CLINICAL STUDY PROTOCOL

Protocol No.	RRx001-211-01
Product	RRx-001
Title:	**RRx-001 in patients with small cell carcinoma, high-grade neuroendocrine carcinoma, EGFR mutation positive non-small cell lung cancer, ovarian cancer (including Malignant Mixed Mullerian Tumor (MMMT) of the ovary or uterus) previously treated with a platinum-based regimen (QUADRUPLE THREAT)**
Development Phase	Phase 2
IND #:	107,674
Version: Original	October 7, 2014
Amendment No.	Amendment 10
Date:	July 20, 2018
Sponsor:	EpicentRx, Inc. 11099 North Torrey Pines Rd, Suite 160 La Jolla, CA 92037
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INVESTIGATOR AGREEMENT PAGE

EpicentRx, Inc.

Protocol No. RRx001-211-01

RRx-001 in patients with small cell carcinoma, high-grade neuroendocrine carcinoma, EGFR mutation positive non-small cell lung cancer, ovarian cancer (including Malignant Mixed Mullerian Tumor (MMMT) of the ovary or uterus) previously treated with a platinum-based regimen (QUADRUPLE THREAT)

July 20, 2018

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: **RRx-001 in patients with small cell carcinoma, high-grade neuroendocrine carcinoma, EGFR mutation positive non-small cell lung cancer, ovarian cancer (including Malignant Mixed Mullerian Tumor (MMMT) of the ovary or uterus) previously treated with a platinum-based regimen (QUADRUPLE THREAT)**

SPONSOR:

EpicentRx, Inc.
11099 North Torrey Pines Rd, Suite 160
La Jolla, CA 92037

Bryan Oronsky, M.D. — 20 JUL 2018 Date

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LIST OF ABBREVIATIONS

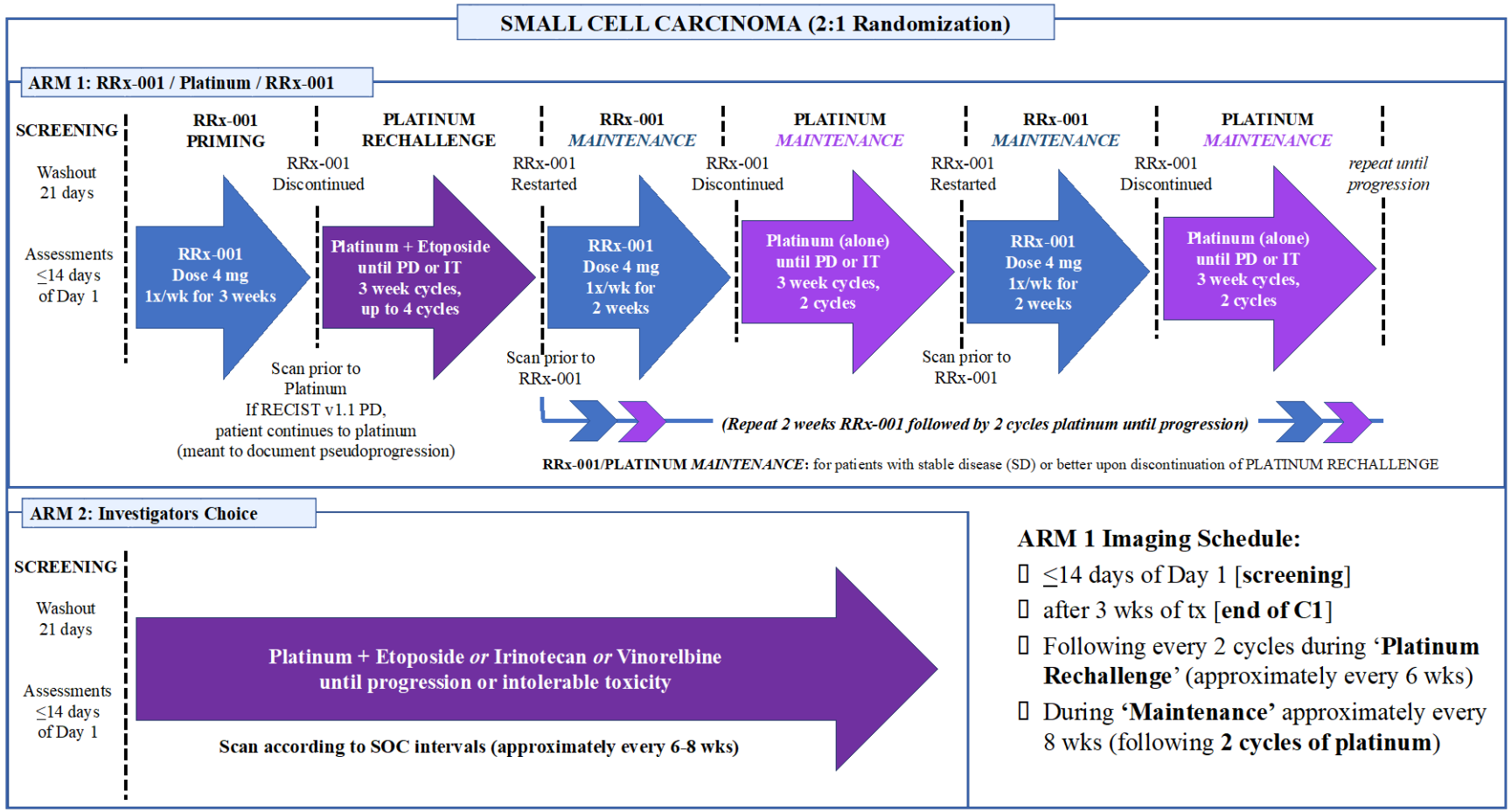
AABB	American Association of Blood Banks
AE	Adverse Event
ALT	Alanine Aminotransferase
AST	Aspartate Aminotransferase
BID	Twice a day
BUN	Blood Urea Nitrogen
CBC	Complete Blood Count
CFI	Chemotherapy Free Interval
CMH	Cochran-Mantel-Haenszel Test
CMP	Comprehensive Metabolic Panel
CPT	Cold Pressor Test
CR	Complete Response
CT	Computed Tomography
CTCAE	Common Terminology Criteria for Adverse Events
DLT	Dose Limiting Toxicity
ECOG	Eastern Cooperative Oncology Group
EOC	Epithelial Ovarian Cancer
ES-SCLC	Extensive Stage Small Cell Lung Cancer
FDG	Fluorodeoxyglucose
FMP	Family Member Prefix
GI	Gastrointestinal
GU	Genitourinary
HCC	Hepatocellular Carcinoma
HGNEC	Extrapulmonary High Grade Neuroendocrine Tumors
HRPP	Human Research Protections Program
INR	International Normalized Ratio
IRB	Institutional Review Board
miRNA	MicroRNA
MMMT	Malignant Mixed Mullerian Tumor
MRI	Magnetic Resonance Imaging
MRN	Medical Record Number
NCI	National Cancer Institute
NSCLC	Non-Small Cell Lung Cancer
NYHA	New York Heart Association
OS	Overall Survival
PET	Positron Emission Tomography
PFS	Progression Free Survival
PD	Progressive Disease
PLD	Pegylated Liposomal Doxorubicin
p.o.	per os/by mouth/orally

PR	Partial Response
PS	Phosphatidylserine
PT	Prothrombin Time
q.d.	quaque die/every day
RBC	Red Blood Cell
rEOC	Resistant/Refractory Epithelial Ovarian Cancer
rSCLC	Resistant/Refractory Small Cell Lung Cancer
RECIST	Response Evaluation Criteria in Solid Tumors
SAE	Serious Adverse Event
SCLC	Small Cell Lung Cancer
SCC	Small Cell Carcinoma
SD	Stable Disease
SGOT	Serum Glutamic Oxaloacetic Transaminase
SPGT	Serum Glutamic Pyruvic Transaminase
SSN	Social Security Number
TAM	Tumor Associated Macrophages
T790M	Threonine (amino acid position 790) Methionine
TEAE	Treatment Emergent Adverse Events
TFI	Treatment-Free Interval
TKI	Tyrosine Kinase Inhibitor
ULN	Upper Limit of Normal
VAS	Visual Analog Scale
WBC	White Blood Cells

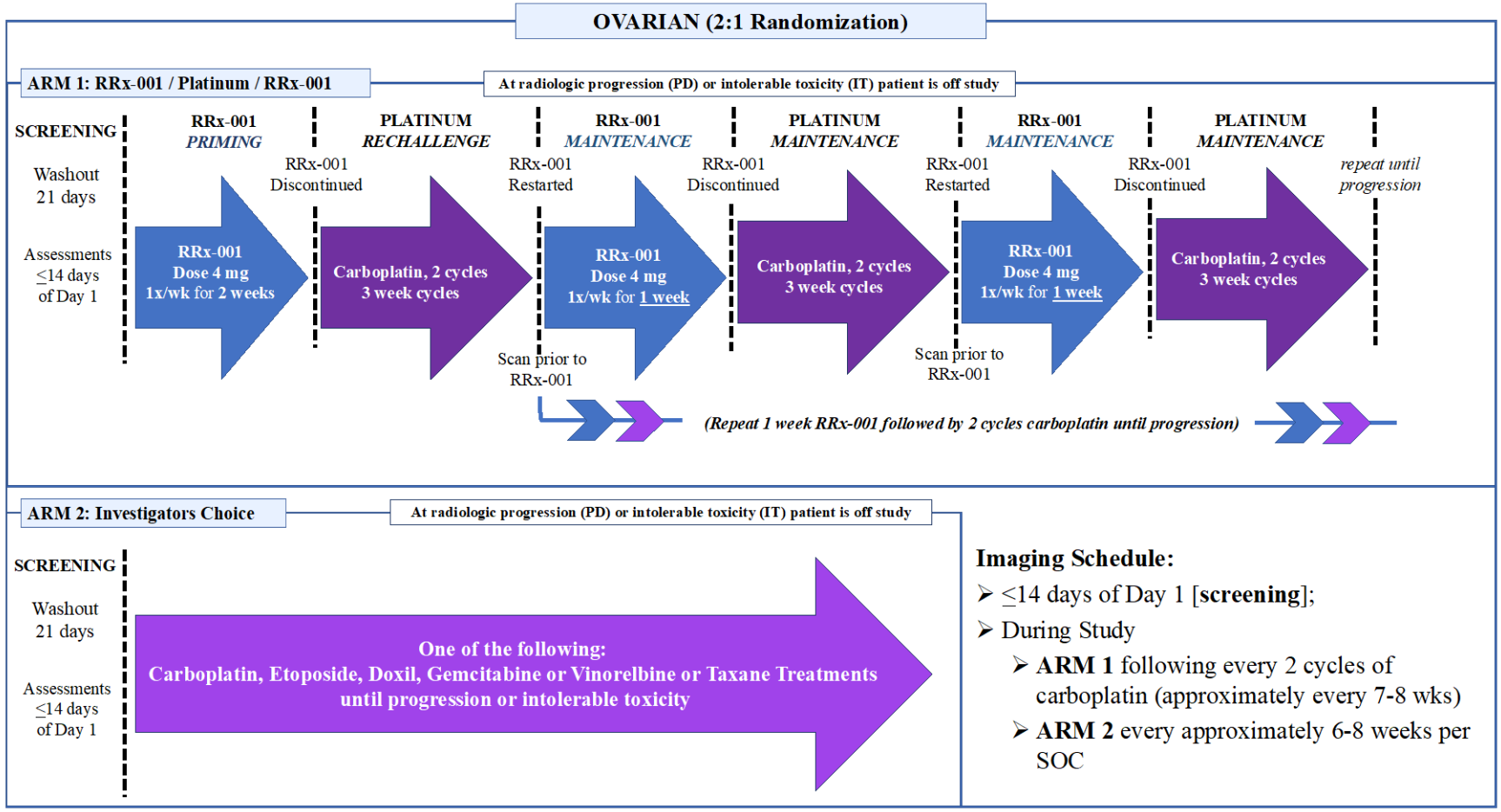
1 STUDY SCHEMAS

1.1 Treatment Schemas [SCC, EOC, NET, NSCLC]

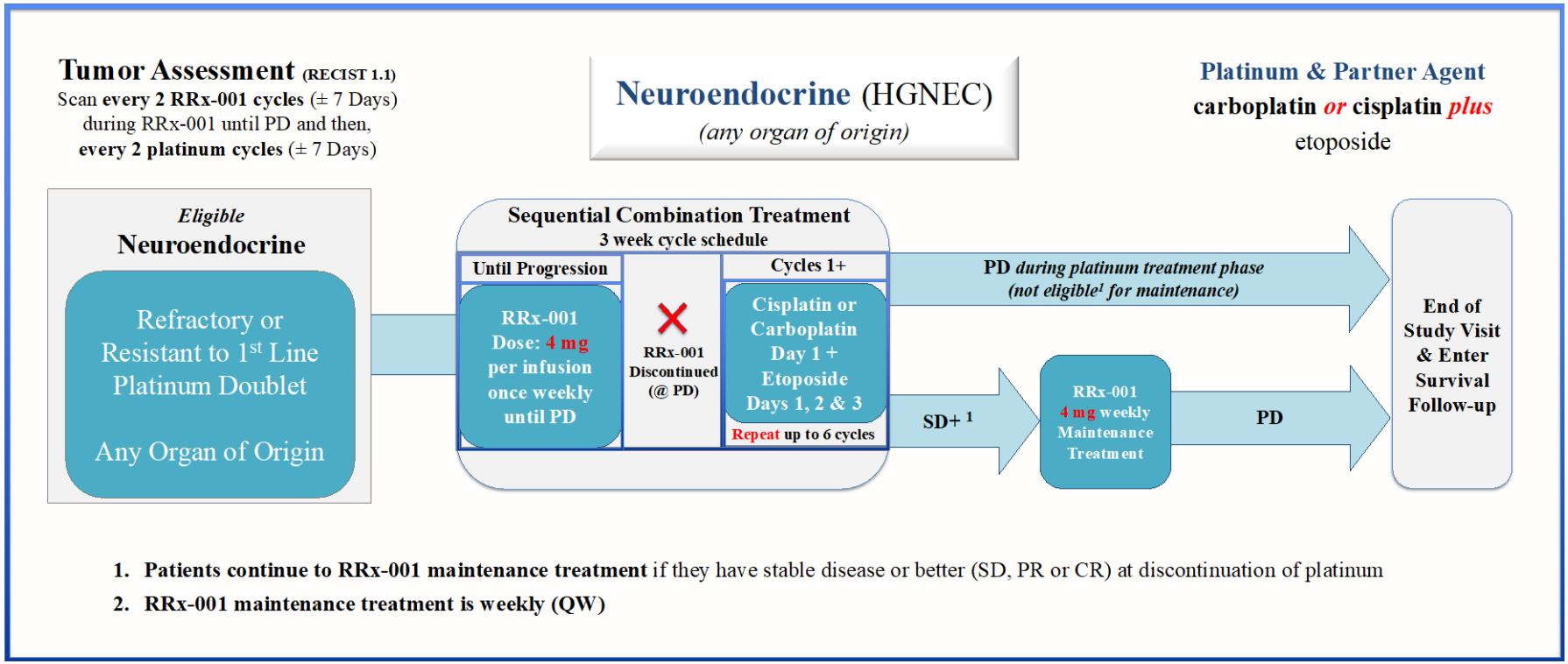
SCC



EOC

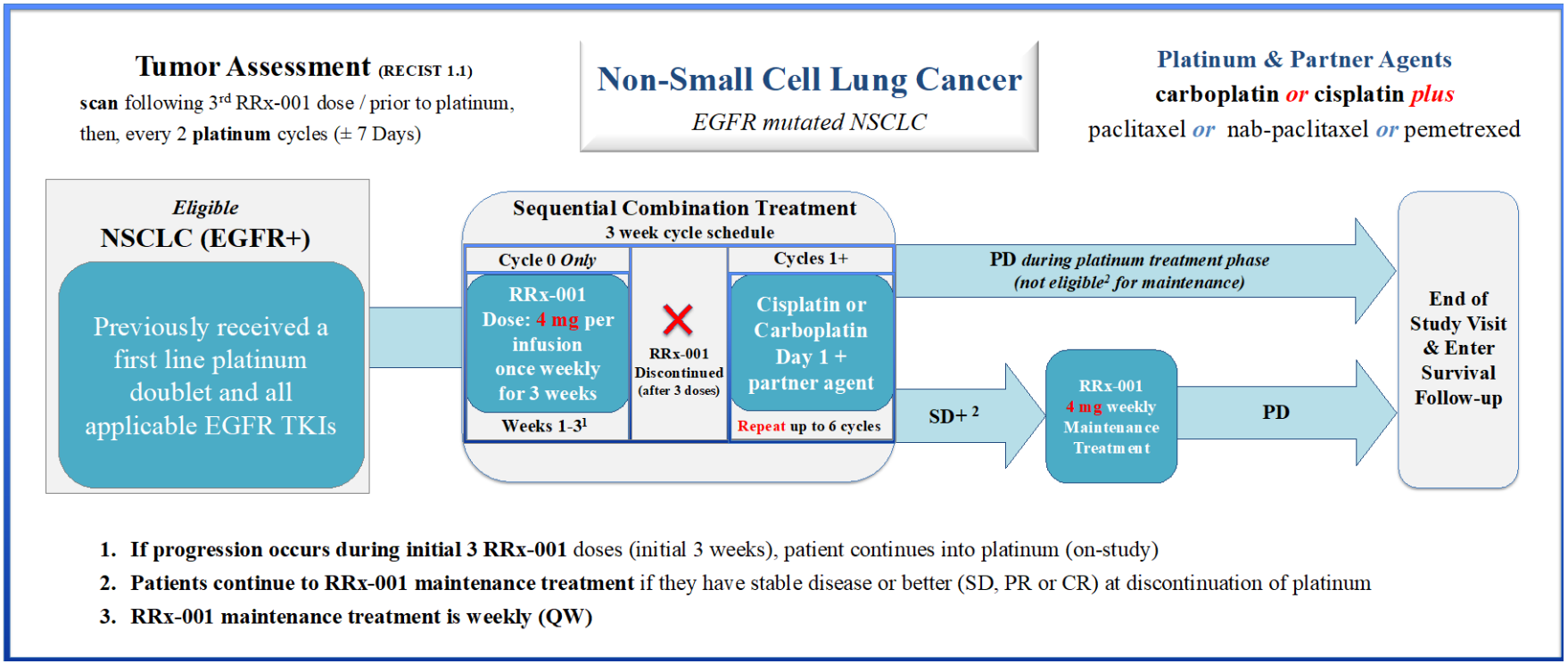

OVARIAN (2:1 Randomization)
ARM 1: RRx-001 / Platinum / RRx-001
At radiologic progression (PD) or intolerable toxicity (IT) patient is off study
SCREENING
Washout 21 days
Assessments ≤14 days of Day 1
RRx-001 PRIMING
RRx-001 Dose 4 mg 1x/wk for 2 weeks
RRx-001 Discontinued
PLATINUM RECHALLENGE
Carboplatin, 2 cycles 3 week cycles
RRx-001 Restarted
Scan prior to RRx-001
RRx-001 MAINTENANCE
RRx-001 Dose 4 mg 1x/wk for 1 week
RRx-001 Discontinued
PLATINUM MAINTENANCE
Carboplatin, 2 cycles 3 week cycles
RRx-001 Restarted
Scan prior to RRx-001
RRx-001 MAINTENANCE
RRx-001 Dose 4 mg 1x/wk for 1 week
RRx-001 Discontinued
PLATINUM MAINTENANCE
Carboplatin, 2 cycles 3 week cycles
repeat until progression
(Repeat 1 week RRx-001 followed by 2 cycles carboplatin until progression)
ARM 2: Investigators Choice
At radiologic progression (PD) or intolerable toxicity (IT) patient is off study
SCREENING
Washout 21 days
Assessments ≤14 days of Day 1
One of the following:
Carboplatin, Etoposide, Doxil, Gemcitabine or Vinorelbine or Taxane Treatments
until progression or intolerable toxicity
Imaging Schedule:
≤14 days of Day 1 [screening];
During Study
ARM 1 following every 2 cycles of carboplatin (approximately every 7-8 wks)
ARM 2 every approximately 6-8 weeks per SOC

NET



1. **Patients continue to RRx-001 maintenance treatment** if they have stable disease or better (SD, PR or CR) at discontinuation of platinum
2. **RRx-001 maintenance treatment is weekly (QW)**

NSCLC



1. **If progression occurs during initial 3 RRx-001** doses (initial 3 weeks), patient continues into platinum (on-study)
2. **Patients continue to RRx-001 maintenance treatment** if they have stable disease or better (SD, PR or CR) at discontinuation of platinum
3. **RRx-001 maintenance treatment is weekly (QW)**

2 STUDY SUMMARY

Title:	RRx-001 in patients with small cell carcinoma, high-grade neuroendocrine carcinoma, EGFR mutation positive non-small cell lung cancer, ovarian cancer (including Malignant Mixed Mullerian Tumor (MMMT) of the ovary or uterus) previously treated with a platinum-based regimen (QUADRUPLE THREAT)
Descriptive Title:	RRx-001 for Sensitization/Resensitization to Platinum Based Chemotherapy in Gynecologic, Thoracic, and Extrathoracic Malignancies in Patients Who Previously Received and Eventually Progressed on or after a Platinum Doublet Regimen
Phase:	Phase 2 Study
Methodology:	The study is designed to explore the potential of the epigenetic and tumor associated macrophage (TAM)-targeting agent RRx-001 to sensitize patients who previously received and now have progressed on a platinum based doublet regimen. This is an open label study for administration of RRx-001 with autologous blood. Small cell carcinoma and ovarian cohort patients will be randomized to 1 of 2 treatment arms, respectively. Neuroendocrine and NSCLC patients will be enrolled to single arms, respectively, as stated below. **SCC cohort patients** (enrolled as of Amendment 10) will be randomized (2:1) to 1 of 2 treatment arms: **Arm 1):** RRx-001 weekly for 3 weeks followed by up to 4 cycles of platinum plus etoposide chemotherapy 'rechallenge' and then RRx-001 & platinum maintenance (for patients with stable disease (SD) or better at discontinuation of platinum rechallenge) **Arm 2):** Standard of Care Investigator's Choice Control Arm, treatment options of one of the following: platinum plus etoposide, irinotecan or vinorelbine until progression or intolerable toxicity **Ovarian cohort patients** (enrolled as of Amendment 10) will be randomized (2:1) to 1 of 2 treatment arms: **Arm 1):** RRx-001 weekly for 2 weeks followed by 2 cycles of carboplatin 'rechallenge' and then 'maintenance', cycling between 1 dose of RRx-001 followed by 2 cycles of carboplatin, which repeats until progression or intolerable toxicity **Arm 2):** Standard of Care Investigator's Choice Control Arm, treatment options of one of the following: carboplatin, etoposide, doxil, gemcitabine, vinorelbine or taxane treatments until progression or intolerable toxicity **Neuroendocrine cohort patients**: Will receive RRx-001 weekly until progression followed by up to 6 cycles of platinum doublet chemotherapy. ➢ **Maintenance RRx-001** is given for patients with stable disease or better at discontinuation of platinum and administered weekly (QW) until progression. **NSCLC cohort patients**: Will receive RRx-001 weekly for 3 weeks followed by up to 6 cycles of platinum doublet chemotherapy. ➢ **Maintenance RRx-001** is given for patients with stable disease or better at discontinuation of platinum and administered weekly (QW) until progression.

Objectives:	Primary Objective To evaluate Overall Survival (OS) and Overall Response Rate (ORR). Secondary Objectives • To estimate the transition probability between disease progression and disease amelioration attributable to resensitization • To estimate the mean sojourn time in a platinum sensitized state • To evaluate disease control rate (DCR) and PFS by RECIST v1.1 criteria in adult patients with advanced or metastatic SCC, NSCLC, EOC or HGNEC after re-treatment with platinum-based therapy following exposure to RRx-001 • To evaluate the toxicity of RRx-001 monotherapy • To evaluate the toxicity of platinum-based therapy following prior exposure to these agents and treatment with RRx-001 monotherapy Exploratory Objectives • To investigate: o Circulating Tumor Cells o Circulating Endothelial Cells (CEP and CEC) o Immune Subsets o Epigenetic markers e.g., Protein Hyperacetylation and gene methylation o Status of tumor suppressors such as p53, pre and post RRx-001 o Expression of TGF-beta and its receptor and fibrosis status pre and post dose of RRx-001. o Relative density of tumor associated macrophages in patient biopsies o Status of microRNAs (miRNAs) pre and post RRx-001. o To evaluate changes in a panel of tumor biomarkers. (i.e., CA-125 for ovarian cancer and chromogranin A and neuron specific enolase (NSE) for neuroendocrine tumors) o To evaluate the overall response rate (ORR), disease control rate (DCR) and PFS by immune response criteria in adult patients with advanced or metastatic SCC, NSCLC, EOC or HGNEC during RRx-001 treatment period
Number of Patients:	Approximately 135 (original study target), approximately **213 total** (updated as of Amendment 10) Amendment 10 enrolled subjects added: **Small Cell Carcinoma:** 2:1 randomization, 26 ARM 1, 13 ARM 2; **39 additional** **Ovarian:** 2:1 randomization, 26 for ARM 1, 13 for ARM 2; **39 additional patients** Total Study Enrollment Target with Amendment 10 expansion: 135 + 78 = **213 (approximately)**
Patient Population:	Inclusion Criteria 1. Patients must have histologically or cytologically confirmed advanced or metastatic: A. Resistant/Refractory Small Cell Carcinoma (SCC) patients in 3rd line or beyond that have previously received platinum or patients in 2nd line with platinum-refractory or platinum-resistant disease B. EGFR mutated non-small cell lung cancer (NSCLC) that has previously received a first line platinum doublet and all applicable EGFR TKIs C. Epithelial Ovarian Cancer (EOC), fallopian tube or primary peritoneal cancer and Malignant Mixed Mullerian Tumor (MMMT) of the ovary or uterus. Excludes other non-epithelial ovarian tumors and ovarian tumors with low malignant potential. Patients must have previously received a platinum based regimen for advanced/metastatic disease or have platinum resistant or refractory disease defined as relapse within 6 months. EOC – specific criteria: Patients who progress or have

stable disease during first-line treatment or who relapse within 1 month are considered to be 'platinum-refractory'. Patients who respond to primary treatment and relapse within 6 months are considered 'platinum-resistant', and patients who relapse more than 6 months after completion of initial therapy are characterized as 'platinum-sensitive'. Patients who relapse 6-12 months following the end of their initial regimen are classified as 'partially sensitive'.

