Statistical Analysis Plan

Protocol No. 0911010739

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 Pancreatic Adenocarcinoma or Colorectal Cancer

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APPROVALS

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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	Cancer antigen
CEA	Carcinoembryonic antigen
CI	Confidence interval
CRA	Clinical Research Associate
CRF	Case report form
CSR	Clinical study report
CT	Computerized 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
GCA	Global clinical assessment
GGT	Gamma glutamyl-transpeptidase
ICF	Informed consent form
Ig	Immunoglobulin
IL	Interleukin
INR	International normalized ratio
KPS	Karnofsky Performance Status
LLT	Lowest level term
MedDRA®	Medical Dictionary for Regulatory Activities
MRI	Magnetic resonance imaging
NK	Natural killer
PA	Posteroanterior
PCR	Polymerase chain reaction
PET-CT	Positron emission tomography - computed tomography

PFS	Progression-free survival
PI	Principal Investigator
PT	Preferred term
PT	Prothrombin time
PTT	Partial thromboplastin time
QLQ-C30	Quality of life questionnaire - C30
RENCA	Renal adenocarcinoma
SAS®	Statistical Analysis System
SAP	Statistical analysis plan
SOC	System organ class
TEAE	Treatment-emergent adverse event
TNF	Tumor necrosis factor
T_0	Time of origin
VAS	Visual analog scale
VSI	Vital Systems, Inc.
WHOdd	World Health Organization drug dictionary

List of Definitions

Concomitant Medication	Medication taken up to ≤ 30 days before the first implantation up to 90 days after the last implantation
End of Study	When all patients have died or have been lost to follow-up, whichever occurs first
Enrolled Patients	Eligible patients who have signed an Informed Consent Form (ICF)
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	Patients who received at least one implant
Treatment-Emergent Adverse Event (TEAE)	An adverse event which occurred during or after the first implantation and up to 120 days after the 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 analyses of safety and efficacy are being performed under contract with Vital Systems, Inc. (VSI), in collaboration with the Sponsor.

This SAP supersedes any statistical considerations identified in the study protocol. Any differences between this statistical analysis plan and the study protocol will be presented and explained in the CSR.

1.1 Data Quality Assurance

The Investigator and site staff will be responsible for the validity of data collected at the clinical site and will be subject to the various monitoring procedures put in place for the study. Study monitoring will be done by a Clinical Research Associate (CRA) to ensure that:

- the rights and well-being of human subjects are protected
- trial data are accurate, complete, and verifiable with source data
- 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 (Clinical Research Associate; CRA) to inspect all Case Report Forms (CRFs) and corresponding source documents, e.g., original medical records and other patient-related data sources, laboratory raw data, and records of surgical implantation as requested, and to provide adequate time and space for monitoring visits.

The study 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 of the study monitor, the reason for the visit, and the monitor's signature. Activities performed by the study monitor 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. CRFs and laboratory reports will be transferred to DM via traceable courier with a transmission log of the documents sent. DM personnel will verify receipt of every page expected and will review the CRFs for legibility, completeness and internal consistency. A comprehensive page inventory will also be reviewed and verified with the site prior to database lock to confirm receipt of all available pages for all study subjects.

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 or queried to the site for clarification if necessary. Computerized algorithms will be used to check for incomplete, inconsistent or illogical values and any issues will be investigated via queries to the site. Data points that trigger edit check failures (e.g. values which are outside of the algorithms) but which are subsequently confirmed to be valid values will be suppressed in the edit check system and documented by DM as known data anomalies.

All data will be compiled into Statistical Analysis System (SAS) datasets, and an initial sample (10%) will undergo a quality control audit requiring no more than 5 discrepancies per 10,000 fields

(0.05%). If this limit is exceeded, the data sample will be expanded to a full (100%) audit for the offending data module. All discrepancies will be documented and corrected, where possible, in the final locked database.

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 No. 0911010739, Amendment 10, dated 27 June 2013. Related documents are the study protocol and CRF.

From experiences gained from this and other studies of macrobeads containing mouse renal adenocarcinoma (RENCA) cells, it has become apparent that tumor measurements often cannot be obtained from patients with such advanced disease due to a lack of tolerance to imaging contrast. As a result, certain efficacy parameters (such as response rate) described in the protocol have been modified to better fit the patient population. Therefore this SAP supersedes the statistical considerations identified in the protocol.

