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Brief Communication

Subset analysis of safety and efficacy in asian patients treated with RRx-001 across three clinical trials

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Abstract: RRx-001, a CD47 antagonist via its inhibition of MYC and the γ-subtype of the peroxisome proliferator-activated receptor (PPAR) has been associated to date with minimal toxicity. The aim of this *post-hoc* analysis was to evaluate the toxicity and efficacy of RRx-001 in Asian patients since RRx-001, in the context of multiple Phase 3 studies, will be administered in China and Chinese territories as well as potentially throughout the rest of Asia. Patients received 4 mg of RRx-001 in three different antitumor clinical trials with chemotherapy and/or radiation and a retrospective subset efficacy and toxicity analysis was conducted for patients with Asian ancestry in comparison to patients with other ethnic backgrounds. The toxicity and efficacy data from these studies were similar between Asians and the rest of the treated patients. While the sample sizes are too small to draw definitive conclusions, at a dose of 4 mg, when RRx-001 is combined with chemotherapy, no apparent differences in terms of safety and efficacy are observed in cancer patients with Asian ancestry.

Keywords: Cancer, RRx-001, chemotherapy, immunotherapy, toxicity

Introduction

Pharmacoethnicity, or ethnic differences in drug response or toxicity [1], is known to influence interpatient susceptibility to particular drugs. These susceptibility factors, which may derive from race/ethnicity, are intrinsic or genetic e.g., polymorphisms of drug metabolizing enzymes and transporters, hepatic/renal function, age, gender and differences in body weight or mutations in drug target proteins that are associated with or lead to particular drug-related sensitivities or resistance and extrinsic or non-genetic e.g., tobacco and alcohol use, diet, climate, pollution exposure and complementary and herbal medicine use (**Table 1**) [2, 3].

Medicine's succinctly stated prime axiom is "first do no harm". On that basis, since manifestly all patients do not respond to the same medicine and the same dose in the same way, clear delineation of biomarkers that identify patients most likely to benefit (or to not benefit) and/or those predisposed to toxicity from a particular treatment and a particular treatment dose is of the utmost importance [4].

Controversial overtones aside, differences due to race, culture and ethnicity may potentially reveal particularly relevant biomarker information in oncology, given the increasing emphasis on precision medicine i.e, right drug for the right patient at the right time and the importance of optimal drug selection and dosing to reduce adverse drug reactions and drug-drug interactions for better treatment outcomes [5]. For example, 5-FU and its oral prodrug capecitabine are better tolerated by Chinese patients than Caucasians [6], possibly due to the major drug target of 5-FU and capecitabine, thymidylate synthase (TS), which is encoded by the *TYMS* gene. The *TYMS* promoter region contains a tandemly-repeated 28 base pair segment, which usually occurs as a duplet (2R) or triplet (3R) polymorphism, with the latter being approximately twice as common among the Chinese population (67%) compared with the Caucasian population (38%) [7]. Retrospective analyses

Table 1. Selected pharmacoethnic factors

Intrinsic factors	Extrinsic factors
Genetic polymorphism	Diet
Age	Climate
Gender	Use of alcohol or tobacco
Ancestry	Cultural practices
Organ function or dysfunction	Pollution exposure

have reported significantly lower grade 3/4 toxicity rates from fluorouracil-based chemotherapy in patients with the 3R/3R genotype compared to the 2R/2R genotype [8].

In addition, interethnic variations with respect to drug metabolizing enzymes such as CYP2D6, CYP2A6, CYP2C19, and CYP2C9, drug transporters such as P-glycoprotein and alpha-1 acid glycoprotein, and drug receptors such as EGFR and KRAS may underpin, influence and potentially predict in selected cases not only the efficacy and safety of anticancer agents in particular populations, but also the potential for drug interactions [9].

RRx-001 is an aerospace-derived small molecule in a Phase 3 clinical trial with a unique dinitroazetidine pharmacophore, whose polarity allows RRx-001 to penetrate the membrane of red blood cells (RBCs), which transport the molecule directly to the tumor, from whence it exerts anticancer effects. On the basis of this Trojan Horse-like method of delivery, wherein RBCs encapsulate and shield the molecule from host normal tissues and *vice versa*, and selectively accumulate in the tumor vasculature prior to phagocytosis by tumor associated macrophages (TAMs), RRx-001 is not a substrate for drug metabolizing enzymes and no drug-drug interactions have been observed to date [10].