D. High-Grade Neuroendocrine Carcinoma (HGNEC), any organ of origin, including a pathology of neuroendocrine features, in patients previously been treated with chemotherapy

i. Although neuroendocrine tumors may be classified differently based on organ of origin, in the context of this protocol they are defined as high grade on the basis of either

1. Aggressive clinical behavior requiring previous treatment with chemotherapy even if histologic features such as the Ki67 index or mitotic rate corresponds with low or intermediate grade.
2. Histologic features:
   a. Neuroendocrine tumors of lung origin are considered high grade if in any part of the tumors, there are >10 mitoses/2mm^2 or 10 high power field (HPF). Large zones of necrosis are usually present. This includes small cell lung carcinoma and large cell neuroendocrine lung carcinoma. [SCLC will not enroll in the HGNEC cohort.]
   b. Neuroendocrine tumors of gastroenteropancreatic origin are considered high grade if in any part of the tumors there are either >20 mitoses/2mm^2 or 10 high power field (HPF) OR Ki67.

2. Radiographically measurable disease by RECIST v1.1
3. A washout period of 3-weeks from last treatment (prior to Day 1 of study).
4. Patients must have previously received a platinum based regimen for advanced/metastatic disease and progressed or have platinum resistant or refractory disease defined as relapse within 6 months.
5. Age ≥18 years.
6. Life expectancy of ≥12 weeks.
7. ECOG performance status 0-2.
8. Participants must have adequate organ and marrow function as defined below both prior to administration of RRx-001 and prior to administration of platinum based regimen:
   A. Absolute neutrophil count ≥1,500/mcL
   B. Platelets ≥100,000/mcL (non-transfused platelet count)
   C. Hemoglobin ≥9 g/dL (transfused Hgb allowed)
   D. Creatinine ≤1.5 x the upper limit of normal
   E. Total bilirubin ≤2.0 x the upper limit of normal or ≤3.0 xULN if patient has a history of Gilbert's syndrome
   F. AST (SGOT)/ALT (SGPT) ≤5 X institutional upper limit of normal if with liver metastases; ≤2.5 X ULN if no liver metastases
9. Patient must consent to the access, review and analysis of previous medical and cancer history, including tumor archival tissue (if available) and imaging data by the sponsor or a third party nominated by the sponsor.
10. Ability to understand and sign a written informed consent document.
11. Women of child-bearing potential and men with partners of child-bearing potential must agree to use adequate contraception (hormonal or barrier method of birth control; abstinence) prior to study entry, for the duration of study participation, and for 90 days following completion of therapy.

	Note: A woman of child-bearing potential is any female (regardless of sexual orientation, having undergone a tubal ligation, or remaining celibate by choice) who meets the following criteria: • Has not undergone a hysterectomy or bilateral oophorectomy; or • Has not been postmenopausal for at least 12 consecutive months <u>Exclusion Criteria</u> 1. Receiving concurrent investigational therapy 2. Symptomatic central nervous system metastasis (e.g., patients requiring increasing doses of steroids) 3. History of needing to *permanently* discontinue prior platinum doublet-based regimen for toxicity (e.g., cisplatin causing renal impairment, ototoxicity, or severe neuropathy). 4. Known severe hypersensitivity to the platinum agent (i.e., carboplatin or cisplatin) or prior partner of platinum agent (i.e., etoposide for SCC and HGNEC; nab-paclitaxel, paclitaxel, or pemetrexed for NSCLC; paclitaxel, pegylated liposomal doxorubicin, docetaxel or gemcitabine for ovarian) planned for the platinum therapy period. If the patient has had prior hypersensitivity reaction to the drug partner of platinum, a patient may enroll as long as it is acceptable to treat with platinum and one of the alternative chemotherapy partner agents. 5. Any significant medical diseases or conditions, as assessed by the investigators and sponsor that would substantially increase the medical risks of participating in this study (i.e., uncontrolled diabetes, NYHA II-IV congestive heart failure, myocardial infarction within 6 months of study, severe chronic pulmonary disease or active uncontrolled infection, uncontrolled or clinically relevant pulmonary edema). 6. Pregnant or nursing
Statistical Analysis:	**<u>Primary Efficacy Endpoints</u>:** OS is defined as the time from enrollment to date of death, and its analysis will be similar to PFS in an intent-to-treat (ITT) population. The Kaplan-Meier estimate of the active cohort survival curve, its median survival times (with 95% confidence CI) will be derived. A hazard ratio will be estimated using the historical control (as a reference). The hazard ratio (HR) and its 95% CI will be calculated. Overall response rate (ORR) of re-introduced platinum therapy, which will be calculated as confirmed response (CR + PR). The treatment effect on ORR will be quantified using the odds ratio. Clopper-Pearson 2-sided 95% confidence limits will be calculated. ORR analyses will be performed for the Efficacy Evaluable population. Patients who do not have measurable disease at baseline will be excluded from the population. **<u>Secondary Efficacy Endpoints</u>:** The transition probability between disease progression and disease amelioration attributable to sensitization/resensitization will be estimated. A semi-Markov chain model will be used to capture the transition probability matrix between disease progression states. The average time each patient spends in a given disease state will be estimated (mean sojourn time) and its 95% confidence interval derived. The expected time spent healthy (or diseased) before death will also be estimated. The analysis of PFS will be similar to OS. Patients will be followed until their date of death, loss to follow-up, withdrawal of consent for further follow-up for survival, or final database closure. Patients who are lost-to-follow-up or are not known to have disease progression at the time of data-cut-off for analysis will be censored at last date shown to be alive. Patients who do not have any follow up since enrollment will be censored at the date of enrollment.

Rate of Grade 3 and Grade 4 non-hematologic toxicities for reintroduced platinum based chemotherapy. Disease control rate (DCR) defined as the sum of complete responses (CR) + partial responses (PR) + stable disease (SD) between topotecan and reintroduced platinum therapy, the rate of Grades 3 and 4 non-hematologic toxicities between topotecan and reintroduced platinum based chemotherapy will be analyzed in a manner similar to ORR.

Safety Variables: Safety data will include adverse events (AEs), serious adverse events (SAEs), ECOG performance status, clinical laboratory tests, vital signs and physical examination results. Safety summaries will be based on the Safety Population, and presented by treatment group using summary tables and listings. Adverse events will be coded by system organ class (SOC) and preferred term using MedDRA (Version 18.1), and severity will be based on NCI CTCAE Grade criterion (Version 5.0).

A Treatment Emergent Adverse Event (TEAE) is defined as an AE that was not present prior to treatment with study drug, but appeared following treatment or was present at treatment initiation, but worsened during treatment. Incidence of TEAEs by MedDRA SOC, preferred term and relationship (Related/Not Related) to study drug will be summarized based on the safety population. Adverse event incidence rates will be summarized using frequency and percentage. Adverse event data will be descriptively evaluated by treatment disease cohort and for overall patients.

Amendment 10 Statistical updates:

General design considerations, effective as of Amendment 10:

1. ***Small Cell Carcinoma:*** *Newly enrolled patients (post Amendment 10) will be allocated to one of two treatment arms using a 2-to-1 randomization ratio,(approximately 26 to Arm 1 and 13 to Arm 2).*

   *The **two treatment arms** are as follows:*

   Arm 1: RRx-001 weekly for 3 weeks followed by up to 4 cycles of platinum plus etoposide chemotherapy 'rechallenge' and then RRx-001 & platinum maintenance (for patients with stable disease (SD) or better at discontinuation of platinum rechallenge)

   Arm 2: Standard of Care Investigator's Choice Control Arm, treatment options of platinum plus etoposide, irinotecan or vinorelbine until progression or intolerable toxicity

2. ***Ovarian:*** *Newly enrolled patients (post Amendment 10) will be allocated to one of two treatment arms using a 2-to-1 randomization ratio (approximately 26 to Arm 1 and 13 to Arm 2).*

   *The **two treatment arms** are as follows:*

   Arm 1: RRx-001 weekly for 2 weeks followed by 2 cycles of carboplatin 'rechallenge' and then 'maintenance', cycling between 1 dose of RRx-001 followed by 2 cycles of carboplatin, which repeats until progression or intolerable toxicity

   Arm 2: Standard of Care Investigator's Choice Control Arm, treatment options of one of the following: carboplatin, etoposide, doxil, gemcitabine, vinorelbine or taxane treatments until progression or intolerable toxicity

3. ***Neuroendocrine****: The only modification with Amendment 09 forward to the existing treatment schedule is the addition of a RRx-001 maintenance for patients with ≥ SD following discontinuation of platinum based chemotherapy (for up to 6 cycles).*

4. ***NSCLC****: Patients enrolled post amendment 09 will receive 3 consecutive doses of RRx-001, after which, RRx-001 is discontinued and platinum based chemotherapy is started for up to 6 cycles. In addition, a RRx-001 maintenance for patients with ≥ SD following discontinuation of platinum based chemotherapy (for up to 6 cycles) was added.*

	Sample size determination and power considerations: *The extension stage of the study will approximately enroll 39 patients to the small cell carcinoma cohort and also 39 patients to the ovarian cohort. In each cohort, a 2-to-1 randomization allocation ratio will be employed (approximately 26 in Arm 1 and 13 in Arm 2, in each cohort). The proposed sample size modification is motivated by recent clinical observations arising from current study data results. This upward sample size adjustment should provide sufficient precision to derive estimates of responses and time-to-event endpoints. Inferential statistics are not the main focus of this newly proposed focus study extension.* ***Analysis of Activity Data:*** *Descriptive statistics arranged by treatment group (within each of the four cohorts) are planned. Graphical depiction of the statistical summaries (ORR, DCR, OS, PFS) will accompany the tabular formatted data results for a more complete presentation of the statistical findings. Specifically, Kaplan-Meier curves and estimation of time-to-event medians with their corresponding 95% confidence intervals will be produced. ORR and DCR responses will be derived and the Clopper-Pearson method will be used to derive the responses 95% confidence intervals.* *Standard safety data will include adverse events (AEs), serious adverse events (SAEs), ECOG performance scale, clinical laboratory tests, vital signs and physical examination results. Safety summaries will use the safety population and will be presented separately by treatment group (within cohort) and across all cohorts aggregated. All safety data will be presented in data listings.* *AEs will be coded by system organ class (SOC) and preferred term using MedDRA, version 14.1; severity will be based on NCI CTCAE Grade (version 5.0). Incidence of TEAEs by MedDRA SOC, preferred term and relationship (Related/Not Related) to study drug will be summarized based on the safety population. Adverse event incidence rates will be summarized using frequency and percentage. Adverse event data will be descriptively evaluated by treatment arm and for overall patients.*
Study Product(s), Dose, Route, Regimen:	RRx-001 Drug Product is supplied as a sterile solution in PEG-400. Prior to administration, Diluent for RRx-001, 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). 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 and re-infused into the patient once a week over an expected time period of less than an hour. The procedure is described in detail in the latest version of the 'Blood Administration Best Practices & Guidelines for IV Infusion of RRx-001 + Blood Mix' guide. All doses of RRx-001 will be administered on an open-label basis. Following treatment with RRx-001, one of the regimens referenced in the methodology section will be administered.
Duration of administration:	In the absence of treatment delays due to adverse events, RRx-001 treatment may continue as outlined in the assigned cohort schema or until disease progression, unacceptable toxicity or physician discretion. Per the standard of care, the platinum based therapy will be given for two cycles of therapy and, if tumor assessments show stable disease or a partial response, an additional two cycles of chemotherapy will be given.

3 BACKGROUND AND RATIONALE

3.1 Background

Lung cancer is the leading cause of death among men and women in North America (Jemal, 2009). An estimated 172,016 subjects have been diagnosed with non small cell lung cancer (NSCLC) in 2009 (Jemal, 2009). Of these subjects more than 55% will present with advanced stage disease (stage IV or stage IIIB) that is not amenable to curative treatment. Of the remaining 45% that are treated with curative intent only 20% of these will undergo surgery while the remaining will be treated with definitive chemoradiation. More than half of these subjects will relapse and eventually succumb to their disease.

1. EGFR$^+$ NSCLC: For EGFR-mutation-positive NSCLC patients who progress on tyrosine kinase inhibitors (TKIs), the most common cause (in 60% of patients) is a second site exon 20 EGFR mutation in the kinase domain of EGFR called T790M (the "gatekeeper" mutation), which prevents drug from binding to the receptor. Several mutant-selective TKIs, including rocelitinib and osimertinib, inhibit both activating mutations as well as the T790M gatekeeper resistance mutation, but do not target wild type (WT) EGFR. Preliminary clinical results from these agents indicate high response rates with long duration in T790M+ cases of acquired resistance. By contrast, the optimal treatment for patients with T790M negative resistance to EGFR TKIs remains unclear. Histologic and molecular investigations of tumor tissue obtained at progression have revealed multiple mechanisms of resistance. These include transformation to a small cell histology or epithelial-to-mesenchymal transformation; amplification of other receptor tyrosine kinases including MET, HER2 and WT EGFR; and point mutations in downstream genes including PIK3CA and BRAF. Thus, NSCLC patients who have failed treatment with TKIs and whose tumors do not express the T790M mutation represent a group with fatal disease and unmet need. (Yu, 2013)

   The current chemotherapy standard for subjects with advanced NSCLC is one of a number of platinum-based doublets; however, in the United States the most commonly used combination is solvent-based paclitaxel (sb-paclitaxel) plus carboplatin. The 130-nm albumin-bound formulation of paclitaxel (nab-paclitaxel [Abraxane]), which may reach the tumor microenvironment more efficiently than sb-paclitaxel, is indicated for the first-line treatment of locally advanced or metastatic non-small cell lung cancer, in combination with carboplatin, in subjects who are not candidates for curative surgery or radiation therapy (Desai, 2006). The median survival of all subjects with advanced NSCLC is 10-12 months (Carbone, 1995). The fraction of subjects who are alive one year after diagnosis has only increased slightly over the past decade (Carbone, 1995). Treating subjects with more than 4 cycles of the same chemotherapy, or adding a third chemotherapy agent to the platinum-based doublet has not improved overall survival (Carbone, 1995). Non-platinum-based regimens have been evaluated in several Phase II and Phase III clinical trials, showing similar survival rates to platinum based treatments (Rodriguez, 2000; Douillard, 2001; Kosmidis, 2002; Georgoulias, 2001, Alberola, 2003; Gridelli, 2003). The EORTC-08975 (Smit, 2003) randomized 483 subjects to three arms -- two cisplatin based regimens and one non-cisplatin based (paclitaxel/gemcitabine). The response rates were similar (27.7% to 36.6%) as was the median survival (between 6.7 months to 8.9 months), but progression free

survival was inferior in the non-platinum based regimen. Other studies have reported somewhat worse results with non-platinum combinations, therefore platinum is still considered a preferred agent for combination chemotherapy in fit subjects with advanced NSCLC.

Second line treatment for recurrent or progressive disease includes treatment with the chemotherapy agents docetaxel and pemetrexed, or treatment with an oral EGFR antagonist, erlotinib. Docetaxel was approved for second line treatment in 2000 after a randomized trial demonstrated that docetaxel at 75 mg/m^2 given every 3 weeks offered a clinically meaningful benefit to subjects with advanced NSCLC whose disease had relapsed or progressed after platinum-based chemotherapy with a response rate of approximately 7% (Fossella, 2000). Pemetrexed was approved for second line treatment based on a non-inferiority study as compared to docetaxel. Treatment with pemetrexed resulted in clinically equivalent efficacy outcomes, but with significantly fewer side effects compared with docetaxel in the second-line treatment of subjects with advanced NSCLC (Hanna, 2004). With these findings pemetrexed has now become increasingly used in the second line setting, and recent clinical trials have extended its use in first line setting for the treatment of subjects with non-squamous cell carcinoma NSCLC (Scagliotti, 2008). A Phase III trial compared pemetrexed/cisplatin to gemcitabine/cisplatin. This trial has demonstrated an improvement in overall survival over the combination cisplatin/gemcitabine in subjects with adenocarcinoma NSCLC (12.6 vs. 10.9 months) and in large cell NSCLC (10.4 vs. 6.7 months) (Scagliotti, 2008).

The decision to use pemetrexed depends on the histology of NSCLC. A recent review of two large pemetrexed based trials have concluded that although pemetrexed is well tolerated in squamous cell histology subjects, pemetrexed based regimens result in a shorter overall survival than non-pemetrexed based regimens in treatment of recurrent squamous cell NSCLC (Scagliotti, 2009). With pemetrexed being used with increased frequency in the first-line setting for adenocarcinoma and limiting the use of pemetrexed to non-squamous cell histology, the need to develop improved second line agents has become increasingly important. Currently, subjects with advanced NSCLC who have progressed after 2nd-line treatment have limited options. Nivolumab has recently received FDA approval for use in the 2nd line setting for subjects with metastatic squamous cell carcinoma who have progressed on or after platinum-based chemotherapy based on the results of a Phase II trial, and data from the Phase III CheckMate-017 trial.

Retrospective analysis using chemotherapy for 3rd line treatment show response rates of only 2% and median survival of 4 months (Massarelli, 2003).

Oral agents gefitinib and erlotinib are small molecule inhibitors of the EGFR tyrosine kinase activity, which have demonstrated clinical benefit after failure of first line chemotherapy (Fukuoka, 2003; Perez-Soler, 2004). Erlotinib was approved in 2004 for the treatment of subjects with locally advanced or metastatic NSCLC after the failure of one or two prior chemotherapy regimens with a single agent response rate of 8.3 % and a median overall survival of 6.3 months (Shepherd, 2005). To date it remains the only approved third line therapy for NSCLC.

2. SCLC: In contrast to the ferment and rapidly changing status of NSCLC, in which significant inroads have been made with targeted agents, the small cell lung cancer landscape has remained, like its name, disappointingly *small* and static. Small cell lung cancer (SCLC) accounts for about 13% (Govindan, 2006) of all lung cancers and is strongly correlated with a history of smoking. It is an aggressive subtype of lung cancer associated with rapid growth, early spread to distant sites, and distinct paraneoplastic syndromes (Kazarian, 2011), including hypercalcemia, Eaton-Lambert syndrome, and syndrome of inappropriate diuretic hormone, that is treated with chemotherapy alone in the metastatic setting. The most commonly used classification is the Veterans Administration Lung Study Group (VALG) staging system, in which the disease is subdivided into limited stage (LS) and extensive stage (ES) (Allen, 2008; Dowell, 2010; Drivsholm, 1999). Without treatment extensive stage small cell lung cancer (ES-SCLC), representing approximately two-thirds of all cases (LS-SCLC comprises the other one-third), is rapidly and invariably fatal within two to four months (Pelayo, 2009). With combination chemotherapy, the cornerstone of management (DeVore, 1996) in subjects without localized symptoms (i.e. superior vena cava syndrome, lobar obstruction, or painful bone metastases), responses are dramatic but sadly short-lived: SCLC inevitably relapses (Hann, 2009) and relapse is associated with a median OS often <6 months (Davies, 2004), a survival rate which has scarcely improved over the last 40 years (Shepherd, 2007).

   The current standard of first-line care for ES-SCLC is platinum based with a combination of cisplatin and etoposide (or cisplatin-irinotecan or cisplatin-topotecan) with or without concurrent radiation therapy, followed in general by topotecan, the sole agent with FDA approval specifically for the second line setting in platinum-sensitive disease and relapsed disease at least 45 days from the end of first-line chemotherapy. (Chan, 2013). A standard third line treatment is lacking although single agent paclitaxel, irinotecan, gemcitabine and vinorelbine are commonly tried in subjects with acceptable performance status. With relapse the prognosis is poor, with about a 20% to 30% response, and a median survival of weeks to months (Allen, 2008; Dowell, 2010; Drivsholm, 1999).

   In the case of resistant or refractory relapse classified as a progression free survival of greater <3 months or progression during treatment, rechallenge is not warranted whereas it is warranted with *sensitive* relapse classified as a progression free survival of greater >3 months (Ardizzoni, 2014) on the basis of a meta analysis by Garassino et al in which 30% of subjects experienced clinical benefit (i.e. stable disease + partial response) with rechallenge chemotherapy (Garassino, 2011).

   The ability to improve on these clinical benefit rates with an agent like RRx-001 that may predispose to successful platinum rechallenge represents a breakout opportunity to change the rules of the 'game' from a treatment paradigm of 'one (or hopefully more) and done' to 'if at first you succeed try and try again' thereby permanently altering a therapeutic landscape that for the last four decades has remained largely stagnant.

3. HGNEC: Unlike lung cancer, which is the second most common tumor type and the leading cause of cancer-related deaths among both men and women in the world (Abbasi, 2011), extrapulmonary high-grade neuroendocrine carcinomas (HGNECs) (Shia, 2008) are rare, aggressive tumors, with a poor prognosis, biologically similar to small cell lung cancer, that

most commonly develop in the gastrointestinal (GI) and the genitourinary (GU) tracts (Strosberg, 2010). Since cisplatin-based regimens, especially the cisplatin and etoposide regimen, are the most studied and widely used in metastatic small-cell lung cancer, they have also been investigated in metastatic NECAs of the GI tract. The first such study by Moertel et al reported a response rate of 67% with response duration of 8 months and a median survival of 19 months (Moertel, 1991).

A subsequent study reported a response rate of 42% with response duration of 9 months and a median survival of 15 months (Mitry, 1999).

On the basis of these clinical trials, the combination of cisplatin and etoposide is recommended as standard first-line therapy; carboplatin and irinotecan are offered as substitutes for cisplatin and etoposide, respectively. However, the optimal duration of chemotherapy is unknown and unclear, as is the question of whether to continue treatment beyond 4 cycles. While there is no data for a standard regimen in second line, retreatment with platinum and etoposide is an option especially if an initial response was seen and relapse occurred more than three months afterwards.

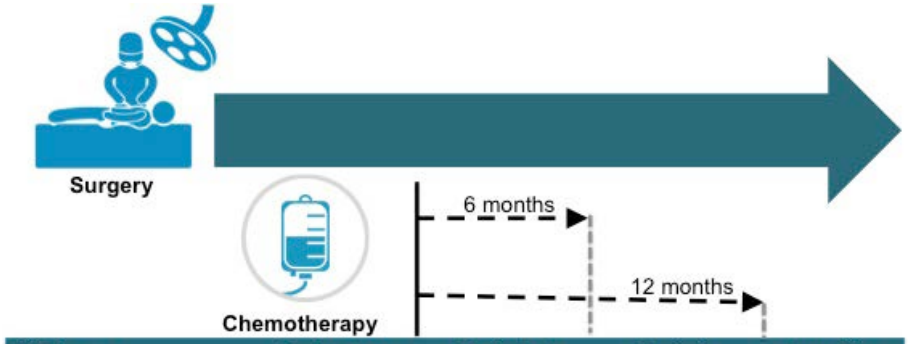
4. Gynecologic Cancers: Epithelial ovarian cancer or EOC (70% of all ovarian cancers with stromal and germ cell tumors comprising the rest) is the fifth most lethal gynecologic malignancy and the leading cause of cancer deaths in women in industrialized countries (Jemal, 2005). Since early ovarian cancer causes minimal to no symptoms, 75% of subjects present with advanced disease (stage III – IV), where the five-year survival rate falls below 25% (Rien, 2011). Malignant Mixed Mullerian Tumor (MMMT) of the ovary or uterus are dedifferentiated (metaplastic) epithelial tumors comprised of carcinomatous and sarcomatous elements arising from a single malignant clone. MMMT is also referred to as Carcinosarcoma and accounts for between 2 to 7.5 percent of ovarian carcinomas but is perhaps the most lethal of all subtypes (Seidman, 2003). These tumors tend to present in more advanced stages and are often large, necrotic and/or hemorrhagic. MMMT generally progresses rapidly and responds briefly to platinum-based chemotherapy, which portends a poor prognosis (Silasi, 2008), (Mano, 2007). Uterine MMMTs are generally excluded from endometrial clinical trials because of the belief that they are of dedifferentiated epithelial origin with a much more aggressive, sarcoma-like clinical behavior (Vaidya, 2006). For this reason, we are including them in this cohort with their more closely related ovarian MMMT cousins.

   Standard initial treatment involves tumor debulking and platinum-based chemotherapy with a taxane derivative to which the response is high (approximately 70%), however, 60–80% will relapse under two years with a platinum-resistant metastatic disease that is uniformly fatal (Gubbels, 2010). The Gynecologic Oncology Group (GOG) adopted the definition of sensitivity to chemotherapy (or sensitivity to platinum) in EOC based on the interval between the last dose of platinum and the development of resistance (Harter 2006) (Figure 1).
   In general, progression or stable disease during first-line treatment or relapse within 1 month is characterized as 'platinum-refractory'. Subjects who respond to primary treatment and relapse within 6 months are considered 'platinum-resistant', and subjects who relapse more than 6 months after completion of initial therapy are characterized as 'platinum-sensitive'. The longer the platinum free interval (PFI) the better the chances for benefit with platinum

re-challenge. This is especially the case for PFI longer than 12 months. Subjects that relapse 6-12 months after the end of their initial regimen, and who are usually classified as so-called 'partially sensitive', tend to be less responsive (Pisano, 2009).

Figure 1: Platinum resistance definition by Gynecologic Oncology Group (GOG)

Platinum sensitivity is classified as resistant, partially sensitive, or sensitive, according to the time elapsed since finishing first-line treatment. Probability of re-treatment response is shown.



