Statistical Analysis Plan

Protocol No. RI-MB-203

An Open-Label, Phase 2 Efficacy Trial of the Implantation of Mouse Renal Adenocarcinoma Cell-Containing Agarose-Agarose Macrobeads in the Treatment of Patients with Treatment-Resistant, Metastatic Colorectal Carcinoma

The Rogosin Institute
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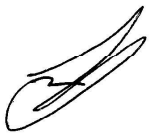

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LIST OF ABBREVIATIONS

ADL	Activities of Daily Living
AE	Adverse Event
ALT	Alanine aminotransferase
AST	Aspartate aminotransferase
BUN	Blood urea nitrogen
CA 19-9	Cancer Antigen 19-9
CA 125	Cancer Antigen 125
CEA	Carcinoembryonic Antigen
CRA	Clinical Research Associate
CRF	Case Report Form
CSR	Clinical Study Report
CT	Computerized Axial Tomography
CTCAE	Common Terminology Criteria for Adverse Events
DM	Data Management
ECG	Electrocardiogram
ECOG	Eastern Cooperative Oncology Group
EORTC	European Organisation for Research and Treatment in Cancer
EOS	End of Study
ESR	Erythrocyte Sedimentation Rate
GGT	Gamma-glutamyl transferase
ICF	Informed Consent Form
Ig	Immunoglobulin
IL	Interleukin
INR	International normalized ratio
LLT	Lowest Level Term
MCH	mean corpuscular hemoglobin
MCV	mean corpuscular volume
MedDRA	Medical Dictionary for Regulatory Activities
MRI	Magnetic Resonance Imaging
NCI	National Cancer Institute
NK	Natural killer
PET-CT	Positron emission tomography - computed tomography
PI	Principal Investigator
PT	prothrombin time
PT	Preferred Term
PTT	Partial thromboplastin time
QLQ-C30	Quality of life questionnaire - C30
RBC	red blood cell
RDW	red blood cell distribution width
RENCA	Renal Adenocarcinoma
RT-PCR	reverse transcriptase polymerase chain reaction
SAP	Statistical Analysis Plan

SAS®	Statistical Analysis System
SD	standard deviation
SOC	System Organ Class
T0	Time of origin
TEAE	Treatment-Emergent Adverse Event
TNF	Tumor necrosis factor
ULN	upper limit of normal
US(A)	United States (of America)
VAS	Visual Analog Scale
VSI	Vital Systems, Inc.
WBC	white blood cell
WHO DD	World Health Organization Drug Dictionary

LIST OF DEFINITIONS

Post Progression Study Day: The difference in days between the date of last radiological scan and the date of data collection.

Baseline: Last available pre-treatment measurement;

Concomitant Medication: Medication taken at most 6 days before implantation and/or after first implantation.

Discontinued Subject: A subject who goes "off protocol" (discontinues enrollment in this study) for any reason, such as withdrawal of consent, protocol violation, adverse event leading to discontinuation, death, or investigator decision. Subjects will continue to be followed outside of this study for long term safety.

Date of origin – survival analysis: Date of the latest scan showing disease progression after completion of prior treatment and prior to first bead implantation

End of Study: 12 months after the last active subject is implanted or the day the last active subject discontinues for any reason, including death, whichever occurs first. After 12 months on study subjects will enter the long-term follow-up period and are expected to be observed until death for any cause.

Enrolled Subjects: Eligible subjects who signed an Informed Consent Form.

Most Frequently-Reported Treatment-Emergent Adverse Events: Adverse events that occur in at least 10% of all subjects combined.

Screen Failures: Subjects who signed informed consent but were ineligible for the study.

The Sponsor: The Rogosin Institute

Time of origin (T_0): Date of the first scan showing disease progression after completion of prior treatment. Scan must be prior to first implant. Used for mortality analyses only.

Treated Population: Subjects who received at least one implant.

Treatment-Emergent Adverse Event (TEAE): in Group A an adverse event that began or worsened after the first implantation and within 90 days after the subject's last implantation.