3 INVESTIGATIONAL PLAN

3.1 Study Objectives

The primary objective of the study is to determine the efficacy of RENCA cell-containing macrobeads in each of two patient populations (Stage IV colorectal carcinoma or pancreatic carcinoma). The secondary objective is to determine the safety and tolerability of implanted macrobeads in each population and in both populations combined. The exploratory objective is to identify mechanisms associated with the antitumor activity of implanted macrobeads, which could include examination of the niches of cancer stem and other cells within the niche bodies of the tumors.

3.2 Study Design

This is an open-label, non-randomized, single-center Phase II trial to evaluate the efficacy, safety and tolerability of RENCA cell-containing macrobeads implanted in Stage IV subjects with colorectal or pancreatic cancer in whom standard and accepted therapy such as chemotherapy, radiation and/or surgery have failed and who have chosen to not pursue other experimental therapies. Patients will be implanted with RENCA macrobeads, which will permanently remain in the peritoneal cavity even if patients discontinue from the study or begin a new therapy (e.g., chemotherapy).

Screening will occur within 28 days prior to implantation. Each eligible subject who signs an Informed Consent Form (ICF) will be considered as “enrolled”. Subjects who sign an ICF but who are not implanted will be replaced. A total of 30 subjects (20 with colorectal cancer and 10 with pancreatic cancer) will be implanted. Detailed inclusion and exclusion criteria are given in Protocol Section 4.3.

Subjects will receive up to 4 macrobead implantations, with at least 3 months between each implantation procedure. The primary focus of the trial is to estimate specific clinically important parameters for use in planning subsequent regulatory trials designed to more fully assess efficacy, safety and tolerability. Subjects will undergo formal safety and efficacy assessments for

120 days after their final implantation. After this formal phase of the trial has been completed, subjects will be followed for the duration of their lives.

Data output and analyses will be stratified by cancer type. There are no pre-specified comparisons between the two cancer types.

The study will end 120 days after the last active subject undergoes their last implantation.

3.3 Study Outcomes

3.3.1 Efficacy

The primary efficacy outcome is post-implantation all-cause mortality, where time to death is defined as the time from the first scan showing disease progression after completion of prior treatment (time of origin, T_0) to death from any cause.

Secondary efficacy outcomes are (if feasible):

- Time from first implantation to death.
- Time from disease Stage IV diagnosis to death.
- Changes from baseline based on Magnetic Resonance Imaging (MRI), computerized tomography (CT) or positron emission tomography (PET)-CT scan, and other appropriate imaging techniques (e.g., sonography, bone scans, other x-rays) as indicated, if feasible.
  - In primary and/or secondary tumor size (volume, area) and
  - In state (necrosis, vascularization) on MRI, CT or PET-CT scan, and other appropriate imaging techniques (e.g., sonography, bone scans, other x-rays) as indicated.
- Change from baseline in tumor markers (CEA, CA19-9)
- Changes from baseline in CA125 (as a marker of inflammation)
- Changes from baseline in
  - Clinician Global Clinical Assessment
  - Activities of daily living
  - Symptom rating
  - Quality of life (QCQ-C30)
  - Pain scale
  - ECOG
- Additional exploratory efficacy outcomes may be analyzed if feasible and will be defined in the CSR.

3.3.2 Safety

Safety outcomes will include:

- Reason for study discontinuation (coming off protocol).
- Incidence of adverse events (AEs).
- Changes from baseline in physical examination parameters, including weight, vital signs, and electrocardiogram (ECG).

- Changes from baseline in laboratory parameters (see Section 11.1.3).
- Changes from baseline in murine antigens skin test.
- Changes from baseline in status of murine leukemia virus as detected by polymerase chain reaction (PCR).

3.3.3 Exploratory

Exploratory outcomes will include presence or absence of circulating tumor cells, examination of pathology specimens (when possible / available) for cancer stem cell niches, and any other analyses of interest as the current state of research in this area evolves.

3.4 Sample Size / Power

As there will be no formal hypothesis testing in this study, the sample size of 30 patients was based on practical, rather than statistical, considerations.