Platinum sensitivity classification	Refractory	Resistant	Partially sensitive	Sensitive
Probability of second platinum response	0%	<10%	30%	>50%

In the setting of platinum resistant disease, a poor prognosis population with an OS <12 months, no universal standard for treatment exists; single agent therapy with paclitaxel, topotecan, pegylated liposomal doxorubicin (PLD) and gemcitabine is generally recommended in second line based on some evidence of activity in Phase III trials, with overall response rates <15% and a median PFS of 3–4 months. (Gordon, 2004; Markman, 2006) In contrast with platin-sensitive recurrences, combination chemotherapy has been shown to increase toxicity without benefit (Ledermann, 2013). The possible exception is bevacizumab, which in the 2012 AURELIA trial, significantly improved the PFS in combination with an investigator's choice of pegylated liposomal doxorubicin, weekly paclitaxel, or topotecan but not the overall survival. (Pujade-Lauraine, 2014).

RRx-001 is a small molecule administered by i.v. that selectively and with great affinity binds to hemoglobin and free sulfhydryl groups such as reduced glutathione present in red blood cells. RRx-001 modified, oxidatively stressed red blood cells exhibit conformational and biochemical alterations under hypoxia, which collectively may lead to adhesion to the tumor vascular endothelium, entrapment in the microvasculature, and engulfment by tumor associated macrophages (TAMs), which undergo M2 to M1 polarization. Preclinical and Phase 1 data suggests that RRx-001 altered DNA methylation of genes and cancer pathways restores sensitivity to previously failed therapies resulting in a prolonged overall survival. On this basis, reintroduction of platinum doublet-based therapies is mandated on progression. In addition, immunohistochemistry of tumor biopsies from subjects on the QUADRUPLE THREAT trial

have revealed an influx of CD8 expressing tumor-infiltrating lymphocytes, confirming that RRx-001 has immunotherapeutic properties (Brzezniak, 2016).

Before co-infusion with blood, the primary adverse event related to RRx-001 was pain during infusion that manifested together with local venodilation (Reid, 2015), presumably due to the displacement of nitric oxide (NO) from its binding site on the beta Cys 93 residue on hemoglobin. This infusional pain that was subject to considerable inter-subject variability resolved within seconds to minutes after administration was stopped. In the same way that capsaicin evokes a sensation of burning without producing tissue damage, RRx-001, likely through the intermediary of nitric oxide, a well-known algetic stimulus on intravascular application in humans, activated nociceptors in the venous endothelium to produce pain.

Subjects enrolled and treated on the QUADRUPLE THREAT study with RRx-001 blood mix has been well tolerated without any significant drug related toxicity reported.

RRx-001 has demonstrated the capacity to reverse resistance to first and second line chemotherapy in selected subjects treated on the Phase I trial (Reid, 2014). Reintroduction of first-line platinum doublet-based therapies after treatment with RRx-001, therefore, potentially represents an important and highly desirable strategy to improve clinical outcomes and prolong survival by significantly impacting the natural histories of SCC, NSCLC, ovarian and HGNEC.

3.2 RRx-001 as a Tumor-Associated Macrophage Targeting Agent with Tumor Sensitizing Properties

RRx-001 (previously known as ABDNAZ) is a TAM-targeting agent with epigenetic and tumor-sensitizing properties that has been investigated in a completed Phase I study at UCSD and Sarah Cannon Research Institute (SCRI) (Reid, 2015) and an ongoing randomized Phase 2 study vs. regorafenib in 3rd and 4th line colorectal cancer.

3.3 Clinical Experience with RRx-001

To date, RRx-001 has been studied in a single Phase 1 clinical trial (Protocol RRx001-11-01, Reid, 2015). 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.

The open-label, Phase I dose-escalating clinical trial in heavily pretreated subjects with refractory metastatic solid tumors investigated the safety and tolerability of RRx-001 when administered as monotherapy. Key inclusion criteria were histologically proven solid tumor for which no satisfactory therapy was available or had failed, adequate organ and hematologic function, ECOG performance status of ≤2 and life expectancy of at least 3 months. Key exclusion criteria included previous cancer therapy within 42 days of baseline visit. 26 subjects were enrolled and 25 subjects were treated. The treatment was continued until disease progression, intolerable toxicity, or subject withdrawal of consent.

RRx-001 was tolerated at all doses from 10-83 mg/m^2 i.v. and a maximum tolerated dose was not reached. Twenty-five subjects received the study drug and are therefore considered evaluable for analysis of safety. All 25 subjects experienced at least one adverse event. Events considered definitely related to protocol therapy were reported in 23 of 25 subjects (92%). Inflammation and/or burning along the course of the injected vein were the most common AEs. Two events of Grade 3, infusion site pain and anxiety related to infusion site pain, were reasonably possible or definitely related to study drug in the opinion of the Investigator. Three subjects experienced adverse events or other problems leading to premature termination from the study and before an assessment of activity could be determined. Subject 001-002 withdrew consent due to infusion site reaction, 002-005 died on study due an SAE arising from a preexisting infection and 002-014 withdrew due to an AE (bowel obstruction) that was considered to be unlikely related to RRx-001 administration. In one subject, Grade 3 anxiety was observed associated with the localized pain on infusion. However, this event was not considered dose limiting, as it was transitory, and promptly disappeared after the infusion was discontinued. Other Grade 1 to Grade 2 related toxicities included infusion site tenderness, vein hardening, vein occlusion, skin discoloration over the site of injection, chest discomfort, cough, dyspnea and mouth tingling but the relative contributions of RRx-001 and malignant disease in the etiology of these toxicities is not known.

No specific laboratory abnormalities were attributed RRx-001; any abnormalities appeared to be more indicative of the underlying systemic disease rather than RRx-001. No RRx-001 related adverse effects on the major physiological systems (cardiovascular, respiratory, hepatic, renal and central nervous systems) occurred in any subject.

In contrast to standard IV administration, which is lengthy (up to 6 hours), time consuming and acutely painful, the RRx-001 blood mix is rapidly administered in under an hour and painless; hence the reason that all of the RRx-001 protocols have been converted to this method of administration.

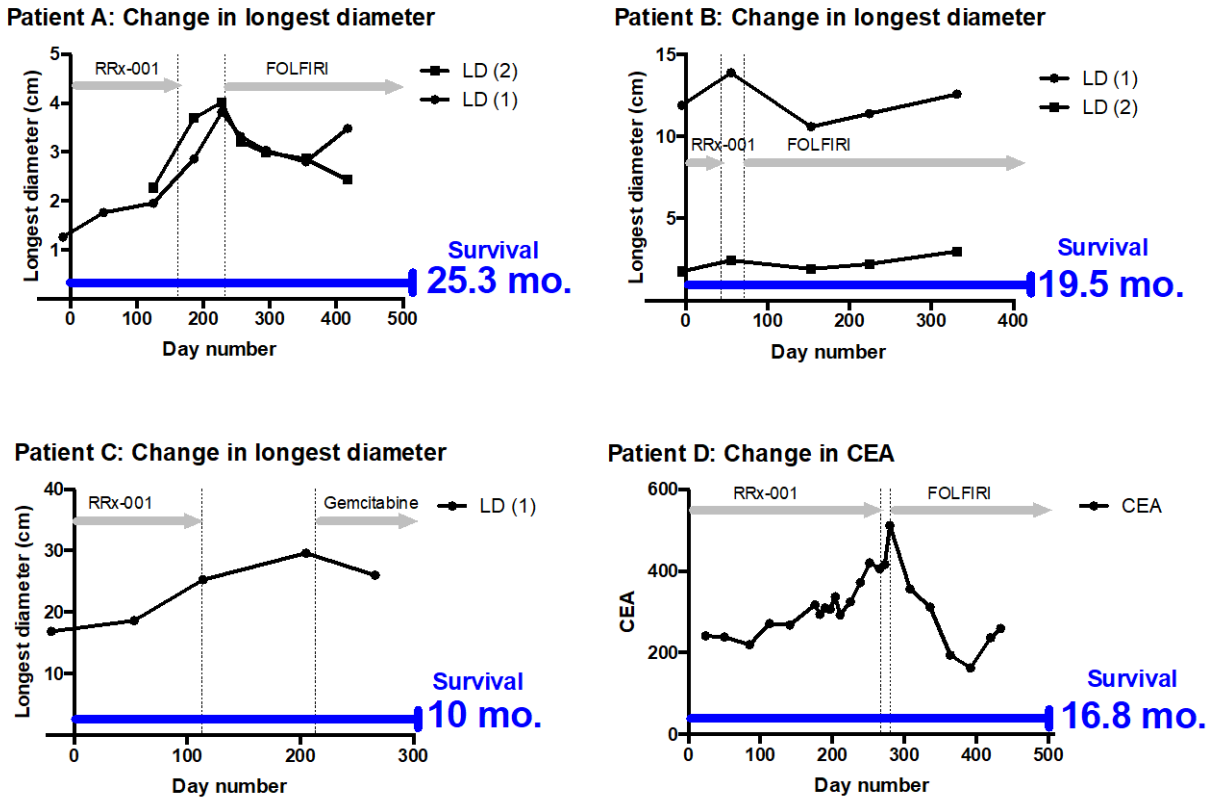
Solutions of RRx-001 for Injection were previously tested for hemolytic potential:

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 the Phase I study, antineoplastic activity was detected in several solid tumor types: non-small cell lung cancer, colorectal cancer, ovarian cancer, hepatocellular cancer, pancreatic cancer and head and neck cancer. One objective partial response was observed. There was no obvious

correlation between the antitumor activity and the dose level. After single agent therapy with RRx-001, four subjects became responsive to previously failed FOLFIRI, as shown by changes in CEA and by imaging.



A further three subjects appeared to respond favorably to subsequent chemotherapy and radiation post RRx-001.

3.3.1 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 1). 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 1: 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) bilrubinemia; 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 when administering by direct IV infusion.*

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. 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.

In summary, other than localized venous dilation and pain on infusion, RRx-001 was very well tolerated. 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.

3.3.2 Pharmacokinetics

As part of the Phase I protocol, the pharmacokinetics of RRx-001 was investigated. PK samples were taken at Day 1 and Day 50 within 15 min predose, 15 min after the start of the infusion, at the end of the infusion (0±1 min) then at 15±2 and 30±5 min after the end of infusion followed by 1, 2, 3, 4.5, 6 and 24 hours ±5 min post infusion. The 24 hour sample was taken for Day 1

only. As part of change in cycle duration from 4 weeks to 2 weeks in Amendment 1.3, Day 50 samples were redefined as Day 22 and the requirement for a 6 h sample on Day 22 was removed. Based on the available data, in Amendment 1.4, the Day 1 the 4.5 and 6 h as well as the Day 22 samples were removed.

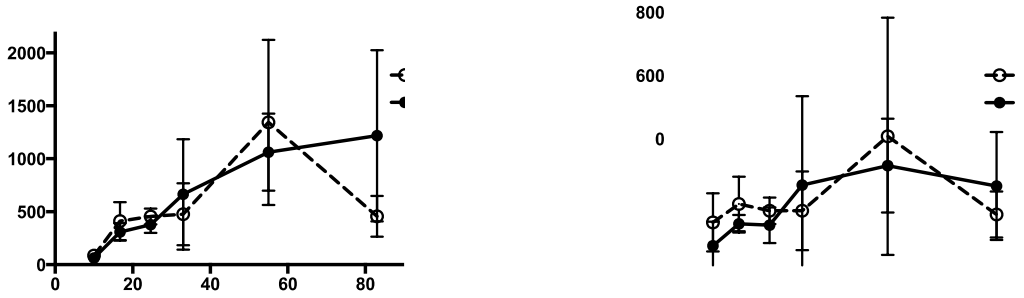
The following parameters were calculated for each subject: Cmax, AUCinf, and half-life and is shown in Table 2. Half-life did not vary greatly across dose levels or between Day 1 and Day 22/50 samples and was found to be 0.46 h. The calculated average Cmax and AUCinf for both Day 1 and Day 22/50 for each cohort, was found to be dose dependent with the exception of the highest dose cohort. Figure 2 shows the plots of average AUCinf (left) and Cmax (right) for Day 1 and Day 22/50 against dose. These data suggest that analysis of RRx-001-GSH is indicative of exposure to RRx-001 for the range 10 to 55 mg/m^2. However, the pharmacokinetics of RRx-001-GSH do not correlate well with the pharmacodynamics of RRx-001. Accordingly no justification for dosing decisions based upon PK information of the glutathione adduct can be made.

Table 2: Pharmacokinetic Properties for RRx-001-GSH vs Dose. Values are shown ± SD

Dose	AvgCmax (D1) (ng/mL)	AvgCmax (D22/50) (ng/mL)	AvgAUCinf (D1) (ng*hr/mL)	AvgAUCinf (D22/50) (ng*hr/mL)	AvgHL (D1) (h)	AvgHL (D22/50) (h)
10	136.46 ± 92	62.7 ± 76	88.0 ± 29	63.2 ± 43	0.38 ± 0.20	0.37 ± 0.17
16.7	194.6 ± 86	132.0 ± 28	411.6 ± 180	309.6 ± 81	0.42 ± 0.16	0.56 ± 0.26
24.6	173.0 ± 42	127.2 ± 56	455.1 ± 75	378.5 ± 79	0.47 ± 0.07	0.51 ± 0.20
33	172.8 ± 124	254.0 ± 281	477.0 ± 292	664.1 ± 522	0.47 ± 0.22	0.44 ± 0.17
55	408.0 ± 375	315.3 ± 148	1343.8 ± 779	1063.1 ± 364	0.42 ± 0.06	0.42 ± 0.13
83	161.3 ± 73	251.1 ± 170	457.4 ± 192	1217.5 ± 808	0.60 ± 0.10	0.45 ± 0.06
Average					**0.46**	**0.46**

Abbreviations: AvgCmax: Max. concentration, averaged over cohort; AvgAUCinf: Area under the plasma concentration-time curve from time zero to infinity, averaged over cohort; AvgHL: Half-life, averaged over cohort.

Figure 2: Left: Plot of AvgAUCinf for Day 1 and Day 22/50 against dose. Right: Plot of AvgCmax for Day 1 and Day 22/50 against dose.



An overview of relevant nonclinical information is presented below.

3.3.3 Preclinical Studies of RRx-001

RRx-001 is a *de-energized* analog of the explosive, TNAZ, the widely-used replacement for TNT, with a closed strained ring structural backbone called a dinitroazetidine, developed as an anticancer agent.

Preclinical and clinical studies support the rationale for the clinical development of RRx-001 in the setting of metastatic refractory cancer both as monotherapy and in combination with standard cytotoxic chemotherapy.

RRx-001 is a nitrogen oxide donor. In hamsters infused with RRx-001 through a central vein at a dose of 5 mg/kg vs. hamsters infused with saline as vehicle controls, significantly increased levels of exhaled nitric oxide in breath condensate were measured in the treated cohort during the infusion; these levels returned rapidly to baseline almost immediately after cessation of the infusion.

With infusion into the antecubital veins, the nitric oxide dissipation effect during infusion is clearly visible as a network of dilated, palpable superficial veins that travel up the forearm proximally in the clinical trial subjects, confined to and persisting only for a distance of 8-10 inches from the site of infusion. The discomfort of the infusion in the forearm varied greatly from subject to subject and did not appear to correspond to the amount of visible dilation.

The anticancer mechanism of action is related to modification of the intracellular milieu of the red blood cell and repolarization of tumor associated macrophages. RRx-001 covalently binds to the beta Cysteine 93 residue on hemoglobin, which significantly upregulates the nitrite reductase activity of hemoglobin, catalyzing the conversion of the endogenous anion nitrite to nitric oxide under hypoxic conditions. This overproduction of NO under hypoxic conditions oxidizes the red blood cell, leading to the expression of phosphatidylserine (PS) and vascular cell adhesion molecules at the RBC surface. RBC adhesion to the tumor endothelial cells sequestrates the RBCs and occludes the tumor microvasculature. Macrophages, which engulf and degrade the adherent and PS-expressing RRx-001 RBCs, extravasate into the extravascular stroma

(Figure 3), as demonstrated by the intracellular lipid accumulation and, consequently, foam cell formation or vacuolation seen on tumor biopsies (Figure 4). Engulfment of the RBCs induces TAM repolarization to antitumor M1 macrophages that secrete proinflammatory cytokines and produce free radicals (Figure **5**). The secreted cytokines recruit more immune cells and the increased production of reactive oxygen and nitrogen species inhibit activity of the hypomethylating enzyme DNMT1 involved in epigenetic processes.

Figure 3: Adhesion of RRx-001-Modified Red Blood Cells (Blue Arrows) to the Tumor Vasculature Leading to Vaso-Occlusion. The Orange Arrows Indicate Presence of the RBCs in the Tumor Parenchyma.

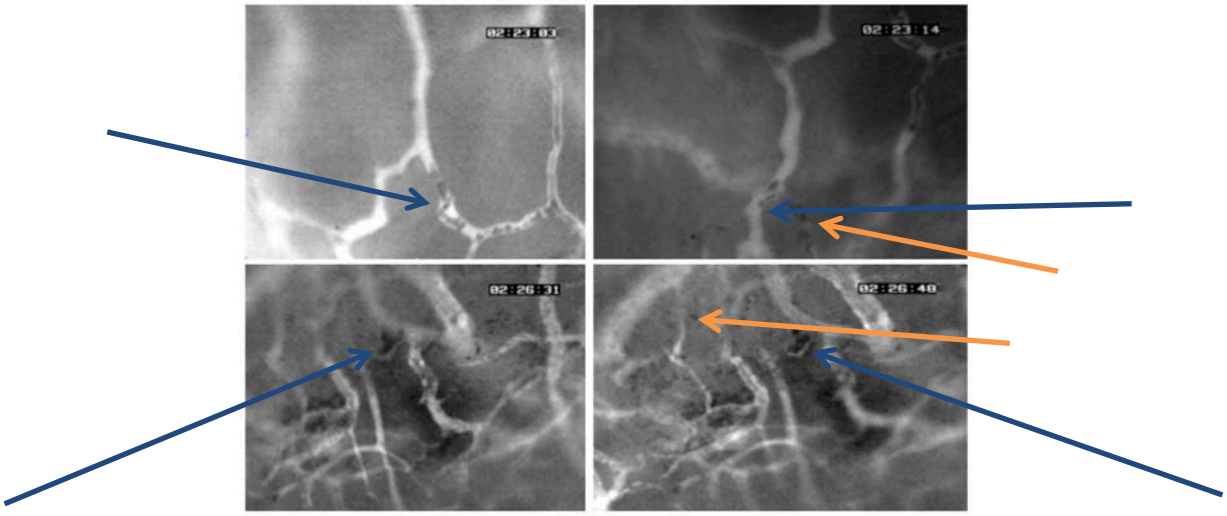


Figure 4: Appearance of Vacuolation (Foamy Cell Changes) (Orange Arrows) Seen Over Time in Serial Biopsies of the Tumor an RRx-001-Treated Patient on QUADRUPLE THREAT

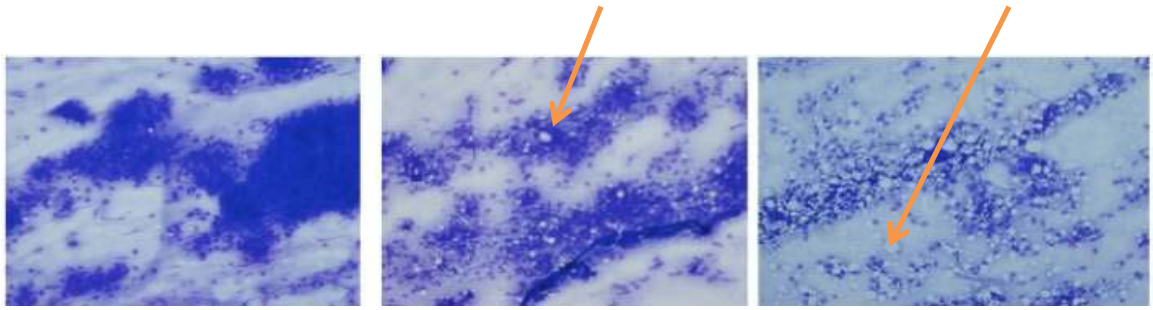


Figure 5: ***In Vivo*** **Experiment Demonstrating RRx-001-Induced Polarization of Tumor Associated Macrophages**

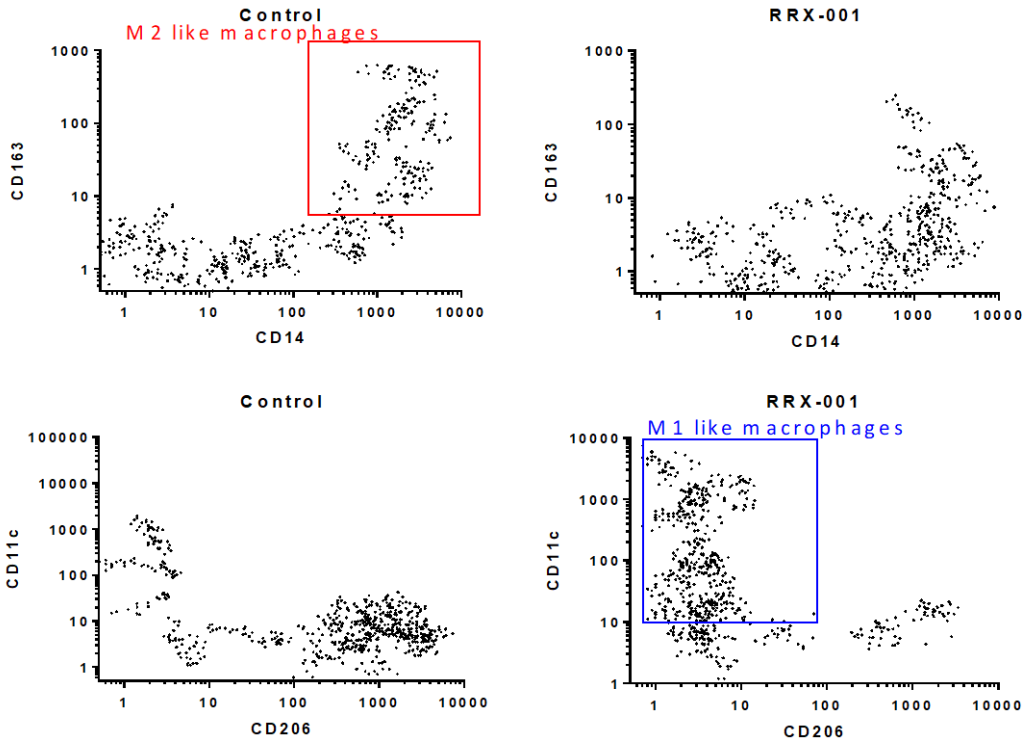
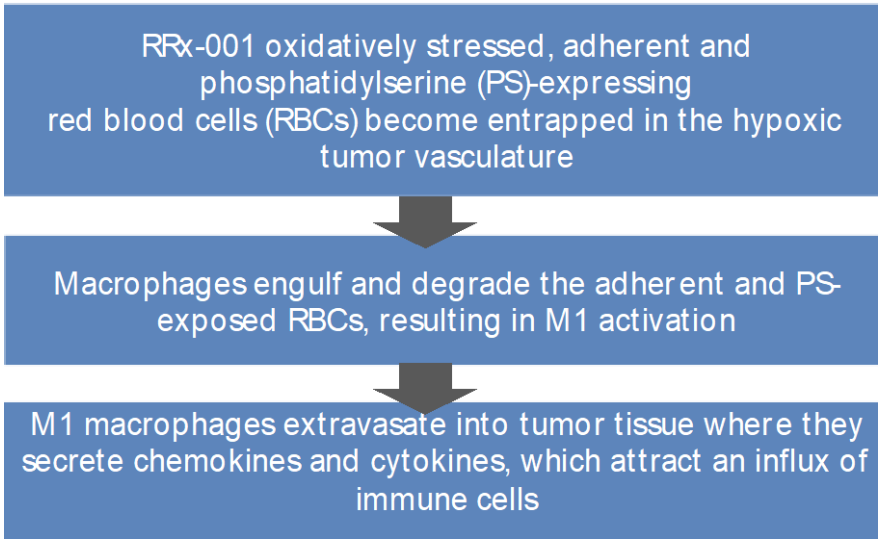


Figure 6: **Three Step Macrophage-Mediated Anti-Tumor Mechanism of Action**



3.3.4 Preclinical Studies of RRx-001 (continued): Chemoprotection with Cisplatin

The chemoprotective effect of RRx-001 was studied on cisplatin-induced nephro-, myelo- and genotoxicity in BALB/c mice. The mice were divided into three groups: (1) no treatment, (2) vehicle and cisplatin only, and (3) RRx-001 and cisplatin. RRx-001 treatment (5 mg/kg every other day for three days) was initiated 3 days prior to cisplatin administration. Renal dysfunction was evaluated biochemically by measuring the concentration of blood urea nitrogen (BUN) and serum creatinine. Genotoxicity was evaluated by metaphase spreads from whole bone marrow cells. Myelotoxicity was evaluated with measurement of serum hemoglobin, leukocyte and platelet concentrations.

Cisplatin significantly elevated the levels of blood urea nitrogen, serum creatinine, and the kidney to body weight ratio, but pretreatment with RRx-001 significantly attenuated the cisplatin-induced nephrotoxicity. After administration of cisplatin, the frequency of chromosomal abnormalities distinctly increased. However, in mice pretreated with RRx-001, Consistent improvement in chromosome spreading with lower frequencies of broken metaphases was obtained in RRx-001-pretreated mice compared with mice injected with only cisplatin, as seen in the figure below.

Figure 7: Preclinical Evidence of Chemoprotection. RRx-001 Treated Mice Prior to Treatment with Cisplatin

The red arrows mark gaps, breaks, or rearrangements in metaphase chromosomes.