The mechanistic basis of its anticancer effects involves vascular normalization for better delivery of chemotherapy and oxygen to hypoxic regions and, hence, reoxygenation of the tumor as well as TAM repolarization from protumor M2 to antitumor M1 and CD47 antagonism via inhibition of MYC and the γ-subtype of the peroxisome proliferator-activated receptor (PPAR) [11].

Changes in tumor blood flow, and the concomitant changes in oxygen and chemotherapy delivery to tumor tissue, are partially responsible for the chemoradiosensitization activity of RRx-001. Since TAMs protect tumors from the effects of chemotherapy, immunotherapy and radiation, reprogramming them from an M2 to M1 phenotype is also thought to drive single agent antitumor activity and chemoimmunoradiosensitization; radiation, immunotherapy and certain types of chemotherapy are known to mediate "immunogenic cell death" (ICD), a process that involves the release of "eat-me" signals such as ATP and high-mobility group B1 (HMGB1) as well as the enhancement of the antigen-presenting capacity of phagocytes and the promotion of T cell responses (**Figure 1**). In fact, unpublished data from clinical biopsies have shown an association between TAM-rich solid tumors and *better* patient responses with RRx-001, which contravenes the established relationship between high TAM density and increased metastasis, immunosuppression, therapeutic resistance, and poor clinical outcomes [12, 13].

To date, RRx-001 has been dosed in over 400 patients in 12 clinical trials in the United States. Of these 12 trials, 3 of them, ROCKET in colorectal cancer (NCT02096354), QUADRUPLE THREAT in small cell lung cancer (SCLC) (NCT02489903) and G-FORCE in glioblastoma (GBM) (NCT02871843) have enrolled patients with Asian background. Since RRx-001 will be administered in China and Chinese territories as well as potentially throughout the rest of Asia as part of multiple Phase 3 trials, the purpose of this *post-hoc* analysis was to compare the toxicity and efficacy data from these Asian patients to the rest of the mostly Caucasian clinical trial populations. For completeness, the pharmacokinetic (PK) data from the Phase 1 first-in-man study is presented; however, its usefulness for this manuscript is limited because, firstly, only 1 Asian patient was enrolled, secondly, because there was considerable inter-patient and inter-dose variability and, thirdly, because the PK adduct that was followed, RRx-001-glutathione (GSH) is not thought to be a relevant driver of the pharmacodynamic effect given that its rapid excretion (elimination half-life ~15-30 min) likely prevents accumulation in tissues or in tumors.

Methods

Study protocols

ROCKET: This phase 2, open-label, randomized (2:1), two-arm study called ROCKET (NCT02096354), which was conducted in the mainland

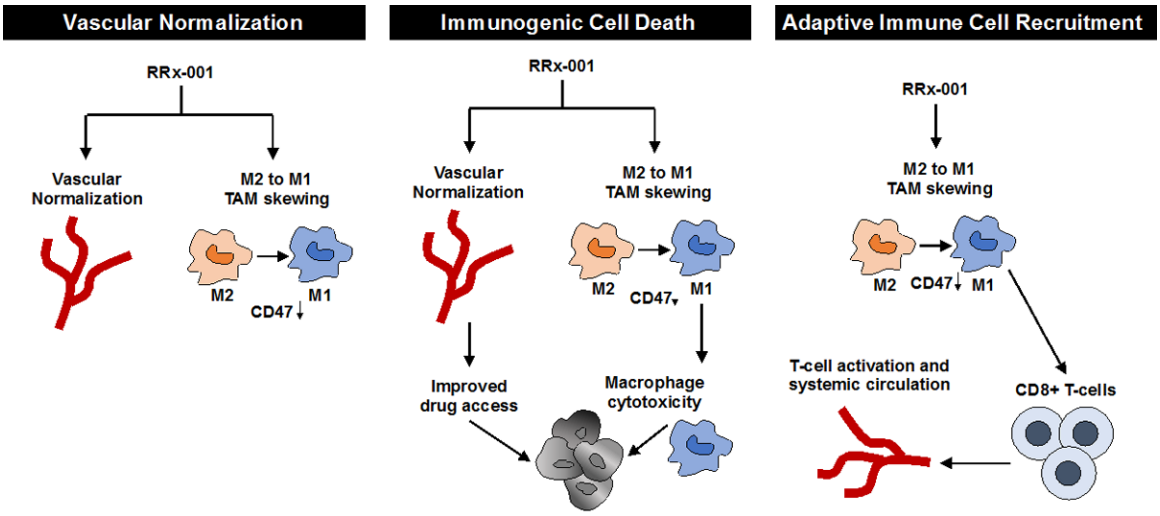

Figure 1. Anticancer mechanism overview of RRx-001.

