[INSERT SITE NAME]
Consent to Act as a Research Subject

RRx-001 in patients with small cell carcinoma, high-grade neuroendocrine carcinoma, EGFR mutation positive non-small cell lung cancer or ovarian cancer (including Malignant Mixed Mullerian Tumor (MMMT) of the ovary or uterus) previously treated with a platinum-based regimen (QUADRUPLE THREAT)
Protocol No. RRx001-211-01

INTRODUCTION

[INSERT PI] and his/her colleagues are conducting a research study sponsored by EpicentRx, Inc. to find out more about the experimental drug called RRx-001. You are being asked to take part because you have Small Cell Carcinoma (SCC), EGFR Positive T790M Negative, T790M Negative or T790M Positive Non-Small Lung Cancer (NSCLC), High Grade Neuroendocrine Cancer (HGNEC), or Resistant or Refractory Epithelial Ovarian Cancer (EOC) or Malignant Mixed Mullerian Tumors (MMMT) of the uterus or ovaries.

This study is being done for research. Your participation in this research study is voluntary. The purpose of this Informed Consent Form is to give you the information necessary to make an informed, voluntary choice about whether you would like to participate in this study. Any new information or knowledge, which develops during the course of this study that may impact your safety or your willingness to participate will be shared with you. Should you decide that you do not wish to participate in this study, you will not lose any benefits and/or access to treatment(s) to which you would have been otherwise entitled. If you have any questions, please ask your study doctor or coordinator to explain any words or information that you do not understand.

PURPOSE

One of the biggest obstacles in oncology (cancer treatment) is the almost inevitable development of drug resistance, which leaves patients with fewer and fewer options for further treatment. The expression “what does not kill me makes me stronger” also applies to cancer cells, which are able to actively adapt to the threat of chemotherapy and survive, even if they were initially slowed down or stopped by it. The unwritten rule in oncology is ‘once resistant, always resistant’, which means that cancer cells are able to ‘remember’ how to outsmart particular chemotherapy drugs that they have seen before, and this is why doctors tend to abandon them completely in favor other drugs or treatment strategies once resistance develops. The purpose of this study is to see if the investigational drug, RRx-001, can overturn this unwritten rule, and make chemotherapy that you previously received, and either initially responded to or not, have an effect, in other words, *sensitize* (or *resensitize*) your tumors to chemotherapy. The ability to sensitize or go back to failed chemotherapy may

improve and increase your options and, ultimately, your overall survival. Like the title of this study, it is hoped that RRx-001 will have "quadruple threat" activity and resensitize to chemotherapy in three forms of lung cancer and ovarian cancer.

The study has four (4) 'cohorts;' one for each of the types of tumors being studied: Small Cell Carcinoma (SCC), EGFR Positive Non-Small Cell Lung Cancer (NSCLC), High Grade Neuroendocrine Cancer (HGENC) and Resistant or Refractory Epithelial Ovarian Cancer (EOC) or Malignant Mixed Mullerian Tumors (MMMT) of the uterus or ovaries. The terms "resistant" and "refractory" refer to the lack of responsiveness of the tumor to previous therapy such as carboplatin and cisplatin, which is what you received previously to treat your cancer. The term "EGFR positive" refers to tumors that carry a mutation or change in the EGFR protein, which causes cells to grow uncontrollably. The EGFR protein has 1,210 amino acids. Amino acids form the building blocks of proteins. EGFR with no mutation at amino acid position 790 has a threonine, or T for short; this is called T790M negative cancer, which, as a participant on this trial, is what you may have. The amino acid at position 790 in EGFR with the T790M mutation is a methionine, or M for short; this is called T790M positive cancer. In general, T790M negative cancer is more aggressive than T790M positive cancer.

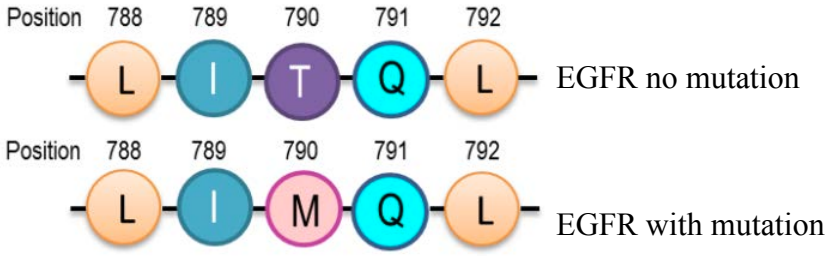

Figure 1: EGFR T790 mutation.

You will be treated with the standard of care chemotherapy as well as best supportive care, regardless of which study group or cohort you participate in. Subjects in some groups will also receive the experimental drug, RRx-001. The timing or schedule of your treatment will depend on the cohort you are in. The four cohorts are shown in Figure 2 and described below.

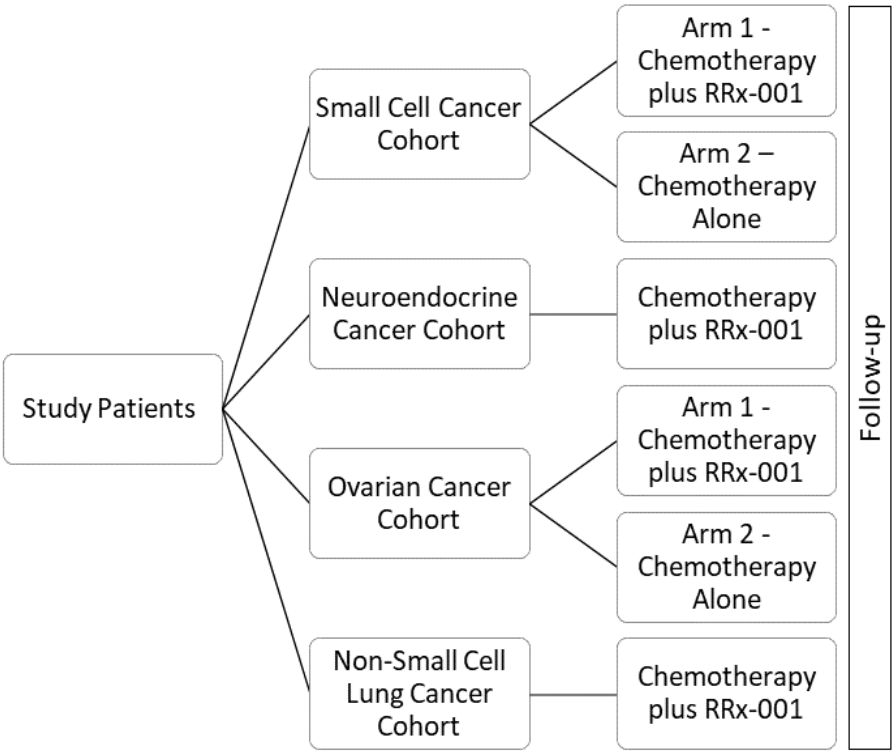

Figure 2: Study treatment group schema.

Small Cell Carcinoma Cohort:

Subjects with small cell carcinoma will be assigned randomly or randomized to one of two different study groups or "arms". Subjects assigned to arm 1 will receive a) RRx-001 for 3 weeks b) *followed by* cisplatin/carboplatin plus etoposide for up to four cycles c) *followed by* a repeating pattern of RRx-001 given once every week for two weeks and then two three-week cycles of cisplatin/carboplatin plus etoposide. If at the end of your second cycle of cisplatin/carboplatin plus etoposide your tumors are stable to smaller, part "c" repeats. When and if your tumors enlarge or get worse your participation on study ends. Subjects assigned to arm 2 will receive cisplatin/carboplatin plus etoposide chemotherapy until your tumors worsen or progress. You do not get to choose which arm you are assigned to. A computer program will choose which arm you are assigned to. Twice as many patients will be randomized to arm 1 than arm 2. In other words, there is a 2/3 or 66% chance that you will be randomized to arm 1, which is RRx-001 plus chemotherapy and 1/3 or 33% chance that you will be randomized to arm 2, which is chemotherapy only.