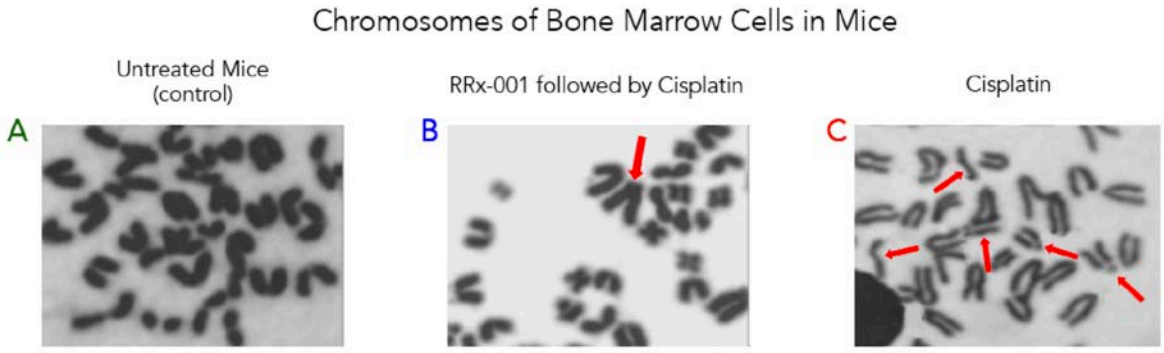
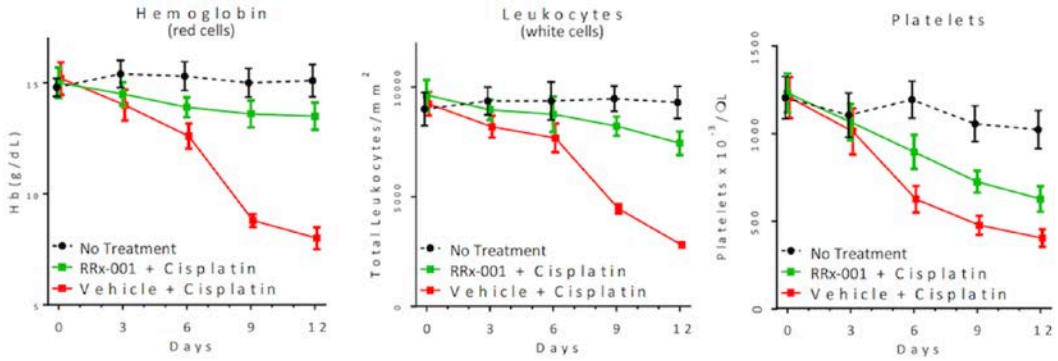


Figure 8: Hemoglobin Concentration, Platelets, and WBC Counts Significantly Reduced in Mice Pretreated with RRx-001



As a consequence of damage to the bone marrow, production of red cells, white cells, and platelets is affected by Cisplatin (red line). Pre-treatment with RRx-001 attenuates or reduces the decline in platelets, red cells and white cells (green line), which indicates partial bone marrow protection. The black dotted line illustrates no treatment.

The results suggest that RRx-001 has a protective effect against cisplatin-induced nephro-, myelo- and genotoxicity.

3.4 Rationale

Survival of SCC, NSCLC, resistant/refractory EOC/MMMT and HGNEC cancer subjects remains poor, and new effective and well-tolerated therapeutics for chemorefractory subjects are urgently needed. We propose a Phase 2 study of RRx-001 administered at a dose of 4 mg once weekly in SCC, NSCLC, EOC/MMMT and HGNEC subjects until progression followed by re-administration of a platinum based regimen specific to the four tumor types outlined in the methodology section. To be eligible for this trial, subjects must have received platinum doublet therapy as standard therapy for advanced disease and now have progressive disease.

This study design is based upon clinical experience of subjects who were treated with RRx-001 monotherapy in the phase I setting, followed by the off-trial re-treatment with therapies that they may have previously failed. Two subjects, both with colorectal cancer (CRC), were noted to have responses both in tumor burden and CEA upon re-challenge with FOLFIRI, which they had each previously failed. The first subject had a 7-month duration of response. The second subject was restarted on FOLFIRI in 7/2013 and responded to this therapy (Reid, 2014). Two additional subjects, one with colorectal cancer (CRC) and one with lung cancer, both achieved prolonged stable responses after treatment with RRx-001 and re-challenge with a previously failed therapy: sorafenib and gemcitabine, respectively.

Early data analysis in the QUADRUPLE THREAT trial demonstrated 8/13 (61%) of patients had been newly sensitized to platinum doublets, indicative of reversal of chemoresistance. Given the limited choices of subjects with advanced thoracic malignancies, this reversal of resistance, which in theory 'primes' tumors to respond subsequent chemotherapy may allow previous responders to derive benefit from retreatment of the same chemotherapy after previous exposure to RRx-001. In addition, immunohistochemical staining of HC of tumor biopsies from two subjects on the TRIPLE THREAT trial revealed the infiltration of cytotoxic $CD3^+$ $CD8^+$ lymphocytes.

4 STUDY OBJECTIVES

4.1 Primary Objectives

To evaluate Overall Survival and Overall Response Rate

4.2 Secondary Objectives

1. To estimate the transition probability between disease progression and disease amelioration attributable to resensitization.
2. To estimate the mean sojourn time in a platinum sensitized state
3. To evaluate disease control rate (DCR), and PFS/MMMT.
4. To evaluate the toxicity of platinum-based therapy following prior exposure to these agents and treatment with RRx-001 monotherapy.
5. To evaluate changes in a panel of tumor biomarkers. (i.e., CA-125 for ovarian cancer and chromogranin A and neuron specific enolase (NSE) for neuroendocrine tumors)

4.3 Exploratory Objectives

To investigate:

- Circulating Tumor Cells
- Circulating Endothelial Cells (CEP and CEC)
- Immune Subsets
- Epigenetic markers e.g., Protein Hyperacetylation and gene methylation
- Status of tumor suppressors such as p53, pre and post RRx-001
- Expression of TGF-beta and its receptor and fibrosis status pre and post dose
- Relative density of tumor associated macrophages in patient biopsies
- Status of microRNAs (miRNAs) pre and post RRx-001

4.4 Endpoints

4.4.1 Primary Endpoints

1. **Overall Survival (OS):** the time from enrollment until the time of death from any cause or last follow-up. Patients will be followed clinically as outlined in the treatment schedule and will be followed off study for death.
2. **Overall Response Rate (ORR):** The proportion of patients who achieve a reduction in the sum of target lesions by 30% following the re-administration of chemotherapy. Radiographic assessment of disease burden will be evaluated by CT and disease RR will be documented using RECIST v1.1.

4.4.2 Secondary Endpoints

1. **Disease Control Rates (DCR):** The percentage of patients who have achieved complete response, partial response and stable disease (as per RECIST v1.1).
2. **Progression free survival (PFS):** the time from enrollment to the time of the first radiographic documentation of objective progression as defined by RECIST v1.1 or death from any cause.
3. **Toxicity:** Rate of Grade 3 and Grade 4 hematologic and non-hematologic toxicities of reintroduced platinum based chemotherapy.
4. The transition probability between disease progression and disease amelioration attributable to sensitization/resensitization and the mean sojourn time.

4.4.3 Exploratory Endpoints

1. **Circulating Tumor Cells:**
   Peripheral blood will be collected to correlate changes in circulating tumor cells with clinical response. CTCs will be assessed using ferrofluidic enrichment and multi-parameter flow cytometric detection. CTCs are identified by positive expression of epithelial markers and a viability marker and negative expression of hematopoietic markers.
2. **Circulating Endothelial Cells (CEP and CEC):**
   Circulating endothelial progenitor cells (CEP) and mature circulating endothelial cells (CEC) will be assessed by multiparameter flow cytometry. Cells will be analyzed for forward and side scatter, and cells expressing hematopoietic markers will be excluded. Endothelial cells will be identified using co-expression of markers, such as CD31 and CD146 for CEC, and CD31 and CD133 for CEP. The cell populations will also be analyzed for viability using scatter profiles and a vital stain, such as Hoechst 33258. Percentages of stained cells will be determined and compared with appropriate negative controls. Multi-parameter flow analysis will be performed with a Miltenyi Quant equipped with FlowJo software, using a minimum of 500,000 events per analysis.
3. **Immune Subsets:**
   The immune infiltrate will be analyzed in tumor biopsies obtained pre- and post-therapy. The tissue will be dissociated into single cells and assessed by multiparameter flow cytometry for immune subsets. The immune populations analyzed will be dependent on the number and viability of infiltrating immune cells. Subsets analyzed may include regulatory T cells (Tregs), myeloid-derived suppressor cells (MDSC), effector and exhausted CD8+ T-cells, and type II polarized macrophages (TAMs). As sample permits, assessment will include functional markers, i.e., PD-1, PD-L1, Tim-3, CTLA-4 and CD40. Peripheral blood mononuclear cells (PBMC) will be assessed using multiparameter flow cytometry for immune subsets including but not necessarily limited to Tregs, MDSC, effector and exhausted CD8+ T-cells. Assessment will include functional markers, i.e., PD-1, Tim-3, CTLA-4 and/or CD40.

4. **Epigenetic markers e.g., Protein Hyperacetylation and gene methylation:**
   Protein hyperacetylation pre- and post-therapy will be assessed in peripheral blood mononuclear cells (PBMC) using multiparameter flow cytometry. Gene acetylation and methylation will be carried out by PCR and IHC techniques. The impact of RRx-001 on the epigenetic status of genes that are closely correlated to resistance to platinum therapy will be studied.
5. **Status of tumor suppressors such as p53, pre and post RRx-001:**
   Expression and mutational status of tumor suppressors such as p53, p21 will be studied by PCR and IHC techniques to see if silenced genes can be reactivated.
6. **TGF-beta and its receptor and fibrosis status:**
   Radiotherapy has been shown to induce increased expression of both TGF-beta and its receptor, which is associated with an increase in fibrosis. Due to the pro-oxidant effect of RRx-001 in tumors, it is hypothesized that a similar effect may occur with RRx-001. Pre and post biopsy samples will be used to investigate this effect.
7. **MicroRNAs (miRNAs) relating to gene expression:**
   MicroRNAs (miRNAs) are short noncoding RNAs that influence gene expression. Increased miRNA levels downregulate genes; conversely, decreased miRNA levels may result in upregulated genes. RRx-001 has been shown to decrease a specific set of miRNAs in the tumor that result in upregulation of type III hypersensitivity genes. Profiling of these perturbed miRNAs in the context of RRx-001 treatment may help to predict drug responses. The PAXgene blood tubes are provided to isolate miRNA and total RNA for analysis.
8. **The relative macrophage density:**
   TAMs will be immunohistochemically labeled using a monoclonal (CD68) antibody in biopsy specimens from patients. CD68-positive cells will be counted with the aid of a microscope and expressed as TAMs/mm^2. TAMs will be quantified by systematically screening the entire cancer area and by counting at the hot spot in a cancer area where macrophages accumulated at highest density in the specimens. The densities of these cells will scored as +, low; ++, moderate; and +++, high.

5 STUDY DESIGN

5.1 Description of the Study

The study is designed to explore the potential tumor associated macrophage (TAM)-targeting agent RRx-001 to sensitize patients who previously received and now have failed a platinum based regimen.

RRx-001 is administered with autologous blood once weekly followed by or in combination with reintroduction of platinum-based therapy according to the treatment schedule illustrated in Section 1.1 Treatment Schemas [SCC, EOC, NET, NSCLC]).

As of Amendment 10, an investigator's choice control arm has been added to small cell carcinoma and ovarian enrolled patients, randomized 2:1 to 1 of 2 Arms. The investigational ARM 1 will enroll an additional 26 patients, with the 'investigators choice' control arm enrolling 13 patients total, per patient group.

In addition, in neuroendocrine and NSCLC cohorts, after up to 6 cycles of the reintroduced platinum doublet, patients with stable disease or better (≥SD) start on maintenance RRx-001 administered weekly (QW) until progression.

5.1.1 Toxicity

Toxicity will be graded according to the National Cancer Institute (NCI) Common Toxicity Criteria for Adverse Events (CTCAE) version 5.0.

Serious and unexpected toxicity is defined as ANY Grade 3 or higher toxicity considered by the investigator to be possibly, probably or definitely related to the study drug, RRx-001, or to its potentiation of protocol defined therapy toxicity, occurring after the initial dose of RRx-001 until up to 30 days after discontinuation of protocol defined therapy. The following exceptions are not considered serious and unexpected toxicity related to RRx-001 or protocol defined therapy:

- Grade 3 or 4 anemia, or neutropenia that resolve to ≤Grade 2 within 10 days. Patients should have repeat labs within 10 days to document resolution.
- Grade 3 or 4 thrombocytopenia without clinically significant bleeding that resolves to ≤Grade 2 within 10 days. Patients should have repeat labs within 10 days to document resolution.
- Grade 3 or 4 leukopenia/lymphopenia without clinically significant consequences (i.e., infection).
- Grade 3 nausea, vomiting or diarrhea with maximal medical support that resolves to ≤Grade 2 within 72 hours.

If 5 patients develop serious and unexpected toxicity in a particular RRx-001 cohort, which is thought to be directly or indirectly related to RRx-001, then enrollment in that particular cohort will stop. Management and dosing modifications are outlined in Section 6.2.6.

5.2 Administrative Structure

This trial is performed under the IND of EpicentRx, Inc.

The Principal Investigator is responsible for the conduct of the clinical trial at the site in accordance with Title 21 of the Code of Federal Regulations and/or the Declaration of Helsinki. The Principal Investigator is responsible for personally overseeing the treatment of all study patients and assuring that all study site personnel adhere to the study protocol and all FDA/GCP/NCI regulations and guidelines regarding clinical trials both during and after study completion.

5.3 Compliance with Laws and Regulations

This study will be conducted according with FDA regulations, the International Conference on Harmonization (ICH) E6 Guideline for Good Clinical Practice (GCP), and applicable local, state, and federal laws.

6 MATERIALS AND METHODS

6.1 Study Population

Patients must meet all of the Inclusion Criteria to participate in this study.

Patients meeting any of the Exclusion Criteria at baseline will be excluded from study participation.

6.2 Study Treatment

Study treatment refers to both RRx-001 and the chosen protocol defined therapy.

6.2.1 RRx-001 Formulation

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). Please refer to pharmacy manual for drug storage conditions and drug preparation instructions.

RRx-001 is not light sensitive. The product should be used soon after dilution. RRx-001 solutions diluted with saline are not stable and saline should not be used. The osmolality of the 2.0 mg/mL dosing solution was determined to be 614 mOsm/kg.

The study product is stored in a secured site with restricted access.

6.2.2 RRx-001 Dose, Procedure and Dose Schedule

Treatment will be administered on an outpatient basis. Patients will receive 4 mg of RRx-001, premixed with the patient's blood prior to reinfusion, in the schedule described in the Schedule of Assessments.

The administration procedure of RRx-001 incorporates the use of an in-line filter 'device' as an added patient safety element; though likely unnecessary, given the patient's own blood is being drawn into a syringe containing anticoagulant, where the study drug (RRx-001) is subsequently transferred to mix with the blood, followed by the treated blood being reinfused back into the patient, within approximately 15 minutes from start of blood draw, all inside a closed sterile assembly.

The filter 'device' is a clinical use in-line blood filter and is part of an FDA approved Neonatal Syringe Set that is used to deliver small aliquots of whole blood. Modification was made for our use by the manufacturer, both to the tubing length (adding approximately 3") and tubing ends (changing the previously female luer connector to a male luer connector on 1 end, and a removing an IV bag spike and replacing it with a male luer connector on the opposite end), thus making this technically 'off label' use.

Appropriate in-use studies have been conducted with this filter 'device' and these results along with the following device labeling: 'CAUTION—Investigational device for use with RRx-001. Limited by Federal law to investigational use under IND 107,674' have been shared with the FDA by way of an information amendment submission, dated December 14, 2017.

A description of the pretreatment regimen is further outlined in Table 3 below. Appropriate dose modifications are described in Section 6.2.6.

Table 3: RRx-001 Regimen Premedication Description

Agent	Premedication	Route	Schedule
RRx-001	10 mg Dexamethasone (or equivalent dose of another corticosteroid) IV or PO up to 2 hours prior to administration of RRx-001	IV or oral	Days 1, 8 and 15 of each cycle
RRx-001	Low-Dose Aspirin 81 mg or Acetaminophen 500 mg up to 2 hours prior to administration of RRx-001	Oral	Days 1, 8 and 15 of each cycle

The patient's identification must be verified by two people prior to starting the blood draw and infusion process. Ensure that the RRx-001 and anticoagulant doses, both provided from pharmacy, are 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 that the mixture is 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 preferred) 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 is important each step is followed in the order outlined in the guide to maintain sterility at all times.**

6.2.3 Protocol Defined Therapies

Standard of care protocol defined therapies will be administered per institutional standard of care and in accordance with the United States Package Insert (USPI) approved by the US FDA. Any patient with a history of toxicity that required permanent discontinuation of any of the chemotherapy agents is ineligible.

- SCC
  - ARM 1:
    - Carboplatin or cisplatin + etoposide
  - ARM 2 "investigators choice" one of the following:
    - Carboplatin or cisplatin + etoposide, irinotecan, vinorelbine

- EOC:
  - ARM 1:
    - Carboplatin (single agent)
  - ARM 2 "investigators choice" <u>one</u> of the following:
    - Carboplatin
    - Etoposide
    - Pegylated liposomal doxorubicin
    - Taxane Treatments
    - Gemcitabine
    - Vinorelbine

- Neuroendocrine:
  - Carboplatin or cisplatin + etoposide
- NSCLC:
  - Carboplatin or cisplatin + paclitaxel *or*
  - Carboplatin or cisplatin + nab-paclitaxel *or*
  - Carboplatin or cisplatin + pemetrexed

Treatment interruption and/or dose reduction may be needed to manage suspected adverse drug reactions in line with standard treatment practice. Refer to the United States Package Insert (USPI) for dose interruption and modification instructions. Patients who previously required dose reduction selected treatment in the first line setting may start treatment at a reduction of the standard dosing, at the discretion of the investigator.

6.2.4 Other Considerations

The hydration for cisplatin should occur pre and post infusion and additionally, supportive diuretics (i.e., mannitol) may be used per investigator discretion. For those treatments considered highly emetogenic anti-nausea regimens will be followed per standard of care. Hematopoietic growth factors may be used per standard of care.

Hematopoietic growth factors (i.e., G- or GM-CSF).

- The use of filgrastrim (neupogen) will be allowed for treatment of Grade 3 or 4 neutropenia or febrile neutropenia. Filgrastrim (neupogen) must be discontinued at least 48 h prior to initiation of the next dose of chemotherapy and prior to the initiation of the next cycle of therapy.
- The use of pegfilgrastim (neulasta) will be allowed as secondary prophylaxis if there was evidence of Grade 3 or 4 neutropenia on a previous cycle.

6.2.5 Criteria for Continuing Treatment

Patients will be evaluated during the treatment period to determine if continued treatment is appropriate. If, at any time during treatment the criteria are not met, treatment will be held or the dose adjusted per protocol and/or per the United States Package Insert (USPI) for treatment parameters.

6.2.6 Dosing Delays/Dosing Modifications: RRx-001

Mild or moderate infusion-related reactions were reported as the most common infusion reaction with RRx-001 when infused directly, and these responded to a reduction in the rate of injection. Although mild reactions were observed when RRx-001 was infused using the Blood-Mix dosing procedure, if a reduction in dose is required or desired, for any reason, whether or not toxicity is present, it is permissible to decrease the dose from 4 mg to 2 mg. Dose modification or drug discontinuation for toxicity may take place at the discretion of the Investigator and will be reported. If a Grade 3 or 4 study drug-related adverse event occurs after a dose reduction, RRx-001 will be discontinued. The dose modifications are listed below in the table below.

Table 4: Dose Modifications for RRx-001 Administration

Sequential Dose Modifications	RRx-001 Dose in mg	RRx-001 Dose in mg/m^2	mL	Infusion Time	Frequency & Interval
Initial	4	2.3	2.0	Not to exceed 4 hours from extraction of blood	Refer to Schedule of Assessments
Dose reduction	2	1.15	1.0	Not to exceed 4 hours from extraction of blood	Refer to Schedule of Assessments

6.2.7 Dosing Delays/Dosing Modifications: Platinum Based Therapy

This section applies to treatment regimens that include the investigational agent RRx-001 as follows:

- Small Cell Carcinoma ARM 1 only
- Ovarian ARM 1 only
- Neuroendocrine
- Non-Small Cell Lung Cancer (NSCLC)

For SCC (ARM2) and EOC (ARM 2), "investigator's choice" enrolled subjects, follow standard of care practice in accordance with the USPI FDA package insert and investigator discretion.

In the event that a patient previously required a dose reduction during first line treatment, the patient may be started on a dose reduction during the initial cycle. This will be at the discretion of the principal investigator. At any time during study the investigator may choose to discontinue the partner agent due to toxicity, maintaining the platinum based agent (as a single agent).

Any treatment delays beyond the protocol allowed 3-week (21 day) break must be approved by the medical monitor.

The following regimens are allowed as defined in the respective treatment schema:

1) Platinum agent: Carboplatin or Cisplatin. Platinum agents are given per the initial approval by the package insert (USPI FDA). The following starting options are:
   a) Cisplatin will be initially dosed at 60-80 mg/m^2 on day 1 every 3 weeks.
   b) Carboplatin will be initially dosed at an AUC of 5-6 on day 1 every 3 weeks.

2) For the cohorts where a second agent will be combined with platinum, the partner agent will be given per the initial approval by the package insert (USPI FDA). The following starting options are:
   a) Etoposide will be initially dosed at 80-100 mg/m^2 Days 1-3 every 3 weeks
   b) Paclitaxel will be initially dosed at 175-225 mg/m^2 on Day 1 of every 3 weeks.
   c) Nab-Paclitaxel will be initially dosed at 100 mg/m^2 on Days 1, 8, and 15 every 3 weeks
   d) Pemetrexed will be initially dosed at 500 mg/m^2 IV over 10 minutes on Day 1 every 3 weeks for up to 6 cycles

Table 5: Dose Delays / Modifications based on Absolute Neutrophil Count: Platinum Doublets

ANC (On Day 1 of treatment cycle)*	**Chemotherapy (Platinum based doublet)**
≥ 1.5 x 10^9/L	Full dose
< 1.5 x 10^9/L	Hold up to 3 weeks until ANC are ≥ 1.5 x 10^9/L Use G-CSF support

ANC nadir	**Chemotherapy (Platinum based doublet)**
Any	No dose delays or adjustments will be done based on nadir ANC.

ANC (On Day 8 of treatment cycle)**	**Chemotherapy (Day 8 chemotherapy)**
≥ 1.5 x 10^9/L	Full dose
< 1.5 x 10^9/L	Hold Day 8 of treatment Use G-CSF support, next cycle

ANC	**Chemotherapy (Day 8 chemotherapy)**
Any	No dose delays or adjustments will be done based on nadir ANC.

ANC (On Day 15 of treatment cycle)***	**Chemotherapy (Day 15 chemotherapy)**
≥ 1.5 x 10^9/L	Full dose
< 1.5 x 10^9/L	Hold Day 15 of treatment Use G-CSF support, next cycle

ANC	**Chemotherapy (Day 15 chemotherapy)**
Any	No dose delays or adjustments will be done based on nadir ANC.

*Dose adjustments will be based only on ANC measured on Day 1 of each cycle (samples drawn up to 3 days prior to cycle Day 1 are allowed).
**Dose adjustments are only for treatment that requires Day 8 dosing of chemotherapy.
***Dose adjustments are only for treatment that requires Day 15 dosing of chemotherapy.
As previously mentioned, G-CSF (Filgrastim or Pegfilgrastim) will be allowed either therapeutically to allow recovery from Grade 3 or 4 neutropenia between cycles or as secondary prophylaxis to prevent a second episode of neutropenia in future cycles.

Table 6: Dose Delays / Modifications based on Platelet Count: Platinum Doublets

Platelets (On Day 1 of treatment cycle)*	**Chemotherapy (Platinum based doublet)**
≥ 100 x 10^9/L	Full dose
>50 x 10^9/L but < 100 x 10^9/L	Hold up to 3 weeks until platelets are ≥ 100 x 10^9/L, then full dose

Platelets	**Chemotherapy (Platinum based doublet)**
< 25 x 10^9/L or < 50 x 10^9/L associated with bleeding	Hold Chemotherapy and once platelets increase to ≥ 100 x 10^9/L 25% dose reduction of both chemotherapy agents

Platelets (On Day 8 of treatment cycle)**	**Chemotherapy (Day 8 chemotherapy)**
≥ 75 x 10^9/L	Full dose
> 25 x 10^9/L but < 75 x 10^9/L	Hold Day 8 chemotherapy

Platelets	**Chemotherapy (Day 8 chemotherapy)**
< 25 x 10^9/L or < 50 x 10^9/L associated with bleeding	Hold chemotherapy and next cycle will be a 25% dose reduction of both chemotherapy agents

Platelets (On Day 15 of treatment cycle)***	**Chemotherapy (Day 15 chemotherapy)**
≥ 75 x 10^9/L	Full dose
> 25 x 10^9/L but < 75 x 10^9/L	Hold Day 15 chemotherapy

Platelets	**Chemotherapy (Day 15 chemotherapy)**
< 25 x 10^9/L or < 50 x 10^9/L associated with bleeding	Hold chemotherapy and next cycle will be a 25% dose reduction of both chemotherapy agents

* Dose adjustments will be based only on platelet count measured on day 1 of each cycle (samples drawn up to 3 days prior to cycle day 1 are allowed).
** Dose adjustments are only for treatment that requires Day 8 dosing of chemotherapy.
*** Dose adjustments are only for treatment that requires Day 15 dosing of chemotherapy.

6.2.7.1 Dose Delays / Modification for Non-Hematologic Toxicities: Platinum Therapies

Dose modification should be made for drug-induced non-hematologic toxicities, with the exception of alopecia, according to the table below.

Non-hematological toxicities must have improved to NCI-CTC Grade ≤ 2 prior to re-treatment. Treatment may be resumed according to the guidelines below.

For Grade 4 toxicities the suggested dose reductions listed below and continuation of treatment should only be implemented if considered by the investigator to be in the best interest of the patient.

