The following protocol information is provided solely to describe how the authors conducted the research underlying the published report associated with the following article:

Safety and Survival with GVAX Pancreas Prime and Listeria Monocytogenes-Expressing Mesothelin (CRS-207) Boost Vaccines for Metastatic Pancreatic Cancer

Le, et al

DOI: 10.1200/JCO.2014.57.4244

CLINICAL PROTOCOL

TITLE OF STUDY:

A Phase 2, Randomized, Multicenter, Open-Label Study of the Efficacy and Immune Response of the Sequential Administration of GVAX Pancreas Vaccine (with Cyclophosphamide) Alone or Followed by CRS-207 in Adults with Metastatic Pancreatic Adenocarcinoma

Protocol ID: **ADU-CL-01**

Sponsor: **Aduro BioTech**
626 Bancroft Way, #3C
Berkeley, CA 94710-2224
Phone: 510-848-4400
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IND: **14,678**

Date of Issue: **06 July 2011, Version 3**

Signatures of Approval for Protocol (Version 3)

Affiliation	Name	Signature	Date:
Investigator:	Dung Le, MD		
Sponsor:	Dirk Brockstedt, Ph.D.		
Medical Monitor:	John Grous, M.D.	MD	July 7, 2011

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Affiliation	Name	Signature	Date:
Investigator:	Dung Le, MD		7/7/11
Sponsor:	Dirk Brockstedt, Ph.D.		7/8/2011
Medical Monitor:	John Grous, M.D.		

This study is to be performed in accordance with Good Clinical Practice, the ethical principles that have their origin in the Declaration of Helsinki: Title 21 of the Code of Federal Regulations Parts 50 (Protection of Human Subjects), 56 (Institutional Review Boards), and 312 (Investigational New Drug Application); and International Conference on Harmonisation E6 (Guideline for Good Clinical Practice).

Study Sponsor:	Aduro BioTech 626 Bancroft Way, #3C Berkeley, CA 94710-2224 Phone: 510-848-4400 Fax: 510-848-5614
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STUDY SYNOPSIS

Name of Sponsor Company: Aduro BioTech	**Individual Study Table Referring to Part of the Dossier**	***(For National Authority Use Only)***
Name of Finished Product: Cytoxan; GVAX pancreas vaccine; CRS-207	**Volume:**	
Name of Active Ingredients: Cyclophosphamide; Panc 10.05 pcDNA1/GM-Neo, Panc 6.03 pcDNA1/GM-Neo; *Lm* Δ*actA*/Δ*inlB*/hMesothelin	**Page:**	

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Primary Investigator: Dung Le, M.D.

Number of Sites: Up to 12

Phase of Development: Phase 2	**Treatment Period:** 5 months	**Study Duration:** 42 months

Objectives:

Primary:

- To compare overall survival in subjects receiving sequential administration of cyclophosphamide, GVAX pancreas vaccine and CRS-207 with overall survival in subjects receiving cyclophosphamide and GVAX vaccine alone

Secondary:

- To assess safety of the cyclophosphamide, GVAX pancreas vaccine, and CRS-207 treatment regimen

Exploratory:

- To assess the association of *Listeria monocytogenes (Lm)* and mesothelin-specific T-cell and other immunological responses with overall survival in subjects receiving test treatments
- To evaluate overall response rate in subjects with measureable disease per Response Evaluation Criteria in Solid Tumors (RECIST) receiving test treatments
- To measure tumor marker kinetics in subjects receiving test treatments

Methodology:

The study is an open-label, randomized, multicenter clinical study in adults with metastatic pancreatic adenocarcinoma who have received or refused at least one chemotherapy treatment.

At least 90 subjects will be enrolled and randomized in a 2:1 fashion into two treatment arms. Both treatment arms will receive up to six doses of vaccine 3 weeks apart (one cycle). Treatment Arm A will receive two doses of cyclophosphamide and GVAX pancreas vaccine and up to four doses of CRS-207. Treatment Arm B will receive up to six doses of cyclophosphamide and GVAX pancreas vaccine.

Treatment Arm	Number of Subjects	Treatment and Dose	Treatment Cycle
A	60	Cyclophosphamide (200 mg/m^2), GVAX pancreas vaccine (5×10^8 cells), CRS-207 (1×10^9 CFU)	Weeks 1 and 4: Cyclophosphamide (Day 1) GVAX pancreas vaccine (Day 2) Weeks 7, 10, 13, and 16: CRS-207 (Day 1)
B	30	Cyclophosphamide (200 mg/m^2), GVAX pancreas vaccine (5×10^8 cells)	Weeks 1, 4, 7, 10, 13, and 16: Cyclophosphamide (Day 1) GVAX pancreas vaccine (Day 2)

CFU = colony-forming unit.