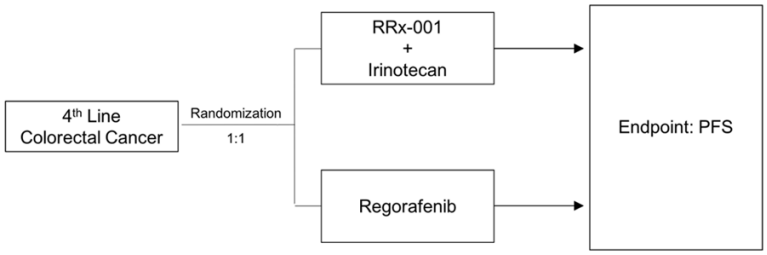

Figure 2. ROCKET study schema.

United States and Hawaii and enrolled 49 patients, compared 4 mg weekly iv RRx-001 + 180 mg/m^2 irinotecan given iv on Day 1 every two weeks vs. 160 mg oral regorafenib given on a 21/28 day cycle in 3rd/4th line patients with metastatic colorectal cancer previously treated with at least oxaliplatin- and irinotecan-based regimens with bevacizumab and cetuximab or panitumumab (if KRAS wildtype). The main endpoint was progression free survival (PFS). Key inclusion/exclusion criteria included age >18 years old, measurable disease, acceptable baseline hematologic and non-hematologic laboratory values, an ECOG performance status of 0-2, no history of intolerance to irinotecan, and no clinically significant cardiovascular disease (**Figure 2**).

QUADRUPLE THREAT: In this open label, non-randomized, exploratory Phase 2 study called QUADRUPLE THREAT (QT) (NCT02489903) 26 patients with SCLC in third-line or beyond that had previously received- and previously progressed on- a platinum doublet i.e., cisplatin/carboplatin + etoposide were enrolled in the United States, of which 2 were of Asian descent. Patients were treated with RRx-001 4 mg IV on day 1 of each week of a 21-day cycle followed at progression by re-challenge with etoposide 80-100 IV mg/m^2 on days 1, 2 and 3 and cisplatin 60-80 mg/m^2 IV on day 1 or carboplatin AUC 5-6 IV on day 1, every 21 days. Key inclusion/exclusion criteria included histological evidence of SCLC, 18 years or older, evidence of measurable disease, ECOG performance status 0-2, adequate organ and marrow function, history of receiving prior platinum doublet and no history of intolerance to it. The primary end points were overall survival (OS) and overall response rate to platinum regimen (**Figure 3**).

G-FORCE: In this non-randomized, open-label, two part trial called G-FORCE-1 (NCT02871-843), the first four cohorts of adult patients with histologically confirmed high grade gliomas received fractionated radiotherapy (60 Gy in 30 fractions over 6 weeks), daily 75 mg/m^2 temozolomide (TMZ) and escalating doses of once weekly RRx-001 from 0.5 mg to 4 mg according to a 3+3 design followed by a 6 week no treatment interval and then standard maintenance TMZ (150 mg/m^2 Cycle 1 and 200

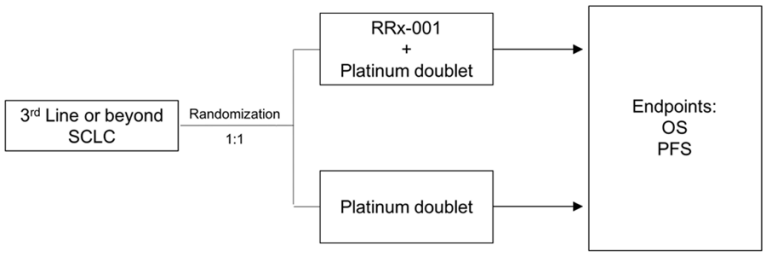

Figure 3. QUADRUPLE THREAT study schema.

mg/m^2 in subsequent cycles) until disease progression. The second two cohorts of patients received fractionated radiotherapy (60 Gy in 30 fractions over 6 weeks), daily 75 mg/m^2 temozolomide and once weekly RRx-001 4 mg followed by a 6 week no treatment interval and then two different maintenance schedules until disease progression according to the same 3+3 design:

1. 0.5 mg RRx-001 once weekly + 100 mg/m^2 TMZ 5 days/week for up to 6 cycles of therapy;
2. 4 mg RRx-001 once weekly + 100 mg/m^2 TMZ 5 days/week for up to 6 cycles of therapy.