Table 7: Platinum Therapies - Adverse Event Dose Modifications: Non-Hematological

Adverse event (AE)	Dose reduction / Modification
> Grade 2 neurotoxicity, ototoxicity	Reduce cisplatin by 25% or change to carboplatin
> Grade 2 Serum creatinine (> 1.6 – 2.5 mg/dl)	Reduce cisplatin by 25% or change to carboplatin
Any other Grade 3 or 4 toxicities not previously mentioned.	Reduce Chemotherapy (Both Chemotherapy in a platinum based doublet) by 25%.

If the above AEs occur following previous dose reduction, then reduce agent by another 25% from the previously administered dosage. If more than 2 dose reductions are needed, the patient will be taken off the study. This may exclude nausea/vomiting/diarrhea, without maximal symptomatic treatment and metabolic toxicities that are easily correctable within 24 hours such as glucose, hypokalemia, hypomagnesemia, hypophosphatemia and hyponatremia, and fatigue.

In the case of nausea/vomiting/diarrhea without maximal symptomatic treatment, implementation of current practice guidelines for this toxicity will take place.

If despite maximal symptomatic treatments the toxicities do not improve to ≤ Grade 2 then all protocol defined therapies will be held until toxicity improves to ≤ Grade 1 or pre-treatment baseline.

6.2.7.2 Nab-Paclitaxel (Abraxane) Dose Modifications

Table 8: Dose Modifications for Hepatic Impairment: Nab-Paclitaxel (Abraxane)

	SGOT (AST) Levels		Bilirubin Levels	Abraxane Dose
Mild	< 10 x ULN	AND	> ULN to ≤ 1. 5 x ULN	100 mg/m^2
Moderate	< 10 x ULN	AND	> 1.5 to ≤ 3 x ULN	80 mg/m^2 *
Severe	< 10 x ULN	AND	> 3 to ≤ 5 x ULN	80 mg/m^2 *
	> 10 x ULN	OR	> 5 x ULN	Not recommended

* If the patient tolerates the reduced dose for two cycles, a dose increase to 100 mg/m^2 in subsequent courses should be considered

Table 9: Dose Modifications for neurologic and hematologic adverse drug reactions: Nab-Paclitaxel (Abraxane)

Do not administer nab-paclitaxel on Day 1 of a cycle until absolute neutrophil count (ANC) is at least 1500 cells/mm^3 and platelet count is at least 100,000 cells/mm^3
In patients who develop severe neutropenia or thrombocytopenia withhold treatment until counts recover to an absolute neutrophil count of at least 1500 cells/mm^3 and platelet count of at least 100,000 cells/mm^3 on Day 1 or to an absolute neutrophil count of at least 500 cells/mm^3 and platelet count of at least 50,000 cells/mm^3 on Days 8 or 15 of the cycle. Upon resumption of dosing, permanently reduce nab-paclitaxel and carboplatin doses as outlined in the table excerpted from the nab-paclitaxel package insert
Withhold nab-paclitaxel for Grade 3-4 peripheral neuropathy. Resume nab-paclitaxel and carboplatin at reduced doses (see excerpted table below) when peripheral neuropathy improves to Grade 1 or completely resolves

From: http://www.abraxane.com/downloads/Abraxane_PrescribingInformation.pdf

Table 10: Permanent Dose Reductions for Hematologic and Neurologic Drug Reactions in NSCLC: Nab-Paclitaxel (Abraxane)

Adverse Drug Reaction	Occurrence	Weekly ABRAXANE Dose (mg/m^2)	Every 3-Week Carboplatin Dose (AUC mg•min/mL)
Neutropenic Fever (ANC less than 500/mm^3 with fever >38°C) OR Delay of next cycle by more than 7 days for ANC less than 1500/mm^3 OR ANC less than 500/mm^3 for more than 7 days	First	75	4.5
	Second	50	3
	Third	Discontinue Treatment	
Platelet count less than 50,000/mm^3	First	75	4.5
	Second	Discontinue Treatment	
Severe sensory Neuropathy – Grade 3 or 4	First	75	4.5
	Second	50	3
	Third	Discontinue Treatment	

6.2.7.3 Paclitaxel Dose Modifications

- If baseline PMN <1500/m^3, do not re-treat until PMN >1500/m^3 and platelet count >100,000/m^3.
- If severe neutropenia occurs (PMN <500/m^3 for 7 days), reduce subsequent doses by 20%.
- If Grade 2 peripheral neuropathy occurs reduce dose to 70 mg/m^2. If ≥ Grade 3 discontinue.
- Renal impairment: No dosage adjustment required

- For hepatic impairment:
  - AST/ALT <10 x ULN and bilirubin up to 2 x ULN: 135 mg/m² over 3 hr
  - AST/ALT <10 x ULN and bilirubin 5 x ULN: 90 mg/m² over 3 hr
  - AST/ALT ≥10 x ULN OR bilirubin >5 x ULN: Do not administer
- For other ≥ Grade 2 toxicity (except alopecia) defer therapy for 1 week until resolved to ≤ Grade 1 and then resume at 70 mg/m^2.

6.2.7.4 Etoposide Dose Modifications

The following table describes etoposide dose modifications based on renal function.

Table 11: Etoposide Dose Modifications for Renal Function

Measured Creatinine Clearance	>50 mL/min	15-50 mL/min
Etoposide	100%	75%

(From: http://packageinserts.bms.com/pi/pi_etophos.pdf)

Data are not available in patients with creatinine clearances <15 mL/min and further dose reduction should be considered in these patients.

Etoposide is associated with:

a) Dose-limiting bone marrow suppression. The occurrence of a platelet count below 50,000/mm^3 or an absolute neutrophil count below 500/mm^3 is an indication to withhold further therapy until the blood counts have sufficiently recovered

b) The possible occurrence of an anaphylactic reaction manifested by chills, fever, tachycardia, bronchospasm, dyspnea, and hypotension. In case of anaphylactic reaction, the infusion should be terminated immediately, and may be followed by the administration of pressor agents, corticosteroids, antihistamines, or volume expanders at the discretion of the physician

c) Injection site reactions. Closely monitor the infusion site for possible infiltration during drug administration. No specific treatment for extravasation reactions is known.

6.2.7.5 Pemetrexed Dose Modifications

Hepatic impairment: no dose adjustments

Hematological toxicity: neutrophils <1.5 x 10^9/L or platelets <100 x 10^9/L. Delay for one week. Repeat complete blood count. If within normal parameters resume treatment with 100% doses. If 2 or more delays, consider a 25% dose reduction.

Renal impairment: CrCl (mL/min) ≥45 give 100% dose. If CrCl <45 not recommended.

Other toxicities: Grade 3 or 4 mucositis, give 50% of previous dose. Any other Grade 3 or 4 toxicities or any diarrhea requiring hospitalization give 75% of previous dose.

6.3 Concomitant and Excluded Therapies

All concomitant medications and blood products, as well as interventions, received by patients from the first dose of study drug until the end of study visit must be recorded.

6.3.1 Supportive Care guidelines

Palliative and supportive care for disease-related symptoms, including palliative radiotherapy, blood transfusions, pain medications, anti-inflammatories, radiation and antiemetics, bisphosphonates and RANK ligand inhibitors, is permitted. Hematopoietic growth factors such as erythropoietin or G-CSF are allowed if clinically indicated (see Section 6.2.4 for additional detail).

6.3.2 Anti-neoplastics

Use of anti-neoplastic or anti-tumor agents not part of the study therapy, including chemotherapy, immunotherapy, and hormonal anticancer therapy, is not permitted while participating in this study.

6.3.3 Investigational Agents

Use of concurrent investigational agents is not permitted.

6.3.4 Warfarin/Coumarin Anticoagulants

Avoid if possible with paclitaxel, as use often causes an elevation or fluctuation in the INR – consider switching patient to a low molecular weight heparin during treatment or if the patient continues taking an oral anticoagulant monitor the INR at least once a week and adjust dose accordingly.

6.4 Study Assessments

A flowchart of scheduled study assessments is provided in Appendix G.

All patients will be closely monitored for safety and tolerability during all cycles of therapy, at study treatment completion/early study treatment discontinuation, and during the survival follow-up period.

6.4.1 Definitions of Study Assessments

a. Medical History
Medical/Oncology history should include history of malignancy (date of first diagnosis, disease course, and prior therapies), surgeries, current ECOG performance status, current symptom inventory, past medical history, all medications taken during the 30 days prior to start of study treatment (including prescriptions, over-the-counter, and herbal/homeopathic remedies), social history (including smoking history and alcohol history), family history and allergies.

b. Demographics
Demographics consist of age, gender, race, and ethnicity.

c. Vital Signs
Vital signs will include measurement of height (at Screening only), weight, pulse rate, blood pressure and temperature.

d. Physical Examination
Changes from baseline abnormalities should be recorded at each subsequent physical examination. New or worsened abnormalities should be recorded as adverse events if appropriate. During the screening visit, a full, comprehensive history and physical exam will be conducted. Thereafter the history and physical exam may be problem focused in accordance with the protocol Schedule of Assessments (Appendix G).

e. Performance Status
Performance status will be evaluated according the ECOG criteria listed in Appendix B.

f. Laboratory Assessments
Clinical laboratory assessments as described in the Schedule of Assessments will be performed by local institutional lab.

In addition, results of tumor markers as drawn per standard of care/ institutional practice are to be provided to sponsor as available.

g. Central Laboratory Samples
Tumor markers from CTCs, CEPs, CECs as well as immune subsets, and protein hyperacetylation will be studied (see Section 4.4.3). For further description see the latest study lab manual.

h. Tumor Biopsy and/or collection of archival tissue
New tumor biopsy, if feasible, will performed on an optional basis prior to infusion of RRx-001 (baseline) and prior to initial platinum rechallange Day 1 (up to 7 Days prior but following discontinuation of RRx-001). Archival tissue, if available, will be collected at baseline. For details regarding the processing of samples please refer to the latest study lab manual.

i. Tumor Assessment
CT (diagnostic with contrast) will be used as the primary imaging tool for response assessment. Anatomical areas should be imaged per institutional standard of care per disease cohort. Imaging will be performed at the time points outlined in the Schedule of Assessments (Appendix G).

Assessment of radiographic response will occur according to RECIST v1.1 (Appendix A). In case partial response (PR), CR, or progressive disease (PD) is observed according to RECIST v.1.1, confirmatory tumor assessments may be repeated at least 4 weeks after initial documentation. Study treatments will continue until disease progression is confirmed by the Investigator, patients' refusal, or unacceptable toxicity, whichever occurs first.

6.4.2 Screening and Pretreatment Assessments

Diagnostic or laboratory studies performed exclusively to determine eligibility for this trial will be done only after obtaining written informed consent. Documentation of the informed consent for screening will be maintained in the patient's research chart and medical record. Studies or procedures that were performed for clinical indications (not exclusively to determine study

eligibility) may be used for baseline values even if the studies were done before informed consent was obtained, so long as they fall within the protocol Screening window.

The study population for this trial will consist of patients with pathologically confirmed advanced resistant/refractory SCC, EGFR positive NSCLC, resistant/refractory EOC or HGNEC. All patients must have measurable disease. CT imaging will confirm measurable lesions within the schedule defined in the Schedule of Assessments. All patients who meet the inclusion and exclusion criteria will be offered enrollment into this study. To confirm patient eligibility for study participation, the following assessments and procedures will be completed during the screening period.

All screening procedures must be performed within the schedule defined in the Schedule of Assessments. The screening procedures include:

a. Written informed consent.
b. Review of inclusion and exclusion criteria.
c. Complete medical/oncology history.
d. Documentation of concomitant medications.
e. Demographics.
f. Complete physical examination, including vital signs and physical measurements (body weight and height).
g. Optional tumor biopsy, if feasible, and/or collection of archival tissue
h. ECOG performance status assessment.
i. Documentation of tumor status (radiologic tumor assessment)
j. Local Laboratory Assessments: CBC and CMP.

   Note: if blood samples are taken within 5 days of the first dose of study treatment, Day 1 samples do not need to be re-collected.
k. Central Laboratory Samples: CTC, Immune Subsets, Lysine Acetylation, CEC/CEP, Serum miRNA analysis
l. Single-item Visual Analogue Fatigue Scale to be completed by the patient
m. Pregnancy test, if female of childbearing potential.

6.4.3 Treatment Discontinuation Assessments

Patients should be seen in the clinic or contacted by telephone to determine if any serious or non-serious adverse events have occurred within 30 days of termination of protocol defined treatment.

Patients may withdraw from the study at any time. Any patient who stops study treatment will be encouraged to return to the study center for a follow-up visit within 4-6 weeks of discontinuation. The primary reason for discontinuation should be documented.

6.4.4 Follow-Up Assessments

Patients will be followed until death, or withdrawal of informed consent. Follow-up will consist of phone calls approximately every 8 weeks (± 7 days) to document survival. If a patient, family member or healthcare proxy cannot be reached, medical records or the Social Security Death Index (SSDI) may be used to document survival. For patients continuing to be imaged at the study site, a copy of the imaging and local radiology report will be made available upon request. Patients may choose to withdraw from making their imaging available during the follow-up period.

6.5 Patient Discontinuation

Patients may discontinue study treatment at any time. Any patient who discontinues treatment will be encouraged to return to the study center to undergo treatment discontinuation assessments. The primary reason for discontinuation should be recorded. Reasons for discontinuation of a patient by the investigator include, but are not limited to, the following:

- Voluntary withdrawal from treatment (follow-up permitted); patients that withdraw from radiology follow-up should still be followed for overall survival
- Voluntary withdrawal of consent (termination of treatment and follow-up),
- Documented disease progression by RECIST v1.1 criteria after start of platinum doublets
- Clinically significant deterioration of the patient's condition prior to treatment discontinuation,
- Patient noncompliance,
- Experience of serious and unexpected toxicity, as defined in Section 5.1.1,
- Investigator determination that it is not in the patient's best interest to continue participation,
- Pregnancy,
- Development of second malignancy (except for basal cell carcinoma, squamous cell carcinoma of the skin, localized prostate, or cervical cancer) that requires treatment which would interfere with the study,
- Lost to follow-up.

6.6 Study Discontinuation

Reasons for terminating the study may include, but are not limited to, the following:

- Completion of the study.
- The incidence or severity of adverse events in this study indicates a potential health hazard.
- Withdrawal of EpicentRx Inc. approval.
- Inaccurate or incomplete data recording.
- Suggested by early stopping guidelines for futility of second or third line chemotherapy.
- Suggested by early stopping guideline for risk of clinical deterioration during RRx-001 treatment period.

7 STATISTICAL METHODS OF DATA ANALYSIS

7.1 Study Design

This study is designed to explore the potential of the epigenetic agent RRx-001 to sensitize patients who previously received a platinum based doublet regimen. RRx-001 is administered with autologous blood once weekly followed by or in combination with a protocol defined therapy.

The primary endpoint is Overall Survival (OS) and Overall Response Rate (ORR).

The four cohorts under consideration are patients with NSCLC, SCC, High Grade Neuroendocrine Tumors, or refractory resistant epithelial ovarian tumors (or MMMT of ovary or uterus) and who meet eligibility criteria defined in the inclusion / exclusion criteria.

Stopping guidelines for safety in platinum therapy period of treatment - Stage 2

If the limiting toxicity events convincingly exceed 30%, we will temporarily halt the study pending safety consultation. Specifically, we will apply a Bayesian toxicity monitoring rule that suspends the enrollment if the posterior probability of risk being larger than 0.30 is 70% or higher. The prior distribution was chosen to be beta (1, 5), representing our prior guess that limiting toxicities occur in 1 out of 6 patients and there is 90% chance that this toxicity rate is between 1.0% and 45%. The stopping boundaries along with corresponding operating characteristics are presented in the following tables based on 5000 simulations.

Stop if # Serious & Unexpected Toxicity	3	4	5	6	7	8	9	10	11	12
Out of N	3-4	5-7	8-10	11-13	14-16	17-19	20-22	23-25	26-28	29-30

Underlying risk of adverse events	Probability of early stopping	Average sample size
0.10	0.8%	29.8
0.20	9.2%	28.1
0.30	36.5%	23.4
0.40	74.7%	16.2
0.50	94.9%	10.4

Amendment 10 Statistical updates:

General design considerations, effective as of Amendment 10:

1. ***Small Cell Carcinoma**: Newly enrolled patients (post Amendment 10) will be allocated to one of two treatment arms using a 2-to-1 randomization ratio, (approximately 26 to Arm 1 and 13 to Arm 2).*

   The two treatment arms are as follows:

   ***Arm 1**: RRx-001 weekly for 3 weeks followed by up to 4 cycles of platinum plus etoposide chemotherapy 'rechallenge' and then RRx-001 & platinum maintenance (for patients with stable disease (SD) or better at discontinuation of platinum rechallenge)*

   ***Arm 2**: Standard of Care Investigator's Choice Control Arm, treatment options of platinum plus etoposide, irinotecan or vinorelbine until progression or intolerable toxicity*
2. ***Ovarian**: Newly enrolled patients (post Amendment 10) will be allocated to one of two treatment arms using a 2-to-1 randomization ratio, (approximately 26 to Arm 1 and 13 to Arm 2).*

   The two treatment arms are as follows:

   ***Arm 1**: RRx-001 weekly for 2 weeks followed by 2 cycles of carboplatin 'rechallenge' and then 'maintenance', cycling between 1 dose of RRx-001 followed by 2 cycles of carboplatin, which repeats until progression or intolerable toxicity*

   ***Arm 2**: Standard of Care Investigator's Choice Control Arm, treatment options of one of the following: carboplatin, etoposide, doxil, gemcitabine, vinorelbine or taxane treatments until progression or intolerable toxicity*
3. ***Neuroendocrine**: The only modification with amendment 09 forward to the existing treatment schedule is the addition of a RRx-001 maintenance for patients with > SD following discontinuation of platinum based chemotherapy (for up to 6 cycles).*
4. ***NSCLC**: Patients enrolled post Amendment 09 will receive 3 consecutive doses of RRx-001, after which, RRx-001 is discontinued and platinum based chemotherapy is started for up to 6 cycles. In addition, a RRx-001 maintenance for patients with > SD following discontinuation of platinum based chemotherapy (for up to 6 cycles) was added.*

Sample size determination and power considerations:

The extension stage of the study will approximately enroll 39 patients to the small cell carcinoma cohort and also 39 patients to the ovarian cohort. In each cohort, a 2-to-1 randomization allocation ratio will be employed (approximately 26 in Arm 1 and 13 in Arm 2, in each chort). The proposed sample size modification is motivated by recent clinical obersvations arising from current study data results. This upward sample size adjustment should provide sufficient precision to derive estimates of responses and time-to-event endpoints. Inferential statistics are not the main focus of this newly proposed focus study extension.

7.2 Efficacy Variables

7.2.1 Primary Efficacy Variables

The primary efficacy endpoint is OS defined as the time from the date of enrollment to disease progression or death from any cause. Patients will be followed until their date of death, loss to follow-up, withdrawal of consent for further follow-up for survival or final database closure.

Patients who are lost to follow-up or are not known to have disease progression at the time of data cut-off for analysis will be censored at last date shown to be alive. Patients who do not have any follow up since enrollment will be censored at the date of enrollment.

The primary efficacy analysis of OS will be based on the modified ITT population. Kaplan-Meier estimates of the survival curves and the median survival times and their corresponding 95% CI will be presented.

Subgroup analyses of OS will be performed to assess whether the treatment effect is concordant among subgroups. The planned subgroup analyses are based on age category (<40 years, 40 to <65 years, and ≥65 years), race (Caucasian vs. other). Other subgroup analyses may be performed and specified in the statistical analysis plan.

ORR is the other primary endpoint, which will be assessed at each radiographic assessment using RECIST v1.1 criterion. ORR will be defined as the proportion of patients with a CR or a PR per RECIST v1.1 based upon the best response as assessed; confirmation of response is not required.

ORR will be analyzed using the CMH test stratified by the randomization stratification factors to assess the significance of the treatment effect on ORR. The treatment effect on ORR will be quantified using the odds ratio relative to the historical control. Clopper-Pearson 2-sided 95% confidence limits will be calculated for the proportion of patients with ORR.

ORR analyses will be performed for the Efficacy Evaluable population. Patients who do not have measurable disease at baseline will be excluded from the population.

In addition to representing ORR, the best response using response categories CR, PR, SD, PD and NE will be tabulated. The proportion of the response in each response category will be calculated. Patients who do not have any post-baseline tumor assessment will be counted under the category NE.

ORR rate at best-confirmed response will also be assessed and analyzed using a similar approach as for Overall Response Rate. All patients meeting the eligibility criteria that have signed a consent form and have begun treatment will be evaluable for the primary endpoint. Statistical analyses will be primarily descriptive in nature. Evidence of efficacy will consist of an ORR rate of 10% or higher in a particular treatment cohort.

7.2.1.1 Transition Probability

The transition probability between disease progression and disease amelioration attributable to resensitization will be estimated. A semi-Markov model will be used to capture the transition probability matrix between disease progression states (Jackson 2015, Sharples 2003).

The average time each patient spends in a given disease state will be estimated and its 95% confidence interval derived. The expected time spent healthy (or diseased) before death will also be estimated.

7.2.1.2 Disease Control Rates (DCR)

The percentage of patients who have achieved complete response, partial response and stable disease (as per RECIST v1.1).

7.2.1.3 Progression Free Survival

PFS defined from the time from registration to the time of the first radiographic documentation of objective progression as defined by RECIST v1.1 for platinum therapy or death from any cause. The analysis of PFS will be similar to the analysis of OS.

7.2.1.4 Toxicity

Rate of Grade 3 and Grade 4 hematologic toxicities between reintroduced platinum based chemotherapy and historical data. The analysis of this toxicity rate will use the CMH test stratified by the randomization stratification factors. The proportion of patients experiencing the given toxicity (by grade) will be quantified using the odds ratio relative to the historical control. Clopper-Pearson 2-sided 95% confidence limits will be calculated for the toxicity proportion (by grade).

7.2.1.5 Analysis of Activity Data

Descriptive statistics arranged by treatment group (within each of the four cohorts) are planned. Graphical depiction of the statistical summaries (ORR, DCR, OS, PFS) will accompany the tabular formatted data results for a more complete presentation of the statistical findings. Specifically, Kaplan-Meier curves and estimation of time-to-event medians with their corresponding 95% confidence intervals will be produced. ORR and DCR responses will be derived and the Clopper-Pearson method will be used to derive the responses 95% confidence intervals.

Small Cell Carcinoma and Ovarian Patients *enrolled to Amendment 10 or later will be analyzed separately (from patients enrolled prior to Amendment 10), the corresponding activity data analyses will be separated accordingly. Safety data summaries will be provided separately and in aggregation (pre-and-post Amendment 10). As of the time of Amendment 10 (and its execution), only newly enrolled patients (to the extension of the study, as of Amendment 10) will be required to consent and follow all required eligibility/randomization requirements.*

There will be two databases with separate database locks:

1. *An original database for patients enrolled prior to Amendment 10. This database will have its own database procedures and lock timelines.*
2. *An extension database for patients enrolled to Amendment 10 or later with its own database lock procedures and timelines.*

NSCLC and Neuroendocrine *enrolled to the study (pre & post Amendment 10) will be analyzed as a single group for each cancer type.*

7.3 Safety Variables

Safety data summary will be presented by study stage. Adverse events with RRx-001 and cumulative adverse events with a protocol defined therapy (description, timing, grade severity, seriousness, and relatedness) will be summarized using sample size frequency of occurrence percentage. Adverse event data will be descriptively evaluated by cohort and for overall patients. Incidence of TEAEs by MedDRA SOC, preferred term and relationship (Related/Not Related) to study drug will be summarized based on the safety population. Changes in the level of serum biomarkers, clinical laboratory abnormalities, and changes in physical exam and vital signs will be compared to baseline samples using one-sample tests (e.g., paired t test or Wilcoxon signed rank test).

Adverse events will be coded by SOC and preferred term using MedDRA, version 18.1. Adverse event severity will be based on NCI CTCAE Grade (version 5.0). A TEAE is defined as an AE that was not present prior to treatment with study drug, but appeared following treatment or was present at treatment initiation, but worsened during treatment.

Percentage and Time to non-hematologic toxicity Grades 3-5 adverse events will also be summarized using time-to-event techniques such as Kaplan-Meier curves. The median time to a given toxicity event (by grade) will be estimated (along with its 95% confidence interval) and descriptively compared to historical toxicity information. The hematologic toxicity Grade 3-5 under consideration comprises anemia, thrombocytopenia, neutropenia, febrile neutropenia and infections.

Amendment 10 Section Updates (Small Cell Carcinoma & Ovarian):

In addition to the safety summary described above, safety summaries will be presented by treatment arm within the small cell carcinoma and ovarian cohorts.

7.4 Statistical and Analytical Methods

Besides explicitly mentioned variables and their analyses, all collected variables will be presented at least descriptively. Categorical data will be analyzed using frequency tables. Longitudinal data will also be presented as change from baseline, if appropriate.

The statistical analysis plan, including a comprehensive list of planned output, will describe all analyses in more depth.

7.4.1 Statistical Model

A two-sided log-rank test will be used to compare each disease cohort to the historical control cohort. Kaplan-Meier estimates will be derived for the one-sample disease cohort and the median with its 95% confidence interval estimates will be derived.

7.4.2 Hypothesis Testing

OS, ORR and PFS endpoints will be compared between the disease cohorts and the corresponding historical control.

7.4.3 Analysis Populations

The following population definitions will be used to analyze selected endpoints using the appropriate subpopulation of the enrolled patients. If the need arises, additional subpopulations will be defined in the statistical analysis plan.

7.4.3.1 Safety Analysis Population

The Safety Population will comprise all study patients who receive at least 1 dose of any study medication. The safety population will be used for the analysis of all safety parameters. For the purposes of this analysis, patients will be assigned to the treatment groups based on the treatments they actually received.

7.4.3.2 Efficacy Analysis Population(s)

- In NSCLC and neuroendocrine cohorts, all enrolled patients who receive study treatment will be included in the modified ITT population and analyzed according to the treatment schedule they were enrolled to.
- For the small cell carcinoma and ovarian randomized patients, the modified intention-to-treat will comprise all randomized patients who receive study drug, and will be analyzed as randomized.
- The Per Protocol population is defined as the subset of modified ITT population who received at least one study treatment cycle and had no major violation of the protocol inclusion and exclusion criteria.