1 ADMINISTRATIVE STRUCTURE

This study is being conducted under the sponsorship of The Rogosin Institute ("the Sponsor"). The clinical monitoring, data management and statistical (safety and efficacy) analyses are being performed under contract with Vital Systems, Inc. (VSI), in collaboration with the Sponsor.

1.1 Data Quality Assurance

The Investigator/site staff will be responsible for the validity of data collected at the clinical site and will be subject to the various monitoring procedures to be used. Monitoring will be done by a Clinical Research Associate (CRA) to ensure that the rights and well-being of human subjects are protected; that trial data are accurate, complete, and verifiable with source data; and that the trial is conducted in compliance with the protocol, Good Clinical Practices, and the applicable regulatory requirements. The Principal Investigator and VSI will agree to allow the study monitor to inspect all Case Report Forms (CRFs) and corresponding source documents, e.g., original medical records, subject records, laboratory raw data, and records of surgical implantation as requested, and to provide adequate time and space for monitoring visits.

The monitor will query the site on missing or spurious data and these will be resolved in a timely manner. A monitoring log will be maintained recording each visit, the reason for the visit, and the monitor's signature. Activities performed by the CRA will be recorded in a monitoring report to be reviewed by the Sponsor.

Sources of data are detailed in the Data Management (DM) Plan; these include CRFs, laboratory and imaging reports, and additional laboratory data. The FDA Guidance for Industry "Electronic Source Data in Clinical Investigations" (FDA, September 2013) will be followed while an Electronic Data Capture (EDC) system will be implemented for data collection. This guidance will be followed with respect to source data used to fill the predefined fields in an electronic case report form (eCRF), according to the protocol.

The eCRF is an auditable electronic record of information that generally is reported to the sponsor on each trial subject, according to a clinical investigation protocol. The eCRF enables clinical investigation data to be systematically captured, reviewed by investigator and DM personnel, managed, stored, analyzed, and reported. Data can be entered into the eCRF either manually or electronically. To comply with the requirement to maintain accurate case histories clinical investigators should review and electronically sign the completed eCRF for each subject before the data are archived or submitted to FDA.

Non EDC data will be independently entered by two operators into a validated computer system. Any discrepancies between the entries will be resolved by the Data Manager and/or queried to the site for clarification. Computerized algorithms will be used to check for incomplete, inconsistent or illogical values. Any issues will be investigated via queries to the site. Data points that trigger edit check failures but are truly outside of the algorithms will be suppressed in the edit check system and documented by DM as known data anomalies.

2 INTRODUCTION

This Statistical Analysis Plan (SAP) describes the statistical analysis methods and data presentations to be used in the summary and analysis of Protocol RI-MB-203. Related documents are the study protocol and CRF. This SAP supersedes the statistical considerations identified in the protocol. Any deviation(s) from the approved SAP will be described and justified in the final Clinical Study Report (CSR).

3 INVESTIGATIONAL PLAN

3.1 Study Objectives

3.1.1 Primary Objective

The primary objective of this study is to descriptively evaluate the efficacy of RENCA macrobead implantation, as assessed by overall survival, in patients with treatment-resistant, metastatic colorectal carcinoma. As only small number of patients were enrolled in the control group, no statistical comparisons between RENCA and control arms will be performed.

3.1.2 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
- 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 after first implantation 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 test for presence of ecotropic murine leukemia virus (eMuLV)
- murine allergen skin test

3.2 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. As very few patients were enrolled into the control group, no comparisons between active and control groups will be performed. The data for patients in the control group will be listed.

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

- Group A (n=41) – patients who underwent up to 4 implantations of RENCA macrobeads, at an amount of 8 RENCA macrobeads /kg body weight
- Group B (n=3) – patients who received or are receiving best supportive care, defined as management of symptoms aimed at maintaining or improving quality of life, not including approved therapies targeting the patient's malignancies

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 120-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 rescue therapy. 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 verified in their entirety; however, patients must continue to be surgical candidates, as deemed by the investigator.

