subject receiving study drug. Subjects will complete QOL questionnaire (Appendix 4) at their clinical visits every 2 weeks for the first 8 weeks on study (Cycles 1 and 2), then every 4 weeks (Cycle 3+), and at each visit during Stage 2 The QOL Questionnaire is not required at Cycle 1 Day 1 if screening QOL Questionnaire is completed within 48 hours prior.
10. Adverse Events and Concomitant Medications: Adverse event assessment should be recorded in all subjects who have received at least one dose of either RRx-001 or regorafenib beginning with Cycle 1, Day 1, and continue until the Progression on irinotecan (if continuing to Stage 2) or at Progression on either RRx-001 or regorafenib if not proceeding to Stage 2. In either case the SAE will be followed to resolution if not resolved to Grade ≤ 1 or baseline at time of

progression. Adverse events will be collected at each clinical visit. Concomitant Medications should be recorded at Screening and continuously throughout the same period as AEs, unless indication is for the treatment of an ongoing AE; in this case it should be recorded until resolution of AE to Grade ≤ 1 or baseline or discontinuation of medication. For a list of prohibited medications, see protocol Section 6.0. Best supportive care procedures and therapies should be documented in the concomitant medications/procedures.

11. RRx-001 administration and clinical visits: RRx-001 will be administered at a dose of 4 mg IV once a week, with infusions performed every 7 days ±1 day apart, over a period of up to 4 hours, on Days 1, 8, 15, and 22 of each 4-week cycle. Pre-medication with a corticosteroid (e.g. 10 mg dexamethasone IV) is required. Other agents, for example ibuprofen (see Section 6.0), may be administered as needed for pain relief at the discretion of the PI. The use of palliative radiation and/or surgical intervention is under the discretion of the Investigator and with agreement of the Sponsor.
12. Regorafenib dosing: Regorafenib will be administered as directed in the package insert, at 160 mg orally once daily for the first 21 days of a 28 day cycle. Dose interruptions and reductions, if required, should strictly adhere to the guidelines in the package insert. The use of palliative radiation and/or surgical intervention is under the discretion of the Investigator and with agreement of the Sponsor.
13. Progression Visit: Subjects found to have progressive disease as defined by irRC and clinical deterioration or intolerable toxicity (see ESASr below) will complete the assessments and enter Stage 2 of the study. All subjects will receive an irinotecan (180 mg/m^2 IV) on Day 1 of each 2 week cycle. On progression, study patients will need to meet eligibility criteria #10 regarding required laboratory parameters (a-e) before moving to Stage 2 of the protocol (see Inclusion Criteria).
14. Post-Progression Follow-up and Survival Follow-up: Following disease progression on RRx-001 or regorafenib, all subjects will enter Stage 2 and receive an irinotecan-based therapy until progression. After progression on irinotecan, subjects will be followed through their subsequent lines of treatment to collect treatment intervention information and overall response assessments during the Post-Progression Treatment Period. During Survival Follow-Up, subjects will be followed every 8 weeks until death from any cause or withdrawal of consent.
15. CEUS Imaging: CEUS will be performed in newly enrolled subjects at Stanford University before and after RRx-001 treatment at C1W1, C1W2, C1W4 and C2W4. CEUS will also be used to assess tumor response with irinotecan post-RRx-001 at least 1 week after the start of irinotecan. See Appendix 6. This schedule may be reduced at the discretion of the primary investigator in agreement with the study radiologist and sponsor.
16. Optional biopsy: may include fine needle aspiration or core biopsy before start of treatment and at Week 4.
17. Edmonton Symptom Assessment System (revised): The ESASr consists of 9 visual analog scales (VAS) for pain, tiredness, drowsiness, nausea, appetite, shortness of breath, depression, overall wellbeing and an extra empty VAS for the assessment of a less frequent symptom that might be important. The severity of each symptom is rated on a scale from 0 to 10 with 10 being the most severe. The physician completes this assessment at Screening and the first week of every cycle. Questionnaire is not required at Cycle 1 Day 1 if screening ESASr Assessments completed within 48 hours prior. An increase of 2 or more points is classified as deteriorated, a change of 0 or ±1 as stable, and a decrease of 2 or more as improved. If the ESAS increases by two or more points, compared to baseline, indicating deterioration, then the patient should be scanned for progression. If the scan is stable or better the decision about whether to continue RRx-001 or Regorafenib or restart irinotecan should be made in consultation with the Medical Monitor.

LIST OF ABBREVIATIONS

Abbreviation or Term	Definition/Explanation
5-FU	5-Fluorouracil, fluorouracil
ADR	Adverse Drug Reaction
AE	Adverse Event
ALT (SGPT)	Alanine aminotransferase (Serum Glutamic Pyruvic Transaminase)
ANC	Absolute neutrophil count
AP or Alk P	Alkaline Phosphatase
AR	Adverse reaction
AST (SGOT)	Aspartate aminotransferase (Serum Glutamic Oxaloacetic Transaminase)
BSA	Body Surface Area
BSC	Best Supportive Care
BUN	Blood Urea Nitrogen
C	Celsius
CEA	Carcinoembryonic antigen
CEUS	Contrast enhanced ultrasound
CAPEOX	Capecitabine, Oxaliplatin
CRC	Colorectal cancer
CFR	Code of Federal Regulations
Cm	Centimeter
CMP	Complete Metabolic Profile
CPT	Cold Pressor Test
CR	Complete Response
CRC	Colorectal cancer
CRF	Case Report Form
CRO	Contract Research Organization
CT	Computerized Tomography
dL	Deciliter
DLT	Dose limiting toxicity
DMA	N,N-Dimethylacetamide
ECG	Electrocardiogram
ECOG	Eastern Cooperative Group
eCRF	Electronic-Based Case Report Form
EGFR	Epidermal growth factor receptor
EORTC	European Organisation for Research and Treatment of Cancer
ESASr	Edmonton Symptom Assessment System (revised)

Abbreviation or Term	Definition/Explanation
ESR	Erythrocyte sedimentation rate
FDA	Food and Drug Administration
FDG	Fluorodeoxyglucose
FOLFIRI	Combination of 5-FU, leucovorin and Irinotecan
FOLFOX	Combination of 5-FU, leucovorin and Oxaliplatin
g	Gram
GCP	Good Clinical Practice
GSH	Glutathione
h, hr	Hour
HGB, hgb	Hemoglobin
HNSTD	Highest Non Severely Toxic Dose
ICF	Informed Consent Form
ICH	International Conference on Harmonization
IEC	Independent Ethics Committee
IRB	Institutional Review Board
irRC	Immune Related Response Criteria
IV, i.v.	Intravenous
kg	Kilogram
L	Liter
LD	Longest Diameter
LFT	Liver Function Test
MedDRA	Medical Dictionary for Regulatory Activities
mg	Milligram
mL	Milliliter
mmHg	Millimeters of Mercury
MRI	Magnetic Resonance Imaging
MTD	Maximum Tolerated Dose
NCI CTCAE	National Cancer Institute Common Terminology Criteria for Adverse Events
NO	Nitric oxide
NOx	Nitrogen oxides
NOAEL	No Observable Affect Effect Level
NSAID	Non-steroidal Anti Inflammatory Drug
OS	Overall Survival
PD	Progressive Disease
PDI	Protein Disulfide Isomerase

Abbreviation or Term	Definition/Explanation
PE	Physical examination
PEG	Polyethylene glycol
PET	Positron emission tomography
PFS	Progression Free Survival
pH	A measure of the acidity or alkalinity of a solution.
PI	Principal Investigator
PR	Partial response
prn	Pro re nata (as the situation demands, as needed)
QLQ	Quality of Life Questionnaire
QOL	Quality of life
RBC	Red Blood Cell
RECIST	Response Evaluation Criteria in Solid Tumors
SAE	Serious Adverse Event
SAR	Suspected Adverse Reaction
SSAR	Suspected Serious Adverse Reaction
TMF	Trial Master File
UCSD	University of California San Diego, San Diego, CA
VEGF	Vascular Endothelial Growth Factor
WFI	Water for Injection
WHO	World Health Organization
WOCBP	Women of Childbearing Potential
X-ray CT, CT	Computerized tomography using X-ray radiation transmission

2.0 BACKGROUND

2.1 Colorectal Cancer

Stage IV colorectal cancer is an aggressively morbid disease, with a poor prognosis: the median and 5-year survival rates are between 28 and 30 months and 10%, respectively (Goldberg, 2013), with treatment. Over the last decade, the incidence of colorectal cancer has decreased slightly, due to improved screening programs and detection of precancerous polyps, however the burden of disease remains high, and is disproportionate within demographic subpopulations such as African-American men (Haggar, 2009). According to the American Cancer Society, colorectal cancer ranks 3rd in terms of incidence and mortality (American Cancer Society. Colorectal Cancer Facts & Figures 2011-2013, Rebecca Siegel). The natural history of the disease is associated with rapid systemic dissemination predominantly to the liver although extrahepatic hematogenous spread to the lung, peritoneum and bone with significant morbidity is not uncommon (Kufe, 2003).

While surgical resection is the cornerstone of treatment for early-stage colorectal cancer, palliative chemotherapeutic management to prolong overall survival and maintain quality of life is the first treatment option in medically inoperable metastatic disease (Chibaudel, 2012).

Three cytotoxic drugs are available for the treatment of metastatic colorectal cancer in the therapeutic continuum between first and third line therapy: fluoropyrimidines (e.g. capecitabine and 5-fluorouracil), oxaliplatin, and irinotecan. These drugs can be administered either in combination (doublets: fluoropyrimidine/ oxaliplatin, 5-FU/ irinotecan; triplets: 5-FU/ oxaliplatin/irinotecan; or as monotherapy (fluoropyrimidine alone). Although there is much variability in prescription, and other combinations are available, typically the combination FOLFOX (5-FU/leucovorin/oxaliplatin) or XELOX (capecitabine/oxaliplatin) is used as first line therapy and FOLFIRI (5-FU/leucovorin/irinotecan) is used as the most common second line treatment (Hess, 2010).

Newer biological agents, particularly bevacizumab, an anti-VEGF monoclonal antibody, have been shown to be potentiate the activity of the combination therapies described above and are usually added to these multi-drug regimens in the first or second line setting.

The anti-EGFR monoclonal antibodies cetuximab and panitumumab have been shown to increase survival in patients lacking the KRAS mutation (KRAS wild type) giving an additional treatment option in the second or greater line setting.

This crowded and creatively chaotic therapeutic landscape (Goldberg, 2006) became even more active with the approval of the multiple tyrosine kinase inhibitor, regorafenib, in September 2012, in the setting of 3rd line KRAS mutant or 4th line KRAS wild-type metastatic colorectal cancer.

Based on the stop and go, that is intermittent maintenance therapy approaches investigated in such large scale trials as ‘OPTIMOX 1’, ‘OPTIMOX 2’, ‘DREAM’, and ‘CAIRO’, where the intermittent therapy arm involving rechallenge to the previous induction therapy post progression

performed worse than the continuous therapy arm, the strategy of resensitization to a previously effective but resistant therapy is not expected to be successful. (Oronsky, 2014)

2.2 Target Indication

RRx-001 is a small first-in-class cytotoxic molecule being developed for the treatment of subjects with advanced, metastatic colorectal cancer, who have been previously treated with, oxaliplatin- and irinotecan-based chemotherapy, including the adjuvant setting, with or without anti-VEGF therapy, and, if KRAS wild type, anti-EGFR therapy that are refractory to irinotecan. This study will enroll subjects with both wild type and mutant KRAS status. It will provide data to support an expanded Phase 2b or a Phase 3 study of RRx-001 therapy in colorectal cancer.

2.3 RRx-001

RRx-001 (N-(bromoacetyl)-3,3-dinitroazetidine) is a novel small-molecule, polynitro-substituted cytotoxic with pro-oxidant induced anticancer activity and a favorable toxicity profile compared with standard cytotoxic agents. RRx-001 is the first of an entirely new class of red blood cell modulators that react with hemoglobin and specific intracellular antioxidants. RRx-001 co-opts a small number of red blood cells to serve as a cellular biocarrier that relies on physiologic cues unique to cancer cells, such as hypoxia, for the delivery of cytotoxic reactive oxygen and nitrogen species to promote tumor cell death.

2.4 Nonclinical Studies with RRx-001

On dosing, RRx-001 rapidly permeates into red blood cells and reacts with the most nucleophilic free thiols (Scicinski, 2012). Because of the high reactivity of RRx-001, the only reaction products that have been observed are the glutathione (GSH) and cysteine adducts and the binding product of RRx-001 to the beta Cysteine 93 on hemoglobin.

In an in vitro blood distribution study using labeled RRx-001 and blood from three human volunteers, approximately 30% of the label was found bound to hemoglobin with the remainder in the plasma. The plasma soluble products were found to be the GSH and cysteine adducts. The toxicology of these metabolites has not been fully explored, however they are rapidly excreted and preliminary investigation of the toxicology of RRx-001-Cysteine found that a dose of 300 mg/kg in rats had no effects, compared to an IV 25 mg/kg dose of RRx-001, which was toxic.

Binding to the beta Cysteine 93 residue of hemoglobin has been reported to increase hemoglobin oxygen affinity. Indeed, endogenous compounds such as nitric oxide that binds to this residue left shift the p50 curve. A large increase in oxygen affinity could suggest impaired systemic oxygen delivery.

In vitro experiments confirmed that high doses (3 mM) of RRx-001 induces a left shift of the p50 curve, but the change in the p50 curve was not observed at physiologically meaningful doses ($< 20\ \mu M$).

Compounds that bind to beta Cys-93 and change the oxygen affinity of hemoglobin, can also enhance hemoglobin's nitrite reductase activity, which generates nitric oxide under hypoxic conditions. RRx-001 has intra-tumoral vasoactive properties, inducing acute changes in tumor

microvascular blood flow up to 72 hours in squamous cell carcinoma (SCCVII) tumor-bearing mice, which could arise from the red blood cell-mediated production of nitric oxide.

An *in vitro* screen of RRx-001 activity revealed micromolar growth inhibitory (GI_{50}) values against a broad spectrum of both human and murine tumors, similar to the activity of cisplatin (Ning, 2012).

As part of the non-clinical safety evaluation program for RRx-001, repeat-dose (4-week) toxicity studies, a cardiopulmonary safety pharmacology study, an *in vitro* genetic toxicology study (non-GLP), and an evaluation of blood/plasma compatibility were conducted. Formulations containing up to 2.0 mg/mL RRx-001, prepared in 3% N,N-Dimethylacetamide (DMA), 6% Polyethylene glycol 400 (PEG 400) in sterile Water for Injection (WFI) were administered *via* intravenous infusion three times a week. In animals, clinical changes and mortality/morbidity were present beginning at 20.1 mg/kg in rats and 8.0 mg/kg in dogs. In these repeat-dose toxicology studies, mortality/morbidity in both species was associated with acute exudative pulmonary edema. Decreased erythrocytes and hemoglobin and increased total bilirubin occurred in rats beginning at 12.0 mg/kg. In dogs, decreased erythrocytes and hemoglobin occurred beginning at 3 mg/kg and increased total bilirubin occurred at 5 mg/kg. In both rats and dogs, the erythrocyte, hemoglobin and bilirubin changes were reversible. The dog was considered to be the most sensitive test species. As outlined in International Conference on Harmonization (ICH) Guidance S9 (NonClinical Evaluation for Anticancer Pharmaceuticals), the highest non-severely toxic dose (HNSTD), also described as the no observable affect effect level (NOAEL) in dogs, was considered to be 5 mg/kg. However, based on the gross pathology findings indicative of pulmonary and liver toxicities, the lower dose of 3.0 mg/kg in dog is used as a dose level from which to set the starting dose.

Rats administered a single intravenous (IV) dose of 12.5 mg/kg RRx-001 had transient elevations in blood pressure (20 – 25 mmHg), and mild, reversible effects on heart rate and several respiratory parameters. At 25 mg/kg, transient elevations in blood pressure (20 – 25 mmHg) and mild to moderate effects on heart rate, and respiratory parameters were observed when RRx-001 was administered at a rate of 15 mL/hr. When the 25 mg/kg dose was given at a slower rate (2 mL/hr vs. 15 mL/hr) signs of overt toxicity and mortality occurred. The mechanism for this finding is under examination. Macroscopic findings of red fluid in the thoracic cavity and mild to moderate red, discoloration in multiple lobes in the lungs were present. Because of this preclinical observation, each dose of RRx-001 was initially administered intravenously over 20 minutes.

Solutions of RRx-001 for Injection were previously tested for hemolytic potential:

Test formulations of 0 (vehicle), 0.5, 1.0, or 2.0 mg/mL RRx-001 were tested (1:1) with human whole blood and plasma. Hemolysis was evaluated by determining the amount of hemoglobin in the supernatant following incubation. Plasma compatibility was determined macroscopically. Formulations of 0.5, 1.0, and 2.0 mg/mL were prepared by mixing RRx-001 powder with the vehicle (3% DMA, 6% PEG 400 NF, and sterile WFI USP). Osmolality values were 618, 612, and 614 mOsm/kg for the 0.5, 1.0, and 2.0 mg/mL formulations, respectively, compared with the control value of 606 mOsm/kg. RRx-001 at concentrations of 0.5, 1.0, or 2.0 mg/mL or vehicle alone did not cause hemolysis or macroscopic changes in plasma.

A time course following dilution of human whole blood (5 parts) to RRx-001 infusion solution (1 part) was followed over two hours. CBC parameters were collected at 1, 5, 15, 60 and 120 min. At this dilution and over this time period, only mild changes in cell size were noted. No evidence of clotting or hemolysis was seen.

In a genetic toxicology screening assay, RRx-001 tested positive in both TA 98 and TA 100 in either the absence or presence of metabolic activation and was concluded to be mutagenic in the bacterial reverse mutation assay. *In vitro*, RRx-001 at concentrations of 0.5, 1.0, or 2.0 mg/mL or vehicle alone did not cause hemolysis or macroscopic changes in plasma.