Key inclusion/exclusion criteria included histological evidence of glioma, evidence of measurable disease, Karnofsky Performance Score of $\geq$ 70%, stable to decreasing dose within first dose of study drug, acceptable laboratory parameters, no infratentorial component, no recurrent gliomas previously treated with radiotherapy and/or chemotherapy, no prior temozolomide, no prior chemotherapy or radiosensitizers for cancers of the head and neck region and no active connective tissue disorders, such as lupus or scleroderma that in the opinion of the treating physician may put the patient at high risk for radiation toxicity. The primary endpoint was the recommended dose/maximally tolerated dose of the combination of RRx-001, TMZ and radiotherapy.

A total of 18 patients were enrolled in the United States.

Toxicity analysis

Adverse events were coded by system organ class and preferred term using MedDRA, version 22. Adverse event severity was based on NCI-CTCAE Grade (version 5.0). Incidence of TEAEs by MedDRA SOC, preferred term, and relationship (Related/Not Related) to study drug were summarized based on the safety population. Adverse event incidence rates were summarized using frequency and percentage.

Statistical analysis

Progression free survival (PFS) was summarized for the sub-populations comprising Asian and non-Asian patients via Kaplan-Meier method based on the intention-to-treat analysis set. For each sub-population, the PFS survival curve, median PFS and its 95% CI (Brookmeyer-Crowley 1982) were produced. Incidence rates of adverse events were summarized using frequency and percentage.

Results

Thirty-four randomized patients comprised ROCKET intention-to-treat analysis set (24 RRx-001 + irinotecan, 10 regorafenib). There were 5 Asian patients and 4 that received RRx-001 + irinotecan achieved a median PFS of 9.3 and 1 patient that received regorafenib achieved a median PFS of 0.16 months. 20 non-Asian patients that received RRx-001 + irinotecan achieved a median PFS of 4.8 months (95% CI (2.0, NA)), while 9 non-Asian patients that received regorafenib achieved a median PFS of 1.7 months (95% CI (0.66, NA)) (**Figure 4**).

Toxicity

The toxicity was evaluated in 49 patients in the ROCKET study (5 Asian patients vs. 44 Non-Asian patients) and the incidence of notable treatment-emergent adverse events (preferred term by system organ class) are shown in **Table 2**, and categorized by ethnicity (Non-Asian vs. Asian).

QUADRUPLE THREAT SCLC: There were two Asian patients in QUADRUPLE THREAT. The adverse events in the Asian and non-Asian subpopulations were comparable. **Table 3** lists Grade $\geq$ 2 adverse events in the Asian sub-population (n=2).

G-FORCE: There were two Asian patients in G-FORCE. The adverse events in the Asian and non-Asian subpopulations were comparable. **Table 4** lists Grade $\geq$ 2 adverse events in the Asian sub-population (n=2).