Non-Small Cell Lung Cancer (NSCLC) Cohort:

- If you have EGFR Positive Non-Small Cell Lung Cancer (NSCLC) you will receive RRx-001 for 3 weeks followed by cisplatin/carboplatin plus one of the following: paclitaxel, albumin bound paclitaxel (this is called nab-paclitaxel or Abraxane), or pemetrexed for up to 6 cycles. If, at the end of cisplatin/carboplatin plus another chemotherapy agent, your tumors are stable to smaller, you will receive weekly

treatment with RRx-001 until your tumors worsen or progress. At this point, if tumor worsening or progression occurs, your participation on study ends.

High Grade Neuroendocrine Cancer (HGNEC) Cohort:

- If you have High Grade Neuroendocrine Cancer (HGNEC), you will receive RRx-001 until your cancer gets worse followed by up to 6 cycles of chemotherapy, which is cisplatin/carboplatin plus etoposide. If, at the end of cisplatin/carboplatin plus etoposide, your tumors are stable to smaller, you will receive weekly treatment with RRx-001 until your tumors worsen or progress. At this point, if tumor worsening or progression occurs, your participation on study ends.

Resistant/Refractory Epithelial Ovarian Cancer (EOC) or Malignant Mixed Mullerian Tumors Cohort:

- Subjects with Resistant/Refractory Epithelial Ovarian Cancer (EOC) or Malignant Mixed Mullerian Tumors of the uterus or ovaries will be assigned randomly or randomized to one of two different study groups or "arms". Subjects assigned to arm 1 will receive a) RRx-001 for 2 weeks b) *followed by* carboplatin for 3 cycles or 3 times c) *followed by* a repeating pattern of RRx-001 for 1 time, carboplatin for 3 cycles or 3 times, RRx-001 for 1 time, carboplatin for 3 cycles or 3 times etc. until your tumors worsen or progress on carboplatin. When and if tumor worsening or progression occurs, your participation on study ends. If you are assigned to arm 2, you will receive standard of care chemotherapy, which may include carboplatin, etoposide, doxil, gemcitabine, vinorelbine, or taxane until your tumors worsen or progress. You do not get to choose which arm you are assigned to. A computer program will choose which arm you are assigned to. Twice as many patients will be randomized to arm 1 than arm 2. In other words, there is a 2/3 or 66% chance that you will be randomized to arm 1, which is RRx-001 plus chemotherapy and 1/3 or 33% chance that you will be randomized to arm 2, which is chemotherapy only.

Cisplatin and carboplatin are a type of platinum-based chemotherapy. These are combinations of chemotherapy drugs that contain derivatives of the metal platinum. Another example of a platinum-based chemotherapy is oxaliplatin. The combination of cisplatin or carboplatin with another chemotherapy agent is called a "platinum doublet", a term, which is used throughout, since the word doublet, refers to "a pair".

Approximately 213 patients will be enrolled in this study nationwide.

A detailed explanation of what will take place during the study is explained below. If you have any questions, or if there is any word or procedure(s), which do not make sense, ask the doctor or study staff to explain them to you before signing this form (should you wish to participate).

DESCRIPTION OF RRX-001

RRx-001 stimulates immune cells in the tumor called macrophages (literally "big eaters"). The job of a macrophage is to engulf or swallow up invaders like bacteria, viruses and even cancer cells. The best analogy or comparison for how a macrophage behaves is the famous "hungry" character named Pac-Man from the popular arcade game in the 1980s. (Figure 3) Like Pac-Man, who is guided through an electronic maze as he "chomps on" yellow dots or pellets, the macrophage or "Mac-Man", in this case, normally travels through the bloodstream seeking out and gobbling up hostile or foreign invaders. Unfortunately for the patient, however, in advanced cancer the job description of a macrophage is changed from a killer of cancer cells to the protector or bodyguard of cancer cells, which explains why they are often found in high numbers in the tumor.

Figure 3. Like Pac-Man that gobbles up yellow energy dots, macrophages normally engulf or swallow foreign or hostile invaders except in advanced cancer where their role becomes that of tumor cell protectors instead of tumor cell killers.

DURATION OF THE STUDY / HOW LONG IS EACH VISIT?

While you participate in this study, you will receive chemotherapy with or without the study drug, RRx-001. The duration of the study depends on which cohort you are in (as described above). Each of your study visits can last from approximately 1 to 2 hours.

STUDY PROCEDURES

Screening

Screening will last approximately 28 days. If you agree to be in this research study, you will be asked to sign this consent form before the following screening procedures are performed to determine if you are eligible for the study. These screening tests may be performed over multiple days and can take between 4 and 8 hours to complete.

- An occupational, family, social and medical history which will include questions about your cancer diagnosis and treatment as well as your health and any past or present medical problems and a review of medications, vitamins, and dietary supplements you have taken in the past or are taking now.
- Physical examination
- Measurement of your height, weight and vital signs (including sitting blood pressure, heart rate, breathing rate and oral temperature)
- Approximately 3 teaspoons of blood will be taken to check your overall health and the health of your organs (i.e. liver and kidneys). The blood will be collected from a vein in your arm.
- Approximately 2 teaspoons of blood will be taken for exploratory research studies. The purpose of these studies is to look at the health of your heart, blood vessels and bones before you start the study. The blood will be collected from a vein in your arm.
- A pregnancy test if you are female and able to get pregnant. You must have a negative pregnancy test to enter this study and receive RRx-001. Women, or men whose partner is of child bearing potential will be asked to continue the use of hormonal or non-hormonal methods of birth control while in the study and for up to 90 days after withdrawal from the study.
- CT imaging of your tumor(s).
    - The CT scanner is a free-standing machine with a large hole in the center. You will be asked to lie on your back with your arms raised above your head on a narrow table that slides into the hole. A dye may be injected into a peripheral vein (veins in the arms, feet, legs and hands that supply oxygenated blood to the body) to better evaluate certain diseases and organs. The radiologist will decide if this is necessary. Tell the technician or radiologist if you have any allergies to contrast dye or have had difficulty with prior CT scans. It is very important that you remain still throughout the exam and hold your breath when asked. This will allow for better images. The actual scan time is usually about two minutes, although the entire procedure may take up to 2 hours.
- If you have **SCC**, you will also have a CT or MRI of the brain
- Tumor Biopsy: If you and the doctor feel that it is in your best interest, based on your health and the current status of your disease, we would like to offer you the ability to get your tumor biopsied prior to starting any study medication. The procedure offered

would be a biopsy of your tumor and/or collection of archival tumor tissue from a previous biopsy of your tumor. If you and the doctor decide that it is in your best interest to undergo a biopsy of your tumor, all risks will be explained to you before the procedure and trained and credentialed staff will perform the procedure. The risks of this procedure include, but are not limited to: pain, bleeding, infection and hospital admissions.

A biopsy and/or collection of archival tissue is not required for your participation in this research study. There may be no direct benefit to you from collection of archival tissue and/or a biopsy; however, the doctor and/or researchers may learn more about your tumor(s) and how to treat them.

Study Treatment

If the exams, tests and procedures show that you can be in the study and you choose to take part, then you will be assigned to one of the four treatment cohorts depending on the type of cancer that you have. In addition to chemotherapy treatment and/or the study drug, RRx-001, , you will also receive best supportive care which includes treatments to help manage side effects and symptoms of cancer. This is an open label study, which means you will know the names of the drugs that you receive.

You will be scheduled to return to the study site for the Day 1 visit of the first (1st) period. Additional study visits will occur weekly. You will be asked to continue the use of hormonal or non-hormonal methods of birth control and to return to all required clinic visits during the entire treatment part of study and for 90 days following completion of therapy.

