CLINICAL STUDY PROTOCOL

Protocol Title:	A Phase IIb, Nonrandomized, Open-Label Trial with Mouse Renal Adenocarcinoma (RENCA) Cell-Containing Agarose-Agarose Macrobeads Compared with Best Supportive Care in Patients with Treatment-Resistant, Metastatic Colorectal Carcinoma
Protocol Number:	RI-MB-203
Investigational Phase:	IIb
IND Number:	IND 10091
Date of Original Protocol:	23 October 2013
Date of Amendment 1 Protocol:	23 December 2013
Sponsor:	The Rogosin Institute 505 East 70th Street New York, NY 10021 USA
Sponsor's Responsible Medical Officer:	Barry H. Smith, MD, PhD President/CEO The Rogosin Institute Telephone: 212-746-1551

DOCUMENT APPROVAL PAGE

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Sponsor Representative: _____ 1/6/2014

Barry H. Smith, MD, PhD — Date
President/CEO
The Rogosin Institute

INVESTIGATOR SIGNATURE PAGE

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I have read the protocol and agree to conduct the study as outlined therein. I will ensure that all study personnel involved with the study are fully informed with regard to the investigational product and the conduct of the study.

Investigator's Signature: _____

Investigator's Name (Print): Thomas J. Fahey III, MD

Date: 3/17/17

Affiliation: Weill Cornell Medical College

ADMINISTRATIVE STRUCTURE OF THE STUDY

Clinical Operations	See the Study Procedures Manual.
Medical Monitor	See the Study Procedures Manual.
Central Laboratory	See the Laboratory Manual.
Clinical Supplies	The Rogosin Institute, Xenia Division 740 Birch Road Xenia, OH USA
Data Management and Statistics	Vital Systems, Inc. 3701 Algonquin Road Suite 310 Rolling Meadows, IL 60008 USA

SYNOPSIS

Sponsor: The Rogosin Institute	**Protocol Number:** RI-MB-203
Name of Study Drug: Not applicable	**Protocol Title:** A Phase IIb, Nonrandomized, Open-Label Trial with Mouse Renal Adenocarcinoma (RENCA) Cell-Containing Agarose-Agarose Macrobeads Compared with Best Supportive Care in Patients with Treatment-Resistant, Metastatic Colorectal Carcinoma
Name of Active Ingredient: Mouse renal adenocarcinoma (RENCA) cell-containing agarose-agarose macrobeads	**Phase of Development:** IIb

Objectives: The primary objective of this study is to evaluate the efficacy of renal adenocarcinoma (RENCA) macrobead implantation compared with best supportive care, as assessed by overall survival, in patients with treatment-resistant, metastatic colorectal carcinoma.

Secondary objectives, defined only for patients with treatment-resistant, metastatic colorectal carcinoma who undergo RENCA macrobead implantation (i.e., Group A), are to determine or evaluate the effect of RENCA macrobead implantation on the following variables:

- change from baseline over the period after the first RENCA macrobead implantation in clinical status, as measured by Eastern Cooperative Oncology Group (ECOG) performance status score and global clinical assessment
- change from baseline over the period after the first RENCA macrobead implantation in quality of life, as measured by the European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire (EORTC QLQ-C30) and Karnofsky Performance Status Scale
- change from baseline over the period after the first RENCA macrobead implantation in erythrocyte sedimentation rate (ESR), C-reactive protein (CRP), and CA 125 levels
- change from baseline over the period after the first RENCA macrobead implantation in levels of tumor markers (including carcinoembryonic antigen [CEA] and carbohydrate antigen 19-9 [CA19-9], with carbohydrate antigen 125 [CA125]) being used as a marker of inflammation (see immediately above).
- tumor marker response rate, defined as the proportion of patients who have a decrease from baseline of 20% or more in CEA or CA 19-9 values
- safety and tolerability of RENCA macrobeads, as measured by the following:
    - adverse events
    - clinical laboratory tests, including chemistry, hematology, coagulation, urinalysis, and test for presence of ecotropic murine leukemia virus (eMuLV)
    - murine allergen skin test

Methodology: This is a Phase IIb, multicenter, nonrandomized, open-label study with RENCA macrobeads in patients with treatment-resistant, metastatic colorectal carcinoma to determine the effect of RENCA macrobead implantation on overall survival compared with that achieved by best supportive care alone.

Two treatment groups will be enrolled in this study, as follows:

- Group A (n=40) – patients who will undergo up to 4 implantations of RENCA macrobeads, at an amount of 8 RENCA macrobeads /kg body weight

- Group B (n=80) – patients who will receive, or are receiving, best supportive care, defined as management of symptoms aimed at maintaining or improving quality of life, but not including approved therapies targeting the patient's malignancy

For patients in Group A, the study will consist of a screening period lasting up to 30 days; up to 4 RENCA macrobead implantation procedures at least 90 days apart: and a 90-day follow-up period after the final implantation procedure. Patients will be expected to participate in a long-term follow-up period until death. RENCA macrobead implantation procedures may be delayed at the investigator's discretion/medical judgment, by patient decision, or due to initiation of a medically necessary or palliative therapy or procedure that is not specifically directed at more effectively treating the cancer itself. No maximum period between implantation procedures will be defined, and patients having treatment delays will not be removed from the study. However, if more than 30 days pass between a Day 90 visit and Day 0 of a subsequent implantation, patients will have re-screening assessments performed to ensure continued eligibility. Re-screening assessments will not include re-administration of informed consent or a new review of medical history. Inclusion/exclusion criteria applied to determine eligibility for the first implant, do not have to be re-applied at this time. However, patients must continue to be acceptable surgical candidates, as per the investigator's and surgeon's medical judgment and the standards of optimal patient care. Discontinuation of the macrobead protocol for a given patient may be the result of the investigator's and/or surgeons decision based on the patient's best medical interest, significant disease progression despite macrobead implantation, an unexpected serious adverse event related or unrelated to the macrobead implantation, or the patient's decision to withdraw for any reason.

After informed consent has been obtained, patients in Group A will undergo screening/baseline assessments. For eligible patients, the first procedure to implant RENCA macrobeads into the peritoneal cavity will be scheduled for Day 0. Patients will be expected to return to the clinic on Days 14, 30, 60, and 90 after each RENCA macrobead implantation procedure for efficacy, exploratory, and safety assessments. Up to 3 additional (for a total of 4) RENCA macrobead implantation procedures will be performed at the investigator's discretion.

Patients will be considered for enrollment in Group B only if they have already decided independently of this study not to pursue further therapeutic treatment of their cancer. For these patients, the study will consist of administration of informed consent, which will include permission to review medical records and record relevant medical information, agreement to be followed for survival, and review of entry criteria to ensure that they are comparable to the patients in Group A. Patients in Group B will not have any assessments performed as part of this study.

It is expected that study centers will enroll patients in either Group A or Group B, and not necessarily both, treatment groups.

Number of patients to be enrolled: A total of 120 patients with treatment-resistant, metastatic colorectal cancer will be entered in the study -- 40 patients who will undergo RENCA macrobead implantation and 80 patients who will receive or are receiving best supportive care.

Criteria for inclusion: Patients in both treatment groups must meet all of the following criteria to be considered eligible to participate in the study:

1. Patients are adult men or women, aged 18 years or older, with histologically-confirmed, metastatic adenocarcinoma of the colon or rectum that is resistant to available treatment options, including at least two such options from available chemotherapy, targeted, and other regimens.
2. Patients have radiographically documented evidence of disease progression.
3. Patients have a life expectancy of at least 6 weeks, in the investigator's opinion, at the time disease progression is documented.

4. Patients are considered surgical candidates on the basis of co-morbidity risks, number and sites of metastases, and ability to withstand general anesthesia.
5. Patients are able to provide written informed consent.

Patients in Group A must also meet all of the following additional criteria:

6. Patients have an ECOG performance status score of 0, 1, or 2.
7. Patients have adequate hematologic function, defined as follows:
   a. absolute neutrophil count (ANC) ≥1500 /mL
   b. hemoglobin ≥9 g/dL
   c. platelets ≥75,000 /mL
8. Patients have adequate hepatic function, defined as follows:
   a. bilirubin ≤1.5 times the upper limit of normal (x ULN)
   b. aspartate transaminase (AST) ≤3 x ULN, or ≤5 x ULN if liver metastases are present
   c. alanine transaminase (ALT) ≤3, x ULN, or ≤5 x ULN if liver metastases are present
9. Patients have adequate renal function, defined as creatinine ≤2.0 mg/dL.
10. Patients have adequate coagulation function, defined as follows:
    a. International Normalized Ratio (INR) ≤1.5 or between 2 and 3 if the patient is receiving anticoagulation
    b. partial thromboplastin time (PTT) ≤5 seconds above the ULN

    Note: Patients receiving full-dose anticoagulation therapy must be receiving a stable dose of oral anticoagulant therapy or low-molecular-weight heparin.
11. Clinically significant toxic effects of chemotherapy (excluding alopecia), radiotherapy, hormonal therapy, or prior surgery must have resolved to Grade 1 or better, with the exception of peripheral neuropathy, which must have resolved to Grade 2 or better.
12. Female patients of childbearing potential must have a negative serum pregnancy test at screening (and a negative urine pregnancy test 2 days prior to the first and each subsequent macrobead implantation if the screening serum pregnancy test result was obtained more than 2 weeks before surgery); patients must agree to use a medically appropriate form of birth control (i.e., barrier method or abstinence) from screening throughout their participation in the study. Male patients and partners must agree to use condoms.

Patients in either treatment group who meet any of the following criteria will be excluded from participating in the study:

1. Patient has hepatic blood flow abnormalities, i.e., portal vein hypertension and thrombosis, and/or a large volume of ascites.
2. Patient has concurrent cancer of any other type, except skin cancers other than melanoma.
3. Patient has a positive test result for human immunodeficiency virus (HIV) or any hepatitis other than A at screening.
4. Patient is considered by the investigator to be unsuitable for participation in the study upon review of medical history, physical examination, or clinical laboratory test results.

Patients in Group A who meet any of the following criteria will be excluded from participating in the study:

5. Patient received FDA-approved chemotherapy within 3 weeks of Day 0, or bevacizumab (or similar drugs) within 4 weeks of Day 0, or radiation therapy at any site within 4 weeks of Day 0.
6. Patient received investigational anticancer therapy within 4 weeks of Day 0.
7. Patient has a positive reaction to the skin test for allergy to mouse antigen (Greer Laboratories, Inc. product #E2 [mouse epithelia], Lenoir, NC).
8. Patient has a history of hypersensitivity reaction that, in the opinion of the investigator, poses an increased risk of an allergic reaction to the RENCA macrobeads, particularly any known allergy to murine antigens or body tissues.
9. The patient has an ongoing or active infection, symptomatic congestive heart failure, unstable angina pectoris, serious cardiac arrhythmias (with the exception of well controlled atrial fibrillation), active bleeding, or psychiatric illness, or social situations that could interfere with the patient's ability to participate in the study.

Duration of treatment: The treatment period consists of up to 4 RENCA macrobead implantation procedures no less than 90 days apart, each followed by a 90-day follow-up period.

Criteria for evaluation:

Efficacy Assessments

For patients in Group A and Group B, the primary efficacy measurement is overall survival, defined as the time interval from the date of radiographically documented disease progression (and therefore failure of the latest available therapy) to the date of death due to any cause. Secondary efficacy measurements include assessment of clinical status (ECOG performance status score and global clinical assessment) and quality of life assessments (EORTC QLQ-30 and Karnofsky Performance Status Scale).

Exploratory Assessments

For patients in Group A, exploratory assessments include assessment of ESR, CRP, and CA 125 levels, tumor marker levels (CEA and CA19-9), CTC levels, tumor changes in size or metabolic activity , analysis of biopsy samples (if obtained), and autopsy (for consenting patients only).

Safety Assessments

For patients in Group A, safety assessments will include monitoring of adverse events, clinical laboratory tests (chemistry, hematology, coagulation, urinalysis, and eMuLV testing), vital signs measurements (blood pressure, pulse, respiration rate, and temperature), physical examinations, 12-lead ECGs, chest x-rays, and murine allergen skin testing.

Investigational product: The investigational product to be used in this study is mouse RENCA cell-containing agarose-agarose macrobeads. Each RENCA macrobead is 6 to 8 mm and contains RENCA cells embedded in 1.0% Lonza HSB-LV agarose, surrounded by a second concentric layer made of 5.0% Lonza HSB-LV agarose layer. It should be noted that 150,000 RENCA are placed initially in each agarose-agarose macrobead and that an estimated 99% of these cells die off with one to two weeks, with the subsequent formation of colonies of tumor cells consisting of RENCA cells with stem cell properties and their daughter cells. It is when these colonies have formed that the macrobead produces the factor or factors that inhibit the growth of tumor cells outside the macrobead, both *in vitro* and *in vivo*.