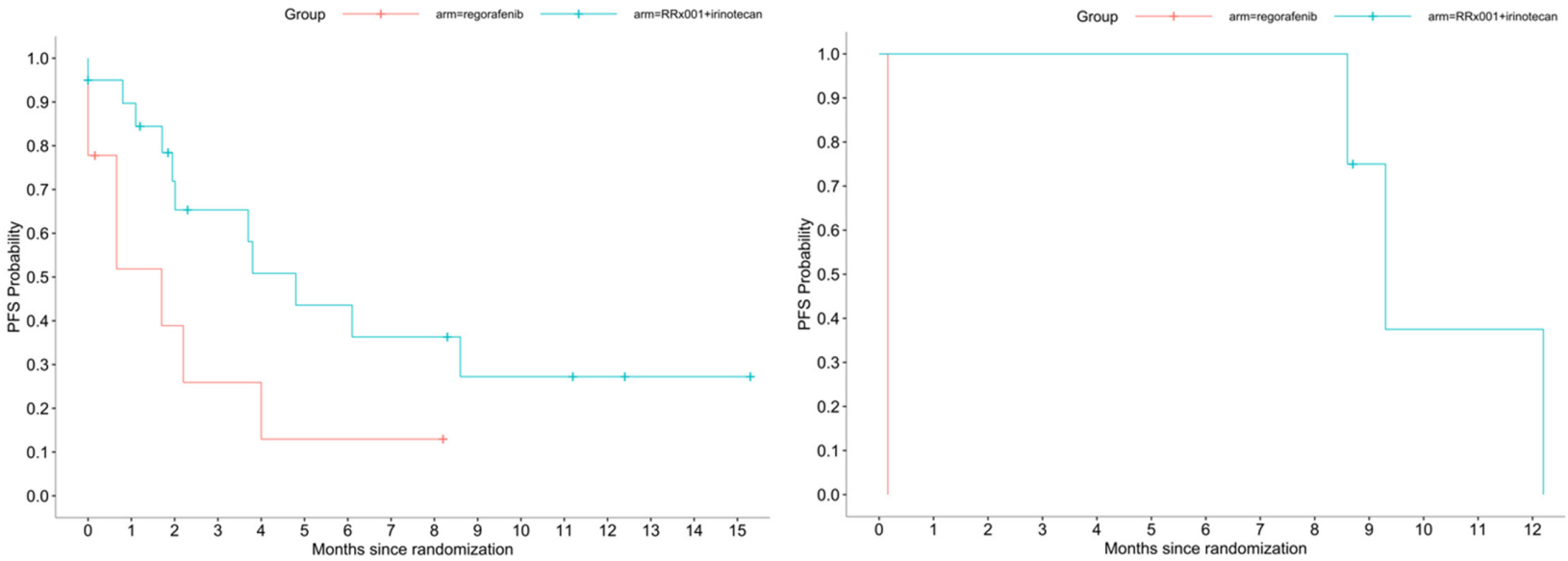

Figure 4. PFS kaplan-meier curve, intent to treat population, Asian vs. Non-Asian patients.

Table 2. Incidence of treatment emergent adverse events preferred terms by system organ class, ROCKET safety population (Asian vs. Non-Asian patients)

System organ class	Preferred term	Regorafenib (n=10)	RRx-001+Irinotecan (n=34)	Total (n=44)
Blood and lymphatic system disorders	Anemia	1 (10)	5 (14.7)	6 (13.6)
	Vomiting	4 (40)	7 (20.6)	11 (25)
	Disease progression	2 (20)	5 (14.7)	7 (15.9)
General disorders and administration site conditions	Fatigue	5 (50)	13 (38.2)	18 (40.9)
	Edema peripheral	0 (0.0)	1 (2.9)	1 (2.3)
Injury, poisoning and procedural complications	Infusion related reaction	0 (0.0)	24 (70.6)	24 (54.5)
	Hypoalbuminemia	0 (0.0)	1 (2.9)	1 (2.3)
	Dyspnea	1 (10)	2 (5.9)	3 (6.8)
System organ class	Preferred term	Regorafenib (n=1)	RRx-001+Irinotecan (n=4)	Total (n=5)
Blood and lymphatic system disorders	Anemia	1 (100)	0 (0.0)	1 (20)
	Vomiting	0 (0.0)	2 (50)	2 (40)
	Disease progression	0 (0.0)	2 (50)	2 (40)
General disorders and administration site conditions	Fatigue	0 (0.0)	3 (75)	3 (60)
	Edema peripheral	1 (100)	1 (25)	2 (40)
Injury, poisoning and procedural complications	Infusion related reaction	0 (0.0)	4 (100)	4 (80)
	Hypoalbuminemia	0 (0.0)	2 (50)	2 (40)
	Dyspnea	1 (100)	1 (25)	2 (40)

Pharmacokinetics

Activity: Pharmacokinetic parameters estimates were derived from a first in man study "A Phase 1, Open-Label, Multiple Ascending Dose Study to Assess the Safety, Tolerability and Pharmacokinetics of RRx-001 in Subjects with Advanced Solid Tumors or Lymphomas For Which There Are No Currently Accepted Curative Therapies". The study enrolled 25 subjects (1 Asian subject).

