A Phase 1/2 Open-Label, Safety, Pharmacokinetic, Pharmacodynamic and Efficacy Study of RX-3117 in Combination with Abraxane® in Subjects with Metastatic Pancreatic Cancer

Rexahn Protocol Number RX3117-003

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Investigator's Agreement

I have read the attached protocol, "A Phase 1/2 Open-Label, Safety, Pharmacokinetic, Pharmacodynamic, and Efficacy Study of RX-3117 in Combination with Abraxane® in Subjects with Metastatic Pancreatic Cancer", Amendment 03 dated 08 August 2018, and agree to abide by all provisions set forth therein.

I agree to comply with the International Conference on Harmonisation Tripartite Guideline on Good Clinical Practice and applicable regulations/guidelines.

I agree to ensure that Financial Disclosure Statements will be completed by:

- me (including, if applicable, my spouse [or legal partner] and dependent children)
- my sub-investigators (including, if applicable, their spouses [or legal partners] and dependent children)

before study initiation, during the study if there are changes that affect my financial disclosure status, and after the study is completed.

I agree to ensure that the confidential information contained in this document will not be used for any purpose other than the evaluation or conduct of the clinical investigation without the prior written consent of Rexahn Pharmaceuticals Inc.

_____

Signature

_____ _____

Name of Principal Investigator Date (DD Month YYYY)

As representative of Rexahn, I agree to the provisions described in this protocol.

_____

Signature

_____ _____

Name of Rexahn Representative Date (DD Month YYYY)

Rexahn Pharmaceuticals Inc.

Protocol Synopsis

Title: A Phase 1/2 Open-Label, Safety, Pharmacokinetic, Pharmacodynamic and Efficacy Study of RX-3117 in Combination with Abraxane® in Subjects with Metastatic Pancreatic Cancer

Study Phase: Phase 1b/2a

Indications: Metastatic Pancreatic Cancer

Objectives:

Phase 1 Objectives:

Primary Objectives

To evaluate the safety and tolerability of RX-3117 in combination with Abraxane® in subjects with metastatic pancreatic cancer

To determine the Recommended Phase 2 Dose (RP2D) of RX-3117 when administered orally in combination with Abraxane® to subjects with metastatic pancreatic cancer

Secondary Objectives

To determine the pharmacokinetic (PK) profiles of RX-3117 and Abraxane® on Day 1 (single dose) and Day 15 (steady-state) in Cycle 1

To evaluate the antitumor activity of RX-3117 in combination with Abraxane®

Exploratory Objective

To investigate predictive and pharmacodynamic blood or tumor biomarkers suggested from nonclinical studies/literatures which may be predictive of response or resistance to RX-3117 treatment

Phase 2 Objectives:

Primary Objective

To estimate the antitumor activity of RX-3117 in combination with Abraxane® as first-line therapy in subjects with metastatic pancreatic cancer

Secondary Objectives

To assess additional measures of antitumor activity

To characterize the safety profile of RX-3117 in combination with Abraxane®

To evaluate the PK of RX-3117 and Abraxane® at the recommended Phase 2 dose (RP2D)

Exploratory Objectives

To investigate the effect of RX-3117 in combination with Abraxane® on potential cellular or molecular biomarkers in blood or tumor samples

To evaluate the change in tumor burden response

To evaluate the effect on Quality of Life (QOL)

Endpoints:

Phase 1 Endpoints:

- **Primary Endpoints**
  - Overall safety profile characterized by the type, frequency, severity, timing of onset, duration and relationship to study therapies of any adverse events (AEs), clinical laboratory abnormalities, vital signs, and electrocardiograms (ECGs)
  - Enumeration and description of any dose limiting toxicities (DLTs) that occur during Cycle 1, serious adverse events (SAEs), or AEs leading to discontinuation of study treatment.
- **Secondary Endpoints**
  - RX-3117 and Abraxane® plasma PK parameters (e.g., time to maximum observed concentration [T_{max}], maximum observed concentration [C_{max}], and area under the concentration-time curve [AUC])
  - Indices of anti-tumor activity (e.g., overall response rate [ORR], time to response [TTR], duration of response [DOR], and progression-free survival [PFS]) during treatment.
- **Exploratory Endpoint**
  - Expression or concentration of various cellular or molecular biomarkers

Phase 2 Endpoints:

- **Primary Endpoint**
  - An adequate number of responders based on PFS and/or objective clinical response
- **Secondary Endpoints**
  - Time to progression, ORR and DOR
  - Overall safety profile of RX-3117 in combination with Abraxane®
  - RX-3117 and Abraxane® PK parameters
- **Exploratory Endpoints**
  - Enumeration, expression, or concentration of various cellular or molecular biomarkers
  - Changes in tumor burden
  - QOL

Study Design:

This will be a Phase 1b/2a multicenter 2-stage study.

Phase 1 will be conducted as a dose-finding, open-label study of oral RX-3117 administered in combination with Abraxane® to subjects with metastatic pancreatic cancer. The recommended phase 2 dose (RP2D) of RX-3117, in combination with Abraxane®, will be determined based on the safety profile, dose modification, and PK.

Phase 1 will be conducted using a combination of the single agent MTD for RX-3117 and the Abraxane® dose as per the package insert when Abraxane® is given in combination for patients with pancreatic cancer. A safety committee will assess the safety and the tolerability of the combination after the first 5 patients and may make recommendation to confirm the MTD or RP2D in another 5 patients. For dosing information, please refer to Investigational Product Dosage and Administration.

After completion of the Phase 1 portion, a Phase 2a study will be conducted using a 2-stage, open-label design, of RX-3117 and Abraxane® in combination to treat subjects with metastatic pancreatic cancer as first-line therapy. Approximately 10 subjects will participate in the Stage 1 at the dose identified in Phase 1 (RP2D). Subjects will be treated for up to 8 cycles of combined therapy. An interim analysis will be conducted after 10 evaluable subjects have been treated at the RP2D, have completed a minimum of 4 cycles of therapy, or have discontinued therapy due to progressive disease before completing 4 cycles. If an adequate number of Responders are observed out of the initial 10 evaluable subjects, then approximately 30 additional evaluable subjects will be enrolled to participate in Stage 2. Subjects will be treated for up to 8 cycles of combined therapy.

Sample Size:

The number of planned subjects is approximately 50 (approximately 10 subjects in the Phase 1, depending upon the number of dose levels needed to identify the RP2D, 10 evaluable subjects in Stage 1 of Phase 2 and approximately 30 evaluable subjects in Stage 2 of the Phase 2).

Duration:

The study will consist of a screening period (up to 14 days; [up to 21 days for tumor imaging]), up to eight 28-day treatment cycles, an end-of-treatment visit, and a follow up visit approximately 30 days after the last dose of RX-3117. Subject participation is anticipated to be approximately 9 months. Additional cycles of therapy may be provided following discussions with the investigator, sponsor and medical monitor.

Subjects may be discontinued from study treatment due to progressive disease (PD), an intolerable treatment-related toxicity, withdrawal of consent, pregnancy, substantial noncompliance with study procedures, principal investigator judgment that it is in the best interest of the subject to stop treatment, or study discontinuation.

Subject Eligibility Criteria:

Inclusion Criteria

Disease Related

1. Subject has confirmed histologic or cytologic evidence of pancreatic cancer, metastatic pancreatic cancer by at least radiographic evidence, and has no prior treatment for metastatic pancreatic cancer. Subjects who received gemcitabine in the neoadjuvant or adjuvant setting can be considered.

2. Subject has measurable disease using Response Evaluation Criteria in Solid Tumors (RECIST) ver. 1.1.
3. Subject has a life expectancy of at least 3 months.
4. Subject has an ECOG performance status 0 or 1.

Demographic

5. Males or females ≥ 18 years of age
6. Subject must be able to swallow capsules
7. Subject must have adequate venous access for intravenous (IV) infusion

Laboratory

8. Subject has hemoglobin ≥ 9.0 g/dL at Screening
9. Subject has absolute neutrophil count (ANC) ≥ 1.5 x 10^9/L at Screening
10. Subject has platelet count ≥ 100 x 10^9/L at Screening
11. Subject has serum creatinine ≤ 1.5 times the upper limit of normal (ULN) at Screening.
    - Subjects with serum creatinine levels > 1.5 times the ULN must have a 24-hour urine creatinine clearance ≥ 50 mL/min
12. Subject has serum bilirubin ≤ 1.5 times the ULN (except in subjects with Gilbert's Syndrome who must have serum bilirubin < 3.0 x ULN)
13. Subject has aspartate aminotransferase (AST; SGOT) and alanine aminotransferase (ALT; SGPT) ≤ 2.5 times the ULN (OR, AST and ALT ≤ 5 times the ULN in the presence of known liver metastases)
14. Subject has alkaline phosphatase ≤ 2.5 times the ULN (OR ≤ 5 times the ULN in the presence of known liver or bone metastases)
15. Subject has normal coagulation parameters (prothrombin time [PT] and/or international normalized ratio [INR], and partial thromboplastin time [PTT] within normal limits [<1.2 x ULN])
16. Subject has potassium concentration within normal range, or correctable with supplements.
17. Oxygen saturation by pulse oximetry ≥ 92% at rest.
18. For women of childbearing potential: Negative serum pregnancy test during screening and negative serum or urine pregnancy test at start of study therapy (Cycle1 Day 1).

Reproductive

19. For female subjects of childbearing potential, willingness to abstain from heterosexual intercourse or use a protocol-recommended method of contraception from the screening visit throughout the study treatment period and for 30 days following the last dose of study drug.

20. Female subjects of non-childbearing potential defined as having amenorrhea for at least 24 consecutive months, a documented hysterectomy, or a documented bilateral oophorectomy)
21. For fertile male subjects having intercourse with females of childbearing potential, willingness to abstain from heterosexual intercourse or use a protocol-recommended method of contraception from the start of study therapy throughout the study treatment period and for 30 days following the last dose of study drug and to refrain from sperm donation from the start of study treatment throughout the study treatment period and for 30 days following the last dose of study drug.

Ethical

22. In the judgment of the investigator, participation in the protocol offers an acceptable benefit-to-risk ratio when considering current disease status, medical condition, and the potential benefits and risks of alternative treatments for the subject's cancer.
23. Before any study-specific procedure, the appropriate written informed consent must be obtained

Exclusion Criteria:

Disease Related

1. Subject has primary brain tumors or clinical evidence of active brain metastasis
2. Subject has undergone major surgery within 4 weeks of the start of study treatment. Laparoscopy and central venous catheter placement are not considered major surgery

Medications

3. Subject has a history of systemic corticosteroid use within 7 days before Day 1 of Cycle 1

General

4. Subject has an active infection requiring parenteral or oral antibiotics within 2 weeks before planned start of study therapy
5. Subject has uncontrolled diabetes as assessed by the investigator
6. Subject has a second malignancy other than curatively resected basal cell carcinoma of the skin, squamous cell carcinoma of the skin, in situ carcinoma of the cervix, or other cancers treated with curative intent and no known active disease within 3 years before planned start of study therapy
7. Subject has an active infection of hepatitis B, hepatitis C or human immunodeficiency virus
8. Female subjects who are pregnant, planning a pregnancy or breast feeding during the study
9. Subject has a high cardiovascular risk, including, but not limited to, subjects with congestive heart failure (New York Heart Association [NYHA] Class III or IV), cardiac arrhythmia, unstable angina, coronary stenting or acute coronary syndromes within 6 months before planned start of study therapy or myocardial infarction within one year before planned start of study therapy

10. ~~Subject has a history of peripheral artery disease (e.g., claudication, Leo Buerger's disease).~~ [Criterion removed]
11. Subject has a history of prior allogeneic bone marrow progenitor cell or solid organ transplantation.
12. Subject has known acute or chronic pancreatitis.
13. Subject has persistent diarrhea, malabsorption, or known sub-acute bowel obstruction ≥ NCI CTCAE Grade 2, despite medical management.
14. Subject has any disorder that may interfere with drug absorption, distribution, metabolism, or excretion (including gastrointestinal surgery and bariatric surgery)
15. All acute toxic effects of any prior antitumor therapy resolved to Grade ≤ 1 before the start of study therapy (with the exception of alopecia [Grade 1 or 2 permitted], or neurotoxicity [Grade 1 or 2 permitted], or anemia [Grade 2 permitted, Grade 3 or higher is excluded]
16. Subject has any other medical, psychiatric, or social condition, which in the opinion of the investigator, would preclude participation in the study, pose an undue medical hazard, interfere with the conduct of the study, or interfere with interpretation of the study results
17. Subject has a history of interstitial lung disease, slowly progressive dyspnea and unproductive cough, sarcoidosis, silicosis, idiopathic pulmonary fibrosis, pulmonary hypersensitivity pneumonitis or multiple allergies. Any lung disease that may interfere with the detection or management of suspected drug-related pulmonary toxicity.
18. Subject is currently enrolled in any other clinical protocol or investigational trial that involves administration of experimental therapy and/or therapeutic devices, or investigational drug.
19. Subject has a history of hypersensitivity to RX-3117, gemcitabine, azacytidine cytosine arabinoside, paclitaxel, nab-paclitaxel, or their excipients.
20. Subject is unwilling or unable to comply with study requirements or planned unavailability for follow-up assessments.

Investigational Product Dosage and Administration:

RX-3117

RX-3117 will be provided as 200 and 500-mg capsules. The capsules will consist of hydroxypropylmethyl cellulose and be packaged in a high-density polyethylene (HDPE) bottle with a child-resistant closure and an induction seal.

Subjects will take RX-3117 five times per week (i.e. 5 consecutive days followed by 2 days off) for 3 consecutive weeks followed by 1 week of rest during each 28-day cycle. Subjects should fast for a minimum of 8 hours prior to RX-3117 administration. RX-3117 will be taken orally with 4 to 8 ounces of water. A light meal is permitted approximately 1 hour after dosing.

For Cycle 1, RX-3117 doses will be dispensed each week. For Cycles 2 and higher, RX-3117 doses will be dispensed at the start of each cycle.

During Phase 1, 700 mg of RX-3117 will be investigated in combination with Abraxane® as per Table 1.

Additional doses may be recommended by the review committee which includes investigators, medical monitor and sponsor. For Phase 2, RX-3117 be administered based on the RP2D identified after completion of Phase 1.

Abraxane®

Abraxane® for Injectable Suspension (paclitaxel albumin-bound particles for injectable suspension) is formulated as nanoparticles with a mean particle size of approximately 130 nanometers. Paclitaxel exists in the particles in a non-crystalline, amorphous state. Abraxane® is supplied as a white to yellow, sterile, lyophilized powder for reconstitution with 20 mL of 0.9% Sodium Chloride Injection, USP prior to intravenous infusion. Each single-use vial contains 100 mg of paclitaxel (bound to human albumin) and approximately 900 mg of human albumin (containing sodium caprylate and sodium acetyltryptophanate). Each milliliter (mL) of reconstituted suspension contains 5 mg paclitaxel formulated as albumin-bound particles. Abraxane® is free of solvents.

Abraxane® will be administered as follows:

Intravenously at a dose of 125, 100 or 75 mg/m^2 as per Table 1 infused over 30 to 40 minutes once a week for 3 weeks (Days 1, 8, and 15) followed by 1 week of rest during each 28-day cycle.

On days when both RX-3117 and Abraxane® are administered on the same day, Abraxane® should be administered first followed by RX-3117. RX-3117 will be administered no sooner than 1 hour after the start of the Abraxane® infusion.

Control Group: There will be no control group.

Key Screening Procedures: (see Section 7.2 and the Schedule of Assessments for more detail):

- Informed Consent
- Review of inclusion and exclusion criteria
- Medical, surgical, and cancer history including histology report confirming diagnosis of metastatic pancreatic cancer
- Medication history (including cancer therapies)
- Physical examination including height and weight
- Vital signs (heart rate, body temperature, respiratory rate, blood pressure, and pulse oximetry)
- 12-lead ECG

- Performance status assessment (i.e., ECOG)
- Tumor imaging assessment
- Blood and urine collection for clinical laboratory tests (hematology, serum chemistry [including serum pregnancy in females of childbearing potential], coagulation, and urinalysis)
- Blood collection for tumor markers

Key Treatment Procedures (see Section 7.3 and the Schedule of Assessments for more detail):

- QOL (before other study procedures are performed)
- Review inclusion and exclusion criteria
- Study drug dispensing and administration
- Concomitant medication assessments
- AE/SAE assessments
- Vital signs (heart rate, body temperature, respiratory rate, blood pressure)
- 12-lead ECG (Cycle 1 only)
- Body weight
- ECOG performance status
- Blood collection for PK assessments in Cycle 1 only (Phase 1 and Phase 2 - Stage 1)
- Blood and urine collection for clinical laboratory tests (hematology, serum chemistry [including serum pregnancy in females of childbearing potential], coagulation, and urinalysis)
- Blood collection for appropriate biomarkers at baseline and at the time of tumor imaging assessments
- Collection of blood for tumor markers
- Collection of archival tumor tissue if available
- Collection of tumor biopsy for biomarker (optional)
- Tumor imaging assessments (after every 2 cycles of treatment)

Adverse Event Evaluation: AEs will be coded using the Medical Dictionary for Regulatory Activities (MedDRA) and will be graded using NCI CTCAE, Version 4.03. The CTCAE will also be used to grade abnormalities in vital signs, laboratory assessments (serum chemistry, hematology, coagulation and urinalysis) and ECGs.

Statistical Considerations:

Analysis Methods

This section provides a brief summary of the planned analysis methods for this protocol. More information will be provided in the formal Statistical Analysis Plan (SAP), which will be developed and finalized before database lock.

For Phase 1, the statistical methods will be descriptive in nature. Appropriate data analysis populations will be defined within Section 10.4 and further described in the SAP. Subject characteristics and safety profiles will be summarized including summaries of RX-3117 dose levels, RX-3117 plasma concentrations, and PK parameters (Cmax, Tmax, Half-life, AUC, etc.). Pharmacodynamic markers will also be described and summarized for the PK analysis set. PK parameters will be derived from the RX-3117 concentration-time profiles using non-compartmental methods for the relevant analysis sets.

Phase 2 will follow a simple 2-stage design. An interim analysis will be conducted when 10 response-evaluable subjects have been enrolled and treated with the RP2D, and have had the opportunity to complete a minimum of 4 cycles of therapy or have discontinued therapy due to disease progression (PD). The study will proceed to Stage 2 if an adequate number of Responders are seen. An adequate number of Responders is defined as either at least 2 out of the 10 subjects (20%) having a measured benefit in PFS noted as PFS >= 4 months/ cycles or if at least 1 subject (10%) has an objective clinical response (partial or complete response) supported by acceptable safety and tolerability reviewed through the conduct of the study by the investigators, medical monitor and sponsor. The study may stop after the interim analysis if an adequate number of Responders are not seen. However, if an adequate number of Responders are seen, approximately 30 evaluable subjects will be enrolled and evaluated.

Sample Size Calculations

For the Phase 1 dose-finding, approximately 10 subjects are planned. The sample size is not based on formal statistical hypothesis testing but will be determined based on observed number of first-cycle DLTs at each dose level. The intent is to limit the number of subjects who are exposed to excessively toxic doses or sub-therapeutic doses of a drug in a Phase 1 evaluation of anticancer agents being used in combination for the first time.

For Phase 2, approximately 40 subjects are planned. Once the RP2D is identified approximately 10 subjects will participate in Stage 1. Depending on the results of the interim analysis, approximately 30 additional subjects will participate in Stage 2.