The effects of RRx-001 on the colorectal cell line HT-29 cells were evaluated via a clonogenic assay. The impact of RRx-001 on cell cycle kinetics and on apoptosis was analyzed using flow cytometry. RRx-001 triggered replicative cessation through the G1 to S phases. As a measure of HT-29 DNA damage after treatment, γ-H2AX foci were determined as a function of time after RRx-001; exposure to RRx-001 resulted in a greater number of γ-H2AX foci than control. Tumor growth delay was used to evaluate the effects of RRx-001 on *in vivo* cytotoxicity. *In vivo* tumor syngeneic studies demonstrated that administration of RRx-001 resulted in significant tumor growth inhibition both alone and when combined with radiation.

Tumor specific imaging with a thiol-based gadolinium contrast agent revealed accumulation of thiol modifications in a variety of mouse tumor xenograft models after exposure to RRx-001. The effect of this reversible and even irreversible oxidation of cysteine thiols on the methylation pathway of promoters in the Nrf2 pathway in cancer cells was evaluated. Treatment of cancer cells, exposed to RRx-001 in fetal calf serum, epigenetically modified DNA of the Keap1 promoter, which stimulates Keap1 expression, and increases proteosomal degradation of Nrf2, a master regulator of several antioxidant genes, perhaps tipping the redox-balance in the cancer cell toward a more oxidant milieu.

These results suggest that the mechanism of cytotoxicity of RRx-001 is reactive oxygen and nitrogen (RONS)-mediated in association with delayed repair of induced DNA damage. The arrest of the cells in the G2-M-S phases may partially explain the higher susceptibility to induced DNA damage, reflected in the increase of γ-H2AX. Although much remains to be clarified regarding the action of RRx-001 on the cell cycle, the ability of RRx-001 to induce mitotic arrest has implications for the targeting of cancerous cells with ensuing apoptosis or premature senescence. RRx-001 treated SCCVII cells analyzed by Western blot analysis revealed that RRx-001 induced apoptosis through the apoptosis-inducing factor (AIF).

It is unclear whether apoptosis or premature senescence is the predominant response to the RRx-001 cytotoxic insult. Immunohistochemical analysis of a glioma U87 xenograft revealed a central zone of intact cells with a senescent-like, “stunned” phenotype. Although these cells resemble senescent cells in several ways, senescence-specific markers were not measured. It is possible that RRx-001 is able to produce a mixture of senescence-like growth arrest, apoptosis and necrosis. Given the lack of off-target toxicities, and the effect of RRx-001 on elements of the stroma (the tumor vasculature and blood flow) as well as the tumor cells themselves, it seems appropriate to characterize RRx-001 as a therapy, which is targeted to the tumor microenvironment as a whole.

Preclinical and Phase 1 data suggests that RRx-001 restored sensitivity to previously failed therapies resulting in a prolonged overall survival through altered DNA methylation of genes and cancer pathways. On this basis, reintroduction of irinotecan is mandated, if feasible, on progression. In addition, immunohistochemistry of tumor biopsies from patients on an ongoing trial in lung cancer (TRIPLE THREAT, NCT02489903) have revealed an influx of CD8 expressing tumor-infiltrating lymphocytes, confirming that RRx-001 is an immunotherapeutic as well as an epigenetic inhibitor (Brzezniak, 2016).

2.5 Clinical Studies with RRx-001

To date, RRx-001 has been studied in a single Phase 1 clinical trial (Protocol RRx001-11-01). The study design was standard '3+3' dose escalation cohorts based on a modified Fibonacci scheme. The primary endpoint was safety and pharmacokinetics with the objective of defining a maximum tolerated dose (MTD) and the recommended Phase 2 dose (RP2D). RRx-001 was administered to subjects intravenously through a peripheral line on a weekly and twice-weekly schedule.

2.5.1 Safety

Twenty-five subjects were treated at 6 dose levels of 10 (n=6), 16.7 (n=3), 24.6 (n=3), 33 (n=4), 55 (n=3), and 83 (n=6) mg/m^2. RRx-001 was generally well tolerated. Adverse events were mostly Grades 1 and 2, with one Grade 3 infusion site pain and one Grade 3 anxiety. Pain at the site of injection was most common (84%), mostly Grades 1 and 2, and related to study drug (Table 2). RRx-001 was initially infused intravenously weekly over 20 minutes. With increasing doses of RRx-001, infusion site pain required increasing the infusion time up to 8 hours and splitting the total dose and administering RRx-001 twice-weekly at the highest dose of 83 mg/m^2. No dose-limiting toxicities (Grade 3 infusion site pain was not considered a DLT) were observed in any cohort, and therefore the maximum tolerated dose was not reached. However, due to the infusion site pain that could be mitigated by slowing the infusion rate, 83 mg/m^2 was considered to be the maximum feasible dose when delivered over up to 8 hours.

Table 2: Treatment Emergent Adverse Events (TEAEs) Considered Related to Study Drug RRx-001 in Decreasing Order of Frequency

TEAE	Cohort 1 (n=6) 10 mg/m^2	Cohort 2 (n=3) 16.7 mg/m^2	Cohort 3 (n=3) 24.6 mg/m^2	Cohort 4 (n=4) 33 mg/m^2	Cohort 5 (n=3) 55 mg/m^2	Cohort 6 (n=6) 83 mg/m^2	Total (n=25)
Infusion Site Pain	4	3	1	4*	3	6	21 (84%)
Arm Swelling/Edema		1		1	2	4	8 (32%)
Vein Hardening				1	1	5	7 (28%)
Dyspnea/Wheezing§	1				1	3	5 (20%)
Mouth tingling/burning					2	2	4 (16%)
Anxiety					2**	1	3 (12%)
Chest Discomfort	1	1				1	3 (12%)
Cough					1	2	3 (12%)
Fatigue				1		2	3 (12%)
Skin Discoloration				1		2	3 (12%)
Flushing¶	1					1#	2 (8%)
Throat Discomfort						2	2 (8%)
Vasodilation	1			1			2 (8%)
Vein Occlusion/DVT						2	2 (8%)
Weakness					2		2 (8%)
Abdominal pain upper	1						1 (4%)
Bilateral hand numbness	1#						1 (4%)
Blood Tinged Sputum						1	1 (4%)
Decreased Respirations						1	1 (4%)
Dizziness	1						1 (4%)
Elevated Blood Pressure						1	1 (4%)
Infusion reaction	1						1 (4%)
Nasal discomfort	1						1 (4%)
Runny Nose/Sinus Drainage					1		1 (4%)
Site Tenderness				1			1 (4%)
Throat irritation	1						1 (4%)
Urinary Incontinence						1	1 (4%)
Vasculitis			1#				1 (4%)
Vision Changes				1#			1 (4%)
Vomiting	1#						1 (4%)

*1 subject had Grade 3 infusion site pain
** 1 subject had Grade 3 anxiety
# Outstanding queries
§ Terms 'Wheezing', 'Dyspnea' and Dyspnea/Wheezing' were combined
¶ Terms 'Flushing' and 'Intermittent Flushing' were combined

There were 12 serious adverse events (SAEs) reported in 10 subjects, all of which were considered unrelated to study drug. The SAE terms were 1) seizures secondary to brain mets; 2) hypercalcemia; 3) cerebral bleed; 4) increased somnolence; 5) atelectatic changes right lung base; 6) bilirubinemia; 7) klebsiella septicemia; 8), upper gastrointestinal bleed; 9) pleural effusion (two SAEs in the same subject); 10) bowel obstruction; and 11) dehydration. Overall, the types of serious AEs reported among this study population were consistent with the severity of illness and underlying disease. No ECG effects or clinically relevant RRx-001-related changes in vital signs or laboratory values were seen in the study.

There were 4 deaths on study or within 30 days of last dose of study drug, all considered unrelated to RRx-001, and related to the subjects' underlying malignancy.

RRx-001 was administered through a peripheral vein. 84% of subjects across the 6 cohorts experienced a prominent and transient, dose-dependent forearm vasodilation and transient mild to moderate pain that was ameliorated with slowing of the infusion time, stopping and restarting the infusion at a slower rate, and concomitant administration of analgesics (short-acting opioids), benzodiazepines or anti-inflammatory medications such as corticosteroids as needed. In particular, *premedication treatment with corticosteroids and ibuprofen at the day of dosing was found to be effective. Premedication with corticosteroids is required at every RRx-001 administration.*

Several subjects in the highest dose cohort (83 mg/m^2) complained of moderately severe injection pain, that was inadequately addressed with adjunctive opioid analgesics and have received a reduced total dose or a split dosing schedule (twice-weekly). Overall, higher doses tend to result in a concomitant escalation in pain, which has become more severe in the later cohorts. At present, 83 mg/m^2 is the maximum feasible dose using the current infusion rates.

Most subjects recovered from the injection site pain and vasodilation within minutes of the infusion being stopped or slowed down and without sequelae; four subjects temporarily developed a non-tender, non-erythematous cord-like induration over the vein of injection, which resolved spontaneously within a few weeks. Duplex ultrasound was negative for venous thrombosis and in the absence of warmth, swelling, redness or tenderness, the diagnosis was more suggestive of focal venous dilation than superficial phlebitis. Initially, RRx-001 was administered through a central IV line over 20 min. However, based on complaints from one subject in the first cohort of an unpleasant nasopharyngeal burning sensation, which led to his (voluntary) discontinuation from the study, IV administration was moved to the antecubital or forearm area and the infusion rate was reduced. One Phase I subject received seven (7) doses of RRx-001 through a central line over 48 hours as part of a single subject protocol (RRx001-11-08) with no localized pain, and no acute or latent systemic toxicity. Similarly, a Phase II patient (under this protocol, RRx001-21-02) received RRx-001 through a central line over five (5) hours with minimal complaints of pain and no acute or latent systemic toxicity.

An emergency use protocol of 2 mg (1 mL) RRx-001 co-infused with autologous blood, developed and approved for one subject on the Phase 1 trial with intolerable local pain, demonstrated safety and feasibility: it was well-tolerated, systemically non-toxic, relatively easy to administer and the subject reported a sense of well-being for several days after the co-infusion. Subsequently, a Phase 2 protocol "An Open-label, Three Stage, Three Arm Pilot Study of RRx-

001 For Second Line or greater Small Cell Lung Cancer, Third Line or greater Non-Small Lung Cancer, and Second Line or greater High Grade Neuroendocrine Tumors Prior to Re-administration of Platinum Based Doublet Regimens (TRIPLE THREAT)" (RRx001-211-01) has been initiated, in which patients are dosed with 4 mg RRx-001 (nominal 2 mg/m^2 for BSA of 2.0 m^2) mixed with 100 mL autologous blood. The dosing schedule in this protocol is based on the ongoing RRx001-211-01 TRIPLE THREAT study. RRx-001 blood co-infusion has the advantage of shorter infusion times, improved tolerability and increased convenience compared to the current protracted venous infusion. Moreover, the fact that, to date, all 9 treated patients in the TRIPLE THREAT trial have demonstrated a markedly improved clinical status suggests that a trade-off of anticancer activity for convenience is unlikely. Shorter overall treatment times will also improve the feasibility of same-day radiotherapy.

In summary, other than localized venous dilation and pain on infusion, RRx-001 was very well tolerated. In the Phase 1 study, the pain was dose related and resulted in attempts to slow the infusion and split the dose between two days within a week. The maximum feasible dose appears to be 83 mg/m^2 at the present time and under the present infusion conditions.

2.5.2 Pharmacokinetics

On infusion, RRx-001 is rapidly metabolized in blood; consequently a bioanalytical method was developed and validated for the RRx-001-glutathione conjugate, a major soluble metabolite of RRx-001. Blood samples taken prior to the start of infusion, during infusion, at the end of the infusion then at time intervals post infusion were analyzed for RRx-001-GSH. Preliminary data suggests rapid clearance of RRx-001-GSH (median terminal half life: 10-25 min). AUCt and C_{max} of RRx-001-GSH were found to increase in a dose-dependent manner for doses from 10 mg/m^2 to 55 mg/m^2.

2.5.3 Preliminary Anti-Tumor Activity

Subjects were evaluated for preliminary anti-tumor activity if their disease was measurable by imaging at baseline and post treatment. Most subjects in the study had CT scans performed at 8-week intervals for response assessment per RECIST v1.1. Twenty (20) out of 25 enrolled subjects were evaluable for response per protocol criteria. Subjects were considered evaluable if they have a screening/baseline CT scan and at least one follow up CT scan following dosing with at least one dose of RRx-001. One partial response (PR) was observed in a 58-year-old subject with parotid adenoid cystic carcinoma who received RRx-001 at a dose of 16.7 mg/m^2 weekly. The subject had previously failed radiotherapy and imatinib. A partial response was reported in this subject at the first 8-week scan and was durable for just over a year. Nine (9) out of 20 evaluable subjects (45%) had stable disease (SD) of $\geq$ 4 months in duration.

Table 3: Subject Response by Cohort per RECIST v1.1

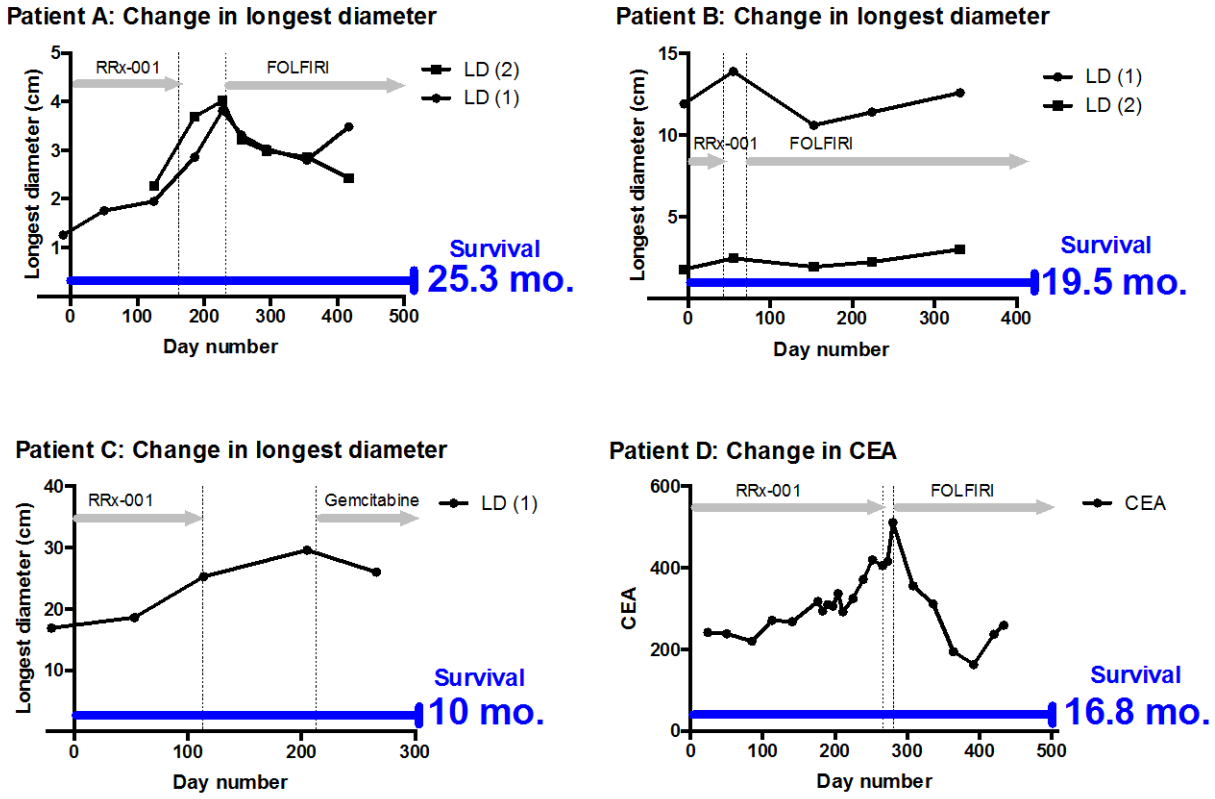
Cohort	Dose (mg/m^2)	Subjects Enrolled	Evaluable Subjects	Response at 1st post-RRx-001 Scan*	% Response at 1st post-RRx-001 Scan*	Disease Control (CR+PR+SD ≥4 mos)	Disease Control Rate
1	10	6	5	3 (SD)	60%	1 (SD)	20%
2	16.7	3	3	2 (SD+PR)	67%	2 (SD+PR)	67%
3	24.6	3	2	1 (SD)	50%	0	0%
4	33	4	3	3 (SD)	100%	2 (SD)	67%
5	55	3	3	2 (SD)	67%	1 (SD)	33%
6	83	6	5	4 (SD)	80%	3 (SD)	60%
TOTAL	**-**	**25**	**20**	**15**	**75%**	**9**	**45%**

* CT scans were performed at 4 or 8 weeks

Disease control (CR+PR+SD≥ 4 months) was seen over all dose levels with no apparent dose response (Table 3). Disease control rate, defined as the sum of subjects achieving CR+PR+SD≥ 4 months divided by all evaluable subjects, was 45% in this study. Subjects who derived clinical benefit had metastatic CRC (n=4), adenoid cystic carcinoma (n=2), pancreatic cancer (n=1), ovarian cancer (n=1) and hepatocellular carcinoma (n=1).

Eleven subjects (44%) dosed in the Phase 1 study had a diagnosis of metastatic colorectal cancer (CRC). Ten of the 11 CRC subjects had failed multiple cycles of standard therapy, including 5-FU, oxaliplatin, irinotecan, bevacizumab, and, in some cases, also experimental therapies. Per investigators, all subjects had rapidly progressing disease and had failed multiple therapies (≥ 2) on enrollment. Only one subject had previously been treated with one line of therapy, 5-FU only, having rejected other standard therapies. Four of 9 evaluable (44%) subjects, regardless of KRAS status or RRx-001 dose, had SD for ≥ 4 months. These subjects received RRx-001 at a dose of 10 mg/m^2, 55 mg/m^2 and 83 mg/m^2 (n=2). Four subjects, three with colorectal cancer (A, C and D) and one with squamous cell carcinoma of the lung (Subject B) became responsive to previously failed therapy after exposure to RRx-001, as shown by changes in CEA and by imaging. One subject (D) had SD for approximately 10 months with RRx-001, and appears to have regained sensitivity to FOLFIRI, a regimen he had previously failed, based on a decrease in his CEA level from 511 to 162 ng/mL. Subject A had SD for approximately 6 months with RRx-001 and regained sensitivity to FOLFIRI, a regimen he had previously failed with a survival of over 25 months (Reid, 2014).