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 (This day will be expressed as a post progression day for the analysis purposes). 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 were 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 consisted of administration of informed consent, which included 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 did not have any assessments performed

as part of this study, they will be followed for mortality only. However, if relevant information is available from their charts (for example, tumor markers, inflammation markers, etc.), it will be listed.

Patients for group B were selected from a large pool of patients substantially similar to those enrolled in Group A based on the baseline parameters and patient history.

Study centers enrolled patients in either Group A or Group B and not necessarily both treatment groups.
Detailed inclusion and exclusion criteria are given in Protocol Section 3.1.

3.3 Study Outcomes

3.3.1 Primary Efficacy Endpoint

Time of Origin for Mortality Evaluation.

Assumptions regarding time of origin for proportional hazard model (P. Allison, Survival Analysis Using SAS, 2nd edition, SAS Institute, 2010).

1) Time of origin should be a single time point defined for all patients in the analysis. Time of origin cannot be a function of the baseline covariates (such as age or severity).
2) The distribution of all other origins of risk exposures (additional to the principal one) is balanced between treatment groups (such as time of diagnosis, time of first treatment, etc.). If it is not balanced – it may impact survival analysis and should be included as either covariate in the mortality analysis model or a covariate to determine propensity scores.
3) Time of origin should have strong effect on death hazard.

The Time of Origin Date for mortality analysis purposes is the date of the last radiological scan showing progression after available treatment for both Group A and group B. Group B includes patients with a progression as determined by radiological scan who decided not to be on any cancer therapy, rely on the best supportive care and agree to participate in the study based on their chart review. No measurements will be obtained from the subjects who agreed to be included in Group B (relevant chart data may be used for analysis, if feasible).

Length of time in days between last available radiological scan (Baseline for mortality analysis purposes) and enrollment (signing of informed consent) may vary substantially between patients and between treated and control groups.

Primary Efficacy Endpoint: Death from Any Cause

Overall survival is defined as the time from Time of Origin to death from any cause. Death will be recorded in the database. A listing will be provided showing mortality status (status=1 if patient is dead and status=0 if patient is alive and censored at the end of observation period) and time to death, if applicable. Deaths will be summarized and analyzed at the end of observation period as determined by sponsor. Subjects still alive at the time of analysis will be considered censored for the analysis purposes.

3.3.2 Secondary Efficacy Endpoints

Secondary efficacy measurements include assessment of clinical status (ECOG performance status score and global clinical assessment) and two quality of life assessments (EORTC QLQ-C30 and Karnofsky Performance Status Scale). If any of the data below are available for both patients in Group A and Group B at the respective time points, the comparative analysis will be performed. Otherwise, the analysis will be limited to the patients in Group A.

Activities of Daily Living (ADL)/Karnofsky Performance Status Scale

ADL/Karnofsky is a self-rated scale that measures the patient's ability to perform daily functions, ranging from 0 ("dead") to 100 ("normal, no complaints, no evidence of disease).

Quality of Life Scale/EORTC QLQ-C30

Quality of life will be assessed using the EORTC QLQ-C30 version 3.0 (Aaronson et al., 1993) which uses discretely-scaled responses to 30 questions to derive global health status/quality of life, functionality, and symptom scales. The raw data will be used to calculate the derived scales using the EORTC QLQ-C30 Scoring Manual (Fayers et al., 2001). Per the manual, any derived scale for which more than half of the individual questions that comprise the scale are missing will be set to missing; otherwise, missing values will be ignored (which has the same effect as imputing the average response among non-missing questions that comprise the scale).

Eastern Cooperative Oncology Group (ECOG) Performance Status

The ECOG Performance Status is used by clinicians to assess disease progression and how the disease is affecting the daily living abilities of the patient; it is scaled as follows:

- 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.

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. 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.

3.3.3 Exploratory Endpoints

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

- ESR, LDH, 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
- tumor marker response rate, defined as the proportion of patients who have a decrease from baseline of 20% or more after first implantation in CEA or CA 19-9 values; mortality analysis adjusted for tumor marker response
- 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
- Immunohistochemical and gene array analysis of tumor biopsy samples, when possible
- Examination of tumor state and any inflammatory or connective tissue reaction to the RENCA macrobeads after autopsy, if applicable

If any of the measurements above are available for Group B, the comparative analysis may be performed, if feasible. For patients in Group B the last available value will be used for the analysis purposes unless data are outdated based on investigator's judgment. However, this analysis will only be performed if the information for Group B patients is relatively current (as determined by medical review).