Study Glossary

Abbreviation	Definition
ANC	Absolute neutrophil count
AUC	Area under the plasma concentration time curve
C_{max}	Maximum observed plasma concentration
CYP	Cytochrome P450
DLT	Dose-limiting toxicity
DNA	Deoxyribonucleic acid
DOR	Duration of Response
ECG	Electrocardiography, electrocardiogram
ECOG	Eastern Cooperative Oncology Group
GCP	Good Clinical Practice
G-CSF	Granulocyte colony stimulating factor
GLP	Good Laboratory Practice
IC_{50}	Half maximum inhibitory concentration
INR	International normalized ratio
IRB	Institutional Review Board
IV	Intravenously
MedDRA	Medical Dictionary for Regulatory Activities
MRI	Magnetic Resonance Imaging
MTD	Maximum tolerated dose
NCI CTCAE	National Cancer Institute Common Terminology Criteria for Adverse Events
ORR	Overall Response Rate
PD	Progressive disease
PFS	Progression free survival
PK	Pharmacokinetics
PR	Partial response
PT	Prothrombin time
PTT	Partial thromboplastin time
QTcF	Corrected QT interval using Fridericia's formula
RECIST	Response Evaluation Criteria in Solid Tumors
RP2D	Recommended Phase 2 Dose
RNA	Ribonucleic Acid
SAP	Statistical Analysis Plan
SD	Stable disease
T_{max}	Time to maximum observed plasma concentration
TTR	Time to response
UCK	Uridine-cytidine kinase
ULN	Upper limit of normal

Study Definitions

Baseline Value	The "baseline value" is the value measured before first administration of study specified treatment. For variables/assessments not scheduled to be performed on study day 1 or that are missing at baseline, the baseline value is the value from the screening period measured closest to study day 1.
Duration of Response	The time from the date of first documentation of a response to the first documented progressive disease.
Enrollment	The date the subject is assigned a dose of RX-3117 and Abraxane®.
Investigational Product	RX-3117
On-Study Death	Any death that occurs after receiving protocol directed therapy through 30 days after the last dose of investigational product. The cause of any on-study death will be reported as a serious adverse event.
Overall Response Rate	The number of complete responders and partial responders in the response evaluable population
Progression Free Survival	The time from the date of first study drug administration to the date of documented progressive disease or death due to any cause, whichever occurs first. The progression-free survival rate will also be measured. It is defined as the proportion of subjects with stable disease (SD) for at least 4 months.
Safety Follow-up	This period is planned for approximately 30 days after a subject discontinues investigational product administration.
Screen Failure	A subject who signs an informed consent but does not qualify to be enrolled into the study.
Screening Period	The period that occurs between the signing of the informed consent and day of enrollment (14 day maximum).
Study Day 1	The day that the first dose of investigational product is administered.
Study Start	Occurs when the first subject has been enrolled.
Treatment emergent adverse event	An adverse event that occurs following the first administration of a study specified treatment.
Time to Progression	The time from the date of first study drug administration to the date of documented progression
Time to Response	The interval from the start of study treatment to the first documentation of CR or PR or other measure of response

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1. OBJECTIVES

1.1 Phase 1 Primary

- To evaluate the safety and tolerability of RX-3117 in combination with Abraxane® in subjects with metastatic pancreatic cancer
- To determine the Recommended Phase 2 Dose (RP2D) of RX-3117 when administered orally in combination with Abraxane® to subjects with metastatic pancreatic cancer

1.2 Phase 1 Secondary

- To determine the pharmacokinetic (PK) profiles of RX-3117 and Abraxane® on Day 1 (single dose) and Day 15 (steady-state) in Cycle 1
- To evaluate the antitumor activity of RX-3117 in combination with Abraxane®

1.3 Phase 1 Exploratory

- To investigate predictive and pharmacodynamic blood or tumor biomarkers suggested from nonclinical studies/literatures which may be predictive of response or resistance to RX-3117 treatment

1.4 Phase 2 Primary

- To estimate the antitumor activity of RX-3117 in combination with Abraxane® as first-line therapy in subjects with metastatic pancreatic cancer

1.5 Phase 2 Secondary

- To assess additional measures of antitumor activity
- To characterize the safety profile of RX-3117 in combination with Abraxane®
- To evaluate the PK of RX-3117 and Abraxane® at the recommended Phase 2 dose (RP2D)

1.6 Phase 2 Exploratory

- To investigate the effect of RX-3117 in combination with Abraxane® on potential cellular or molecular biomarkers in blood or tumor samples
- To evaluate the change in tumor burden response
- To evaluate the effect on Quality of Life (QOL)

2. BACKGROUND AND RATIONALE

2.1 Disease

According to the latest statistics (American Cancer Society, 2015), cancer causes around 7.6 million deaths worldwide each year. Deaths from cancer are projected to continue rising to an estimated 21.4 million worldwide in 2030 (Globocan, 2012).

For patients presenting with confined local-regional cancer, the development of systemic therapies as adjuvants to primary surgery or irradiation have substantially improved outcomes by delaying recurrence of disease. However, for patients who present with large

primary tumors or metastases or who develop recurrent metastatic disease, cancer becomes a life-threatening disorder. Therapy for patients with advanced cancer has focused on the sequential use of systemic treatments to impede the disease progression that leads to disabling symptoms and death. Depending upon the tumor type, hormonal therapies, therapeutic monoclonal antibodies, or tyrosine kinase receptor inhibitors may be employed, and most commonly, cytotoxic chemotherapy in various sequences and combinations is administered.

The current National Comprehensive Cancer Network recommendations suggest acceptable chemotherapy combinations for patients with good performance status (i.e., Eastern Cooperative Oncology Group performance status [ECOG] of 0 or 1), good pain management, patent biliary stent, and adequate nutritional intake; these combinations include FOLFIRINOX, gemcitabine plus nab-paclitaxel, and gemcitabine plus erlotinib. The only recommended option for patients with poor performance status is gemcitabine monotherapy. Clinical trials are still recommended for first-line patients. The guidelines for choosing an appropriate treatment regimen for patients with metastatic pancreatic cancer thus remain ambiguous, and in the absence of a randomized trial comparing the combination regimens head to head, the dilemma remains regarding appropriate first-line therapy for these patients.

2.2 Cytidine Analogs in the Therapy of Cancer

Cytidine analogs have been widely used as antivirals and for the treatment of various types of cancer, both hematologic as well as solid tumors. These agents include cytarabine, 5-azacytidine, 5-aza-2'deoxycytidine (decitabine) and gemcitabine.

Among these, gemcitabine is the most broadly used anticancer agent. Initially developed as an antiviral agent, gemcitabine (2',2'-difluoro-2'-deoxycytidine) is structurally similar to cytarabine differing due to a fluorine substitution at position 2' of the furanose ring. Gemcitabine is a prodrug that requires cellular uptake and intracellular phosphorylation. Within the cell, gemcitabine is phosphorylated to gemcitabine monophosphate (dFdCMP) by deoxycytidine kinase which ultimately is converted to either the di- or triphosphate forms (gemcitabine diphosphate [dFdCDP] and gemcitabine triphosphate [dFdCTP]; Heinemann et al, 1992.

2.3 RX-3117

RX-3117 is a small-molecule, cyclopentyl pyrimidyl nucleoside being developed by Rexahn Pharmaceuticals, Inc. RX-3117 was synthesized as a new oral antimetabolite with the potential to overcome gemcitabine resistance and offer a favorable pharmacologic profile. Its chemical name is 4-amino-1-[(1S,4R,5S)-2-fluoro-4,5-dihydroxy-3-(hydroxymethyl)cyclopent-2-en-1-yl]pyrimidin-2-one. The RX-3117 monohydrate drug substance is a white to yellow crystalline solid. The molecular weight is 257.22 daltons for the anhydrous form and 275.24 daltons for the monohydrate form. Its molecular formula is $C_{10}H_{12}N_3O_4F \bullet H_2O$.

2.3.1 Mechanism of Action and Nonclinical Pharmacology Studies

The mechanism of action of RX-3117 has been investigated extensively. RX-3117 is an antimetabolite that mimics the building blocks of DNA or ribonucleic acid (RNA). Antimetabolites are incorporated into DNA or RNA of cells, where they interfere with cell division. RX-3117 is activated by uridine-cytidine kinase 2 (UCK2), and thus differs from gemcitabine, which is activated by deoxycytidine kinase. In addition, gemcitabine is inactivated by cytidine deaminase at a fast rate, whereas RX-3117 is inactivated by cytidine deaminase at a slow rate, thus allowing higher cellular concentrations of RX-3117 to enhance its anticancer activity.

In vitro mechanism studies characterized the effects of RX-3117 on cell cycle, apoptosis, and further elucidated its mode of action. Cell-cycle analysis by flow cytometry demonstrated that RX-3117 inhibited the cell cycle in G1 phase and also induced programmed cell death (apoptosis). The effect of RX-3117 on DNA and RNA was also evaluated; the majority of cell lines investigated showed a concentration-dependent inhibition of DNA and RNA synthesis after exposure to RX-3117, and RX-3117 showed inhibition of DNA synthesis more than RNA synthesis in most cell lines. Moreover, RX-3117 inhibited the proliferation of a variety of cancer cell lines of different origins, including bladder, bone, brain, breast, cervical, colon, liver, lung, muscle, ovary, pancreas, prostate, renal, and skin.

RX-3117 demonstrated an anti-proliferative IC50 of 6.3 μM against 5 pancreatic cancer cell lines tested, with one cell line being resistant (PANC1). RX-3117 demonstrated an added anti-proliferative effect when combined with paclitaxel in MiaPaca2 pancreatic cancer cell line. In a MiaPaca-2 xenograft model, RX-3117 at oral doses of 50 mg/kg (5 days/2 days off, 3 weeks) and 500 mg/kg (3 times a week for 3 weeks) demonstrated tumor growth delays of 30-50%.

2.3.2 Nonclinical Safety Pharmacology Studies

Safety pharmacology studies by the oral route evaluated potential functional effects of RX-3117 on the cardiovascular system, respiratory system, and central nervous system. Effects on the central nervous system and the cardiovascular system were also evaluated as part of the 28-day oral repeated dose toxicity study in dogs. In vitro, RX-3117 displayed no human ether-a-go-go-related gene (hERG) potassium channel inhibition, no cardiac cytotoxicity, and had no effect on spontaneous beating in Cor.At® pure embryonic stem cell derived cardiomyocytes. In vivo, RX-3117 did not elicit any changes in blood pressure parameters, electrocardiography (ECG) parameters, or heart rate in dogs. RX-3117 had no significant effects on respiratory parameters in mice. In addition, RX-3117 had no effects on the central or autonomic nervous systems, or on peripheral motor and sensory systems in both mice and dogs. Finally, RX-3117 had no effects on electroencephalography activity following an intravenous (IV) dose of 100 mg/kg in monkeys.

Further nonclinical safety pharmacology information can be found in the RX-3117 Investigator's Brochure.

2.3.3 Nonclinical Pharmacokinetic and Drug Metabolism Studies

The pharmacokinetic properties of RX-3117 were investigated in mice, dogs, and monkeys in conjunction with toxicity studies, as well as in separate pharmacokinetic studies.

Pharmacokinetic studies indicate that RX-3117 is orally bioavailable in mice and dogs, in contrast to gemcitabine, which can only be administered by the IV route only. RX-3117 is only poorly orally bioavailable in monkeys. For all species investigated in which the drug was orally bioavailable, RX-3117 displayed generally biphasic plasma profiles, with fast absorption and a relatively fast initial distribution phase followed by a slower terminal phase. Nonclinical pharmacokinetic parameters characterize a longer terminal elimination half-life (t½) of RX-3117 than that of gemcitabine. Following repeated administration, although plasma concentrations were detectable before the last dose, the extent of RX-3117 accumulation was minimal, with similar exposure parameters on the first and last days of administration. No sex-related differences of pharmacokinetic parameters were observed in any of the species tested.

2.3.4 Nonclinical Toxicology Studies

In mice, a single oral administration of RX-3117 at doses up to 1000 mg/kg did not induce toxicity signs on the day of treatment or during a 14-day recovery period, at any of the doses tested. Following daily oral administration of RX-3117 at 180/100 mg/kg/day (male/female mice), 60 and 30 mg/kg/day (both male and female mice) for up to 28 days, mortality occurred at the high dose in male and female mice (180 and 100 mg/kg, respectively) and in the mid-dose female mice (60 mg/kg). Clinical signs were observed mainly in high-dose groups and included hunched posture, piloerection, decreased activity, lethargy, tremors, semi-closed eyes, and cold to touch. Clinical signs mostly appeared just prior to the death or unscheduled sacrifice of the animals. Specific observations are detailed in the RX-3117 Investigator's Brochure. The dose of 60 mg/kg/day was considered as the severely toxic dose (STD).

In a non-GLP study in mice in which RX-3117 was given orally 3 times a week at 500, 1000, and 1500 mg/kg for a total of 5 administrations, a similar picture of toxicity appeared, yet at much higher doses as compared with the daily dosing regimen. Mortality occurred in the mid- and the high-dose groups (1000 and 1500 mg/kg, respectively). The dose of 500 mg/kg/day was considered to be the maximum tolerated dose (MTD) in this study.

In dogs, the main effects following a single oral administration of RX-3117 at doses up to 300 mg/kg were bone marrow toxicity, consisting of significant changes in hematologic parameters, and reductions in weights of the thymus and male sexual glands in mid- (100 mg/kg) and high-dose (300 mg/kg) groups. Following daily oral administration of RX-3117

for up to 28 days at doses of 1, 2.5, and 5 mg/kg, isolated episodes of emesis and liquid feces, along with reductions in body weight and food consumption, were seen in high-dose groups. Hematologic changes were noted in high-dose groups, which were fully recoverable by the end of the recovery period. The dose of 5 mg/kg/day was determined as the highest nonseverely toxic dose (HNSTD) while the dose of 2.5 mg/kg/day was determined as the no-observed-adverse-effect level (NOAEL).

In a non-GLP study in which RX-3117 dogs were given orally at doses of 15 and 30 mg/kg 3 times per week for a total of 6 administrations. Overall, the toxicity profile of RX-3117 in this study was similar to that observed during the 28-day repeated dose toxicity study, yet toxic effects were observed at higher doses in the thrice-weekly dosing regimen. The dose of 30 mg/kg/day was considered to be the MTD in this study.

Intravenous administration of high doses of RX-3117 in dogs and monkeys was associated with marked central nervous system toxicity, which was not observed in any of the tested species following dosing by the oral route. Daily IV doses of 35 mg/kg in monkeys (given for 5 consecutive days) were not associated with any signs of central nervous system toxicity.

RX-3117 was tested in a dedicated electroencephalography study in monkeys, in order to set safe doses and exposure levels based on electroencephalography measurements. Following a single IV dose of 100 mg/kg, no effects were noted on electroencephalographic activity and no clinical or electrophysiologic findings suggesting proconvulsant or seizure liability were observed.

RX-3117 was not mutagenic in the Ames in vitro reverse mutation assay using 5 strains of bacteria. However, RX-3117 was mutagenic to mammalian cells, when tested in the mouse lymphoma cell assay.

No studies on reproductive toxicity and carcinogenicity with RX-3117 have been performed.

2.3.5 Exploratory Clinical Study

RX-3117 was evaluated in an exploratory pharmacokinetic study of a single oral dose (50 or 100 mg) or a single IV dose (20 mg) of RX-3117 performed at 2 centers in Hungary. Subjects had advanced solid tumors and had not received any chemotherapy for 2 weeks prior to receiving the study drug.

No adverse events, treatment-emergent adverse events, deaths, or other serious adverse events were reported. No significant findings resulted from assessments of clinical laboratory test results, vital sign measurements, ECG, or physical examination findings. No safety issues (including cardiac toxicity) were reported although it should be noted that data were only collected on Days 1 through 3 and Day 7 after the study drug administration.

Further nonclinical safety information can be found in the RX-3117 Investigator's Brochure.

2.4 Phase 1b/2a, dose-ranging study of RX-3117 in patients with advanced malignancies

A Phase 1 study (NCT02030067) was designed to evaluate safety, tolerability and pharmacokinetics (PK) following increasing doses and schedules of RX-3117 to identify a recommended Phase 2 dose. Subjects received oral RX-3117 3, 5 or 7 times per week for 3 weeks followed by 1 week of rest for up to 8 cycles. RX-3117 PK demonstrated a dose proportional exposure and was rapidly absorbed without a marked lag time, and a median T_{max} between 2 to 3 hours; accumulation was generally minimal. The most frequent related adverse events were moderate to severe anemia, mild to moderate fatigue and nausea, mild diarrhea, vomiting, and anorexia. The recommended phase 2 dose and schedule was 700 mg daily for 5 times per week for three weeks, followed by a week off in a 28-day cycle. (Rasco 2016)

2.4.1 Stage 1 Phase 2a, study of RX-3117 in patients with metastatic pancreatic cancer

The Phase 1 study (NCT02030067) was amended to evaluate safety, tolerability and efficacy following treatment with the recommended phase 2 dose identified earlier. Eligible subjects (aged ≥ 18 years) were those with relapsed/refractory metastatic pancreatic cancer. The most frequent adverse events were moderate to severe anemia, mild to severe fatigue, mild diarrhea, and moderate to severe leukopenia (Rasco 2017). This ongoing trial is designed to detect an early efficacy signal using single agent RX-3117 in subjects with advanced pancreatic cancer. In the first stage of Phase 2, 2 of the 10 evaluable subjects reached the study endpoint of 4 months progression free survival. Data collection is ongoing in the second stage of Phase 2.

Further clinical safety information can be found in the RX-3117 Investigator's Brochure.

3. Experimental Design

3.1 Study Design

This will be a Phase 1b/2a multicenter 2-stage study.

Phase 1 will be conducted as a dose-finding, open-label study of oral RX-3117 administered in combination with Abraxane® to subjects with metastatic pancreatic cancer. The recommended phase 2 dose (RP2D) of RX-3117, in combination with Abraxane®, will be determined based on the safety profile, dose modification, and PK. Phase 1 will be conducted using a combination of the single MTD for RX-3117 and the Abraxane® dose as per the package insert when Abraxane® is given in combination for patients with pancreatic cancer. A safety committee will assess the safety and the tolerability of the combination after the first 5 patients and may make recommendation to confirm the MTD

in another 5 patients. For dosing information, please refer to Section 6.1 Study Drug Administration.

After completion of the Phase 1 portion, a Phase 2a study will be conducted using a 2-stage, open-label design, of RX-3117 and Abraxane® in combination to treat subjects with metastatic pancreatic cancer as first-line therapy. Approximately 10 subjects will participate in the Stage 1 at the dose identified in Phase 1 (RP2D). Subjects will be treated for up to 8 cycles of combined therapy. An interim analysis will be conducted after 10 evaluable subjects have been treated at the RP2D, have completed a minimum of 4 months/ cycles of therapy, or have discontinued therapy due to progressive disease before completing 4 cycles. If an adequate number of Responders are observed out of the initial 10 evaluable subjects, then 30 evaluable additional subjects will be enrolled to participate in Stage 2. An adequate number of Responders is defined as either at least 2 out of the 10 subjects (20%) having a measured benefit in PFS noted as PFS ≥ 4 months/ cycles or if at least 1 subject (10%) has an objective clinical response (partial or complete response) supported by acceptable safety and tolerability reviewed through the conduct of the study by the investigators, medical monitor and sponsor. The study may stop after the interim analysis if an adequate number of Responders are not seen. However, if an adequate number of Responders are seen, approximately 30 evaluable subjects will be enrolled and evaluated. Subjects will be treated for up to 8 cycles of combined therapy.

RX-3117 will be administered orally for 5 consecutive days followed by 2 days off each week for 3 weeks and a 1-week hiatus in repeated 4-week cycles.

Abraxane® will be administered intravenously over 30-40 min. on Days 1, 8, and 15 of each cycle at the dose level assigned in Phase 1 or the RP2D determined for Phase 2. Subjects will receive up to 8 cycles of RX-3117 in combination with Abraxane® or until disease progression (per RECIST ver. 1.1 see Appendix E), clinical progression, an intolerable RX-3117 related adverse event, withdrawal of consent, pregnancy, substantial noncompliance, or if the principal investigator feels it is in the best interest of the subject to stop treatment.

After 8 cycles of therapy, if in the opinion of the investigator a subject is receiving clinical benefit (as determined by patient care, quality of life, and tumor reduction), additional cycles of RX-3117 in combination with Abraxane® may be administered following discussions with the sponsor and medical monitor.

The study endpoints are defined in Section 10.1.

3.2 Number of Centers

Approximately 5 sites will participate in the Phase 1 portion and up to 15 enrolling sites in the US will participate in the Phase 2 study. Sites that do not enroll subjects within 3 months of site initiation may be terminated.

3.3 Number of Subjects

Number of planned subjects is approximately 5040 subjects (approximately 10 subjects in the Phase 1, depending upon the number of dose levels needed to identify the RP2D, approximately 10 evaluable subjects in Stage 1 of Phase 2 and approximately 30 evaluable subjects in Stage 2 of the Phase 2).

3.4 Estimated Study Duration

3.4.1 Study Duration for Participants

The study will consist of a screening period (up to 14 days; up to 21 days for tumor assessments), up to 8 treatment cycles (i.e., cycle = 28 days), an end-of-treatment visit, and a safety follow-up visit 30 +7 days after the last dose of RX-3117. Subject participation is anticipated to be approximately 9 months.

Subjects may receive RX-3117 until the earliest sign of disease progression (per RECIST ver. 1.1 see **Error! Reference source not found.**), clinical progression, an intolerable R X-3117-related toxicity, withdrawal of consent, pregnancy, substantial noncompliance with study procedures, principal investigator judgment that it is in the best interest of the subject to stop treatment, or study discontinuation.

3.4.2 End of Study

The study will end when all subjects have completed the study or have been discontinued.

4. SUBJECT ELIGIBILITY

This clinical trial can fulfill its objectives only if appropriate participants are enrolled. The following eligibility criteria are designed to select subjects for whom study participation is considered appropriate. All relevant medical and non-medical conditions should be taken into consideration when deciding whether this protocol is suitable for a particular subject. Eligibility criteria may not be waived by the investigator.. Any questions regarding a subject's eligibility should be discussed with the study sponsor and medical monitor prior to enrollment.

4.1 Screening Log

Investigators will be expected to maintain a screening log of all potential study candidates that includes limited information about the potential candidate (i.e., age, sex, race), date, and outcome of the screening process (e.g., enrolled into study, reason for ineligibility, or declined to participate).