Figure 1: Subjects Resensitized to Previously Failed Therapies



2.6 Rationale for Study

Preclinical studies have supported the rationale for current clinical development of RRx-001 in colorectal cancer. RRx-001 potently inhibited survival of colorectal HT-29 cells, as measured by inhibition of a modified mitochondrial dehydrogenase activity (MTT assay). These effects were enhanced by ionizing radiation. The findings are consistent with immunohistochemical analysis of *in vivo* treated HCT116 and Colo205 colorectal tumors where RRx-001 reduced tumor cell proliferation rates, an effect magnified by bevacizumab pretreatment. Moreover, excessive ROS levels in colorectal tumors (Inokuma 2009) presumably render these cancer cells highly susceptible to redox active therapies.

Based on the preliminary anti-tumor activity observed in the limited number of CRC subjects in the Phase 1 study detailed in Section 2.5.3 above, it would appear that RRx-001 and regorafenib may have approximately the same clinical activity by providing prolonged stable disease for subjects with a significantly more favorable safety profile for RRx-001. While the number of CRC subjects treated with RRx-001 in the Phase 1 study is limited, the anti-tumor activity observed appears to be independent of subjects' KRAS status and RRx-001 dose. Several CRC subjects had an excellent response to subsequent chemo/radiotherapy after progression and this study will investigate whether treatment with RRx-001 has an impact on clinical benefit with irinotecan post-RRx-001 with overall survival as the primary endpoint.

In summary, the available preclinical and preliminary clinical data identify RRx-001, with its pro-oxidant mechanism of action and lack of systemic toxicities due to an apparent selectivity for malignant cells, as a potential novel agent for the treatment of CRC.

2.7 Clinical Dose Selection for RRx-001

The RRx-001 dose selected for this study is based on experience from the Phase 1 clinical study. Although an MTD was not determined, the maximum feasible dose of 83 mg/m^2 was determined based on a prolonged IV infusion time of up to 8 hours to ameliorate the drug-related infusion site pain with faster infusion rates. The infusion site pain associated with iv drug administration was characterized by rapid, almost immediate onset and just as rapid resolution upon discontinuation. This adverse event, experienced at all dose levels studied, was accompanied by a palpably prominent focal venous dilation, presumably due to the focal generation of nitric oxide within the vessel that generally returned to baseline immediately after discontinuation of the infusion. The intensity of the pain, which was associated with increased dose and rate of administration, was managed by prolonging the infusion rate to 8 hours and concurrent administration of anti-inflammatory medications, benzodiazepines and/or opiates.

Twice-weekly infusions separated by at least 2 days were evaluated in the highest cohort of 83 mg/m^2 to ameliorate infusion site pain and to explore any effects on preliminary anti-tumor activity. The twice-weekly dosing schedule was not associated with increased toxicity or an apparent loss of clinical benefit. One subject with colorectal cancer developed an upper extremity DVT during the study.

Clinical benefit (PR + SD $\geq$ 4 months) was observed in 9 of 20 (45%) evaluable subjects in the Phase 1 study at all dose levels. There does not appear to be a dose-response curve based on the limited clinical data available. Based on the safety and preliminary clinical activity observations from the Phase 1 study, an initial dose of 16.5 mg/m^2 and infused intravenously once weekly was chosen for this Phase 2 study in CRC subjects. This dose was chosen as the highest well-tolerated dose that could be infused within a 4-8 hour time window.

Amendment 06 replaces conventional IV infusion with administration with autologous blood. As described above RRx-001 has been previously dosed by co-infusion with autologous blood over a shorter duration. Aside from the convenience and time factor both for the patient and the radiotherapist since RT is administered immediately after RRx-001, clinical experience with 5 patients to date (1 on an emergency use protocol and 4 patients on an ongoing Phase 2 protocol entitled "An Open-label, Three Stage, Three Arm Pilot Study of RRx-001 For Second Line or greater Small Cell Lung Cancer, Third Line or greater Non-Small Lung Cancer, and Second Line or greater High Grade Neuroendocrine Tumors Prior to Re-administration of Platinum Based Doublet Regimens (TRIPLE THREAT)" (RRx001-211-01)) has demonstrated significantly better tolerability. The improved tolerability is related to RRx-001 penetration of the RBC membrane and binding of to hemoglobin resulting in an acute burst of nitric oxide. This burst appears to cause pain or discomfort at the site of intravenous injection, related to the release of nitric oxide. When RRx-001 is mixed with whole blood outside of the body, the released nitric oxide is sequestered by proteins in the blood and therefore is not available to induce pain once the mixed blood is re-infused.

Moreover, in the TRIPLE THREAT study, increased convenience of treatment has been accompanied by promising indications of activity at a dose corresponding to 2 mg/m^2; in the BRAINSTORM study, under Amendment 02, the starting level of 5 mg/m^2 has resulted in at least two Partial Responses.

Subjects randomized to the RRx-001 treatment arm will receive a once-weekly dose of RRx-001 at 4 mg by mixing with autologous blood over a time period, not to exceed 4 hours from the time of extraction of the patient's blood on Days 1, 8, 15, and 22 of each 4-week cycle. The dosing schedule window may vary ± 1 day for subject convenience or clinic schedules.

2.8 Clinical Dose Selection for Regorafenib

Per the FDA package insert, subjects randomized to regorafenib will receive regorafenib at 160 mg orally daily on Days 1-21 of a 4-week cycle.

2.9 Clinical Dose Selection for Irinotecan and Bevacizumab Therapies

The recommended dose for irinotecan and bevacizumab will be 180mg/m^2 iv over 30–90 min and 5 mg/kg iv over 30-90 min, respectively, every 2 weeks.

3.0 STUDY OBJECTIVES

3.1 Primary Objectives

- To assess and compare the overall survival in the RRx-001 vs regorafenib treatment arms.

3.2 Secondary Objectives

Secondary objectives in this study are to assess the following efficacy and safety variables:

- To assess and compare Progression Free Survival 2 (PFS2) as a surrogate for overall survival (OS) in the RRx-001 vs. regorafenib treatment arms.
- To assess and compare the safety and tolerability in the RRx-001 vs. regorafenib treatment arms.
- To assess and compare objective response rate (ORR) in the RRx-001 vs. regorafenib treatment arms.
- To assess and compare the clinical benefit rate (CBR = CR+PR+SD≥4 months) in the RRx-001 vs. regorafenib treatment arms.
- To assess and compare the progression free survival (PFS) in the RRx-001 vs. regorafenib treatment arms.
- To assess and compare the duration of response (DOR) in the RRx-001 vs. regorafenib treatment arms.

- To assess and compare the duration of clinical benefit (DCB) in the RRx-001 vs. regorafenib treatment arms.
- To assess and compare the response and clinical benefit to subsequent therapies in the RRx-001 vs. regorafenib treatment arms.
- To assess and compare the quality of life (QOL) in the RRx-001 vs. regorafenib treatment arms using the EORTC QLQ-C30 questionnaire.

3.3 Exploratory Objectives

Exploratory objectives are non-optional for newly enrolled patients.

- To assess the impact of RRx-001 on tumor blood flow by Contrast Enhanced Ultrasound (CEUS)

4.0 OVERALL STUDY DESIGN

This is a two-stage, phase 2, open-label, randomized (2:1), two-arm study comparing RRx-001 vs. regorafenib in subjects with metastatic colorectal cancer who have been treated with at least oxaliplatin- and irinotecan-based regimens with bevacizumab and cetuximab or panitumumab (if KRAS wildtype).

Effective August 15th, 2016, general enrollment for this protocol has been closed to new enrollment. An expansion cohort remains open at Stanford University with the potential to enroll up to 10 patients. The following content is maintained for intent of overall evaluation of previously enrolled and new patients enrolled by Stanford:

Stage 1

- Arm 1 – subjects will receive once-weekly intravenous RRx-001 at a dose of 4 mg on Days 1, 8, 15, and 22 of a 4-week cycle. Subjects will have the option of changing to twice weekly dosing if the Investigator and subject feel it is necessary to mitigate infusion pain.
- Arm 2 – subjects will receive regorafenib at 160 mg orally daily on Days 1-21 of a 4-week cycle.

Stage 2

On progression all subjects will receive irinotecan. The recommended doses will be 180 mg/m^2, administered once every two weeks. Study patients will need to meet eligibility criteria #10 regarding required laboratory parameters (a-e) before beginning Stage 2 (see Inclusion Criteria). In addition, the following criteria need to be met:

- In order to allow continued administration of RRx-001 (or regorafenib) despite progression of disease based on appearance of a new lesion (per irRC), patients must have absence of symptoms and signs of clinically important morbidity due to disease progression (e.g., requirement for additional medical management to control symptoms

or irradiation to prevent morbidity), absence of symptomatic rapid disease progression requiring urgent medical intervention (e.g., spinal cord compression), and no decline in ECOG or Karnofsky performance status.

- Patients are re-consented using a written informed consent document at the time of progression of disease.

The study is designed to compare the safety and activity between RRx-001 against regorafenib in a parallel comparative study. Subjects with confirmed progression from their last treatment will be randomized 2:1 to receive either RRx-001 or regorafenib in 4-week cycles until confirmed radiologic progressive disease per irRC and clinical deterioration or intolerable toxicity (Section 9.1.2). The study is also designed to investigate potential resensitization to irinotecan post RRx-001 or regorafenib. Subjects will undergo long term follow up for their response to subsequent therapy and for overall survival. Approximately 190 subjects will be randomized and followed for between 6 months and 18 months: 127. Arm 1 (RRx-001) will enroll approximately 127 subjects and 63 Arm 2 (regorafenib).

4.1 Duration of Treatment

In the absence of unacceptable treatment-related toxicity or disease progression as defined by the protocol (Section 9.1.2), subjects may receive the treatment to which they have been randomized (Arm 1, RRx-001 or Arm 2, regorafenib) for up to 1 year at the discretion of the Investigator and beyond 1 year with the agreement of the Investigator and the Sponsor. Subjects will remain on study as long as they continue to receive RRx-001, regorafenib or irinotecan-based therapies. It is expected that the primary analysis will take place 6 months after the last subject is randomized.

Subjects that have been randomized to regorafenib are not permitted to crossover to receive RRx-001.

4.2 Study Procedures

Subjects will be screened for eligibility within the twenty-eight (28) days prior to enrollment according to the *Schedule of Assessments*. Radiologic tumor assessment diagnostic CT (with contrast), will be performed at Screening unless imaging was performed within 28 days of enrollment. Diagnostic CT scans at Stage 2 (i.e. receiving irinotecan-based therapies) will be carried out at the first scheduled imaging visit after starting irinotecan. In addition to safety labs as indicated in the Schedule of Assessments, for subjects randomized to receive RRx-001, blood may be drawn for biomarker assays at Screening, Cycle 2, Day 1 and at Progression.

Tumor biopsies may be performed following discussion and concurrence with the Medical Monitor.

Subjects will undergo all protocol-required assessments including laboratory evaluations, vital signs, physical exam and QOL questionnaire every 2 weeks during Cycles 1 and 2, then every 4 weeks from Cycle 3+. Subjects will be imaged by contrast-enhanced chest/abdomen/pelvis CT

every 8 weeks per institutional standard of care. MRI is permitted if the subject is intolerant of CT contrast agent or if MRI is the best imaging modality for a given tumor site. The same imaging modality for tumor assessments for each subject should be performed throughout the study. Response assessments will be based on the Investigator per irRC for RRx-001 and Regorafenib and RECIST v1.1 for irinotecan to enable comparison with historic response data. Females of childbearing potential will receive a serum pregnancy test at Screening and at Day 1 of each four-week cycle. Adverse events (AEs) and concomitant medications will be collected throughout the study at the clinic visits.

4.3 Long-term Follow-up

All subjects will undergo long-term follow up for overall survival. Subjects will be followed every two (2) months by chart review and/or phone contact until death or withdrawal of consent.

4.4 Data Monitoring Committee

On further review, given the lack of systemic toxicity observed to date, a data monitoring committee will only be convened to review significant serious adverse events and unacceptably frequent adverse events. There will be 2 planned analyses; an interim analysis once 61 (50%) OS events have occurred, and a final analysis once enrollment has been completed and 123 OS events have occurred. Safety will be assessed by periodic physical examinations, clinical laboratory assessments, and monitoring of AEs. Adverse events will be graded using NCI CTCAE v4.03.

4.5 Response Assessment

Radiographic and/or physical assessments of the malignancy will be made at Screening/Baseline (within 28 days prior to the first dose of RRx-001 or regorafenib) and every 3 cycles (8 weeks ± 7 days) thereafter. However, to capture non-radiologic progression, Physicians will administer the well validated questionnaire: the Edmonton Symptom Assessment System (ESASr) to patients at Screening and during the first week of every cycle. The ESASr consists of 9 visual analog scales (VAS) for pain, tiredness, drowsiness, nausea, appetite, shortness of breath, depression, overall wellbeing and an extra empty VAS for the assessment of a less frequent symptom that might be important. The severity of each symptom is rated on a scale from 0 to 10 with 10 being the most severe. The physician completes this assessment starting at Screening. An increase of 2 or more points is classified as deteriorated, a change of 0 or ±1 as stable, and a decrease of 2 or more as improved. If the ESAS increases by two or more points, compared to baseline, indicating deterioration, then the patient should be scanned for progression. If the scan is stable or better the decision about whether to continue RRx-001 or regorafenib or restart irinotecan should be made in consultation with the Medical Monitor.

Objective response (CR+PR) as determined by the subject's best tumor response, duration of response and time to progression will be assessed by the Investigator radiologic review using irRC for RRx-001 and regorafenib and RECIST v1.1 for irinotecan. A confirmatory CT/MRI scan should be performed at approximately 4 weeks from the previous scan for all patients with an objective response of ≥ PR. The clinical benefit rate (CBR = CR+PR+SD≥4 months) will also be determined. Tumor markers, as applicable, will also be assessed on a monthly basis, but

will not be used as a basis for disease progression or response in the absence of radiologic findings consistent with disease progression or response.

4.6 RRx-001 Treatment

RRx-001 treatment arm patients will receive once-weekly intravenous RRx-001 premixed with the patient's blood prior to reinfusion, at a set rate of 3 mL/minute for the first 15 minutes, increased by 1 mL/minute every 10 minutes thereafter until completion of the infusion, in the schedule described in the Schedule of Assessments..

All subjects will receive premedication with corticosteroids (e.g., dexamethasone 10 mg IV or PO) prior to RRx-001 administration, along with ibuprofen, benzodiazepines, gabapentin, and/or opiates as needed to ameliorate infusion site pain.

The patient's identification must be verified by two people prior to starting the blood draw and infusion process. Ensure the RRx-001 and anticoagulant dose both provided from pharmacy, is for the correct patient (using patient identifiers noted on labeling), that the RRx-001 and anticoagulant are mixed with the patient's autologous blood, and re-infused back to the correct patient. DO NOT proceed with administration if any discrepancies are noted.

Proper Handling:

The methodology for administering the RRx-001 dose by premixing with the patient's blood is based on procedures used in blood product transfusions. Standard procedures for avoiding hemolysis will be followed. These include the use of large gauge IV needles (19g or larger) and slow consistent rate during blood draw to avoid undue mechanical shear stress to red blood cells.

Whenever blood is present during the administration procedure, handle with care and do not shake. Avoid excessive temperatures, (both high and low temperatures can cause hemolysis). Avoid conditions that create high turbulence or trauma to the red blood cells.

Anticoagulant & RRx-001 Doses Prepared by the Pharmacy:

The Anticoagulant and RRx-001 doses will be prepared by the pharmacy for the clinic, where the patient administration procedure takes place. For details of the pharmacy procedure, please refer to the latest version of the pharmacy manual.

Administration Procedure in the Clinic:

The RRx-001 and anticoagulant doses should be properly labeled per institutional standards and in accordance with the latest pharmacy manual guidelines.

Administration procedure steps should be followed carefully and can be found in the latest version of the 'Blood Administration Best Practices & Guidelines for IV Infusion of RRx-001 + Blood Mix'. Safety guidelines are based on procedures used in blood product transfusions. **It's important each step is followed in order outlined in the guide to maintain sterility at all times.**

4.6.1 RRx-001 Storage and Accountability

RRx-001 for infusion is stored as follows: Vial 1, a 10 mL glass vial, containing sterile RRx-001 in PEG 400 is stored between -25°C and -15°C. Vial 2, a 5 mL glass vial containing the diluent, DMA, is stored at controlled room temperature.

RRx-001 is not light sensitive. The product should be used immediately after dilution. RRx-001 SOLUTIONS DILUTED WITH SALINE ARE NOT STABLE AND SALINE SHOULD NOT BE USED. DO NOT put the RRx-001 into an intravenous bag or large-volume syringe that does not contain WFI. Always first add the organic diluent (Vial 2) to RRx-001. Mix thoroughly by inverting several times. Subsequently, add the resulting mixture to WFI and mix thoroughly.

All transfer procedures for preparing RRx-001 solutions require strict adherence to aseptic techniques, preferably employing a vertical laminar flow safety hood while wearing gloves and protective clothing.

The study product should be stored in a secured site with restricted access. Study product accountability will be performed by the site pharmacist or designee, verified by the Sponsor's designee, and recorded in the study Pharmacy Binder. The pharmacist or designee will:

- Maintain records of product delivery inventory and return.
- Maintain temperature monitoring.
- Maintain up-to-date accountability of the study drug in the trial study drug accountability log (or equivalent).
- Document the use of study product by each subject.
- Return or destroy unused study product as per Sponsor's instructions.