The number of RENCA macrobeads to be surgically implanted in each patient in Group A is based on body weight and will be calculated to provide a dosage of 8 macrobeads /kg body weight.

Reference therapy: For patients in Group B, best supportive care is defined as management of symptoms aimed at maintaining or improving quality of life and does not include approved therapies specifically targeting the patient’s malignancy.

Statistical methods: All available data will be listed and summarized by treatment group (if applicable) and study visit. Categorical variables will be summarized using frequencies and percentages for each category. Continuous variables will be summarized using number of patients, mean, standard deviation, median, and range. All programs for data output and analyses will be written in Statistical Analysis System® (SAS) version 9.1.3 or higher (SAS Institute, Inc., Cary, NC).

Efficacy Variables and Analyses

The primary efficacy variable, overall survival, will be defined as the time interval between the date of radiographically documented disease progression and the date of death due to any cause.

Because treatment group assignment in this study is not randomized, balance of baseline covariates potentially related to both treatment and survival between Group A and Group B will be achieved through the use of propensity scores. A propensity score for each patient will be defined as the probability of being in Group A given a vector of observed baseline covariates x_i and will be derived using logistic regression. The final propensity score model will be selected based on univariable relationships between covariates derived from the baseline characteristics and group membership, collinearity among the candidate covariates, and number of patients enrolled (with the standard target of 10 patients per covariate).

Estimated survival functions will be presented graphically. A proportional hazards model will be used to estimate and compare functions for overall survival for Groups A and B. Patients who are lost to follow-up before the time of the analysis endpoint (t_e) will be considered censored as of the day the patient was last known to be alive. Patients who are still alive as of t_e will be considered censored at t_e.

The proportion of patients having improvement in ECOG performance status score at any time point will be summarized. The proportion of patients having improvement in the global clinical assessment score at any time point will be summarized. Observed values for responses to the EORTC QLQ-C30 will be used to calculate the derived scales for physical functioning, emotional functioning, cognitive functioning, social functioning, role functioning, individual symptoms, and financial difficulties (Fayers et al. 2001). The proportion of patients having improvement in any of the derived scales of the EORTC QLQ-C30 at any time point will be summarized. The proportion of patients having improvement at any time point in scores for the Karnofsky Performance Status Scale will be summarized.

Exploratory Variables and Analyses

Observed values and changes from baseline to each time point after each RENCA macrobead implantation in levels of tumor markers (CEA and CA19-9) will be summarized using descriptive statistics. The proportion of patients who have a tumor marker response (i.e., at least 20% decrease from baseline in CEA or CA19-9) will also be summarized.

Observed values and changes from baseline to each time point after each RENCA macrobead implantation in levels of CTCs, immunoglobulin levels (IgA, IgE, IgG, and IgM) and markers of cellular immune function (T cells, B cells, and NK cells [i.e., CD16 count]) will be summarized using descriptive statistics.

Characterization of changes from baseline to 90 days after each RENCA macrobead implantation in tumors will be listed. Depending on available results, these data may be summarized.

Results for analysis of any tumor biopsy samples obtained will be listed. Any autopsy results will be listed.

Safety Variables and Analyses

Exposure to study treatment, i.e., number of implantations and amount of macrobeads implanted, will be summarized using descriptive statistics.

Adverse events will be coded using MedDRA (Medical Dictionary for Regulatory Activities) version 10.1. A treatment-emergent adverse event will be defined as an adverse event that began or worsened after the first implantation and within 90 days after the last implantation. Summaries of treatment-emergent adverse events will be provided separately by implantation and for all implantations.

Treatment-emergent adverse events will be summarized by overall incidence, by severity, and by relationship. Summaries will also be provided for deaths, serious adverse events, and adverse events leading to discontinuation of study treatment. Listings will be provided for all adverse events, deaths, serious adverse events, and adverse events leading to discontinuation of study treatment.

For clinical laboratory parameters (chemistry (including metabolic, liver and renal function), hematology (including markers of inflammation), coagulation, and urinalysis), absolute values and changes from baseline to each time point after each RENCA macrobead implantation will be summarized. The proportion of patients with abnormal results will be summarized. Shifts from normal at baseline to abnormal after RENCA macrobead implantation will also be provided. Abnormal clinical laboratory results and NCI CTCAE v4.0 toxicity grade (if applicable) will be noted in the listings, and a separate listing for Grade 3 or higher laboratory values will be provided. Results from eMuLV testing will be listed.

Vital signs measurements (blood pressure, pulse, respiration rate, and temperature) will be listed.

Weight changes, along with calculated Body Mass Index (BMI) based on height measurement, will be listed.

Physical examination findings will be listed.

For 12-lead ECGs, results (normal, abnormal but not clinically significant, or abnormal and clinically significant) will be summarized by time point as frequencies and percentages of patients.

For chest x-rays, results (normal, abnormal but not clinically significant, or abnormal and clinically significant) will be summarized by time point as frequencies and percentages of patients.

Results from murine allergen skin testing will be listed.

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LIST OF ABBREVIATIONS

Abbreviation	Definition
ALT	alanine transaminase
AST	aspartate transaminase
BMI	Body Mass Index
BUN	blood urea nitrogen
CA19-9	carbohydrate antigen 19-9, marker for certain gastrointestinal tumors
CA125	carbohydrate antigen 125, marker for ovarian cancer but, in this case, for intraperitoneal inflammation
CEA	carcinoembryonic antigen, marker for colorectal cancer
CFR	Code of Federal Regulations
CI	confidence interval
COPD	chronic obstructive pulmonary disease
CRF	case report form
CRP	C-reactive protein
CTC	circulating tumor cell assay
DNA	deoxyribonucleic acid
DSMB	Data Safety Monitoring Board
ECG	electrocardiogram
ECOG	Eastern Cooperative Oncology Group
eMuLV	ecotropic murine leukemia virus
EORTC QLQ-C30	European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire
ESR	erythrocyte sedimentation rate
FDA	Food and Drug Administration
FOLFIRI	leucovorin/5-fluorouracil/irinotecan
FOLFOX	leucovorin/5-fluorouracil/oxaliplatin
GCP	Good Clinical Practice
GGT	gamma-glutamyltransferase
HIV	human immunodeficiency virus
ICH	International Conference on Harmonisation
IEC	Independent Ethics Community
IgA	immunoglobulin A
IgE	immunoglobulin E
IgG	immunoglobulin G
IgM	immunoglobulin M
IL-6	interleukin 6
IND	Investigational New Drug
INR	International Normalized Ratio
IPTW	inverse probability treatment weight
IRB	Institutional Review Board
LDH	lactate dehydrogenase
HIV	human immunodeficiency virus
HSB-LV	HSB low-viscosity agarose (Lonza Group Ltd.)

Abbreviation	Definition
MCH	mean corpuscular hemoglobin
MCHC	mean corpuscular hemoglobin concentration
MCV	mean corpuscular volume
MedDRA	Medical Dictionary for Regulatory Activities
MRI	magnetic resonance imaging
NCI CTCAE	National Cancer Institute Common Terminology Criteria for Adverse Events
NK	natural killer cell
PET-CT	positron emission tomography-computed tomography
PT	prothrombin time
PTT	partial thromboplastin time
QTcB	QT interval corrected using Bazett's formula
RBC	red blood cell
RDW	red blood cell distribution width
RENCA	renal adenocarcinoma
RT-PCR	reverse transcriptase polymerase chain reaction
SAP	Statistical Analysis Plan
SD	standard deviation
SOC	system organ class
SUV	standardized uptake value
TNF	tumor necrosis factor
ULN	upper limit of normal
US(A)	United States (of America)
WBC	white blood cell

1. BACKGROUND INFORMATION

1.1. Introduction

Treatment for cancer has traditionally consisted of surgery, radiation therapy, and chemotherapy. The advent of targeted, biological therapies, such as tyrosine kinase inhibitors, inhibitors of angiogenesis, inhibitors of, and antibodies to, specific receptors such as mTOR, HER-2, VEGF, and EGFR, and immune cell activation has changed the face of anti-cancer therapy. Although advances have produced encouraging prognoses in certain types of cancer, much remains to be accomplished with respect to the treatment of solid tumors, including some of the most common and deadly cancers such as those of the lung, colon, breast, ovary, prostate, pancreas, and kidney. New types of less toxic, less debilitating, and more effective therapies are needed.

Cancer of the colon is a highly treatable and often curable disease when localized to the bowel (Wolpin and Mayer 2008). Surgery is the primary form of treatment and results in cure in approximately 50% of patients. Recurrence following surgery is a major problem and is often the ultimate cause of death. The prognosis of patients with colon cancer is clearly related to the degree of penetration of the tumor through the bowel wall, the presence or absence of nodal involvement, and the presence or absence of distant metastases. Beyond those characteristics, elevated pretreatment serum levels of carcinoembryonic antigen (CEA) have a negative prognostic significance. The fact is, however, that, even with good prognostic factors and aggressive chemotherapy with regimens such as leucovorin/5-fluorouracil/oxaliplatin (FOLFOX) and leucovorin/5-fluorouracil/irinotecan (FOLFIRI), with or without the addition of bevacizumab and cetuximab (the latter for patients without the KRAS mutation), many patients become resistant to available chemotherapies and targeted biological therapies. In addition, other surgical and ablative techniques may no longer be an option. With liver and lung metastases being common problems, and brain metastases being less common, but potentially devastating, there is clearly a need for new, more effective therapeutic measures, especially for those patients who have metastatic spread of their tumors (Gleisner et al. 2008, Onaitis et al. 2009).

Among the therapeutic possibilities currently being explored for colorectal cancer, as well as other solid tumors, those that involve cellular biological control mechanisms are both appealing and promising. Many such modalities, such as induction of terminal differentiation, enhancement of growth-inhibitory (negative) feedback, selective programmed cell death (apoptosis), targeted insertion of viral or other genes into the proliferating cancer cell, and growth arrest at either the G1-S or G2-M checkpoints of the cell cycle, seem to be feasible with significant potential for clinical use (Littlepage et al 2007). Furthermore, studies have suggested that a subpopulation of cells within a tumor, i.e., the so-called cancer stem or progenitor cells, which have been described and characterized in certain tumor types such as those of the brain (glioma series), colon, and breast, may, in fact, be responsible for tumor survival, progression, resistance, and metastasis (Clark and Fuller 2006, Moore and Lemischka 2006). These cell populations may represent a novel and fundamental target for anti-neoplastic therapy.

The development of new and more effective therapeutic approaches to the treatment of neoplastic disease requires exploration into the nature of cancer and tumor cell growth. It is increasingly clear that cancer is not simply the result of a rogue mutated cell or clone of cells exhibiting unrestricted proliferative and metastatic behavior. Rather, cancer is itself a complex and multivariate biological system, in a sense a kind of (undesirable) organ or organ system. Adding to this complexity is the fact that the genomic patterns of the primary tumors may differ from among themselves within the same organ type and their metastases, but also the metastases may differ among themselves in this regard. Furthermore, cancer is not an entirely separate entity within the host, but rather dependent on complex interactions with the host as a whole and its own microenvironment, just as a normal organ is. The local microenvironment may, in fact, aid and abet the neoplastic cells, providing them with blood flow and nutrition. The "normal" host cells in the microenvironment may not be normal at all, but may become incorporated into the structure and workings of the tumor. In other words, the tumor is a heterogeneous collection of interdependent cells, the least desirable of which may be the frankly neoplastic cells.

The fact that cancer can be considered an alternative organ system, suggests that it should be subject to at least some of the same regulatory processes that govern normal, physiologic system function. One such process, the control of proliferation in a normal organ, is quite strict. Although it has long been thought that cancer cells and the tumors they form are not subject to the same regulatory growth-control feedback mechanisms as are normal cells and organs, increasing evidence suggests that they are subject to such regulation. Not surprisingly, an important signal in the growth-regulatory process for tumor cells is the mass of tumor present (Prehn 1991). Tumor growth slows as the mass of both primary and metastatic tumors increase (Keir CH, Ocean AJ, Fahey TJ, Berman N, Wadke A, Kelly-Rossini L, Goldstein MJ, Leeser DB, Michelassi F, Smith BH. Treatment of advanced, epithelial-derived cancer (AEC) with intraperitoneal implantation of agarose-agarose macrobeads (MB) containing mouse renal adenocarcinoma cells (RENCA). American Society of Clinical Oncology (ASCO) Annual 2011 Meeting; J Clin Oncol 29: 2011 (suppl; abstr e13594).