4.2 Inclusion Criteria

Disease Related

1. Subject has confirmed histologic or cytologic evidence of pancreatic cancer, at least radiographic evidence of metastatic pancreatic cancer, and has no prior treatment for metastatic pancreatic cancer. Subjects who received gemcitabine in the neoadjuvant or adjuvant setting can be considered.
2. Subject has measurable disease using Response Evaluation Criteria in Solid Tumors (RECIST) ver. 1.1
3. Subject has a life expectancy of at least 3 months
4. Subject has an ECOG performance status 0 or 1

Demographic

5. Males or females ≥ 18 years of age
6. Subject must be able to swallow capsules
7. Subject must have adequate venous access for intravenous (IV) infusion

Laboratory

8. Subject has hemoglobin ≥ 9.0 g/dL at Screening
9. Subject has absolute neutrophil count (ANC) ≥ 1.5 x 10^9/L at Screening
10. Subject has platelet count ≥ 100 x 10^9/L at Screening
11. Subject has serum creatinine ≤ 1.5 times the upper limit of normal (ULN) at Screening.
    - Subjects with serum creatinine levels > 1.5 times the ULN must have a 24-hour urine creatinine clearance ≥ 50 mL/min
12. Subject has serum bilirubin ≤ 1.5 times the ULN (except in subjects with Gilbert's Syndrome who must have serum bilirubin < 3.0 x ULN)
13. Subject has aspartate aminotransferase (AST; SGOT) and alanine aminotransferase (ALT; SGPT) ≤ 2.5 times the ULN (OR, AST and ALT ≤ 5 times the ULN in the presence of known liver metastases)
14. Subject has alkaline phosphatase ≤ 2.5 times the ULN (OR ≤ 5 times the ULN in the presence of known liver or bone metastases)
15. Subject has normal coagulation parameters (prothrombin time [PT] and/or international normalized ratio [INR], and partial thromboplastin time [PTT] within normal limits [<1.2 x ULN])
16. Subject has potassium concentration within normal range, or correctable with supplements
17. Oxygen saturation by pulse oximetry ≥ 92% at rest
18. For women of childbearing potential: Negative serum pregnancy test during screening and negative serum or urine pregnancy test at start of study therapy (Cycle1 Day 1)

Reproductive

19. For female subjects of childbearing potential, willingness to abstain from heterosexual intercourse or use a protocol-recommended method of contraception from the screening visit throughout the study treatment period and for 30 days following the last dose of study drug
20. Female subjects of non-childbearing potential defined as having amenorrhea for at least 24 consecutive months, a documented hysterectomy, or a documented bilateral oophorectomy)
21. For fertile male subjects willingness to abstain from heterosexual intercourse or use a protocol-recommended method of contraception from the start of study therapy throughout the study treatment period and for 30 days following the last dose of study drug and to refrain from sperm donation from the start of study treatment throughout the study treatment period and for 30 days following the last dose of study drug.

Ethical

22. In the judgment of the investigator, participation in the protocol offers an acceptable benefit-to-risk ratio when considering current disease status, medical condition, and the potential benefits and risks of alternative treatments for the subject's cancer.
23. Before any study-specific procedure, the appropriate written informed consent must be obtained

4.3 Exclusion Criteria:

Disease Related

1. Subject has primary brain tumors or clinical evidence of active brain metastasis
2. Subject has undergone major surgery within 4 weeks of the start of study treatment. Laparoscopy and central venous catheter placement are not considered major surgery

Medications

3. Subject has a history of systemic corticosteroid use within 7 days before Day 1 of Cycle 1

General

4. Subject has an active infection requiring parenteral or oral antibiotics within 2 weeks before planned start of study therapy
5. Subject has uncontrolled diabetes as assessed by the investigator
6. Subject has a second malignancy other than curatively resected basal cell carcinoma of the skin, squamous cell carcinoma of the skin, in situ carcinoma of the cervix, or other cancers treated with curative intent and no known active disease within 3 years before planned start of study therapy
7. Subject has an active infection of hepatitis B, hepatitis C or human immunodeficiency virus

8. Female subjects who are pregnant, planning a pregnancy or breast feeding during the study
9. Subject has a high cardiovascular risk, including, but not limited to, subjects with congestive heart failure (New York Heart Association [NYHA] Class III or IV), cardiac arrhythmia, unstable angina, coronary stenting or acute coronary syndromes within 6 months before planned start of study therapy or myocardial infarction within one year before planned start of study therapy
10. ~~Subject has a history of peripheral artery disease (e.g., claudication, Leo Buerger's disease).~~ [Criterion removed]
11. Subject has a history of prior allogeneic bone marrow progenitor cell or solid organ transplantation.
12. Subject has known acute or chronic pancreatitis.
13. Subject has persistent diarrhea, malabsorption, or known sub-acute bowel obstruction ≥ NCI CTCAE Grade 2, despite medical management.
14. Subject has any disorder that may interfere with drug absorption, distribution, metabolism, or excretion (including gastrointestinal surgery and bariatric surgery)
15. All acute toxic effects of any prior antitumor therapy resolved to Grade ≤ 1 before the start of study therapy (with the exception of alopecia [Grade 1 or 2 permitted], or neurotoxicity [Grade 1 or 2 permitted], or anemia [Grade 2 is permitted; Grade 3 or higher is excluded]
16. Subject has any other medical, psychiatric, or social condition, which in the opinion of the investigator, would preclude participation in the study, pose an undue medical hazard, interfere with the conduct of the study, or interfere with interpretation of the study results
17. Subject has a history of interstitial lung disease, slowly progressive dyspnea and unproductive cough, sarcoidosis, silicosis, idiopathic pulmonary fibrosis, pulmonary hypersensitivity pneumonitis or multiple allergies. Any lung disease that may interfere with the detection or management of suspected drug-related pulmonary toxicity.
18. Subject is currently enrolled in any other clinical protocol or investigational trial that involves administration of experimental therapy and/or therapeutic devices, or investigational drug.
19. Subject has a history of hypersensitivity to RX-3117, gemcitabine, azacytidine cytosine arabinoside, paclitaxel, nab-paclitaxel, or their excipients.
20. Subject is unwilling or unable to comply with study requirements or planned unavailability for follow-up assessments.

5. SUBJECT ENROLLMENT

5.1 Subject Recruitment

Subjects will be enrolled from the cancer population being followed at or referred to the investigational sites. The site personnel will discuss the possibility of participation directly with subjects being seen in the center who may be appropriate candidates for the study. A description of the protocol will be posted on the www.clinicaltrials.gov website.

5.2 Subject Registration, Enrollment and Treatment Assignment

Before subjects may be entered into the study, the sponsor requires a copy of the site's written institutional review board approval of the protocol, informed consent form, and all other subject information and/or recruitment material, if applicable (see Section 12.3).

All subjects must personally sign and date the consent form before study specific procedures are performed during the screening period. After a subject has completed the necessary screening assessments, any questions regarding the eligibility of a subject should be discussed with the study sponsor before enrollment of the subject into the study.

The study sponsor or its designee will assign each subject a unique subject identification number (a 2-digit site number followed by a 3-digit subject number) at screening. The subject number must be used for subject identification on all study-related documents (e.g., electronic case report forms [eCRFs], clinic notes, laboratory samples, CT scans, MRIs, etc.). In order to obtain a subject number, the site must notify the sponsor or its designee that the subject has completed consent. In order for the subject to begin study treatment, the site must provide completed eligibility documents to the study sponsor or designee and the study sponsor or designee will provide confirmation of eligibility by either fax or e-mail to the site. Of note, subjects may be rescreened only once for laboratory values not meeting the criteria for study eligibility.

Please note: a subject will be enrolled when the treatment dose has been assigned. Ideally subjects will be dosed no later than 3 business days after enrollment.

5.3 Subject Replacement

In the Phase 1 and Phase 2-Stage 1, subjects who are enrolled but not treated and subjects who discontinue treatment before completion of Cycle 1 for reasons other than the occurrence of a DLT may be replaced. Any replacement subject will be enrolled into the same dosing level as that for the subject who withdrew.

In the Phase 2-Stage 2 portion, subjects who are enrolled but not treated will be replaced.

6. TREATMENT PROCEDURES

The investigational product in this study is RX-3117. RX-3117 will be administered in combination with Abraxane®. Abraxane® will not be provided by the sponsor. For details on RX-3117 description, storage and handling see Section 11.

6.1 Study Drug Administration

6.1.1 RX-3117 Dosing Schedule

RX-3117 will be administered on a cyclical basis. A cycle is defined as the period elapsing from the first day of RX-3117 administration through Day 28 of the cycle or to the recovery

from any adverse events sufficient that a new cycle can be administered (e.g., on Day 36 or Day 43), whichever occurs later. Once a new cycle is initiated, the prior cycle is considered to be completed.

In each 28-day cycle, RX-3117 will be taken by the subject 5 times per week (i.e., for 5 consecutive days followed by 2 days off) for 3 consecutive weeks followed by 1 week of rest in each 4 week cycle. Study drug should be taken at approximately the same time each day (e.g., at ~8 AM on each planned day of dosing). Ideally, doses should be taken at ~24- hour intervals. While it is realized that variations in dosing schedule may occur in the outpatient setting, the prescribed regimen should be followed as closely as possible, especially in the clinic.

At specified clinic visits in Cycle 1, RX-3117 will be administered in the clinic with dosing appropriately timed relative to blood sampling for Abraxane® and RX-3117 pharmacokinetics. As detailed in Section 7, clinic staff should record RX-3117 administration information, including the exact time each dose of RX-3117 is administered in the clinic or hospital.

6.1.2 RX-3117 Dose Administration

At each RX-3117 dose administration, the capsule types and numbers corresponding to the appropriate dose of RX-3117 are to be swallowed whole with approximately 100 to 200 mL (~ 4 to 8 ounces) of water. Subjects should be instructed not to bite or chew on the capsules. In case of breakage of the capsules in the oral cavity, additional water should be taken as a rinse that is then swallowed.

Subjects will be instructed to refrain from eating for 8 hours before each dose is administered. Subjects may eat ≥ 1 hour after dose administration.

6.1.3 Abraxane® Dose Schedule and Administration

Abraxane® will be administered once a week for 3 weeks on Days 1, 8, and 15 followed by 1 week of rest during each 28 day cycle. Abraxane® will be administered intravenously infused over 30 to 40 minutes. The date, time (i.e., start and stop) and volume infused (i.e., either initial and remaining volumes or volume infused off the pump) will be recorded in the subject's medical record and eCRFs.

On days when both RX-3117 and Abraxane® are administered on the same day, Abraxane® should be administered first, followed by RX-3117 dose given no sooner than 1 hour after the start of Abraxane® infusion. Abraxane® should not be mixed with or administered as an infusion simultaneously with other medicinal products.

At specified clinic visits in Cycle 1, Abraxane® will be administered in the clinic with dosing appropriately timed relative to blood sampling for Abraxane® and RX-3117

pharmacokinetics, if applicable. Pharmacokinetic samples should not be obtained from a port or PICC line if the line is used for the administration of Abraxane®.

6.2 Dose Finding and Stopping Rules

During Phase 1, 700 mg or lower doses of RX-3117 may be investigated in combination with Abraxane®, RX-3117 dosing will begin at 700 mg daily/ 5 days consecutively per week with 2 days rest for 3 weeks and then 1 week of rest in each Cycle. The Abraxane® starting dose will be 125 mg/m^2 administered on Days 1, 8 and 15 of each cycle. Abraxane® and RX-3117 dose reductions will follow Table 1 below.

Table 1. Dosage Reductions

Dose Level	Abraxane® (mg/m^2)	RX-3117 (mg)
Full dose	125	700
1st dose reduction	100	600
2nd dose reduction	75	500

This will be a Phase 1b/2a multicenter 2-stage study. The Phase I portion of the study is similar in nature to the traditional 3+3 design however it allows for a target DLT probability of 0.40 or 40%. The decision to increase the threshold from 33% to 40% is due to the known AE profiles of both drugs, the current recommended dose of Gemcitabine plus Abraxane®, and the desire not to expose first line subjects to subtherapeutic doses. Therefore if 0 or 1 of the first 5 subjects that complete one cycle of treatment experience a DLT, then the full dose may be confirmed as the RP2D. If 3 or more of the first 5 subjects that complete one cycle of treatment experience a DLT, then there will be a dose reduction and 5 subjects will be treated at the next lowest dose level. If 2 of the first 5 subjects that complete one cycle of treatment experience a DLT, then the safety review committee may recommend an additional 5 subjects are to be treated at the full dose. In this case, if 3 or less of the 10 subjects experience a DLT, then the full dose will be confirmed as the RP2D. Otherwise, if 4 or more of the 10 subjects experience a DLT, then a dose reduction will occur. Additional doses may be recommended by the review committee which includes investigators, medical monitor and sponsor. For Phase 2, the RX-3117 and Abraxane® dosing will be administered based on the RP2D identified after completion of Phase 1.

The RX-3117 doses will be administered from the least number of capsules available at the time of dosing shown in Table 2.

Table 2. RX-3117 Capsule Size and Dosing

Actual daily dose, mg	Number of capsules/ day		Total weekly dose, mg	Total cycle dose, mg
	200 mg	500 mg		
500	0	1	2,500	7,500
600	3	0	3,000	9,000
700	1	1	3,500	10,500

If a DLT occurs at one dose and dosing schedule (e.g., Abraxane® administered for once weekly for 3 weeks), that dose will follow the rules described below for enrolling additional subjects.

Since the frequency and severity of treatment related toxicities associated with single agent Abraxane® and RX-3117 do not overlap, a dose de-escalation design will be used.

In the event that attribution of causality, of potential DLTs, to study drug may be equivocal, discussions with the investigators, medical monitor and sponsor will occur and additional subjects may be enrolled at that dose level of RX-3117 and/or Abraxane®. Reviews will be conducted by the investigators, medical monitor and sponsor of all available safety data on an ongoing basis throughout the study. The study sponsor or its designee will notify the sites when enrollment into a dose level is complete and when the next dose level is open to enrollment.

6.3 Determination of MTD and Recommended Phase 2 Starting Dose

The establishment of the recommended Phase 2 dose will be based on a review of the overall safety data by the investigators, medical monitor and sponsor. Selection of a recommended Phase 2 starting dose from within the tested doses of RX-3117 and/or Abraxane® will be based on evaluation of short- and long-term safety information but also considering findings regarding compliance, pharmacokinetics, pharmacodynamics and antitumor activity, if applicable. The review committee may recommend that a lower dose level of RX-3117 and/or Abraxane® be considered the recommended Phase 2 dose or that another dose level of RX-3117 and/or Abraxane® between the highest previously tolerated dose level, and the dose level exceeding the MTD be tested in additional subjects.

Upon review of the Phase 1 safety data, the investigators, medical monitor, and the sponsor determined the Phase 2 dose to be 700 mg RX-3117 and 125 mg/m^2 Abraxane following the schedules defined in Sections 6.1.1 and 6.1.3.

6.4 Definitions of Dose-Limiting Toxicity

Reference should be made to the CTCAE, Version 4.03 for grading of the severity of adverse events and laboratory abnormalities. The DLT assessment period is defined as

the first cycle of treatment in the Phase 1 portion of the study. The minimum exposure to the investigation regimen for DLT assessments will be defined as subjects who receive at least 10 doses of RX-3117 and 2 doses of Abraxane. A DLT will be defined as any of the following adverse events that is considered by the investigator as possibly, probably or definitely-related to RX-3117, Abraxane or the combination:

- Grade 4 neutropenia (ANC < 0.5 x 10^9/L)
- Grade ≥ 3 neutropenia (ANC < 1.0 x 10^9/L) with fever greater than 38.5°C (101.3°F)
- Grade 4 thrombocytopenia (platelet count < 25 x 10^9/L)
- Grade 3 nausea or vomiting lasting >3 days despite optimal management
- Grade 3 fatigue lasting > 7 days
- Grade 4 fatigue
- Treatment interruptions of ≥ 7 days
- Any Grade thrombocytopenia that occurs with clinically significant bleeding

Any other non-hematological Grade ≥ 3 adverse events will be considered DLTs with the exception of the following:

- Alopecia
- Grade 1 or 2 sensory neuropathy
- For subjects with bone or liver metastases and baseline levels of AST or ALT > 2.5 x ULN or alkaline phosphatase > 2x ULN, DLTs do not include elevations in AST, ALT, and alkaline phosphatase unless the following criteria are met:
- AST > 8 x ULN, if the baseline level was between 2.5 to 5 x ULN in subjects with liver metastases
- ALT > 8 x ULN, if the baseline level was between 2.5 to 5 x ULN in subjects with liver metastases
- Alkaline phosphatase > 8 x ULN, if the baseline level was between 2 to 5 x ULN in subjects with bone or liver metastases

6.5 Delayed, Missed and Vomited Doses of RX-3117

Subjects who have a delay in the administration of a dose of RX-3117 of ≤ 8 hours should take the planned dose as soon as possible after the intended time of administration. For subjects who have a delay in administration of RX-3117 of ≥ 8 hours, the dose should not be taken. RX-3117 administration may continue but the missed dose should not be made up and the planned timing of subsequent RX-3117 dosing should not be altered.

Vomited doses should not be retaken.

6.6 Delayed and Missed Doses of Abraxane®

If a subject has an AE or other event causing the delay or missed dose of Abraxane®, the investigator should discuss, whenever possible, the restart and potential dose modifications of Abraxane® with the sponsor and medical monitor.

6.7 Dosage Modifications

Whenever possible, dose and scheduling modifications should be discussed between the investigator and the sponsor prior to implementation. The appropriate clinic staff should dispense the study drug for the new dose level and instruct the subject/caregiver about the change in dose level.

6.7.1 Dose Modifications During a Cycle

RX-3117

If a subject experiences a RX-3117-related DLT or AE (as defined in Section 6.4) and requires a dose reduction, RX-3117 administration should be interrupted, as necessary, until the adverse event resolves or stabilizes to an acceptable degree (generally to the pretreatment severity grade). If appropriate, more frequent laboratory monitoring may be instituted until abnormalities have recovered to the pretreatment severities. Thereafter, RX-3117 may be reinstituted, but the dose of RX-3117 for the remainder of that cycle should be reduced by 1 dose level or as directed by the Sponsor. Successive adjustments to progressively lower dose levels can be made. If the subject cannot tolerate RX-3117 at the lowest dose level (500 mg/day for 5 days) then the subject should be discontinued from RX-3117 therapy. If necessary, the subject should be instructed to return to the clinic to receive RX-3117 of the appropriate strength(s) for the reduced dose level. Missed days of treatment should not be made up (e.g., if a subject experiences an RX-3117-related adverse event, after 1 week of treatment, and the event lasts for 1 week, the missed doses during week 2 should be omitted and the new reduced dose level should be administered only for the remaining doses so that the total planned cycle duration remains 28 days).

Abraxane®

In Phase 1, dose adjustments for Abraxane® will be made after discussion amongst the investigator, medical monitor, and sponsor.

In Phase 2, dose adjustments for Abraxane® will be allowed for adverse events according to the approved package insert. Refer to Table 1. Dosage Reductions for the dose reduction schedule. Additional dose recommendations and modifications due to adverse reactions are detailed in Table 3 and Table 4. If the start of a cycle (i.e., day 1 of a cycle) is delayed due to an Abraxane®-related toxicity, then RX-3117 dosing may continue on schedule.

Table 3. Dose Recommendation and Modifications of Abraxane® for Neutropenia and/or Thrombocytopenia at the Start of a Cycle or within a Cycle

Cycle Day	ANC (cells/mm^3)		Platelet count (cells/mm^3)	Abraxane®
Day 1	< 1500	OR	< 100,000	Delay dose until recovery

Day 8	500 to < 1000	OR	50,000 to 75,000	Reduce 1 dose level
	< 500	OR	< 50,000	Withhold dose
Day 15: IF Day 8 dose was reduced or given without modification:				
	500 to < 1000	OR	50,000 to 75,000	Reduce 1 dose level
	< 500	OR	< 50,000	Withhold dose
Day 15: IF Day 8 dose was withheld				
	≥ 1000	OR	≥ 75,000	Reduce 1 dose level from Day 1
	500 to < 1000	OR	50,000 to < 75,000	Reduce 2 dose levels from Day 1
	< 500	OR	< 50,000	Withhold dose

https://www.accessdata.fda.gov/drugsatfda_docs/label/2013/021660s037lbl.pdf

Table 4. Dose Modifications of Abraxane for Other Adverse Drug Reactions

Adverse Drug Reaction	**Abraxane®**
Febrile Neutropenia: Grade 3 or 4	Withhold until fever resolves and ANC ≥ 1500; resume at next lower dose level
Peripheral Neuropathy: Grade 3 or 4	Withhold until improves to ≤ Grade 1; resume at next lower dose level
Cutaneous Toxicity: Grade 2 or 3	Reduce to next lower dose level; discontinue treatment if toxicity persists
Cutaneous Toxicity: Grade 3 mucositis or diarrhea	Withhold until improves to ≤ Grade 1; resume at next lower dose level

https://www.accessdata.fda.gov/drugsatfda_docs/label/2013/021660s037lbl.pdf

RX-3117 and Abraxane®

If an adverse event occurs that is related to RX-3117, Abraxane® may continue on schedule.