Venous PK blood samples (5 mL) were collected on days 1 and 50 (Amendment 1.3 allowed collection at Day 22 instead of Day 50). Samples were collected as follows: Pre-dose (within 15 minutes prior to the start of infusion), 15 min post the start of the infusion, 0 (± 1 min) at the completion of the infusion, 15 ± 2, 30 ± 5 minutes, 1, 2, 3, 4.5, 6, 24 hours (Day 2 only) ± 5 minutes after the end of infusion. The plasma concentration of the glutathione adduct of RRx-001 was determined by a bioanalytical laboratory. Due to the rapid excretion of the glutathione adduct (elimination half-life ~15-30 min), subsequent protocol amendments reduced the number of time points and total time the clearance of the analyte was followed.

Quantification of the levels of the RRx-001-glutathione adduct in human plasma was determined using a validated LCMS/MS method.

Non-linear pharmacokinetics were concluded since higher doses of RRx-001 did not result in a proportionally higher estimated (median) AUC_{all} (see **Table 5**). Large interpatient and intercohort variability was observed, and covariant analysis did not reveal significant relationships with any pharmacokinetic parameter.

Dose-dependency was not detected due to the high interpatient variability, which is likely a function of the main toxicity of RRx-001, that of localized pain on infusion, that required slowing or stopping of the infusion rate to ameliorate the pain. Due to a new method of administration, pain on infusion has largely been eliminated but at the time of the first-in-man trial it was still present.

Traditionally, substantial pharmacokinetic variability is indicative of differing efficacy and toxicity in patients; however, RRx-001 has a large therapeutic window, as evidenced by the absence of dose limiting toxicities (DLTs) and a maximally tolerated dose (MTD). Moreover, the dose-response relationship is rather flat in the

Table 3. Listing of Grade >2 treatment emergent adverse events preferred terms by system organ class, QUADRUPLE THREAT, safety population (Asian patients)

Subject ID	Treatment	System organ class	Preferred term	NCI-CTC Grade	Relation to drug	Outcome	Serious AE	AE start date	AE end date
001-001	Platinum	Metabolism and nutrition disorders	Phosphorus metabolism disorders	2	Unrelated	Resolved	No	11/24/2015	11/30/2015
001-001	Platinum	Metabolism and nutrition disorders	Phosphorus metabolism disorders	2	Unrelated	Resolved	No	12/7/2015	12/21/2015
001-001	Platinum	Endocrine disorders	Hyperglycemia	2	Unrelated	Resolved	No	12/14/2015	1/4/2016
001-001	RRx-001	Gastrointestinal disorders	Diarrrhea	2	Unrelated	Resolved	No	6/25/2015	6/25/2015
001-001	RRx-001	Injury, poisoning and procedural complications	Infusion related reaction	2	Related	Resolved	No	6/29/2015	6/30/2015
001-001	RRx-001	Respiratory, thoracic and mediastinal disorders	Pulmonary embolism	3	Unrelated	Resolved	yes	8/29/2015	9/1/2015
001-001	RRx-001	Respiratory, thoracic and mediastinal disorders	Pulmonary embolism	3	Unrelated	Resolved	No	9/1/2015	9/3/2015
001-001	Platinum	Skin and subcutaneous tissue disorders	Alopecia	2	Related	Resolved	No	9/30/2015	2/1/2016
001-001	Platinum	General disorders and administration site conditions	Fatigue	2	Unrelated	Resolved	Yes	9/30/2015	12/10/2015
001-001	RRx-001	Respiratory, thoracic and mediastinal disorders	Pulmonary embolism	2	Unrelated	Resolved	No	9/1/2015	9/1/2015
001-001	RRx-001	Injury, poisoning and procedural complications	Infusion related reaction	2	Unrelated	Resolved	No	9/1/2015	9/1/2015
001-001	Platinum	Respiratory, thoracic and mediastinal disorders	Cough	2	Unrelated	Resolved	No	11/30/2015	12/15/2015
001-001	Platinum	Respiratory, thoracic and mediastinal disorders	Upper respiratory tract infection	2	Unrelated	Resolved	No	11/30/2015	12/8/2015
004-014	RRx-001	Gastrointestinal disorders	Diarrrhea	2	Unrelated	Resolved	No	1/11/2018	1/14/2018

Table 4. Listing of Grade >2 treatment emergent adverse events preferred terms by system organ class, G-FORCE, safety population (Asian patients)