Refer to the Pharmacy Manual for full details on reconstitution and preparation.

4.6.2 RRx-001 Packaging and Labeling

Each vial will be labeled with the study drug name, volume, Sponsor name, Manufacturer name and address, storage conditions, lot number and the following cautionary statements "New Drug Limited by Federal Law to Investigational Use."

RRx-001 and Diluent for RRx-001 will be supplied in glass vials in individual cartons packaged in boxes of 6 vials per box.

The product reconstitution and handling details are provided in the Pharmacy Manual.

4.7 Regorafenib

Subjects that have been randomized to the regorafenib treatment arm will receive regorafenib at a dose of 160 mg orally QD as outlined in the FDA package insert. Regorafenib will be supplied commercially via a prescription per standard of care and paid for by the subject's medical insurance. Subjects will have to be pre-authorized by the site prior to randomization. Subjects will also record their daily administration of regorafenib using a medication diary, which will be reviewed at each clinic visit.

Regorafenib will be stored and dosed according to the package insert.

4.8 Irinotecan Therapies

All subjects proceeding to Stage 2 of the study will receive treatment with commercially available irinotecan *via* a prescription per standard of care paid for by the subject's medical insurance.

See Section 6.1.3 for more information about dose modifications.

Table 4: Dose and Dose Schedule for Irinotecan and Bevacizumab Therapies

Regimen	Duration	Dose(s) and Schedule
Irinotecan	Every 2 weeks	Day 1: Irinotecan 180 mg/m^2 IV over 30–90 min

5.0 SUBJECT SELECTION

All subjects must sign an Institutional Review Board (IRB)-approved informed consent form prior to any protocol-required procedures are performed. All subjects enrolled into this study must satisfy all eligibility criteria.

6.0 CONCOMITANT MEDICATIONS

All subjects will be asked about concomitant medications at study entry. For subjects entering the study on a chronic concomitant medication, adequate clarification of the reason for taking that medication must be documented in the medical history. Information about medications, including over the counter medications, used during the study must also be recorded. Subjects must observe the restrictions listed here throughout the study. The following medications are restricted per the US FDA-approved product information for regorafenib.

- Strong CYP3A4 inducers (e.g., rifampin, phenytoin, carbamazepine, phenobarbital, and St. John's Wort)
- Strong inhibitors of CYP3A4 activity (e.g., clarithromycin, grapefruit juice, itraconazole, ketoconazole, posaconazole, telithromycin, and voriconazole)

All subjects will receive premedication with corticosteroids (e.g., dexamethasone 10 mg IV or PO) prior to RRx-001 administration to reduce the potential for infusion site pain. Ibuprofen (400-800 mg), opioids, benzodiazepines, gabapentin (300-2400 mg PO), pregabalin (600 mg/day, PO), and/or aprepitant may also be used as needed at the discretion of the Investigator to ameliorate infusion site pain in addition to increasing the infusion time in subjects who experience this adverse event. As testosterone levels may influence pain perception (Basaria 2013), male subjects who are intolerant of RRx-001 infusion should be tested for both free and total testosterone. Testosterone supplementation is permitted only in this instance and at the discretion of the Investigator and with the agreement of the Sponsor.

6.1 Dose Modification

6.1.1 RRx-001

Dose modifications arising from subject intolerance of the RRx-001 infusion are permitted and are justified based on the observation of activity at all dose levels in the Phase 1 study. The dosing schedule window may vary ± 1 day for subject convenience or clinic schedules. Dose modifications are shown in Table 5.

During dosing of RRx-001, the infusion rate should be titrated to subject tolerance. Stopping and restarting the infusion is permitted. It is recommended that reductions or increases in the rate of infusion should be carried in increments of 0.5 mL/hour.

Dose modifications for any other study drug-related adverse events should be discussed with and approved by the Sponsor prior to implementation.

Table 5: Dose Modifications for RRx-001 Administration

Sequential Dose Modification	RRx-001 Dose	Infusion Time	Frequency	Interval
Initial	4 mg	Up to 4 h from time of blood extraction	1 x week	Separated by 7 days ± 1 day
Dose reduction option	2 mg	Up to 4 h from time of blood extraction	1 x week	Separated by 7 days ± 1 day

6.1.2 Regorafenib

The initial dose for regorafenib is 160 mg QD, as described in the FDA package insert. Dose modifications for regorafenib due to drug-related adverse events should be performed based on guidance provided in the FDA package insert, as excerpted below. Please review the FDA package insert for more information.

Interrupt regorafenib for the following:

- NCI CTCAE Grade 2 hand-foot skin reaction (HFSR) [palmar-plantarerythrodysesthesia (PPE)] that is recurrent or does not improve within 7 days despite dose reduction; interrupt therapy for a minimum of 7 days for Grade 3 HFSR
- Symptomatic Grade 2 hypertension
- Any NCI CTCAE Grade 3 or 4 adverse reaction

Reduce the dose of regorafenib to 120 mg:

- For the first occurrence of Grade 2 HFSR of any duration
- After recovery of any Grade 3 or 4 adverse reaction
- For Grade 3 aspartate aminotransferase (AST)/alanineaminotransferase (ALT) elevation; only resume if the potential benefit outweighs the risk of hepatotoxicity

Reduce the dose of regorafenib to 80 mg:

- For re-occurrence of Grade 2 HFSR at the 120 mg dose
- After recovery of any Grade 3 or 4 adverse reaction at the 120 mg dose (except hepatotoxicity)

Discontinue regorafenib permanently for the following:

- Failure to tolerate 80 mg dose
- Any occurrence of AST or ALT more than 20 times the upper limit of normal (ULN)
- Any occurrence of AST or ALT more than 3 times ULN with concurrent bilirubin more than 2 times ULN
- Re-occurrence of AST or ALT more than 5 times ULN despite dose reduction to 120 mg
- For any Grade 4 adverse reaction; only resume if the potential benefit outweighs the risks

6.1.3 Irinotecan

The recommended dose for irinotecan will be 180 mg/m^2 every two (2) weeks. Recommended dose alterations for toxicity from the FDA approved irinotecan product information are shown in Table 7 below.

Table 6: Dose Modifications for Irinotecan Administration

Table 11. Recommended Dose Modifications for CAMPTOSAR/5-Fluorouracil (5-FU)/Leucovorin (LV) Combination Schedules

Patients should return to pre-treatment bowel function without requiring antidiarrhea medications for at least 24 hours before the next chemotherapy administration. A new cycle of therapy should not begin until the granulocyte count has recovered to ≥1500/mm^3, and the platelet count has recovered to ≥100,000/mm^3, and treatment-related diarrhea is fully resolved. Treatment should be delayed 1 to 2 weeks to allow for recovery from treatment-related toxicities. If the patient has not recovered after a 2-week delay, consideration should be given to discontinuing therapy

Toxicity NCI CTC Grade[a] (Value)	During a Cycle of Therapy	At the Start of Subsequent Cycles of Therapy[b]
No toxicity	Maintain dose level	Maintain dose level
Neutropenia		
1 (1500 to 1999/mm^3)	Maintain dose level	Maintain dose level
2 (1000 to 1499/mm^3)	↓ 1 dose level	Maintain dose level
3 (500 to 999/mm^3)	Omit dose until resolved to ≤ grade 2, then ↓ 1 dose level	↓ 1 dose level
4 (<500/mm^3)	Omit dose until resolved to ≤ grade 2, then ↓ 2 dose levels	↓ 2 dose levels
Neutropenic fever	Omit dose until resolved, then ↓ 2 dose levels	
Other hematologic toxicities	Dose modifications for leukopenia or thrombocytopenia during a cycle of therapy and at the start of subsequent cycles of therapy are also based on NCI toxicity criteria and are the same as recommended for neutropenia above.	
Diarrhea		
1 (2-3 stools/day > pretx[c])	Delay dose until resolved to baseline, then give same dose	Maintain dose level
2 (4-6 stools/day > pretx)	Omit dose until resolved to baseline, then ↓ 1 dose level	Maintain dose level
3 (7-9 stools/day > pretx)	Omit dose until resolved to baseline, then ↓ 1 dose level	↓ 1 dose level
4 (≥ 10 stools/day > pretx)	Omit dose until resolved to baseline, then ↓ 2 dose levels	↓ 2 dose levels
Other nonhematologic toxicities[d]		
1	Maintain dose level	Maintain dose level
2	Omit dose until resolved to ≤ grade 1, then ↓ 1 dose level	Maintain dose level
3	Omit dose until resolved to ≤ grade 2, then ↓ 1 dose level	↓ 1 dose level
4	Omit dose until resolved to ≤ grade 2, then ↓ 2 dose levels	↓ 2 dose levels
	For mucositis/stomatitis decrease only 5-FU, not CAMPTOSAR	*For mucositis/stomatitis decrease only 5-FU, not CAMPTOSAR.*

[a] National Cancer Institute Common Toxicity Criteria (version 1.0)
[b] Relative to the starting dose used in the previous cycle
[c] Pretreatment
[d] Excludes alopecia, anorexia, asthenia

Table 7: Recommended Dose Reductions for Irinotecan

Starting Dose of Irinotecan (mg/m^2)	Dose level -1 (mg/m^2)	Dose level -2 (mg/m^2)
180	140-150	110-120

7.0 STUDY VISITS

7.1 Screening Visit Within 28 Days Prior to Randomization

Required Procedures and Assessments

- Written Informed Consent
- Medical history/Demographics: Includes demographic data (age, race, ethnicity, etc.), medical history, surgical history, cancer history, cancer treatment history
- Clinic visit: Includes full physical exam and recording of PE findings (abnormalities only), ECOG Performance Status, vitals, weight, height. Clinic visit should be performed by the treating Investigator or sub-investigator.
- QOL assessment: EORTC QLQ-C30

- Physician administered Edmonton Symptom Assessment System (ESAS)
- Tumor imaging by CT/MRI and RECIST v1.1 assessment
- RRx-001 randomized subjects will be imaged by diagnostic CT with contrast
- Clinical laboratory assessments by local lab:
    - Hematology includes: red blood cells, hematocrit, hemoglobin, platelets, and white blood cells with differential (neutrophil, lymphocyte, monocyte, basophil, and eosinophil).
    - Complete metabolic panel includes: sodium, potassium, chloride, bicarbonate, BUN, creatinine, glucose, calcium, total protein, albumin, AST, ALT, total bilirubin, alkaline phosphatase, and LDH.
    - CEA tumor marker.
    - Serum pregnancy test on women of child-bearing potential (WOCBP)
    - Urinalysis
- Archival tumor sample submission: Archived tissue will be collected for all subjects when available. It is preferred that tumor biopsies be submitted for biomarker analysis as a formalin fixed paraffin-embedded (FFPE) blocks; however at least 10 unstained slides are also acceptable. See Appendix 3 for detailed instructions.
- Concomitant medications review and documentation. For subjects entering the study on a chronic concomitant medication, adequate clarification of the reason for taking that medication must be documented in the medical history. For a list of prohibited medications, see protocol Section 6.0
- AE/SAE assessment: The AE/SAE reporting period will extend from first dose of study drug (regorafenib or RRx-001) through the Study Termination Visit, until 30 days after the last dose of study drug, or the resolution or stabilization of the AE to Grade ≤1 or baseline, whichever is longer. AEs/SAEs occurring from time of signed informed consent to first dose of study drug should be recorded in the Medical History CRF page.
- Inclusion/Exclusion criteria assessment
- Randomization: May be performed up to 7 days prior to Cycle 1 Day 1

For additional detail on Screening Procedures, refer to Section 1.1 *Schedule of Assessments.*

7.2 Treatment Schedule

Procedure and Cycle Windows:

- Cycle 1 Day 1 should be performed within 7 days after Randomization
- Cycle 1 Day 1 Repeat Assessments:
    - If screening clinic visit is performed within 7 days prior to Cycle 1 Day 1, it does not need to be repeated.
    - If screening labs (hematology and complete metabolic panel) are completed within 48 hours prior to Cycle 1 Day 1, these do not need to be repeated.
- All Day 1 procedures should be performed within 48 hours prior to the start of the cycle.
- Following Cycle 1 Day 1, visits are to be executed ± 24 hours from the scheduled time point.
- Cycle length = 4 weeks (28 days).

Cycle 1 Day 1 (Week 1)

- Clinic Visit: Includes symptom directed physical exam and recording of PE findings (abnormalities only), ECOG Performance Status, Vitals, Weight
- Clinical laboratory assessments by local lab (not required if screening labs performed within 48 hours prior):
    - Hematology includes: red blood cells, hematocrit, hemoglobin, platelets, and white blood cells with differential (neutrophil, lymphocyte, monocyte, basophil, and eosinophil).
    - Complete Metabolic Panel includes: sodium, potassium, chloride, bicarbonate, BUN, creatinine, glucose, calcium, total protein, albumin, AST, ALT, total bilirubin, alkaline phosphatase, and LDH.
    - CEA tumor marker.
- QOL Questionnaire: EORTC QLQ-C30. Should be completed at the beginning of the visit, prior to any other assessments.
    - Not required if screening QOL Questionnaire is completed within 48 hours prior.
- Physician administered Edmonton Symptom Assessment System (ESAS)
    - Not required if screening ESAS is completed within 48 hours prior.
- Concomitant Medications Review and Documentation, including BSC
- Adverse Event Assessment
- Study Drug Administration:
    - RRx-001 will be administered intravenously either centrally or peripherally once a week, on Day 1 (at least 7 days ±1 day apart), over up to 4 hours. For additional detail on dosing and premedication, refer to protocol Sections 2.7 and 6.0 and to Section 1.1 *Schedule of Assessments.*
    - Best Supportive Care should be administered according to the Institutional Standard of Care. Best Supportive Care includes any method to preserve the comfort of the subject, including palliative radiation and surgical intervention. The use of palliative radiation and/or surgical intervention is under the discretion of the Investigator and with agreement of the Sponsor. Best Supportive Care excludes systemic anti-cancer therapy.
    - Regorafenib will be administered orally as directed in the package insert at 160 mg once daily for the first 21 days of a 28-day cycle. Dose interruptions and reductions, if required, should strictly adhere to the guidelines in the package insert.
- Subjects enrolled at Stanford University may have CEUS imaging at the discretion of the Principal Investigator and Radiologist.

Cycle 1 Day 8 (Week 2)

- Study Drug Administration:
    - RRx-001 will be administered intravenously either centrally or peripherally once a week, on Day 8 (at least 7 days ±1 day apart), over up to 4 hours. For additional detail on dosing and premedication, refer to protocol Sections 2.7 and 6.0 and Section 1.1 *Schedule of Assessments*
    - Best Supportive Care should be administered according to the Institutional Standard of Care.

  - Regorafenib will be administered orally as directed in the package insert at 160 mg once daily for the first 21 days of a 28-day cycle.
  - Adverse Event Assessment
- Subjects enrolled at Stanford University may have CEUS imaging at the discretion of the Principal Investigator and Radiologist.

Cycle 1 Day 15 (Week 3)

- Clinic Visit: Includes symptom-directed physical exam and recording of PE findings (abnormalities only), ECOG Performance Status, Vitals, Weight
- Clinical laboratory assessments by local lab:
  - Hematology includes: red blood cells, hematocrit, hemoglobin, platelets, and white blood cells with differential (neutrophil, lymphocyte, monocyte, basophil, and eosinophil).
  - Complete Metabolic Panel includes: sodium, potassium, chloride, bicarbonate, BUN, creatinine, glucose, calcium, total protein, albumin, AST, ALT, total bilirubin, alkaline phosphatase, and LDH.
  - CEA tumor marker.
- QOL Questionnaire: EORTC QLQ-C30. Should be completed at the beginning of the visit, prior to any other assessments.
- Concomitant Medications Review and Documentation, including BSC
- Adverse Event Assessment
- Study Drug Administration:
  - RRx-001 will be administered intravenously either centrally or peripherally once a week, on Day 15 (at least 7 days ±1 day apart), over up to 4 hours. For additional detail on dosing and premedication, refer to protocol Sections 2.7 and 6.0 and to Section 1.1 *Schedule of Assessments*
  - Best Supportive Care should be administered according to the Institutional Standard of Care.
  - Regorafenib will be administered orally as directed in the package insert at 160 mg once daily for the first 21 days of a 28-day cycle.

Cycle 1 Day 22 (Week 4)

- Study Drug Administration:
  - RRx-001 will be administered intravenously either centrally or peripherally once a week, on Day 22 (at least 7 days ±1 day apart), over up to 4 hours. For additional detail on dosing and premedication, refer to protocol Sections 2.7 and 6.0 and Section 1.1 *Schedule of Assessments*
  - Best Supportive Care should be administered according to the Institutional Standard of Care.
  - Adverse Event Assessment
- Subjects enrolled at Stanford University may have CEUS imaging at the discretion of the Principal Investigator and Radiologist.

Cycle 2 Day 1 (Week 1)

- Clinic Visit: Includes symptom-directed physical exam and recording of PE findings (abnormalities only), ECOG Performance Status, Vitals, Weight
- Clinical laboratory assessments by local lab:
  - Hematology includes: red blood cells, hematocrit, hemoglobin, platelets, and white blood cells with differential (neutrophil, lymphocyte, monocyte, basophil, and eosinophil).
  - Complete Metabolic Panel includes: sodium, potassium, chloride, bicarbonate, BUN, creatinine, glucose, calcium, total protein, albumin, AST, ALT, total bilirubin, alkaline phosphatase, and LDH.
  - CEA tumor marker.
  - Serum pregnancy test on women of child-bearing potential (WOCBP)
- QOL Questionnaire: EORTC QLQ-C30. Should be completed at the beginning of the visit, prior to any other assessments.
- Physician administered Edmonton Symptom Assessment System (ESAS)
- Concomitant Medications Review and Documentation, including BSC
- Adverse Event Assessment
- Study Drug Administration:
  - RRx-001 will be administered intravenously either centrally or peripherally once a week, on Day 1 (at least 7 days ±1 day apart), over up to 4 hours. For additional detail on dosing and premedication, refer to protocol Sections 2.7 and 6.0 and to Section 1.1 *Schedule of Assessments*
  - Best Supportive Care should be administered according to the Institutional Standard of Care.
  - Regorafenib will be administered orally as directed in the package insert at 160 mg once daily for the first 21 days of a 28-day cycle.