If an adverse event occurs that is related to Abraxane®, RX-3117 may continue on schedule.

If an adverse event occurs that is related to the combination of RX-3117 and Abraxane®, dosing of both drugs may be delayed until the event is resolved.

6.7.2 Dose Modifications at the Beginning of the Next Cycle

A new cycle of RX-3117 treatment may be delayed, as necessary, until adverse events or laboratory abnormalities have returned to baseline levels. If adverse events or laboratory abnormalities are not resolved to baseline, weekly delays in initiating the new cycle of treatment should be instituted. Once all toxicities have returned to baseline, the next cycle

of therapy can be initiated. If the start of a cycle (i.e., day 1 of a cycle) is delayed due to RX-3117 related toxicity, then Abraxane® dosing may continue on schedule.

Subjects receiving a lower dose but who the principal investigator feels are benefiting from treatment, may after discussions with the Sponsor, receive a higher dose of either RX-3117 or Abraxane®, for which there is already safety data.

6.7.3 Dose Re-Escalation

After a dose reduction for either RX-3117 or Abraxane®, the dose need not be re-escalated, even if there is minimal or no toxicity with the reduced dose. However, if the subject tolerates a reduced dose of RX-3117 or Abraxane® for ≥ 4 weeks then the RX-3117 and/or Abraxane® doses may be increased to the next higher dose level, at the discretion of the investigator. Such re-escalation may be particularly warranted if further evaluation reveals that the adverse event that led to the dose reduction was not RX-3117 or Abraxane®-related. Successive adjustments to progressively higher dose levels can be made at 4-week intervals but the dose must not exceed the highest dose level for which there is already Cycle 1 safety data.

6.8 Discontinuation of Study Treatment

All study participants may receive study treatment for up to 8 cycles. Therapy beyond 8 cycles may be considered following discussions among the sponsor, investigator and medical monitor. However:

- Any subject has the right to withdraw from study treatment or study follow-up at any time.
- Any subject who has objective evidence of cancer progression should be withdrawn from study treatment.
- Any subject who cannot tolerate 500 mg RX-3117 or 75 mg/m^2 Abraxane® despite appropriate supportive care should be withdrawn from study treatment.
- Any subject whose medical condition substantially changes after entering the study should be carefully evaluated by the investigator in consultation with the sponsor; such subjects should be withdrawn from study treatment if continuing would place them at risk.
- Any subject who becomes pregnant or begins breastfeeding should be withdrawn from study treatment.
- Any subject who becomes significantly noncompliant with study drug administration, study procedures, or study requirements should be withdrawn from

study treatment in circumstances that increase risk or substantially compromise the interpretation of study results.

- The investigator, in consultation with the sponsor, may withdraw any subject from the study treatment, if, in the investigator's opinion, it is not in the subject's best interest to continue.

- The sponsor, relevant regulatory agencies, or the institutional review board may request discontinuation of the study at any time.

The date the subject is withdrawn from study treatment or from the study and the reason for discontinuation will be recorded in the subject's medical record and on the appropriate eCRF.

When a subject is withdrawn from study treatment or is permanently removed from study treatment (regardless of the reason), all of the evaluations required at the end-of-treatment visit should be performed and any additional evaluations should be completed that may be necessary to ensure that the subject is free of untoward effects. The subject should be encouraged to seek appropriate follow up for any continuing health problems.

Subjects who discontinue study treatment may still continue on study follow-up. Thus, all subjects receiving study drug will be followed during the post treatment follow-up assessments unless the subject withdraws consent for such follow-up.

6.9 Concomitant and Supportive Therapy

To the extent possible, administration of any prescription or over-the-counter drug products other than study medication should be minimized during the study period. Subjects should be discouraged from use of street drugs, herbal remedies, self-prescribed drugs, tobacco products, or excessive alcohol at any time during the clinical study.

If considered necessary for the subject's well-being, drugs for concomitant medical conditions or for symptom management may be given at the discretion of the investigator. The decision to authorize the use of any drug other than protocol prescribed therapies should take into account subject safety, the medical need, the potential for drug interactions, the possibility for masking symptoms of a more significant underlying event, and whether use of the drug will compromise the outcome or integrity of the study

Subjects should be instructed about the importance of the need to inform the clinic staff of the use of any drugs or remedies (whether prescribed, over-the-counter, recreational or illicit) before and during the course of the study. Any concomitant drugs taken by a subject during the course of the study and the reason for use should be recorded on the electronic case report forms (eCRFs).

6.9.1 Analgesics

Investigators may give analgesics, as necessary, for pain control.

6.9.2 Antibiotics

For subjects who develop an infection, appropriate medical therapy (e.g., with antibiotics, antifungals, or antivirals) or other interventions should be instituted. Investigators should use appropriate medical judgment in determining whether a subject continues with RX-3117 or Abraxane® during treatment for the infection.

6.9.3 Anticancer or Experimental Systemic Therapies Other than Investigational Treatments

No other systemic anticancer therapies (including chemotherapy, antibody therapy, immunotherapy, or other experimental therapies) of any kind are permitted while the subject is receiving protocol prescribed therapy. Subjects are not allowed to participate concurrently in any other therapeutic clinical study.

6.9.4 Antidiarrheals

For subjects who develop diarrhea, causes related to existing medical conditions, concomitant medications, or gastrointestinal infection should be considered and eliminated. Depending upon the clinical circumstances, endoscopy and biopsy may be warranted.

Antidiarrheals are not allowed prior the administration of Abraxane® or RX-3117 on Cycle 1 Day 1 and antidiarrheals should not be taken prophylactically in subsequent cycles. However, antidiarrheals can be administered on subsequent treatment days and in subsequent cycles, based on the judgment of the treating physician and local institutional practices. Subjects should be instructed to begin taking antidiarrheal medication at the first sign of any of the following: (1) poorly formed or loose stool, (2), occurrence of more bowel movements than usual in 1 day, or (3) an unusually high volume or increased liquidity of stool.

A recommended symptomatic antidiarrheal is loperamide, which may be taken in the following manner: 4 mg at the first onset of diarrhea, then 2 mg every 2 hours around the clock until diarrhea-free for at least 12 hours. Subjects may take loperamide 4 mg every 4 hours during the night. Subjects who appear prone to drug-related diarrhea should be provided with loperamide so that they have sufficient supply on hand in case antidiarrheal support is required. Alternate or additional antidiarrheal measures may be used at the discretion of the treating physician. Subjects should be instructed to increase fluid intake to help maintain hydration during episodes of diarrhea.

Depending upon the type and severity of the diarrhea, interruption of Abraxane® or RX-3117 and rechallenge at the same or a reduced dose level and frequency of either and with appropriate support care should be considered.

6.9.5 Antiemetics

Antiemetics are not allowed prior the administration of Abraxane® or RX-3117 on Cycle 1 Day 1 in Phase 1. However, antiemetics can be administered on subsequent treatment days and in subsequent cycles and prophylactically in Phase 2, based on the judgment of the treating physician and local institutional practices.

At the occurrence of drug-related nausea or vomiting of severity Grade $\geq$ 1, it is suggested that the subject receive an oral or transdermal serotonin antagonist (e.g., dolasetron, granisetron, ondansetron, tropisetron, palonosetron). The neurokinin receptor antagonist, aprepitant, may also be considered. Other classes of antiemetic medications that may be employed include dopamine antagonists or benzodiazepines. If possible, systemic corticosteroids should be avoided due to their many non-specific effects.

Depending upon the type and severity of the vomiting, interruption of Abraxane® or RX-3117 and rechallenge at the same or a reduced dose level and with appropriate support care should be considered.

6.9.6 Contraception

Sexually active females of childbearing potential must accept continuous heterosexual abstinence as a lifestyle choice or agree to use a protocol-recommended method of contraception during heterosexual intercourse throughout the study treatment period and for 30 days following discontinuation of RX-3117. A female subject is considered to be of childbearing potential unless she has had a hysterectomy, bilateral tubal ligation, or bilateral oophorectomy; has medically documented ovarian failure (with serum estradiol and follicle-stimulating hormone [FSH] levels within the institutional postmenopausal range and a negative serum or urine β-human chorionic gonadotropin [β-HCG]), or is menopausal (age $\geq$ 55 years with amenorrhea for $\geq$ 6 months). Protocol-recommend methods of contraception include barrier method with spermicide, intrauterine device (IUD), or steroidal contraceptive (oral, transdermal, implanted, or injected).

Sexually active male subjects who can father a child (i.e., are fertile) must accept continuous heterosexual abstinence as a lifestyle choice; limit intercourse to female partners who are surgically sterile, post-menopausal, or using effective contraception (as noted in Table 3; or agree to use a protocol-recommended method of contraception during heterosexual intercourse throughout the study treatment period and for 30 days following discontinuation of RX-3117 (as noted in Table 3). A male subject is considered fertile unless he has had a bilateral vasectomy with documented aspermia or a bilateral orchiectomy. The investigator should counsel subjects on the most effective methods for

avoiding pregnancy during the trial. Protocol-recommended contraceptive methods are described in Table 3.

Table 3. Protocol-Recommended Contraceptive Methods

Individual Methods	Combination Methods	
	Hormonal Methods (One method to be used with a barrier method)	**Barrier Methods (Both of these methods to be used OR one of these methods to be used with a hormonal method)**
IUD • Copper T 380A IUD • LNg 20 IUD Tubal sterilization Hysterectomy	Estrogen and progesterone • Oral contraceptives • Transdermal patch • Vaginal ring Progesterone • Injection • Implant	• Diaphragm with spermicide • Male condom (with spermicide)

Abbreviation**:** IUD=intrauterine device

The sponsor should be consulted regarding any questions relating to childbearing status or contraception.

6.9.7 Corticosteroids

Systemic or enteric corticosteroids are not allowed prior the administration of Abraxane® or RX-3117 on Cycle 1 Day 1. Subjects may receive topical or inhaled corticosteroids while on study. In addition, subjects who develop conditions that may be alleviated by systemic or enteric corticosteroid therapy are permitted to receive such drugs and are not required to discontinue study participation

6.9.8 Diet

There are no specific dietary restrictions in the study other than that subjects should refrain from eating for 8 hours before and for 1 hour after RX-3117 is taken.

6.9.9 Drugs with Potential for Interactions with RX-3117 and Abraxane

As described in Section 2.2.4, in vitro studies indicate that RX-3117 does not inhibit drug transporters or CYP enzymes at clinically relevant concentrations; thus, it is not expected that RX-3117 would induce interactions with drugs for which absorption or metabolism would be modulated by inhibition of these enzymes.

The package insert for Abraxane indicates that Abraxane is metabolized by CYP2C8 and CYP3A4. Refer to the current package insert for potential drug interactions with Abraxane (https://www.accessdata.fda.gov/drugsatfda_docs/label/2013/021660s037lbl.pdf).

6.9.10 Erythropoietin and Granulocyte Colony-Stimulating Factors

Use of erythropoietic agents (e.g., erythropoietin or darbepoetin alpha) is not permitted during Cycle 1 of therapy. Thereafter, such agents may be administered for Grade ≥ 3 anemia, but their use in this study is discouraged.

Granulocyte-macrophage colony-stimulating factor (GM-CSF) should not be administered given the potential for GM-CSF-related inflammatory symptoms.

Use of granulocyte colony-stimulating factor (G-CSF; e.g., filgrastim, PEG-filgrastim, lenograstim) is not allowed in Cycle 1 of therapy. Prophylactic administration of G-CSF and concomitant administration of RX-3117 and G-CSF is not permitted in support of protocol therapy. In addition, therapeutic use of G-CSF in subjects with serious neutropenic complications such as tissue infection, sepsis syndrome, fungal infection, etc., may be considered at the investigator's discretion

Reference may be made to the American Society of Clinical Oncology guidelines (Rizzo et al, 2008; Smith et al, 2006).

6.9.11 Immunization

Due to its potential effects on lymphoid cells, Abraxane® and/or RX-3117 might theoretically impair primary or secondary responses to immunization. For subjects who are at substantial risk of an infection (e.g., influenza) that might be prevented by immunization, consideration should be given to providing the vaccine prior to initiation of study therapy.

If a vaccine is administered during Abraxane® and RX-3117 therapy, vaccination should not be performed during Cycle 1 or during any other cycle in a period when the patient is experiencing Grade ≥ 2 leukopenia. The safety of immunization with live viral vaccines during RX-3117 has not been evaluated and vaccination with live virus vaccines during study treatment is not recommended. There have been reports of Abraxane® having major interactions with various drugs, including live vaccines.

6.9.12 Radiation Therapy

Radiation therapy is not permitted during Cycle 1 of study treatment. Thereafter, short-term, palliative radiation therapy can be used for the management of known, non-progressing bony metastatic lesions if refractory to standard pain management algorithms.

RX-3117 appears to sensitize tumor cells to radiotherapy in an *in vitro* setting. However, since the radiosensitizing properties of RX-3117 have not yet been established, it is recommended that the study drug be stopped ≥ 2 days before radiation and re-started ≥ 2 days after the completion of the course of radiation. Before treatment occurs, the investigator should discuss the method/frequency of radiation administration with the sponsor.

Abraxane® is a radiosensitizing agent. Discontinuation of Abraxane® before radiation should follow institutional standards.

6.9.13 Surgery or Other Invasive Procedures

The effects of RX-3117 on coagulation or wound healing are unknown. Potential RX-3117 myelosuppressive or immunosuppressive effects could enhance the risk of peri-procedural bleeding or infection.

Elective surgical procedures (other than placement of IV access devices) should be avoided during RX-3117 or Abraxane® administration. However, subjects may undergo necessary surgical or invasive procedures for serious intercurrent medical problems; in these circumstances, study drug should be interrupted. Investigators should use appropriate medical judgment in determining whether to resume study drug in the post-procedure period. For subjects resuming study drug, any myelosuppressive effects of the drug should have returned to baseline levels and the subject should be clinically stable before reinitiating therapy.

6.9.14 Transfusions

Red blood cell or platelet transfusions may be administered, as clinically indicated.

7. STUDY PROCEDURES

Refer to the Schedule of Assessments (for details see Appendix A, Appendix B, and Appendix C) for outlines of procedures required at each visit. All safety blood and urine samples should be collected and submitted to the local laboratory on the day of collection. Blood for evaluation of RX-3117 or Abraxane® pharmacokinetics, any archived tumor tissue, any tumor biopsy samples, and biomarker samples should be prepared and shipped to the central laboratories for analysis.

Unless otherwise specified, all assessments will be done on the planned visit date.

7.1 General Study Procedures

A signed and dated institutional review board approved informed consent must be obtained before any study specific screening procedures are performed. Assessments that are performed as standard of care procedures may be used for screening if performed

before the informed consent is signed, provided that they are still within the screening period.

7.2 Screening Procedures

The following screening assessments must be performed and results available within 14 days (unless otherwise noted - 21 days allowed for imaging assessments) before enrollment:

- Written informed consent
- Review of inclusion and exclusion criteria
- Medical, surgical, cancer and psychiatric history review, documentation of diagnosis and previous treatments with responses including details of tumor diagnosis (e.g., date of diagnosis, histology, stage at diagnosis and current stage) and most recent disease assessment
- Prior medication usage within the previous 28 days before planned study drug administration.
- Resting vital signs: pulse, respiration rate, temperature, blood pressure (i.e., after the subject has been seated for at least 5 minutes) and oxygen saturation (to be assessed by pulse oximetry while subject is breathing room air)
- ECOG Performance status
- Physical examination (excluding genitourinary system) including weight and height

Laboratory tests (for analyte details see

- Appendix D)
    - Urinalysis
    - Hematology panel
    - Chemistry panel
    - Serum pregnancy test for female subjects of childbearing potential
    - Coagulation: PT/INR and PTT
    - Tumor marker
- 12-lead electrocardiogram will be taken after the subject has been supine or recumbent (same position must be used for all measurements) for at least 5 minutes (within 7 days before enrollment). All electrocardiogram reports must include the HR, QRS, QT, QTcF, and PR intervals. A duplicate printout of the electrocardiogram report must be printed when the assessment is performed for review by a central vendor.
- Radiological imaging to assess disease extent. Radiological assessment must include computerized tomography or magnetic resonance imaging of disease sites and the modality selected should be the same throughout the study. Disease assessment should be according to RECIST ver. 1.1 (for details see Appendix E) within 21 days before enrollment. Some imaging assessments may be collected for a second review by a central imaging vendor.
- Review of subject eligibility by the study sponsor or assigned designee
- Subject is enrolled when they receive the treatment assignment from the sponsor or assigned designee

7.3 Treatment Period – Cycle 1 Day 1

7.3.1 Pre-dosing Assessments

The following procedures will be performed within 5 days **before** the 1st dose of Abraxane® and RX-3117 are administered on Cycle 1 Day 1, unless otherwise described:

Laboratory tests within 5 days before dosing (for analyte details see

- Appendix D)
    - Hematology panel
    - Chemistry panel
    - Urinalysis
    - Pregnancy test for female subjects of childbearing potential must be negative before study drug dosing can occur. If a serum pregnancy test was done and determined negative within 72 hours of dosing a urine pregnancy test is not needed.
    - Coagulation tests: PT/INR and PTT
    - Tumor marker
- Subject will complete Quality of Life Questionnaires before any of the following study procedures are performed.
    - EORTC-QLQ-30 and EORTC-PAN26
    - FACT-Hep
- Review medication usage for any medications started since the screening visit
- Weight
- ECOG performance status
- Collection of a tumor biopsy sample pre-treatment from enrolled subjects (optional)
- 12 lead electrocardiogram taken while the subject is supine or recumbent (same position must be used for all measurements). All electrocardiogram reports in this study must include HR, QRS, QT, QTcF, and PR intervals. A duplicate printout of the electrocardiogram report must be printed when the assessment is performed for review by a central vendor. (Phase 1 and Phase 2 – Stage 1 only)
- Resting vital signs: pulse, respiration rate, body temperature, and blood pressure (i.e., after the subject has been seated for at least 5 minutes).
- Collect a blood sample for pre-dose Abraxane® and RX-3117 pharmacokinetics (with recording of the date and actual clock time of blood collection).(Phase 1 and Phase 2 – Stage 1)
- Collect blood sample for biomarker analysis.

7.3.2 Post-dosing Assessments – Cycle 1 Day 1

The following procedures will be performed **after** the administration of Abraxane® but before the administration of RX-3117:

- Blood samples for Abraxane® pharmacokinetics will be collected (Phase 1 and Phase 2 – Stage 1):

- At the end of infusion of Abraxane on Cycle 1 Day 1, and just prior (no more than15 minutes) to RX-3117 administration (pre-dose).

RX-3117 will be administered no earlier than 1 hour after the start of Abraxane® infusion. The following procedures will be performed **after** the administration of RX-3117:

- The required order of assessments is electrocardiogram, followed by vital signs and pharmacokinetic sampling when applicable.

Post-RX-3117 Dose Procedure (Phase 1 and Phase 2 – Stage 1 only)				
Time *(in hours)* elapsed since dose		12 lead ECG[a]	Vital Signs[b]	PK
	0.5 *(±5 minutes)*		X	X
	1 *(±10 minutes)*	X	X	X
	2 *(±10 minutes)*	X	X	X
	3 *(±10 minutes)*		X	X
	4 *(±10 minutes)*	X	X	X
	6 *(±10 minutes)*	X	X	X

[a] while the subject is supine or recumbent (same position must be used for all measurements). All electrocardiogram reports in this study must include HR, QRS, QT, QTcF, and PR intervals. A duplicate printout of the electrocardiogram report must be printed when the assessment is performed for review by a central vendor.

[b] pulse, respiration rate, body temperature, and blood pressure (i.e., after the subject has been seated for at least 5 minutes)

- Recording of concomitant medication(s)
- Record adverse event(s). Serious adverse events will be reported immediately. Any adverse event that is considered related to study drug will be followed to resolution or return to baseline.
- Collection of archived tumor samples from eligible treated subjects within 4 weeks of Cycle 1 Day 1.
- Dispensing of study drug and instructions for dosing at home (Phase 2 – Stage 2 only)
- Dispensing of diary cards (Phase 2- Stage 2 only)

7.4 Treatment Period – Cycle 1 Day 2 (Phase 1 and Phase 2 - Stage 1)

- Recording of adverse event(s). Serious adverse events will be reported immediately. Any adverse event that is considered related to study drug will be followed to resolution or return to baseline.
- Record concomitant medication(s).
- 12 lead electrocardiogram taken at 24 hours after the RX-3117 administration while the subject is supine or recumbent (same position must be used for all measurements). All electrocardiogram reports in this study must include HR, QRS, QT, QTcF, and PR intervals. A duplicate printout of the electrocardiogram report must be printed when the assessment is performed for review by a central vendor.