Subject ID	Site #	Treatment	System organ class	Preferred term	NCI-CTC Grade	Relation to drug	Outcome	Status	Serious AE	AE start date	AE end date
01-007	001	RRx-001+TMZ	General disorders and administration site conditions	Fatigue	2	Unrelated	RRx-001 dose not changed	Resolved	No	4-Apr-18	29-May-18
01-007	001	RRx-001+TMZ	Skin and subcutaneous tissue disorders	Rash	2	Unrelated	RRx-001 dose not changed	Resolved	No	17-Apr-18	5-May-18
01-007	001	RRx-001+TMZ	Nervous system disorders	Headache	2	Unrelated		Resolved	No	1-Jun-18	12-Jun-18
01-007	001	RRx-001+TMZ	Musculoskeletal and connective tissue disorders	Muscular weakness	2	Unrelated		Not Resolved	No	2-Jun-18	
01-007	001	RRx-001+TMZ	General disorders and administration site conditions	Fatigue	2	Unrelated		Not Resolved	No	12-Jun-18	
01-007	001	RRx-001+TMZ	Nervous system disorders	Vision blurred	2	Unrelated		Not Resolved	No	14-May-18	
01-007	001	RRx-001+TMZ	Nervous system disorders	Headache	2	Unrelated		Not Resolved	No	7-Sep-18	
01-007	001	RRx-001+TMZ	Nervous system disorders	Seizure	2	Unrelated		Resolved	No	14-Oct-18	14-Oct-18
01-007	001	RRx-001+TMZ	Nervous system disorders	Seizure	2	Unrelated		Resolved	Yes	14-Oct-18	16-Oct-18
01-007	001	RRx-001+TMZ	Injury, poisoning and procedural complications	Brain edema	2	Unrelated	RRx-001 dose not changed	Resolved	No	20-Jun-18	3-Jul-18
01-010	001	RRx-001+TMZ	Gastrointestinal disorders	Intestinal perforation	5	Unrelated	RRx-001 withdrawn/discontinud	Fatal	Yes	15-Dec-18	29-Dec-18
01-010	001	RRx-001+TMZ	Renal and urinary disorders	Urinary tract infection	2	Unrelated	RRx-001 dose not changed	Not resolved	No	30-Nov-18	

Table 5. AUC_{all} summary statistics by dose, First In Man Phase 1 study, PK population

Dose (ng/m^2)	N	Mean	Median	Min	Max	Std Dev	Std Error	Coefficient of Var (CV)
10.0	8	77.1	75.7	31.2	127.9	34.4	24.3	44.6
16.7	6	357.9	352.8	216.1	602.1	135.8	96.0	37.9
24.6	6	415.6	417.9	296.7	501.3	80.6	57.0	19.4
33.0	7	555.9	377.3	157.4	1264.4	378.6	267.7	68.1
55.0	6	1153.7	1081.7	659.5	1892.9	472.5	334.1	41.0
83.0	6	870.6	631.1	288.3	1781.2	646.3	457.0	74.2

range of 10 mg/m^2-83 mg/m^2 (20-166 mg). True non-linear pharmacokinetic behavior is usually secondary to saturation of drug elimination pathways (e.g. metabolizing enzymes) and the higher drug levels in plasma tend to correspond to higher amounts of drug in the tissues, which is not the case here, since RRx-001-GSH is rapidly eliminated and, therefore, unlikely to distribute in tissues and tumors. Hence, it may be more apt to describe the PK behavior, which was heavily influenced by the slowing and stopping of the infusion due to pain, as pseudo-non-linear rather than non-linear.

Discussion

Per ICH guidance, the following properties of a compound make it less likely to be sensitive to ethnic factors.

Linear pharmacokinetics (pK)

With the caveat that the RRx-001-GSH adduct is a non-relevant driver of efficacy, its PK behavior is best described as pseudo-non-linear because the more-than-proportional increase in plasma AUC with dose does not correspond to higher levels in tissues or in the tumor given the rapid elimination kinetics ($t_{1/2}$ of 15-30 minutes) and, therefore, a corresponding more-than-proportional increase in pharmacodynamic effects is absent.