Laird 1965; Norton et al, 1976; Speer et al., 1984; Norton, 1988; Norton, 2008; Weedon-Fekjaer et al, 2008). Surgeons, for example, have observed that surgical excision of part of a tumor mass can be associated with rapid re-growth of the remaining tumor and distant metastases. The same phenomenon has been demonstrated in animal models of tumors (De Wys 1972, Fisher et al. 1989). In these studies, removal of the primary tumor at an early stage of development of the malignancy resulted in the appearance of dramatically greater numbers of distal metastases. Other work in breast cancer has confirmed and extended the understanding of growth control in tumors (Norton L, Simon R, Bereton HD, Bogden AE. Predicting the course of Gompertzian growth. Nature 1976:264:542-5.

Norton L. Gompertzian model of human breast cancer growth. Cancer Res 1988:48:7067-71.

Norton et al 2008). Taking these various findings into account, it is not unreasonable to argue that a promising therapeutic approach to the biological control of tumor growth could consist of "fooling" tumors into sensing that their mass is greater than it actually is, thereby slowing or halting tumor growth (Prehn, 1991).

The proposed cancer treatment to be evaluated in this study is based, at least in part, on the concept that tumor growth can be controlled by tumor mass or signals that indicate that such mass is present. In this case, the induction of inhibitory signals is brought about not by true tumor mass, but rather by placing cancer cells in a proliferation-restrictive hydrophilic matrix composed of agarose (Smith et al. 2011a, b). The release of such inhibitory signals from cancer cells in a proliferation-restrictive environment has been shown to inhibit the proliferation of freely growing cancer cells without specificity of species or target tumor cell type in both nonclinical and clinical studies.

Beyond the specifics of tumor growth inhibition by mass, it is important to add that the RENCA macrobead represents a complex biological system in and of itself. In its interactions with tumor cells outside the macrobead, whether *in vitro* or *in vivo*, this complex system interacts with the target neoplastic cells and tumors to produce a variety of inhibitory and stimulating actions that cause gene expression changes in the target cells. These changes range from the down-regulation of genes involved in DNA replication and angiogenesis to striking up-regulation of genes concerned with programmed cell death (apoptosis) so that tumor cell proliferation is inhibited and cell survival is shortened (Smith et al, 2011b). Thus, the RENCA macrobeads represent one cancer cell system trapped in an agarose matrix regulating the "behavior" of tumor cells outside the bead, suggesting a potentially new and important approach to biologically-based anti-cancer therapy.

1.2. Name and Description of Investigational Product

The investigational product to be used in this study is mouse RENCA cell-containing agarose-agarose macrobeads. Each RENCA macrobead is 6 to 8 mm and contains RENCA cells embedded in 1.0% Lonza HSB-LV agarose, surrounded by a second concentric layer made of 5.0% Lonza HSB-LV agarose layer. It should be noted that 150,000 RENCA are placed initially in each agarose-agarose macrobead and that an estimated 99% of these cells die off with one to two weeks, with the subsequent formation of colonies of tumor cells consisting of RENCA cells with stem cell properties and their daughter cells. It is when these colonies have formed that the macrobead produces the factor or factors that inhibit the growth of tumor cells outside the macrobead, both *in vitro* and *in vivo*.

1.3. Findings from Nonclinical and Clinical Studies

1.3.1. Summary of Nonclinical Studies

Nonclinical studies in mouse tumor models, both *in vivo* and *in vitro*, have indicated statistically significant activity of the RENCA macrobeads with respect to suppression of tumor growth.

RENCA macrobead-conditioned medium demonstrated growth inhibition of human epithelial cell lines including prostate cancer cells (36% to 40%), bladder cancer cells (17% to 43%), and colorectal cancer cells (43 to 58%), demonstrating that the inhibitory effect of RENCA macrobeads operates across species lines and is not specific to tumor cell type (Smith et al. 2011a).

In mice injected with RENCA tumor cells under the renal capsule, animals which were implanted with 4 RENCA macrobeads had significantly smaller tumors (30% to -60%) compared with those implanted with empty macrobeads or sham surgery (Smith et al. 2011a). When implanted in the peritoneal cavity of 11 dogs with prostate adenocarcinoma, RENCA macrobeads significantly extended survival compared with no treatment (177 days vs 21 to 30 days). Improvements in appetite and/or weight and activity level were observed in 39 of 51 cats and dogs after RENCA macrobead implantation. Long-term survivals without further macrobead treatment were also observed in these veterinary patients.

1.3.2. Summary of Clinical Studies

Two clinical studies with RENCA macrobeads have been initiated, one Phase I study and two Phase II studies.

1.3.2.1. Study RI-MB-101 (Formerly Known as Study 0407007343 and Including Study 0610008795)

Study RI-MB-101 (formerly known as Study 0407007343) was an investigator-sponsored, exploratory, Phase I, open-label study to evaluate the safety of RENCA macrobead implantation patients with a stage IV, treatment-resistant, epithelial-derived tumors. An exception protocol (Study 0610008795) was initiated to allow patients with non-epithelial-derived tumors to be included in Study RI-MB-101. Tumor types for patients enrolled in this study included colorectal carcinoma, gall bladder cancer, gastric carcinoma, pancreatic carcinoma, ovarian carcinoma, and non-small cell lung carcinoma. Each patient was scheduled for 1 implantation procedure; however, a maximum of 4 implants, no less than 120 days apart, was allowed on a case-by-case basis. Thirty-one patients underwent RENCA macrobead implantation (28 subjects with epithelial-derived tumors and 3 subjects with non-epithelial-derived tumors).

The mean (standard deviation [SD]) age of all patients was 59 (8.6) years. Similar numbers of men and women were enrolled (15 and 16, respectively). The number of RENCA macrobeads implanted was 8 or 16 macrobeads /kg body weight; the mean (SD) number of RENCA macrobeads implanted during the first implantation procedure was 661 (296.9) macrobeads /kg body weight. Twenty-three (74%) patients had a single implantation, and 8 (26%) patients had multiple implantations.

All 31 patients died. Median overall survival, measured as date of first implantation to date of death due to any cause, was 5.4 months (95% confidence interval [CI]: 2.2, 7.0 months) for all patients and 7.0 months (95% CI: 1.1, 9.7 months) for patients with colorectal cancer (n=12).

Most patients had increases in erythrocyte sedimentation rate (ESR), C-reactive protein (CRP), CA 125, and IL-6, levels after the implantation procedure, indicating a systemic inflammatory response. These values remained elevated for up to several weeks after the implantation procedure, but returned to baseline or near-baseline values by 90 days after implantation.
The RENCA macrobeads were generally well tolerated. No deaths or serious adverse events were considered related to the RENCA macrobead implantations. The most common adverse events that were considered related to study treatment involved systemic inflammation as the underlying problem (Keir et al, 2011).

1.3.2.2.Study RI-MB-201 (Formerly Known as Study 0911010739)

Study RI-MB-201 (formerly known as Study 0911010739) is an ongoing, Phase II, open label study to evaluate the efficacy and safety of RENCA macrobead implantation in patients with advanced pancreatic or colorectal cancer. Patients could have had a maximum of 4 implants, with a minimum of 90 days between each implant.

As of the data cutoff date of 9 April 2013, 46 patients had undergone RENCA macrobead implantation, 30 patients with colorectal and 16 patients with pancreatic cancer.

The mean (SD) age of all patients was 59 (8.9) years. The number of RENCA macrobeads implanted was 8 macrobeads /kg body weight; the mean (SD) number of macrobeads implanted during the first implantation procedure was 617 (136.1) macrobeads. Thirty-three (72%) patients had a single implantation, and 13 (28%) patients had multiple implantations.

Overall survival was defined as the date of first implantation to date of death due to any cause. Overall, 36 (78%) patients died. Median overall survival was 5.6 months (95% CI: 4.2, 8.7) for the combined analysis of the colorectal and pancreatic patients. Twenty-two (76%) patients with colorectal cancer died, and median overall survival of patients with colorectal cancer was 7.2 months (95% CI: 5.0, 12.3). Among patients with colorectal cancer, product-limit median survival was 10.1 months (95% CI: 4.3, 13.5) for patients who had a tumor marker response* compared with 5.6 months (95% CI: 2.4, 6.0 months) for patients who did not have a tumor marker response (p=0.51, log-rank test).

No new safety or tolerability concerns were discovered during this study (Ocean et al, 2013).
* Tumor marker response was defined as a 20% or greater decrease in either or both CEA and CA 19-9 levels within the first thirty days after implantation.

1.4. Known Benefits and Risks

Treatment with RENCA macrobeads has been shown to increase survival in patients who have an increase in ESR, CRP, and interleukin 6 (IL-6) levels and a concurrent decrease in tumor markers (Ocean et al. 2013). Implantation with RENCA macrobeads has also

been associated with tumor necrosis in patients with longer overall survival after 1 implantation. RENCA macrobeads have been generally well tolerated with no treatment-related adverse events of Grade 3 or higher being reported in clinical studies.

The surgical procedure required for implantation of RENCA macrobeads in the peritoneal cavity is simple and minimally invasive as it is performed by laparoscopy. There are risks associated with any surgical procedure, including those related to anesthesia, infection, and bleeding, and with laparoscopic surgery, in particular, accidental damage to the bowel or blood vessels within the abdomen. The screening process will take into account individual patient risk factors, and patients with any condition that makes them an unsuitable surgical candidate will not be enrolled.

As with any xenograft procedure, allergic reaction to foreign antigens (in this case, mouse antigens) is a potential risk (Chapman et al 1995). Patients who undergo RENCA macrobead implantation will have skin testing performed during their participation in the study to detect an allergy to mouse antigens.

Theoretically, there is a potential for transmission of a murine virus to a patient implanted with RENCA macrobeads. However, the only virus identified to date in the RENCA cell line is the ecotropic (non-xenotropic) variant of the murine leukemia virus (eMuLV), an endogenous retrovirus that is not known to infect human cells (National Research Council, 1991). Precautions taken to avoid transmission of a murine virus include screening for known murine viruses, including those that present a possible risk of infection for humans and routine testing for microbiological contaminants, during their maintenance in culture as well as after their incorporation into the RENCA macrobeads. It is important to note that no evidence of viral or other infection related to RENCA macrobead implantation has been observed in any of the animals or clinical study patients who have undergone RENCA macrobead implantation over the past 8 years.

1.5. Justification for Dose Selection

In the Phase I, open-label study of RENCA macrobead implantation in 31 patients with end-stage, treatment-resistant tumors, single implantations of 8 macrobeads /kg body weight were determined to be well tolerated when implanted in the abdominal cavity. RENCA macrobeads in the amount of 16 macrobeads/kg body weight were also determined to be well tolerated, but did not appear to offer any additional treatment effect. Therefore, the amount of RENCA macrobeads to be implanted in patients in this study will be 8 macrobeads /kg body weight. Both dose levels were derived from the animal studies summarized above (see Section 1.3.1 above).

RENCA macrobeads have been shown to produce an inhibitory effect for at least 3 years *in vitro* and up to 6 months *in vivo* animal studies. Data from the Phase I clinical trial indicate that RENCA macrobeads have a functional longevity of 3 to 4 months in the human peritoneal cavity, Therefore, the minimum time between successive RENCA macrobead implantations in this study will be no less than 90 days.

A maximum of 4 RENCA macrobead implantations has its basis in results from the veterinary patient studies and previous human clinical studies in which the majority of

patients had 1 or 2 implantations. This number is also considered sufficient to provide potential benefit to patients with advanced disease and lack of other treatment options.

1.6. Compliance Statement

This study will be conducted in compliance with the United States IND regulations (21 Code of Federal Regulations [CFR] Parts 50, 54, 56, 312, and 314), International Conference on Harmonization (ICH) Guidance for Industry, E6 Good Clinical Practice (GCP), the Nuremberg Code, and the most recent guidelines of the Declaration of Helsinki.

1.7. Population to be Studied

A total of 120 patients with treatment-resistant, metastatic colorectal cancer will be entered in the study. Forty patients will undergo RENCA macrobead implantation and 80 patients will receive, or are receiving, best supportive care.

2. STUDY OBJECTIVES AND ENDPOINTS

2.1. Primary Objective

The primary objective of this study is to evaluate the efficacy of RENCA macrobead implantation compared with that seen with best supportive care, as assessed by overall survival, in patients with treatment-resistant, metastatic colorectal carcinoma.