- Resting vital signs: pulse, respiration rate, body temperature, and blood pressure (i.e., after the subject has been seated for at least 5 minutes).
- Blood sample for RX-3117 pharmacokinetics will be collected:
    - At 24 hours ± 1 hour (Cycle 1 Day 2) after the first dose of the RX-3117 and before the second dose
- Dispensing of study drug and instructions for dosing at home
- Dispensing of diary cards
- RX-3117 will be taken orally at the clinic. The time of the dosing will be recorded.

7.5 Treatment Period – Cycle 1 Day 8

The following procedures and assessments will be performed **before** Abraxane® dosing on Cycle 1 Day 8, unless otherwise described:

- Subject will complete Quality of Life Questionnaires before any other study procedures are performed:
    - EORTC-QLQ-30 and EORTC-PAN26
    - FACT-Hep
- Collection of unused RX-3117
- Review subject study drug compliance
- Record concomitant medication(s)
- Recording of adverse event(s). Serious adverse events will be reported immediately. Any adverse event that is considered related to study drug will be followed to resolution or return to baseline.

Laboratory tests within 3 days before dosing (for details see

- Appendix D)
    - Hematology panel
    - Chemistry panel
    - Urinalysis
    - Coagulation tests: PT/INR and PTT
- Resting vital signs: pulse, respiration rate, body temperature, and blood pressure (i.e., after the subject has been seated for at least 5 minutes).

The following procedures and assessments will be performed after the completion of Abraxane® dosing on Cycle 1 Day 8:

- Record concomitant medication(s)
- Dispensing of study drug and instructions for dosing at home
- Dispensing of diary cards
- RX-3117 may be taken orally in the clinic or at home.

7.6 Treatment Period – Cycle 1 Day 15

7.6.1 Pre-dosing Assessments

The following procedures will be performed **before** Abraxane® dosing on Cycle 1 Day 15, unless otherwise described. If Abraxane® is not being administered on Cycle 1 Day 15, the following procedures will be performed **before** RX-3117 dosing unless otherwise described:

Laboratory tests within 3 days before dosing (for details see

- Appendix D)
    - Hematology panel
    - Chemistry panel
    - Urinalysis
    - Coagulation tests: PT/INR and PTT
- Subject will complete Quality of Life Questionnaires before any other study procedures are performed (except the laboratory tests listed above):
    - EORTC-QLQ-30 and EORTC-PAN26
    - FACT-Hep
- Collection of unused study drug
- Review subject study drug compliance
- Record concomitant medication(s)
- Recording of adverse event(s). Serious adverse events will be reported immediately. Any adverse event that is considered related to study drug will be followed to resolution or return to baseline.
- Collect blood sample for pre-dose pharmacokinetics (with recording of the date and actual clock time of blood collection) (Phase 1 and Phase 2 - Stage 1).
- Resting vital signs: pulse, respiration rate, body temperature, and blood pressure (i.e., after the subject has been seated for at least 5 minutes).

7.6.2 Post-dosing Assessments – Cycle 1 Day 15

The following procedures will be performed **after** the administration of Abraxane® but before the administration of RX-3117:

- Blood samples for Abraxane® pharmacokinetics will be collected (Phase 1 and Phase 2 – Stage 1):
    - At the end of infusion of Abraxane® on Cycle 1 Day 15, and just prior (no more than15 minutes) to RX-3117 administration (pre-dose).

The following procedures will be performed **after** the administration of RX-3117 on Cycle 1 Day 15:

- The required order of assessments is vital signs followed by pharmacokinetic sampling when applicable.

Time *(in hours)* elapsed since dose	**Post-RX-3117 Dose Procedure (Phase 1 and Phase 2 – Stage 1 only)**	
	Resting Vital Signs[a]	PK
0.5 *(±5 minutes)*	X	X
1 *(±10 minutes)*	X	X
2 *(±10 minutes)*	X	X
3 *(±10 minutes)*	X	X
4 *(±10 minutes)*	X	X
6 *(±10 minutes)*	X	X

[a] pulse, respiration rate, body temperature, and blood pressure (after the subject has been seated for at least 5 minutes)

- Record concomitant medication(s)
- Record adverse event(s). Serious adverse events will be reported immediately. Any adverse event that is considered related to study drug will be followed to resolution or return to baseline.
- Dispensing of study drug and instructions for dosing at home
- Dispensing of diary cards

7.7 Treatment Period – Cycle 1 Day 22

- Subject will complete Quality of Life Questionnaires before any other study procedures are performed:
  - EORTC-QLQ-30 and EORTC-PAN26
  - FACT-Hep
- Collection of unused study drug
- Review subject study drug compliance
- Recording of concomitant medication(s)
- Recording of adverse event(s). Serious adverse events will be reported immediately. Any adverse event that is considered related to study drug will be followed to resolution or return to baseline.

Laboratory tests within 3 days before dosing (for details see

- Appendix D)
    - Hematology panel
    - Chemistry panel
- Resting vital signs: pulse, respiration rate, body temperature, and blood pressure (i.e., after the subject has been seated for at least 5 minutes).

7.8 Treatment Period – Cycles 2 – 8, Day 1

For subjects receiving treatment beyond Cycle 1 the following procedures will be performed within 3 days **before** dosing on Day 1 of each new cycle, unless otherwise described.

- Subject will complete Quality of Life Questionnaires before any other study procedures are performed and before the subject is informed of their disease status:
    - EORTC-QLQ-30 and EORTC-PAN26
    - FACT-Hep
- Weight
- ECOG performance status

Laboratory tests (for details see

- Appendix D)
  - Hematology panel
  - Chemistry panel
  - Urinalysis
  - Coagulation tests: PT/INR and PTT
  - Tumor marker
- Collect blood sample for biomarker analysis (Cycle 2 only)
- Resting vital signs: pulse, respiration rate, body temperature, and blood pressure (i.e., after the subject has been seated for at least 5 minutes)
- Record concomitant medication(s)
- Recording of adverse event(s). Serious adverse events will be reported immediately. Any adverse event that is considered related to study drug will be followed to resolution or return to baseline.
- Dispensing of study drug and instructions for dosing at home (on Day 1)
- Dispensing of diary cards (on Day 1)

7.9 Treatment Period – Cycles 2 – 8, Days 8 and 15

For subjects receiving treatment beyond Cycle 1 the following procedures will be performed **before** dosing on Days 8 and 15 of each new cycle, unless otherwise described.

- Subject will complete Quality of Life Questionnaires before any other study procedures are performed:
  - EORTC-QLQ-30 and EORTC-PAN26
  - FACT-Hep

Laboratory tests within 3 days before dosing (for details see

- Appendix D) (Day 15 only)
  - Hematology panel
  - Chemistry panel
- Resting vital signs: pulse, respiration rate, body temperature, and blood pressure (i.e., after the subject has been seated for at least 5 minutes)
- Collection of unused study drug
- Review subject study drug compliance
- Record concomitant medication(s)
- Recording of adverse event(s). Serious adverse events will be reported immediately. Any adverse event that is considered related to study drug will be followed to resolution or return to baseline.

7.10 Treatment Period – Cycles 2 – 8, Day 22

- Subject will complete Quality of Life Questionnaires before any other study procedures are performed:
  - EORTC-QLQ-30 and EORTC-PAN26
  - FACT-Hep
- Collection of unused study drug
- Review subject study drug compliance
- Tumor assessment, including CT/MRI as applicable between Days 22 and 28 of Cycles 2, 4, 6 and 8. Results of the assessment must be available and reviewed before dosing begins in the next cycle.
- Record concomitant medication(s)
- Recording of adverse event(s). Serious adverse events will be reported immediately. Any adverse event that is considered related to study drug will be followed to resolution or return to baseline.

7.11 Treatment Period: ≥ Cycle 9, Day 1

For subjects receiving treatment beyond Cycle 8 the following procedures will be performed within 3 days **before** dosing on Day 1 of each new cycle, unless otherwise described. Visit schedule deviations may be permitted following discussions with the sponsor.

- Subject will complete Quality of Life Questionnaires before any other study procedures are performed and before the subject is informed of their disease status:

- EORTC-QLQ-30 and EORTC-PAN26
- FACT-Hep

- Record concomitant medication(s)
- Recording of adverse event(s). Serious adverse events will be reported immediately. Any adverse event that is considered related to study drug will be followed to resolution or return to baseline.
- Weight
- ECOG performance status
- Resting vital signs: pulse, respiration rate, body temperature, and blood pressure (i.e., after the subject has been seated for at least 5 minutes.

Laboratory tests (for details see

- Appendix D)
  - Hematology panel
  - Chemistry panel
  - Tumor marker
- Dispensing of study drug and instructions for dosing at home (on Day 1)
- Dispensing of diary cards (on Day 1)

7.12 Treatment Period: ≥ Cycle 9, Days 8, 15, and 22

The following procedures will be performed unless otherwise described:

- Subject will complete Quality of Life Questionnaires before any other study procedures are performed:
  - EORTC-QLQ-30 and EORTC-PAN26
  - FACT-Hep
- Collection of unused study drug
- Review subject study drug compliance
- Record concomitant medication(s)
- Recording of adverse event(s). Serious adverse events will be reported immediately. Any adverse event that is considered related to study drug will be followed to resolution or return to baseline
- Dispensing of study drug and instructions for dosing at home (Days 8 and 15)
- Dispensing of diary cards (Days 8 and 15)
- Tumor Assessment(s) as applicable between Days 22 and 28 of each even numbered cycle before the Day 1 of the next odd numbered cycle. Results to be evaluated before dosing at the next odd numbered cycle. Some imaging assessments may be collected for a review by a central imaging vendor.

7.13 End of Treatment Visit or Early Termination

An End of Treatment Visit will be performed when a subject discontinues study treatment (see Section 6.8). The following procedures will be performed unless otherwise described:

- Subject will complete Quality of Life Questionnaires before any other study procedures are performed and the subject obtains knowledge of their disease status.
  - EORTC-QLQ-30 and EORTC-PAN26
  - FACT-Hep
- Collect unused study drug

- Review subject study drug compliance
- Record concomitant medication(s)
- Recording of adverse event(s). Serious adverse events will be reported immediately. Any adverse event that is considered related to study drug will be followed to resolution or return to baseline.
- Weight
- ECOG performance status
- Resting vital signs: pulse, respiration rate, body temperature, and blood pressure (i.e., after the subject has been seated for at least 5 minutes).

Laboratory tests (for details see

- Appendix D)
    - Hematology panel
    - Chemistry panel
    - Urinalysis
    - Coagulation tests: PT/INR and PTT
    - Tumor marker
- Tumor assessment, including CT/MRI as applicable. End of study tumor assessment (if the subject withdraws from the study for reasons other than tumor progression on a routine imaging/scan) should be performed if the last assessment was performed ≥ 4 weeks earlier. Some imaging assessments may be collected for a second review by a central imaging vendor.
- A biomarker blood sample will be collected.

7.14 Safety Follow-Up Visit

Subjects will undergo the safety follow-up visit approximately 30-37 days after the subject receives their last dose of RX-3117. If the End of Treatment/ Early Termination Visit occurs within the safety follow-up visit window (i.e. 30-37 days after last dose of RX-3117) due to unforeseen circumstances (i.e. hospitalization, 30-day drug interruption leading to discontinuation, etc.), the procedures for both visits may be performed during the same visit.

The following procedures will be performed:

- Subject will complete Quality of Life Questionnaires before any other study procedures are performed:
    - EORTC-QLQ-30
    - FACT-Hep and EORTC-PAN26
- Recording of concomitant medication(s), including any anticancer therapies administered subsequent to the administration of study drug
- Recording of adverse event(s). Serious adverse events will be reported immediately. Any adverse event that is considered related to study drug will be followed to resolution or return to baseline.
- Weight
- ECOG performance status
- Resting vital signs: pulse, respiration rate, body temperature, and blood pressure (i.e., after the subject has been seated for at least 5 minutes).
- Laboratory tests
    - Hematology panel

- Chemistry panel

- Tumor assessment, including CT/MRI as applicable. Subjects first meeting criteria for complete response or partial response at the last on-treatment tumor assessment should have a Safety Follow-up tumor assessment if the last assessment was performed ≥ 4 weeks, in order to confirm the response based on RECIST ver. 1.1 criteria. Some imaging assessments may be collected for a second review by a central imaging vendor.

7.15 Unscheduled Visit(s)

An unscheduled visit may be performed at any time during the study at the request of the subject or as deemed necessary by the investigator. The date and reason for the unscheduled visit will be documented in the subject's medical record and the eCRFs, as well as any other data obtained (e.g., adverse events, concomitant medications and treatments, and results from procedures or tests).

7.16 RX-3117 Dosing

RX-3117 will be administered orally, at the assigned dose, with the subject in a fasted state (i.e., ≥ 8 hours after a meal) with approximately 100 to 200 mL (4 to 8 ounces) of water. The subject may have a small glass of juice, except grapefruit juice, (4- to 6 ounces) no earlier than 10 minutes after dosing as needed. Food may be taken ≥ 1 hour after the dose has been administered. The time of last meal and dosing must be documented.

On days when the subject is scheduled to come into the clinic, RX-3117 will be administered orally in the presence of site personnel, per the assigned dose. This is important for days when blood is collected for pharmacokinetic analysis (i.e., Days 1, 8, and 15 of Cycle 1), on those days dosing will occur after that pre-dose pharmacokinetic sample is collected.

When subjects self-administer RX-3117 at home, RX-3117 will be taken orally at approximately the same time every day after fasting for a minimum of 8 hours and with approximately 4-8 ounces of water. The subject may have a small glass of juice (4-6 ounces) no earlier than 10 minutes after dosing as needed. Food may be taken approximately 1 hour after the dose has been administered.

7.17 Tumor measurements

Radiographic tumor assessment(s) performed during the screening period will be used to prospectively identify all sites of disease present at the start of treatment. Subjects with symptoms suggestive of disease progression should be objectively evaluated for tumor progression.

On-study tumor assessment(s) will be performed by the investigator. Response and progression will be evaluated using modified RECIST ver. 1.1 (see Appendix E) after

Cycle 2 and every 8 weeks thereafter or upon early termination if an assessment has not been done in the previous 4 weeks. The results of the tumor assessment must be available before the beginning of the next cycle.

Radiographic tumor assessment(s) must include CT/MRI of chest, abdomen, and pelvis, sufficient to evaluate major sites of disease. Throughout the study, the same method of assessment and the same technique should be used to characterize each identified and reported lesion at screening. Computed tomography (CT) and/or magnetic resonance imaging (MRI) (spiral CT or MRI with ≤ 5 mm cuts) should be used for tumor assessment unless another modality of radiographic disease assessment is necessary for the lesions including bone lesions per RECIST guidelines Version 1.1,

See Appendix E for detailed information on RECIST ver. 1.1 to be used in this study. Some imaging assessments may be collected for a second review by a central imaging vendor.

Special Considerations Regarding Lesion Measurability

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

Bone Lesions

Bone scan, positron emission tomography (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 nonmeasurable.

Cystic Lesions

Lesions that meet the criteria for radiographically defined simple cysts should not be considered as malignant lesions (neither measurable nor nonmeasurable) 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 not considered measurable unless there has been demonstrated progression in the lesion.

8.Other Assessment(s)

8.1 Predictive and Pharmacodynamic Biomarkers

Biomarkers are objectively measured and evaluated indicators of normal biologic processes, pathogenic processes, or pharmacologic responses to a therapeutic intervention. In oncology, there is particular interest in the molecular changes underlying the oncogenic processes that may identify cancer subtypes, stage disease, assess the amount of tumor growth, or predict disease progression, metastasis, responses, or resistance to therapeutic agents. These investigations may be useful in developing markers to identify disease subtypes, guide therapy, and/or predict disease progression.

A blood sample will be collected prior to treatment with RX-3117 and on Day 1 in Cycles 1 and 2, and during the Early Termination or End of Treatment visit to measure biomarkers in whole blood, any of its components and/or circulating tumor cells (CTCs) that may be involved in the response to RX-3117, alone or in combination with other agents or relevant to pancreatic cancer biology.

In addition, any paraffin-embedded tumor samples collected independent from this study (whether before or during for the assessment of cancer) and the corresponding pathology report will be gathered by investigational sites. If paraffin blocks cannot be shipped, unstained slides and a core punch biopsy will be prepared from paraffin embedded tumor samples collected independent of the study before and during the study from each subject for analysis.

Measurements may include, but are not limited to, nucleoside transporters; uridine-cytidine kinase 2 (UCK2); DNA methyltransferases (DNMTs); ribonucleotide reductases (RRM); RX-3117 incorporation into DNA/RNA as well as other genes and/or proteins that may be identified to be involved in the response to RX-3117 or are relevant to pancreatic cancer biology.

A tumor biopsy will be collected pre-treatment (optional).

Refer to the laboratory manual for detailed collection and handling procedures for all predictive biomarker samples.

8.1.1 Sample Storage and Destruction

These blood and tumor samples and any other components from the cells may be stored for up to 20 years to research scientific questions related to cancer and/or RX-3117. The

subject retains the right to have the sample material destroyed at any time by contacting the principal investigator.

The sponsor will be the exclusive owner of any data, discoveries, or derivative materials from the sample materials and is responsible for the destruction of the sample(s) at the request of the research subject through the principal investigator or at the end of the storage period. The principal investigator will provide the sponsor with the required study and subject numbers so that any remaining blood and tumor samples and any other components from the cells can be located and destroyed. If a commercial product is developed from this research project, the sponsor will own the commercial product. The subject will have no commercial rights to such product and will have no commercial rights to the data, information, discoveries, or derivative materials gained or produced from the sample. See Section 12.4 for subject confidentiality.

8.2 Quality of Life (QOL) Questionnaires

Three QOL questionnaires will be used in this study: EORTC QLQ-C30 version 3 with, EORTC PAN-26 and the Functional Assessment of Cancer Therapy-Hepatobiliary (FACT-Hep) version 4. The purpose is to pilot both assessments before being used in a larger trial and to determine which instrument covers all the relevant issues in a reliable and meaningful way.

In principle it is the patient him/herself who has to fill out quality of life forms and preferably without help from others. Some patients may need help, e.g. because of reduced sight. Another person could then read the questions, without making any suggestions to the patient, and report the answers on the form.

All subjects will complete the assessments before study treatment at baseline and at every visit (except Cycle 1 Day 2) until disease progression or withdrawal from the study. Patient reported outcomes assessments are to take place prior to any other study procedures performed on a particular study day.

8.2.1 EORTC QLQ-C30 and PAN26

The QLQ-C30 Version 3.0 is a validated questionnaire developed by the European Organisation for Research and Treatment of Cancer (EORTC) to assess the quality of life of cancer patients. It is supplemented by the disease-specific module for pancreatic cancer (PAN26). The majority of people can complete the questionnaires within 10 to 15 minutes. However, patients should be given the time they need to complete the questionnaire.

8.2.2 FACT-Hep

The Functional Assessment of Chronic Illness Therapy (FACIT) Measurement System is a collection of QOL questionnaires targeted to the management of chronic illness. FACT-

Hep is designed for use with patients with Hepatobiliary cancer (liver, bile duct and pancreas).

9. Safety Data Collection, Recording, and Reporting

9.1 Definitions

9.1.1 Adverse Events

An adverse event is any untoward medical occurrence in a trial subject who is administered a drug or biologic (medicinal product) or who is using a medical device; the event does not necessarily have a causal relationship with study drug administration or usage.

For this protocol, untoward medical occurrences that should be reported as adverse events include the following:

- Any unfavorable and unintended symptom, sign (including an abnormal laboratory finding), or disease temporally associated with the use of study drug, whether or not related to the study drug.

- Any pre-existing condition that increases in severity or changes in nature during or as a consequence of study drug administration.

- Any complication that occurs as a result of a protocol-mandated procedure (e.g., venipuncture, ECG) in the screening, study drug administration, or follow-up periods.

- Any injury or accident occurring during the screening, study drug administration, or follow-up periods. If a medical condition is known to have caused the injury or accident (e.g., a fall secondary to dizziness), the medical condition (dizziness) and the accident (fall) should be reported as 2 separate adverse events.

- Any abnormality in physiological testing or a physical examination finding that requires clinical intervention or further investigation (beyond ordering a repeat [confirmatory] test).

- Any laboratory (e.g., clinical chemistry, hematology, urinalysis) or investigational abnormality (e.g., ECG, X-ray) independent of the underlying medical condition that requires clinical intervention, results in further investigation (beyond ordering a repeat [confirmatory] test), or leads to investigational medicinal product interruption or discontinuation unless it is associated with an already reported clinical event. If the laboratory abnormality is part of a syndrome, the syndrome or diagnosis (e.g., anemia) not the laboratory result (e.g., decreased hemoglobin) should be recorded.

- A complication related to pregnancy or termination of a pregnancy (see Section 9.7.2 for additional information).

None of the following events is considered an adverse event:

- Laboratory abnormalities not requiring clinical intervention or further investigation. Such abnormalities will be captured as part of overall laboratory monitoring.