About RRx-001 treatment

Depending on what arm you are assigned to, you may receive the study drug, RRx-001. RRx-001 is given once a week through a vein in your arm or through a catheter or 'port' in your chest. When you come into the clinic for treatment, the doctor or study staff will withdraw approximately 12 mL of your own blood through a vein in your arm or through a catheter or 'port' in your chest into a syringe containing 4 mg (2 mL) of RRx-001; for comparison, a teaspoon is equal to 5 mL, therefore 12 mL of blood is about 2 ½ teaspoons in volume. Using an investigational device called the eLOOP, the blood will be mixed with the study drug, RRx-001, and re-infused through a vein in your arm over a period of up to 30 minutes. This process is called "autohemotransfusion." The handling of blood by the study staff at [INSERT SITE] will be done according to the Institutional Standard of Care guidelines at [INSERT SITE]. Approximately 30 minutes before the infusion of RRx-001, you will receive pre-medications, such as dexamethasone, or another corticosteroid, and a Baby Aspirin (81 mg) or Acetaminophen (500 mg), to help with any pain associated with the infusion, although this is unlikely. Sometimes it may be necessary to slow down the infusion and administer RRx-001 over a longer time. Based on any side effects you are experiencing, dose interruptions and/or dose reductions are allowed if the doctor feels that it is in your best interest to do so. **When you do leave the clinic for the day**, **you should be accompanied by a caregiver that can carefully observe your physical condition and symptoms overnight and call the hospital if necessary.**

Below is a detailed description of the study procedures for each disease cohort and arm.

Small Cell Carcinoma Cohort – Arm 1

Period 1: RRx-001

During Period 1, the doctors and/or study staff will perform the following tests and/or procedures:

- A symptom directed physical exam and measurement of your height, weight and vital signs (to include your sitting blood pressure, heart rate, breathing rate and oral temperature).
- You will be asked about the medications you are currently taking ('Concomitant Medications') and any side effects you are experiencing.
- Approximately 2 teaspoons of blood will be taken weekly to check your overall health and the health of your organs (i.e. liver and kidneys).
- Approximately 9 teaspoons of blood will be taken on day 1 only for exploratory research studies. The purpose of these studies is to examine and analyze the genes, proteins, and cells found in the blood. The blood will be collected from a vein in your arm.
- You will receive RRx-001 once a week for 3 weeks.
- You will have a CT scan at the end of week 3.

Period 2: Platinum Chemotherapy

During Period 2, you will receive the following platinum-based chemotherapy regimen:

1) One of the following platinum agents:
   a) Cisplatin will be given through a vein in your arm 60-80 mg/m^2 on day 1 every 3 weeks.
   b) Carboplatin will be initially dosed through a vein in your arm at an area under the curve (AUC) or concentration of 5-6 on day 1 every 3 weeks.
2) Second agent to be combined with the platinum-based agent
   a) Etoposide will be initially dosed at 80-100 mg/m^2 days 1-3 every 3 weeks

You will also receive best supportive standard of care to help manage any side effects associated with your disease or the treatments you receive.

During Period 2, the doctors and/or study staff will perform the following tests and/or procedures:

- Prior to starting chemotherapy, you may have an optional biopsy of your tumor and/or collection of archival tumor tissue. This procedure is being done for research.

- A physical exam and measurement of your height, weight and vital signs (to include your sitting blood pressure, heart rate, breathing rate and oral temperature).
- You will be asked about the medications you are currently taking ('Concomitant Medications') and any side effects you are experiencing.
- Approximately 9 teaspoons of blood will be taken at the beginning of your platinum doublet treatment for exploratory research studies. The purpose of these studies is to examine and analyze the genes, proteins, and cells found in the blood. The blood will be collected from a vein in your arm.
- Approximately 2 teaspoons of blood will be taken on the first day of your last cycle of platinum doublet treatment for exploratory research studies. The purpose of these studies is to look at the health of your heart, blood vessels and bones before you start the study. The blood will be collected from a vein in your arm.
- Approximately 2 teaspoons of blood will be taken weekly to check your overall health and the health of your organs (i.e. liver and kidneys)
- You will receive a CT scan every 2 cycles during treatment with platinum doublets. Therefore, this will happen at the end of Cycle 2, or (6) weeks after your first day receiving platinum chemotherapy, and at the end of Cycle 4.

Period 3: Maintenance

You will receive a repeating pattern of RRx-001 for 1 time, carboplatin for 2 cycles or 2 times, RRx-001 for 1 time, carboplatin for 2 cycles or 2 times etc. until your tumors worsen or progress on carboplatin. When and if tumor worsening or progression occurs, your participation on study ends.

During Period 3, the doctors and/or study staff will perform the following tests and/or procedures:

- A physical exam and measurement of your height, weight and vital signs (to include your sitting blood pressure, heart rate, breathing rate and oral temperature).
- You will be asked about the medications you are currently taking ('Concomitant Medications') and any side effects you are experiencing.
- Approximately 2 teaspoons of blood will be on Day 1 of each RRx-001 and each platinum cycle to check your overall health and the health of your organs (i.e. liver and kidneys)
- You will receive a CT scan every 2 platinum chemotherapy cycles. Therefore, this will happen at the end of Cycle 2, or (8) weeks after starting period 3. This will continue every eight (8) weeks, or two (2) cycles, for as long as you continue on study.

Small Cell Carcinoma Cohort – Arm 2

Period 1: Standard of Care

During Period 1, you will receive one of the following treatment regimens. Your study doctor will decide what regimen is best for you:

1) Cisplatin or carboplatin plus etoposide
2) Irinotecan
3) Vinorelbine

You will also receive best supportive standard of care to help manage any side effects associated with your disease or the treatments you receive.

During Period 1, the doctors and/or study staff will perform the following tests and/or procedures:

- A physical exam and measurement of your height, weight and vital signs (to include your sitting blood pressure, heart rate, breathing rate and oral temperature).
- You will be asked about the medications you are currently taking ('Concomitant Medications') and any side effects you are experiencing.
- Approximately 2 teaspoons of blood will be taken weekly (for the first 2 weeks of each cycle) to check your overall health and the health of your organs (i.e. liver and kidneys)
- You will receive a CT scan approximately every 6-8 weeks during treatment.

Ovarian Cancer Cohort – Arm 1

Period 1: RRx-001

During Period 1, the doctors and/or study staff will perform the following tests and/or procedures:

- A symptom directed physical exam and measurement of your height, weight and vital signs (to include your sitting blood pressure, heart rate, breathing rate and oral temperature).
- You will be asked about the medications you are currently taking ('Concomitant Medications') and any side effects you are experiencing.
- Approximately 2 teaspoons of blood will be taken weekly to check your overall health and the health of your organs (i.e. liver and kidneys).
- Approximately 9 teaspoons of blood will be taken on day 1 only for exploratory research studies. The purpose of these studies is to examine and analyze the genes, proteins, and cells found in the blood. The blood will be collected from a vein in your arm.
- You will receive RRx-001 once a week for 2 weeks.

Period 2: Platinum Chemotherapy

During Period 2, you will receive carboplatin. Carboplatin will be initially dosed through a vein in your arm at an area under the curve (AUC) or concentration of 5-6 on day 1 every 3 weeks for two cycles.

You will also receive best supportive standard of care to help manage any side effects associated with your disease or the treatments you receive.

During Period 2, the doctors and/or study staff will perform the following tests and/or procedures:

- Prior to starting chemotherapy, you may have an optional biopsy of your tumor and/or collection of archival tumor tissue. This procedure is being done for research.
- A physical exam and measurement of your height, weight and vital signs (to include your sitting blood pressure, heart rate, breathing rate and oral temperature).
- You will be asked about the medications you are currently taking ('Concomitant Medications') and any side effects you are experiencing.
- Approximately 9 teaspoons of blood will be taken at the beginning of your platinum treatment for exploratory research studies. The purpose of these studies is to examine and analyze the genes, proteins, and cells found in the blood. The blood will be collected from a vein in your arm.
- Approximately 2 teaspoons of blood will be taken weekly to check your overall health and the health of your organs (i.e. liver and kidneys)
- You will receive a CT scan every 2 cycles during treatment with platinum chemotherapy. Therefore, this will happen at the end of Cycle 2.

Period 3: Maintenance

You will receive a repeating pattern of RRx-001 given once followed by two three-week cycles of carboplatin. If at the end of your second cycle of carboplatin your tumors are stable to smaller this treatment repeats. When and if your tumors enlarge or get worse your participation on study ends.