4 SCHEDULE OF STUDY PROCEDURES

The following data collection time table was abstracted from Appendix 2 of the protocol, Schedule of Assessments:

Implant	Screening	1					2					3					4						Follow-Up [12]
Day		0	14	30	60	90	0	14	30	60	90	0	14	30	60	90	0	14	30	60	90	120	
Visit		1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19	20	21	
Informed Consent	X																						
PE / VS / Medical History	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	
ConMed / AE Review	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	
Global Clinical Assessment Questionnaire	X			X	X	X			X	X	X			X	X	X			X	X	X	X	
Activities of Daily Living Rating	X			X	X	X			X	X	X			X	X	X			X	X	X	X	
Symptoms Rating / Severity Assessment	X			X	X	X			X	X	X			X	X	X			X	X	X	X	
Quality of Life Scale	X			X	X	X			X	X	X			X	X	X			X	X	X	X	
Pain Scale Assessment	X		X	X	X	X		X	X	X	X		X	X	X	X		X	X	X	X	X	
ECOG Performance Scale	X			X	X	X			X	X	X			X	X	X			X	X	X	X	
Neurological Examination	X		X	X	X	X		X	X	X	X		X	X	X	X		X	X	X	X	X	
Phlebotomy	X		X	X	X	X		X	X	X	X		X	X	X	X		X	X	X	X	X	
12-Lead ECG	X					X					X					X							
Urinalysis	X					X					X					X							
Tumors Markers (CEA, CA19-9)	X		X	X	X	X		X	X	X	X		X	X	X	X		X	X	X	X	X	
CA125	X		X	X	X	X		X	X	X	X		X	X	X	X		X	X	X	X	X	
Hematology Profile [1]	X		X	X	X	X		X	X	X	X		X	X	X	X		X	X	X	X	X	
Coagulation Panel [2]	X		X	X	X	X		X	X	X	X		X	X	X	X		X	X	X	X	X	
Sedimentation Rate	X		X	X	X	X		X	X	X	X		X	X	X	X		X	X	X	X	X	
Comprehensive Metabolic Panel [3]	X		X	X	X	X		X	X	X	X		X	X	X	X		X	X	X	X	X	

Implant	Screening	1					2					3					4						Follow-Up [12]
Day		0	14	30	60	90	0	14	30	60	90	0	14	30	60	90	0	14	30	60	90	120	
Visit		1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19	20	21	
GGT [4]	X		X	X	X	X		X	X	X	X		X	X	X	X		X	X	X	X	X	
Amylase [5]	X																						
Lipase [5]	X																						
Lactate Dehydrogenase	X		X	X	X	X		X	X	X	X		X	X	X	X		X	X	X	X	X	
C-Reactive Protein	X		X	X	X	X		X	X	X	X		X	X	X	X		X	X	X	X	X	
Bilirubin, Direct	X			X	X	X			X	X	X			X	X	X			X	X			
Hepatitis Panel [6]	X																						
HIV	X																						
Serum Pregnancy (Qualitative) [7]	X					X					X					X							
Immunoglobulin Levels [8]	X					X					X					X							
Cytokine Panel [9]	X		X	X	X	X		X	X	X	X		X	X	X	X		X	X	X	X	X	
Cellular Immune Function [10]	X					X					X					X							
Ecotropic Murine Leukemia Virus	X			X		X			X		X			X		X				X		X	
Immunohistochemical & Gene Array Analysis (when indicated)		X					X					X					X						
Murine Allergen Skin Test	X					X					X					X							
Positive and Negative Skin Test	X					X					X					X							
Circulating Tumor Cells	X			X		X			X		X			X		X			X				
Macrobeads Implantation (8 per kg body weight)		**X**					**X**					**X**					**X**						
Cefazolin (Prophylaxis – 1 gm)		X					X					X					X						
Chest X-Ray (PA / lateral)	X					X					X					X							

Implant	Screening	1					2					3					4						Follow-Up [12]
Day		0	14	30	60	90	0	14	30	60	90	0	14	30	60	90	0	14	30	60	90	120	
Visit		1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19	20	21	
CT Scan Chest (Non-Contrast) [11]	X																						
MRI of Abdomen [11]	X				X	X				X						X				X		X	
MRI of Pelvis [11]	X				X	X				X						X				X		X	
Tumor Mass Biopsy (where indicated)		X					X					X					X						
PET-CT Scan Whole Body	X					X				X						X				X		X [11]	
Radionuclide Bone Scan [11]																							