3.3.4 Safety Endpoints

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
- murine allergen skin test at Day 90 after RENCA macrobead implantation

3.4 Sample Size

There were 41 patients treated in Group A, and there were 3 patients enrolled in Group B.

4 SCHEDULE OF STUDY PROCEDURES

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	
Viral screening (HIV, hepatitis B, C, E)	X						
Pregnancy test (females of childbearing potential only)	X[d]	X[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	X		X	X	X	X	
Tumor markers (CEA, CA19-9, CA125)	X		X	X	X	X	
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 screening/re-screening/baseline visits..

[e] A urine pregnancy test at Day 0 is required only if the screening serum pregnancy test result was obtained more than 2 weeks before Day 0.

[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.

[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, tumor biopsies may be performed during the implantation procedure; samples will be tested for immunohistochemical and gene array analysis.

ALT=alanine aminotransferase; AST=aspartate aminotransferase; BUN=blood urea nitrogen; CA19-9=cancer antigen 19-9; CA125=cancer 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.

5 ANALYSIS POPULATIONS

All subjects who receive at least one implant will be included in all efficacy and safety evaluations and will be referred to as the Treated Population.

Control population: patients who will receive or are receiving best supportive care, defined as management of symptoms aimed at maintaining or improving quality of life, not including approved therapies targeting the patient's malignancies. 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 review of entry criteria. Patients in Group B will not have any assessments performed as part of this study. The relevant data from their charts (tumor markers, inflammation markers, etc.) may be used for the comparison purposes, if feasible. However, this analysis will only be performed if the information for Group B patients is relatively current (as determined by medical review).

6 GENERAL DATA HANDLING/PRESENTATION CONSIDERATIONS

6.1 Listing, Table, and Figure Formats

- In general, tables and figures will include all subjects in the Treated Population only.
- Listings will be ordered by Group, unique subject identifier, study day, visit date, and data collection time, if appropriate.
- Tables and figures will be ordered by study day. Listings will include Group, subject identification, study day, date, and data collection time, as applicable.
- Unscheduled data, such as repeat laboratory tests, will be listed but not summarized.
- Partial dates will be listed as recorded; i.e., there will be no imputation of partial dates for listings.
- Fully populated dates will be presented as ddmmmyyyy.
- Times will be presented as hh:mm (24-hour clock).
- Laboratory data will be presented in conventional units.
- Missing data will be represented on listings as "NA" with the footnote "not applicable,", "ND" with the footnote "not done", or another entry with an explanatory footnote, whichever is appropriate.

- Missing descriptive statistics or p-values will be output as a hyphen with an explanatory footnote.
- Each listing, table, and figure will be numbered using a decimal-point system for identifying related listings, tables, and figures.
- Each listing, table, and figure will be titled with the listing/table/figure number and a description of the presentation.
- Column headers will contain the unit of measurement, if applicable.
- In tables, column headers will contain the overall sample size of the group associated with the column. The overall sample size will include subjects with missing values for the data presented in the column. The number of subjects with available data for the column will be shown in the body of the table.
- Footnotes will appear at the bottom of each page of listings and tables or at the end of output, as appropriate.
- All listings, tables, and figures will be presented in the landscape orientation with 1-inch margins on all sides.
- In general, the main body of listings and tables will be 9 pt courier new font.
- Footnotes will be at least 9 pt courier new font.
- Headers will be 9 pt courier new font (unless other font/size are appropriate) and will contain the protocol number and the page number and total number of pages of the particular listing, table, or figure.
- Footers will be 9 pt courier new font (unless other font/size are appropriate) and will contain the data source (listings) or listing source (tables and figures), data sets used, program name, run time, and page number and total number of pages of the entire output file (e.g., the listings file).
- All listings, tables, and figures will be presented in black and white.
- Listings and tables will be produced by SAS® version 9.1.3 or higher (SAS Institute, Inc., Cary, NC).
- Figures will be produced by SAS® version 9.1.3 or higher, Microsoft® Excel version 2007 or higher (Microsoft Corp., Redmond, WA), and/or SigmaPlot version 11.0 (Build 11.1.0.102) or higher.