- A diagnostic, medical or surgical procedure (e.g., surgery, endoscopy, tooth extraction, transfusion). However, the medical condition for which the procedure was performed should be reported if it meets the definition of an adverse event. For example, an acute appendicitis that begins during the adverse event reporting period should be reported as the adverse event and the resulting appendectomy should be recorded in the subject's medical records and eCRFs.

- A pre-existing disease or condition or laboratory abnormality present or detected before the initial screening visit and that does not worsen.

- An intervention not associated with an untoward medical occurrence (e.g., hospitalization for elective surgery or for social and/or convenience reasons).

- An overdose without clinical sequelae.

9.1.2 Serious Adverse Events

A serious adverse event is defined as an untoward medical occurrence that results in any of the following outcomes:

- Death (i.e., all deaths occurring between signing of the consent form to within 30 days after last study drug administration), including deaths due to disease progression. Deaths that occur as a result of an adverse event that started during the study period should be reported. The reported adverse event should be the event that caused the death. Death is the outcome of this serious adverse event.

- Life-threatening situation (i.e., with an immediate risk of death from the event as it occurred but not including an event that, had it occurred in a more serious form, might have caused death).

- In-patient hospitalization or prolongation of existing hospitalization. Of note, an untoward medical occurrence that occurs during hospitalization is an adverse event but a complication that prolongs hospitalization is a serious adverse event. In-patient hospitalization comprises formal admission to a hospital for medical reasons, for any length of time, whether or not hospitalization extends overnight. However, hospital admissions for administration of the study drug, procedures

required by the study protocol, or tumor-related diagnostic procedures are not considered serious.

- Persistent or significant incapacity or substantial disruption of the ability to conduct normal life functions

- Congenital anomaly/birth defect in the offspring of a subject who received the study drug.

- Other important medical events. Such events may not be immediately life-threatening or result in death or hospitalization, but based upon appropriate medical and scientific judgment, may jeopardize the subject or may require medical or surgical intervention to prevent one of the outcomes listed above. Examples of such events might include:

  - Allergic bronchospasm requiring intensive treatment in an emergency room or at home

  - New cancers or blood dyscrasias

  - Convulsions that do not result in hospitalization

  - Development of drug dependency or drug abuse

9.2 Other Events Requiring Rapid Reporting

DLTs are events [toxicities] specifically identified in this protocol that must be reported to the Sponsor or designee in an expedited manner. Information regarding DLTs should be recorded on a protocol-designated DLT report form and faxed or emailed to the study sponsor or designee within 24 hours of site personnel becoming aware of the event. DLTs may or may not be serious adverse events as Unexpected Adverse Event

An unexpected adverse event is defined as an event that has a nature or severity, or specificity that is not consistent with the applicable investigator brochure or that is symptomatically and pathophysiologically related to a known toxicity but differs because of greater severity or specificity. For example, under this definition, hepatic necrosis would be unexpected (by virtue of greater severity) if the investigator brochure only referred to elevated hepatic enzymes or hepatitis. Similarly, cerebral thromboembolism and cerebral vasculitis would be unexpected (by virtue of greater specificity) if the investigator brochure only listed cerebral vascular accidents. “Unexpected,” as used in this definition, refers to an adverse drug experience that has not been previously observed and reported rather than an experience that has not been anticipated based on the pharmacological properties of the study drug.

9.2.1 Eliciting Adverse Event Information

The investigator is to report all directly observed adverse events and all adverse events spontaneously reported by the study subject. In addition, each study subject will be questioned about adverse events at each scheduled clinic visit or during each telephone contact with the subject following initiation of study drug administration. The type of question asked should be open-ended, e.g., *"Have you had any new health problems?"* or a similar type of query.

9.3 Reporting Procedures for All Adverse Events

All adverse events will be assessed by the investigator or qualified designee and recorded in the eCRFs. The investigator should attempt to establish a diagnosis of the event on the basis of signs, symptoms and/or other clinical information. In such cases, the diagnosis should be documented as the adverse event and/or serious adverse event and not described as the individual signs or symptoms. The following information should be recorded:

- Description of the adverse event using concise medical terminology
- Description as to whether or not the adverse event is serious (see Section 9.1.2)
- The start date (date of adverse event onset)
- The stop date (date of adverse event resolution)
- The severity of the adverse event (see Section 9.4)
- A description of the potential relatedness of the adverse event to study drug or a study procedure (see Section 9.5)
- The action taken due to the adverse event
- The outcome of the adverse event

9.4 Grading of the Severity of an Adverse Event

The severity of adverse events will be graded using the Common Terminology Criteria for Adverse Events (CTCAE), Version 4.03 (available at *http://evs.nci.nih.gov/ftp1/CTCAE/CTCAE_4.03_2010-06-14_QuickReference_8.5x11.pdf*). For each episode, the highest severity grade attained should be reported.

If a CTCAE criterion does not exist, the investigator should refer to the Grades definition on page 2 of the CTCAE v4.03.

The distinction between the seriousness and the severity of an adverse event should be noted. Severe is a measure of intensity; thus, a severe reaction is not necessarily a serious reaction. For example, a headache may be severe in intensity, but would not be classified as serious unless it met one of the criteria for serious events listed in Section 9.1.2 above.

9.5 Describing Adverse Event Relationship to Study Drug and Study Procedures

The relationship of an adverse event to study drug should be assessed using clinical judgment, describing the event as either unrelated (no) or related (yes) consistent with the following definitions:

- No: Evidence exists that the adverse event had an etiology other than the study drug. For serious adverse events, an alternative causality must be provided (e.g., pre-existing condition, underlying disease, intercurrent illness, or concomitant medication).

- Yes: A temporal relationship exists between the adverse event onset and administration of the investigational medicinal product that cannot be readily explained by the subject's clinical state or concomitant therapies. Furthermore, a suspected adverse reaction means any AE for which there is a *"reasonable possibility"* that the drug caused the AE. For the purpose of reporting under this protocol, "reasonable possibility" means there is evidence to suggest a causal relationship between the drug and the AE, and the adverse event appears with some degree of certainty to be related to the study drug based on the known therapeutic and pharmacologic actions or adverse event profile of the investigational medicinal product. In case of cessation or reduction of the dose, the adverse event abates or resolves. In case of interruption and rechallenge, the event reappears upon rechallenge.

Of note, even in circumstances when the study drug is given intermittently or is interrupted temporarily before the onset of the adverse event, consideration should be given as to whether the study drug may have contributed to the event.

The relationship to protocol-mandated study procedures (e.g., procedures such as venipuncture or performance of an ECG) should be assessed using the following considerations:

- No: Evidence exists that the adverse event has an etiology other than the study procedure.

- Yes: The adverse event occurred as a result of a protocol-mandated procedure.

9.6 Adverse Event Reporting Requirements

9.6.1 Site Reporting Requirements

Classification of an event as serious or nonserious (see Section 9.1.2) determines the reporting procedures to be followed by the site.

Site reporting requirements for adverse events are summarized in Table 5 below.

Table 5. Site Reporting Requirements for Adverse Events

Classification	Reporting Time	Reporting Action
Serious	Within 24 hours	Fax or email completed serious adverse event report form to sponsor or designee, and to the site IRB, as per local IRB requirements; include copies of relevant source documents (e.g., progress notes, autopsy reports, laboratory and diagnostic test results, discharge summaries)
	Within 24 hours	Telephone call or e-mail to the study sponsor medical monitor[a]
	Within 3 days	Fax or email follow up information in a serious adverse event report to sponsor or designee; include copies of relevant source documents ((e.g., progress notes, autopsy reports, laboratory and diagnostic test results, discharge summaries)
	Per CRF submission procedure	Record and submit information on appropriate CRFs
Nonserious	Per CRF submission procedure	Record and submit information on appropriate CRFs

a See Operations Manual for study contact information
Abbreviations: CRF=case report form, IRB=institutional review board

For serious adverse events, the Serious Adverse Event Report Form must be completed in addition to completing the adverse event portion of the CRF. The information in the adverse event portion of the Serious Adverse Event Report Form(s) and CRF must match or be reconciled. Where the same data are collected, the forms must be completed in a consistent manner. For example, the same adverse event term should be used on both forms.

Particularly for fatal or life-threatening events, copies of progress notes, autopsy reports, laboratory and diagnostic test results, discharge summaries, and other relevant documents should be e-mailed or faxed when requested and applicable. Follow-up information to the serious adverse event should be clearly documented as “follow up” in the serious adverse event report form and must be faxed or emailed to these same parties. The study sponsor may request additional information from the investigator to ensure the timely completion of accurate safety reports.

The subject's name, address, and other personal identity information should be obscured on any source documents (e.g., progress notes, nurses' notes, laboratory and diagnostic test results, discharge summaries) but without losing the traceability of a document to the study subject identifiers. Only the subject's study number, initials, or date of birth are to be provided.

In the rare event that the investigator does not become aware of the occurrence of a serious adverse event immediately (for example, if a subject initially seeks treatment elsewhere), the investigator is to report the event within 24 hours after learning of it and to document his/her first awareness of the adverse event.

Contact details for the study sponsor medical monitor are provided in the Operations Manual.

9.6.2 Study Sponsor Reporting Requirements

Each serious adverse event report received from the investigator must be evaluated by the investigator as well as the study sponsor medical monitor. Each is required to review all unanticipated problems involving risk to subjects or others, serious adverse events, and all subject deaths associated with the protocol and provide an unbiased written report of the event. At a minimum, the study sponsor medical monitor should comment on the outcomes of the event or problem, and in the case of a serious adverse event or death, comment on the relationship to participation in the study. The designated study sponsor medical monitor should also indicate whether they concur with the details of the report provided by the study investigator.

For regulatory reporting purposes, the event is classified as related if any of the investigator or study sponsor medical monitor determines that the event is related to the study drug (see Section 9.5). For reporting purposes, an expected adverse event will be considered expected by the study sponsor if the event is listed in the current IB, is an event known to be consequences of the underlying disease or condition under investigation (e.g., symptoms, disease progression) or an event unlikely to be related to the underlying disease or condition under investigation but common in the study population (see Section 9.2).

The study sponsor awareness date will be used in determining adverse event regulatory reporting timelines. The study sponsor awareness date is defined as the earliest date the study sponsor or an agent (e.g., a site monitor) becomes aware of an adverse event. This is the date the regulatory reporting clock begins and the date is considered Day 0.

The study sponsor serious adverse event regulatory reporting requirements are described in Table 6.

Table 6. Study Sponsor Reporting Requirements for Adverse Events

Type of Event			Type of Report	Timeframe for Reporting To Health Authorities
Fatal or Life-Threatening	Unexpected	Related		
Yes	Yes	Yes	Letter notification (may also include MedWatch form)	Within 7 calendar days of study sponsor awareness date or according to local regulations
			MedWatch form	Within 15 calendar days of study sponsor awareness date or according to local regulations
No	Yes	Yes	MedWatch form	Within 15 calendar days of study sponsor awareness date or according to local regulations
Yes	No	Yes	Annual report	Annually
No	No	Yes		
Yes	Yes	No		
No	Yes	No		
Yes	No	No		
No	No	No		

Abbreviations: CIOMS= Council for International Organizations of Medical Sciences

If notification of an adverse event requiring expedited reporting is received, the study sponsor (or designees) will contact each clinical investigator prescribing RX-3117 by e-mail, fax, or overnight mail such that the investigator can promptly notify the site IRB (within 7 calendar days for deaths or life-threatening events or within for 15 calendar days for other reportable events from the study sponsor awareness date). All unanticipated problems involving risk to subjects or others, serious adverse events related to participation in the study, and subject deaths related to participation in the study will also be promptly reported via telephone, facsimile, or e-mail by the study sponsor (or designees) to appropriate health regulatory authorities.

9.7 Special Situation Reporting Requirements

9.7.1 Definitions of Special Situations

Special situation include pregnancy; medication error, abuse, misuse, or overdose.

- Information regarding pregnancy is provided in Section 9.7.2.
- A medication error is any preventable event that can cause or lead to inappropriate medication use or subject harm while the medication is in the control of a healthcare professional or subject.
- Abuse is defined as persistent, sporadic or intentionally excessive use of a drug by a subject when such use is accompanied by harmful physical and/or psychological effects.

- Misuse is defined as any use of a drug in a way that is not in accordance with the protocol instructions and may be accompanied by harmful physical and/or psychological effects.

- An overdose is defined as a dose taken (accidentally or intentionally) that meets the criteria for overdose prescribed by the protocol (see Section 11.9). In cases of a discrepancy in drug accountability, overdose will be established only when it is clear that the subject has taken excessive amounts of drug or the investigator has reason to suspect that the subject has taken excessive amounts of drug. Cases of study drug overdose will result in specific reporting requirements (see Section 9.6.1).

9.7.2 Pregnancy

The following safety reporting instructions related to pregnancy are included as a precaution.

Each female subject should be instructed to discontinue further study therapy and inform the investigator immediately if she becomes pregnant at any time between the first dose of study drug until 30 days after the last ingestion of study drug.

Each male subject should be instructed to inform the investigator immediately if he impregnates a woman at any time between the first dose of study drug until 30 days after the last ingestion of study drug

The investigator should counsel the subject regarding the possible effects of investigational medicinal product exposure on the fetus and the need to inform the study site of the outcome of the pregnancy.

Neither a pregnancy itself nor an induced elective abortion to terminate the pregnancy without medical reasons is considered an adverse event; such occurrences should be reported on the appropriate pregnancy report forms. However, if the outcome of the pregnancy meets the criteria for classification as a serious adverse event (i.e., spontaneous abortion, induced abortion due to complications, stillbirth, neonatal death, or congenital anomaly [including that in an aborted fetus]), the investigator should follow the procedures for reporting serious adverse events (see Section 9.6.1).

Additional information regarding reporting pregnancy outcomes may be required:

- Any spontaneous abortion, including miscarriage and missed abortion will be reported as a serious adverse event.

- An induced therapeutic abortion to terminate any pregnancy due to complications or other medical reasons will be recorded as a serious adverse event. The

underlying medical reason for this procedure should be recorded as the adverse event term.

- All neonatal deaths that occur within 1 month of birth should be reported, without regard to causality, as serious adverse events. In addition, any infant death after 1 month that the investigator assesses as related to the in-utero exposure to the study drug should also be reported.

- In the case of a live birth, the "normality" of the newborn can be assessed at time of birth (i.e., there is no required minimum follow-up of a presumably normal infant before the Pregnancy Outcome Report CRF can be completed).

- The "normality" of an aborted fetus can be assessed by gross visual inspection unless there are pre-abortion laboratory findings suggestive of a congenital anomaly, in which case pathologic examination should be requested.

9.7.3 Instructions for Reporting Special Situations

Information regarding any pregnancy in a study subject or the female partner of a male subject must be documented on a Pregnancy Reporting Form and forwarded to the sponsor or designee within 24 hours of learning of the pregnancy. Monitoring of the pregnancy in both female study subjects and female partners of male study subjects should continue until the conclusion of the pregnancy. The outcome of the pregnancy should be reported on the Pregnancy Outcome Report Form within 5 days of the conclusion of the pregnancy. If the end of the pregnancy occurs after the study has been completed, the outcome should be reported directly to the study sponsor.

Along with information regarding the circumstances of the special situation, any clinical sequelae occurring in association with that situation should be reported as adverse events or serious adverse events according to the reporting requirements for those events (see Section 9.6). Details of signs or symptoms, clinical management and outcome should be reported, if available defined in this protocol but may be serious adverse events if they meet one or more of the criteria for serious adverse events (see Section 9.1.2). If a DLT is also a serious adverse event, it should be reported both on the DLT report form and per the instructions for reporting serious adverse events (see Section 9.6.1). Recording of a DLT in the relevant CRFs will also be required.

10. STATISTICAL CONSIDERATIONS

A Statistical Analysis Plan (SAP) will be finalized prior to database lock and will include more details of analysis populations and summary strategies. Any changes from the statistical analyses described in this document will be described in the SAP, and any deviation from the final SAP will be described in the final clinical study report.

10.1 Study Endpoints

Endpoints:

Phase 1 Endpoints:

- **Primary Endpoints**
  - Overall safety profile characterized by the type, frequency, severity, timing of onset, duration and relationship to study therapies of any adverse events (AEs), clinical laboratory abnormalities, vital signs, and electrocardiograms (ECGs)
  - Enumeration and description of any dose limiting toxicities (DLTs) that occur during Cycle 1, serious adverse events (SAEs), or AEs leading to discontinuation of study treatment.
- **Secondary Endpoints**
  - RX-3117 and Abraxane® plasma PK parameters (e.g., time to maximum observed concentration [T_{max}], maximum observed concentration [C_{max}], and area under the concentration-time curve [AUC])
  - Indices of anti-tumor activity (e.g., overall response rate [ORR], time to response [TTR], duration of response [DOR], and progression-free survival [PFS]) during treatment.
- **Exploratory Endpoint**
  - Expression or concentration of various cellular or molecular biomarkers

Phase 2 Endpoints:

- **Primary Endpoint**
  - An adequate number of Responders based on PFS and/or objective clinical response
- **Secondary Endpoints**
  - Time to progression, ORR and DOR
  - Overall safety profile of RX-3117 in combination with Abraxane®
  - RX-3117 and Abraxane® PK parameters
- **Exploratory Endpoints**
  - Enumeration, expression, or concentration of various cellular or molecular biomarkers
  - Changes in tumor burden
  - QOL

10.2 General Statistical Considerations

Safety, Efficacy, QOL, PK, and Pharmacodynamic assessments will be summarized separately for Phase 1 and Phase 2 (Stage 1 and Stage 2 combined). Additional summaries and analyses of pooled Phase 1 and 2 data may also be generated based on applicability of dosing regimens.

Descriptive and summary statistics will be presented by dose level and overall, as appropriate. Summary statistics for continuous variables will include number of observations, mean, standard deviation, median, and range (minimum and maximum). Categorical variables will be summarized using the number and percentage of responses with 95% confidence intervals if appropriate. Unless otherwise indicated, 95% confidence intervals for binary variables will be calculated using the binomial distribution (exact method) and will be 2-sided. Data listings will be created for all eCRF modules to supplemental the tabulations. Graphical techniques (e.g., Kaplan-Meier curves, line plots) may be used when such methods are appropriate and informative.

As appropriate, changes from baseline to each visit timepoint will be described and summarized along with the value at each visit timepoint. The baseline value is defined as the last (most recent), non-missing value immediately prior to the first exposure to study medication. Unless otherwise specified, all analyses will be 2-sided at the 0.05 level of significance.

10.3 Sample Size Calculation

For the Phase 1 dose-finding, approximately 10 subjects are planned. The sample size is not based on formal statistical hypothesis testing but will be determined based on observed number of first-cycle DLTs at each dose level. The intent is to limit the number of subjects who are exposed to excessively toxic doses or sub-therapeutic doses of a drug in a Phase 1 evaluation of anticancer agents being used in combination for the first time.

For Phase 2, approximately 40 evaluable subjects are planned. This sample size is not based on statistical hypothesis but rather to further evaluate efficacy and safety endpoints in order to plan future trials. Once the RP2D is identified approximately 10 evaluable subjects will participate in Stage 1. Depending on the results of the interim analysis, approximately 30 evaluable subjects will participate in Stage 2.

10.4 Analysis Populations

10.4.1 Intent-to-Treat (ITT) Analysis Population

The Intent-to-Treat (ITT) population will include all subjects who were enrolled in the study regardless of if they actually received study medication.

10.4.2 Modified Intent-to-Treat (mITT) Analysis Population

The Modified Intent-to-Treat (mITT) set includes all ITT subjects who receive $\geq$ 1 dose of RX-3117. The mITT population may also be thought of as the Safety population and is the primary population to be used for safety evaluations such as summaries of baseline characteristics, study drug exposure, subject disposition and assessment of DLTs and MTDs. In addition, this population will be used in the analyses of efficacy assessments such as overall response rate and progression free survival.

A subset of the mITT population will be used in the analyses of time to response and duration of response. This subset will include those who have measurable tumor, who can be evaluated for tumor response with both baseline and on-study tumor evaluations, and who achieve a complete response or partial response. This analysis set will be used in the analyses of time to response and duration of response.

Another subset of the mITT population will be used in the analysis of PK and Pharmacodynamic parameters. It will include those from the mITT population who have baseline and on-study measurements to provide interpretable results for specific parameters of interest.

10.4.3 Per Protocol (PP) Analysis Population

The Per Protocol (PP) population includes all subjects from the mITT population with the exclusion of any subjects with protocol deviations/violations that would compromise the safety and/or efficacy of the study treatment. Any subjects excluded from this population will be identified and documented prior to database lock.

10.5 Randomization and Blinding

This is a non-randomized, open-label study. Therefore, randomization and blinding are not applicable.

10.6 Missing Data and Other Data Handling Conventions

All summaries and analyses will be based upon the observed data unless methods for handling missing data are specified otherwise. The details for handling of missing data will be described in addition detail in the SAP. It is not anticipated that any missing data will be imputed with the exceptions below:

- For QOL measurements, missing data will be handled as described in the scoring manuals and/or algorithms.
- For time to event analyses:
    - Subjects without any efficacy evaluations will be considered as censored at time 0.
    - Subjects without the event of interest will be censored on the date they were last known to be event-free.
- For Adverse Events:
    - Missing dates will not be imputed; however, if partial dates are available, they will be used to assess if the AE occurred during the treatment period.
    - Missing severities of AEs will not be imputed and will be considered missing in any tabulations of AE severity.