1. Hematology Profile: WBC, RBC, hemoglobin, hematocrit, MCV, MCH, MCHC, RDW, platelets, automated differential WBC
2. Coagulation Panel: PT, PTT, INR
3. Comprehensive Metabolic Panel: CO_2, sodium, potassium, chloride, creatinine, BUN, calcium, total protein, albumin, total bilirubin, alkaline phosphatase, AST, ALT, glucose
4. GGT: gamma glutamyl-transpeptidase
5. Amylase and lipase are done at baseline, then as medically necessary for individual subjects
6. Hepatitis Panel: Hepatitis B, C and E
7. Serum pregnancy only for females of childbearing potential
8. Immunoglobulin Levels: IgA, IgG, IgE and IgM
9. Cytokine Panel: IL-6, TNF-α, TNF receptors p55, TNF receptors p75
10. Cellular Immune Function: T cells; B cells; antibodies to diphtheria, tetanus, mumps, rubella; quantitative IgG subclasses, NK cells count (CD16)
11. Only if clinically indicated.
12. Long-term follow-up will begin after the patient's EOS visit, and will continue for the duration of each subject's life, at 6-month intervals during the first 2 years of follow-up and then yearly thereafter. All examinations and treatment during this time will be guided by optimal patient care principles and the decisions of the physicians providing overall health care to the patient.

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.

6 GENERAL DATA HANDLING / PRESENTATION CONSIDERATIONS

6.1 Listing, Table, and Figure Formats

- In general, listings, tables, and figures will include all subjects in the Treated Population.
- Listings will be ordered by cancer type, unique subject identifier, study day, visit date, and data collection time, if appropriate.
- Tables and figures will be ordered by cancer type and study day and will include summaries for both cancer types individually as well as for all subjects combined.
- The order of cancer type presentation in listing, tables, and figures will be colorectal, then pancreatic.
- Listings will include subject identification, subject initials, subject age and sex, cancer type, study day, date, and data collection time, as applicable.
- Unscheduled data, such as repeat laboratory tests, will be listed but will not be summarized or analyzed.
- Partial dates will be listed as recorded; i.e., there will be no imputation of partial dates for listings.
- Dates will be presented as ddmmmyy.
- 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 either a hyphen (“-”) with a corresponding footnote (e.g., “unknown” or “not evaluated”), as “N/A” with the footnote “not applicable,” 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.

- 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 10 pt Times Roman font (or similar).
- Footnotes will be 8 pt Times Roman font (or similar).
- Headers will be 12 pt Times Roman font (or similar).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 8 pt Times Roman font (or similar).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).

6.2 Data Analysis

- All analyses will be done using SAS® version 9.1.3 or higher.
- All analyses will be exploratory. No confirmatory statistical testing will be done.
- Categorical variables will be summarized as frequencies and percentages in each category. In general, continuous variables will be summarized by numbers of patients, 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.
- All p-values will be presented as illustrated below:

p-value	Presentation
≥ 0.01	2 decimal places
< 0.01 but ≥ 0.001	3 decimal places
< 0.001 but ≥ 0.0001	4 decimal places
< 0.0001	< 0.0001

- All analyses will be exploratory and, as such, there will be no significance level adjustments to control type I error.
- All statistical tests will be two-sided.
- Unscheduled data will not be summarized or analyzed (but will be listed, as noted above).

6.3 Missing Data

For dates, year and month are required. If day is missing, it will be imputed to be the 15th of the month. Otherwise, missing values will not be imputed for descriptive statistics or analyses unless otherwise specified.

6.4 Visit Windows

6.4.1 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 Assessments (Section 4). Study visit labels in the Schedule of Assessments differ somewhat from those that are used in the text of the protocol and in the SAP (see samples below):

SAP	Text of Protocol	Schedule of Assessments
Implant 2 / Day 0	Visit 6 / Implant 2 / Day 0	Visit 6 / Implant 2
Implant 3 / Day 0	Visit 11 / Implant 3 / Day 0	Visit 11 / Implant 3
Implant 4 / Day 0	Visit 16 / Implant 4 / Day 0	Visit 16 / Implant 4

In the time-to-death analyses, the time of origin (T_0) will be defined separately for each analysis:

- Time from first scan showing disease progression after completion of prior treatment to death (primary analysis)
- Time from first implantation to death (secondary analysis)
- Time from diagnosis of Stage IV disease to death (secondary analysis)

6.4.1.1 Screening

Screening will occur after the ICF has been signed and within 28 days of the first implantation. Subjects will undergo all screening procedures during this time.

6.4.1.2 Baseline

Individual baselines will be established for each implant. For a given parameter, baseline for each implant will be the last recorded observation prior to the implant.