6.2 Data Analysis

- All analyses will be done using SAS® version 9.1.3 or higher and/or the statistical software package R as appropriate.

- Categorical variables will be summarized as frequencies and percentages in each category. In general, continuous variables will be summarized by numbers of subjects, means, standard deviations, medians, and ranges. The number of decimal places for minimums and maximums will be the same as the original data. The number of decimal places for means, medians, and interquartile ranges will be the same as the original data plus one. The number of decimal places for measures of variance will be the same as the original data plus two.

- Laboratory data with qualifiers (e.g., "<") will be listed with but summarized without the qualifier.

- P-values will be presented to four decimal places. P-values < 0.0001 will be presented as "< 0.0001."

- There is a single primary endpoint. There will be no significance level adjustment for secondary and exploratory endpoints. All statistical tests will be two-sided, statistical significance will be evaluated at the 0.05 level.

- Unscheduled data may not be summarized or analyzed (but will be listed, as noted above).

6.3 Missing Data

For mortality analysis purposes if incomplete date of either last radiological scan or death is present, the following imputations will be made: if year is missing – no imputations; if year is present and month is missing, July 1 will be imputed, if year and month are present but day is missing, the 15th of the month will be imputed.

Missing values will not be imputed for descriptive statistics or analyses unless otherwise specified.

6.4 Study Time Points

The following study time points are critical in terms of screening procedures, implantation, and study termination. Study time point labels correspond to those that are used in the protocol (minus visit numbers) and that will be used in listings and tables. A complete description of all study time points is contained in the Schedule of Study Procedures. Patients in Group A 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. For the mortality analysis purposes post progression days will be utilized with the Day 0 defined as the last available radiological scan.

Baseline

For Group A the Baseline is defined as screening (except for mortality analysis where it is defined as the last radiological scan). If re-screening is performed, the values obtained at re-screening will be utilized as baseline values. If any analysis other than mortality is performed for the group B subjects, the Baseline will be the last recorded observation based on the subject's chart.

Time of Origin and End of Study (EOS)

EOS will be defined as 12 months after last RENCA implant or death. Long-term follow-up will continue until patient dies (unless long-term follow-up is terminated by the Sponsor).
The Time of Origin Date for mortality analysis purposes is the date of the last radiological scan showing progression after available treatment. Actual study days correspond to the difference between date of data collection/observation and the Origin Date.

Study Day Window

The study day window is defined as pre-specified data collection date +/- 5 days (+/- 3 days for Day 14 following implant). If multiple non-missing observations exist for a Study Day window, the last valid observation in that window will be used for summaries and analyses (but all data will be listed).

7 BASELINE CHARACTERISTICS

Baseline characteristics for Group B (Control) will be collected from the subjects' charts only.

7.1 Demographics

Demographics (age, sex, weight, height and race/ethnicity) at Screening will be recorded in the CRF and will be included in the Baseline Characteristics listing and summary table. Age at baseline will be calculated by subtracting the date of birth from the date of last radiological scan, dividing by 365.25, and rounding down to the nearest integer.

7.2 Other Baseline Characteristics

The Subject Eligibility listing will include whether or not inclusion/exclusion criteria were met, waivers granted (if any), confirmation that eligibility was evaluated and study procedures were understood, and ICF signature and approval dates. These data will be recorded in the CRF.

Medical history at Screening will be recorded in the CRF. Each subject's medical history including condition, onset date, end date, and whether or not the condition is ongoing will be listed.

Current oncology diagnoses, if available, will be recorded in the CRF. Metastases locations, location of primary tumor, date of diagnosis, date of stage 4 diagnosis and date of last available radiologic scan will be listed and/or summarized, as appropriate.