STUDY SYNOPSIS (continued)

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To monitor initial safety of the sequential vaccine regimen, no more than one subject will be enrolled per week for the first six subjects. If any limiting toxicities are observed during the study (see Section 3.6 of the Protocol), the data will be reviewed with the Data Monitoring Committee (DMC) and the dose may be lowered to 1×10^8 colony-forming units (CFU) for all subsequent dosing with CRS-207.

Subjects will return to the study site approximately 4 weeks after their final treatment for safety and immune response evaluations. They will continue to be followed by phone or optional clinic visit for subsequent cancer-related therapies, overall response rate, and *Lm*- and mesothelin-specific immune responses (at clinic visits only) for the duration of the study until all subjects have reached at least 24 months of follow-up or death.

At the investigator's discretion, subjects may receive additional treatment cycles of the assigned treatment regimen if they are clinically stable and meet dosing requirements.

Number of subjects (planned):
At least 90 subjects with metastatic pancreatic adenocarcinoma satisfying all eligibility criteria will be enrolled. With an expected enrollment rate of five patients per month, the accrual period would be 18 months, which, with the 24 months of follow-up of each patient, yields a maximum total study time 42 months. An interim analysis will be conducted after 33 subjects have died; this is one-half the total number of deaths required for the final analysis. The study may be terminated after that interim analysis if results meet prespecified stopping criteria or if the DMC recommends stopping on the basis of clinical judgment and guidelines in their charter and the sponsor accepts the recommendation. Details of the interim analysis and criteria are outlined in the Protocol and will be fully described in the DMC charter and statistical analysis plan (SAP).

Subject discontinuation:
A subject may be removed from the study for the following reasons:
(1) Occurrence of an adverse event that presents an unacceptable consequence or risk to the subject
(2) Development of an illness or complication (including progressive disease) that justifies withdrawal from the study, as determined by the investigator and medical monitor
(3) Noncompliance: failure to receive clinical study medication or treatment as mandated by the protocol, failure to comply with protocol requirements, or unauthorized subject-initiated changes in dosing regimen
(4) Refusal of clinical trial material administration by the subject
(5) Dose cohort, treatment arm, or study discontinued by the sponsor

Subjects who withdraw consent or are removed from the study before completing one treatment cycle may be replaced at the discretion of Aduro BioTech. The replacement subject will be enrolled in the same treatment arm as the dropout. Subjects who have disease progression may be allowed to continue in the study if the investigator believes they are deriving some benefit from the therapy.

STUDY SYNOPSIS (continued)

Name of Sponsor Company: Aduro BioTech	**Individual Study Table Referring to Part of the Dossier**	***(For National Authority Use Only)***
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Inclusion criteria:

(1) Have histologically proven malignant adenocarcinoma of the pancreas; measurable disease is not required (Subjects with mixed histology will be included if the predominant component is adenocarcinoma. Subjects must have metastatic disease.)
(2) Have received or refused at least one chemotherapy regimen
(3) Be at least 18 years of age
(4) Have an Eastern Cooperative Oncology Group performance status of 0 or 1
(5) Have an anticipated life expectancy of greater than 12 weeks
(6) For women and men of childbearing potential, a medically acceptable method of highly effective contraception (oral hormonal contraceptive, condom plus spermicide, or hormone implants) must be used throughout the study period and for 28 days after their final vaccine administration (A barrier method of contraception must be employed by all subjects [male and female], regardless of other methods.)
(7) Be willing and able to give written informed consent, and be able to comply with all study procedures
(8) Have adequate organ function, as defined by the laboratory values in Table 1

Table 1. Required Laboratory Values for Study Inclusion

Hematologic	Renal	Hepatic
WBC ≥3,500/μL ANC ≥1,500/μL Platelets ≥90 × 10^3/μL Hemoglobin ≥9 g/dL CD4 ≥0.2 × 10^9/L	Creatinine ≤2.0 × ULN	AST/ALT <2.0 × ULN Alkaline phosphatase <2.5 × ULN Bilirubin < ULN

ALT = alanine aminotransferase; ANC = absolute neutrophil count; AST = aspartate aminotransferase; ULN = upper limit of normal; WBC = white blood cell.