All efficacy analyses will be based on the modified ITT population. The primary and secondary efficacy analyses will be repeated using the Per Protocol population to confirm the overall study results. Further efficacy analyses may be conducted as described in the statistical analysis plan.

7.5 Power Considerations and Sample Size Determination

The extension stage of the study will approximately enroll 39 patients to the small cell carcinoma cohort and also 39 patients to the ovarian cohort, both in a 2:1 randomization, respectively (26 in ARM 1 and 13 in ARM 2 for each). The sample size is based on clinical observations motivated by currently available study data results, and should provide sufficient precision to derive estimates of responses and time-to-event endpoints. Inferential statistics are not the main focus of this newly proposed focus study extension.

7.6 Interim Analysis and Data Monitoring

Safety data will be reviewed periodically to examine safety information, including TEAEs, SAEs, and deaths, and factors relating to quality of trial conduct will be reviewed. During Part 2, an IDMC will be established to review the safety data summaries and examine the findings of the interim futility analysis.

All patients will be evaluable for toxicity from the time of their first treatment with protocol specified treatment until the end of protocol specified treatment. However, cumulative adverse

events during the period of treatment will be continuously monitored. If the limiting toxicity events exceed 30%, the trial will be temporarily halted pending safety consultation.

Efficacy will be assessed on a periodic basis to determine the best course for future development. OS, PFS and ORR will be evaluated at each data review when appropriate data maturity is achieved.

Data Monitoring: Safety data will be reviewed periodically to examine safety information, including TEAEs, SAEs, toxicity, deaths, and factors relating to quality of trial conduct will be reviewed. An informal DMC will be established to review the safety data summaries and examine the findings of the interim data summaries, and will consist of two physicians not involved in the conduct of this trial and one biostatistician. Administrative staff will assist the informal DMC with operational details and coordinate the generation of DMC minutes.

DMC members will review safety analyses in order to investigate potential safety risks to the patients participating in the study that would suggest a change in study conduct or in the ICF. The DMC charter describes details including the primary responsibilities of the DMC, its relationship with other trial components, its membership, the purpose and timing of its meetings, statistical monitoring guidelines to be implemented, and statistical analysis for the open and closed sessions (if appropriate). The informal DMC Charter and meeting minutes will be submitted as part of the final Clinical Study Report.

7.7 Institutional Review Board

The PI must obtain IRB approval for the investigation. Initial IRB approval and all materials approved by the IRB for this study including the patient consent form and recruitment materials must be maintained by the Investigator and made available for inspection.

7.8 Data Quality Assurance

Data will be collected via notes in the electronic medical record, radiological imaging and outside reports and entered into the appropriate Electronic Data Capture (EDC) Case Report Forms (CRFs).

8 ASSESSMENT OF SAFETY

The safety of RRx-001 and other protocol defined therapy will be assessed through collection and analyses of adverse events (AEs) and laboratory tests. Patients will be assessed for safety through the duration of study while receiving protocol defined treatment.

8.1 Specification of Safety Variables

Safety assessments will consist of monitoring and reporting adverse events (AEs) and serious adverse events (SAEs) that are considered related to RRx-001 or protocol specified standard of care therapy (e.g., carboplatin, cisplatin, investigator's choice treatment), all events of death, and any study specific issue of concern.

8.1.1 Adverse Events

An adverse event (AE) is defined as any new untoward medical occurrence or worsening of a pre-existing medical condition in a patient or clinical investigation patient administered an investigational (medicinal) product and that does not necessarily have a causal relationship with this treatment. An AE can therefore be any unfavorable or unintended sign (including abnormal laboratory finding, for example), symptom or disease temporally associated with the use of investigational product, whether or not considered related to the investigational product.

This includes the following:

- AEs not previously observed in the patient that emerge during the protocol specified AE reporting period, including signs or symptoms associated with SCC, T790M$^-$ NSCLC, HGNEC, rEOC that were not present prior to the AE reporting period.
- Complications that occur as a result of protocol-mandated interventions (e.g., invasive procedures such as biopsies).
- Preexisting medical conditions (other than the condition being studied) judged by the investigator to have worsened in severity or frequency or changed in character during the protocol-specified AE reporting period.
- Clinical progression of SCC, EGFR+ NSCLC, HGNEC or EOC should not be reported as an AE.

8.1.2 Serious Adverse Events

An AE should be classified as an SAE if:

- It results in death (i.e., the AE actually causes or leads to death).
- It is life threatening (i.e., the AE, in the view of the investigator, places the patient at immediate risk of death. It does not include an AE that, had it occurred in a more severe form, might have caused death.).
- It requires or prolongs inpatient hospitalization.

- It results in persistent or significant disability/incapacity (i.e., the AE results in substantial disruption of the patient's ability to conduct normal life functions).
- It results in a congenital anomaly/birth defect in a neonate/infant born to a mother exposed to the investigational product.
- It is considered a significant medical event by the investigator based on medical judgment (e.g., may jeopardize the patient or may require medical/surgical intervention to prevent one of the outcomes listed above).

All AEs that do not meet any of the criteria for serious should be regarded as non-serious AEs.

The terms "severe" and "serious" are not synonymous. Severity (or intensity) refers to the grade of a specific AE, e.g., mild (Grade 1), moderate (Grade 2), or severe (Grade 3) myocardial infarction. "Serious" is a regulatory definition (see previous definition) and is based on patient or event outcome or action criteria usually associated with events that pose a threat to a patient's life or functioning. Seriousness (not severity) serves as the guide for defining regulatory reporting obligations from the Sponsor to applicable regulatory authorities.

Severity and seriousness should be independently assessed when recording AEs and SAEs on the CRF.

8.2 Methods and Timing for Assessing and Recording Safety Variables

The investigator is responsible for ensuring that all AEs and SAEs that are observed or reported during the study are collected and reported to the FDA, IRB, and EpicentRx, Inc. in accordance with CFR 312.32 (IND Safety reporting).

8.2.1 Adverse Event Reporting Period

The study period during which all AEs and SAEs must be reported begins after informed consent is obtained and ends 30 days following the last administration of protocol specified treatment (i.e., RRx-001, carboplatin, cisplatin, investigator's choice treatment, etc.) or study discontinuation/termination, whichever is earlier. After this period, investigators should only report SAEs that are attributed to prior study treatment.

8.2.2 Assessment of Adverse Events

Investigators will assess the occurrence of AEs and SAEs at all patient evaluation time points during the study. All AEs and SAEs whether volunteered by the patient, discovered by study personnel during questioning, or detected through physical examination, laboratory test, or other means will be recorded in the patient's medical record and on the appropriate AE or SAE CRF page.

Each recorded AE or SAE will be described by its duration (i.e., start and end dates), severity (see Table 12), regulatory seriousness criteria if applicable, suspected relationship to the investigational product (see following guidance), and actions taken.

The AE grading (severity) scale found in the National Cancer Institute Common Terminology Criteria for Adverse Events (NCI-CTCAE), Version 5.0, will be used for AE reporting.

Table 12: Adverse Event Grading (Severity) Scale

Grade	Severity	Alternate Description [a]
1	Mild (apply event-specific NCI-CTCAE grading criteria)	Transient or mild discomfort (< 48 hours); no interference with the patient's daily activities; no medical intervention/therapy required
2	Moderate (apply event-specific NCI-CTCAE grading criteria)	Mild to moderate interference with the patient's daily activities; no or minimal medical intervention/therapy required
3	Severe (apply event-specific NCI-CTCAE grading criteria)	Considerable interference with the patient's daily activities; medical intervention/therapy required; hospitalization possible
4	Very severe, life threatening, or disabling (apply event-specific NCI-CTCAE grading criteria)	Extreme limitation in activity; significant medical intervention/therapy required, hospitalization probable
5	Death related to AE	

Note: Regardless of severity, some events may also meet regulatory serious criteria. Refer to definitions of an SAE (see Section 8.1.2).

[a]Use these alternative definitions for Grade 1, 2, 3, and 4 events when the observed or reported AE is not in the NCI-CTCAE listing.

To ensure consistency of AE and SAE causality assessments, investigators should apply the following general guideline:

- **YES**

There is a plausible temporal relationship between the onset of the AE and administration of the investigational product, and the AE cannot be readily explained by the patient's clinical state, intercurrent illness, or concomitant therapies; and/or the AE follows a known pattern of response to the investigational product; and/or the AE abates or resolves upon discontinuation of the investigational product or dose reduction and, if applicable, reappears upon re-challenge.

- **NO**

Evidence exists that the AE has an etiology other than the investigational product (e.g., preexisting medical condition, underlying disease, intercurrent illness, or concomitant medication); and/or the AE has no plausible temporal relationship to administration of the investigational product (e.g., cancer diagnosed 2 days after first dose of study drug).

Expected adverse events are those adverse events that are listed or characterized in the Product Label or current Investigator Brochure.

Unexpected adverse events are those not listed in the Product Label or current Investigator Brochure or not identified. This includes adverse events for which the specific or severity is no consistent with the previous description.

8.2.3 Specific Instructions for Recording Adverse Events

Investigators are strongly encouraged to use correct medical terminology/concepts when reporting AEs or SAEs and to avoid colloquialisms and abbreviations.

a. Diagnosis vs. Signs and Symptoms

If known at the time of reporting, a diagnosis should be reported rather than individual signs and symptoms. However, if a constellation of signs and/or symptoms cannot be medically characterized as a single diagnosis or syndrome at the time of reporting, it is ok to report the information that is currently available. If a diagnosis is subsequently established, it should be reported as follow-up information.

b. Deaths

All deaths that occur during the protocol-specified AE reporting period (see Section 8.1.2), regardless of attribution, will be reported to the appropriate parties. When recording a death, the event or condition that caused or contributed to the fatal outcome should be reported as the single medical concept. If the cause of death is unknown and cannot be ascertained at the time of reporting, report "Unexplained Death".

c. Preexisting Medical Conditions

A preexisting medical condition is one that is present at the start of the study. Such conditions should be reported as medical and surgical history. A preexisting medical condition should be re-assessed throughout the trial and reported as an AE or SAE only if the frequency, severity, or character of the condition worsens during the study. When reporting such events, it is important to convey the concept that the preexisting condition has changed by including applicable descriptors (e.g., "more frequent headaches").

d. Hospitalizations for Medical or Surgical Procedures

Any AE that results in hospitalization or prolonged hospitalization should be documented and reported as an SAE. If a patient is hospitalized to undergo a medical or surgical procedure as a result of an AE, the event responsible for the procedure, not the procedure itself, should be reported as the SAE. For example, if a patient is hospitalized to undergo coronary bypass surgery, record the heart condition that necessitated the bypass as the SAE.

Hospitalizations for the following reasons do not require reporting:

- Hospitalization or prolonged hospitalization for diagnostic or elective surgical procedures for preexisting conditions
- Hospitalization or prolonged hospitalization required to allow efficacy measurement for the study or
- Hospitalization or prolonged hospitalization for scheduled therapy of the target disease of the study.

e. Pregnancy

If a female patient becomes pregnant while receiving investigational therapy or within 90 days after the last dose of study drug, a report should be completed and expeditiously submitted to the EpicentRx, Inc. Follow-up to obtain the outcome of the pregnancy should also occur. Abortion,

whether accidental, therapeutic, or spontaneous, should always be classified as serious, and expeditiously reported as an SAE. Similarly, any congenital anomaly/birth defect in a child born to a female patient exposed to the investigational product should be reported as an SAE.

f. Post-Study Adverse Events

The investigator should expeditiously report any SAE occurring after a patient has completed or discontinued study participation if attributed to prior investigational product exposure. If the investigator should become aware of the development of cancer or a congenital anomaly in a subsequently conceived offspring of a female patient who participated in the study, this should be reported as an SAE.

8.3 Reporting Requirements for Adverse Events

8.3.1 Expedited Reporting Requirements for Serious Adverse Events

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 patient 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 patient death, a summary of available autopsy findings must be submitted as soon as possible to Sponsor or designee.

The completed SAE CRF page or MedWatch form should be emailed to EpicentRx's Drug Safety Department at:

SAEREPORTING@epicentrx.com

The **Medical Monitor**, Dr. Bryan Oronsky can be reached at **(408) 569-3202 (cell) or boronsky@epicentrx.com** should any questions arise regarding an SAE or SAE reporting.

Relevant follow-up information should be submitted to EpicentRx's Drug Safety as soon as it becomes available and/or upon request.

MedWatch 3500A Reporting Guidelines

In addition to completing appropriate patient demographic and suspect medication information, the report should include the following information within the Event Description (Section 5) of the MedWatch 3500A form (http://www.fda.gov/medwatch/index.html):

- Treatment regimen (dosing frequency, combination therapy)
- Protocol description (and number, if assigned)
- Description of event, severity, treatment, and outcome, if known
- Supportive laboratory results and diagnostics
- Investigator's assessment of the relationship of the adverse event to each investigational product and suspect medication

Follow-up information

Additional information may be added to a previously submitted report by any of the following methods:

- Adding to the original MedWatch 3500A report and submitting it as follow-up
- Adding supplemental summary information and submitting it as follow-up with the original MedWatch 3500A form
- Summarizing new information and faxing it with a cover letter including patient identifiers (i.e., D.O.B., initials, patient number), protocol description and number, if assigned, suspect drug, brief adverse event description, and notation that additional or follow-up information is being submitted (The patient identifiers are important so that the new information is added to the correct initial report.)

Occasionally, EpicentRx may contact the reporter for additional information, clarification or current status of the patient for whom an adverse event was reported. For questions regarding STEAE reporting, you may contact the EpicentRx Drug Safety representative (Bryan Oronsky, MD, (408) 569-3202).

- The Human Research Protections Program (HRPP) must be notified within 10 business days of "any unanticipated problems involving risk to patients or others" (UPR).

  The following events meet the definition of UPR:

  1. Any serious event (injuries, side effects, deaths or other problems), which in the opinion of the Principal Investigator was unanticipated, involved risk to patients or others, and was possibly related to the research procedures.
  2. Any serious accidental or unintentional change to the IRB-approved protocol that alters the level of risk.
  3. Any deviation from the protocol taken without prior IRB review to eliminate apparent immediate hazard to a research patient.

4. Any new information (e.g., publication, safety monitoring report, updated sponsor safety report), interim result or other finding that indicates an unexpected change to the risk/benefit ratio for the research.
5. Any breach in confidentiality that may involve risk to the patient or others.
6. Any complaint of a patient that indicates an unanticipated risk or that cannot be resolved by the Principal Investigator.

8.3.2 Routine Reporting of Adverse Events

- The HRPP will be notified of any adverse events that are not unanticipated problems involving risk to patients or other (non-UPRs) at the time of the annual Continuing Review.

8.4 Type and Duration of Follow-Up of Patients After Adverse Events

All AEs and SAEs that are encountered during the protocol-specified AE reporting period that are considered at least possibly related to the study drug should be followed to their resolutions, or until the investigator assesses them as stable, or the patient is lost to follow-up. Resolution of AEs and SAEs (with dates) should be documented on the appropriate AE CRF page and in the patient's medical record to facilitate source data verification.

Recording of Adverse Events includes the study period during protocol specified treatment (i.e., RRx-001, carboplatin, cisplatin, investigator's choice treatment, etc.) until the patient is off study.

For some SAEs, the Sponsor or its designee may follow-up by telephone, fax, electronic mail, and/or a monitoring visit to obtain additional case details deemed necessary to appropriately evaluate the SAE report (e.g., hospital discharge summary, consultant report, or autopsy report).

9 SPONSOR AND INVESTIGATOR REQUIREMENTS

The Principal Investigator is responsible for the conduct of the clinical trial at the site in accordance with Title 21 of the Code of Federal Regulations and/or the Declaration of Helsinki. The Principal Investigator is responsible for personally overseeing the treatment of all study patients. The Principal Investigator must assure that all study site personnel, including sub-investigators and other study staff members, adhere to the study protocol and all FDA/GCP/NCI regulations and guidelines regarding clinical trials both during and after study completion.

The Principal Investigator will be responsible for assuring that all the required data will be collected and entered onto the Case Report Forms. Periodically, monitoring visits will be conducted and the Principal Investigator will provide access to his/her original records to permit verification of proper entry of data. At the completion of the study, all case report forms will be reviewed by the Principal Investigator and will require his/her final signature to verify the accuracy of the data.

9.1 Study Initiation

Before the start of this study and the shipment of investigational agent to the study site, the following documents must be on file at EpicentRx, Inc.

- U.S. Food and Drug Administration (FDA) Form 1572, signed by the Principal Investigator
- The names of any sub-investigators must appear on this form. Investigators must also complete all regulatory documentation as required by local regulations
- Current curricula vitae and license of the Principal Investigator
- Final Protocol and ICF
- A signed and dated investigator brochure acceptance form
- Written documentation of IRB approval of protocol and ICF (identified by title and date of approval) for each site
- A signed Confidentiality Agreement
- A signed Research Agreement

9.2 Informed Consent

The informed consent documents must be signed by the patient, or the patient's legally authorized representative, before his or her participation in the study. The case history for each patient shall document that informed consent was obtained prior to participation in the study. A copy of the informed consent documents must be provided to the patient or the patient's legally authorized representative. If applicable, they will be provided in a certified translation of the local language.

Original signed consent forms must be filed in the site study binder or in each patient's study file.

9.3 Institutional Review Board Approval

This protocol, the informed consent document, and relevant supporting information must be submitted to the IRB for review and must be approved before the study is initiated. In addition, any advertising materials must be approved by the IRB. The study will be conducted in accordance with U.S. FDA, applicable national and local health authority, and IRB requirements.

The Principal Investigator is responsible for keeping the IRB apprised of the progress of the study and of any changes made to the protocol as deemed appropriate, but in any case, the IRB must be updated at least once a year. The Principal Investigator must also keep the IRB informed of any significant adverse events.

Investigators are required to promptly notify their respective IRB of all adverse drug reactions that are both serious and unexpected. This generally refers to serious adverse events that are not already identified in the Investigator Brochure and that are considered possibly or probably related to the study drug by the investigator. Investigators must forward to their IRB any written safety report or update provided by EpicentRx (e.g., IND safety report, Investigator Brochure, safety amendments and updates, etc.).

9.4 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. Monitoring may also be carried out remotely. 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 patient 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.

9.5 Data Collection

Study documentation includes all Case Report Forms, data correction forms or queries, source documents, correspondence, monitoring logs/letters, and regulatory documents (e.g., protocol and amendments, IRB correspondence and approval, signed patient consent forms).

Source documents include all recordings of observations or notations of clinical activities and all reports and records necessary for the evaluation and reconstruction of the clinical research study. 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, and redacted copies may be requested by Sponsor.

9.6 Study Medication Accountability

EpicentRx will provide all study drug (RRx-001) required for completion of this study. The recipient will acknowledge receipt of the drug by returning the drug receipt form indicating shipment content and condition. Damaged supplies will be replaced.

Study drug accountability records should be maintained by the site in accordance with the regulations.

All drug supply requests of RRx-001 will be submitted directly to EpicentRx from the site per instructions in the study Pharmacy Manual.

At the time of study closure, the unused, used and expired study drug will be destroyed at the site per Institutional SOPs and EpicentRx should be provided with documentation when this has occurred.

9.7 Disclosure of Data

Patient medical information obtained by this study is confidential, and disclosure to third parties other than those noted below is prohibited.

In accordance with the Health Information Portability and Accountability Act (HIPAA), patients who have provided written informed consent must also sign a patient authorization to release medical information to his or her personal physician or other appropriate medical personnel responsible for his or her welfare, to EpicentRx and authorized representatives of EpicentRx, upon request, for source verification of study documentation.

Data generated by this study must be available for inspection upon request by representatives of the U.S. FDA, local health authorities, EpicentRx, Inc., and their authorized representative(s), collaborators and licensees, and the HRPP.

9.8 Retention of Records

U.S. FDA regulations (21 CFR §312.62[c]) require that records and documents pertaining to the conduct of this study and the distribution of investigational drug, including CRFs, consent forms, laboratory test results, and medication inventory records, must be retained by the Principal Investigator for 2 years after marketing application approval. If no application is filed, these records must be kept 2 years after the study is discontinued and the U.S. FDA and the applicable national and local health authorities are notified.

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11 APPENDICES

Appendix A. Response evaluation criteria in solid tumors

Tumor assessments will be made according to the schedule of assessments. Response and progression will be evaluated using RECIST v1.1 [Eisenhauer et al. 2009].

A1 MEASURABILITY OF TUMOR AT BASELINE

A1.1 Definitions

At baseline, tumor lesions will be categorized as follows:

A1.1.1 Measurable

Tumor lesions: must be accurately measured in at least one dimension (longest diameter in the plane of measurements is to be recorded) with a minimum size of:

- 10 mm by CT scan (CT scan slice thickness no greater than 5 mm).
- 10 mm caliper measurement by clinical exam (lesions which cannot be accurately measured with calipers should be recorded as non-measureable).
- 20 mm by chest X-ray.

Malignant lymph nodes: to be considered pathologically enlarged and measurable, a lymph node must be >= 15 mm in *short* axis when assessed by CT scan. At baseline and in follow-up, only the *short* axis will be measured and followed.

A1.1.2 Non-measurable

All other lesions, including small lesions (longest diameter < 10 mm or pathological lymph nodes with >= 10 to < 15 mm short axis) as well as truly non-measurable lesions. Lesions considered truly non-measurable include: leptomeningeal disease, ascites, pleural or pericardial effusion, inflammatory breast disease, lymphangitic involvement of skin or lung, abdominal masses/abdominal organomegaly identified by physical exam that is not measurable by reproducible imaging techniques.

A1.1.3 Special considerations regarding lesion measurability

Bone lesions, cystic lesions, and lesions previously treated with local therapy require particular comment:

Bone lesions:

- Bone scan, PET scan or plain films are not considered adequate imaging techniques to measure bone lesions. However, these techniques can be used to confirm the presence or disappearance of bone lesions.
- Lytic bone lesions or mixed lytic-blastic lesions, with *identifiable soft tissue components*, that can be evaluated by cross sectional imaging techniques such as CT or MRI can be considered as measurable lesions if the soft tissue component meets the definition of measurability described above.
- Blastic bone lesions are non-measurable.

Cystic lesions:

- Lesions that meet the criteria for radiographically defined simple cysts should not be considered as malignant lesions (neither measurable nor non-measurable) since they are, by definition, simple cysts.
- 'Cystic lesions' thought to represent cystic metastases can be considered as measurable lesions, if they meet the definition of measurability described above. However, if noncystic lesions are present in the same subject, these are preferred for selection as target lesions.

Lesions with prior local treatment:

- Tumor lesions situated in a previously irradiated area, or in an area subjected to other loco-regional therapy, are usually not considered measurable unless there has been demonstrated progression in the lesion. Study protocols should detail the conditions under which such lesions would be considered measurable.

A1.2 Specifications by methods of measurements

A1.2.1 Measurement of lesions

All measurements should be recorded in metric notation, using calipers if clinically assessed. All baseline evaluations should be performed as close as possible to the treatment start and never more than 4 weeks before the beginning of the treatment.

A1.2.2 Method of assessment

A diagnostic CT with contrast imaging will be permitted as the baseline evaluation at the screening assessment and for lesion assessment. Imaging based evaluation should always be done rather than clinical examination unless the lesion(s) being followed cannot be imaged but are assessable by clinical exam.

Clinical lesions: Clinical lesions will only be considered measurable when they are superficial and P10mm diameter as assessed using calipers (e.g. skin nodules). For the case of skin lesions, documentation by color photography including a ruler to estimate the size of the lesion is suggested. As noted above, when lesions can be evaluated by both clinical exam and imaging, imaging evaluation should be undertaken since it is more objective and may also be reviewed at the end of the study.

Chest X-ray: Chest CT is preferred over chest X-ray, particularly when progression is an important endpoint, since CT is more sensitive than X-ray, particularly in identifying new lesions. However, lesions on chest X-ray may be considered measurable if they are clearly defined and surrounded by aerated lung.

CT: For the purposes of this study a diagnostic CT with contrast will be used for lesion assessment.

Ultrasound: Ultrasound is not useful in assessment of lesion size and should not be used as a method of measurement. Ultrasound examinations cannot be reproduced in their entirety for independent review at a later date and, because they are operator dependent, it cannot be guaranteed that the same technique and measurements will be taken from one assessment to the next. If new lesions are identified by ultrasound in the course of the study, confirmation by MRI is advised.

Endoscopy, laparoscopy: The utilization of these techniques for objective tumor evaluation is not advised. However, they can be useful to confirm complete pathological response when biopsies are obtained or to determine relapse in trials where recurrence following complete response or surgical resection is an endpoint.

Tumor markers: Tumor markers alone cannot be used to assess objective tumor response. If markers are initially above the upper normal limit, however, they must normalize for a patient to be considered in complete response. Because tumor markers are disease specific, instructions for their measurement should be incorporated into protocols on a disease specific basis.

Cytology, histology: These techniques can be used to differentiate between PR and CR in rare cases if required by protocol (for example, residual lesions in tumor types such as germ cell tumors, where known residual benign tumors can remain). When effusions are known to be a potential adverse effect of treatment (e.g. with certain taxane compounds or angiogenesis inhibitors), the cytological confirmation of the neoplastic origin of any effusion that appears or worsens during treatment can be considered if the measurable tumor has met criteria for response or stable disease in order to differentiate between response (or stable disease) and progressive disease.

B2 TUMOR RESPONSE EVALUATION

B2.1 Baseline documentation of 'target' and 'non-target' lesions

When more than one measurable lesion is present at baseline all lesions up to a maximum of five lesions total (and a maximum of two lesions per organ) representative of all involved organs should be identified as target lesions and will be recorded and measured at baseline (this means in instances where patients have only one or two organ sites involved a maximum of two and four lesions respectively will be recorded).