Cycle 2 Day 8 (Week 2)

- Study Drug Administration:
  - RRx-001 will be administered intravenously either centrally or peripherally once a week, on Day 8 (at least 7 days ±1 day apart), over up to 4 hours. For additional detail on dosing and premedication, refer to protocol Sections 2.7 and 6.0 and Section 1.1 *Schedule of Assessments*
  - Best Supportive Care should be administered according to the Institutional Standard of Care.
  - Regorafenib will be administered orally as directed in the package insert at 160 mg once daily for the first 21 days of a 28-day cycle.
  - Adverse Event Assessment

Cycle 2 Day 15 (Week 3)

- Clinic Visit: Includes symptom-directed physical exam and recording of PE findings (abnormalities only), ECOG Performance Status, Vitals, Weight
- Clinical laboratory assessments by local lab:
  - Hematology includes: red blood cells, hematocrit, hemoglobin, platelets, and white blood cells with differential (neutrophil, lymphocyte, monocyte, basophil,

and eosinophil).
    - Complete Metabolic Panel includes: sodium, potassium, chloride, bicarbonate, BUN, creatinine, glucose, calcium, total protein, albumin, AST, ALT, total bilirubin, alkaline phosphatase, and LDH.
    - CEA tumor marker.
- QOL Questionnaire: EORTC QLQ-C30. Should be completed at the beginning of the visit, prior to any other assessments.
- Concomitant Medications Review and Documentation, including BSC
- Adverse Event Assessment
- Study Drug Administration:
    - RRx-001 will be administered intravenously either centrally or peripherally once a week, on Day 15 (at least 7 days ±1 day apart), over up to 4 hours. For additional detail on dosing and premedication, refer to protocol Sections 2.7 and 6.0 and to Section 1.1 *Schedule of Assessments*
    - Best Supportive Care should be administered according to the Institutional Standard of Care.
    - Regorafenib will be administered orally as directed in the package insert at 160 mg once daily for the first 21 days of a 28-day cycle.

Cycle 2 Day 22 (Week 4)

- Study Drug Administration:
    - RRx-001 will be administered intravenously either centrally or peripherally once a week, on Day 22 (at least 7 days ±1 day apart), over up to 4 hours. For additional detail on dosing and premedication, refer to protocol Sections 2.7 and 6.0 and Section 1.1 *Schedule of Assessments*
    - Best Supportive Care should be administered according to the Institutional Standard of Care.
- Adverse Event Assessment
- Subjects enrolled at Stanford University may have CEUS imaging at the discretion of the Principal Investigator and Radiologist.

Cycle 3+

- Cycle 3+ has the same procedures as Cycle 1 and 2.
- Tumor Imaging by CT and irRC Assessment at 12 weeks with 4 week confirmatory scan for response or progression, if indicated

Progression Visit

- Diagnostic CT (with contrast)
- Concomitant Medications Review and Documentation, including BSC
- Adverse Event Assessment

Refer to *Schedule of Assessments* for additional details.

7.2.1 Stage 2: Irinotecan

Following progression on RRx-001 or regorafenib (see Section 9.1.2), subjects will receive irinotecan therapies. See Section 4.8, Table 4 for more details about the dose and schedule. Subjects enrolled at Stanford University may have CEUS imaging at the discretion of the Principal Investigator and Radiologist. A diagnostic CT (with contrast) scan for RRx-001 randomized subjects that are at Stage 2 (i.e. receiving irinotecan) will be carried out at the first scheduled imaging visit after starting irinotecan.

Study patients will need to meet Inclusion Criterion #10 regarding required laboratory parameters (a-e) before beginning Stage 2 (see Inclusion Criteria). In addition, the following criteria need to be met:

- ***In order to allow continued administration of RRx-001 (or regorafenib) despite progression of disease based on appearance of a new lesion (per irRC), patients must have absence of symptoms and signs of clinically important morbidity due to disease progression (e.g., requirement for additional medical management to control symptoms or irradiation to prevent morbidity), absence of symptomatic rapid disease progression requiring urgent medical intervention (e.g., spinal cord compression), and no decline in ECOG or Karnofsky performance status.***

- ***Patients are re-consented using a written informed consent document at the time of progression of disease.***

7.2.2 Long-Term Follow Up

Following progression on irinotecan-based therapies, subjects will be followed through their subsequent lines of treatment to collect overall survival. Subjects will be followed every eight (8) weeks by chart review (at a minimum) until death or withdrawal of consent to collect overall survival. Follow up will continue until study closure.

7.3 Subject Withdrawal from Study Treatment

Subjects may discontinue the trial at any time, for any reason, without prejudice to further treatment.

Subjects may be withdrawn from the study for any of the following reasons but will be followed for safety until 30 days after last dose of study drug, resolution or permanent sequelae of all toxicities attributable to the study drug, whichever is earliest:

- The subject withdraws consent; or
- Unacceptable toxicity; or
- The cessation of study treatment is medically necessary in the opinion of the Investigator; or
- The subject is lost to follow-up; or
- Non-compliance with study procedures; or

- Sponsor decides to end study.

7.4 Withdrawal Procedure

In the event of a subject's withdrawal from the study, the Investigator will promptly notify the Medical Monitor. All treatment emergent adverse drug events will be followed until resolution, improvement to ≤ Grade 1 or baseline, or permanent sequelae, subject death, commencement of other anticancer therapy or up to the end of the study, whichever is longer. Final outcome for AEs ongoing at time of termination visit will be captured as "Not Recovered/Not Resolved".

7.5 Early Termination of Study/Center Closure

The study may be terminated at any time by the Sponsor in the event of unacceptable toxicity or new information that significantly impacts subject safety. The study may be terminated at a study site if the Investigator does not adhere to the protocol. In the event that the clinical development of the investigational product is discontinued for any reason, the Sponsor shall immediately inform all study Investigators/IRBs and Regulatory Authorities.

8.0 SUBJECT ASSESSMENTS

Subjects must provide written informed consent for participation in this study prior to start of any study procedures.

Subjects must meet all inclusion and exclusion criteria prior to randomization and study drug dosing.

8.1 Tumor Assessments Using irRC Criteria by X-Ray Computed Tomography, Magnetic Resonance Imaging and FDG-PET

X-ray computed tomography (CT) with contrast procedures will be performed to establish a baseline for the tumor, and disease progression will be monitored as detailed in Section 4.4. Imaging should be performed with the use of contrast. The Screening CT procedure does not need to be repeated if a CT was performed within 28 days of Randomization. Subsequent assessments will be performed according to the *Schedule of Assessments*. Subjects that are intolerant to the CT contrast agent are eligible for tumor assessment by MRI. In addition, MRI may be used if it is the best imaging modality for a given tumor site. The same imaging modality for tumor assessments for each subject should be performed throughout the study. As described in Section 9.1.2, an FDG-PET scan may be carried out at the Investigator's discretion for informational purposes since RRx-001 is associated with treatment-related tumor inflammation if CT or MRI progression is observed. Imaging in this study will be carried out as described in (Table 8).

Table 8: Imaging Events and Modalities

Imaging Event	Imaging Modality	RRx-001 Arm	Regorafenib Arm	Irinotecan-based Therapies
Baseline	CT or MRI	Y	Y	Y
Every 12 weeks	CT or MRI	Y	Y	N
Every 8 weeks	CT or MRI	N	N	Y
On suspected progression by CT or MRI	FDG-PET	Y*	N	N
First scheduled imaging visit post start of irinotecan	PET-CT	Y	N	Y

* = Recommended, but at Investigators' discretion

An exploratory endpoint is to assess the impact of p53 status on response. As one measure of response will be change in SUV by FDG-PET, it will be important to have an even distribution of p53 wild type and mutant subjects. Therefore, as the study is progressing, it may be necessary to limit the number of subjects being imaged based on the ratio of wild-type to mutant subjects enrolled.

8.2 Contrast Enhanced Ultrasound (CEUS) Imaging

Contrast Enhanced Ultrasound imaging will be carried to assess impact of RRx-001 on tumor blood flow and perfusion and to assess tumor response with irinotecan post-RRx-001. The decision as to who (which patients), on what therapies and when to image at any given time is entirely at the discretion of the Stanford University PI, and the Stanford University radiologist. See Appendix 6 for full details.

8.3 Tumor Biopsies

See Appendix 4 for further details concerning tumor biopsy methodology, labeling and shipment instructions for a central pathology service. Determination of p53 and PDI (RRx-001 subjects): Documentation of p53 status or level of PDI expression can occur via the following: 1) Prior genetic testing/profiling results; 2) Submission of archival tissue to local laboratory if site has the required capabilities; or 3) Submission of archival tissue to central laboratory. Only in the event that p53 status is unknown and there is not sufficient archival tissue to be submitted, the patient should undergo a research biopsy of the primary tumor if deemed clinically appropriate.

8.4 Laboratory Assessments

Clinical laboratory (hematology, chemistry, and tumor marker), urinalysis and serum or urine pregnancy (on females of childbearing potential) will be performed according to the *Schedule of Assessments* and under Institutional Standard of Care.

The Investigator will monitor the laboratory test findings. If any laboratory test is abnormal, it will be followed at the discretion of the Investigator.

Abnormal laboratory tests may, in the opinion of the Investigator, be considered clinically significant and, thus, constitute or be associated with an AE. In such cases, they must be reported

on the AE page of the case report form (CRF). Any abnormal clinical lab that is determined not to be clinically significant will have a description of the reason for this determination documented on the lab CRF.

8.5 Clinical Features of RRx-001 Toxicity and Management

In the Phase 1 trial, the most common adverse event associated with RRx-001 was transient discomfort or vascular pain at the injection site, for the length of the infusion, which was unpleasant to the clinical trial participants. Pretreatment with a parenteral or oral corticosteroid and NSAID on dosing days mitigated the intensity of pain and is a prerequisite and cornerstone of pain management in this Phase 2 trial. However, the administration of corticosteroids outside of dosing days on a chronic or subchronic basis is contraindicated except in emergencies and in clinically symptomatic disease pseudoprogression (see below). In these cases, the lowest possible dose for symptom management should be used. As immunosuppressants, corticosteroids may alter the release of RRx-001-induced pro-inflammatory cytokines and chemokines and thus impact negatively on anti-tumor activity.

Empirically prolongation of the infusion time was also effective and any intervention for refractory pain or discomfort should include slowing of the infusion rate; however pain perception is individualized and because no single approach was universally effective in the Phase 1 trial, pain management must be addressed on a case-by-case basis, with individualized infusion rates and the co-administration of opioids, and benzodiazepines as required.

Another complication is the potential for treatment-related necrosis and tumor enlargement or pseudoprogression with RRx-001. The clinical significance of this complication is variable, ranging from none to requiring medical intervention. The management is individualized, depending on the size of the acutely enlarged mass, and its relation to adjacent anatomical structures. An acutely enlarged necrotic mass may present with compressive symptoms, mimicking other more common conditions including true progression and therefore even nonspecific complaints such as abdominal pain or nausea should increase the index of suspicion and the reflex to image and/or biopsy suspected cases aggressively.

9.0 ASSESSMENT OF EFFICACY

9.1 Tumor Assessments

Tumor assessments will be made according to the *Schedule of Assessments*. Response and progression will be evaluated as defined per irRC for RRx-001 and regorafenib and RECIST v1.1 for irinotecan study stages.

All subjects must have radiographic tumor measurements performed at the participating study center.

The RECIST v 1.1 guidelines (January 2009) will be used as one component to determine response. Grading for best response will be categorized as complete response (CR), partial response (PR), stable disease (SD) or progressive disease (PD).

Immune Related Response Criteria will be used as described in Appendix 5.

Sites will provide all scans to EpicentRx for later review.

9.1.1 Definitions

For guidelines on definitions and evaluation of measurable and non-measureable disease and target and non-target lesions, see Appendix 5: RECIST v1.1 and irRC.

9.1.2 Determination of Conditions for Entry to Stage 2 of Study: RRx-001

Tumors will be assessed by CT or MRI every 12 weeks with a confirmatory scan 4 weeks later per irRC, for progression or response, if indicated, to determine the conditions for entry to Stage 2 of the clinical study, resensitization to irinotecan.

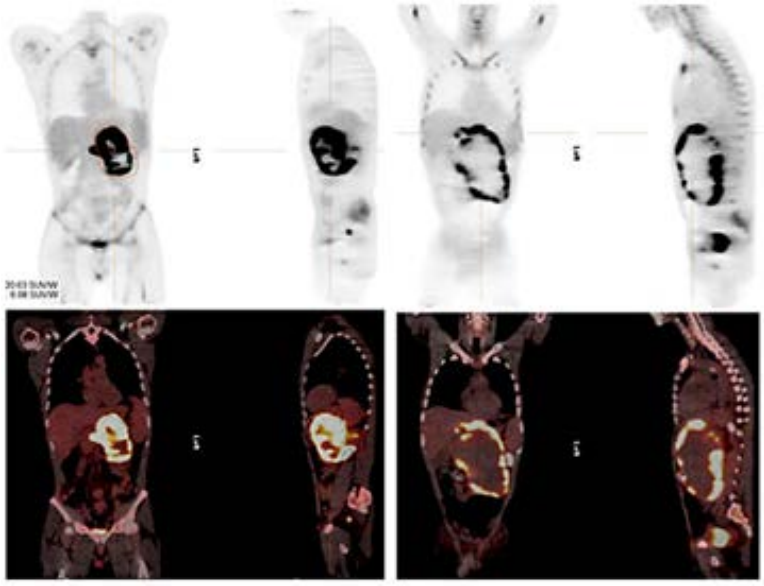
Subjects that have been randomized to the regorafenib arm will enter Stage 2 on diagnosis of Progressive Disease by CT or MRI per irRC, provided that their performance status is adequate i.e. 0 or 1 and it is warranted in the opinion of the Investigator, taking into account the whole clinical picture.

Study patients will need to meet Inclusion Criterion #10 regarding required laboratory parameters (a-e) before beginning Stage 2 (see Inclusion Criteria).

9.2 Pseudoprogression and Immune Related Response Criteria (irRC)

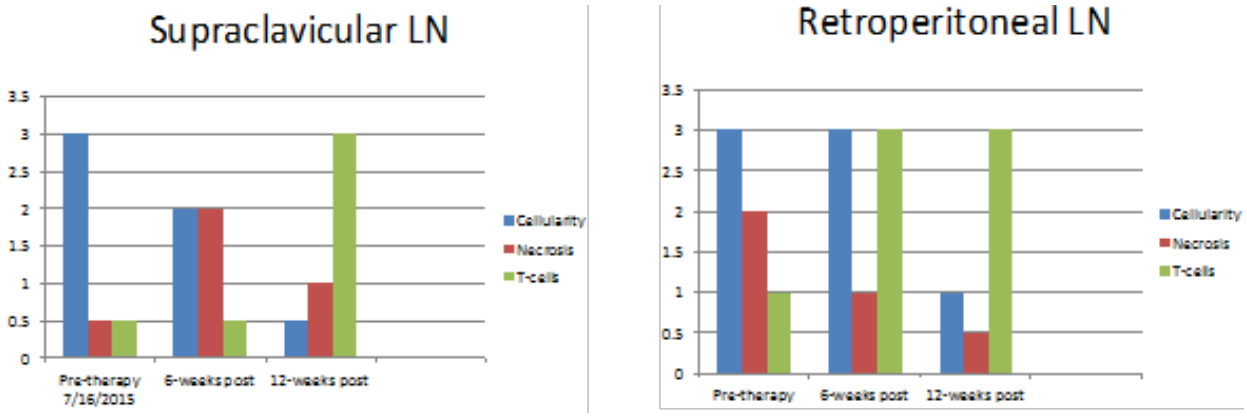
Based on preclinical experiments, RRx-001 increases anti-tumor T cell activation. Clinical observations of RRx-001-treated tumors suggest that RECIST response assessment criteria are not sufficient to fully characterize patterns of response, which typically include treatment-related necrosis and rapid radiologic enlargement of lesions in the context of symptomatic stabilization or improvement; this subjective improvement or stabilization is consistent with pseudoprogression i.e. temporary reversible increase in size due to RRx-001 exposure. The before-and-after images of this $EGFR^+$ NSCLC TRIPLE THREAT patient taken from a published case report are a case in point. [Brzezniak et al. 2016]. A biopsy of this tumor revealed infiltration of T lymphocytes and only scant surviving tumor cells. Over time presumably due to resorption of the necrotic debris, the lesion shrunk in size. Therefore the apparent increase or decrease in size of RRx-001-treated tumors may in reality be a function of the development or subsidence of inflammatory swelling.

Figure 2: Baseline FDG-PET/CT (left) demonstrating an FDG avid tumor is compared to interim FDG-PET/CT after 5 weeks of treatment with RRx-001 (right). The treatment effect is indicated by extensive central tumor necrosis with a thin halo of the apparently viable tumor, which may be an immune infiltrate.



Serial biopsies from another TRIPLE THREAT patient demonstrated an increased T cell infiltrate and decreased cellularity and size at 12 weeks; prior to 12 weeks the patient's tumors increased in size although not enough to be considered progressive disease per RECIST v. 1.1 criteria.

Figure 3: Graph of cellularity, necrosis and T cell infiltrate in a two serially biopsied lymph nodes from the same patient on a 40x field of view. The y-axis is graded on a scale of 0 to 3 where 0=none 1=slight 2=moderate 3=extensive. By 12 weeks T cell infiltrate has significantly increased while cellularity has significantly decreased.