During Period 3, the doctors and/or study staff will perform the following tests and/or procedures:

- A physical exam and measurement of your height, weight and vital signs (to include your sitting blood pressure, heart rate, breathing rate and oral temperature).
- You will be asked about the medications you are currently taking ('Concomitant Medications') and any side effects you are experiencing.
- Approximately 2 teaspoons of blood will be on Day 1 of each RRx-001 and each platinum cycle to check your overall health and the health of your organs (i.e. liver and kidneys)

- You will receive a CT scan every 2 platinum chemotherapy cycles. Therefore, this will happen at the end of Cycle 2, or (7) weeks after starting period 3. This will continue every seven (7) weeks, or two (2) cycles, for as long as you continue on study.

Ovarian Cancer Cohort – Arm 2

Period 1: Standard of Care

During Period 1, you will receive one of the following treatment regimens. Your study doctor will decide what regimen is best for you:

1) Carboplatin
2) Etoposide
3) Doxil
4) Gemcitabine
5) Vinorelbine
6) Taxane

You will also receive best supportive standard of care to help manage any side effects associated with your disease or the treatments you receive.

During Period 1, the doctors and/or study staff will perform the following tests and/or procedures:

- A physical exam and measurement of your height, weight and vital signs (to include your sitting blood pressure, heart rate, breathing rate and oral temperature).
- You will be asked about the medications you are currently taking ('Concomitant Medications') and any side effects you are experiencing.
- Approximately 2 teaspoons of blood will be taken weekly (for the first 2 weeks of each cycle) to check your overall health and the health of your organs (i.e. liver and kidneys)
- You will receive a CT scan approximately every 6-8 weeks during treatment.

Neuroendocrine Cancer Cohort

Period 1: RRx-001

During Period 1, the doctors and/or study staff will perform the following tests and/or procedures:

- A symptom directed physical exam and measurement of your height, weight and vital signs (to include your sitting blood pressure, heart rate, breathing rate and oral temperature).
- You will be asked about the medications you are currently taking ('Concomitant Medications') and any side effects you are experiencing.

- Approximately 2 teaspoons of blood will be taken weekly to check your overall health and the health of your organs (i.e. liver and kidneys).
- Approximately 9 teaspoons of blood will be taken on day 1 only for exploratory research studies. The purpose of these studies is to examine and analyze the genes, proteins, and cells found in the blood. The blood will be collected from a vein in your arm.
- You will receive RRx-001 once a week until your tumors worsen or progress.
- You will receive a CT scan every six weeks (2 cycles) during treatment with RRx-001.

Period 2: Platinum Chemotherapy

During Period 2, you will receive the following platinum-based chemotherapy regimen:

1) One of the following platinum agents:
   a) Cisplatin will be given through a vein in your arm 60-80 mg/m^2 on day 1 every 3 weeks.
   b) Carboplatin will be initially dosed through a vein in your arm at an area under the curve (AUC) or concentration of 5-6 on day 1 every 3 weeks.
2) Second agent to be combined with the platinum-based agent
   a) Etoposide will be initially dosed at 80-100 mg/m^2 days 1-3 every 3 weeks

You will also receive best supportive standard of care to help manage any side effects associated with your disease or the treatments you receive.

During Period 2, the doctors and/or study staff will perform the following tests and/or procedures:

- Prior to starting platinum chemotherapy, you may have an optional biopsy of your tumor and/or collection of archival tumor tissue. This procedure is being done for research.
- A physical exam and measurement of your height, weight and vital signs (to include your sitting blood pressure, heart rate, breathing rate and oral temperature).
- You will be asked about the medications you are currently taking ('Concomitant Medications') and any side effects you are experiencing.
- Approximately 9 teaspoons of blood will be taken at the beginning of your platinum treatment for exploratory research studies. The purpose of these studies is to examine and analyze the genes, proteins, and cells found in the blood. The blood will be collected from a vein in your arm.
- Approximately 2 teaspoons of blood will be taken weekly to check your overall health and the health of your organs (i.e. liver and kidneys)
- You will receive a CT scan prior to starting period 2 and then every six weeks (2 cycles) during treatment with platinum chemotherapy.

Period 3: Maintenance

You will receive a RRx-001 given once a week until your tumors enlarge or get worse.

During Period 3, the doctors and/or study staff will perform the following tests and/or procedures:

- A physical exam and measurement of your height, weight and vital signs (to include your sitting blood pressure, heart rate, breathing rate and oral temperature).
- You will be asked about the medications you are currently taking ('Concomitant Medications') and any side effects you are experiencing.
- Approximately 2 teaspoons of blood will be taken on Day 1 of each cycle for exploratory research studies. The purpose of these studies is to examine and analyze the genes, proteins, and cells found in the blood. The blood will be collected from a vein in your arm.
- Approximately 2 teaspoons of blood will be on Day 1 and Day 15 of each cycle to check your overall health and the health of your organs (i.e. liver and kidneys)
- You will receive a CT scan every 2 cycles. Therefore, this will happen at the end of Cycle 2, or (6) weeks after starting period 3. This will continue every six (6) weeks, or two (2) cycles, for as long as you continue on study.

Non-Small Cell Lung Cancer Cohort

Period 1: RRx-001

During Period 1, the doctors and/or study staff will perform the following tests and/or procedures:

- A symptom directed physical exam and measurement of your height, weight and vital signs (to include your sitting blood pressure, heart rate, breathing rate and oral temperature).
- You will be asked about the medications you are currently taking ('Concomitant Medications') and any side effects you are experiencing.
- Approximately 2 teaspoons of blood will be taken weekly to check your overall health and the health of your organs (i.e. liver and kidneys).
- Approximately 9 teaspoons of blood will be taken on day 1 only for exploratory research studies. The purpose of these studies is to examine and analyze the genes, proteins, and cells found in the blood. The blood will be collected from a vein in your arm.
- You will receive RRx-001 once a week for 3 weeks.

Period 2: Platinum Chemotherapy

During Period 2, you will receive the following platinum-based chemotherapy regimen:

1) One of the following platinum agents:
   a) Cisplatin will be given through a vein in your arm 60-80 mg/m^2 on day 1 every 3 weeks.
   b) Carboplatin will be initially dosed through a vein in your arm at an area under the curve (AUC) or concentration of 5-6 on day 1 every 3 weeks.

2) Second agent to be combined with the platinum-based agent:
   a) Nab-Paclitaxel will be initially dosed at 100 mg/m^2 on days 1, 8, and 15 every 3 weeks
   b) Paclitaxel will be initially dosed at 175-225 mg/m^2 IV over 3 hours on day 1 every 3 weeks
   c) Pemetrexed will be initially dosed at 500 mg/m^2 IV over 10 minutes in 100 mL 0.9% NaCl on day 1 every 21 days for up to 6 cycles.

You will also receive best supportive standard of care to help manage any side effects associated with your disease or the treatments you receive.

During Period 2, the doctors and/or study staff will perform the following tests and/or procedures:

- Prior to starting platinum chemotherapy, you may have an optional biopsy of your tumor and/or collection of archival tumor tissue. This procedure is being done for research.
- A physical exam and measurement of your height, weight and vital signs (to include your sitting blood pressure, heart rate, breathing rate and oral temperature).
- You will be asked about the medications you are currently taking ('Concomitant Medications') and any side effects you are experiencing.
- Approximately 9 teaspoons of blood will be taken at the beginning of your platinum treatment for exploratory research studies. The purpose of these studies is to examine and analyze the genes, proteins, and cells found in the blood. The blood will be collected from a vein in your arm.
- Approximately 2 teaspoons of blood will be taken weekly to check your overall health and the health of your organs (i.e. liver and kidneys)
- Approximately 2 teaspoons of blood will be taken on the first day of your last cycle of platinum doublet treatment for exploratory research studies. The purpose of these studies is to look at the health of your heart, blood vessels and bones before you start the study. The blood will be collected from a vein in your arm.
- You will receive a CT scan prior to starting period 2 and then every six weeks (2 cycles) during treatment with platinum chemotherapy.

Period 3: Maintenance

You will receive a RRx-001 given once a week until your tumors enlarge or get worse.