6.4.1.3 Implant 1 / Study Day 0

The day of the first implant will be designated as Implant 1 / Study Day 0.

6.4.1.4 Implant 1 / Study Day 90 ± 5 Days

Subjects will be evaluated for a second implantation which, if cleared, will occur as soon as possible after the visit on Implant 1 / Study Day 90 ± 5 days.

6.4.1.5 Implant 2 / Study Day 0

The day of the second implant will be designated as Implant 2 / Study Day 0.

6.4.1.6 Implant 2 / Study Day 90 ± 5 days

Subjects will be evaluated for a third implantation which, if cleared, will occur as soon as possible after the visit on Implant 2 / Study Day 90 ± 5 days.

6.4.1.7 Implant 3 / Study Day 0

The day of the third implant will be designated as Implant 3 / Study Day 0.

6.4.1.8 Implant 3 / Study Day 90 ± 5 days

Subjects will be evaluated for a fourth implantation which, if cleared, will occur as soon as possible after the visit on Implant 3 / Study Day 90 ± 5 days.

6.4.1.9 Implant 4 / Study Day 0

The day of the fourth and final implant will be designated as Implant 4 / Study Day 0.

6.4.1.10 End of Study (EOS) Visit

For each patient, active safety and efficacy assessments will be completed 120 days after the patient's final implant.

6.4.1.11 Follow-up

Long-term follow-up will begin after the patient's EOS visit, and will continue for the duration of each subject's life, at 6-month intervals during the first 2 years of long-term follow-up and then yearly thereafter. All examinations and treatment during this time will be guided by optimal patient care principles and the decisions of the physicians providing overall health care to each subject.

6.4.2 Assignment of data to study time points

Each data observation will be assigned both a nominal study day and an actual study day.

Type of Study Day	Definition
Actual study day	Calculated as the difference in days between date of collection and date of the **first** implant and will be used as the x-axis for plots of individual subject data over time.
Nominal study day	Calculated as the difference in days between the date of collection and the date of the **most recent implant** prior to the date of collection, regardless of the study day to which the observation was assigned at data entry (e.g., from the CRF).

Nominal study day will be Observations that do not fall within a nominal study day window (see Section 6.4.4) will be labeled as "Unscheduled" and will be listed but not summarized or analyzed. Nominal study day will be used for listings and tables (unless otherwise noted), and for figures of grouped observations over time. See Section 6.4.1.2 for the definition of Baseline observations.

6.4.3 Selection of data in the event of multiple records in a study day window

If multiple non-missing observations exist for a nominal Study Day window, all data will be listed however the last valid observation in that window will be used for summaries and analyses.

6.4.4 Visit windows definitions

The following visit window definitions will be used:

Implant	Time Window			Comment
	From Day (inclusive)	Assessment Day	To Day (inclusive)	
Pre-implant	-28	**< 0**	0	Implant 1 Baseline
1	---	**0**	---	Implant 1 Day 0
	7	**14**	21	Implant 1 Day 14 (I1 / D14)
	23	**30**	37	Implant 1 Day 30 (I1 / D30)
	53	**60**	67	Implant 1 Day 60 (I1 / D60)
	83	**90**	97	Implant 1 Day 90 (I1 / D90) if before Implant 2 or there is no Implant 2
2	---	**0**	---	≥ 98 days after Implant 1, Day 0 Implant 2 Day 0 (I2 / D0)
	7	**14**	21	Implant 2 Day 14 (I2 / D14)
	23	**30**	37	Implant 2 Day 30 (I2 / D30)
	53	**60**	67	Implant 2 Day 60 (I2 / D60)
	83	**90**	97	Implant 2 Day 90 (I2 / D90) if before Implant 3 or there is no Implant 3
3	---	**0**	---	≥ 98 days after Implant 2, Day 0 Implant 3 Day 0 (I3 / D0)
	7	**14**	21	Implant 3 Day 14 (I3 / D14)
	23	**30**	37	Implant 3 Day 30 (I3 / D30)
	53	**60**	67	Implant 3 Day 60 (I3 / D60)
	83	**90**	97	Implant 3 Day 90 (I3 / D90) if before Implant 4 or there is no Implant 4
4	---	**0**	---	≥ 98 days after Implant 3, Day 0 Implant 4 Day 0 (I4 / D0)
	7	**14**	21	Implant 4 Day 14 (I4 / D14)
	23	**30**	37	Implant 4 Day 30 (I4 / D30)
	53	**60**	67	Implant 4 Day 60 (I4 / D60)
	83	**90**	97	Implant 4 Day 90 (I4 / D90)

Implant	Time Window			Comment
	From Day (inclusive)	Assessment Day	To Day (inclusive)	
	113	**120**	127	EOS
Any visit which occurs outside the above time windows is considered "unscheduled".				