Given these observations, RECIST v. 1.1 criteria have been replaced with irRC to assess response at 12 weeks. Measurable lesions are defined as ≥5×5 mm. The longest diameters of new lesions, if any, are also measured, according to irRC. The cut-off values defined by irRC are: ≥25% increase from the nadir for progression, ≥50% decrease from baseline for partial response, and disappearance of all lesions for complete response. Confirmation by two consecutive observations not less than 4 weeks apart is required for CR, PR and PD for both assessments, as defined by irRC to assign best response for each patient. Refer to Appendix E for more information about irRC. However, to capture potential non-radiological progression, physicians will administer a well-validated questionnaire called Edmonton Symptom Assessment System (ESAS) to patients starting at Week 8. Note that tumor assessment for the Platinum Doublet Stage will continue to use RECIST v1.1 criteria to enable comparison with historic responses.

10.0 ASSESSMENT OF SAFETY

Safety will be evaluated according to the *Schedule of Assessments* per Institutional Standard of Care.

10.1 Coding Adverse Events

This trial will use the most current version of the Medical Dictionary for Regulatory Activities (MedDRA) for coding all AEs. Adverse events within each system will be summarized by preferred term, system organ class, NCI CTCAE, Version 4.03 (published June 14, 2010 or later) grade of severity, and relationship to the study medication. Serious adverse events (SAEs) will be summarized separately.

10.2 Adverse Events

An AE is any untoward medical occurrence in a subject or clinical investigation subject administered a pharmaceutical product and that does not necessarily have a causal relationship with this treatment. An AE can therefore be any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease temporally associated with the use of a medicinal (investigational) product, whether or not related to the medicinal (investigational) product.

Pre-existing events, which increase in frequency or severity or change in nature during or as a consequence of use of the study medication will also be considered as AEs. AEs may also include pre-treatment or post-treatment complications that occur as a result of protocol-mandated procedures. Any medical condition or clinically significant laboratory abnormality with an onset date before any study required procedures is considered to be pre-existing, and should be documented in the CRF as such. Any AE (i.e. a new event or an exacerbation of a pre-existing condition) with an onset after the administration of study required procedures up to the last day on study (end-of-treatment visit) should be recorded as an AE on the appropriate CRF page(s).

For the purposes of this study an AE will not include the following:

- A medical or surgical procedure (e.g., biopsy, surgery, endoscopy, tooth extraction, or transfusion); associated with the underlying condition that leads to the procedure;
- Pre-existing diseases or conditions present or detected before start of study medication

administration and which do not worsen or increase in severity or frequency after the administration of study medication; situations where an untoward medical occurrence has not occurred (e.g., hospitalization for elective surgery for a condition that has not worsened on study, social and/or convenience admissions to grant families a respite in caring for a subject).
- Progressive disease.

10.2.1 Abnormal Test Findings

Abnormal laboratory findings (e.g., clinical chemistry, hematology, urinalysis, tumor marker) or other abnormal assessments (e.g., electrocardiogram, X-rays, vital signs) per se are not reported as AEs. However, those abnormal findings that are deemed clinically significant by the Investigator or are associated with signs and/or symptoms must be recorded as AEs if they meet the definition of an adverse event (and recorded as an SAE if they meet the criteria of being serious). The criteria for determining whether an abnormal objective test finding should be reported as an AE include the following:

- Test result is associated with accompanying symptoms;
- Test result requires additional diagnostic testing or medical/surgical intervention;
- Test result leads to a change in study dosing or discontinuation from the study, significant additional concomitant drug treatment, or other therapy.

Merely repeating an abnormal test, in the absence of any of the above conditions, does not constitute an AE. Any abnormal test result that is determined to be an error does not require reporting as an AE.

10.3 Monitoring Adverse Events

All AEs will be assessed by the Investigator and recorded on the appropriate CRF; the reported verbatim term will be documented including the date of onset and resolution, NCI-CTCAE grade of severity, relationship to study medication, outcome, and action taken. Adverse events will be reported starting at the Cycle 1 Day 1 clinical visit and be recorded continuously through the treatment period and until the Study Termination Visit (STV) or resolution if not resolved to baseline at time of STV.

Adverse Events Data Elements:

- Verbatim description of event.
- NCI-CTCAE v4.03 grade for AE severity.
- Start and stop date of AE.
- Relationship to study drug (attribution).
- Whether or not the subject was discontinued from the study due to the AE.
- Action taken with regard to the administration of study drug.
- Whether or not the event met the criteria for a SAE; if yes, an SAE form needs to be completed and submitted to the Sponsor within 24 hrs.

10.3.1 Grading of AEs

The severity of an event and the seriousness are not to be considered synonymous. The severity is grading the intensity of an event. The seriousness of an event is based on the subject/event outcome. All AEs will be assessed for severity using the NCI-CTCAE v4.03.

If a particular AE is not listed in the NCI-CTCAE v4.03, the following criteria will be used:

- Grade 1 = Mild
- Grade 2 = Moderate
- Grade 3 = Severe
- Grade 4 = Life threatening or disabling
- Grade 5 = Death

10.3.2 Causality Relationship of AEs

The relationship of each AE to the study medication will be evaluated by the Investigator using the following definitions:

- Unrelated: The AE is unlikely or clearly not related to the study drug. The AE can be explained to be likely related to other factors such as concomitant medications, underlying disease, or the subject's clinical state.
- Related: The AE is possibly or definitely related to the study drug. A plausible temporal sequence exists between the time of administration of the study drug and the development of the AE and it follows a known response pattern to the study drug. The AE cannot be reasonably explained by the known characteristics of the subject's clinical state or other concomitant therapies or interventions administered to the subject.

If the Investigator determines an SAE is associated with study procedures, the Investigator must record his causal relationship in the source documents and CRF, as appropriate, and report such an assessment in accordance with the SAE reporting requirements, if applicable.

10.3.3 Study Procedures

Although adverse events are typically considered in the context of arising as a consequence of study drug exposure, it is important for the safety of study subjects to identify study-related procedures that may produce untoward events. For example, following study enrollment a protocol may stipulate that a diagnostic test be performed. It is possible that the diagnostic test poses a particular risk to the study population. It would be important to identify this risk, particularly serious risks so that steps could be taken to reduce the risk to study subjects. If an adverse event occurs as a result of a protocol-directed procedure, it is important to record the adverse event and assign the causality assessment as related to "study procedure".

10.3.4 Deaths

Death is an outcome of an adverse event and not an adverse event in itself. All reports of subject death should include an Adverse Event term for the cause of the death. For all reports in which an Adverse Event term is not provided (other than 'Death'), follow-up for the cause of death will be required. Only in the rare occurrence that no verbatim description of an adverse event can be

obtained from the investigative site, then "Death – Unknown Cause" will be used as the event term.

10.4 Serious Adverse Event (SAE)

An AE is considered "serious" if, in the view of either the Investigator or Sponsor, it results in any of the follow outcomes:

- Death;
- Life-threatening (subject is at immediate risk of death);
- Inpatient hospitalization or prolongation of existing hospitalization;
- Results in persistent or significant incapacity or substantial disruption of the ability to conduct normal life functions;
- Congenital anomaly/birth defect in the offspring of a subject who received study medication;
- Other: Important medical events that may not result in death, be immediately life-threatening, or require hospitalization, may be considered a SAE when, based upon appropriate medical judgment, they may jeopardize the subject and may require medical or surgical intervention to prevent one of the outcomes listed in this definition, examples of such events are: intensive treatment in an emergency room or at home for allergic response, blood dyscrasias or convulsions that do not result in hospitalization, development of drug dependency or drug abuse, etc.

Death: Death is an outcome of an AE, and not an AE in itself. All deaths regardless of causality must be reported. See Section 10.3.4.

Life-Threatening**:** "Life-threatening" means that the subject was at immediate risk of death from the event as it occurred. This does not include an event that might have led to death, if it had occurred with greater severity.

An AE is considered "life-threatening" if, in the view of either the Investigator or Sponsor, its occurrence places the subject at immediate risk of death. It does not include an AE, that, had it occurred in a more severe form, might have caused death.

Hospitalization**:** "Inpatient hospitalization" means the subject has been admitted to a hospital for medical reasons for any length of time.

The Investigator should attempt to establish a diagnosis of the event based on signs, symptoms, and/or other clinical information. In such cases, the diagnosis should be documented as the AE and/or SAE and not the individual signs/symptoms. AEs associated with hospitalization or prolongations of hospitalization in study subjects are considered serious. Any initial admission (even if less than 24 hours) to a healthcare facility meets these criteria.

Hospitalization does not include the following:

- Rehabilitation facilities;
- Hospice facilities;

- Respite care (e.g., caregiver relief);
- Skilled nursing facilities;
- Nursing homes;
- Routine emergency room admissions;
- Scheduled or elective same day surgeries (as outpatient/same day/ambulatory procedures).

Hospitalization of prolongation of hospitalization in the absence of a precipitating clinical AE is not in itself a SAE.

All SAEs require reporting to the Sponsor within 24 hours of a site's knowledge of the SAE.

Diagnostic and therapeutic non-invasive procedures, and surgery, should not be reported as AEs. However, the medical condition for which the procedure was performed should be reported if it meets the definition of an AE. For example, an acute appendicitis that begins during the AE reporting period should be reported as an AE and the resulting appendectomy should be recorded as treatment of the AE.

10.4.1 Adverse Reaction

An adverse reaction (AR) means any AE caused by a drug. An AR or adverse drug reaction (ADR) is a subset of all suspected adverse reactions (SARs) as defined below for which there is reason to conclude that the drug caused the event. Adverse reactions are a subset of all suspected AEs for which there is reason to conclude that the drug caused the AE.

10.4.2 Suspected Adverse Reaction (SAR)

Suspected adverse reaction means any AE for which there is a reasonable possibility that the drug caused the AE. For the purposes of IND safety reporting, ''reasonable possibility'' means there is evidence to suggest a causal relationship between the drug and the AE. Suspected adverse reaction implies a lesser degree of certainty about causality than adverse reaction, which means any AE caused by a drug.

For reporting purposes, AEs assigned a relationship to treatment of "related" will be classified as SARs.

AEs assigned a relationship to treatment of "unrelated" will not be classified as SARs.

10.4.3 Unexpected Suspected Adverse Reactions

An AE or SAR is considered "unexpected" if it is not listed in the Investigator Brochure (IB) or the FDA package insert or is not listed at the specificity or severity that has been observed. For approved drugs (i.e., regorafenib) used in this study please refer to the currently approved product label for a summary of the AEs associated with that product.

The IB provides Investigators with information (clinical and nonclinical) about the investigational product. The IB includes those AEs for which a causal relationship is suspected or confirmed (SARs or ADRs) as well as AEs that may be predicted to occur based on the

pharmacological properties of the investigational product. The IB is used as the basis for the Sponsor's determination of "unexpected" for reporting purposes.

"Unexpected" SARs are AEs not currently listed in the IB. An AE or SAE may also be considered "unexpected" if it is not listed in the IB at the specificity or severity that has been observed.

10.5 Withdrawal Due to Adverse Events

Withdrawal due to an AE should be distinguished from withdrawal due to insufficient response or any other reason, according to the definition of AE noted earlier and recorded on the appropriate AE CRF page or electronic-based CRF (eCRF) screen.

When a subject withdraws due to an SAE, the SAE must be reported in accordance with the reporting requirements defined below.

In case the AE has not resolved up to 30 days after last dose of study drug, the final outcome of these ongoing and new unrelated AEs will be captured as "Not Recovered/Not Resolved" or "Recovering/Resolving" whichever is applicable.

10.6 Reporting Responsibility

An IND safety report will be submitted for any SAR that is both Serious and Unexpected. Before submitting this report, need to ensure that the event meets the following criteria:

- SAR
- Serious
- Unexpected

If the AE does not meet all three of the definitions, it should not be submitted as an expedited IND safety report.

10.6.1 Investigator Reporting

Except for study endpoints, the Investigator must immediately report to the Sponsor all SAEs, regardless of whether the investigator believes that they are drug related, including those events listed in the protocol as anticipated to occur in the study population independent of drug exposure or in the Investigator Brochure as predicted to occur with the drug. Study endpoints that are also SAEs are reported to the Sponsor.

10.6.2 Instructions for Notification of SAEs:

The SAE reporting period will extend from the signature of the informed consent through the Study Termination Visit, until 30 days after the last dose of study drug, or the resolution or stabilization of the AE to Grade ≤1 or baseline, whichever is longer.

If an SAE occurs, the Sponsor and its designee are to be notified within 24 hours of awareness of the event by the Investigator. In particular, if the SAE is fatal or life threatening, notification to the Sponsor or designee must be made immediately, irrespective of the extent of the available

SAE information. This timeframe also applies to additional new information (follow up) on previously forwarded SAE reports as well as to the initial and follow up reporting of Exposure in Utero (Pregnancy) cases.

In the rare event that the Investigator does not become aware of the occurrence of an SAE immediately (e.g., if an outpatient trial subject initially seeks treatment elsewhere), the Investigator is to report the event within 24 hours of first awareness of the SAE and to document the time of his/her first awareness of the SAE.

For all SAEs, the Investigator is obligated to pursue and provide information to the Sponsor or designee in accordance with the timeframes for reporting specified above. In addition, an Investigator may be requested by the Sponsor or designee to obtain specific additional follow up information in an expedited fashion. This information may be more detailed than information captured on the AE CRF. In general, this will include a description of the AE in sufficient detail to allow for a complete medical assessment of the case and independent determination of possible causality. Information on other possible causes of the event, such as concomitant mediations and illnesses must be provided. In the case of a subject death, a summary of available autopsy findings must be submitted as soon as possible to Sponsor or designee.

For all AEs, the details must be recorded in the source documents and the Investigator must pursue and obtain information adequate both to determine the outcome of the AE and to assess whether it meets the criteria for classification as an SAE requiring prompt notification to Sponsor or designee. For all AEs, sufficient information should be obtained by the Investigator to determine causality of the AE. The Investigator is required to assess causality. Follow up by the Investigator is required to determine the outcome of the event until the event resolution, permanent sequelae, commencement of other anticancer therapy or loss to follow up.

10.6.3 Reporting Serious Events to the IRB and FDA

SAEs and SSARs require immediate notification to the site's IRB as per their reporting guidelines. All correspondence relating to IRB correspondence should be sent to Sponsor or designee for inclusion in the trial master file (TMF).

Any unexpected fatal or life-threatening SAR shall be reported to the FDA as soon as possible but in no case later than seven (7) calendar days after the Sponsor's initial receipt of the information. Notification may be made by telephone with subsequent facsimile reports or electronic records.

The minimum information shall include the subject's study number, age, gender, name of the study drug, and the term for the SAE or SSAR.

The Sponsor must also notify the FDA and all participating Investigators in a written IND safety report of any SAE that is both serious, related, and unexpected, as soon as possible, but in no case later than 15 calendar days after the Sponsor's initial receipt of the information.

Sponsors are specifically required to notify all participating investigators (and FDA) in a written IND safety report of "any adverse experience associated with the use of the drug that is both

serious and unexpected" and "any finding from tests in laboratory animals that suggests a significant risk for human subjects" (§ 312.32(c)(1)(i)(A),(B)).

Any relevant additional information that the Sponsor obtains that pertains to a previously submitted IND safety report must be submitted to FDA as a *Follow-up IND Safety Report* without delay, as soon as the information is available.

10.6.4 Additional Sponsor Responsibility

More generally, Sponsors are required to "keep each participating Investigator informed of new observations discovered by or reported to the Sponsor on the drug, particularly with respect to adverse effects and safe use" (§ 312.55(b)).

10.6.5 Notification of Post-study Serious Adverse Events (SAEs)

If a subject terminates study participation early, any SAEs that occur for a period of up to 30 days after the last dose of study drug should be reported to the Sponsor. SAEs that occur after completion of the study are not required to be reported to the Sponsor unless the Investigator believes the event is related to study drug.

10.7 Following Adverse Events and Serious Adverse Events (SAEs)

Subjects with unresolved previously reported AEs or SAEs, should be followed by the Investigator until 30 days after the last dose of study drug, event resolution or improvement to Grade ≤1 or baseline, permanent sequelae, subject death, commencement of other anticancer therapy, up to end of study, or loss to follow-up, whichever is earlier.

In case the AE has not resolved at the end of the Post Progression Follow-up period, the final outcome of these ongoing and new unrelated AEs will be captured as "Not Recovered/Not Resolved" or "Recovering/Resolving" whichever is applicable.

11.0 STATISTICAL PLAN

11.1 Determination of Sample Size

We hypothesize that the administration of RRx-001 as a single agent for relapsed metastatic colorectal cancer that have failed 2 prior lines of systemic therapy, including adjuvant therapy, will increase median OS by 3 months (i.e., from 6 to 9 months) when compared to the control therapy of regorafenib. Such an increase in median OS corresponds to a 33% reduction in the risk of death (i.e., target hazard ratio of 0.667). As this is a proof of concept study, the comparison between the two arms will be made at a 10% (one-sided) significance level. Based on a log-rank test and 2:1 randomization ratio between treatment arms, a total of 123 death events from the 2 treatment arms are required to detect such an improvement in the RRx-001 treatment arm compared to control with 80% power. As part of these calculations, it has been assumed that there will be uniform enrollment over a 12-month period, there will be a minimum 6 months follow-up per subject and survival data will be obtained for all but an insignificant number of subjects. It is expected that 190 subjects will be randomized with 2:1 randomization to achieve 123 events. Study follow-up will continue until it is projected that there will be approximately 123 events.

The primary inferential comparison between treatment groups will use the log-rank test using the full analysis population defined as randomized subjects receiving at least one dose of study treatment and not violating the following inclusion/exclusion criteria:

Exclusion Criteria:

4. Symptoms or signs of active brain metastases;
6. Cholangitis that required treatment or intervention within 4 weeks of study enrollment

11.2 Safety Analyses

Safety data analysis will be conducted on all subjects receiving at least 1 dose of RRx-001 or regorafenib. Analyses will consist of data summaries for clinical and laboratory parameters, and for AEs. The safety data will be summarized by treatment arm. The number and percentage of subjects experiencing 1 or more AEs will be summarized by the relationship to study drug and severity. Adverse events will be coded using Medical Dictionary for Regulatory Activities (MedDRA) terminology. Laboratory parameters will be summarized using descriptive statistics, by post-dosing shifts relative to baseline, and data listings of clinically significant abnormalities. Vital signs will be summarized by changes from baseline values using descriptive statistics.