- If an AE is missing a response to the question regarding relationship to treatment, the event will be considered to be related.

10.7 Adjustments for Covariates, Multiple Comparisons, and/or Multiplicity

No adjustments for covariates, multiple comparisons, and/or multiplicity are planned for this trial.

10.8 Multi-Center Studies and Pooling of Centers

Approximately 3 enrolling sites in the US will participate in the Phase 1 portion of the study and up to 15 enrolling sites in the US will participate in the Phase 2 study. Due to the nature of this early phase study, data from all sites will be pooled for all analyses.

10.9 Interim Analysis

The interim analyses that are planned to be conducted in the Phase 1 are related to the review of available data during the dose escalation phase of the study. The decision to de-escalate to the next dose level will be made after the evaluation of safety data through at least 28 days of the first cycle of the current dose level. Each review will be conducted by the investigators, medical monitor and sponsor.

The interim analysis after Stage 1 of the Phase 2 will be performed when the first 10 evaluable subjects have been treated at the recommended Phase 2 dose, are evaluable for response, have the opportunity to complete up to 4 cycles of therapy or have discontinued therapy before 4 cycles (see Section 6.8). If an adequate number of Responders are observed out of the initial 10 evaluable subjects, subject enrollment will continue with another 30 evaluable subjects enrolled (approximately 40 evaluable subjects combined in Phase 2). An adequate number of Responders is defined as either at least 2 out of the 10 evaluable subjects (20%) having a measured benefit in PFS noted as PFS ≥ 4 months/ cycles or if at least 1 subject (10%) has an objective clinical response (partial or complete response) supported by acceptable safety and tolerability reviewed through the conduct of the study by the investigators, medical monitor and sponsor. The study may stop after the interim analysis if an adequate number of Responders are not seen. However, if an adequate number of Responders are seen, an additional 30 evaluable subjects will be enrolled and evaluated.

10.10 Data Tabulations and Analyses

Summary tabulations will be provided for disposition, demographic, and baseline characteristics, efficacy, safety, and PK/ Pharmacodynamic data as noted in the following sections. All data collected in the EDC will be provided in data listings to supplement the tabulations.

10.10.1 Tabulation and Analysis of Disposition, Demographics, and Baseline Characteristics

A tabulation of subject disposition will be presented by study phase and dose level including the number in each analysis population, reasons for discontinuing treatment, and reasons for discontinuing from the study.

Demographics and baseline characteristics will be summarized using descriptive statistics by study phase and dose level. This includes but is not limited to medical, surgical, cancer, and psychiatric histories plus prior medications and physical examination results.

10.10.2 Tabulation and Analysis of Efficacy

10.10.2.1 Objective Response Rate and Tumor Burden

Tumor control assessments will be based on the standardized RECIST version 1.1. Tumor control will be documented at each assessment by response category (e.g., CR, PR, SD, PD) as defined for each response parameter, tumor dimension values, percentage change in tumor dimension values from baseline or nadir, date that response is first documented, date that response is confirmed, and date of disease progression. The Objective Response Rate (ORR) will be defined as the rate of a clinical response of CR or PR at the completion of treatment assessment. Subjects with unknown or missing response will be treated as non-responders, i.e. they will be included in the denominator when calculating the proportion. The ORR will be summarized using tabulations and 95% confidence intervals. The change from baseline in tumor change (burden) will be summarized as well using summary statistics.

10.10.2.2 Time-to-Event for TPP, DOR, and PFS

For time-to-event endpoints, only events occurring $\leq$ 30 days following the permanent discontinuation of study treatment will be considered as events; for subjects with events occurring > 30 days following the permanent discontinuation of study treatment, the data will be censored. The following calculations will be applied:

- TTP (defined as the time from first treatment administration to first documentation of RECIST-defined objective tumor progression). Median TTP is to be estimated using the Kaplan-Meier method.

- DOR (defined as the time from the first documentation of RECIST-defined objective tumor response to the first documentation of RECIST-defined objective tumor progression or death). Median DR is to be estimated using the Kaplan-Meier method.

- Progression Free Survival (defined as the time from first treatment administration to first documentation of RECIST-defined objective tumor progression or relapse or death from any cause). Median PFS is to be estimated using the Kaplan-Meier method.

Time to response, duration of response, and progression-free survival will be described in the appropriate analysis set using Kaplan-Meier methods. Medians, ranges, and corresponding 95% confidence intervals will be presented.

10.10.2.3 Quality of Life Questionnaires

The three QOL assessments used in this study will be summarized. These are the EORTC QLQ-C30 version 3, EORTC PAN-26, and the Functional Assessment of Cancer Therapy-Hepatobiliary (FACT-Hep) version 4. Each assessment will be scored according to the appropriate scoring manual and summarized overall and for subscales as available. In addition to the values at each timepoint, the percentage change from baseline to each scheduled visit will be summarized.

10.10.3 Tabulation and Analysis of Safety

10.10.3.1 Exposure to Study Medication and Compliance

Descriptive information will be provided regarding the number of doses of study therapy prescribed, the total number of doses taken, the percent of expected doses taken, the duration of treatment, and the number and timing of prescribed dose reductions, dose interruptions, and dose re-escalations.

RX-3117 compliance will be described in terms of the proportion of study drug actually taken based on subject diaries and returned capsule counts relative to the amount that was dispensed (accounting for physician-prescribed reductions and interruptions).

10.10.3.2 Adverse Events

AEs will be coded using the Medical Dictionary for Regulatory Activities (MedDRA) and displayed in tables and listings using MedDRA system organ class (SOC) and preferred term. The incidence rates of treatment-emergent AEs, SAEs, DLTs, AEs of at least Grade 3 in severity, related AEs, and AEs leading to withdrawal of treatment will be tabulated and summarized. Treatment-emergent adverse events (TEAEs) will be those that start or worsen on or after the first day dose of study treatment, through 30 days after last dose; related AEs will be those with an Investigator determination of related to treatment.

AEs with partial dates will be assessed using the available date information to determine if treatment-emergent. AEs with completely missing dates will be assumed to be treatment-emergent. No formal hypothesis-testing of AE incidence rates will be performed.

The causal relationship between the occurrence of an AE and the study drug will be judged by the investigator as not related, possibly related, or probably related. In the event a subject experiences repeat episodes of the same AE, then the event with the highest severity and/or strongest causal relationship to treatment will be used for purposes of tabulations.

10.10.3.3 Clinical and Biomarker Laboratory Data

For each analyte, the actual value and percentage change from baseline to each visit timepoint will be summarized to include, but not limited to, hematology, clinical chemistry, coagulation, and biomarker data. In the event of repeat values, the last non-missing value per study day will be used.

Severity of select clinical lab measures will be determined using CTCAE criteria (e.g., those measures that have a corresponding CTCAE grade classification). Labs with CTCAE grades greater than or equal to 3 will be presented in a data listing. Shift tables that present changes from baseline to worst on-study and baseline to last on-study values relative to CTCAE classification ranges will be produced.

10.10.3.4 Vital Signs

The actual vital signs values and percentage change from baseline to each visit timepoint will be summarized.

10.10.3.5 ECGs

The ECG parameters (heart rate, PR interval, QRS interval, QT interval, and corrected QT [QTc] interval) at each visit timepoint recorded as well as the percentage change from baseline will summarized. These parameters will be determined electronically by the ECG machine at the clinical site. The QT interval will be corrected by the Fridericia method as follows:

- Fridericia: QTcF = QT/(RR)1/3

The overall ECG assessment will be reported as “Normal” or “Abnormal” with respect to relevant abnormalities by the investigator. A shift table comparing the ECG assessment over the study drug administration period to baseline will be presented.

10.10.4 Pharmacokinetics and Pharmacodynamics

10.10.4.1 Pharmacokinetics

Plasma concentrations and derived pharmacokinetic parameters will be listed and graphs of individual subject concentrations by visit will be presented on linear and semi-logarithmic axes. Pharmacokinetic data will be summarized by visit using graphical and tabular methods considering stage and dose level.

10.10.4.2 Pharmacodynamics

The pharmacodynamics data will be summarized in the same manner as the clinical laboratory data. As data allows, the correlation between PK and Pharmacodynamic results will be investigated.

11. INVESTIGATIONAL PRODUCT

11.1 Abraxane®

Abraxane® will be obtained by the site pharmacy from commercial sources. Administration, storage and handling will follow guidelines detailed in the approved package insert. Sites will track accountability following institutional guidelines and local standard operating procedures.

11.2 RX-3117

RX-3117 will be provided as 200 mg and 500 mg capsules intended for oral administration. The capsules contain approximately 215-mg or 540 mg, respectively, of RX-3117 monohydrate with the additional mass above the nominal respective values of 200 or 500 mg accounting for the water of hydration. RX-3117 capsules are filled only with the active pharmaceutical ingredient (API). No other excipients are contained in the formulation.

The capsules will be a hard gelatin hydroxypropylmethyl cellulose capsule. The 200 mg capsule will be contained in a Size 2 Swedish orange opaque capsule and the 500 mg will be contained in a Size 0 opaque capsule with a Swedish orange cap and grey body.

11.3 Packaging and Labelling

The drug product will be packaged in white, high-density polyethylene (HDPE) bottles with a child-resistant closure and an induction seal. Bottles will contain 10 capsules of 1 of the relevant dose strengths (200 mg or 500 mg).

All labels for study drug bottles will meet all applicable requirements of the Food and Drug Administration, Annex 13 of Current Good Manufacturing Practice (cGMP) (Manufacture of Investigational Medicinal Products, July 2003), and/or other local regulations, as applicable.

11.4 Storage and Handling

Bottles containing capsules of RX-3117 should be stored at a controlled refrigerated temperature of 2-8°C (i.e., 36-46° F).

11.5 Source

RX-3117 will be supplied without charge by Rexahn Pharmaceuticals, Inc.

11.6 Dispensing

The site personnel (e.g., pharmacist or other qualified person) will be responsible for dispensing RX-3117. It is planned that the study drug will be dispensed at 1-week intervals during Cycle 1 of treatment and at 4-week intervals thereafter.

The clinic pharmacist or an alternative qualified person will provide each subject with directions regarding drug storage and instructions regarding how many of each size/color of capsule to use at each dosing. The subject number, subject initials, dose assignment, and number of capsules to be taken will be written on the dispensing bottle label by site personnel.

11.7 Procedures for Monitoring Subject Compliance

Each study site will be responsible for monitoring subject compliance through subject interviews and counting of unused study drug capsules.

At the time of study drug dispensing, the site personnel will show subjects how to complete a subject diary card with a record of the number of capsules of RX-3117 that they have taken daily at home and how to record any problems with drug administration or reasons for noncompliance. Site personnel will instruct subjects that they must bring the diary card back after each study visit. The site personnel will need to evaluate subjects' diary cards for completeness after each dispensing interval and collect the original diary page or make a certified copy.

In addition, subjects should be instructed to return all bottles (used or unused) and any unused study medication to the study site at the end of each dispensing interval. The quantity of RX-3117 and the date when it is returned by the subject should be recorded in the study drug accountability records. All RX-3117 returned by the subject should be retained for review by the study site monitor prior to return to the study sponsor or destruction.

If it is determined that a subject is substantially noncompliant with the study protocol in circumstances that increase risk or substantially compromise the interpretation of study results, the investigator and the sponsor should determine whether the subject should be withdrawn from study treatment. If the subject is withdrawn for noncompliance, the institutional review board should be notified.

11.8 Drug Accountability

The disposition of all RX-3117 should be documented from the time of receipt at the site through dispensing to study subjects, drug return, or drug destruction. All drug supplies and associated documentation will be periodically reviewed and verified by the study monitor over the course of the study.

Study personnel must ensure that all study drug is kept in a secure locked area with access limited to authorized personnel. The study drug must not be used outside the context of this protocol. Under no circumstances should the investigator or site personnel supply study drug to other investigators or clinics, or allow the study drug to be used other than as directed by this protocol.

The investigator and/or the responsible site personnel must maintain accurate records of the receipt of all study drug shipped by the study sponsor or its designee, including, but not limited to: the date received, lot number, amount received, condition of the study drug, and the disposition of all study drug. Study drug accountability records must also be maintained that include the subject number to whom the study drug was dispensed; the date, quantity and lot number of the study drug dispensed; and the identity of the person dispensing the medication.

Depending upon the decision of the study sponsor, remaining unused study drug supply will be returned to the study sponsor or its designee after the study is completed or will be discarded or destroyed at the clinical site. Drug may be returned or destroyed on an ongoing basis during the study if appropriate. If the study drug is discarded or destroyed at the clinical site, standard institutional policy should be followed. Records documenting the date of study drug return or destruction, relevant lot numbers, and the amount returned or destroyed should be maintained.

11.9 Overdose Precautions

There is limited prior clinical experience with RX-3117. Administration of very high single IV doses of RX-3117 to monkeys induced convulsions, tremors, and lack of coordination. Myelotoxicity is a known dose-dependent consequence of anti-metabolite administration.

In this protocol, an overdose is defined as administration of more than the prescribed daily dose of RX-3117. In a subject who experiences an overdose, consideration should be given as to whether RX-3117 administration should be temporarily interrupted. If the overdose ingestion is recent and substantial, and if there are no medical contraindications, use of gastric lavage or induction of emesis may be considered. Observation for any symptomatic side effects should be instituted, and biochemical and hematological parameters should be followed closely (consistent with the protocol or more frequently, as needed). Appropriate supportive management to mitigate adverse effects should be initiated.

The study sponsor should be contacted if a study drug overdose occurs. Cases of study drug overdose will result in specific reporting requirements (see Section 9.6.1).

11.10 Inadvertent Exposure and Spill Precautions

Based on available data from nonclinical studies, RX-3117 may be acutely toxic and genotoxic. It is not anticipated that the study drug would be irritative at levels that are likely to result from inadvertent exposure to the contents of broken capsules.

Personnel handling the drug should use reasonable precautions to avoid ingestion of the study drug product or eye contact, skin contact, or inhalation of the study drug substance. Study subjects should be strongly advised to store the drug appropriately, keep the drug in a secure place out of the reach of children and to avoid mixing study drug capsules with other medications.

For further information regarding inadvertent exposure and spill precautions, please consult the RX-3117 investigator brochure.

12.REGULATORY OBLIGATIONS

12.1 Informed Consent

An initial generic informed consent form will be provided to the investigator for preparing the informed consent document to be used at his or her site. Updates to the template will be communicated in writing from the sponsor or designee to the investigator. The written informed consent document should be prepared in the language(s) of the potential subject population.

Before a subject's participation in the clinical study, the investigator is responsible for obtaining written informed consent from the subject after adequate explanation of the aims, methods, anticipated benefits, and potential hazards of the study and before any protocol-specific screening procedures or any investigational products are administered.

The acquisition of informed consent and the subject's agreement or refusal of his/her notification of the primary care physician should be documented in the subject's medical records, and the informed consent form should be signed and personally dated by the subject and by the person who conducted the informed consent discussion (not necessarily an investigator). The original signed informed consent form should be retained in accordance with institutional policy, and a copy of the signed consent form should be provided to the subject or legally acceptable representative

12.2 Institutional Review Board

A copy of the protocol, proposed informed consent form, other written subject information, and any proposed advertising material must be submitted to the institutional review board for written approval. A copy of the written approval of the protocol and informed consent form must be received by the sponsor before recruitment of subjects into the study and shipment of investigational product.

The investigator must submit and, where necessary, obtain approval from the institutional review board for all subsequent protocol amendments and changes to the informed consent document. The investigator should notify the institutional review board of deviations from the protocol or serious adverse events occurring at the site and other adverse event reports received from the sponsor, in accordance with the institutional review board procedures.

The investigator will be responsible for obtaining annual institutional review board approval/renewal throughout the duration of the study. Copies of the investigator's reports and the institutional review board continuance of approval must be sent to the sponsor or designee.

12.3 Prestudy Documentation Requirements

The investigator is responsible for forwarding the following documents to the sponsor or designee for review before study initiation can occur:

- Signed and dated protocol signature page (Investigator's Agreement)
- Copy of approved informed consent form and subject information sheet, if applicable
- Copy of the institutional review board approval of the protocol, consent form, and subject information sheet
- Up-to-date curricula vitae of principal investigator and all sub-investigators
- Institutional review board composition and/or written statement that institutional review board is in compliance with regulations
- Laboratory normal ranges and documentation of laboratory certification (or equivalent)
- Signed study contract
- Completed Food and Drug Administration (FDA) form 1572
- Financial disclosure document(s)

12.4 Subject Confidentiality

The investigator must ensure that the subject's confidentiality is maintained. On the electronic case report forms or other documents submitted to the sponsor, subjects should be identified by their initials and a subject study number only. Documents that are not for submission to the sponsor (e.g., signed informed consent forms) should be kept in strict confidence by the investigator.

In compliance with Federal regulations/ICH GCP Guidelines, it is required that the investigator and institution permit authorized representatives of the company, of the regulatory agency(s), and the institutional review board direct access to review the subject's original medical records for verification of study-related procedures and data. Direct access includes examining, analyzing, verifying, and reproducing any records and reports that are important to the evaluation of the study. The investigator is obligated to inform and obtain the consent of the subject to permit named representatives to have access to his/her study-related records without violating the confidentiality of the subject.

12.5 Investigator Signatory Obligations

Each clinical study report should be signed by the investigator or, in the case of multicenter studies, the coordinating investigator.

The coordinating investigator, identified by the sponsor, will either be:

- a recognized expert in the therapeutic area
- an investigator who provided significant contributions to either the design or interpretation of the study
- an investigator contributing a high number of eligible subjects

13. ADMINISTRATIVE AND LEGAL OBLIGATIONS

13.1 Protocol Amendments and Study Termination

Protocol amendments, except where necessary to eliminate an immediate hazard to subjects, must be made only with the prior approval of the sponsor. Agreement from the investigator must be obtained for all protocol amendments and amendments to the informed consent document. The institutional review board must be informed of all amendments and give approval. The investigator **must** send a copy of the approval letter from the institutional review board to Rexahn.

Both the sponsor and the investigator reserve the right to terminate the study according to the study contract. The investigator should notify the institutional review board in writing of the study's completion or early termination and send a copy of the notification to the sponsor.

13.2 Study Documentation and Archive

The investigator should maintain a list of appropriately qualified persons to whom he/she has delegated study duties. All persons authorized to make entries and/or corrections on electronic case report forms will be included on the sponsor's Delegation of Authority Form.

Source documents are original documents, data, and records from which the subject's electronic case report form data are obtained. These include but are not limited to hospital records, clinical and office charts, laboratory and pharmacy records, diaries, microfiches, radiographs, and correspondence.

The investigator and study staff are responsible for maintaining a comprehensive and centralized filing system of all study-related (essential) documentation, suitable for inspection at any time by representatives from the sponsor and/or applicable regulatory authorities. Elements should include:

- Subject files containing completed electronic case report forms, informed consent forms, and subject identification list

- Study files containing the protocol with all amendments, investigator's brochure, copies of prestudy documentation (see Section 12.3), and all correspondence to and from the institutional review board and the sponsor
- Proof of receipt, Investigational Product Accountability Record, Return of Investigational Product for Destruction, Final Investigational Product Reconciliation Statement, and all drug-related correspondence

In addition, all original source documents supporting entries in the electronic case report forms must be maintained and be readily available.

No study document should be destroyed without prior written agreement between the sponsor and the investigator. Should the investigator wish to assign the study records to another party or move them to another location, he/she must notify the sponsor in writing of the new responsible person and/or the new location.

13.3 Study Monitoring and Data Collection

The sponsor's representative and regulatory authority inspectors are responsible for contacting and visiting the investigator for the purpose of inspecting the facilities and, upon request, inspecting the various records of the clinical study (e.g., electronic case report forms and other pertinent data) provided that subject confidentiality is respected.

The sponsor's monitor is responsible for verifying the electronic case report forms at regular intervals throughout the study to verify adherence to the protocol; completeness, accuracy, and consistency of the data; and adherence to local regulations on the conduct of clinical research. The monitor should have access to subject medical records and other study-related records needed to verify the entries on the electronic case report forms.

The investigator agrees to cooperate with the monitor to ensure that any problems detected in the course of these monitoring visits, including delays in completing electronic case report forms, are resolved.

In accordance with ICH GCP and the sponsor's audit plans, this study may be selected for audit by sponsor or its designee. Inspection of site facilities (e.g., pharmacy, drug storage areas, laboratories) and review of study-related records will occur to evaluate the study conduct and compliance with the protocol, ICH GCP, and applicable regulatory requirements.