During Period 3, the doctors and/or study staff will perform the following tests and/or procedures:

- A physical exam and measurement of your height, weight and vital signs (to include your sitting blood pressure, heart rate, breathing rate and oral temperature).
- You will be asked about the medications you are currently taking ('Concomitant Medications') and any side effects you are experiencing.
- Approximately 2 teaspoons of blood will be taken on Day 1 of each cycle for exploratory research studies. The purpose of these studies is to examine and analyze the genes, proteins, and cells found in the blood. The blood will be collected from a vein in your arm.
- Approximately 2 teaspoons of blood will be on Day 1 and Day 15 of each cycle to check your overall health and the health of your organs (i.e. liver and kidneys)
- You will receive a CT scan every 2 cycles. Therefore, this will happen at the end of Cycle 2, or (6) weeks after starting period 3. This will continue every six (6) weeks, or two (2) cycles, for as long as you continue on study.

PROGRESSIVE DISEASE STUDY PROCEDURES:

If the scan(s) show that your tumor(s) has/have progressed, for NSCLC and neuroendocrine tumors only, you will be scheduled to return to the clinic for the following assessments / procedures:

- A clinical assessment
- A physical exam and measurement of your height, weight and vital signs (to include your sitting blood pressure, heart rate, breathing rate and oral temperature).
- You will be asked about the medications you are currently taking ('Concomitant Medications') and any side effects you are experiencing.
- Approximately 3 teaspoons of blood will be taken to check your overall health and the health of your organs (i.e. liver and kidneys).

POST-TREATMENT SURVIVAL FOLLOW-UP

After your final visit to the clinic, you will be contacted every eight (8) weeks until you are unable to be contacted. During this period, the clinic staff may contact you by phone or in person.

If you are continuing to be imaged at the study site after your participation in this study is over, a copy of imaging may be requested by the study sponsor to see how your tumors respond to future therapies. You may choose to withdraw from making your imaging available during the follow-up period.

_____ **Yes,** you give permission for your imaging to be made available upon request following your completion of this study.

_____ **No,** you do **not** give permission for your imaging to be made available upon request following your completion of this study.

_____ _____
Signature of Participant Date

GENERAL DISCUSSION OF GENETICS

EpicentRx, Inc. will be responsible for deciding how your samples will be used. Blood taken from you may be used to establish products that could be patented and licensed. There are no plans to provide you with financial compensation should this occur. This blood and tissue and its derivatives may have significant therapeutic or commercial value. You consent to such uses. Your study doctor has no personal or financial interest in this research. If you decide later that you do not want the specimens collected from you to be used for future research, you may tell this to [INSERT PI], who will use his/her best efforts to stop any additional studies. However, in some cases, such as if your specimens have already undergone testing, it may be impossible to locate and remove the data collected from those tests because the data collection is no longer linked to you directly.

EpicentRx, Inc. will be responsible, have control over the long-term storage location and will keep your DNA specimen and/or the information derived from it indefinitely.

There will be no direct benefit to you from this study since you will not be provided with any results or information regarding your DNA test. The investigator, however, may learn more about SCC, NSCLC, HGNEC, or EOC/MMMT.

Instances are known in which a subject in research has been required to furnish genetic information as a precondition for in applying for health insurance and/or a job. Participation in this study does not mean that you have had genetic testing. Genetic testing means having a test performed and the results provided to you and your doctor. If you are interested in having genetic testing performed you should consult your doctor, as some commercial tests are available. Your doctor can provide you with the necessary information to determine if such a test would be appropriate for you.

Some people involved in genetic studies have felt anxious about the possibility of carrying an altered gene that they could possibly pass on to their children. Even though we will do our best to keep your information confidential, there is the possibility that your genetic risk for certain diseases is accidently divulged to the wrong source, if that happens you might be discriminated against obtaining life or health insurance, employment or ability to adopt children.

Federal and State laws generally make it illegal for health insurance companies, group health plans, and most employers to discriminate against you based on your genetic information. This law generally will protect you in the following ways:

a) Health insurance companies and group health plans may not request your genetic information that we get from this research.

b) Health insurance companies and group health plans may not use your genetic information when making decisions regarding your eligibility or premiums.

c) Employers with 5 or more employees may not use your genetic information that we get from this research when making a decision to hire, promote, or fire you or when setting the terms of your employment.

Be aware that these laws **do not** protect you against genetic discrimination by companies that sell life insurance, disability insurance, or long-term care insurance.

RISKS OF PARTICIPATION

Participation in this study may involve some added risks or discomforts. While you are on this study, you are at risk for the side effects listed below. You should discuss these with your doctor. There may also be other side effects that we cannot predict. Other drugs will be given to make side effects less serious and uncomfortable. Many side effects go away shortly after the study drug is stopped, but in some cases, side effects may be serious, long lasting, and may even cause death.

There may be other risks associated with participation in this study that are currently unforeseeable.

In the initial clinical trial of RRx-001 in which 25 patients with various different types of cancers received RRx-001 intravenously, the main side effect in 84% of patients was temporary pain and/or a stinging, burning sensation at the injection site in the forearm and along the length of the vein as well as swollen veins (vasodilation). Pain and swollen veins, when they occurred, lasted during the entire time of infusion of RRx-001 and, generally, both of these side effects went away almost immediately (within minutes) of stopping the infusion of RRx-001.

This discomfort experienced by patients during infusion was when the drug was injected directly into a vein and now the administration process has been updated to mix with blood

prior to infusion, eliminating all or most of the discomfort associated with direct IV infusion. To minimize the risk of discomfort, you will receive a pain reliever (Baby Aspirin or Acetaminophen) and anti-inflammatory medications (corticosteroids) before the infusion. Your study doctor may also slow down the infusion.

Side Effects Related to RRx-001	
Common (occurring in 10% or more of patients)	• Swelling and redness in the arm or site of the medication injection • Vein hardening • Shortness of breath • Mouth tingling/burning • Anxiety • Chest discomfort • Cough • Fatigue • Skin discoloration
Less common (less than 10% of patients)	• Flushing • Throat discomfort • Vein swelling (vasodilation) • Vein blockage • Weakness • Pain • Bleeding of the tumor • Constipation • Redness and pain around the mouth and lips • Diarrhea • Anemia, which may cause tiredness, or may require blood transfusion • Loss of appetite • Dry skin • Rash • Stroke • Clostridium difficile colitis (an infection of the colon). The symptoms of C. difficile colitis include fever, diarrhea, and abdominal pain.
Rare (less than 1% of patients)	• Abdominal pain • Hand numbness • Bloody mucus • Decreased respirations • Dizziness • High blood pressure • Discomfort in the nose • Runny nose • Involuntary leakage of urine • Vision changes • Vomiting

There were no serious side effects that were thought to be related to RRx-001 during the initial study which were life-threatening or required hospitalization of the patient.

During a recent study of RRx-001 in combination with irinotecan, an FDA-approved anticancer agent, one RRx-001-treated patient died on study due to low blood counts and infection (sepsis); which can occur with irinotecan. While it is unlikely that RRx-001 contributed to these side effects, based on its overall favorable safety track record, it is also impossible to definitely rule it out since this was the first such treated patient. It is also important to note that by choosing to participate in this study, you will not be receiving combination therapy with RRx-001 plus irinotecan.

Because RRx-001 is an investigational drug and not a lot of patients have received the drug, not all of the side effects are known at this time. It is not known if additional side effects will be seen with this drug. Also, it is important to be aware that, even though precautions and prevention practices are in place, treatment of your blood with RRx-001 outside of the body before it is returned to you is a risk factor for bacterial contamination of the blood. The administration of contaminated blood may possibly lead to life threatening or fatal infections. For this reason you will be watched closely for known and other unknown, possibly serious side effects.