2.2. Secondary Objectives

Secondary objectives, defined only for patients with treatment-resistant, metastatic colorectal carcinoma who undergo RENCA macrobead implantation (i.e., Group A), are to determine or evaluate the effect of RENCA macrobead implantation on the following variables:

- change from baseline over the period after the first RENCA macrobead implantation in clinical status, as measured by Eastern Cooperative Oncology Group (ECOG) performance status score and global clinical assessment
- change from baseline over the period after the first RENCA macrobead implantation in quality of life, as measured by the European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire (EORTC QLQ-C30) and Karnofsky Performance Status Scale
- change from baseline over the period after the first RENCA macrobead implantation in erythrocyte sedimentation rate (ESR) and C-reactive protein (CRP) levels. CA-125 will also be used as a marker of inflammation, especially that localized in the peritoneal cavity.
- change from baseline over the period after the first RENCA macrobead implantation in levels of tumor markers (including carcinoembryonic antigen [CEA] and carbohydrate antigen 19-9 [CA19-9])
- tumor marker response rate, defined as the proportion of patients who have a decrease from baseline of 20% or more in CEA or CA 19-9 values
- change from baseline over the period after the first RENCA macrobead implantation in circulating tumor cells (CTCs)
- safety and tolerability of RENCA macrobeads, as measured by the following:
    - adverse events
    - clinical laboratory tests, including chemistry, hematology, coagulation, urinalysis, and PCR-based testing for presence of ecotropic murine leukemia virus (eMuLV) in serum
    - murine allergen skin test

3. INVESTIGATIONAL PLAN

3.1. Overall Study Design

This is a Phase IIb, multicenter, nonrandomized, open-label study with RENCA macrobeads in patients with treatment-resistant, metastatic colorectal carcinoma to determine the effect of RENCA macrobead implantation on overall survival compared with best supportive care.

Two treatment groups will be enrolled in this study, as follows:

- Group A (n=40) – patients who will undergo up to 4 implantations of RENCA macrobeads, at an amount of 8 RENCA macrobeads /kg body weight
- Group B (n=80) – patients who will receive or are receiving best supportive care, defined as management of symptoms aimed at maintaining or improving quality of life, but not including approved therapies targeting the patient's malignancy

For patients in Group A, the study will consist of a screening period lasting up to 30 days, up to 4 RENCA macrobead implantation procedures at least 90 days apart, and a 90-day follow-up period after the final implantation procedure. Patients will be expected to participate in a long-term follow-up period until death. RENCA macrobead implantation procedures may be delayed at the investigator's discretion, by patient decision, or due to initiation of another approved or experimental therapy other than localized radiation for symptom relief or therapeutic or palliative surgery (see Section 5.4.2). No maximum period between implantation procedures will be defined, and patients having treatment delays will not be discontinued from the study. However, if more than 30 days pass between a Day 90 visit and Day 0 of a subsequent implantation, patients will have re-screening assessments performed to ensure continued eligibility. Re-screening assessments will not include administration of informed consent, review of medical history, or murine allergen skin test. Inclusion/exclusion criteria do not have to be applied at this time. However, patients must continue to be surgical candidates, as per the medical judgment of the investigator and surgeon and consistent with the standards of optimal patient care.

After informed consent has been obtained, patients in Group A will undergo screening/baseline assessments. For eligible patients, the first procedure to implant RENCA macrobeads into the peritoneal cavity will be scheduled for Day 0. Patients will be expected to return to the clinic on Days 14, 30, 60, and 90 after each RENCA macrobead implantation procedure for efficacy, exploratory, and safety assessments. Up to 3 additional (for a total of 4) RENCA macrobead implantation procedures will be performed dependent on the patient's disease state and at the investigator's discretion.

Patients will be considered for enrollment in Group B only if they have already decided independently of this study not to pursue therapeutic treatment of their cancer. For patients in Group B, the study will consist of administration of informed consent, which will include permission to review medical records and record relevant medical information, agreement to be followed for survival, and evaluation of the appropriate

inclusion/exclusion entry criteria. Patients in Group B will not have any subsequent assessments performed as part of this study.

It is expected that study centers will enroll patients in either Group A or Group B, but not necessarily both treatment groups.

3.2. Measures and Endpoints

3.2.1. Efficacy Measures and Endpoints (All Patients)

For all patients, the primary efficacy variable is overall survival, defined as the time interval from the date of radiographically documented disease progression to the date of death due to any cause. Secondary efficacy measurements include assessment of clinical status (ECOG performance status score and global clinical assessment) and quality of life assessments (EORTC QLQ-30 and Karnofsky Performance Status Scale).

3.2.2. Exploratory Measures and Endpoints (Group A)

For patients in Group A, exploratory measures and endpoints are as follows:

- ESR, CRP, and CA 125 levels at Days 14, 30, 60, and 90 after each RENCA macrobead implantation
- Tumor marker (including CEA and CA19-9) levels at Days 14, 30, 60, and 90 after each RENCA macrobead implantation
- CTCs at Day 90 after each RENCA macrobead implantation
- Immunoglobulin (IgA, IgE, IgG, and IgM) levels at Day 90 after each RENCA macrobead implantation
- Cellular immune function, as measured by T cell count; B cell count, NK cell counts (e.g., CD16 count), at Day 90 after each RENCA macrobead implantation
- Characterization of tumor changes at Day 90 after each RENCA macrobead implantation using PET-CT scans
- Appropriate histopathological analysis of tumor biopsy samples, when medically indicated and at the investigator's discretion
- Examination of tumor state and any inflammatory or connective tissue reaction to the RENCA macrobeads after autopsy, if applicable

3.2.3. Safety Measures and Endpoints (Group A)

For patients in Group A, the safety of treatment with RENCA macrobeads will be assessed as follows:

- Monitoring of adverse events throughout the study
- Clinical laboratory tests (including chemistry, hematology, coagulation, urinalysis) at Days 14, 30, 60, and 90 after RENCA macrobead implantation
- eMuLV test at Days 30 and 90 after RENCA macrobead implantation
- Vital signs measurements at Days 14, 30, 60, and 90 after RENCA macrobead implantation

- Physical examinations at Days 14, 30, 60, and 90 after RENCA macrobead implantation
- 12-lead ECG at Day 90 after RENCA macrobead implantation
- Chest x-ray at Day 90 after RENCA macrobead implantation
- Murine allergen skin test at Day 90 after RENCA macrobead implantation

3.3. Measures Taken to Avoid Bias

This study has a nonrandomized, open-label design. Previous clinical studies with RENCA macrobead implantation have not included a control group, primarily because a blinded placebo control is not feasible with the surgical procedure required for treatment with RENCA macrobeads. In this study, RENCA macrobead implantation will be compared to best supportive care with regard to overall survival as the primary endpoint. Secondary efficacy parameters will also be evaluated as specified in section 2.2.

In addition, the advanced disease state that characterizes the patient population selected for this study precludes the use of an active control since no alternative therapies exist currently. Patients considered for RENCA macrobead implantation will be those patients who are seeking alternative treatment for their disease. Patients in the best supportive care treatment group will have already decided independently of this study that they are not seeking additional treatment for their disease. Randomization of patients into 1 of the 2 treatment groups would take away the patient's decision to seek or not to seek further treatment and would have unacceptable ethical implications. The survival of the best supportive care group (Group B) will be compared to Group A using the inclusion/exclusion criteria of the protocol and propensity score matching statistical techniques in accord with best statistical practice and draft FDA guidance and consultation.

Comparison of RENCA macrobead implantation and best supportive care, where applicable and using appropriate statistical methods referred to above, will allow for an informative statistical analysis of the efficacy data collected during this study and will provide a context for data collected in previous studies.

3.4. Study Treatment and Dosage

The investigational product to be used in this study is mouse RENCA cell-containing agarose-agarose macrobeads. Each RENCA macrobead is 6 to 8 mm and contains RENCA cells embedded in 1.0% Lonza HSB-LV agarose, surrounded by a second concentric layer made of 5.0% Lonza HSB-LV agarose layer. It should be noted that 150,000 RENCA are placed initially in each agarose-agarose macrobead and that an estimated 99% of these cells die off with one to two weeks, with the subsequent formation of colonies of tumor cells consisting of RENCA cells with stem cell properties and their daughter cells. It is when these colonies have formed that the macrobead produces the factor or factors that inhibit the growth of tumor cells outside the macrobead, both *in vitro* and *in vivo*.

The amount of RENCA macrobeads to be surgically implanted in each patient will be 8 macrobeads /kg body weight. Only patients in Group A will undergo implantation with RENCA macrobeads.

The RENCA macrobeads are prepared, counted, and packaged in vials at The Rogosin Institute, Xenia Division (Xenia, Ohio) for each individual patient scheduled for an implantation procedure. An extra vial containing 10 RENCA macrobeads will be included with each shipment. The label on each package of RENCA macrobeads contains the following information: patient number, lot number, date of production, date of shipment, and intended implant date. The RENCA macrobeads are then sent by courier to the study center to be available the night before the scheduled day of implantation. After the RENCA macrobeads arrive, they are stored at room temperature until implanted, which should occur within 24 hours after receipt. If the RENCA macrobeads are not used within the designated 24-hour period, they are to be returned to The Rogosin Institute, Xenia Division.

More information regarding the implantation procedure is provided in Section 5.1.

3.5. Duration of Patient Participation

Patients in Group A are expected to participate in a screening period lasting a maximum of 30 days, a treatment period including up to 4 RENCA macrobead implantation procedures no less than 90 days apart (and no maximum period between implantations defined), a follow-up period after the last implantation procedure lasting 90 days and a long-term follow-up period lasting the duration of their lives. Not including the long-term follow-up period, the total expected duration is a minimum of 120 days (for 1 implantation procedure) or 390 days (for 4 implantation procedures).

Patients in Group B are expected to participate in this study for the duration of their lives, though no active participation is required.

3.6. Stopping Rules and Discontinuation Criteria

3.6.1. Stopping Rules

If the sponsor, investigator, study monitor, Data Safety Monitoring Board (DSMB) (see also Section 7), or officials from the Food and Drug Administration (FDA) discover conditions arising during the study that indicate that the study should be halted or that the study center should be terminated, this action may be taken after appropriate consultation between the sponsor and investigator. Conditions that may warrant termination of the study include, but are not limited to, the following:

- The discovery of an unexpected, serious, or unacceptable risk to the patients enrolled in the study
- A decision on the part of the sponsor to suspend or discontinue testing, evaluation, or development of the product

Conditions that may result in termination of participation by a particular study center may include, but are not limited to, the following:

- Failure of the investigator to enroll patients into the study at an acceptable rate
- Failure of the investigator to comply with pertinent FDA regulations
- Submission of information known to be false from the research facility to the sponsor, study monitor, or the FDA
- Insufficient adherence to protocol requirements

3.6.2. Discontinuation Criteria

Study termination and follow-up would be performed in accordance with 21 CFR 312.50 and 21 CFR 312.56.

For individual patients in Group A, it is planned that the RENCA macrobeads will remain in the peritoneal cavity for the life of the patient unless it is considered in the best interest of the patient to consider removal of the macrobeads. Removal of RENCA macrobeads may be considered for reasons including, but not limited to, the following:

- Evidence of active infection by eMuLV, as evidenced by a viral load detected through RT-PCR
- Occurrence of a Grade 4 or Grade 5 adverse event that is considered unexpected and related to the RENCA macrobeads
- Occurrence of a Grade 3 or higher chronic peritonitis reaction, as described in the National Cancer Institute Common Terminology Criteria for Adverse Events, version 4.0 (NCI CTCAE v4.0):
    - Grade 3 – symptomatic and severely altered gastrointestinal function (e.g., inadequate oral caloric or fluid intake); intravenous fluids, tube feedings, or total parenteral nutrition indicated for more than 24 hours
    - Grade 4 – life-threatening consequences

3.7. Clinical Supplies and Accountability

The investigator must maintain accurate records of receipt of the RENCA macrobeads, inventory at the site, use by each patient, and the prompt return of unused supplies. These records must include dates, quantities, and batch numbers.

3.8. Study Procedures

A schedule of study procedures for patients in Group A is provided in Table 1.

Participation in the study by patients in Group B will consist of administration of informed consent, which will include permission to review medical records and record relevant medical information, agreement to be followed for survival, and review of entry criteria. Patients in Group B will not have any assessments performed as part of this study.