All available safety data will be provided to an independent Data Monitoring Committee (DMC) at the interim and final efficacy analyses (see below). Periodic safety reviews will be conducted by the DMC approximately every 3-6 months.

11.3 Efficacy Analyses

The primary efficacy endpoint is OS, defined as the number of months from randomization to death due to any cause. OS will be summarized descriptively using the Kaplan-Meier method. Median OS will be estimated for each treatment group from the 50th percentile of the corresponding Kaplan-Meier estimates. The primary inferential comparison between treatment groups will use an unstratified, log-rank test. The hazard ratio will be estimated using a Cox proportional hazards model without covariates. Similar analyses will be performed for progression free survival and Progression Free Survival 2. Efficacy based upon response outcomes will be assessed using RECIST (version 1.1). Such outcomes will be determined by the local Investigator and will serve as the data source for the analyses. A summary of anticancer therapies received after ending protocol therapy will be provided. Objective response rate and clinical benefit rate as well as other rate-based estimates will be compared using the chi-square test. For all estimates, 95% confidence intervals will be calculated. The duration of objective response and clinical benefit response will be described descriptively using the Kaplan-Meier method for subjects with such responses.

Exploratory subgroup analyses will be conducted using the following subgroups:

1. Subjects with KRAS, BRAF or P53 mutations
2. Subjects with prior bevacizumab, cetuximab or panitumumab therapy
3. Subjects with prior oxaliplatin therapy
4. Subjects with prior irinotecan therapy
5. Subjects with prior 5-FU based therapy

A single interim analysis for futility is planned at the time that 50% of the total death events are expected. The objective of the futility analysis is to stop randomization to the study if there is sufficient evidence that such therapy is not improving outcomes relative to the control therapy. As the intent of the interim analysis is for futility only, no adjustment to the type I error at the final analysis is proposed. An independent statistical service provider will perform the interim efficacy analysis in conjunction with the DMC. As noted previously, the DMC also will review safety data every 3-6 months.

Exploratory Analyses:

Screening Data: All baseline subject characteristics of demographic data (age, height, weight, race, ethnicity, etc.), medical history (abnormalities only), cancer history, cancer treatment history, PE findings (abnormalities only), and concomitant medications at study entry will be listed by subject. Demographics will be tabulated and summarized.

Due to the changes in Amendment 01, particularly with respect to inclusion/exclusion criteria and study design, subjects that were enrolled prior to Amendment 01 will be analyzed for safety only.

12.0 INVESTIGATOR REQUIREMENTS

12.1 Protocol Adherence

Investigators must adhere to the protocol as detailed in this document and agree that the Sponsor must approve any change to the protocol prior to seeking approval from the IRB/IEC. Investigators will be responsible for enrolling only those subjects who have met all the protocol inclusion and none of the exclusion criteria, or must have obtained prior approval from the Medical Monitor for deviations from the study inclusion/exclusion criteria.

12.2 Disclosure

All information provided regarding the study, as well as all information collected/documented during the course of the study will be regarded as confidential. The Investigator agrees not to disclose such information in any way without prior written permission from the Sponsor.

Any publication of the results, either in part or in total (articles in journals or newspapers, oral presentations, abstracts, etc.) by the Investigator(s) or their representative(s), shall require prior notification and review, within a reasonable time frame, by the Sponsor, and cannot be made in violation of the Sponsor's confidentiality restrictions or to the detriment of the Sponsor's intellectual property rights.

12.3 Case Report Forms

Electronic or paper-based case report forms (eCRF or CRF, respectively) may be used for this study. The Sponsor will provide paper-based CRFs or appropriate data entry screens for electronic data capture to allow for the recording of all information and study data as specified by this protocol. All CRFs must be completed by the examining personnel or data coordinator. Each Investigator is responsible for ensuring that accurate eCRFs or paper-based CRFs are submitted to the Sponsor in a timely manner.

12.4 Source Document Maintenance

Source documents are defined as documentation related to original observations and activities of a clinical investigation. Source documents may include, but are not limited to, study progress notes, e-mail correspondences, computer printouts, laboratory data, and recorded data from automated instruments. All source documents produced in this study will be maintained by the Investigator and made available for inspection by the Sponsor, regulatory authorities, or both. The original signed informed consent document, signed by the subject (or other legally acceptable representative), for each participating subject shall be filed with records kept by the Investigator, and a copy of each given to the subject.

12.5 Study Monitoring Requirements

The Sponsor will designate a Sponsor's Study Monitor (i.e., clinical research associate (CRA)) who will be responsible for monitoring this clinical trial. The Sponsor's Study Monitor will monitor the study conduct; insure the proper completion and retention of source documentation completion and retention, accurate study drug accountability records and prompt data entry to CRF. To this end, the Sponsor's Study Monitor will visit the study site at suitable intervals and be in frequent contact through verbal and written communication. It is essential that the Sponsor's Study Monitor have access to all documents (related to the study and the individual participants) at any time these are requested. In turn, the Sponsor's Study Monitor will adhere to all requirements for subject confidentiality as outlined in the Informed consent form (ICF). The Investigator(s) or their representative(s) will be expected to cooperate with the Sponsor's Study Monitor, to be available during a portion of the monitoring visit to answer questions, and to provide any missing information. Investigator(s) or their representative(s) are required to respond in writing to any deficiencies or protocol deviations noted by the monitor in the site visit report.

12.6 Quality Control and Quality Assurance

Accurate, consistent and reliable data will be ensured through the use of standard practices and procedures. Site initiation visits will be conducted at the clinical site. Experienced CRAs will monitor the study and verify that the data is accurate. Sponsor may contract with a qualified contract research organization(s) (CRO) to perform the data management of this trial. The Medical Monitor, CRAs and site personnel will be trained by the CRO and/or Sponsor.

Drug Safety Reporting will be the responsibility of Sponsor or its representative. System backups for data stored at the CRO/Sponsor, and records retention for the study data will be consistent with the standard procedures for the CRO/Sponsor.

12.7 Study Completion

The Sponsor requires the following data and materials before a study can be considered complete or terminated:

1. Laboratory findings, clinical data, and all special test results from baseline through the Study Termination.
2. Data collection using paper-based CRFs (including correction forms) or eCRFs properly completed by appropriate study personnel and signed and dated by the Investigator.
3. Complete drug accountability records (drug inventory log and an inventory of returned or

destroyed clinical material).
4. Copies of protocol amendments and IRB/ independent ethics committee (IEC) approval and notification, if appropriate.
5. A summary of the study prepared by the Investigator (an IRB/IEC summary letter is acceptable.).

13.0 PROTECTION OF HUMAN SUBJECTS AND GENERAL STUDY ADMINISTRATION

This study will be conducted in compliance with the ICH of Technical Requirements for Registration of Pharmaceuticals for Human Use E6 Good Clinical Practice (GCP); Consolidated Guidelines, the ethical principles of the Declaration of Helsinki; FDA GCP guidelines: and any additional national or IRB/IEC-required procedures.

13.1 Informed Consent

This study will be conducted in compliance with ICH E6 GCP: Consolidated Guidelines pertaining to informed consent. Each subject or other legally acceptable representative will give written consent for the subject to participate in the study prior to initiation of any study-related procedures, after having been informed about the nature and purpose of the study, participation and termination conditions, risks, and benefits. The informed consent document must be signed and dated by the subject (or legal representative) and the subject's consent process must be documented prior to the subject's study participation. A copy of the informed consent document must be provided to the subject. If applicable, it will be provided in certified translation for non-English-speaking subjects. Signed informed consent forms must remain in the subject's study file and be available for verification by the Sponsor, regulatory authorities, or both, at any time.

13.2 Institutional Review Board (IRB) Approval

In accordance with 21 CFR 56, the protocol, advertisement, and Informed Consent Form (ICF) and assents will be reviewed and approved by the IRB. The Sponsor will supply relevant material for the Investigator to submit to the IRB for the protocol's review and approval. Verification of the IRB unconditional approval of the protocol, the written ICF any advertisement materials will be transmitted to the Investigator. Approval by the IRB of the protocol, informed consent document any advertisement materials must be obtained before the study may be initiated.

The IRB will be informed by the Investigator(s) or their representative(s) of subsequent protocol amendments and of serious and unexpected AEs and ARs. Approval for protocol amendments will be transmitted in writing to the Investigator. If requested, the Investigator(s) or their representative(s) will permit audits by the IRB and Regulatory inspections by providing direct access to source data/documents.

The Investigator(s) or their representative(s) will provide the IRB with progress reports at appropriate intervals (not to exceed one year) and a Study Progress Report following the completion, termination, or discontinuation of the Investigator(s)' participation in the study.

14.0 DATA HANDLING AND RECORD KEEPING

The results from Screening and data collected during the study will be recorded in the subject's CRF (either paper or electronic CRF). To maintain confidentiality, only numbers and/or initials will identify the subjects.

Training sessions, regular monitoring of the investigative site by Sponsor-designated personnel, instruction manuals, data verification, crosschecking, and audits will be performed to ensure quality of all study data.

The Sponsor will review and validate study data as defined in the data-monitoring plan.

It will be the responsibility of the Investigator to ensure that the essential documents are available in the Investigator's files or at the institutional site. Any or all of these documents may be subject to, and should be available for, monitoring by the Sponsor or inspection by the regulatory authorities as defined in the monitoring plan.

If applicable, the completed CRFs will be transferred to the Sponsor or designee and the Investigator will retain copies of each CRF. All source documents, records, and reports will be retained by the study site in accordance with 21 CFR 312.62(c). All primary data, or copies thereof (e.g., laboratory records, CRFs, data sheets, correspondence, radiology reports, photographs, and computer records), which are a result of the original observations and activities of the study and are necessary for the reconstruction and evaluation of any study report, will be retained in the study site archives.

14.1 Direct Access to Source Data/Documents

The Investigator agrees by his or her participation that the results of this study may be used for submission to national or international registration authorities. If required, these authorities will be provided with the names of the Investigator, and his or her address, qualifications, and extent of involvement. It is understood that the Investigator is required to provide the Sponsor with all study data, complete reports, and access to all study records.

Data generated by this study must be available for inspection by any regulatory authorities, by the Sponsor, and by the IRB/IEC, as appropriate. At the request of the subject medical information may be given to the subject's personal physician or other appropriate medical personnel responsible for his or her welfare. Medical information obtained from subjects during the course of this study is confidential and disclosure to third parties other than those noted above is prohibited.

14.2 Archiving of Data

The Investigator shall arrange for the retention of the subject identification codes for at least 15 years after completion or discontinuation of the study. Subject files and other source data shall be kept for the maximum period of time permitted by the hospital or institution. The Investigator shall retain the trial related essential documents until the Sponsor informs the Investigator these documents are no longer needed.

All data and documents shall be made available at the request of relevant authorities. The Investigator shall inform the Sponsor before any records are destroyed.

15.0 ETHICAL CONSIDERATIONS

This study will be conducted according to US and international standards of Good Clinical Practice (FDA regulations 21 CFR 312 for IND studies and FDA guidance E6) for all studies.

All subjects for this study will be provided a consent form describing this study and providing sufficient information for subjects to make an informed decision about their participation in this study. This consent form will be submitted with the protocol for review and approval by the IRB. The formal consent of a subject, using the IRB-approved consent form, will be obtained before that subject is submitted to any study procedure. The subject or legally acceptable surrogate must sign this consent form, and the investigator-designated research professional obtaining the consent.

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Appendix 1: Eastern Cooperative Group (ECOG) Performance Status

ECOG PERFORMANCE STATUS*

Grade	ECOG
0	Fully active, able to carry on all pre-disease performance without restriction
1	Restricted in physically strenuous activity but ambulatory and able to carry out work of a light or sedentary nature, e.g., light house work, office work
2	Ambulatory and capable of all self-care but unable to carry out any work activities. Up and about more than 50% of waking hours
3	Capable of only limited self-care, confined to bed or chair more than 50% of waking hours
4	Completely disabled. Cannot carry on any self-care. Totally confined to bed or chair
5	Dead

* As published in Am. J. Clin. Oncol.:*Oken, M.M., Creech, R.H., Tormey, D.C., Horton, J., Davis, T.E., McFadden, E.T., Carbone, P.P.: Toxicity And Response Criteria Of The Eastern Cooperative Oncology Group. Am J Clin Oncol 5:649-655, 1982.*

Appendix 2: Bioassay Sample Collection

-Removed-

No Exploratory Biomarkers in this Amendment

Appendix 3: Biopsy Tissue and/or Slides Collection and Shipping General Guidelines

Cancers are often heterogeneous in molecular pathogenesis, clinical course, and treatment responsiveness. The ability to develop biomarkers which correlate with prognostic and predictive activity of RRx-001 and then select subjects in phase 1b or II with susceptible tumors based on the analysis of a unique biomarker 'signature' would be invaluable. EpicentRx has preliminary evidence that immunohistochemical markers predict benefit from RRx-001, and it may be possible to assay the marker in archived specimens.

Therefore EpicentRx proposes to collect convenience samples of fixed archival tissue specimens, if they happen to be available, and assay them with immunohistochemistry for prognostic and predictive markers, with no prospectively determined subject eligibility, power calculations, or analytical plans. An expert tumor biologist will process the samples. In some cases where applicable these archival specimens will be compared with 'freshly cut' tumor samples from the same subject.

The data from these samples may be published. It is not known whether archived specimens collected for unknown reasons, processed and stored in a variety of ways, that happen to be available for assay, will yield meaningful biological information.

Biopsy tissue and/or slides may be sent to a pathologist for an independent reading.

If requested, send tissue or slides to: Uniformed Services University of the Health Sciences

- The specimen should be representative.
- Tissue specimens optimally are received fresh/unfixed.
- Always use a sharp razor blade or scalpel to avoid crushing tissue.
- Excisional or incisional biopsies are generally preferred.
- Needle aspiration is discouraged.
- Avoid necrotic areas of tumor.
- Specimens should contain the following information:
  - Clinical Information:
    - RRx-001 study
    - Institution name
    - Subject identifier
    - Identification as either pre- or post-treatment with RRx-001 specimen
    - Responsible physician(s)
    - Date of procedure
  - Procedure (e.g., core biopsy, wedge biopsy)
  - Anatomic site(s) of specimen

  ***Note**: De-identify ALL study participants' personal identifying information (participant name, medical record number, social security number, etc.) on all of the material before sending to the central pathologist.*
- Macroscopic Examination:
  - Specimen:
    - Unfixed/fixed (specify fixative)

  - Number of pieces
  - Dimensions
  - Descriptive features (e.g., hemorrhage, necrosis)
  - Primary tumor or metastasis
  - Orientation, if designated by surgeon
- Tissue submitted for microscopic examination, as appropriate:
  - Entire specimen
  - Selected sample
- Additional pathologic findings, if present (e.g., necrosis).

- Labels should be attached to each tissue block.
- Ship samples on ice packs to prevent sample degradation in transit:
  - Cold Ice Pack Shipping: Pack secondary containers in a styrofoam container with cold pack and sufficient packing material to maintain temperature:
    - Seal the Styrofoam container with tape.
    - Place the sealed Styrofoam container in a durable shipping cardboard box.
  - Frozen Dry Ice Pack Shipping: Pack secondary containers in a styrofoam container with dry ice and sufficient packing material to maintain temperature:
    - Seal the Styrofoam container with tape.
    - Place the sealed Styrofoam container in a durable shipping cardboard box.
    - Label the shipping box with DRY ICE labels; note the weight of the dry ice on the label.
- Ship overnight express to central storage at Uniformed Services University of the Health Sciences, Bethesda, MD:

Attn: Prof Regina Day
Uniformed Services University of the Health Sciences
Department of Pharmacology
Room C2051
4301 Jones Bridge Road
Bethesda, Maryland 20814-4799

Phone: (301) 295-3236
FAX: (301) 295-3220

Email: regina.day@usuhs.edu

Please send samples so that they arrive on weekdays. No weekend shipping. Please email Prof Regina Day and the Sponsor to notify of intended shipment prior to shipment.

Full details will be provided in a separate Lab Manual

- The central pathology lab will confirm receipt of the specimens.
  Note*: If there are problems with the specimen and shipment contents, the central pathology facility will contact the clinical study coordinator at the respective clinical site to inquire and resolve the issue.*
- The central pathologist will cut the necessary slides and send the tissue block back to the originator site.

Expenses related to pathology specimens and shipment: All costs incurred at the local site as a result of obtaining pathology specimens and the Sponsor will pay for shipment of the specimens.

Appendix 4: Quality of Life Questionnaire – EORTC QLQ-C30

The EORTC QLQ-C30 (version 3) questionnaire will be used to assess changes in subject's Quality of Life. This will be applied at each study visit before any other procedure. The questionnaire will take 11-12 min to complete (see next page).

EORTC QLQ-C30 (version 3)

We are interested in some things about you and your health. Please answer all of the questions yourself by circling the number that best applies to you. There are no "right" or "wrong" answers. The information that you provide will remain strictly confidential.