7 BASELINE CHARACTERISTICS

7.1 Demographics

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

7.2 Other Baseline Characteristics

A listing of satisfaction of each inclusion / exclusion criteria recorded in the CRF will be provided. A separate Subject Eligibility listing will include whether or not all 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.

Disease history, including cancer type, date and method of first diagnosis, treatment history and current status will be recorded in the CRF. For current diagnosis, locations of metastases and time from diagnosis to first implantation will be summarized; for previous diagnosis, tumor location will be summarized.

Contraceptive methods will be ascertained at Screening and will be recorded in the CRF. For women, childbearing potential and contraceptive methods or reason for non-childbearing potential will be listed and summarized; for men, vasectomy status and contraceptive methods will be listed and summarized.

Height and weight at Screening will be recorded in the CRF and will be included in the Baseline Characteristics listing and summary table.

8 MACROBEAD IMPLANTATION

Details of macrobead implantations will be recorded in the CRF. For each implantation, date, start and end time of the implantation procedure, the number of beads implanted with associated lot numbers, subject vital signs, anesthesia and cefazolin status will be listed. The total number of implantations, and the number of macrobeads implanted per implantation, will be summarized.

9 MEDICATION USE

Prescription, over-the-counter, and alternative medication use within 30 days of implantation and through the EOS visit will be recorded in the CRF and will be coded to generic terms using the World Health Organization Drug Dictionary (WHOdd) version 2008Q1 (March 2008) or later, B2 format. Coding will be done by DM using a computer algorithm for exact matches or manual coding for incomplete or non-matches. All coding will be reviewed by a second member of the DM team. 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 WHOdd drug class, WHOdd 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 WHOdd drug class and preferred name within drug class. Medications that were stopped within a 7-day window prior to 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, stratified by cancer type. There will be no formal hypothesis testing and no group comparisons are currently planned. The primary efficacy outcome will be all-cause mortality, as defined above in Section 3.3.1.

Secondary efficacy outcomes will be:

- Time from first implantation to death
- Time from diagnosis of Stage IV disease to death
- Changes from baseline based on MRI, CT or PET-CT scan, and other appropriate imaging techniques (e.g., sonography, bone scans, other x-rays) as indicated, if feasible.
  - In primary and/or secondary tumor size (volume, area) and
  - In state (necrosis, vascularization) on MRI, CT or PET-CT scan, and other appropriate imaging techniques (e.g., sonography, bone scans, other x-rays) as indicated.
- Change from baseline in tumor markers (CEA, CA19-9)
- Change from baseline in CA125 (as a marker of inflammation)
- Changes from baseline in:
  - Clinician Global Clinical Assessment
  - Activities of daily living
  - Symptom rating
  - Quality of life (QCQ-C30)
  - Pain scale
  - ECOG

- Additional exploratory efficacy outcomes may be analyzed if feasible and will be defined in the CSR

10.1 Efficacy Outcomes

10.1.1 All-cause mortality

All-cause mortality for primary analysis is defined as time from date of the first scan showing disease progression after completion of prior treatment (time of origin, T_0) to death from any cause. Subjects still alive at the time of analysis will be censored at that time point.

Secondary analyses of time from first implantation to death, and time from diagnosis of Stage IV disease to death, will be analyzed similarly.

For all time-to-death analyses the Kaplan-Meier curves will be presented; respective 95% two-sided confidence intervals (CIs) will be calculated.

10.1.2 Changes in tumor size and state

All available measurements will be obtained from various radiological assessments

If available, the volume of all measureable lesions will be calculated as length x width x height. Observed values and changes from baseline in relationship to both first and most recent implant will be listed for each study time point at which these data are recorded. For continuous parameters, at each time point, observed values and changes from baseline will be summarized. Nominal outcomes will be categorized and summarized as frequencies and percentages of subjects at each time point. In listings, all available measurements of all lesions and malignant lymph nodes will be shown. For summaries, mean longest diameters, volumes, and densities for a given lesion / node class (e.g., target) for each subject will be calculated and summarized, if available and feasible.