Table 1: Schedule of Study Procedures

	Screening/Re-screening[a]/ Baseline	Active Treatment (Implants 1, 2, 3, and 4)					Long-Term Follow-Up[b]
	Days –30 to –1	Day 0	Day 14±3	Day 30±5	Day 60±5	Day 90±5	
Visit number		*1, 6, 11, 16*	*2, 7, 12, 17*	*3, 8, 13, 18*	*4, 9, 14, 19*	*5, 10, 15, 20*	
Procedure							
Informed consent	X[a]						
Inclusion/exclusion criteria	X[a]						
Medical history, including prior anticancer treatments	X[a]						
Physical exam, including weight, and height (height at screening/baseline only)	X		X	X	X	X	
Vital signs[c]	X	X	X	X	X	X	
12-Lead ECG	X					X	
Chest x-ray	X					X	
Viral screening (HIV, hepatitis B, C, E)	X						
Pregnancy test (females of childbearing potential only)	X[d,e]						
Chemistry[f]	X		X	X	X	X	
Hematology[g]	X		X	X	X	X	
Coagulation (PT, PTT, INR)	X		X	X	X	X	
Urinalysis[h]	X					X	
eMuLV	X			X		X	X
Murine allergen skin test	X[a]					X	
CRP, ESR, CA 125	X		X	X	X	X	
Tumor markers (CEA, CA19-9)	X		X	X	X	X	
Circulating Tumor Cells (CTCs)	X					X	
Immunoglobulins (IgA, IgE, IgG, IgM)	X					X	
Cellular immune function[i]	X					X	
PET-CT for assessment of tumor changes[j]	X					X	
ECOG Performance Scale	X		X	X	X	X	
Global clinical assessment	X		X	X	X	X	
EORTC QLQ-C30	X		X	X	X	X	
Karnofsky Performance Status Scale	X		X	X	X	X	
Macrobead implantation[k]		X					
Tumor mass biopsy[l]		X					
Concomitant medications	X	X	X	X	X	X	
Adverse events	X	X	X	X	X	X	

[a] If more than 30 days pass between a Day 90 visit and Day 0 of a subsequent implantation, patients will have re-screening assessments performed to ensure continued eligibility. Re-screening assessments will not include administration of informed consent, review of medical history, or murine allergen skin test. Inclusion/exclusion criteria do not have to be verified in their entirety; however, patients must continue to be surgical candidates, as deemed by the investigator.
[b] Additional procedures may be performed at long-term follow-up visits, as clinically indicated. Long-term follow-up visits will occur every 6 months (±14 days) for 2 years, then every year (±1 month) thereafter until death to determine overall survival status, to test for the presence of eMuLV, and to determine whether any adverse events that would be considered related to the RENCA macrobeads occurred.
[c] Vital signs measurements include blood pressure, pulse, respiration rate, and temperature.
[d] A serum pregnancy test will be performed at baseline screening/re-screening baseline visits.
[e] If the screening serum pregnancy test result was obtained more than 2 weeks before Day 0 of each implant, then a urine pregnancy test must be done 2 days prior to the planned laparoscopic procedure. If this has not been (or cannot be done) done, the procedure should be postponed until the result is available and the patient can be cleared for surgery based on a negative result.
[f] Chemistry parameters include AST, ALT, GGT, lactate dehydrogenase, alkaline phosphatase, total bilirubin, direct bilirubin, albumin, creatinine, BUN, total protein, glucose, carbon dioxide, sodium, potassium, chloride, and calcium. Amylase and lipase will be done at baseline. If within normal limits, they need not be repeated.
[g] Hematology parameters include WBC count, RBC count, hemoglobin, hematocrit, MCV, MCH, MCHC, RDW, platelets, and automated differential WBC.
[h] Urinalysis parameters include color, appearance, glucose, bilirubin, ketones, specific gravity, pH, blood, protein, urobilinogen, nitrite, leukocyte esterase, and urine sediments.
[i] Cellular immune function will be assessed by measuring the following: T cells; B cells, and NK cells (i.e., CD16 count).
[j] Additional imaging techniques (i.e., MRI, CT, sonography, bone scans, or x rays) may be performed for further assessment of tumor changes, as clinically indicated.
[k] All patients will receive antibiotic prophylaxis prior to the implantation procedure.
[l] At the investigator's discretion during the implantation procedure, tumor biopsy samples may be collected for appropriate, medically-indicated histopathological analysis.
ALT=alanine aminotransferase; AST=aspartate aminotransferase; BUN=blood urea nitrogen; CA19-9=carbohydrate antigen 19-9; CA125=carbohydrate antigen 125; CEA=carcinoembryonic antigen; CRP=C-reactive protein; CTCs=circulating tumor cells; ECG=electrocardiogram; ECOG=Eastern Cooperative Oncology Group; eMuLV=ecotropic murine leukemia virus; EORTC QLQ-C30=European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire; ESR=erythrocyte sedimentation rate; HIV=human immunodeficiency virus; Ig=immunoglobulin; IL-6=interleukin 6; INR=International Normalized Ratio; MCH=mean corpuscular hemoglobin; MCHC=mean corpuscular hemoglobin concentration; MCV=mean corpuscular volume; NK=natural killer; PET-CT=positron emission tomography-computed tomography; PT=prothrombin time; PTT=partial thromboplastin time; RBC=red blood cell; RDW=red blood cell distribution width; TNF=tumor necrosis factor; WBC=white blood cell.

3.8.1. Screening/Re-Screening/Baseline Visit

For patients in Group A, the screening/re-screening/baseline visit will occur within 30 days of Day 0 (day of implantation procedure). All of the following procedures or assessments will be performed at the screening/re-screening/baseline visit:

- Informed consent (not to be performed at the re-screening visit)
- Inclusion/exclusion criteria (not to be performed in entirety at the re-screening visit; patients must continue to be surgical candidates, as deemed by the investigator)
- Medical history (at the screening visit only)
- Physical examination, including height (baseline only) and weight
- Vital signs (blood pressure, pulse, respiration rate, and temperature)
- 12-lead ECG
- Chest x-ray
- Collection of blood samples
    - Viral screening for HIV and hepatitis B, C, and E
    - eMuLV test
    - Serum pregnancy test for women of childbearing potential only
    - Clinical laboratory tests (chemistry, hematology, coagulation)
    - CRP, ESR, CA 125
    - Tumor markers (CEA, CA19-9)
    - CTCs
    - IgA, IgE, IgG, and IgM
    - Cellular immune function (T cells; B cells, and NK cells [i.e., CD16])
- Collection of urine sample for urinalysis
- Murine allergen skin test (not to be performed at a re-screening visit)
- Assessment of tumor changes, using PET-CT scans (and additional imaging techniques [i.e., MRI, CT, sonography, bone scans, or x-rays], as clinically indicated)
- ECOG performance status
- Global clinical assessment
- EORTC QLQ-C30
- Karnofsky Performance Status Scale
- Concomitant medications
- Adverse events (re-screening only)

3.8.2. Day 0 (Day of Each Implantation Procedure)

Unless a serum pregnancy test result for females of childbearing potential in Group A only was obtained within the 2 weeks before Day 0, female patients of childbearing potential must have a urine pregnancy test performed 2 days prior to the RENCA macrobead implantation procedure or otherwise the procedure should be postponed until the result is available and negative for pregnancy. RENCA macrobeads implanted in the amount of 8 macrobeads per kilogram, based on the body weight obtained during the pretreatment evaluations. See also Section 5.1.

A review of concomitant medications and adverse events should be performed at this visit. Vital signs (blood pressure, pulse, respiration rate, and temperature) will also be measured.

At the investigator's discretion during the implantation procedure, tumor biopsy samples may be collected for appropriate, medically-indicated histopathological analysis.

3.8.3. Days 14, 30, and 60 After Implantation Procedure

For patients in Group A, the following assessments will be performed on Days 14 (±3), 30 (±5), and 60 (±5), unless otherwise noted:

- Physical examination, including weight
- Vital signs (blood pressure, pulse, respiration rate, and temperature)
- Collection of blood samples
    - Clinical laboratory tests (chemistry, hematology, coagulation)
    - eMuLV test (Day 30 only)
    - CRP, ESR, CA 125
    - Tumor markers (CEA, CA19-9)
- ECOG performance status
- Global clinical assessment
- EORTC QLQ-C30
- Karnofsky Performance Status Scale
- Concomitant medications
- Adverse events

3.8.4. Day 90 After Implantation Procedure

For patients in Group A, the following procedures or assessments will be performed at the Day 90 (±5) visit:

- Physical examination, including weight
- Vital signs (blood pressure, pulse, respiration rate, and temperature)
- 12-lead ECG
- Chest x-ray
- Collection of blood samples
    - Clinical laboratory tests (chemistry, hematology, coagulation)
    - eMuLV test
    - CRP, ESR, and CA 125
    - Tumor markers (CEA, CA19-9)
    - CTCs
    - IgA, IgE, IgG, and IgM
    - Cellular immune function (T cells; B cells, and NK cells (i.e., CD16])
- Collection of urine sample for urinalysis
- Murine allergen skin test

- Assessment of tumor changes using PET-CT scans (and additional imaging techniques [i.e., MRI, CT, PET-CT, sonography, bone scans, or x-rays], as clinically indicated)
- ECOG performance status
- Global clinical assessment
- EORTC QLQ-C30
- Karnofsky Performance Status Scale
- Concomitant medications
- Adverse events

3.8.5. Long-Term Follow-Up (Every 6 Months for 2 Years, Then Annually Thereafter)

For patients in Group A, long-term follow-up visits will occur every 6 months (±14 days) after the Day 90 visit following the last implantation procedure for 2 years and annually (±1 month) thereafter until death to test for presence of eMuLV, to determine overall survival status, and to determine whether any adverse events considered related to the RENCA macrobeads occurred.

Attempts to contact patients by telephone should be made on a regular basis as determined by the investigator to document survival.

4. SELECTION AND WITHDRAWAL OF PATIENTS

A total of 120 patients with treatment-resistant, metastatic colorectal carcinoma will be entered in the study at a maximum of 6 study centers in the US. Forty patients will undergo RENCA macrobead implantation, and 80 patients will receive or are receiving best supportive care. It is expected that study centers will enroll patients in either Group A or Group B and not necessarily both treatment groups.

4.1. Inclusion Criteria

4.1.1. Inclusion Criteria for All Patients

Patients in both treatment groups must meet all of the following criteria to be considered eligible to participate in the study:

1. Patients are adult men or women, aged 18 years or older, with histologically-confirmed, metastatic adenocarcinoma of the colon or rectum that is resistant to available treatment options, including at least two such options from available chemotherapy, targeted, and other regimens.
2. Patients have radiographically documented evidence of disease progression.
3. Patients have a life expectancy of at least 6 weeks, in the investigator's opinion, at the time disease progression is documented.
4. Patients are considered surgical candidates on the basis of co-morbidity risks, number and sites of metastases, and ability to withstand general anesthesia.
5. Patients are able to provide written informed consent.

4.1.2. Additional Inclusion Criteria for Patients Who Will Undergo RENCA Macrobead Implantation (Group A)

Patients in Group A must also meet all of the following additional criteria:

6. Patients have an ECOG performance status score of 0, 1, or 2.
7. Patients have adequate hematologic function, defined as follows:
   a. absolute neutrophil count (ANC) ≥1500 /mL
   b. hemoglobin ≥9 g/dL
   c. platelets ≥75,000 /mL
8. Patients have adequate hepatic function, defined as follows:
   d. bilirubin ≤1.5 times the upper limit of normal (x ULN)
   e. aspartate transaminase (AST) ≤3 x ULN, or ≤5 x ULN if liver metastases are present
   f. alanine transaminase (ALT) ≤3 x ULN, or ≤5 x ULN if liver metastases are present
9. Patients have adequate renal function, defined as creatinine ≤2.0 mg/dL.
10. Patients have adequate coagulation function, defined as follows:

g. International Normalized Ratio (INR) ≤1.5 or between 2 and 3 if the patient is receiving anticoagulation

h. partial thromboplastin time (PTT) ≤5 seconds above the ULN

Note: Patients receiving full-dose anticoagulation therapy must be receiving a stable dose of oral anticoagulant therapy or low-molecular-weight heparin.

11. Clinically significant toxic effects of chemotherapy (excluding alopecia), radiotherapy, hormonal therapy, or prior surgery must have resolved to Grade 1 or better, with the exception of peripheral neuropathy, which must have resolved to Grade 2 or better.
12. Female patients of childbearing potential must have a negative serum pregnancy test at screening (and a negative urine pregnancy test 2 days prior to the first and each subsequent macrobead implantation if the screening serum pregnancy test result was obtained more than 2 weeks before surgery); patients must agree to use a medically appropriate form of birth control (i.e., barrier method or abstinence) from screening throughout their participation in the study. Male patients and partners must agree to use condoms.

4.2. Exclusion Criteria

4.2.1. Exclusion Criteria for All Patients

Patients in both treatment groups who meet any of the following criteria will be excluded from participating in the study:

1. Patient has hepatic blood flow abnormalities, i.e., portal vein hypertension and thrombosis, and/or a large volume of ascites.

2. Patient has concurrent cancer of any other type, except skin cancers other than melanoma.

3. Patient has a positive test result for human immunodeficiency virus (HIV) or any hepatitis other than A at screening.

4. Patient is considered by the investigator to be unsuitable upon review of medical history, physical examination, or clinical laboratory test results.

4.2.2. Additional Exclusion Criteria for Patients Who Will Undergo RENCA Macrobead Implantation (Group A)

Patients in Group A who meet any of the following additional criteria will be excluded from participating in the study:

5. Patient received FDA-approved chemotherapy within 3 weeks of Day 0, or bevacizumab (or similar drugs) within 4 weeks of Day 0, or radiation therapy at any site within 4 weeks of Day 0.

6. Patient received investigational anticancer therapy within 4 weeks of Day 0.

7. Patient has a positive reaction to the skin test for allergy to mouse antigen (Greer Laboratories, Inc. product #E2 [mouse epithelia], Lenoir, NC).