Please fill in your initials: __ __ __

Your birthdate (Month, Day, Year): __ __ / __ __ / __ __ __ __

Today's date (Month, Day, Year): __ __ / __ __ / __ __ __ __

		NOT AT ALL	A LITTLE	QUITE A BIT	VERY MUCH
1.	Do you have any trouble doing strenuous activities, like carrying a heavy shopping bag or a suitcase?	1	2	3	4
2.	Do you have any trouble taking a long walk?	1	2	3	4
3.	Do you have any trouble taking a short walk outside of the house?	1	2	3	4
4.	Do you need to stay in bed or a chair during the day?	1	2	3	4
5.	Do you need help with eating, dressing, washing yourself or using the toilet?	1	2	3	4

DURING THE PAST WEEK:

		NOT AT ALL	A LITTLE	QUITE A BIT	VERY MUCH
6.	Were you limited in doing either your work or other daily activities?	1	2	3	4
7.	Were you limited in pursuing your hobbies or other leisure time activities?	1	2	3	4
8.	Were you short of breath?	1	2	3	4
9.	Have you had pain?	1	2	3	4
10.	Did you need to rest?	1	2	3	4
11.	Have you had trouble sleeping?	1	2	3	4
12.	Have you felt weak?	1	2	3	4
13.	Have you lacked appetite?	1	2	3	4
14.	Have you felt nauseated?	1	2	3	4
15.	Have you vomited?	1	2	3	4
16.	Have you been constipated?	1	2	3	4

Please go on to the next page

DURING THE PAST WEEK:

	NOT AT ALL	A LITTLE	QUITE A BIT	VERY MUCH
17. Have you had diarrhea?	1	2	3	4
18. Were you tired?	1	2	3	4
19. Did pain interfere with your daily activities?	1	2	3	4
20. Have you had difficulty in concentrating on things, like reading a newspaper or watching television?	1	2	3	4
21. Did you feel tense?	1	2	3	4
22. Did you worry?	1	2	3	4
23. Did you feel irritable?	1	2	3	4
24. Did you feel depressed?	1	2	3	4
25. Have you had difficulty remembering things?	1	2	3	4
26. Has your physical condition or medical treatment interfered with your family life?	1	2	3	4
27. Has your physical condition or medical treatment interfered with your social activities?	1	2	3	4
28. Has your physical condition or medical treatment caused you financial difficulties?	1	2	3	4

FOR THE FOLLOWING QUESTIONS PLEASE CIRCLE THE NUMBER BETWEEN 1 AND 7 THAT BEST APPLIES TO YOU

29. How would you rate your overall health during the past week?

1	2	3	4	5	6	7
Very poor						Excellent

30. How would you rate your overall quality of life during the past week?

1	2	3	4	5	6	7
Very poor						Excellent

Appendix 5: RECIST v1.1 and Immune Related Response Criteria

Table 1 – Time point response: patients with target (+/– non-target) disease.

Target lesions	Non-target lesions	New lesions	Overall response
CR	CR	No	CR
CR	Non-CR/non-PD	No	PR
CR	Not evaluated	No	PR
PR	Non-PD or not all evaluated	No	PR
SD	Non-PD or not all evaluated	No	SD
Not all evaluated	Non-PD	No	NE
PD	Any	Yes or No	PD
Any	PD	Yes or No	PD
Any	Any	Yes	PD

CR = complete response, PR = partial response, SD = stable disease, PD = progressive disease, and NE = inevaluable.

Table 2 – Time point response: patients with non-target disease only.

Non-target lesions	New lesions	Overall response
CR	No	CR
Non-CR/non-PD	No	Non-CR/non-PD[a]
Not all evaluated	No	NE
Unequivocal PD	Yes or No	PD
Any	Yes	PD

CR = complete response, PD = progressive disease, and NE = inevaluable.

a 'Non-CR/non-PD' is preferred over 'stable disease' for non-target disease since SD is increasingly used as endpoint for assessment of efficacy in some trials so to assign this category when no lesions can be measured is not advised.

Reproduced from: Eisenhauer EA, Therasse P, Bogaerts J et al. New response evaluation criteria in solid tumours: Revised RECIST guideline (version 1.1). Eur J Cancer 2009; 45:228-247.

Immune Related Response Criteria

	Bidimensional irRC assessment [Wolchok et al 2009]
Measurable lesions	≥5×5 mm by bidimensional measurements
Measurement of each lesion	The longest diameter × the longest perpendicular diameter (cm^2)
The sum of the measurements	The sum of the bidimensional measurements of all target lesions and new lesions if any
Response assessment	PD: ≥25% increase from the nadir PR: ≥50% decrease from baseline CR: Disappearance of all lesions
New lesions	The presence of new lesion(s) does not define progression. The measurements of the new lesion(s) are included in the sum of the measurements.
Confirmation	Confirmation by two consecutive observations not less than 4 weeks apart was required for CR, PR and PD

Appendix 6: CEUS Imaging Protocol

Purpose

- To assess tumor response before and after treatment with RRx-001 with CEUS via measurement of tumor blood volume and perfusion
- To assess tumor response with irinotecan post-RRx-001 at least a week post start of irinotecan therapy.
- **CEUS Imaging will be carried out at Stanford University only**

Methodology

- CEUS will be performed in patients with liver metastases prior to infusion of RRx-001 (baseline) and at the end of infusion in accordance with the Schedule of Assessments.
- **The decision as to who (which patients), on what therapies and when to image at any given time is entirely at the discretion of the Stanford University PI, Dr. George Fisher, and the Stanford University radiologist, Dr. Juergen Willmann**

Contrast Agent

- Definity (Lantheus Medical Imaging, Inc., North Billerica, MA) given as a bolus or infusion *via* peripheral IV catheter in the forearm of the patient opposite the side of the ultrasound examination
- Recommended dosage as a bolus: (1) 10 microliters (μL)/kg of the activated product by intravenous bolus injection within 30-60 seconds, followed by a 10 mL saline flush
- Recommended dosage as an IV infusion: 1.3 mL of the activated product added to 30 mL of preservative-free saline where the rate of infusion should be initiated at 2.0-4.0 mL/minute but titrated as necessary to achieve optimal image enhancement

CEUS Procedure

- Image tumors larger than 2 cm in the longest diameter plane
- Assess tumor morphology with B-mode
- Identify target tumor and select best acoustic window for its assessment
- Measure maximum width, length, and depth of the tumor with electronic calipers

- Calculate the tumor volume with the formula for a prolate ellipsoid (volume cm3 = length cm * width cm * height cm * π6)
- After determination of the largest tumor cross-section in sagittal or parasagittal plane, fix the transducer in place and set the contrast specific imaging parameters
- Keep all parameters including gain settings, focus, and depth as well as the position of the probe with respect to the lesion scan plane constant during the study
- Quantify perfusion parameters with destruction-replenishment analysis produce microbubble-replenishment time-intensity curves
    - Image contrast microbubbles without disruption at a low acoustic amplitude pressure or mechanical index (MI)
    - Increase the acoustic pressure amplitude for a few frames causing bubble disruption; immediately after that, return imaging is returned to the non-disrupting level to observe the replenishment of the microbubbles into the ROI. This effectively creates a negative bolus within the imaging plane, which decays as inflow of fresh bubbles replenishes the vasculature. The initial rate of replenishment is related to flow; the steady state to vascular volume.

Imaging Schema

Screening/Baseline	C1W1	C1W2	C1W3	C1W4	C2W1	C2W2	C2W3	C2W4
	X	X		X				X

Appendix 7: Additional Information About Irinotecan Toxicity

The most common toxicities associated with irinotecan, which is generally well tolerated, are neutropenia, anemia, delayed diarrhea, and fatigue (Sargent, 2001). In subjects with an elevated bilirubin >2 mg/dL, 5-FU plus bevacizumab may be preferable to irinotecan, as dose reductions are not necessary to avoid the potential for severe toxicity. In case of ileus, fever or febrile neutropenia, prompt supportive care is necessary including the use of antibiotics. The Warnings Section excerpted below from the package insert describes the risks associated with irinotecan administration (Camptosar, US FDA-approved product information).

Figure 4: Excerpt from the Package Insert for Irinotecan Hydrochloride Describing Observed Toxicity Associated with its Use

WARNINGS

General

Outside of a well-designed clinical study, irinotecan hydrochloride injection should not be used in combination with the "Mayo Clinic" regimen of 5-FU/LV (administration for 4-5 consecutive days every 4 weeks) because of reports of increased toxicity, including toxic deaths. Irinotecan hydrochloride injection should be used as recommended (see **DOSAGE AND ADMINISTRATION**).

Diarrhea

Irinotecan hydrochloride injection can induce both early and late forms of diarrhea that appear to be mediated by different mechanisms. Early diarrhea (occurring during or shortly after infusion of irinotecan hydrochloride injection) is cholinergic in nature. It is usually transient and only infrequently is severe. It may be accompanied by symptoms of rhinitis, increased salivation, miosis, lacrimation, diaphoresis, flushing, and intestinal hyperperistalsis that can cause abdominal cramping. Early diarrhea and other cholinergic symptoms may be prevented or ameliorated by administration of atropine (see **PRECAUTIONS, General**, for dosing recommendations for atropine).

Late diarrhea (generally occurring more than 24 hours after administration of irinotecan hydrochloride injection) can be life threatening since it may be prolonged and may lead to dehydration, electrolyte imbalance, or sepsis. Late diarrhea should be treated promptly with loperamide (see **PRECAUTIONS, Information for Patients**, for dosing recommendations for loperamide). Patients with diarrhea should be carefully monitored, should be given fluid and electrolyte replacement if they become dehydrated, and should be given antibiotic support if they develop ileus, fever, or severe neutropenia. After the first treatment, subsequent weekly chemotherapy treatments should be delayed in patients until return of pretreatment bowel function for at least 24 hours without need for anti-diarrhea medication. If grade 2, 3, or 4 late diarrhea occurs subsequent doses of irinotecan hydrochloride injection should be decreased within the current cycle (see **DOSAGE AND ADMINISTRATION**).

Neutropenia

Deaths due to sepsis following severe neutropenia have been reported in patients treated with irinotecan hydrochloride injection. Neutropenic complications should be managed promptly with antibiotic support (see **PRECAUTIONS**). Therapy with irinotecan hydrochloride injection should be temporarily omitted during a cycle of therapy if neutropenic fever occurs or if the absolute neutrophil count drops < 1000/mm^3. After the patient recovers to an absolute neutrophil count ≥ 1000/mm^3, subsequent doses of irinotecan hydrochloride injection should be reduced depending upon the level of neutropenia observed (see **DOSAGE AND ADMINISTRATION**).

Routine administration of a colony-stimulating factor (CSF) is not necessary, but physicians may wish to consider CSF use in individual patients experiencing significant neutropenia.

Patients with Reduced UGT1A1 Activity

Individuals who are homozygous for the UGT1A1*28 allele (UGT1A1 7/7 genotype) are at increased risk for neutropenia following initiation of irinotecan hydrochloride injection treatment. In a study of 66 patients who received single-agent irinotecan hydrochloride injection (350 mg/m^2 once-every-3-weeks), the incidence of grade 4 neutropenia in patients homozygous for the UGT1A1*28 allele was 50%, and in patients heterozygous for this allele (UGT1A1 6/7 genotype) the incidence was 12.5%. No grade 4 neutropenia was observed in patients homozygous for the wild-type allele (UGT1A1 6/6 genotype).

When administered in combination with other agents, or as a single agent, a reduction in the starting dose by at least one level of irinotecan hydrochloride injection should be considered for patients known to be homozygous for the UGT1A1*28 allele. However, the precise dose reduction in this patient population is not known and subsequent dose modifications should be considered based on individual patient tolerance to treatment (see **DOSAGE AND ADMINISTRATION** and **PRECAUTIONS, Laboratory Tests**).

Hypersensitivity

Hypersensitivity reactions including severe anaphylactic or anaphylactoid reactions have been observed.

Colitis/Ileus

Cases of colitis complicated by ulceration, bleeding, ileus, and infection have been observed. Patients experiencing ileus should receive prompt antibiotic support (see **PRECAUTIONS**).

Renal Impairment/Renal Failure

Rare cases of renal impairment and acute renal failure have been identified, usually in patients who became volume depleted from severe vomiting and/or diarrhea.

Thromboembolism

Thromboembolic events have been observed in patients receiving irinotecan containing regimens; the specific cause of these events has not been determined.

Pulmonary Toxicity

Interstitial Pulmonary Disease (IPD)-like events, including fatalities, have been reported in patients receiving irinotecan for treatment of colorectal cancer and other advanced solid tumors. In the event of an acute onset of new or progressive, unexplained pulmonary symptoms such as dyspnea, cough, and fever, irinotecan and other co-prescribed chemotherapeutic agents should be interrupted pending diagnostic evaluation. If IPD is diagnosed, irinotecan and other chemotherapy should be discontinued and appropriate treatment instituted as needed (see **ADVERSE REACTIONS, Overview of Adverse Events: Respiratory**).

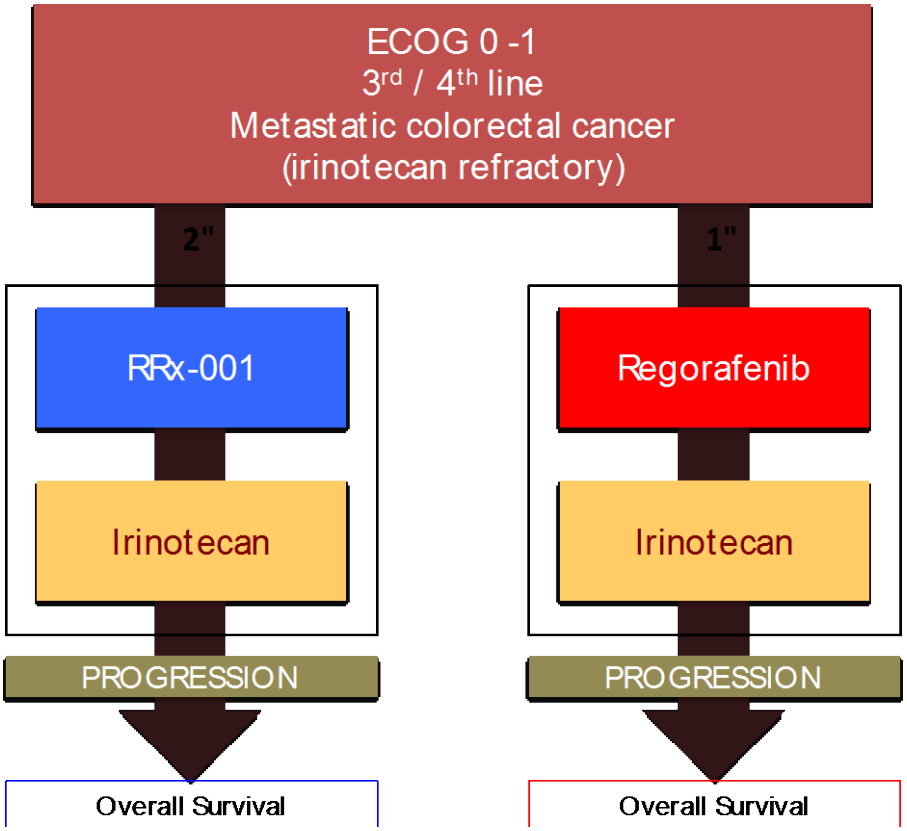
Pregnancy

Irinotecan hydrochloride injection may cause fetal harm when administered to a pregnant woman. Radioactivity related to ^{14}C-irinotecan crosses the placenta of rats following intravenous administration of 10 mg/kg (which in separate studies produced an irinotecan C_{max} and AUC about 3 and 0.5 times, respectively, the corresponding values in patients administered 125 mg/m^2). Administration of 6 mg/kg/day intravenous irinotecan to rats (which in separate studies produced an irinotecan C_{max} and AUC about 2 and 0.2 times, respectively, the corresponding values in patients administered 125 mg/m^2) and rabbits (about one-half the recommended human weekly starting dose on a mg/m^2 basis) during the period of organogenesis, is embryotoxic as characterized by increased post-implantation loss and decreased numbers of live fetuses. Irinotecan was teratogenic in rats at doses greater than 1.2 mg/kg/day (which in separate studies produced an irinotecan C_{max} and AUC about 2/3 and 1/40th, respectively, of the corresponding values in patients administered 125 mg/m^2) and in rabbits at 6.0 mg/kg/day (about one-half the recommended human weekly starting dose on a mg/m^2 basis). Teratogenic effects included a variety of external, visceral, and skeletal abnormalities. Irinotecan administered to rat dams for the period following organogenesis through weaning at doses of 6 mg/kg/day caused decreased learning ability and decreased female body weights in the offspring. There are no adequate and well-controlled studies of irinotecan in pregnant women. If the drug is used during pregnancy, or if the patient becomes pregnant while receiving this drug, the patient should be apprised of the potential hazard to the fetus. Women of childbearing potential should be advised to avoid becoming pregnant while receiving treatment with irinotecan hydrochloride injection.

Appendix 8: Acceptable Infusion Sets

Acceptable infusion sets are based on the in-use stability studies and are fully described in the Pharmacy Manual.

Appendix 9: Study Schema



Appendix 10: Edmonton Symptom Assessment System (revised version)

Edmonton Symptom Assessment System:
(revised version) (ESAS-R)

Please circle the number that best describes how you feel NOW:

No Pain	0	1	2	3	4	5	6	7	8	9	10	Worst Possible Pain
No Tiredness *(Tiredness = lack of energy)*	0	1	2	3	4	5	6	7	8	9	10	Worst Possible Tiredness
No Drowsiness *(Drowsiness = feeling sleepy)*	0	1	2	3	4	5	6	7	8	9	10	Worst Possible Drowsiness
No Nausea	0	1	2	3	4	5	6	7	8	9	10	Worst Possible Nausea
No Lack of Appetite	0	1	2	3	4	5	6	7	8	9	10	Worst Possible Lack of Appetite
No Shortness of Breath	0	1	2	3	4	5	6	7	8	9	10	Worst Possible Shortness of Breath
No Depression *(Depression = feeling sad)*	0	1	2	3	4	5	6	7	8	9	10	Worst Possible Depression
No Anxiety *(Anxiety = feeling nervous)*	0	1	2	3	4	5	6	7	8	9	10	Worst Possible Anxiety
Best Wellbeing *(Wellbeing = how you feel overall)*	0	1	2	3	4	5	6	7	8	9	10	Worst Possible Wellbeing
No _____ Other Problem *(for example constipation)*	0	1	2	3	4	5	6	7	8	9	10	Worst Possible _____

Patient's Name _____

Date _____ Time _____

Completed by (check one):
- ☐ Patient
- ☐ Family caregiver
- ☐ Health care professional caregive
- ☐ Caregiver-assisted

BODY DIAGRAM ON REVERSE SIDE

ESAS-r
Revised: November 2010