Nab-paclitaxel

Risks and side effects related to nab-paclitaxel		
Likely	• Allergic reactions • Neutropenia (lowered white blood cell count) that could lead to infections • Temporary lowering of red blood cells • A feeling of tiredness • Diarrhea	• Nausea • Vomiting • Numbness and tingling in the hands and feet • Aches and pains in muscles and joints • Temporary loss of scalp and body hair
Less Likely	• Low blood pressure • Rash • Decreased appetite • Weight loss • Sores in mouth or throat • Abnormal liver function tests	• Abnormal test of bone health: alkaline phosphatase • Shortness of breath • Abnormal heart rhythm • Possible irritation of skin or tissue if chemotherapy leaks out of vein • Swelling in the arms and legs
Rare, but serious	• Severe allergic reactions	

Cisplatin

Risks and side effects related to cisplatin		
Likely	• Decrease in blood counts that may cause infection, bleeding, and bruising • Loss of appetite	• Nausea and vomiting • Hearing loss or ringing in the ears • Numbness or tingling in the hands or feet
Less Likely	• Muscle cramps or spasms • Loss of coordination • Involuntary movements or shaking • Rash • Vision problems	• Hair loss • Low mineral levels in your blood • Decrease in liver function causing temporary elevation in blood tests • Metallic taste
Rare, but serious	• Loss of muscle or nerve function, which may cause weakness or numbness in your hands and feet • Decreasing ability of the kidneys to handle the body's waste, which may be permanent	• Allergic reactions, which can cause difficulty in breathing, fast heartbeat, and sweating • Secondary cancers

Carboplatin

Risks and side effects related to carboplatin		
Likely	• Leukopenia (decrease in white blood cells in the blood, including low levels of neutrophils), which may affect your body's ability to fight infections • Anemia (decrease in red blood cells in the blood), which may result in symptoms such as fatigue or shortness of breath • Thrombocytopenia (low platelet count, which may make you more likely to bruise or bleed)	• Nausea, vomiting • Infections • Abnormal liver tests (may suggest liver damage) • Abnormal kidney tests (increase blood urea nitrogen and/or creatinine, may suggest kidney damage) • Electrolyte loss (low blood calcium, sodium, potassium, or magnesium) • Pain • Tiredness • Loss of appetite, dehydration
Less Likely	• Numbness, pain or tingling in hands or feet • Diarrhea • Constipation	• Bleeding • Allergic reaction (rash, itching, hives) • Hair loss
Rare, but serious	• Hearing loss, especially if taken in combination with aminoglycoside antibiotics • Vision changes • Injection site reactions • Stomatitis (inflammation of the mouth and lips)	• Hemolytic uremic syndrome (condition associated with decrease in red cells, platelets and kidney function), which can require dialysis or lead to fatal kidney failure • Secondary cancer

Paclitaxel

Risks and side effects related to paclitaxel		
Likely	• Inflammation or degeneration of the peripheral nerves (those nerves outside of the brain and spinal cord) causing numbness, tingling, or burning that may cause problems walking or performing activities of daily living and may be long lasting • Decrease in the total number of white blood cells or in the number of neutrophils, also called granulocytes, which are a type of white blood cells • Lack of enough red blood cells (anemia)	• Irritation or sores in the lining of the mouth and throat • Infection • Nausea • Vomiting • Diarrhea • Hair loss • Pain in joints, bones, or muscles • Allergic reaction
Less Likely	• Decrease in the number of a type of blood cell that helps to clot blood (platelet) • Redness, tenderness, discoloration, or swelling of the skin where the drug is administered • Slow or irregular heartbeat	• Low blood pressure • Fever • Flu-type symptoms (including body aches, fever, chills, tiredness, loss of appetite, cough) • Increased blood levels of liver enzymes
Rare, but serious	• Serious, potentially life-threatening type of allergic reaction that may cause breathing difficulty, dizziness, low blood pressure, and loss of consciousness	• Lung problems such as inflammation of the lungs that can cause shortness of breath, low levels of oxygen in the blood, and damage that could be permanent • Heart problems

Etoposide

Risks and side effects related to etoposide		
Likely	• Fatigue • Lowered white cell counts may increase risk of infection • Lowered red cell counts may lead to anemia, tiredness or shortness of breath • Lowered platelet may lead to an increase in bruising or bleeding • Nausea, vomiting, and diarrhea, abdominal pain, stomach ulcers, constipation, indigestion • Loss of appetite and weight loss • Change in taste • Difficulty swallowing • Swelling, redness at IV site • Decrease in kidney function which may lead to changes in the balance of chemicals in your blood • Numbness, pain or tingling in hands or feet	• Temporary hair loss (not only from the scalp but possibly the underarms, beard, eyelashes, and pubic area) • General discomfort, weakness, drowsiness • Fluid retention, increased weight gain around the stomach and puffy appearance especially in the face • Flu-like symptoms: fever, headache, back pain, chills, muscle aches, weakness, loss of appetite, cough, runny nose, general discomfort, sweating, and trouble sleeping • Increase in blood pressure • Inflammation of the hands and soles of the feet occurs in about ¼ of patients 5-7 days after transplantation
Less Likely	• Sores and/or ulcers and tenderness in mouth or throat or other parts of the body • Liver toxicity including abnormal levels of blood chemistry tests that measure liver function	• Eye and vision problems including blindness and inflammation of the optic nerve • Radiation recall dermatitis • Muscle cramps • Lack of blood supply to the fingers and toes
Rare, but serious	• Fluid in the lungs • Seizures • Allergic reactions (including potentially severe reactions)	• Secondary cancers • Treatment related death

Pemetrexed

Risks and side effects related to pemetrexed		
Likely	• Decrease in white blood cells, which can increase the chance of developing an infection, with or without fever. • Decrease in red blood cells (anemia) • Short-lived increases in some tests that show how the liver is working • Nausea and vomiting • Diarrhea • Hair loss • Loss of appetite • Inflamed mucous membranes (especially the lining of the mouth)	• Skin rash (which may be itchy, or may progress to become serious) • Abdominal pain • Edema (swelling, usually of the limbs and face) • Fever • Weakness or fatigue • Difficulty breathing, cough • Constipation • Headache
Less Likely	• Decreased platelet counts (which may increase the chance of bruising and bleeding after injury) • Cellulitis (inflammation of tissues under the skin) • Decreased kidney function • Urinary tract infection and other types of infection • Difficulty sleeping • Loss of body fluid (dehydration) • Pneumonia	• Allergic reactions • Neuropathy (tingling and/or weakness of the arms, hands, feet, and legs) • Increased heart rate • Conjunctivitis (pink eye) • Heartburn • Taste disturbances • Chest pain, heart attack, and/or irregular heart rate • Renal failure
Rare, but serious	• Injection site reactions • Intestinal obstruction	• Gastrointestinal bleeding • Formation of blood clots in deep veins

This information relates to pemetrexed when taken as a single agent. These effects may also be anticipated when pemetrexed is used together with cisplatin or carboplatin, but certain side effects may occur more frequently, such as decreased platelet counts, hair loss, decreased kidney function, injection site reactions, intestinal obstruction, gastrointestinal bleeding, and formation of blood clots in deep veins and serious skin reactions. Complications of some of the above side effects may lead to life-threatening events such as infections, kidney failure, bleeding, and possibly death. There is slight risk of severe allergic reaction to the drug, which may be life threatening. There is always a risk involved in taking a new drug but every precaution will be taken to minimize the risk.

Gemcitabine

Risks and side effects related to gemcitabine		
Likely	• Nausea, vomiting • Anemia (decrease in red blood cells in the blood), which may result in symptoms such as fatigue or shortness of breath • Leukopenia (decrease in white blood cells in the blood, including low levels of neutrophils or lymphocytes), which may affect your body's ability to fight infections • Abnormal liver tests (may suggest liver damage) • Protein or blood in urine • Hyperglycemia (high blood sugar) • Electrolyte loss (low blood calcium or magnesium) • Stomatitis (inflammation of the mouth and lips)	• Abnormal kidney test (may suggest kidney damage) • Rash • Thrombocytopenia (low platelet count, which may make you more likely to bruise or bleed) • Dyspnea (shortness of breath) • Peripheral edema (swelling in hands and feet) • Hair loss • Abnormal sensation (pins and needles) • Diarrhea • Infection • Fever • Sleepiness • Bleeding • Low blood pressure
Less Likely	• Injection site reactions	• Allergic reaction (breathing difficulty)
Rare, but serious	• Pulmonary toxicity, including interstitial pneumonitis, pulmonary fibrosis, pulmonary edema, and adult respiratory distress syndrome (ARDS), which can lead to fatal respiratory distress • Capillary leak syndrome (leakage of fluids from blood vessels to tissues) • Posterior reversible encephalopathy syndrome (possible headache, confusion, seizure and/or vision loss, may suggest brain damage)	• Hemolytic uremic syndrome (condition associated with decrease in red cells, platelets and kidney function), which can require dialysis or lead to fatal kidney failure • Serious hepatotoxicity, including liver failure and death

Gemcitabine is known to increase toxic side effects of radiation therapy, and should not be used within a week before or after radiation. Gemcitabine causes birth defects and is toxic to embryos and fetuses in mice and rabbits. Gemcitabine can cause fetal harm if taken while pregnant.