8 MACROBEAD IMPLANTATION

Details of macrobead implantations will be recorded in the CRF. For each implantation, date, start and end time of implantation, lot numbers of beads implanted, and whether biopsies were taken will be listed. Total number of implantations will be summarized.

9 MEDICATION USE

Prescription, over-the-counter, and alternative medication use within 30 days of implantation and through the End of Study will be recorded in the CRF and will be coded to generic terms using the World Health Organization Drug Dictionary (WHO DD). Coding will be done by DM using a computer algorithm for exact matches or manual coding for incomplete or non-matches. The Medical Monitor will review and approve the final coding prior to database lock.

Separate listings will be done for pre-implantation and concomitant medications and will include WHO DD drug class (Anatomic and Therapeutic Class Level 1), WHO DD preferred drug name, reported drug name, start and stop date, study day in relationship to both first and most recent implantation, dose, route, regimen, and indication. Concomitant medication use will be summarized by numbers and percentages of subjects reporting each preferred name and also by WHO DD drug class and preferred name within drug class. Medications that were stopped before implantation but no earlier than 7 days before implantation will be considered "pre-implantation." All other medications will be considered concomitant. If medication exposure dates cannot be determined due to missing or partially missing start and/or stop dates, the medication will be considered concomitant.

10 EFFICACY ANALYSES

Efficacy parameters will be listed and summarized for all implanted subjects and for patients enrolled in the control group based on the information available from their charts.

10.1 PRIMARY EFFICACY ANALYSES OVERVIEW

The primary endpoint of the study is all-cause mortality. A Kaplan-Meier curve will be generated for all subjects enrolled in Group A. Kaplan-Meier curves will also be generated for subjects with one implant vs. subjects with >1 implant.

The data for most analyses is based on the one-line-per-patient data structure which includes patient ID, treatment group (TX), date of last radiological scan, date of ICF, time of death OR censoring time (lost to follow-up or end of observation period), event code (0 for censoring, 1 for death). Subject is censored if he is either lost to follow-up or alive at the end of observation period.

10.2 SECONDARY ANALYSES

Secondary endpoints are described in section 3.3.2. The analysis below will be performed for Group A. The time points for each of the secondary assessments below include Baseline, Day 14, Day 30, Day 60, and Day 90 after each macrobead implantation.

Activities of daily living ADL/Karnofsky Performance Status Scale and respective changes from baseline (screening) will be summarized at each time point using descriptive statistics.
The Quality of Life scale (EORTC QLQ-C30), including total score (global health status), functionality, and symptom scales will be analyzed similarly and at the same time points.

ECOG performance status will be summarized as a proportion of patients with each ECOG score at each time point.

Global Clinical Assessment VAS scores will be summarized at each time point.

10.3 EXPLORATORY ANALYSES

For patients in Group A the following analyses will be performed

- The subgroup analysis to evaluate any potential impact of number of macrobead implantations on survival will be performed if feasible. The association of mortality with the number of implants (1 implant vs. >1 implant) will be analyzed using proportional hazards model.

- ESR, LDH, CA 125 and CRP levels will be listed and summarized using descriptive statistics at Baseline, Days 14, 30, 60 and 90; changes from Baseline (screening) to these time points will also be listed and summarized descriptively
- Tumor markers (CEA and CA19-9) will be listed and summarized descriptively at Baseline, Days 14, 30, 60 and 90; changes from Baseline (screening) to these time points will also be listed and summarized descriptively
- tumor marker response rate, defined as the proportion of patients who have a decrease from baseline of 20% or more after first implantation in CEA or CA 19-9 values
- The association of mortality with tumor marker response (responders vs. non-responders) will be analyzed using proportional hazards model.
- CTCs at Day 90 after each implantation (and changes from Baseline) will be listed and summarized descriptively
- Immunoglobulin (IgA, IgE, IgG, and IgM) levels will be listed and summarized descriptively at day 90 after each implantation; changes from Baseline (screening) to this time point will also be listed and summarized descriptively
- Cellular immune function as measured by T cell counts; B cell count, NK cell counts (e.g., CD16 count) will be listed and summarized descriptively at Day 90 after each implantation; changes from Baseline (screening) to this time point will also be listed and summarized descriptively

- Characterization of tumor changes at Day 90 after each implantation will be listed and summarized descriptively based on PET-CT scans
- Immunohistochemical and gene array analysis of tumor biopsy samples will be listed when possible
- Examination of tumor state and any inflammatory or connective tissue reaction to the RENCA macrobeads after autopsy will by listed, if applicable

If comparative analysis is feasible, the changes from last available radiological scan to study time points will be compared between Groups A and B; the models may be adjusted for different time of study entry, if needed.