Target lesions should be selected on the basis of their size (lesions with the longest diameter), be representative of all involved organs, but in addition should be those that lend themselves to reproducible repeated measurements. It may be the case that, on occasion, the largest lesion does not lend itself to reproducible measurement in which circumstance the next largest lesion which can be measured reproducibly should be selected.

Lymph nodes merit special mention since they are normal anatomical structures which may be visible by imaging even if not involved by tumor. Pathological nodes which are defined as measurable and may be identified as target lesions must meet the criterion of a short axis of P15mm by CT scan. Only the short axis of these nodes will contribute to the baseline sum. The short axis of the node is the diameter normally used by radiologists to judge if a node is involved by solid tumor. Nodal size is normally reported as two dimensions in the plane in which the image is obtained (for CT scan this is almost always the axial plane; for MRI the plane of acquisition may be axial, sagittal or coronal). The smaller of these measures is the short axis.

For example, an abdominal node which is reported as being 20mm· 30mm has a short axis of 20mm and qualifies as a malignant, measurable node. In this example, 20mm should be recorded as the node measurement. All other pathological nodes (those with short axis P10mm but <15 mm) should be considered non-target lesions. Nodes that have a short axis <10mm are considered non-pathological and should not be recorded or followed.

A *sum of the diameters* (longest for non-nodal lesions, short axis for nodal lesions) for all target lesions will be calculated and reported as the baseline sum diameters. If lymph nodes are to be included in the sum, then as noted above, only the short axis is added into the sum. The baseline sum diameters will be used as reference to further characterize any objective tumor regression in the measurable dimension of the disease.

All other lesions (or sites of disease) including pathological lymph nodes should be identified as non-target lesions and should also be recorded at baseline. Measurements are not required and these lesions should be followed as 'present', 'absent', or in rare cases 'unequivocal progression' (more details to follow). In addition, it is possible to record multiple non-target lesions involving the same organ as a single item on the case record form (e.g. 'multiple enlarged pelvic lymph nodes' or 'multiple liver metastases').

B2.3 Response criteria

This section provides the definitions of the criteria used to determine objective tumor response for target lesions.

B2.3.1 Evaluation of target lesions

Complete Response (CR):	Disappearance of all target lesions. Any pathological lymph nodes (whether target or non-target) must have reduction in short axis to <10 mm.
Partial Response (PR):	At least a 30% decrease in the sum of diameters of target lesions, taking as reference the baseline sum diameters.
Progressive Disease (PD):	At least a 20% increase in the sum of diameters of target lesions, taking as reference the smallest sum on study (this includes the baseline sum if that is the smallest on study). In addition to the relative increase of 20%, the sum must also demonstrate an absolute increase of at least 5 mm. (Note: the appearance of one or more new lesions is also considered progression).
Stable Disease (SD):	Neither sufficient shrinkage to qualify for PR nor sufficient increase to qualify for PD, taking as reference the smallest sum diameters while on study.

B2.3.2 Special notes on the assessment of target lesions

Lymph nodes. Lymph nodes identified as target lesions should always have the actual short axis measurement recorded (measured in the same anatomical plane as the baseline examination), even if the nodes regress to below 10mm on study. This means that when lymph nodes are included as target lesions, the 'sum' of lesions may not be zero even if complete response criteria are met, since a normal lymph node is defined as having a short axis of <10mm. Case report forms or other data collection methods may therefore be designed to have target nodal lesions recorded in a separate section where, in order to qualify for CR, each node must achieve a short axis <10mm. For PR, SD and PD, the actual short axis measurement of the nodes is to be included in the sum of target lesions.

Target lesions that become 'too small to measure'. While on study, all lesions (nodal and non-nodal) recorded at baseline should have their actual measurements recorded at each subsequent evaluation, even when very small (e.g. 2 mm). However, sometimes lesions or lymph nodes

which are recorded as target lesions at baseline become so faint on MRI scan that the radiologist may not feel comfortable assigning an exact measure and may report them as being 'too small to measure'. When this occurs it is important that a value be recorded on the case report form. If it is the opinion of the radiologist that the lesion has likely disappeared, the measurement should be recorded as 0mm. If the lesion is believed to be present and is faintly seen but too small to measure, a default value of 5 mm should be assigned (Note: It is less likely that this rule will be used for lymph nodes since they usually have a definable size when normal and are frequently surrounded by fat such as in the retroperitoneum; however, if a lymph node is believed to be present and is faintly seen but too small to measure, a default value of 5mm should be assigned in this circumstance as well). The measurement of these lesions is potentially non-reproducible; therefore providing this default value will prevent false responses or progressions based upon measurement error. To reiterate, however, if the radiologist is able to provide an actual measure, that should be recorded, even if it is below 5 mm.

Lesions that split or coalesce on treatment. When non-nodal lesions 'fragment', the longest diameters of the fragmented portions should be added together to calculate the target lesion sum. Similarly, as lesions coalesce, a plane between them may be maintained that would aid in obtaining maximal diameter measurements of each individual lesion. If the lesions have truly coalesced such that they are no longer separable, the vector of the longest diameter in this instance should be the maximal longest diameter for the 'coalesced lesion'.

B2.3.3 Evaluation of non-target lesions

This section provides the definitions of the criteria used to determine the tumor response for the group of non-target lesions. While some non-target lesions may actually be measurable, they need not be measured and instead should be assessed only qualitatively at the time points specified in the protocol.

Complete Response (CR):	Disappearance of all non-target lesions and normalization of tumor marker level. All lymph nodes must be non-pathological in size (<10 mm short axis).
Non-CR/Non-PD:	Persistence of one or more non-target lesion(s) and/or maintenance of tumor marker level above the normal limits.
Progressive Disease (PD):	Unequivocal progression (see comments below) of existing non-target lesions. (Note: the appearance of one or more new lesions is also considered progression).

B2.3.4 Special notes on assessment of progression of non-target disease

The concept of progression of non-target disease requires additional explanation as follows:

When the patient also has measurable disease. In this setting, to achieve 'unequivocal progression' on the basis of the non-target disease, there must be an overall level of substantial worsening in non-target disease such that, even in presence of SD or PR in target disease, the overall tumor burden has increased sufficiently to merit discontinuation of therapy. A modest 'increase' in the size of one or more non-target lesions is usually not sufficient to quality for unequivocal progression status. The designation of overall progression solely on the basis of change in non-target disease in the face of SD or PR of target disease will therefore be extremely rare.

When the patient has only non-measurable disease. This circumstance arises in some phase III trials when it is not a criterion of study entry to have measurable disease. The same general concepts apply here as noted above, however, in this instance there is no measurable disease assessment to factor into the interpretation of an increase in non-measurable disease burden.

Because worsening in non-target disease cannot be easily quantified (by definition: if all lesions are truly non-measurable) a useful test that can be applied when assessing patients for unequivocal progression is to consider if the increase in overall disease burden based on the change in non-measurable disease is comparable in magnitude to the increase that would be required to declare PD for measurable disease: i.e.an increase in tumor burden representing an additional 73% increase in 'volume' (which is equivalent to a 20% increase diameter in a measurable lesion). Examples include an increase in a pleural effusion from 'trace' to 'large', an increase in lymphangitic disease from localized to widespread, or may be described in protocols as 'sufficient to require a change in therapy'. If 'unequivocal progression' is seen, the patient should be considered to have had overall PD at that point. While it would be ideal to have objective criteria to apply to non-measurable disease, the very nature of that disease makes it impossible to do so, therefore the increase must be substantial.

B2.4.5 New lesions

The appearance of new malignant lesions denotes disease progression; therefore, some comments on detection of new lesions are important. There are no specific criteria for the identification of new radiographic lesions; however, the finding of a new lesion should be unequivocal: i.e. not attributable to differences in scanning technique, change in imaging modality or findings thought to represent something other than tumor (for example, some 'new' bone lesions may be simply healing or flare of pre-existing lesions). This is particularly important when the patient's baseline lesions show partial or complete response.

A lesion identified on a follow-up study in an anatomical location that was not scanned at baseline is considered a new lesion and will indicate disease progression. An example of this is the patient who has visceral disease at baseline and while on study has a CT or MRI brain ordered which reveals metastases. The patient's brain metastases are considered to be evidence of PD even if he/she did not have brain imaging at baseline.

If a new lesion is equivocal, for example because of its small size, continued therapy and follow-up evaluation will clarify if it represents truly new disease. If repeat scans confirm there is definitely a new lesion, then progression should be declared using the date of the initial scan.

While FDG-PET response assessments need additional study, it is sometimes reasonable to incorporate the use of FDG-PET scanning to complement CT scanning in assessment of progression (particularly possible 'new' disease). New lesions on the basis of FDG-PET imaging can be identified according to the following algorithm:

a. Negative FDG-PET at baseline, with a positive FDG-PET at follow-up is a sign of PD based on a new lesion.
b. No FDG-PET at baseline and a positive FDG-PET at follow- up:
   If the positive FDG-PET at follow-up corresponds to a new site of disease confirmed by CT, this is PD. If the positive FDG-PET at follow-up is not confirmed as a new site of disease on CT, additional follow-up CT scans are needed to determine if there is truly progression occurring at that site (if so, the date of PD will be the date of the initial abnormal FDG-PET scan). If the positive FDG-PET at follow-up corresponds to a pre-

existing site of disease on CT that is not progressing on the basis of the anatomic images, this is not PD.

B2.4 Evaluation of best overall response

The best overall response is the best response recorded from the start of the study treatment until the end of treatment taking into account any requirement for confirmation. On occasion a response may not be documented until after the end of therapy so protocols should be clear if post-treatment assessments are to be considered in determination of best overall response. Protocols must specify how any new therapy introduced before progression will affect best response designation. The patient's best overall response assignment will depend on the findings of both target and non-target disease and will also take into consideration the appearance of new lesions. Furthermore, depending on the nature of the study and the protocol requirements, it may also require confirmatory measurement. Specifically, in non-randomized trials where response is the primary endpoint, confirmation of PR or CR is needed to deem either one the 'best overall response'. This is described further below.

B2.4.1 Time point response

It is assumed that at each protocol specified time point, a response assessment occurs. Table 1 provides a summary of the overall response status calculation at each time point for patients who have measurable disease at baseline.

When patients have non-measurable (therefore non-target) disease only, Table 2 is to be used.

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	Inevaluable
PD	Any	Yes or No	PD
Any	PD	Yes or No	PD
Any	Any	Yes	PD

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
Not all evaluated	No	Inevaluable
Unequivocal PD	Yes or No	PD
Any	Yes	PD

B2.4.2 Missing assessments and unevaluable designation

When no imaging/measurement is done at all at a particular time point, the patient is not evaluable (NE) at that time point. If only a subset of lesion measurements are made at an assessment, usually the case is also considered NE at that time point, unless a convincing argument can be made that the contribution of the individual missing lesion(s) would not change

the assigned time point response. This would be most likely to happen in the case of PD. For example, if a patient had a baseline sum of 50 mm with three measured lesions and at follow-up only two lesions were assessed, but those gave a sum of 80 mm, the patient will have achieved PD status, regardless of the contribution of the missing lesion.

B2.4.3 Best overall response: all time points

The best overall response is determined once all the data for the patient is known.

Best response determination in trials where confirmation of complete or partial response IS NOT required: Best response in these trials is defined as the best response across all time points (for example, a patient who has SD at first assessment, PR at second assessment, and PD on last assessment has a best overall response of PR). When SD is believed to be best response, it must also meet the protocol specified minimum time from baseline. If the minimum time is not met when SD is otherwise the best time point response, the patient's best response depends on the subsequent assessments. For example, a patient who has SD at first assessment, PD at second and does not meet minimum duration for SD, will have a best response of PD. The same patient lost to follow-up after the first SD assessment would be considered unevaluable.

Best response determination in trials where confirmation of complete or partial response IS required: Complete or partial responses may be claimed only if the criteria for each are met at a subsequent time point as specified in the protocol (generally 4 weeks later). In this circumstance, the best overall response can be interpreted as in Table 3.

Table 3. Best overall response when confirmation of CR and PR required.

Overall response First time point	Overall response Subsequent time point	BEST overall response
CR	CR	CR
CR	PR	SD, PD OR PR
CR	SD	SD provided minimum criteria for SD duration met, otherwise PD
CR	PD	SD provided minimum criteria for SD duration met, otherwise PD
CR	Inevaluable	SD provided minimum criteria for SD duration met, otherwise inevaluable
PR	CR	PR
PR	PR	PR
PR	SD	SD
PR	PD	SD provided minimum criteria for SD duration met, otherwise PD
PR	Inevaluable	SD provided minimum criteria for SD duration met, otherwise inevaluable
Inevaluable	Inevaluable	Inevaluable

B2.4.4 Special notes on response assessment

When nodal disease is included in the sum of target lesions and the nodes decrease to 'normal' size (<10 mm), they may still have a measurement reported on scans. This measurement should be recorded even though the nodes are normal in order not to overstate progression should it be based on increase in size of the nodes. As noted earlier, this means that patients with CR may not have a total sum of 'zero' on the case report form (CRF).

In trials where confirmation of response is required, repeated 'NE' time point assessments may complicate best response determination. The analysis plan for the trial must address how missing data/assessments will be addressed in determination of response and progression. For example, in most trials it is reasonable to consider a patient with time point responses of PR-NE-PR as a confirmed response.

Patients with a global deterioration of health status requiring discontinuation of treatment without objective evidence of disease progression at that time should be reported as 'symptomatic deterioration'. Every effort should be made to document objective progression even after discontinuation of treatment. Symptomatic deterioration is not a descriptor of an objective response: it is a reason for stopping study therapy. The objective response status of such patients is to be determined by evaluation of target and non-target disease as shown in Tables 1–3.

Conditions that define 'early progression, early death and inevaluability' are study specific and should be clearly described in each protocol (depending on treatment duration, treatment periodicity).

In some circumstances it may be difficult to distinguish residual disease from normal tissue. When the evaluation of complete response depends upon this determination, it is recommended that the residual lesion be investigated (fine needle aspirate/biopsy) before assigning a status of complete response. FDG-PET may be used to upgrade a response to a CR in a manner similar to a biopsy in cases where a residual radiographic abnormality is thought to represent fibrosis or scarring. The use of FDG-PET in this circumstance should be prospectively described in the protocol and supported by disease specific medical literature for the indication. However, it must be acknowledged that both approaches may lead to false positive CR due to limitations of FDG-PET and biopsy resolution/sensitivity.

For equivocal findings of progression (e.g., very small and uncertain new lesions; cystic changes or necrosis in existing lesions), treatment may continue until the next scheduled assessment. If at the next scheduled assessment, progression is confirmed, the date of progression should be the earlier date when progression was suspected.

B2.5 Confirmatory measurement/duration of response

B2.5.1 Confirmation

In non-randomized trials where response is the primary endpoint, confirmation of PR and CR is required to ensure responses identified are not the result of measurement error. This will also permit appropriate interpretation of results in the context of historical data where response has traditionally required confirmation in such trials. However, in all other circumstances, i.e. in randomized trials (Phase II or III) or studies where stable disease or progression are the primary endpoints, confirmation of response is not required since it will not add value to the interpretation of trial results. However, elimination of the requirement for response confirmation may increase the importance of central review to protect against bias, in particular in studies that are not blinded.

In the case of SD, measurements must have met the SD criteria at least once after study entry at a minimum interval that is defined in the study protocol.

B2.5.2 Duration of overall response

The duration of overall response is measured from the time measurement criteria are first met for CR/PR (whichever is first recorded) until the first date that recurrent or progressive disease is objectively documented (taking as reference for progressive disease the smallest measurements recorded on study).

The duration of overall complete response is measured from the time measurement criteria are first met for CR until the first date that recurrent disease is objectively documented.

B2.5.3 Duration of stable disease

Stable disease is measured from the start of the treatment (in randomized trials, from date of randomization) until the criteria for progression are met, taking as reference the smallest sum on study (if the baseline sum is the smallest, this is the reference for calculation of PD).

The clinical relevance of the duration of stable disease varies in different studies and diseases. If the proportion of patients achieving stable disease for a minimum period of time is an endpoint of importance in a particular trial, the protocol should specify the minimal time interval required between two measurements for determination of stable disease.

Note: The duration of response and stable disease as well as the progression-free survival are influenced by the frequency of follow-up after baseline evaluation. It is not in the scope of this guideline to define a standard follow-up frequency. The frequency should take into account many parameters including disease types and stages, treatment periodicity and standard practice. However, these limitations of the precision of the measured endpoint should be taken into account if comparisons between trials are to be made.

Reference:

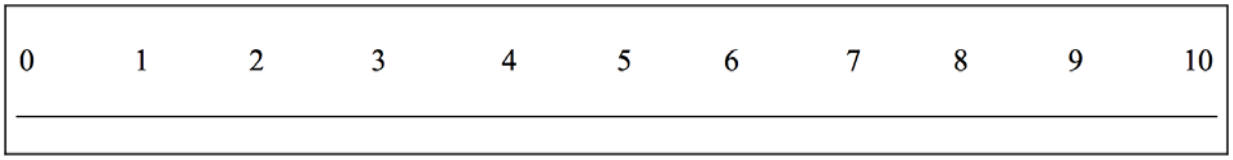
Eisenhauer EA, Therasse P, Bogaerts J et al. New response evaluation criteria in solid tumours: Revised RECIST guideline (version 1.1). Eur J Cancer 2009; 45:228-247.

Appendix B. ECOG performance status scale

Grade	Description
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 housework or office work
2	Ambulatory and capable of all self-care but unable to carry out any work activities. Up and about >50% of waking hours
3	Capable of only limited self-care, confined to a bed or chair >50% of waking hours
4	Completely disabled. Cannot carry on any self-care. Totally confined to bed or chair
5	Dead

Appendix D. Visual Analogue Fatigue Scale

Please mark an "X" on the number scale to indicate your overall fatigue level with 0 being not at all tired and 10 being extremely tired



Appendix F. Imaging Collection for Independent Review:

Upon request, all imaging performed while patient is on-study, including imaging performed during screening, is to be sent to EpicentRx or uploaded to an imaging assessor web based platform within six (6) weeks of procedure visit for independent radiology assessment.

Imaging should be redacted to exclude patient identifiers in accordance with HIPPA regulations and, when provided outside of a web based platform, prepared in electronic format (e.g., CD, USB flash drive, etc.) to include:

a. Site and patient number (XXX-XXX)
b. Imaging procedure date (MM/DD/YYYY)
c. Copy of local radiology report

Attn: Scott Caroen
EpicentRx
11099 North Torrey Pines Rd, Suite 160
La Jolla, CA 92037
Phone: 415-715-7786

Appendix G. Schedules of Assessments

SCC (Arm 1, table 1 of 2**) RRx-001 Priming, Platinum Rechallenge** (3-week cycles)

– RRx-001 / Platinum 'Maintenance' for patients that complete the Platinum Rechallenge with ≥ SD is shown on the subsequent table

Assessment / Procedure	Screening ≤14 days of C0 D1	RRx-001 Priming*			Platinum Rechallenge			Imaging Assessment q2 platinum cycles (± 7 days)	End of Study (EOS)[10]	Follow-up Period[11] (± 7 days)
		±3 day window unless otherwise stated in footnotes								
		C 0 D 1	C 0 D 8	C 0 D 15	C 1 D 1	C 1 D 8	C 2-4 D 1			
Informed Consent	X									
Med/Onc History	X									
Demographics	X									
Physical Exam[1]	X	X	X	X	X	X	X		X	
Vital Signs	X	X	X	X	X	X	X		X	
ECOG Status	X	X	X	X	X	X	X		X	
Lesion Assessment by diagnostic CT with contrast[2]	X			X				X		
Brain Imaging (CT or MRI)	X									
Administer RRx-001[3]		X	X	X						
Administer Platinum-Based Chemotherapy[4]					X		X			
CBC and CMP (incl Magnesium, LDH)[5]	X	X[5]	X[5]	X[5]	X	X	X		X	
Beta Natriuretic Peptide (BNP)[6]	X						X (C4 only)			
Hemoglobin A1C (HbA1C)	X						X (C4 only)			
25-OH vitamin D (25-OHD)	X						X (C4 only)			
Tumor Tissue[7]	X				X					
Pregnancy Test[8]	X									
Record adverse events	X	X	X	X	X	X	X		X	
Record concomitant therapies, medications and/or procedures	X	X	X	X	X	X	X		X	
Visual Analogue Fatigue Scale (Appendix D)	X	X			X		X			
Central Lab Collection: Circulating Tumor Cells (CTCs)[9]		X			X					
Central Lab Collection: Immune Subsets[9]		X			X					
Central Lab Collection: Lysine Acetylation[9]		X			X					
Central Lab Collection: CEC/CEP[9]		X			X					
Central Lab Collection: Serum miRNA Analysis[9]		X			X					
Survival Contact										X

* If patient experiences disease progression during the RRx-001 Priming (initial 3 weeks), subject may discontinue RRx-001 and proceed to Platinum Rechallenge

1. Full physical exam is required at Screening. Subsequent physical exams may be symptom-directed. Each PE must include vital signs and weight.
2. Screening imaging must be obtained within 14 days prior to C0D1. A diagnostic CT with contrast must be performed at the end of Cycle 0, prior to initiation of platinum treatment, then every 2 cycles from start of platinum treatment (every 2 cycles ±7 Days) during the Platinum Rechallenge. SCC patients also require a Brain MRI within 8 weeks prior to C0D1 (does not need to be repeated if SOC imaging performed within window; head CT is allowed if MRI is contraindicated). Lesion assessment will be by RECIST v1.1. In addition to local assessment, upon request, all imaging performed while patient is 'on-study' is to be sent to EpicentRx within six (6) weeks of procedure visit for independent radiology review. Reference Appendix F for format and shipping instructions. During the 'follow-up period', for subjects continuing to be imaged at the study site, a copy of the imaging and local radiology report will be made available upon request. Subjects may choose to withdraw from making their imaging available during the follow-up period (once they are 'off-study').
3. Premedication with 10 mg of dexamethasone, or a similar corticosteroid, and a low-dose aspirin (81 mg) or Acetaminophen (500 mg) is required within 2 hours prior to the infusion of RRx-001 blood mix. If patient is already receiving dexamethasone or equivalent corticosteroid, premedication with dexamethasone should not be given.
4. During the 'Platinum Rechallenege', Administer carboplatin AUC 5-6 IV on day 1 or cisplatin 60-80 mg/m^2 IV on day 1 plus etoposide per protocol and approved package insert every 21 days for up to 4 cycles.
5. During the RRx-001 Priming period for RRx-001 dosing visits on Day 1 and Day 8, the LDH lab value should be processed and sent to EpicentRx (entered into EDC or emailed to study manager) within 48 hours of test blood collection. If LDH value increases by $\geq$ 25% from Day 1 to Day 8, RRx-001 is to be discontinued and Platinum Rechallenge will begin 1 week sooner than scheduled (skipping the RRx-001 Priming Period Day 15 visit).
6. Only to be performed if subject is a smoker. During screening and Day 1 of Cycle 4 only.
7. New tumor biopsy, if feasible, will performed on an optional basis prior to infusion of RRx-001 (baseline) and prior to initial platinum rechallange Day 1 (up to 7 Days prior but following discontinuation of RRx-001). Archival tissue, if available, will be collected at baseline. For details regarding the processing of samples please refer to the latest study lab manual.
8. For women of childbearing potential (WOCBP), a negative serum or urine pregnancy test is required prior to entering this study WOCBP and men whose partners are able to become pregnant will be asked to use non-hormonal methods of contraception for the entire duration of the study and for up to 90 days after their last dose with RRx-001 and through platinum phase.
9. To be collected and sent to sponsor-designated central lab and may be collected up to 3 days prior to treatment administration. Blood samples will be drawn from all subjects by venipuncture or central venous catheter. For detailed collection, processing, and shipment requirements reference the Collection Flow Chart in the latest study lab manual.
10. If subject demonstrates progressive disease (PD) during platinum treatment, treatment will be discontinued and subject will complete End of Study (EOS) visit within 30 days of termination of platinum dosing and move into follow-up period. **If subject has $\geq$ SD at discontinuation of Platinum Rechallenge period, subject continues onto maintenance portion of ARM 1 (see section below)**.
11. Follow-up Period begins when patient has PD during Platinum Rechallenge or RRx-001/Platinum Maintenance treatment, or discontinues treatment for any other reason. Subjects with stable disease or better (SD, PR or CR) at discontinuation of Platinum Rechallenge continue into the RRx-001/Platinum Maintenance until progression. Survival contact will occur via medical record review, telephone call or Social Security Death Index every 8 weeks (± 7 days) until death. For subjects continuing to be imaged at the study site, a copy of the imaging and local radiology report will be made available upon request. Subjects may choose to withdraw from making their imaging available during the follow-up period (once they are 'off-study').