Vinorelbine

Risks and side effects related to vinorelbine		
Likely	• Numbness and tingling of the arms and legs • Diarrhea, • Nausea, vomiting, constipation • Reaction during or following infusion of the drug	• Sores in the mouth • Tiredness, muscle weakness • Hair loss
Less Likely	• Pain • Blood clot • Severe blood infection • Infection, especially when white blood cell count is low • Anemia which may require a blood transfusion	• Bruising, bleeding • Blockage of the airway which may cause cough, wheezing • Damage to the lungs which may cause shortness of breath
Rare, but serious	• Heart attack which may cause chest pain • Allergic reaction which may cause rash, low blood pressure, wheezing, shortness of breath, swelling of the face or throat	• Scarring of the lungs • Blood in urine • A tear or hole in the bowels that may require surgery

Dexamethasone or other corticosteroids

Side Effects Related to Dexamethasone or other corticosteroids	
Common (occurring in 10% or more of patients)	• Edema (fluid retention) • High blood pressure • Sodium (salt) retention (build up) and/or potassium loss. Sodium and potassium are referred to as electrolytes. In the case of sodium build up symptoms may cause swelling due to water retention while potassium loss may cause symptoms such as cramps, weakness and heart palpitations (skipped heartbeats) • Increased appetite and weight gain • Extreme mood swings • Tiredness • Depression • Inability to sleep • Nausea/vomiting
Less common (less than 10% of patients)	• Increased sweating, • Increased blood sugar, which may cause damage to your blood vessels and/or increase your risk of having diabetes. Symptoms of diabetes include increased thirst, dry mouth and increased need to urinate or pee. • Irregularities in the menstrual cycle (periods) • Excess hair • Thinning of bone • Increased risk of infections • Hiccups • Abdominal pain • Stomach ulcers (sores) • Skin disorders
Rare (less than 1% of patients)	• Patients with pre-existing schizophrenia and/or epilepsy may experience worsening of their disease • Patients with heart disease may experience heart failure

Other Study-Related Risks:

***Allergic Reactions*:** As with any drug, there is the chance of an allergic reaction, which may include difficulty breathing, rash, flushing, weakness, dizziness, lightheadedness, and swelling.

Intravenous (IV) Injection Side Effects: If the drug leaks from the vein the shot is given into, it may cause skin irritation at the needle site.

Risks of blood draws: There is a risk of discomfort or pain, bleeding, swelling and a small arm bruise and swelling when blood is drawn. Rarely, a clot or infection may occur at the site of the blood draw. Some people also become faint, dizzy, or light-headed during or immediately after the blood draw.

Risks and Side Effects of a Central Line: Subjects may be required to have placement of a "central line." A central line is a catheter that is placed under your skin and into a large vein. It will allow easy administration of the chemotherapy drugs. Risks of placement of a central line include bleeding or lung collapse when the catheter is placed, as well as inflammation at the site of the catheter, and infection.

Reproductive Risks: You should not become pregnant or father a baby while on this study and for a period of time following your last dose of RRx-001 because the drugs in this study can possibly affect a fetus and cause serious birth defects. Women should not breastfeed a baby while on this study. It is important you understand that you need to use birth control while on this study. If you are female and capable of childbearing, a pregnancy test will be done before the study begins in order to be as sure as possible that you are not pregnant. Your participation requires that you use hormonal (such as birth control pills) or non-hormonal contraception methods (such as abstinence, diaphragm, condom, or intrauterine device) to prevent pregnancy for the duration of the study and for 90 days following your last dose of RRx-001. Ask about counseling and more information about preventing pregnancy.

Risks from CT Scans: During your participation in this research study, you will be exposed to radiation from scheduled CT scans. The total exposure resulting from these imaging studies is calculated to be approximately 117 mSv each year. This amount is *more* than you would receive from one year of natural exposure in the [INSERT CITY AND STATE OF CLINIC] area, which is approximately 1.6 mSv. Cumulative exposure from radiation may increase your risk of developing certain types of cancer in the future.

The principal investigator for this research study has determined and verified that all of the CT scans prescribed for this study would typically be performed as part of the standard medical care required to adequately monitor your current illness. You will have a CT scan of your chest, abdomen and pelvis at Screening and every 6 weeks thereafter during period 1 of this study when you're receiving the study drug, RRx-001, and every 6 weeks once you've started period 2. Additional imaging may be performed if clinically indicated. If you are especially concerned with radiation exposure, or you have had a lot of x-rays or imaging scans already, you should discuss this with the principal investigator for this study, [INSERT PI], or your regular doctor.

Risks of IV Contrast: As part of this study a CT scan may be done. There may be some reactions related to the contrast dye used in CT scans. Contrast dye is usually administered when you get a CT scan. Some people may develop hives and itching or other allergic symptoms from this dye, swelling of the heart, cramps of the voice box, breathing distress caused by narrowing of the airways in lungs, low blood pressure, with loss of consciousness, and in rare cases, severe loss of blood and fluids leading to shock and death, fainting, seizures, and irregular heartbeats. In addition, if you have low kidney function, this dye can temporarily or permanently decrease your kidney function.

Risks of bronchoscopy: If you provide consent, biopsies of your tumor(s) may be performed. As part of this procedure, a bronchoscopy may be performed. This involves using a very small camera to look inside the tubes ("bronchi") within your lungs. Although slight

(occurring in about 5-8% of patients), there are some risks / complications associated with this procedure. These include:

- Pneumothorax – This is when air or gas builds up in the space between the lung and the chest. This is often called "collapsed lung" and can result in difficulty breathing.
- Hypoxemia – This is when not enough oxygen is supplied to the blood circulating in your body causing the lungs to potentially work harder to increase the supply of oxygen.
- Hemorrhage – This is when some blood escapes from the veins and arteries in your body due to a cut, puncture or rupture, resulting in external (outside your body) or internal (inside your body) bleeding.

Risks of Loss of Confidential Information: There is also a small risk that information from your health records will be released to an unauthorized party. We will do our best to make sure that your personal information will be kept private. The chance that this information will be given to someone else is very small. An identification code assigned by the study team to each patient will be used in place of your name to protect your identity when reporting trial-related data.

BENEFITS OF PARTICIPATION

If you agree to take part in this study, there may not be direct medical benefit to you. Others, however, may benefit from the information learned from this research study, and the investigators may learn more about RRx-001.

ALTERNATIVES TO PARTICIPATION

If you choose not to take part in or stop participating in this research study, there may be other treatments. Refusal to take part in this study will not cause penalty or loss of benefits to which you are otherwise entitled.

You do not have to participate in this study to receive treatment for your cancer. Other possible treatments could include treatment with other drugs or drug combinations, participation in other research studies, or supportive care only (no cancer treatment).

Please talk to your doctor about these and other options.

COSTS/COMPENSATION

The study drug, RRx-001, will be supplied at no cost while you take part in this study. The cost of getting the study drug, RRx-001, ready is also provided at no cost. The study drug administration is not paid for by the study sponsor, so you or your health plan/insurance company may have to pay for this.

It is possible the study drug, RRx-001, may not continue to be supplied while you are on the study. Although not likely, if this occurs, your study doctor will talk to you about your options.

You and/or your health plan/insurance company will need to pay for all of the other costs of caring for your cancer while in this study, including the costs of tests, procedures, or medicines to manage any side effects, unless you are told that certain tests are supplied at no cost. Before you decide to be in the study, you should check with your health plan/insurance company to find out exactly what they will pay for.

Examples of procedures and drugs that may be billed include the following: routine clinic visits, routine laboratory tests, CT imaging, pre-medications (baby aspirin/acetaminophen and dexamethasone), and FDA-approved chemotherapy with platinum-based doublets.