10.1.3 Change in tumor markers and other biochemical parameters

See Section 11.1.3 below for details on laboratory data collection and reporting. Clinical laboratory parameters will include the tumor markers CEA and CA 19-9. A tumor marker response is defined as a ≥ 20% decrease from baseline in one or both of CEA or CA 19-9.

Other biochemical parameters include:

- Serum enzymes and proteins
- Kidney function (creatinine, blood urea nitrogen (BUN))
- C-reactive protein
- Hematology (leukocytes, hemoglobin, differential, platelets, erythrocyte sedimentation rate (ESR))
- Cytokines
- Cellular and humoral immunity status (observed values will be clinically reviewed to determine presence / absence of each antibody, etc.)
- CA125 is included as part of the assessment of inflammatory response to macrobead placement.

Along with listings and summaries, graphical displays of individual subject observed values over time will be produced for tumor markers, CA125, C-reactive protein, and ESR.

10.1.4 Clinician and self-rating scales

Clinician and patient self-rating scales will be recorded in the CRF. Observed values and changes from baseline in relationship to both first and most recent implant will be listed for each study time point at which these data are recorded. For continuous or discrete outcomes, observed values and changes from baseline will be summarized at each time point. Nominal outcomes will be categorized and summarized as frequencies and percentages of subjects at each time point. Each rating scale to be evaluated is described below.

10.1.4.1 Global Clinical Assessment (GCA)

The GCA is done by the clinician and measures patient clinical status via a visual analog scale (VAS). GCA 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.

10.1.4.2 Activities of daily living (ADL) rating / Karnofsky performance status (KPS) scale

ADL / KPS 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).

10.1.4.3 Quality of life scale / EORTC QLQ-C30

Quality of life will be assessed using the European Organisation for Research and Treatment in Cancer (EORTC) Quality of Life Questionnaire (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).

10.1.4.4 Pain scale

Subjects will be asked to rate their pain on a discrete scale (from 0 = "no pain" to 10 = "worst pain imaginable, unbearable"). Specific anatomical locations of pain will also be recorded.

10.1.4.5 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:

Status	Description
0	Fully active, able to carry on all pre-disease performance without restriction
1	Restricted in physically strenuous activity but ambulatory and able to carry out work of a light or sedentary nature, e.g., light 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

Status	Description
4	Completely disabled. Cannot carry on any self-care. Totally confined to bed or chair
5	Dead

10.2 Statistical Analysis Methods

- All statistical testing will be considered strictly exploratory as the study was not powered based on statistical considerations.
- Exact 95% CIs will be calculated for rates.
- Survival analysis methods will be used analyze time-to-event outcomes; for non-mortality outcomes, the term “survival” will still be used to describe non-occurrence of the event being analyzed. Kaplan-Meier plots with 95% CIs will be generated to show probability of survival as a function of time since implantation. In addition, Kaplan-Meier estimates of the median survival time will be reported.
- The relationship between times from diagnosis of Stage IV disease diagnosis to the primary analysis time of origin and primary analysis time of origin to death will be examined (if feasible) using Cox regression model and Kaplan-Meier curves.
- The relationship between time-to-event outcomes and tumor markers (and other covariates, if feasible) will be assessed using Cox regression. Kaplan-Meier plots will be produced for descriptive assessment.
- Survival comparisons by implantation number will be performed, if feasible.
- Other explorations of efficacy data may be performed (if feasible), such as:
  - Testing for effects of baseline values of tumor markers and presenting stratified descriptive statistics, if deemed appropriate.
  - Plotting chronological subject profiles of specific parameters; i.e., plotting a set of parameters over time on the same graph for a given subject.

11 SAFETY ANALYSES

Safety parameters will be listed and summarized for all implanted subjects, stratified by cancer type. 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, weight, 12-lead ECG parameters, 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 EOS visit (120 days after the last implant) or at time of patient death or withdrawal, whichever occurs first.

Reasons why surviving patients received < 4 implants will be summarized. These reasons can include patient request (voluntary withdrawal), AE, protocol violation, request of Investigator or Regulatory Authority, request of Sponsor, lost to follow-up or other. One reason will be specified per patient.

Dates of Screening, date of the first scan showing disease progression after completion of prior treatment and the date of each implant will be listed.

Number and percentage of patients receiving 1, 2, 3 or 4 implants will be summarized. For all patients who received at least one implant, the number of days on study after each implantation will be summarized.