To ensure the quality of clinical data across all subjects and sites, a data management review will be performed on subject data received at the sponsor or designee. During this review, subject data will be checked for consistency, omissions, and any apparent discrepancies. In addition, the data will be reviewed for adherence to the protocol and good clinical practice. To resolve any questions arising from the clinical data management

review process, data queries and/or site notifications will be sent to the site for completion and returned to the sponsor or designee.

The principal investigator will electronically sign and date the indicated places on the electronic case report form. These signatures will indicate that the principal investigator inspected or reviewed the data on the electronic case report form, the data queries, and the site notifications, and agrees with the content.

13.4 Language

All written information and other material to be used by subjects and investigative staff must use vocabulary and language that are clearly understood.

13.5 Publication Policy

To coordinate dissemination of data from this study, the sponsor encourages the formation of a publication committee consisting of several principal investigators and appropriate sponsor staff. The committee is expected to solicit input and assistance from other investigators and the sponsor staff as appropriate. Membership on the committee (both for investigators and the sponsor's staff) does not guarantee authorship—the criteria described below should be met for every publication.

Authorship of any publications resulting from this study will be determined on the basis of the Uniform Requirement for Manuscripts Submitted to Biomedical Journals: Writing and editing for biomedical publication (International Committee of Medical Journal Editors, 2010), which states:

- Authorship credit should be based on (1) substantial contributions to conception and design, acquisition of data, or analysis and interpretation of data; (2) drafting the article or revising it critically for important intellectual content; (3) final approval of the version to be published. Authors should meet conditions 1, 2, and 3.
- When a large, multicenter group has conducted the work, the group should identify the individuals who accept direct responsibility for the manuscript. These individuals should fully meet the criteria for authorship defined above, and editors will ask these individuals to complete journal-specific author and conflict-of-interest disclosure forms. When submitting a manuscript authored by a group, the corresponding author should clearly indicate the preferred citation and identify all individual authors as well as the group name. Journals generally list other members of the group in the Acknowledgments. The NLM indexes the group name and the names of individuals the group has identified as being directly responsible for the manuscript; it also lists the names of collaborators if they are listed in Acknowledgments.
- Acquisition of funding, collection of data, or general supervision of the research group, alone, does not justify authorship.
- All persons designated as authors should qualify for authorship, and all those who qualify should be listed.

- Each author should have participated sufficiently in the work to take public responsibility for appropriate portions of the content.

All publications (e.g., manuscripts, abstracts, oral/slide presentations, book chapters) based on this study must be submitted to the sponsor for corporate review. The Clinical Study Agreement among the institution, principal investigator, and the sponsor will detail the procedures for, and timing of, the sponsor's review of publications.

13.6 Compensation

Subject will be treated and/or compensated for any study-related illness/injury pursuant to the information provided in the Compensation for Injury section of the Informed Consent.

14. REFERENCES

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15. APPENDICES

Appendix A. Schedule of Assessments Cycle 1

	SCR[a]	Cycle 1					EOT / ET	SFU[c]
Procedures and Treatments Day	**-14**	**1**	**2**	**8[b]**	**15**	**22[b]**		
Informed consent	X							
Medical, surgical, cancer and psychiatric histories	X							
Prior medication usage	X[d]	X[e]						
Eligibility review, enrollment	X	X[f]						
Quality of Life measurements[g]		X		X	X	X	X	X
Pregnancy test[h]	X	X						
Physical examination excluding GU including height	X							
Weight	X	X					X	X
ECOG performance status	X	X					X	X
Hematology and serum chemistry	X	X[i]		X	X	X	X	X
Coagulation profile and Urinalysis	X	X[i]		X	X		X	
Vital sign measurements[j,k]	X	X	X	X	X	X	X	X
12-lead electrocardiogram[j,l]	X	X	X					
Pharmacokinetic sampling[j,m]		X			X			
Abraxane® infusion[n]		X		X	X			
RX-3117 drug administration[o]		X	X[p]	X	X			
Dispensing of study drug[q] and diary cards		X[q]	X[q]	X[q]	X[q]			
Unused study drug collection & subject compliance				X	X	X	X	
Tumor assessment(s)[r]	X							X[s]
Tumor marker blood samples	X	X[i]					X	
Adverse event assessment[t]		X	X	X	X	X	X	X
Concomitant med review		X	X	X	X	X	X	X
Archived tumor tissue[u]		X						
Biomarker blood sample[v]		X					X	
Tumor biopsy samples (optional)[w]		X						

ECOG = Eastern Cooperative Oncology Group; ET = Early Termination; EOT = End of Treatment; SFU = Safety Follow up; SCR = Screening

Footnotes for Schedule of Assessments

a Screening procedures will be performed within 14 days of enrollment, except baseline tumor assessment, which can be evaluated within 21 days before enrollment. ECG must be done within 7 days before enrollment.
b The Cycle 1 Day 8 and Day 22 visits may occur on Days 8 or 22 (+1 day).
c Safety follow-up visit will be between 30 and 37 days after the last dose of RX-3117.
d Medications taken within 28 days before Cycle 1 Day 1.
e Review prior medication usage for any medications started since the screening visit.
f Confirm that the subject is still is eligible for enrollment in the study.
g QoL questionnaires must be completed prior to any other study procedure.
h A serum pregnancy test will be performed at screening (for women of childbearing potential). A serum pregnancy test or urine pregnancy test will be performed at baseline (Day 1 of Cycle 1) unless the screening serum pregnancy test was performed within 72 hours before dosing on Cycle 1 Day 1.

i If screening laboratory tests were performed within 72 hours before Cycle 1 Day 1, they do not need to be repeated on Cycle 1 Day 1.
j The required order of assessments is ECG, followed by vital signs and then PK sampling when applicable.
k Vital signs measurements will include resting heart rate, blood pressure, pulse, respiratory rate, and temperature. Oxygen saturation (by pulse oximetry while subject is breathing room air) will be assessed at Screening only.
l ECG to be assessed pre-dose of Abraxane®, pre-dose of RX-3117 administration, and at 1, 2, 4, and 6 hours after RX-3117 oral administration on Cycle 1 Day 1. (Phase 1 and Phase 2-Stage 1 only)
m In Phase 1 and Phase 2-Stage 1 only, Pharmacokinetic (PK) samples will be collected at Abraxane® pre-dose, at the end of infusion, at RX-3117 pre-dose (no more than 15 minutes before dosing) and at 0.5, 1, 2, 3, 4, and 6 hours after oral administration of RX-3117 on Day 1 in Cycle 1. A sample will also be taken 24 hours after RX-3117 dosing administration on Cycle 1 Day 1.)
n Abraxane® IV infusion over 30-40 minutes on Days 1, 8, and 15. If a dose is administered on the same day as PK sampling (i.e. pre-dose and 24 hours), the PK sample will be collected first.
o RX-3117 will be administered orally after having fasted for a minimum of 8 hours and no earlier than 1 hour after the start of infusion of Abraxane®.
p Administered for 5 consecutive days followed by 2 days off per week for 3 weeks then 1 week off. If a dose is administered on the same day as PK sampling (i.e., pre-dose and 24 hours), the PK sample will be collected first.
q Study drug and diary cards will be dispensed at 1 week intervals during Cycle 1.
r Tumor assessments will be evaluated using RECIST v1.1 and should include an assessment of all areas of known and suspected malignancy. Depending on the tumor type, specific assessments may include CT (preferred for lung lesions) or MRI scans and any other appropriate radiographic or scintigraphic procedures and/or physical examinations. The method of assessment for an individual tumor or lesion that was used at baseline must be used consistently throughout the study and follow-up visit.
s Subjects meeting criteria for complete response or partial response at the last on-treatment tumor assessment should have a Safety Follow-up tumor assessment if the last assessment was performed ≥ 4 weeks, to confirm the response based upon RECIST.
t Adverse events include all worsening of pre-existing conditions from the time the subject receives study treatment. All adverse events attributed to study drug will be assessed until resolved or returned to baseline.
u To be collected within 4 weeks after enrollment
v Biomarker samples will be collected pre-dose
w Tumor biopsies will be taken following enrollment but before first dose of study treatment (optional)

Appendix B. Schedule of Assessments Cycles 2 to 8

	Cycles 2 - 8				EOT/ET	SFU[a]
Procedures and Treatments **Day**	**1**	**8**	**15**	**22**		
Quality of Life measurements[b]	X	X	X	X	X	X
Weight	X				X	X
ECOG performance status	X				X	X
Hematology and serum chemistry	X		X		X	X
Coagulation profile and Urinalysis	X				X	
Vital sign measurements[c]	X	X	X		X	X
Abraxane® infusion[d]	X	X	X			
RX-3117 drug administration [e,f,]	X	X	X			
Dispensing of study drug and diary cards[g]	X[g]					
Unused study drug collection & subject compliance				X	X	
Tumor assessment(s)[h]				X[i]	X[j]	X
Tumor marker blood samples	X				X	
Adverse event assessment[l]	X	X	X	X	X	X
Concomitant medication review	X	X	X	X	X	X
Biomarker blood sample	X[m]				X	

ECOG = Eastern Cooperative Oncology Group; ET = Early Termination; EOT = End of Treatment; SFU = Safety Follow up; SCR = Screening

Footnotes for Schedule of Assessments

a Safety follow-up visit will be between 30 and 37 days after the last dose of study drug.

b EORTC QLQ-C30; EORTC PAN26; FACT-Hep. QoL questionnaires must be completed prior to any other study procedure.

c Vital signs measurements will include resting heart rate, blood pressure, pulse, respiratory rate, and temperature.

d Abraxane® IV infusion over 30- 40 minutes on Days 1, 8, and 15.

e RX-3117 will be administered orally after having fasted for a minimum of 8 hours and no earlier than 1 hour after the start of infusion of Abraxane®.

f Administered for 5 consecutive days followed by 2 days off per week for 3 weeks then 1 week off.

g Study drug and diary cards will be dispensed at least once every cycle thereafter.

h Tumor assessments will be evaluated using RECIST v1.1 and should include an assessment of all areas of known and suspected malignancy. Depending on the tumor type, specific assessments may include CT (preferred for lung lesions) or MRI scans and any other appropriate radiographic or scintigraphic procedures and/or physical examinations. The method of assessment for an individual tumor or lesion that was used at baseline must be used consistently throughout the study and follow-up visit.

i Tumor evaluation, including CT/MRI/PET will be performed between Days 22-28 of Cycles 2, 4, 6 and 8. The results of the assessments must be available before the start of the next cycle. Results of the assessment must be available before the start of the next cycle.

j For subjects who end treatment on a cycle for which response assessments are not planned (i.e., cycle 5 or 7) and if an assessment has not been done in the previous 4 weeks.

k Subjects meeting criteria for complete response or partial response at the last on-treatment tumor assessment should have a Safety Follow-up tumor assessment if the last assessment was performed ≥ 4 weeks, to confirm the response based upon RECIST.

l Adverse events include all worsening of pre-existing conditions from the time the subject receives study treatment. All adverse events attributed to study drug will be assessed until resolved or returned to baseline.
m Biomarker samples will be collected predose on Cycle 2 only.

Appendix C. Schedule of Assessments Cycle 9 and beyond

	≥Cycle 9				EOT/ET	SFU[a]
Procedures and Treatments **Day**	**1**	**8**	**15**	**22**		
Quality of Life measurements[b]	X	X	X	X	X	X
Weight	X				X	X
ECOG performance status	X				X	X
Hematology and serum chemistry	X				X	X
Coagulation profile and Urinalysis					X	
Vital sign measurements[c]	X				X	X
Abraxane® infusion[d]	X	X	X			
RX-3117 drug administration[e,f]	X	X	X			
Dispensing of study drug and diary cards[g]	X					
Unused study drug collection & subject compliance				X	X	
Tumor assessment(s)[h]				X[i]	X[j]	X[k]
Tumor marker blood samples	X				X	
Adverse event assessment[l]	X	X	X	X	X	X
Concomitant med review	X	X	X	X	X	X
Biomarker blood sample					X	

ECOG = Eastern Cooperative Oncology Group; ET = Early Termination; EOT = End of Treatment; SFU = Safety Follow up; SCR = Screening

Footnotes for Schedule of Assessments

a Safety follow-up visit will be between 30 and 37 days after the last dose of study drug.

b EORTC QLQ-C30; EORTC PAN26; FACT-Hep. QoL questionnaires must be completed prior to any other study procedure.

c Vital signs measurements will include resting heart rate, blood pressure, pulse, respiratory rate, and temperature.

d Abraxane® IV infusion over 30-40 minutes on Days 1, 8, and 15 .

e RX-3117 will be administered orally after having fasted for a minimum of 8 hours and no earlier than 1 hour after the start of infusion of Abraxane®.

f Administered for 5 consecutive days followed by 2 days off per week for 3 weeks then 1 week off.

g Study drug and diary cards will be dispensed at least once every cycle.

h Tumor assessments will be evaluated using RECIST v1.1 and should include an assessment of all areas of known and suspected malignancy. Depending on the tumor type, specific assessments may include CT (preferred for lung lesions) or MRI scans and any other appropriate radiographic or scintigraphic procedures and/or physical examinations. The method of assessment for an individual tumor or lesion that was used at baseline must be used consistently throughout the study and follow-up visit.

i Tumor evaluation, including CT/MRI will be performed between Days 22-28 of Cycle 10 and every 2 cycles thereafter. The results of the assessments must be available before the start of the next cycle. Results of the assessment must be available before the start of the next cycle.

j For subjects who end treatment on a cycle for which response assessments are not planned (i.e., cycle 5 or 7) and if an assessment has not been done in the previous 4 weeks.

k Subjects meeting criteria for complete response or partial response at the last on-treatment tumor assessment should have a Safety Follow-up tumor assessment if the last assessment was performed ≥ 4 weeks, to confirm the response based upon RECIST.

- Adverse events include all worsening of pre-existing conditions from the time the subject receives study treatment. All adverse events attributed to study drug will be assessed until resolved or returned to baseline.

Appendix D. Analytes

Chemistry	Urinalysis	Hematology	Other Labs
Sodium	Specific gravity	RBC	Urine β-HCG
Potassium	pH	Hemoglobin	Serum β-HCG
Chloride		ANC	PT; PTT or INR
Bicarbonate	Protein	Platelets	
Magnesium	Glucose	WBC	Blood samples for RX-3117 and metabolite concentration and PK
Calcium	Bilirubin	Differential	
BUN	Ketones	• Eosinophils	
Serum Creatinine	WBC	• Basophils	Blood samples for biomarkers
AST (SGOT)	RBC	• Lymphocytes	Tumor Marker
ALT (SGPT)	Epithelial cells	• Neutrophils	Blood samples for Abraxane® concentration and PK
Alkaline phosphatase	Bacteria (macroscopy only)	• Monocytes	
Lactate dehydrogenase			
Total bilirubin			
Creatine phosphokinase			
Total protein			
Albumin			
Glucose			

β-HCG = beta human chorionic gonadotropin; ALT = alanine amino transferase; ANC = absolute neutrophil count; AST aspartate amino transferase; BUN = blood, urea, nitrogen, INR = international normalized ratio; PT = prothrombin time; PTT = Partial prothrombin time; RBC = red blood cells; WBC = white blood cells

Appendix E. Response Evaluation Criteria in Solid Tumors

(Eisenhauer et al, 2009)

- **Definitions**

  At baseline, tumor lesions/lymph nodes will be categorized measurable or non-measurable as follows:

  - **Measurable Disease** - the presence of at least one measurable lesion. If the measurable disease is restricted to a solitary lesion, its neoplastic nature should be confirmed by cytology/histology.
  - **Measurable Lesions** - lesions that can be accurately measured in at least one dimension with longest diameter ≥ 20 mm using chest X-ray or ≥ 10 mm with CT scan.
  - **Non-measurable Lesions** - all other lesions, including small lesions (longest diameter <20 mm with chest X-ray or ≥ 10 but < 15 mm with CT scan), i.e., bone lesions, leptomeningeal disease, ascites, pleural/pericardial effusion, inflammatory breast disease, lymphangitis cutis/pulmonis, cystic lesions, and also abdominal masses that are not confirmed and followed by imaging techniques; and.

- All measurements should be taken and recorded in metric notation, using a ruler or calipers. All baseline evaluations should be performed as closely as possible to the beginning of treatment and never more than 28 days before study day 1.
- The same method of assessment and the same technique should be used to characterize each identified and reported lesion throughout the trial.
- Clinical lesions (e.g., skin nodules and palpable lymph nodes) will only be considered measurable target lesions when they ≥ 15 mm. For the case of skin lesions, documentation by color photography, including a ruler to estimate the size of the lesion, is recommended.
- Lymph nodes that are < 10 mm will be considered non-pathological

Methods of Measurement

- CT and MRI are the best currently available and reproducible methods to measure target lesions selected for response assessment. Conventional CT and MRI should be performed with cuts no greater than 5 mm in slice thickness contiguously. This applies to tumors of the chest, abdomen and pelvis. Head and neck tumors and those of extremities usually require specific protocols.
- When the primary endpoint of the study is objective response evaluation, ultrasound should not be used to measure tumor lesions. It is, however, a possible alternative to clinical measurements of superficial palpable lymph nodes, subcutaneous lesions and thyroid nodules. Ultrasound might also be useful to confirm the complete disappearance of superficial lesions usually assessed by clinical examination.

- The utilization of endoscopy and laparoscopy for objective tumor evaluation has not yet been fully and widely validated. Their uses in this specific context require sophisticated equipment and a high level of expertise that may only be available in some centers. Therefore, the utilization of such techniques for objective tumor response should be restricted to validation purposes in specialized centers. However, such techniques can be useful in confirming complete pathological response when biopsies are obtained.
- Cytology and histology can be used to differentiate between partial response and complete response in rare cases (e.g., after treatment to differentiate between residual benign lesions and residual malignant lesions in tumor types such as germ cell tumors).

Baseline Documentation of "Target" and "Non-Target" Lesions

- All measurable lesions up to a maximum of 2 lesions per organ and 5 lesions in total, representative of all involved organs should be identified as target lesions and recorded and measured during screening.
- Target lesions should be selected on the basis of their size (lesions with the longest diameter) and their suitability for accurate repeated measurements (either by imaging techniques or clinically).
- A sum of the longest diameter (LD) for all target lesions will be calculated and reported as the baseline sum LD. The baseline sum LD will be used as reference by which to characterize the objective tumor.
- All other lesions (or sites of disease) should be identified as non-target lesions and should also be recorded during screening. Measurements of these lesions are not required, but the presence or absence of each should be noted throughout the study.

Response Criteria

Evaluation of Target Lesions

* Complete Response (CR):	Disappearance of all target lesions. Any pathologic 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 the diameters of target lesions, taking as reference the baseline sum diameters
* Progressive Disease (PD):	At least a 20% increase in the sum of the diameters of target lesions, taking as reference the smallest sum diameters recorded since the treatment started or the appearance of one or more new lesions. In addition the relative increase of 20%, the sum must also demonstrate an absolute increase of at least 5 mm. 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 progressive disease, taking as reference the smallest sum diameters while on study.

Evaluation of Non-Target Lesions

* Complete Response (CR):	Disappearance of all non-target lesions. All lymph nodes must be non-pathological in size (i.e., < 10 mm short axis)
* Incomplete Response/ Stable Disease (SD):	Persistence of one or more non-target lesion(s)
* Progressive Disease (PD):	Appearance of one or more new lesions and/or unequivocal progression of existing non-target lesions (1)

(1) Although a clear progression of “non-target” lesions only is exceptional, in such circumstances, the opinion of the treating physician should prevail.

Evaluation of Best Overall Response

The best overall response is the best response recorded from the start of the treatment until disease progression/recurrence (taking as reference for progressive disease the smallest measurements recorded since the treatment started). In general, the subject's best response assignment will depend on the achievement of both measurement and confirmation criteria

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

CR = compete response, PR = partial response, SD = stable disease, PD = progressive disease, NE = inevaluable

- Subjects with a global deterioration of health status requiring discontinuation of treatment without objective evidence of disease progression at that time should

be classified as having “symptomatic deterioration”. Every effort should be made to document the objective progression even after discontinuation of treatment.

- In some circumstances it may be difficult to distinguish residual disease from normal tissue. When the evaluation of complete response depends on this determination, it is recommended that the residual lesion be investigated (fine needle aspirate/biopsy) to confirm the complete response status.

Confirmation

- The main goal of confirmation of objective response is to avoid overestimating the response rate observed. In cases where confirmation of response is not feasible, it should be made clear when reporting the outcome of such studies that the responses are not confirmed.
- To be assigned a status of partial response or complete response, changes in tumor measurements must be confirmed by repeat assessments during the study.
- In the case of SD, follow-up measurements must have met the SD criteria no earlier than 49 days after the date of enrollment/randomization during the study.

Duration of Overall Response

- The duration of overall response is measured from the time measurement criteria are met for complete response or partial response (whichever status is recorded first) until the first date that recurrence or progressive disease is objectively documented, taking as reference for progressive disease the smallest measurements recorded since the treatment started.

Duration of Stable Disease

- SD is measured from the start of the treatment until the criteria for disease progression are met, taking as reference the smallest measurements recorded since the treatment started.