There will be no payment to you for participating in this study.

The sponsor, EpicentRx Inc., is paying the institution, [INSERT SITE] to do this study.

COMPENSATION FOR RESEARCH-RELATED INJURY

If you are injured as a direct result of being in this study, treatment will be available. The costs of such treatment will be covered by the [INSERT SITE] or the study sponsor, EpicentRx Inc., depending on a number of factors. The [INSERT SITE] and the study sponsor, EpicentRx Inc., do not normally provide any other form of compensation for injury. You may call the [INSERT SITE] Human Research Protections Program Office at (xxx) xxx-xxxx for more information about this, to inquire about your rights as a research subject, or to report research-related problems.

VOLUNTARY PARTICIPATION

Participation in this study is entirely voluntary. If you choose not to participate or wish to withdraw your consent to participate in these study procedures at any time, it will in no way affect your regular treatments or medical care at this institution or loss of benefits to which you are entitled.

You will be informed of any new findings that might affect your willingness to continue participating in the study.

The study doctor may stop your participation in this study without your consent. If you have any side effects that are very serious or if you become ill during the course of the research study you may have to drop out even if you would like to continue. The study doctor will make the decision and let you know if it is not possible for you to continue. The decision that is made is to protect your health and safety, or because it is part of the research plan that people who develop certain conditions or do not follow the instructions from the study doctor may not continue to participate. In addition, EpicentRx Inc. may end your participation in the study at any time without your consent.

If you withdraw from the study for any reason, you must notify your study doctor, [INSERT PI] at (xxx) xxx-xxxx. You will be asked to return to the clinic so that the study

doctor may perform a final evaluation, which includes laboratory tests. Additional details can be found in the Procedures section of this document.

DO YOU HAVE ANY QUESTIONS?

[INSERT PI] and/or_____ has explained this study to you, and answered your questions. You may contact [INSERT PI] at (xxx) xxx-xxxx. You may also call the hospital 24-hour paging system at (xxx) xxx-xxxx and ask for the oncologist on-call. If you have other questions or research-related problems, you may call the [INSERT SITE] Clinical Trials Office at (xxx) xxx-xxxx.

If you have questions about your rights as a research participant, your participation in this study, and/or concerns about this study, you may call the [INSERT SITE] Human Research Protections Program (a group of people who review the research study to protect your rights and welfare) at (xxx) xxx-xxxx.

CONFIDENTIALITY

The confidentiality of your research records will be maintained to the extent permitted by law. Your medical information will not be made publicly available unless disclosure is required by law or regulation.

Study data is labeled with a code instead of your name or other information that can easily identify you. Your identity will remain confidential.

Data obtained from this study, including your protected health information, will be given to the sponsor of this study, EpicentRx Inc., and/or its representatives, and may be used by and/or disclosed to the Food and Drug Administration (FDA), Department of Health and Human Services (DHHS) agencies, the [INSERT SITE] Institutional Review Board, and other governmental agencies in the United States or other countries in which regulatory approval of RRx-001 may be sought. Once your personal health information is released it may be re-disclosed and no longer protected by privacy laws.

A description of this clinical trial will be available on http://www.ClinicalTrials.gov, as required by U.S. Law. This Web site will not include information that can identify you. At most, the Web site will include a summary of the results. You can search this Web site at any time.

As a rule, the researchers will not continue to use or disclose information about you, but will keep it secure until it is destroyed. Sometimes, it may be necessary for information about you to continue to be used or disclosed, even after you have canceled your permission or the study is over. Examples of reasons for this include:

- To avoid losing study results that have already included your information
- To provide limited information for research, education, or other activities (This information would not include your name, social security number, or anything else that could let others know who you are.)

- To help [INSERT SITE] and government officials make sure that the study was conducted properly.

Your permission allowing the researches and study staff to access your health information expires at the end of the study, unless you cancel it sooner. You may cancel your permission at any time by writing to:

[INSERT PI]
[INSERT CORRESPONDENCE ADDRESS]

You will be asked to sign a separate HIPAA authorization form to allow the study team to access and share information from your medical record.

Information on Alternative Treatments After Progression on RRx-001

Please read below and think about your choice. The purpose of this study is to find out whether treatment with RRx-001 will make your tumor sensitive to retreatment with platinum-doublet chemotherapy. However, it is important to realize that an existing FDA therapy may be available for your cancer and, if it is available, what are the potential benefits and common side effects of that therapy. The table below shows what FDA therapies may be available to you as well as the potential benefits and side effects. After reviewing this information, please initial below.

Cancer Type	Name of FDA Approved Therapy	Type of Therapy	Dosing	Potential Benefits	Common Side Effects
Small Cell Lung Cancer (SCLC)	Topotecan	Chemotherapy (if topotecan is given)	1.5 mg/^{2} oral or IV for 5 days every 3 weeks	Unknown in resistant/refractory SCLC	Nausea, vomiting, shortness of breath, low white and red blood cells and low platelets (cells that are responsible for clotting)
EGFR$^+$ Non Small Cell Lung Cancer (NSCLC)	Erlotinib (Tarceva) (if you have not already received it)	Targeted Therapy	150 mg oral once daily	• Improved progression free survival of 0.4 months compared to no treatment (placebo) • Tumor shrinkage • Symptom improvement	Skin rash and diarrhea
	Checkpoint inhibitors (nivolumab, pembrolizumab)	Immunotherapy	Nivolumab 3 mg/kg IV over 60 minutes every 2 weeks Pembrolizumab 2 mg/kg IV over 30 minutes every 3 weeks	Unknown; in general patients with NSCLC EGFR mutations have not benefited from checkpoint inhibitors	Immune related side-effects in which the body attacks its own cells and tissues

Cancer Type	Name of FDA Approved Therapy	Type of Therapy	Dosing	Potential Benefits	Common Side Effects
	Docetaxel	Chemotherapy	75 mg/m^2 every 3 weeks	• Improved progression free survival • Tumor shrinkage • Symptom improvement	Common side effects include nausea, vomiting, diarrhea, constipation, loss of appetite, feeling weak or tired, muscle pain, missed menstrual periods, temporary hair loss, or fingernail or toenail changes
High Grade Neuroendocrine Tumor (HGNEC)	None	____	____	_____	____
Resistant/Refractory Ovarian Cancer (EOC)	Technically none since this is a resistant form of cancer; however liposomal doxorubicin (doxil) and/or bevacizumab or olaparib may be given	Chemotherapy (doxorubicin) and targeted therapies (olaparib and bevacizumab)	Doxil 50 mg/m^2 IV every 4 weeks + bevacizumab 10-15 mg/kg on days 1 and 15	Improved progression free survival, tumor shrinkage and symptom improvement are possible in theory with these therapies however survival is not usually increased	Mouth and skin sores, heart problems, high blood pressure, kidney problems and wound healing delays
			Olaparib 400 mg twice daily by mouth		Nausea and vomiting, fatigue, and low level of red blood cells (anemia), which are usually manageable
Malignant Mixed Mullerian Tumors (MMMT)	Only 3 therapies are considered effective: cisplatin, paclitaxel and ifosfamide. Ifosfamide is the only agent not offered in this trial	Chemotherapy	2.0 g/m^2 i.v. over 1 h for 2 days (days 1, 2: total dose 4.0 g/m^2	Improved progression-free survival and overall survival	Potential side effects include bladder infection and bleeding, low white cells, red cells and platelets, sleepiness, confusion and hallucinations

_____ Initials

I have reviewed the information provided regarding alternative FDA approved therapies that may be available for my cancer and, if it is available, what are the potential benefits and common side effects of that therapy.

SIGNATURE AND CONSENT

Your participation in this study is voluntary, and you may refuse to participate or withdraw from the study at any time without prejudice or loss of benefits to which you are otherwise entitled. You will receive a signed copy of this consent document and a copy of "The Experimental Subject's Bill of Rights" to keep.

You agree to participate.

_____
Printed Name of Participant

_____ _____
Signature of Participant Date

_____
Printed Name of Person Obtaining Consent

_____ _____
Signature of Person Obtaining Consent Date