8. Patient has a history of hypersensitivity reaction that, in the opinion of the investigator, poses an increased risk of an allergic reaction to the RENCA macrobeads, particularly any known allergy to murine antigens or body tissues.

9. The patient has an ongoing or active infection, symptomatic congestive heart failure, unstable angina pectoris, serious cardiac arrhythmias (with the exception of well controlled atrial fibrillation), active bleeding, or psychiatric illness, or social situations that could interfere with the patient's ability to participate in the study.

4.3. Withdrawal Criteria and Procedures

Patients can withdraw their consent to participate in the study without risk to their individual health care at any time. Patients in Group A may also be removed from consideration for RENCA macrobead implantation by the investigator or the sponsor at any time, if either determines that it is in the best interest of the patient.

If patients in Group A will no longer consider or be considered for RENCA macrobead implantation, they will be encouraged to continue in the 90-day follow-up period, which includes reporting of serious adverse events (see Section 7.1.5) and/or the long-term follow-up period. The primary reason for discontinuation of treatment with RENCA macrobeads will be recorded on the case report form (CRF).

Patients who do not complete the study will not be replaced.

5. TREATMENTS

5.1. Implantation of RENCA Macrobeads

The number of RENCA macrobeads to be surgically implanted in each patient in Group A is based on body weight and will be calculated as 8 RENCA macrobeads /kg body weight. Each patient will have up to 4 macrobead implantations, with at least 90 days between each implantation.

A patient's body weight as measured within 30 days of Day 0 (i.e., at the screening/baseline visit, a Day 90 visit following a previous implantation procedure, or a re-screening visit) will be used to calculate the amount of RENCA macrobeads to be implanted. The investigator will contact The Rogosin Institute, Xenia Division to request shipment of the RENCA macrobeads (see the Study Procedures Manual for details).

Patients will have a small abdominal incision(s) using laparoscopy under general anesthesia, as indicated. The location of the incision(s) will be at the investigator's discretion. Antibiotic prophylaxis should be administered before surgery, as consistent with standard of care.

The RENCA macrobeads will be placed into the peritoneal cavity. Once implanted, the beads should remain in a free-floating state in the intraperitoneal space. The macrobeads do not become vascularized, and thus remain as implants rather than true grafts.

Assuming a patient's post-surgical condition is stable, the patient will be discharged from the surgical recovery room to either home care or hospital admission, as medically indicated, which may be as soon as the same day as the procedure. Hospital admission postoperatively has not been necessary in any of the patients in the RI-MB-201 study.

5.2. Best Supportive Care

For patients in Group B, best supportive care is defined as management of symptoms aimed at maintaining or improving quality of life, but not including approved therapies targeting the patient's malignancies.

5.3. Treatment Compliance

For patients in Group A, compliance with the schedule of RENCA macrobead implantations will be dictated by a patient's ability to meet the clinical requirements for continued treatment and a patient's willingness to continue participation in the study.

The number of implantations and amount of macrobeads implanted will be recorded for each patient.

5.4. Concomitant Medications or Therapies

5.4.1. Prior and Concomitant Medications or Therapies

Medications taken within 30 days before Day 0 will be recorded in the CRF. In addition, patients' prior anticancer treatment will also be recorded.

Antibiotic prophylaxis will be administered prior to RENCA macrobead implantation.

All medications and other treatments taken by patients during the study will be recorded on the CRF.

5.4.2. Other Therapy During Implantation vs. Alternative Therapy

During their participation in this study, patients in Group A will be allowed to have local radiation for symptom relief and/or surgery for therapeutic or palliative purposes. Use of alternative therapy, including chemotherapy or a different investigational product of whatever nature may be indicated for disease progression. In that case, the subject will be removed from the active protocol and will not be eligible for further implantation.* Where procedures to provide palliation or symptom relief have been performed, any subsequent implantations, if indicated, will need to be scheduled at the discretion of the investigator and surgeon. Re-screening procedures to confirm continued eligibility of the subject may be required.

* Removal from the "active" protocol, i.e., that protocol involving continuing eligibility for macrobead implantation, for reasons of disease progression, medical decision, or voluntary patient withdrawal, does not mean complete "termination" since the protocol requires subsequent follow-up to determine the presence or absence of the RT-PCR of the presence of eMuLV DNA. Patients in this category have been released from the active protocol and should be considered "inactive," but subject to lifetime follow-up for viral; detection. "Inactive status" in this case does not require the recording of adverse events associated with other treatments or therapeutic procedures beyond 90 days from the last macrobead implant covered by this protocol.

6. ASSESSMENT OF EFFICACY

6.1. Primary Efficacy Measurement

For patients in Group A and Group B, the primary efficacy measurement is overall survival, defined as the time interval from the date of radiographically documented disease progression to the date of death due to any cause.

6.2. Secondary Efficacy Measurements

For patients in Group A, secondary efficacy measurements include clinician-rated assessments to evaluate clinical status (ECOG and global clinical assessment) and patient-rated assessments to evaluate quality of life (EORTC QLQ-C30 and Karnofsky Performance Status Scale).

6.2.1. Clinician-Rated Assessments of Clinical Status

6.2.1.1.Eastern Conference Oncology Group Performance Status

For patients in Group A, the ECOG performance score is determined by the investigator and ranges from 0 to 5, as follows (Oken et al. 1982):

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

6.2.1.2.Global Clinical Assessment

For patients in Group A, the global clinical assessment is performed by the investigator and measures clinical status using a visual analog scale.

6.2.2. Quality of Life (Patient-Rated Assessments)

6.2.2.1.European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire

For patients in Group A, the EORTC QLQ-C30, version 3.0 is a validated questionnaire completed by the patient and developed to assess quality of life in patients with cancer. It includes subscales measuring physical functioning, social functioning, emotional functioning, cognitive functioning, and role performance as well as subscales and single items assessing symptoms (e.g., fatigue, pain, nausea/vomiting), and financial impact of the disease.

6.2.2.2.Karnofsky Performance Status Scale

For patients in Group A, the Karnofsky Performance Status Scale ranges from 0 to 100, where 0 is death and 100 is perfect health, as follows (Karnofsky and Burchenal 1949).

100%	Normal, no complaints, no signs of disease
90%	Capable of normal activity, few symptoms or signs of disease
80%	Normal activity with some difficulty, some symptoms or signs
70%	Caring for self, not capable of normal activity or work
60%	Requiring some help, can take care of most personal requirements
50%	Requires help often, requires frequent medical care
40%	Disabled, requires special care and help
30%	Severely disabled, hospital admission indicated, but no risk of death
20%	Very ill, urgently requiring admission, requires supportive measures of treatment
10%	Moribund, rapidly progressive fatal disease processes
0	Death

6.3. Exploratory Assessments

For patients in Group A, exploratory assessments include measurement of ESR and CRP levels, tumor marker levels, CTCs, immunoglobulins, cellular immune function, examination of tumor changes, at the investigator's discretion during the implantation procedure, tumor biopsy samples may be collected for appropriate, medically-indicated histopathological analysis, and autopsy (for consenting patients only).

6.3.1. Erythrocyte Sedimentation Rate and C-Reactive Protein

For patients in Group A, erythrocyte sedimentation rate and CRP levels are nonspecific markers of inflammation and will be considered both safety and efficacy assessments. A rise in ESR and CRP levels that is temporally associated with an implantation procedure could be considered an indication of an inflammatory reaction to placement of the macrobeads in the intraperitoneal cavity.

6.3.2. Tumor Markers

For patients in Group A, blood samples will be collected for measurement of tumor markers CEA, CA19-9, and CA125. A decrease in tumor marker levels may be associated with a decrease in tumor activity and biological response. Although CA125 is often used as a tumor marker, for the purposes of this study, its levels will be used as an indication of an inflammatory reaction to placement of the macrobeads.

6.3.3. Circulating Tumor Cells

For patients in Group A, circulating tumor cells (CTCs) in blood will be measured throughout the study and allow for a noninvasive measure of disease status. They may also give some indication of prognosis.

6.3.4. Immunoglobulins

For patients in Group A, immunoglobulin levels will be used to measure the body's immune reaction to RENCA macrobead implantation. Immunoglobulins A, E, G, and M (IgA, IgE, IgG, and IgM) will be measured. A rise in specific immunoglobulin levels reflective of inflammation may be considered part of an inflammatory reaction to placement of the macrobeads in the intraperitoneal cavity. The immunoglobulin measurements are also important in evaluating the humoral immune status of the patient so that they are not only indicative of response to the macrobeads, but also the functional integrity of the humoral immune system after macrobead implantation.

6.3.5. Cellular Immune Function

For patients in Group A, the effect of implantation with RENCA macrobeads on cellular immune function will be assessed by measuring T cells, B cells, and NK cells (i.e., CD16) in blood. This evaluation is to determine both the functional level of this system and any possible stimulation or inhibition by the macrobeads.

6.3.6. Assessment of Tumor Changes

For patients in Group A, tumors will be assessed approximately every 90 days using PET-CT scans with fluorine deoxglucose. Tumor locations (primary and metastatic) volumes, and metabolic assessments (SUVs) will be assessed. Additional imaging techniques (i.e., MRI, CT, sonography, bone scans, and x-rays), may be performed for further assessment, as clinically indicated.

6.3.7. Tumor biopsies

For patients in Group A, at the investigator's discretion during the implantation procedure, tumor biopsy samples may be collected for appropriate, medically-indicated histopathological analysis. It should be emphasized that the performance of the tumor biopsies is not a requirement of the protocol.

6.3.8. Autopsy

Autopsies may be performed on patients in Group A who provide separate consent. However, consent to autopsy is not a condition for participation in the study. Patients may withdraw consent to have an autopsy performed at any time without risk to their participation in the study or medical care. A patient's decision to consent to have an autopsy performed will not be binding on family members, if they do not also agree to the autopsy.

Samples of tumor tissue (primary and metastatic sites), peritoneum, internal organ serosa, and underlying tissue may be taken during an autopsy to evaluate tumor state and any inflammatory or connective tissue reaction to the RENCA macrobeads. Standard histopathological and immunohistochemical analyses may be performed on the tissue obtained.

7. ASSESSMENT OF SAFETY

For patients in Group A, safety assessments will include monitoring of adverse events, clinical laboratory tests including eMuLV testing, vital signs measurements, physical examinations, 12-lead ECGs, chest x-rays, and murine allergen skin testing.

A DSMB will be established to ensure the safety of patients participating in this study. Details regarding the structure, function, and decision-making guidelines for the DSMB are provided in a separate DSMB charter.

7.1. Adverse Events

It is the responsibility of the investigator to document all adverse events that occur during the study.

7.1.1. Definition of an Adverse Event

For the purposes of this study, an adverse event is defined as the appearance of (or worsening of any pre-existing) undesirable sign(s), symptom(s), or medical condition(s) that occur after a patient's signed informed consent has been obtained. Abnormal laboratory values or test results occurring after informed consent constitute AEs only if they induce clinical signs or symptoms, are considered clinically meaningful, require therapy (e.g., hematologic abnormality that requires transfusion), or require changes in study drug treatment. Adverse events (including laboratory abnormalities that constitute adverse events) should be described using diagnosis whenever possible, rather than individual underlying signs and symptoms. When an abnormal laboratory or test result corresponds to a sign or symptom of a previously reported adverse event, it is not necessary to separately record the laboratory/test result as an additional event. Disease progression will not be captured as an adverse event.

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

7.1.2. Recording and Reporting of Adverse Events

Adverse events will be recorded and reported from the time of the patient's signed informed consent through 90 days after the last RENCA macrobead implantation procedure. The occurrence of adverse events should be sought by non-directive questioning of the subject. Adverse events may also be detected when they are volunteered by the subject. Treatment-emergent adverse events are defined as any adverse events that are reported after the first RENCA macrobead implantation procedure through 90 days after the last implantation procedure. An adverse event that occurs outside the reporting period, but in the opinion of the investigator, is related to the study treatment should be reported as described for a treatment-emergent adverse event.

All adverse events should be followed until the event has resolved, the condition has stabilized, or etiology of the event is determined to be not related to study treatment, or the patient is lost to follow-up. For each patient for whom an adverse event was reported that did not resolve before the end of the reporting period, follow-up information on the subsequent course of events must be submitted to the medical monitor. This requirement indicates that follow-up may be required for some adverse events after the patient has completed his/her participation in the study.

7.1.3. Severity of an Adverse Event

The severity of adverse events will be assessed by the investigator according to the NCI CTCAE v4.0. CTCAE Grade 5 (death) will be reported as per DSMB, IRB, and FDA guidelines and, of course, will be used to define the time interval from baseline to provide the survival period. It is to be reported as an outcome and not as an adverse event per se. It is, however, maintained as part of the CTCAE Grades for purposes of completeness and accuracy of reporting. Of specific safety concern would be any death thought to be related directly to the implantation of the macrobeads themselves. If the severity of an adverse event is not described in the NCI CTCAE v4.0, the investigator will use the following scale to determine the severity.