11 SAFETY ANALYSES

Safety parameters will be listed and summarized for all implanted subjects. Safety analyses will involve the examination of incidence and reasons for discontinuation; incidence of AEs and their relationship to study treatment; changes in clinical laboratory results, vital signs, 12-lead ECG interpretations, physical examination findings, murine antigens skin test, and murine leukemia virus.

11.1 Safety Outcomes

11.1.1 Subject Disposition

Subject disposition will be recorded at the termination visit. For subjects who discontinued, the primary reason for discontinuation will be recorded as voluntary withdrawal, AE, protocol violation, request of investigator or regulatory authority, request of sponsor, or lost to follow-up (one reason per subject). Dates of screening, last radiological scan, first and last implant, whether or not the subject discontinued, and the reason for discontinuation (if applicable) will be listed. Number and percentage of subjects completing the study, number and percentage of subjects who discontinued the study by reason for discontinuation, and number of days on study after each implantation will be summarized.

11.1.2 AEs

AE reporting is described in Protocol Section 6. Volunteered, observed, and elicited AEs will be recorded in the CRF from the day the ICF is signed through 90 days after the last implant, and in a registry for the rest of each subject's life. This will include AEs subjects report spontaneously, AEs observed by the investigator, and AEs subjects report in response to open-ended questions. AEs will be coded using MedDRA® (Medical Dictionary for Regulatory Activities). In MedDRA, each reported event is mapped to a Lowest Level Term (LLT), a Preferred Term (PT), and a System Organ Class (SOC). LLTs constitute the lowest level of terminology and can accommodate colloquial or culturally unique terms. Each LLT is linked to only one PT. A PT is a distinct descriptor for a symptom, sign, disease, diagnosis, therapeutic indication, investigation, surgical or medical procedure, or medical, social or family history characteristic; it groups together equivalent LLTs. A PT must be linked to at least one SOC but can be linked to as many SOCs as appropriate. SOCs provide the broadest level of data retrieval and comprise groupings by etiology,

manifestation site, and purpose. Coding will be done by DM using a computer algorithm for exact matches or manual coding for incomplete or non-matches. The Medical Monitor will review and approve the final coding prior to database lock.

A TEAE will be defined as an AE that began or worsened after the first implantation and within 90 days after the last implantation. AEs recorded prior to the first implantation will be considered non-treatment-emergent. AEs with no recorded start date will be considered treatment-emergent, as will AEs with no recorded start time that began on the same day as the first implantation.

All reported AEs (treatment-emergent or not) will be listed. Deaths will be listed separately, as will serious AEs and AEs that resulted in study discontinuation (as previously defined). Listings will include onset and resolution dates, study day in relationship to both first implant and most recent implant, duration (days), whether or not serious criteria apply, severity (mild, moderate, severe, life-threatening/disabling, death), action taken (none, discontinued), whether or not treatment was required, outcome (recovered, not resolved, residual effects, unknown, fatal), and relationship to study treatment (not related, related). Study day of onset in relationship to the first/most recent implantation will be calculated by subtracting the date of first/most recent implant from the AE onset date. AE duration will be calculated by subtracting AE onset date from AE resolution date. AEs that resolve on the same day will have duration = "< 1 day." Duration will not be calculated for AEs with missing or partial onset or resolution dates.