A flat pharmacodynamic (PD) (effect-concentration) curve for both efficacy and safety in the range of the recommended dosage and dose regimen

At all doses, in over 400 treated patients, RRx-001 is associated with a flat PD profile for both safety and efficacy because the drug is largely "trapped" in the plasma compartment, having bound to red blood cells, and the resulting higher total drug levels in plasma do not reflect higher levels in tissues.

A wide therapeutic dose range

A very wide therapeutic dose range is present because to date no dose limiting toxicities have been observed and no maximally tolerated (MTD) dose has been reached.

Minimal metabolism or metabolism distributed among multiple pathways

RRx-001 is not metabolized since it binds covalently and irreversibly to thiols (free cysteine, free GSH and a cysteine residue on the beta chain of hemoglobin).

High bioavailability, thus less susceptibility to dietary absorption effects

RRx-001 is given intravenously and it binds to hemoglobin and therefore it is not susceptible to dietary absorption.

Low potential for protein binding

RRx-001 is unlikely to bind to proteins since the observed plasma adducts are free cysteine, free GSH and a cysteine residue on the beta chain of hemoglobin called beta cysteine 93 (BCys93). In *in vitro* experiments, RRx-001 does bind to albumin in the cysteine 34 position but only after 72 hours whereas binding to free cysteine, free GSH and BCys93 is immediate [11].

Little potential for drug-drug, drug-diet and drug-disease interactions

Little potential for drug-drug, drug-diet and drug-disease interactions is present because RRx-001, when given intravenously, binds immediately, covalently and irreversibly to free cysteine, free GSH and BCys93. Furthermore,

RRx-001 is not metabolized by any enzymes including those that are subject to genetic polymorphism.

Non-systemic mode of action

The mode of action is systemic.

Little potential for inappropriate use

Little potential for inappropriate use or abuse is present because RRx-001 has not been observed to produce euphoria, stimulation, pain relief (other than pain relief due to smaller tumor sizes), relaxation, or lowered inhibitions.

With respect to the clinical trials presented above, and, in particular, the ROCKET trial, the extremely small sample sizes compromise the ability to draw valid conclusions, as previously stated; however, a greater benefit in PFS was observed for RRx-001 vs. regorafenib in both Asians and Non-Asians as well as in the study as a whole. Overall, in the study, the toxicity of regorafenib greatly exceeded and was much less well-tolerated than that of the RRx-001 + irinotecan combination [14], which is not fully reflected in **Table 2**. The main toxicity of RRx-001, present in the majority of patients and MedDRA-coded in **Table 2** as "infusion related reaction", is localized transient pain or discomfort on infusion; the infusion related reaction descriptor is somewhat of a misnomer since systemic hypersensitivity reactions such as anaphylaxis or cytokine release syndrome did not (and do not) occur. In general, RRx-001 is well-tolerated, especially with the new method of administration, and does not appear to worsen the toxicity profiles of the chemotherapy or radiation regimens with which it has been combined.

In summary, then, when RRx-001 is infused, it binds immediately and covalently to thiols including the beta cysteine 93 residue on hemoglobin without enzymatic alteration. Red blood cells (RBCs) are an isolated pharmacokinetic compartment. Therefore, RRx-001 is not metabolized by phase 1 cytochrome-P450 (CYP) enzymes or phase 2 enzymes including UDP-glucuronosyltransferases (UGTs), which may differ between Asians and Caucasians. Since RRx-001 is covalently bound to hemoglobin, it is also unlikely to undergo efflux from transporters such as p-glycoprotein (p-gp). Also, plasma protein binding has no role in the distribution of RRx-001 and body size and weight should similarly not affect drug distribution and elimination. Even hemoglobin and hematocrit levels should not affect the absorption, distribution, metabolism, and excretion (ADME) properties of RRx-001 because the drug only binds to a small subpopulation of red blood cells.

On the other hand, the use of complementary and alternative medicines, including certain herbal medicines that may prevent the binding of RRx-001 to the beta cysteine 93 residue on hemoglobin, either in a direct (competitive) or indirect (allosteric) manner, reversibly or irreversibly, tends to vary widely between Asians and Caucasians and, thus, in theory, has the potential to induce different pharmacologic responses.

In the near future considerably larger and eagerly awaited clinical trials in China will determine whether, in fact, any ethnic differences that may potentially impact or influence the safety and efficacy of RRx-001 are present.

Disclosure of conflict of interest

EpicentRx Inc is the sponsor of these clinical trials featuring RRx-001.

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