SCC (Arm 1, table 2 of 2) RRx-001 & Platinum (single agent) 'Maintenance'

2 Weeks RRx-001 followed by 2 Cycles Platinum (Carboplatin or Cisplatin, single agent), **repeating until PD**

(For Subjects with ≥ SD at Discontinuation of 'Platinum Rechallenge')

Assessment / Procedure	RRx-001 Maintenance		Platinum Maintenance			
	±3 day window unless otherwise stated in footnotes			Imaging Assessment q2 platinum cycles (± 7 days)	End of Study (EOS)[5]	Follow-up Period[6] (± 7 days)
	Each Cycle D 1	Each Cycle D 8	Each Cycle D 1			
Physical Exam[1]	X	X	X		X	
Vital Signs	X	X	X		X	
ECOG Status	X	X	X		X	
Lesion Assessment by diagnostic CT with contrast[2]				X		
Brain Imaging (CT or MRI)						
Administer RRx-001[3]	X	X				
Administer **Single Agent** Platinum Chemotherapy[4]			X			
CBC and CMP (incl Magnesium, LDH)	X	X	X		X	
Record adverse events	X	X	X		X	
Record concomitant therapies, medications and/or procedures	X	X	X		X	
Visual Analogue Fatigue Scale (Appendix D)	X		X			
Survival Contact						X

1. Maintenance RRx-001 and Platinum physical exams may be symptom-directed. Each PE must include vital signs and weight.
2. During the Maintenance RRx-001 and Platinum period, a diagnostic CT with contrast must be performed **every 2 platinum cycles** (approximately every 8 weeks ±7 Days). Lesion assessment will be by RECIST v1.1. In addition to local assessment, upon request, all imaging performed while patient is 'on-study' is to be sent to EpicentRx within six (6) weeks of procedure visit for independent radiology review. Reference Appendix F for format and shipping instructions. During the 'follow-up period', for subjects continuing to be imaged at the study site, a copy of the imaging and local radiology report will be made available upon request. Subjects may choose to withdraw from making their imaging available during the follow-up period (once they are 'off-study').
3. Premedication with 10 mg of dexamethasone, or a similar corticosteroid, and a low-dose aspirin (81 mg) or Acetaminophen (500mg) is required within 2 hours prior to the infusion of RRx-001 blood mix. If patient is already receiving dexamethasone or equivalent corticosteroid, premedication with dexamethasone should not be given.
4. During 'Platinum Maintenance', Administer carboplatin AUC 5-6 IV on day 1 or cisplatin 60-80 mg/m^2 IV on day 1 as **a single agent** per protocol and approved package insert every 21 days for 2 cycles.
5. RRx-001 Maintenance and Platinum Maintenance repeat until progression or intolerable toxicity. If subject demonstrates progressive disease (PD) during RRx-001/Platinum Maintenance, treatment will be discontinued and subject will complete End of Study (EOS) visit within 30 days of termination of treatment and move into follow-up period.
6. Follow-up Period begins when patient has PD during Platinum Rechallenge or RRx-001/ Platinum Maintenance treatment, or discontinues treatment for any other reason. Survival contact will occur via medical record review, telephone call or Social Security Death Index every 8 weeks (± 7 days) until death. For subjects continuing to be imaged at the study site, a copy of the imaging and local radiology report will be made available upon request. Subjects may choose to withdraw from making their imaging available during the follow-up period (once they are 'off-study').

Ovarian (Arm 1, table 1 of 2**) RRx-001 Priming, Platinum Rechallenge**

– RRx-001 / Platinum 'Maintenance' for patients that complete the Platinum Rechallenge with ≥ SD is shown on the subsequent table

Assessment / Procedure	Screening ≤ 14 days of C0 D1	RRx-001 Priming*		Platinum Rechallenge			Imaging Assessment q2 platinum cycles (± 7 days)	End of Study (EOS)[8]	Follow-up Period[9] (± 7 days)
			±3 day window unless otherwise stated in footnotes						
		C 0 D 1	C 0 D 8	C 1 D 1	C 1 D 8	C 2 D 1			
Informed Consent	X								
Med/Onc History	X								
Demographics	X								
Physical Exam[1]	X	X	X	X	X	X		X	
Vital Signs	X	X	X	X	X	X		X	
ECOG Status	X	X	X	X	X	X		X	
Lesion Assessment by diagnostic CT with contrast[2]	X						X		
Administer RRx-001[3]		X	X						
Administer Platinum (Carboplatin) Chemotherapy[4]				X		X			
CBC and CMP (incl Magnesium, LDH)	X	X	X	X	X	X		X	
Tumor Tissue[5]	X			X					
Pregnancy Test[6]	X								
Record adverse events	X	X	X	X	X	X		X	
Record concomitant therapies, medications and/or procedures	X	X	X	X	X	X		X	
Visual Analogue Fatigue Scale (Appendix D)	X	X		X		X			
Central Lab Collection: Circulating Tumor Cells (CTCs)[7]		X		X					
Central Lab Collection: Immune Subsets[7]		X		X					
Central Lab Collection: Lysine Acetylation[7]		X		X					
Central Lab Collection: CEC/CEP[7]		X		X					
Central Lab Collection: Serum miRNA Analysis[7]		X		X					
Survival Contact									X

* If patient experiences disease progression during the RRx-001 Priming (initial 2 weeks), subject may discontinue RRx-001 and proceed to Platinum Rechallenge

1. Full physical exam is required at Screening. Subsequent physical exams may be symptom-directed. Each PE must include vital signs and weight.
2. Screening imaging must be obtained within 14 days prior to C0D1. A diagnostic CT with contrast must be performed at the end of Cycle 0, prior to initiation of platinum treatment, then every 2 cycles from start of platinum treatment (every 2 cycles ±7 Days) during the Platinum Rechallenge. Lesion assessment will be by RECIST v1.1. In addition to local assessment, upon request, all imaging performed while patient is 'on-study' is to be sent to EpicentRx within six (6) weeks of procedure visit for independent radiology review. Reference Appendix F for format and shipping instructions. During the 'follow-up period', for subjects continuing to be imaged at the study site, a copy of the imaging and local radiology report will be made available upon request. Subjects may choose to withdraw from making their imaging available during the follow-up period (once they are 'off-study').
3. Premedication with 10 mg of dexamethasone, or a similar corticosteroid, and a low-dose aspirin (81 mg) or Acetaminophen (500 mg) is required within 2 hours prior to the infusion of RRx-001 blood mix. If patient is already receiving dexamethasone or equivalent corticosteroid, premedication with dexamethasone should not be given.

4. During the 'Platinum Rechallenege', Administer carboplatin AUC 5-6 IV on day 1 per protocol and approved package insert every 21 days for 2 cycles.
5. New tumor biopsy, if feasible, will performed on an optional basis prior to infusion of RRx-001 (baseline) and prior to initial platinum rechallange Day 1 (up to 7 Days prior but following discontinuation of RRx-001). Archival tissue, if available, will be collected at baseline. For details regarding the processing of samples please refer to the latest study lab manual.
6. For women of childbearing potential (WOCBP), a negative serum or urine pregnancy test is required prior to entering this study. WOCBP and men whose partners are able to become pregnant will be asked to use non-hormonal methods of contraception for the entire duration of the study and for up to 90 days after their last dose with RRx-001 and through platinum phase.
7. To be collected and sent to sponsor-designated central lab and may be collected up to 3 days prior to treatment administration. Blood samples will be drawn from all subjects by venipuncture or central venous catheter. For detailed collection, processing, and shipment requirements reference the Collection Flow Chart in the latest study lab manual.
8. If subject demonstrates progressive disease (PD) during platinum treatment, treatment will be discontinued and subject will complete End of Study (EOS) visit within 30 days of termination of platinum dosing and move into follow-up period. **If subject has ≥ SD at discontinuation of Platinum Rechallenge period, subject continues onto maintenance portion of ARM 1 (see section below)**.
9. Follow-up Period begins when patient has PD during Platinum Rechallenge or RRx-001/Platinum Maintenance treatment, or discontinues treatment for any other reason. Survival contact will occur via medical record review, telephone call or Social Security Death Index every 8 weeks (± 7 days) until death. For subjects continuing to be imaged at the study site, a copy of the imaging and local radiology report will be made available upon request. Subjects may choose to withdraw from making their imaging available during the follow-up period (once they are 'off-study').

Ovarian (Arm 1, table 2 of 2) RRx-001 & Platinum (single agent) 'Maintenance'

1 Week RRx-001 followed by 2 Cycles Platinum (Carboplatin), repeating until PD

(For Subjects with ≥ SD at Discontinuation of 'Platinum Rechallenge')

Assessment / Procedure	RRx-001 Maintenance ±3 day window unless otherwise stated in footnotes Each Cycle D 1	Platinum Maintenance ±3 day window unless otherwise stated in footnotes Each Cycle D 1	Imaging Assessment q2 platinum cycles (± 7 days)	End of Study (EOS)[5]	Follow-up Period[6] (± 7 days)
Physical Exam[1]	X	X		X	
Vital Signs	X	X		X	
ECOG Status	X	X		X	
Lesion Assessment by diagnostic CT with contrast[2]			X		
Administer RRx-001[3]	X				
Administer Platinum (Carboplatin) Chemotherapy[4]		X			
CBC and CMP (incl Magnesium, LDH)	X	X		X	
Record adverse events	X	X		X	
Record concomitant therapies, medications and/or procedures	X	X		X	
Visual Analogue Fatigue Scale (Appendix D)	X	X			
Survival Contact					X

1. Maintenance RRx-001 and Platinum physical exams may be symptom-directed. Each PE must include vital signs and weight.
2. During the Maintenance RRx-001 and Platinum period, a diagnostic CT with contrast must be performed **every 2 platinum cycles** (approximately every 7 weeks ±7 Days). Lesion assessment will be by RECIST v1.1. In addition to local assessment, upon request, all imaging performed while patient is 'on-study' is to be sent to EpicentRx within six (6) weeks of procedure visit for independent radiology review. Reference Appendix F for format and shipping instructions. During the 'follow-up period', for subjects continuing to be imaged at the study site, a copy of the imaging and local radiology report will be made available upon request. Subjects may choose to withdraw from making their imaging available during the follow-up period (once they are 'off-study').
3. Premedication with 10 mg of dexamethasone, or a similar corticosteroid, and a low-dose aspirin (81 mg) or Acetaminophen (500 mg) is required within 2 hours prior to the infusion of RRx-001 blood mix. If patient is already receiving dexamethasone or equivalent corticosteroid, premedication with dexamethasone should not be given.
4. During 'Platinum Maintenance', Administer carboplatin AUC 5-6 IV on day 1 as **a single agent** per protocol and approved package insert every 21 days for 2 cycles.
5. If subject demonstrates progressive disease (PD) during RRx-001/Platinum Maintenance, treatment will be discontinued and subject will complete End of Study (EOS) visit within 30 days of termination of treatment and move into follow-up period.
6. Follow-up Period begins when patient has PD during Platinum Rechallenge or RRx-001/ Platinum Maintenance treatment, or discontinues treatment for any other reason. Survival contact will occur via medical record review, telephone call or Social Security Death Index every 8 weeks (± 7 days) until death. For subjects continuing to be imaged at the study site, a copy of the imaging and local radiology report will be made available upon request. Subjects may choose to withdraw from making their imaging available during the follow-up period (once they are 'off-study').

SCC & Ovarian (Arm 2): "Investigator's Choice"

Assessment / Procedure	Screening ≤ 14 days of C1 D1	Investigator's Choice ±3 day window unless otherwise stated in footnotes			Imaging Assessment Per SOC Intervals *approximately every 6-8 wks ± 7 days*	End of Study (EOS)[5]	Follow-up Period[6] (± 7 days)
		C 1 D 1	C 1 D 8	C 2+ D 1			
Informed Consent	X						
Med/Onc History	X						
Demographics	X						
Physical Exam[1]	X	X	X	X		X	
Vital Signs	X	X	X	X		X	
ECOG Status	X	X	X	X		X	
Lesion Assessment by diagnostic CT with contrast[2]	X				X		
Administer Investigator's Choice Chemotherapy[3]		X		X			
CBC and CMP (incl Magnesium, LDH)	X	X	X	X		X	
Pregnancy Test[4]	X						
Record adverse events	X	X	X	X		X	
Record concomitant therapies, medications and/or procedures	X	X	X	X		X	
Visual Analogue Fatigue Scale (Appendix D)	X	X		X			
Survival Contact							X

1. Full physical exam is required at Screening. Subsequent physical exams may be symptom-directed. Each PE must include vital signs and weight.
2. Screening imaging must be obtained within 14 days prior to C1D1. A diagnostic CT with contrast must be performed every 6-8 weeks ±7 Days per standard of care until progression or intolerable toxicity. SCC patients also require a Brain MRI within 8 weeks prior to C1D1 (does not need to be repeated if SOC imaging performed within window; head CT is allowed if MRI is contraindicated). Lesion assessment will be by RECIST v1.1. In addition to local assessment, upon request, all imaging performed while patient is 'on-study' is to be sent to EpicentRx within six (6) weeks of procedure visit for independent radiology review. Reference Appendix F for format and shipping instructions. During the 'follow-up period', for subjects continuing to be imaged at the study site, a copy of the imaging and local radiology report will be made available upon request. Subjects may choose to withdraw from making their imaging available during the follow-up period (once they are 'off-study').
3. Administer Investigator's Choice Treatment per protocol and approved package insert until progression or intolerable toxicity.
4. For women of childbearing potential (WOCBP), a negative serum or urine pregnancy test is required prior to entering this study. WOCBP and men whose partners are able to become pregnant will be asked to use non-hormonal methods of contraception for the entire duration of the study and for up to 90 days after their last dose with RRx-001 and through platinum phase.
5. If subject demonstrates progressive disease (PD) during investigator's choice treatment, treatment will be discontinued and subject will complete End of Study (EOS) visit within 30 days of termination of treatment dosing and move into follow-up period.
6. Follow-up Period begins when patient has PD during investigator's choice treatment, or discontinues treatment for any other reason. Survival contact will occur via medical record review, telephone call or Social Security Death Index every 8 weeks (± 7 days) until death. For subjects continuing to be imaged at the study site, a copy of the imaging and local radiology report will be made available upon request. Subjects may choose to withdraw from making their imaging available during the follow-up period (once they are 'off-study').

Neuroendocrine Sequential Treatment: Weekly RRx-001 Therapy (21-day cycle) until progression followed by Cisplatin/Carboplatin + Etoposide Therapy (21-day cycles) x 4-6 Cycles

Assessment / Procedure	Screening ≤ 28 days of C1 D1	RRx-001 Therapy until progression						Platinum Therapy 4-6 cycles			Imaging Assessment q2 cycles (± 7 days)	End of Study (EOS)[9]	Follow-up Period[10] (± 7 days)
		±3 day window unless otherwise stated in footnotes											
		C 1 D 1	C 1 D 8	C 1 D 15	C 2+ D 1	C 2+ D 8	C 2+ D 15	C 1 D 1	C 1 D 8	C 2-6 D 1			
Informed Consent	X												
Med/Onc History	X												
Demographics	X												
Physical Exam[1]	X	X	X	X	X			X	X	X		X	
Vital Signs	X	X	X	X				X	X	X		X	
ECOG Status	X	X	X	X	X			X	X	X		X	
Lesion Assessment by diagnostic CT with contrast[2]	X							X			X		
Administer RRx-001[3]		X	X	X	X	X	X						
Administer Platinum-Based Chemotherapy[4]								X		X			
CBC and CMP (incl Magnesium, LDH)	X	X	X	X	X			X	X	X		X	
Beta Natriuretic Peptide (BNP)[5]	X									X (C6 only)			
Hemoglobin A1C (HbA1C)	X									X (C6 only)			
25-OH vitamin D (25-OHD)	X									X (C6 only)			
Tumor Tissue[6]	X							X					
Pregnancy Test[7]	X												
Record adverse events	X	X	X	X	X	X	X	X	X	X		X	
Record concomitant therapies, medications and/or procedures	X	X	X	X	X	X	X	X	X	X		X	
Visual Analogue Fatigue Scale (Appendix D)	X	X			X			X		X			
Central Lab Collection: Circulating Tumor Cells (CTCs)[8]		X						X					
Central Lab Collection: Immune Subsets[8]		X						X					
Central Lab Collection: Lysine Acetylation[8]		X						X					
Central Lab Collection: CEC/CEP[8]		X						X					
Central Lab Collection: Serum miRNA Analysis[8]		X						X					
Survival Contact													X

1. Full physical exam is required at Screening. Subsequent physical exams may be symptom-directed. Each PE must include vital signs and weight.
2. Screening imaging must be obtained within 28 days prior to C1D1. A diagnostic CT with contrast must be performed every 2 cycles from start of RRx-001 treatment (every 2 cycles ±7 Days), prior to initiation of platinum treatment, then every 2 cycles from start of platinum treatment (every 2 cycles ±7 Days). Lesion assessment will be by RECIST v1.1. In addition to local assessment, upon request, all imaging performed while patient is 'on-study' is to be sent to EpicentRx within six (6) weeks of procedure visit for independent radiology review. Reference Appendix F for format and shipping instructions. During the 'follow-up period', for subjects continuing to be imaged at the study site, a copy of the imaging and local radiology report will be made available upon request. Subjects may choose to withdraw from making their imaging available during the follow-up period (once they are 'off-study').
3. Premedication with 10 mg of dexamethasone, or a similar corticosteroid, and a low-dose aspirin (81 mg) or Acetaminophen (500 mg) is required within 2 hours prior to the infusion of RRx-001 blood mix. If patient is already receiving dexamethasone or equivalent corticosteroid, premedication with dexamethasone should not be given.
4. Administer carboplatin AUC 5-6 IV on day 1 or cisplatin 60-80 mg/m^2 IV on day 1 plus second agent per protocol and approved package insert every 21 days for 4-6 cycles.
5. Only to be performed if subject is a smoker.
6. New tumor biopsy, if feasible, will performed on an optional basis prior to infusion of RRx-001 (baseline) and prior to initial platinum rechallange Day 1 (up to 7 Days prior but following discontinuation of RRx-001). Archival tissue, if available, will be collected at baseline. For details regarding the processing of samples please refer to the latest study lab manual.
7. For women of childbearing potential (WOCBP), a negative serum or urine pregnancy test is required prior to entering this study. WOCBP and men whose partners are able to become pregnant will be asked to use non-hormonal methods of contraception for the entire duration of the study and for up to 90 days after their last dose with RRx-001 and through platinum phase.
8. To be collected and sent to sponsor-designated central lab and may be collected up to 3 days prior to or after visits. Blood samples will be drawn from all subjects by venipuncture or central venous catheter. For detailed collection, processing, and shipment requirements reference the Collection Flow Chart in the latest study lab manual.
9. If subject demonstrates progressive disease (PD) during platinum treatment, treatment will be discontinued and subject will complete End of Study (EOS) visit within 30 days of termination of platinum dosing and move into long-term follow-up (LTFU).
10. Follow-up Period begins when patient has PD during platinum treatment or RRx-001 Maintenance treatment, or discontinues treatment for any other reason. Subjects with stable disease or better (SD, PR or CR) at discontinuation of platinum treatment continue into the RRx-001 Maintenance Phase until progression (see RRx-001 Maintenance Phase, End of Study Visit, and Follow-up). Survival contact will occur via medical record review, telephone call or Social Security Death Index every 8 weeks (± 7 days) until death. For subjects continuing to be imaged at the study site, a copy of the imaging and local radiology report will be made available upon request. Subjects may choose to withdraw from making their imaging available during the follow-up period (once they are 'off-study').

NSCLC Sequential Treatment: Weekly RRx-001 Therapy (21-day cycle) x 1 Cycle followed by Cisplatin/Carboplatin + Second Agent Therapy (21-day cycles) x 4-6 Cycles

Assessment / Procedure	**Screening ≤28 days of C0 D1**	**C 0 D 1**	**±3 day window unless otherwise stated in footnotes**							**Imaging Assessment**	**End of Study (EOS)[9]**	**Follow-up Period[10] (± 7 days)**
			C 0 D 8	**C 0 D 15**	**C 1 D 1**	**C 1 D 8**	**C1 D 15**	**C 2-6 D 1**	**C 2-6 D 8**	**C 2-6 D 15**	**q2 cycles (± 7 days)**	
Informed Consent	X											
Med/Onc History	X											
Demographics	X											
Physical Exam[1]	X	X	X	X	X	X		X				X	
Vital Signs	X	X	X	X	X	X		X				X	
ECOG Status	X	X	X	X	X	X		X				X	
Lesion Assessment by diagnostic CT with contrast[2]	X			X							X		
Administer RRx-001[3]		X	X	X									
Administer Platinum-Based Chemotherapy[4]					X[4]								
CBC and CMP (incl Magnesium, LDH)	X	X	X	X	X	X		X				X	
Beta Natriuretic Peptide (BNP)[5]	X							X (C6 only)					
Hemoglobin A1C (HbA1C)	X							X (C6 only)					
25-OH vitamin D (25-OHD)	X							X (C6 only)					
Tumor Tissue[6]	X				X								
Pregnancy Test[7]	X												
Record adverse events	X	X	X	X	X	X		X				X	
Record concomitant therapies, medications and/or procedures	X	X	X	X	X	X		X				X	
Visual Analogue Fatigue Scale (Appendix D)	X	X			X			X					
Central Lab Collection: Circulating Tumor Cells (CTCs)[8]		X			X								
Central Lab Collection: Immune Subsets[8]		X			X								
Central Lab Collection: Lysine Acetylation[8]		X			X								
Central Lab Collection: CEC/CEP[8]		X			X								
Central Lab Collection: Serum miRNA Analysis[8]		X			X								
Survival Contact													X

* If patient experiences disease progression during Cycle 0 before 3 doses have been administered, subject may discontinue RRx-001 and proceed to Cisplatin/Carboplatin + Partner Agent Treatment

1. Full physical exam is required at Screening. Subsequent physical exams may be symptom-directed. Each PE must include vital signs and weight.
2. Screening imaging must be obtained within 28 days prior to C0D1. A diagnostic CT with contrast must be performed at the end of Cycle 0, prior to initiation of platinum treatment, then every 2 cycles from start of platinum treatment (every 2 cycles ±7 Days). Lesion assessment will be by RECIST v1.1. In addition to local assessment, upon request, all imaging performed while patient is 'on-study' is to be sent to EpicentRx within six (6) weeks of procedure visit for independent radiology review. Reference Appendix F for format and shipping instructions. During the 'follow-up period', for subjects continuing to be imaged at the study site, a copy of the imaging and local radiology report will be made available upon request. Subjects may choose to withdraw from making their imaging available during the follow-up period (once they are 'off-study').
3. Premedication with 10 mg of dexamethasone, or a similar corticosteroid, and a low-dose aspirin (81 mg) or Acetaminophen (500 mg) is required within 2 hours prior to the infusion of RRx-001 blood mix. If patient is already receiving dexamethasone or equivalent corticosteroid, premedication with dexamethasone should not be given.
4. Administer carboplatin AUC 5-6 IV on day 1 or cisplatin 60-80 mg/m^2 IV on day 1 plus second agent per protocol and approved package insert every 21 days for 4-6 cycles. For subjects receiving pegylated liposomal doxorubicin, cycles will be 4 weeks (28-days) in length.
5. Only to be performed if subject is a smoker.
6. New tumor biopsy, if feasible, will performed on an optional basis prior to infusion of RRx-001 (baseline) and prior to initial platinum rechallange Day 1 (up to 7 Days prior but following discontinuation of RRx-001). Archival tissue, if available, will be collected at baseline. For details regarding the processing of samples please refer to the latest study lab manual.
7. For women of childbearing potential (WOCBP), a negative serum or urine pregnancy test is required prior to entering this study. WOCBP and men whose partners are able to become pregnant will be asked to use non-hormonal methods of contraception for the entire duration of the study and for up to 90 days after their last dose with RRx-001 and through platinum phase.
8. To be collected and sent to sponsor-designated central lab and may be collected up to 3 days prior to or after visits. Blood samples will be drawn from all subjects by venipuncture or central venous catheter. For detailed collection, processing, and shipment requirements reference the Collection Flow Chart in the latest study lab manual.
9. If subject demonstrates progressive disease (PD) during platinum treatment, treatment will be discontinued and subject will complete End of Study (EOS) visit within 30 days of termination of platinum dosing and move into long-term follow-up (LTFU).
10. Follow-up Period begins when patient has PD during platinum treatment or RRx-001 Maintenance treatment, or discontinues treatment for any other reason. Subjects with stable disease or better (SD, PR or CR) at discontinuation of platinum treatment continue into the RRx-001 Maintenance Phase until progression (see RRx-001 Maintenance Phase, End of Study Visit, and Follow-up). Survival contact will occur via medical record review, telephone call or Social Security Death Index every 8 weeks (± 7 days) until death. For subjects continuing to be imaged at the study site, a copy of the imaging and local radiology report will be made available upon request. Subjects may choose to withdraw from making their imaging available during the follow-up period (once they are 'off-study').

RRx-001 Maintenance Treatment Schedule: For Neuroendocrine & NSCLC; 21-Day Cycle (until PD)

Assessment / Procedure	±3 day window unless otherwise stated in footnotes			Imaging Assessment q2 cycles (± 7 days)	End of Study (EOS)[4]	Follow-up Period[5] (± 7 days)
	Each Cycle D 1	Each Cycle D 8	Each Cycle D 15			
Physical Exam[1]	X				X	
Vital Signs					X	
ECOG Status					X	
Administer RRx-001[2]	X	X	X			
Lesion Assessment by diagnostic CT with contrast[3]				X		
CBC and CMP (incl Magnesium, LDH)	X		X		X	
Record adverse events	X	X	X		X	
Record concomitant therapies, medications and/or procedures	X	X	X		X	
Visual Analogue Fatigue Scale (Appendix D)	X					
Central Lab Collection: Circulating Tumor Cells (CTCs)[6]	X					
Survival Contact						X

1. Physical exams may be symptom-directed.
2. Premedication with 10 mg of dexamethasone, or a similar corticosteroid, and a low-dose aspirin (81 mg) or Acetaminophen (500mg) is required within 2 hours prior to the infusion of RRx-001 blood mix. If patient is already receiving dexamethasone or equivalent corticosteroid, premedication with dexamethasone should not be given.
3. A diagnostic CT with contrast must be performed every 2 cycles from start of RRx001 maintenance treatment (every 2 cycles ±7 Days). Assessment will be by RECIST v1.1. In addition to local assessment, upon request, all imaging performed while patient is 'on-study', including screening, is to be sent to EpicentRx within six (6) weeks of procedure visit for independent radiology review. Reference Appendix F for format and shipping instructions.
4. End of Study (EOS) visit is to be performed at the time of progression on RRx-001 Maintenance treatment. Patients will then move into long-term follow-up (LTFU).
5. Follow-up Period begins when patient has PD during platinum + RRx-001 treatment or RRx-001 Maintenance treatment, or discontinues treatment for any other reason. Survival contact will occur via medical record review, telephone call or Social Security Death Index every 8 weeks (± 7 days) until death. For patients continuing to be imaged at the study site, a copy of the imaging and local radiology report will be made available upon request. Patients may choose to withdraw from making their imaging available during the follow-up period (once they are 'off-study').
6. To be collected and sent to sponsor-designated central lab and may be collected up to 3 days prior to or after visits. Blood samples will be drawn from all patients by venipuncture or central venous catheter. For detailed collection, processing, and shipment requirements reference the latest study lab manual.