Grade 1/mild:	transient or mild discomfort, no limitation in activity, and no medical intervention/therapy is required
Grade 2/moderate:	mild to moderate limitation in activity, some assistance may be needed, no or minimal medical intervention/therapy required
Grade 3/severe:	marked limitation in activity, some assistance usually required, medical intervention/therapy required, hospitalizations possible
Grade 4/life-threatening or disabling:	extreme limitation in activity, significant assistance required, significant medical intervention/therapy required, hospitalization or hospice care probable

Grade 5/death

When the intensity of an adverse event changes over time for a reporting period (e.g., between visits), each change in intensity will be reported as an adverse event until the adverse event resolves. For example, 2 separate adverse events will be reported if a subject experiences Grade 1 diarrhea for 3 days, meeting the definition of an adverse event, and then after 3 days the adverse event increases to a Grade 3 intensity that lasts for 2 days and then resolves. The Grade 1 event will be reported as an adverse event with a start date equal to the day the event met the adverse event definition and a stop date equal to the day that the event increased in intensity from Grade 1 to Grade 3. The Grade 3 event will also be reported as an adverse event with the start date equal to the day the event changed in intensity from Grade 1 to Grade 3 and a stop date on the day

that the event changed intensity again or resolved. For analysis purposes, this will be considered one AE for this subject and the maximum intensity will be recorded.

7.1.4. Relationship of an Adverse Event to the Study Treatment

The investigator will assess the relationship of each adverse event to treatment with RENCA macrobeads as unrelated or related.

An adverse event will be considered "not related" to the use of the investigational product if there is not a possibility that the event has been caused by the investigational product. Factors pointing toward this assessment include, but are not limited to, the lack of reasonable temporal relationship between administration of the investigational product and the event, the presence of a biologically implausible relationship between the investigational product and the adverse event (e.g., the event occurred before administration of the product), or the presence of a more likely alternative explanation for the adverse event (e.g., the underlying disease).

An adverse event will be considered "related" to the use of the investigational product if there is a possibility that the event may have been caused by the product under investigation. Factors that point toward this assessment include, but are not limited to, a reasonable temporal sequence between administration of the investigational product and the event, a known response pattern of the investigational product, a biologically plausible relationship between the product and the adverse event, or a lack of an alternative explanation for the adverse event (e.g., the underlying disease).

7.1.5. Serious Adverse Events

7.1.5.1. Definition of a Serious Adverse Event

A serious adverse event (experience) or reaction is any untoward medical occurrence that, at any dose, meets any of the following criteria:

- is fatal or life-threatening (i.e., immediate risk of dying)
- results in persistent or significant disability/incapacity
- constitutes a congenital anomaly or birth defect
- is clinically meaningful, (i.e., defined as an event that jeopardizes the subject or requires potential medical or surgical intervention to prevent 1 of the outcomes listed above), or is considered meaningful by the investigator as an important medical event that may not result in death, be life-threatening, or require hospitalization, but may be considered a serious adverse event when, based upon appropriate medical judgment, it may jeopardize the subject or may require medical or surgical intervention to prevent 1 of the outcomes listed in this definition
- requires in-patient hospitalization or prolongation of existing hospitalization, unless hospitalization is due to one of the following reasons:
    - routine treatment or monitoring of the studied indication, not associated with any deterioration in condition, or elective or pre-planned treatment

for a pre-existing condition that is unrelated to the indication under study and has not worsened since signing the informed consent form
- treatment on an emergency outpatient basis for an event not fulfilling any of the definitions of a serious adverse event given above and not resulting in hospital admission
- social reasons and respite care, in the absence of any deterioration in the subject's general condition
- any serious adverse events that are expected because of the condition being treated, including if the serious adverse event is a primary outcome measure, and whether there has been a clear agreement with regulators not to consider these as serious adverse events, provided the information is collected elsewhere

Medical and scientific judgment should be exercised in deciding whether expedited reporting is appropriate in other situations, such as important medical events that may not be immediately life-threatening or result in death or hospitalization but may jeopardize the patient or may require intervention to prevent one of the other outcomes listed in the definition above. These events should also usually be considered serious.

7.1.5.2.Reporting a Serious Adverse Event

Every serious adverse event, regardless of suspected causality, occurring after the subject has signed informed consent and up to 90 days after the last RENCA macrobead implantation, must be reported to the sponsor or designee within 24 hours of learning of its occurrence. Any serious adverse events experienced after this period should be reported to the Sponsor, or designee, only if the investigator suspects a causal relationship to the study mediation. Recurrent episodes, complications, or progression of the initial SAE must be reported as follow-up to the original episode within 24 hours of the investigator receiving the follow-up information. A serious adverse event occurring at a different time interval or otherwise considered completely unrelated to a previously reported one should be reported separately as a new event. Previously planned surgeries should not be reported as serious adverse events unless the underlying medical condition worsens over the course of the study. All patients (including discontinued patients) with a serious adverse event must be followed until the event resolves or reaches a new baseline, but for a minimum of 90 days after the last implantation procedure. A serious adverse event that occurs outside the reporting period after completion of the study, but in the opinion of the investigator, is related to the study treatment should be reported as described for a serious adverse event.

Investigators should not wait to receive additional information to fully document the event before notifying the sponsor of a serious adverse event. The telephone report should be followed by full written summary detailing relevant aspects of the serious adverse event in question. Where applicable, information from relevant hospital case records and autopsy reports should be obtained. The serious adverse event should also be recorded on the adverse event page of the patient's CRF. If additional information becomes available, follow-up reports must be submitted no more than 7 days after receipt.

Contact telephone and facsimile numbers for serious adverse event reporting will be provided separately.

If the serious adverse event is not previously documented in the Investigator's Brochure for the study drug (new occurrence) and is thought to be related to study treatment, the sponsor may urgently require further information from the investigator for reporting to local regulatory authorities.

Serious adverse events that are considered to be unexpected and related to study treatment will be reported by the sponsor to the FDA, and all participating investigators shall be notified no later than 15 calendar days from the "date learned" of the event. Investigators are responsible for reporting all serious adverse events to their IRB in accordance with local regulations.

7.2. Clinical Laboratory Parameters

For patients in Group A, clinical laboratory tests will include chemistry, hematology, coagulation, urinalysis, and eMuLV. Details of processing, storage, and shipping of samples are provided in a separate Laboratory Manual.

7.2.1. Chemistry, Hematology, Coagulation, and Urinalysis

Chemistry, hematology, coagulation, and urinalysis parameters are listed in Table 2.

Table 2: Chemistry, Hematology, Coagulation, and Urinalysis Parameters

Chemistry	Hematology	Urinalysis
Metabolic glucose carbon dioxide sodium potassium chloride calcium **Hepatic Function** aspartate aminotransferase (AST) alanine aminotransferase (ALT) gamma glutamyltransferase (GGT) lactate dehydrogenase alkaline phosphatase total bilirubin direct bilirubin total protein albumin **Renal Function** creatinine blood urea nitrogen (BUN)	Complete Blood Count (CBC) with differential platelets **Inflammation:** CRP ESR CA 125 **Tumor Markers:** CEA CA 19-9 **Coagulation** Partial thromboplastin time (PTT) Prothrombin time (PT) International Normalized Ratio (INR)	Color appearance glucose bilirubin ketones specific gravity pH blood protein urobilinogen nitrite leukocyte esterase urine sediments

amylase (if clinically indicated) lipase (if clinically indicated)		

7.2.2. Ecotropic Murine Leukemia Virus

For patients in Group A, blood samples will be collected for analysis by a validated reverse transcriptase polymerase chain reaction (RT-PCR)-based assay o detect the presence of eMuLV gene sequences. Over the past eight years of human implantation, the presence of eMuLV sequences has not been documented in any patient, and there have been no clinical symptoms, signs or other evidence of transmission of, or infection with, the eMuLV in any patient.

eMuLV is not known to infect human cells (National Research Council, 1991).

7.3. Vital Sign Measurements

For patients in Group A, vital signs measurements include blood pressure, pulse, respiration rate, and temperature.

7.4. Physical Examinations

For patients in Group A, complete physical examinations will be performed and will include a neurological examination, weight, and height (height to be measured at the screening/baseline visit only). Any abnormalities noted at a post-baseline visit that were not present at screening/baseline should be recorded as adverse events. Weight and height (the latter at baseline only) should be recorded as part of the physical examination.

7.5. Electrocardiograms

For patients in Group A, 12-lead ECGs will be performed, and rhythm results will be recorded as normal, abnormal but not clinically significant, or abnormal and clinically significant.

7.6. Chest X-Rays

For patients in Group A, chest x-rays will be performed, and results will be reported as normal, abnormal but not clinically significant, or abnormal and clinically significant.

7.7. Other Safety Assessments

For patients in Group A, a standard skin test for hypersensitivity response to murine allergens will be performed to ensure that patients do not have an allergy to murine antigens, cells or tissues.

8. STATISTICAL METHODOLOGY

This is a Phase IIb, multicenter, nonrandomized, open-label study to evaluate the safety and efficacy of RENCA macrobead implantation in patients with metastatic, treatment-resistant colorectal carcinoma. The primary efficacy variable is overall survival at 12 months after the last RENCA macrobead implantation, which will be compared between patients who undergo RENCA macrobead implantation (Group A) and patients who receive best supportive care (Group B). For patients in Group A, safety variables include monitoring of adverse events, clinical laboratory tests including testing for eMuLV, vital signs measurements, physical examinations, 12-lead ECGs, chest x-rays and murine allergen skin testing.

8.1. Determination of Sample Size

A total of 120 patients will be entered in this study, 40 patients who will undergo RENCA macrobead implantation (Group A) and 80 patients who will receive or are receiving best supportive care (Group B). For the primary outcome of overall survival, this sample size will provide at least 80% power to detect a hazard ratio of 0.505. For example, assuming a mortality rate of 60% in Group A at 12 months, the mortality rate in Group B would have to be no less than 74% at 12 months. This assumes balance between groups on factors that may be associated with mortality.

8.2. Criteria for Termination of the Study

Stopping rules are described in Section 3.6.1. No statistical criteria for termination of the study are defined.

8.3. Analysis Populations

The full analysis population will include all patients who were implanted with RENCA macrobeads (Group A) and all patients enrolled to receive best supportive care (Group B).

The all treated population will include all patients in Group A who were implanted with RENCA macrobeads.

8.4. Statistical Analysis Methods

All available data will be listed and summarized by treatment group (if applicable) and study visit. Data from unscheduled visits will be listed but may not be summarized or analyzed. Baseline will be defined as the most recent visit or observation before the first implantation. Secondary baselines may be similarly defined for each subsequent implantation. Categorical variables will be summarized using frequencies and percentages for each category. Continuous variables will be summarized using number of patients, mean, standard deviation, median, and range. All programs for data output and analyses will be written in Statistical Analysis System® (SAS) version SAS 9.1.3 or higher, or other specialized analysis software as appropriate (SAS Institute, Inc., Cary, NC). Additional analysis details will be described in the Statistical Analysis Plan (SAP).

For purposes of reporting results, the study will be considered complete 12 months after the last implantation procedure or when all patients have reached the primary endpoint (i.e., death) or have been lost to follow-up, whichever occurs first. If the last patient undergoes less than 4 implantation procedures, then the first, second, or third implantation procedure may be considered to be "the last implantation procedure" if more than 120 days pass before the subsequent procedure. This last patient would not be prohibited from undergoing a subsequent protocol-specified implantation procedure.

8.4.1. Study Population

In general, the full analysis population will be used for study population analyses. The all treated population will be used for those variables that were collected only for Group A.

Disposition of patients will include the numbers of patients in each analysis population, numbers and percentages of patients who discontinued treatment prior to receiving 4 implantations with RENCA macrobeads, and the reasons for discontinuing the study or study treatment (e.g., disease progression, adverse event, investigator decision, patient decision).

Demographics and baseline characteristics, medical history, and concomitant medications will be summarized using descriptive statistics or listed, as appropriate.

8.4.2. Efficacy Analyses

8.4.2.1.Primary Efficacy Analysis

The primary efficacy analysis will be performed using the all treated population.

For all patients, the primary efficacy variable, overall survival, is defined as the date of radiographically documented disease progression to date of death due to any cause assessed at 12 months after the last RENCA macrobead implantation.

Because treatment group assignment in this study is not randomized, balance of baseline covariates potentially related to both treatment and survival between Group A and Group B will be achieved through the use of propensity scores.