11.1.2 Adverse Events

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 120 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) version 10.1 (released by MedDRA MSSO SEP 2007) or higher. 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. All coding will be reviewed by a second member of the DM team. The Medical Monitor will review and approve the final coding prior to database lock.

A treatment-emergent AE (TEAE) will be defined as an AE that began or worsened during or after the first implantation and within 120 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 AEs will be listed, but only TEAEs will be summarized and analyzed.

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, remotely related, possibly related, probably 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, including incidence, severity and relationship to study treatment (implantation). TEAEs will be reported overall, as well as by SOC and PT. 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 over all implantations, as well as by implantation number.

Serious adverse events (SAEs) will also be summarized. SAEs and AEs that resulted in study discontinuation (as previously defined) will be listed separately.

Missing severity will be considered severe and missing relationship will be considered "probably related." If the same TEAE is experienced more than once by a given subject, the TEAE will be counted only once for that subject. 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, only the most related TEAEs will be tabulated.

Deaths will be summarized separately, showing incidence of death overall, cancer-related death and cancer-related death by implantation number.

11.1.3 Clinical laboratory evaluations

Hematology, coagulation, serum chemistry, serum pregnancy, urinalysis, immunology, immunophenotyping, and all other laboratory parameters including those listed in Protocol Section 5.6 will be analyzed at multiple laboratory sites and will be delivered via hard-copy reports to the central data processing center (VSI). 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) v3.0 toxicity grade (if applicable) will be listed. Laboratory observations with Grade 3 or higher toxicity and/or reported as an AE will be listed. For all parameters, study day, date collected, observed value, normal range, and out-of-range flag will be output to a spreadsheet. 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 laboratory 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 and/or toxicity grades from baseline (in relationship to both first and most recent implant) to each subsequent time point at which laboratory data are collected.

11.1.4 Vital signs and weight

Vital signs (blood pressure, respiration rate, heart rate, and temperature) and weight will be obtained at each study visit. In addition, at-home blood pressure, heart rate, and temperature recordings will be logged by subjects or their caregivers twice daily at 8 A.M. and 8 P.M. for the first month after implantation, then once a day for the following two months. The investigators may modify this schedule, depending on clinical circumstances. Both in-clinic and at-home data will be recorded in the CRF. In-clinic and at-home vital signs will be listed separately. Listings will include the study day, date and observed values. In-clinic data will include the change from baseline in relationship to both first and most recent implant. At-home data will be considered unscheduled data, and will be listed but will not be summarized or analyzed.

11.1.5 12-Lead electrocardiogram (ECG)

Data from standard 12-lead ECGs will be recorded in the CRF. The following parameters will be collected: rhythm (normal / abnormal), heart rate, and PR, QRS, QT and QTcB intervals. The listing will include study day, date, observed values, and, for continuous parameters, change from baseline in relationship to both first and most recent implant. At each time point, observed values and changes from baseline in relationship to both first and most recent implant will be summarized for continuous parameters; nominal parameters will be categorized and summarized as frequencies and percentages of subjects at each time point.

11.1.6 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, date, body system, status (normal, abnormal or not examined), and specification (if abnormal) will be listed. Numbers and percentages of subjects with abnormal findings for each body system will be summarized.

11.1.7 Murine antigens skin test

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

11.1.8 Murine leukemia virus

Results from murine leukemia virus testing will be recorded in a separate spreadsheet. 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 (as applicable), and all applicable U.S. Food and Drug Administration regulations. This SAP supersedes any statistical considerations identified in the study protocol. Any differences between this statistical analysis plan and the study protocol will be presented and explained in the CSR.

14 SOFTWARE

Tables, listings, figures, and analyses will be produced using SAS® Version 9.1.3 or higher (SAS Institute Inc., Cary, NC), Microsoft® Excel version 2007 or higher (Microsoft Corp., Redmond, WA).

15 REFERENCES

Aaronson NK, Ahmedzai S, Bergman B, Bullinger M, Cull A, Duez NJ, Filiberti A, Flechtner H, Fleishman SB, de Haes JCJM, Kaasa S, Klee MC, Osoba D, Razavi D, Rofe PB, Schraub S, Sneeuw KCA, Sullivan M, Takeda F. The European Organisation for Research and Treatment of Cancer QLQ-C30: A quality-of-life instrument for use in international clinical trials in oncology. *Journal of the National Cancer Institute* 1993; **85:** 365-376.

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.

16 APPENDICES

16.1 Listings

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End of Analysis Plan