A summary of TEAEs will be provided, showing incidence of TEAEs, serious TEAEs, TEAEs by severity, and TEAEs by relationship to study treatment and to implant procedure. Missing severity will be considered severe and missing relationship will be considered "probably related." Deaths will be summarized separately, showing incidence of death overall, cancer-related death, and cancer-related death by implantation number. In addition, for each SOC and PT within SOCs, the numbers and percentages of subjects reporting a TEAE will be calculated. If the same TEAE is experienced more than once by a given subject, the TEAE will be counted only once for that subject. The number of TEAEs overall and by SOC will be also tabulated. TEAEs will also be summarized by severity and relationship to study treatment and to implant procedure within SOCs and PTs. For summaries by severity, only the most severe TEAE per subject for each SOC and for each PT within SOCs will be tabulated. Similarly, for summaries by relationship to study treatment and to implant procedure, only the most related TEAEs will be tabulated. A summary of serious TEAEs will be provided. A summary of the most frequently reported TEAEs will also be provided, with "most frequently" defined as occurring in at least 10% of all subjects. All TEAE summaries will be done both over all implantations and by implantation number. SOCs and PTs within SOCs will be displayed alphabetically.

11.1.3 Clinical Laboratory Evaluations

Hematology, coagulation, serum chemistry, pregnancy, urinalysis, immunology, and all other laboratory parameters including those listed in Protocol Section 7.2 will be analyzed at multiple laboratory sites and will be captured into the study database. Laboratory test names and units of measurement will be standardized by VSI. For select parameters, study day, collection lab, date and time collected, normal range, observed value, change from baseline in relationship to both first and most recent implant, out-of-range flag, and Common Terminology Criteria for Adverse Events (CTCAE) v4.0 toxicity grade (if applicable) will be listed. Lab observations with Grade 3 or higher toxicity and/or reported as an AE will be listed. For select parameters, observed values

and changes from baseline (in relationship to both first and most recent implant) will be summarized for each time point at which lab data were collected. Separate series of tables will show numbers and percentages of subjects by out-of-range flag and by toxicity grade. Shift tables will be provided that show numbers and percentages of subjects with normal ↔ abnormal shifts based on out-of-range flags from baseline (in relationship to both first and most recent implant) to each subsequent time point at which lab data are collected.

11.1.4 Vital Signs

Vital signs (blood pressure, respiration rate, heart rate, and temperature) will be obtained at each study visit.

11.1.5 12-Lead Electrocardiogram (ECG)

Data from standard 12-lead ECGs will be recorded in the CRF. Summarize rhythm results (normal, abnormal but not clinically significant, or abnormal and clinically significant). The listing will include study day, date, and results.

11.1.6 Chest X-Rays

Chest X-Ray results recorded as normal, abnormal but not clinically significant, or abnormal and clinically significant will be listed.

11.1.7 Physical Examination

Results from physical examinations will be recorded in the CRF. Clinically significant changes from baseline that meet the definition of an AE will be recorded on the AE form. Study day and date will be listed

11.1.8 Murine Antigens Skin Test

Results from murine antigens skin testing will be recorded in the CRF. Study day and test result will be listed.

11.1.9 Murine Leukemia Virus

Results from murine leukemia virus testing will be reported into the study database. Study day and test result will be listed.

12 MISCELLANEOUS DATA COLLECTION

12.1 Subject Progress

A listing of subject progress through the study will be provided that shows visits completed and dates of each visit.

13 STATEMENT OF COMPLIANCE

This analysis will be conducted in full compliance with the analysis plan, the study protocol, and all applicable U.S. Food and Drug Administration regulations.

14 SOFTWARE

Tables, listings, figures, and analyses will be done using SAS® Version 9.1.3 or higher (SAS Institute Inc., Cary, NC), R (Vienna, Austria), Microsoft® Excel version 2007 or higher (Microsoft Corp., Redmond, WA), and/or SigmaPlot version 11.0 (Build 11.1.0.102).

15 REFERENCES

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Fayers PM, Aaronson NK, Bjordal K, Groenvold M, Curran D, Bottomley A, on behalf of the EORTC Quality of Life Group. The EORTC QLQ-C30 Scoring Manual (3rd Edition). Published by: European Organisation for Research and Treatment of Cancer, Brussels 2001.

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