A propensity score for each patient will be defined as the probability of being in Group A given a vector of observed baseline covariates x_i and will be derived using logistic regression. Specifically, for a given patient i,

$$\text{probability}_i\,(\text{Group A} \mid \mathbf{x}_i) = [1 + \exp(-c + \mathbf{b}\mathbf{x}_i)]^{-1},$$

where c and **b** are the logistic regression parameter estimates.

The final propensity score model will be selected based on univariable relationships between covariates derived from the baseline characteristics (to be defined in the SAP) and group membership, collinearity among the candidate covariates, and number of patients enrolled (with the standard target of 10 patients per covariate) (Smith BH, Gazda

LS, Conn BL, et al. Three-dimensional culture of mouse renal carcinoma cells in agarose macrobeads selects for a subpopulation of cells with cancer stem cell or cancer progenitor properties. Cancer Res. 2011;71(3):716-724. (b)

Speer JF, Petrosky VE, Retsky MW, Wardwell RH. A stochastic numerical model of breast cancer growth that simulates clinical data. Cancer Res 1984: 44:4124-30.

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Weitzen et al. 2004). Additional details regarding choice of candidate covariates and specific use of propensity score in the survival analysis will be described in the SAP.

Estimated survival functions will be presented graphically. A proportional hazards model will be used to estimate and compare functions for overall survival for Groups A and B. Patients who are lost to follow-up before the time of the analysis endpoint (t_e) will be considered censored as of the day the patient was last known to be alive. Patients who are still alive as of t_e will be considered censored at t_e.

8.4.2.2.Secondary Efficacy Analyses

Secondary efficacy analyses will be performed using the full analysis population.

Secondary efficacy variables include the following:

- proportion of patients who show improvement in ECOG performance status score at any post-baseline time point
- proportion of patients who show improvement in the global clinical assessment at any post-baseline time point
- proportion of patients who show improvement in any subscale of the EORTC QLQ-30 at any post-baseline time point
- proportion of patients who show improvement in Karnofsky Performance Status Scale score at any post-baseline time point

The proportion of patients having improvement in ECOG performance status score at any time point will be summarized.

Global clinical assessment will be reported as the distance from the left endpoint to the clinician's mark divided by the total length of the horizontal line being marked. The proportion of patients having improvement in the global clinical assessment score will be summarized.

Observed values for responses to the EORTC QLQ-C30 will be used to calculate the derived scales for physical functioning, emotional functioning, cognitive functioning,

social functioning, role functioning, individual symptoms, and financial difficulties (Fayers et al. 2001). The proportion of patients having improvement in any of the derived scales of the EORTC QLQ-C30 at any time point will be summarized.

The proportion of patients having improvement at any time point in scores for the Karnofsky Performance Status Scale will be summarized.

8.4.2.3.Exploratory Analyses

For patients in Group A, exploratory variables include

- Change from baseline in ESR, CRP, and CA 125 levels at Days 14, 30, 60, and 90 after each RENCA macrobead implantation
- Change from baseline in tumor marker (including CEA and CA19-9) levels at Days 14, 30, 60, and 90 after each RENCA macrobead implantation
- Change from baseline in CTCs to Day 90 after each RENCA macrobead implantation
- Change from baseline in immunoglobulin (IgA, IgE, IgG, and IgM) levels at Day 90 after each RENCA macrobead implantation
- Change from baseline in cellular immune function, as measured by T cell count; B cell count, NK cell counts (e.g., CD16 count), at Day 90 after each RENCA macrobead implantation
- Characterization of tumor changes at Day 90 after each RENCA macrobead implantation using PET-CT scans
- At the investigator's discretion during the implantation procedure, tumor biopsy samples may be collected for appropriate histopathological analysis
- Examination of tumor state and any inflammatory or connective tissue reaction to the RENCA macrobeads after autopsy, if applicable

Exploratory analyses will be performed using the all treated population.

Observed values and changes from baseline in relation to the first implant and the most recent implant in ESR, CRP, CA 125 levels and immunoglobulin levels (IgA, IgE, IgG, and IgM) will be summarized using descriptive statistics.

Observed values and changes from baseline to each time point after each RENCA macrobead implantation in levels of tumor markers (CEA and CA19-9) will be summarized using descriptive statistics. The proportion of patients who have a tumor marker response (i.e., at least 20% decrease from baseline in CEA or CA19-9) will also be summarized.

Observed values and changes from baseline to each time point after each RENCA macrobead implantation in levels of CTCs, immunoglobulin levels (IgA, IgE, IgG, and IgM) and markers of cellular immune function (T cells, B cells, and NK cells [i.e., CD16 count]) will be summarized using descriptive statistics.

Characterization of tumor changes from baseline to 90 days after each RENCA macrobead implantation will be listed. Depending on available results, these data may be summarized.

Results of any histopathological analysis will be made part of the patient's permanent medical and protocol records.

Any autopsy results will also be made part of the patient's permanent medical and protocol records.

8.4.3. Safety Analyses

The entire treated population will be used for the analysis of all safety variables. Safety data will be summarized using descriptive statistics; no formal statistical analyses are planned.

8.4.3.1.Exposure to Study Treatment

Exposure to study treatment, i.e., number of implantations and numbers of macrobeads implanted, will be summarized using descriptive statistics.

8.4.3.2.Adverse Events

Adverse events will be coded using MedDRA (Medical Dictionary for Regulatory Activities) version 10.1 or later. A treatment-emergent adverse event will be defined as an adverse event that began or worsened after the first implantation and within 90 days after the last implantation. Summaries of treatment-emergent adverse events will be provided separately by implantation and for all implantations.

Treatment-emergent adverse events will be summarized by overall incidence, by severity, and by relationship. Summaries will also be provided for deaths, serious adverse events, and adverse events leading to discontinuation of study treatment. Listings will be provided for all adverse events, deaths, serious adverse events, and adverse events leading to discontinuation of study treatment.

8.4.3.3.Clinical Laboratory Parameters

For clinical laboratory parameters (chemistry, hematology, coagulation, and urinalysis), absolute values and changes from baseline to each time point after each RENCA macrobead implantation will be summarized. The proportion of patients with abnormal results will be summarized. Shifts from normal at baseline to abnormal after RENCA macrobead implantation will also be provided. Abnormal clinical laboratory results and NCI CTCAE v4.0 toxicity grade (if applicable) will be noted in the listings, and a separate listing for Grade 3 or higher laboratory values will be provided.

Results from eMuLV testing will be listed.

8.4.3.4. Vital Sign Measurements

Vital signs (blood pressure, pulse, respiration rate, and temperature) results will be listed.

8.4.3.5. Physical Examinations

Physical examination findings will be listed.

8.4.3.6. Electrocardiograms

For 12-lead ECGs, results (normal, abnormal but not clinically significant, or abnormal and clinically significant) will be summarized by time point as frequencies and percentages of patients.

8.4.3.7. Chest X-Rays

For chest x-rays, results (normal, abnormal but not clinically significant, or abnormal and clinically significant) will be summarized by time point as frequencies and percentages of patients.

8.4.3.8. Other Safety Assessments

Results from the murine allergen skin tests performed will be listed.

8.5. Interim Analyses

No interim analyses are planned.

8.6. Deviations from the Planned Statistical Analyses

Any changes to the planned statistical analyses will be described and justified in the clinical study report.

9. DIRECT ACCESS TO SOURCE DATA/DOCUMENTS

It is an expectation of regulatory authorities that monitors, auditors, and representatives of national and international government regulatory agency bodies have access to original source documentation (see examples in Section 10.4) to ensure data integrity. "Original" in this context is defined as the first documentation of an observation and does not differentiate between hard copy and electronic records.

The Investigator must make study data accessible to the clinical monitor, to other authorized representatives of the sponsor, and to FDA inspectors.

10. QUALITY CONTROL AND QUALITY ASSURANCE

10.1. Amendments

Any amendments to the protocol will be written and approved by the sponsor. All amendments must be submitted to the IRB for approval prior to implementing the changes. In some instances, an amendment requires changes to the informed consent form, which also must be submitted for IRB approval prior to administration to patients.

10.2. Monitoring

The sponsor is responsible for ensuring the proper conduct of the study with regard to ethics, protocol adherence, site procedures, integrity of the data, and applicable laws and/or regulations. At regular intervals during the study and following completion of the study, the sponsor's study monitors will contact the study site via visits to the site, telephone calls, and letters in order to review study progress, CRF completion, and address any concerns or questions regarding the study conduct. During monitoring visits, the following aspects of study conduct will be carefully reviewed: informed consent of patients, patient recruitment, patient compliance with the study procedures, source data verification, drug accountability, use of concomitant therapy by patients, adverse event and serious adverse event documentation and reporting, and quality of data. Records pertaining to these aspects are expected to be kept current.

10.3. Audits and Inspections

The sponsor, a regulatory authority, or an IRB may visit the study site at any time during the study or after completion of the study to perform audits or inspections. The purpose of a sponsor audit or regulatory inspection is to systematically and independently examine all study-related activities and documents to determine whether these activities were conducted according to the protocol, GCP, ICH guidelines, and any other applicable regulatory requirements. Investigators should contact the sponsor immediately if contacted by a regulatory agency about an inspection at their site.

10.4. Data Quality Assurance

The investigator is responsible for completing and maintaining adequate and accurate CRFs and source documentation. Source documentation constitutes original records, which may include: progress notes, medication administration records, laboratory reports, ECG tracings, chest x-ray images, discharge summaries, etc.

The investigator must sign the investigator's statement in each patient's CRF indicating that the data reported are accurate.

At the study sites, clinical research associates will manually review CRFs against source documentation. Computer-programmed edit checks will be run against the database to check for discrepancies and reasonableness of the data, and the safety database will be reconciled with the clinical database. All issues resulting from the computer-generated checks and the safety database reconciliation will be resolved according to standard data

management practices in conjunction with the medical monitor, clinical study personnel, and the study investigators.

11. ETHICS

11.1. Informed Consent

Written informed consent must be obtained from each patient prior to any protocol-related activities. As part of this procedure, the investigator or appropriate personnel at each site will explain orally and in writing the nature, duration, and purpose of the study, and the action of the study treatment in such a manner that the patient is aware of the potential risks, inconveniences, or adverse effects that may occur. Patients should be informed that they can withdraw from the study at any time. If the patient decides to withdraw from the study, he or she will be asked if they would agree to continue to be monitored (including the long-term screening for the presence of eMuLV viral DNA as requested by the FDA).

One copy of the signed informed consent document will be given to the patient, and the original will be retained by the investigator. Additionally, the participant must be allowed adequate time to consider the potential risks and benefits associated with his/her participation in the study.

The informed consent document must have been reviewed and approved by the sponsor and by the investigator's IRB prior to the initiation of the study.

11.2. Health Insurance Portability and Accountability Act of 1996

The investigator agrees to comply with all applicable federal, state, and local laws and regulations relating to the privacy of patient health information, including, but not limited to, the Standards for Individually Identifiable Health Information, 45 CFR. Parts 160 and 164 (the Health Insurance Portability and Accountability Act of 1996 [HIPAA] Privacy Regulation). The investigator shall ensure that study patients authorize the use and disclosure of protected health information in accordance with HIPAA Privacy Regulation and in a form satisfactory to the sponsor.

11.3. Confidentiality Regarding Study Patients

The privacy of participating patients must be maintained. Patients will be identified by their initials and an assigned patient number on CRFs and other documents submitted to the clinical monitor. Any documents that identify the patient (e.g., the signed informed consent document) must be maintained in strict confidence by the investigator, except to the extent necessary to allow auditing by the FDA, the clinical monitor, or sponsor personnel.

All information regarding the nature of the proposed investigation provided by the sponsor to the investigator (with the exception of information required by law or regulations to be disclosed to the IRB, the patient, or the FDA) must be kept in confidence by the investigator.

12. DATA HANDLING AND RECORD KEEPING

According to 21 CFR Part 312.62 and ICH E6, study-related records must be retained for at least 2 years after the last approval of a marketing application in an ICH region and until there are no pending or contemplated marketing applications in an ICH region, or at least 2 years have elapsed since the formal discontinuation of clinical development of the investigational product. These documents should be retained for a longer period, however, if required by applicable regulatory requirements or by an agreement with the sponsor.

The investigator must not destroy any study-related records without receiving approval from the sponsor. The investigator must notify the sponsor in the event of accidental loss or destruction of any study records. If the investigator leaves the institution where the study was conducted, the sponsor must be contacted to arrange alternative record storage options.

13. FINANCING AND INSURANCE

The investigator shall provide to the sponsor sufficient accurate financial information to allow the sponsor to submit complete and accurate financial certification or disclosure statements to the FDA. The investigator shall promptly update this information if any relevant changes occur in the course of the study and for one year following completion of the study.

14. REPORTING AND PUBLICATION OF RESULTS

The sponsor is responsible for preparing a clinical study report of the result from this study.

All unpublished information given to investigators by the sponsor shall not be published or disclosed to a third party without written authorization by the sponsor.

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