STUDY SYNOPSIS (continued)

Name of Sponsor Company: Aduro BioTech	**Individual Study Table Referring to Part of the Dossier**	***(For National Authority Use Only)***
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Exclusion criteria:

(1) Have a known history or evidence of brain metastases
(2) Have a known allergy to both penicillin and sulfa
(3) Have an artificial (prosthetic) joint or other artificial implant or device that cannot be easily removed (Dental and breast implants are allowed if there is no history of infection of the implants and no clinically significant adverse events associated with the implants. Biliary stents and mediports will be allowed; however mediports cannot be used for infusion or blood draw from time of CRS-207 dosing through 4 days post-dose.)
(4) Have any evidence of hepatic cirrhosis or clinical or radiographic ascites
(5) Have had a pulmonary embolism or venous thromboembolism within 2 months of study enrollment
(6) Have radiographic or clinically significant pleural effusion
(7) Have known or suspected hypersensitivity to GM-CSF, hetastarch, pentastarch, corn, dimethyl sulfoxide, fetal bovine serum, trypsin (porcine origin), yeast, or any other component of GVAX pancreas vaccine or CRS-207 (e.g., glycerol)
(8) Have any immunodeficiency disease or immunocompromised state (e.g., use of immunosuppressive agents, chemotherapy or radiation therapy within 14 days of study treatment)
(9) Have received a diagnosis of HIV, hepatitis B, or hepatitis C (Subjects who are hepatitis C antibody positive may be enrolled if they are confirmed with negative viral load at screening.)
(10) Have active autoimmune disease or history of autoimmune disease requiring systemic steroids or other immunosuppressive treatment
(11) Have used any systemic steroids within 28 days of study treatment
(12) Use more than 3 g/d of acetaminophen
(13) Have received an investigational product within 28 days of study treatment or planned to receive within 28 days after vaccine administration
(14) Have had major surgery or significant traumatic injury occurring within 28 days before treatment administration or anticipated surgery or procedure requiring general anesthesia during the study participation (including 28 days after last dose of CRS-207) (Minor procedures [dental work, skin biopsy, etc.], celiac plexus block, and biliary stents are allowed.)
(15) Have an unhealed surgical wound
(16) Be a woman who is pregnant or breastfeeding
(17) Have clinically significant heart disease (such as uncontrolled angina, myocardial infarction within last 3 months, congestive heart failure of New York Heart Association III or IV)
(18) Have valvular heart disease that requires antibiotic prophylaxis for prevention of endocarditis
(19) Have oxygen saturation <92% on room air, as measured by pulse oximeter
(20) Have an intercurrent illness that is either life-threatening or of clinical significance such that it might limit compliance with study requirements (Such illnesses include, but are not limited to, ongoing or active infection, metabolic or neurologic disease, peripheral vascular disease, or psychiatric illness.)

STUDY SYNOPSIS (continued)

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Exclusion criteria, cont.:

(21) Have insufficient peripheral venous access to permit completion of the study dosing and compliance with study phlebotomy regimen
(22) Be unwilling or unable to follow the study schedule for any reason
(23) Have a history of alcohol dependence or use of illicit drugs (e.g., opioids, cocaine, amphetamines, hallucinogens, etc.) that could potentially interfere with adherence to study procedures or requirements
(24) Be unable to avoid close contact with another individual known to be at high risk of listeriosis (e.g., newborn infant, pregnant woman, HIV-positive individual) during the course of CRS-207 treatment until completion of antibiotic regimen

Dose eligibility:

Subjects must have adequate organ function as defined by the laboratory values in Table 2 before dosing on Day 1 of dosing weeks. Laboratory tests may be done up to 72 hours before dosing on Day 1.

Table 2. Dosing-Eligibility Requirements

Hematologic	Renal	Hepatic
WBC ≥3,500/μL ANC ≥1,500/μL Platelets ≥90 × 10^3/μL Hemoglobin ≥9 g/dL	Creatinine ≤2.0 × ULN	AST/ALT ≤2.5 × ULN Bilirubin ≤1.5 × ULN

ALT = alanine aminotransferase; ANC = absolute neutrophil count; AST = aspartate aminotransferase; ULN = upper limit of normal; WBC = white blood cell.

Prohibited medications:

The following therapies are not permitted during the study treatment period and may result in early termination of the subject from treatment:

- Anticancer chemotherapy or nonstudy immunotherapy (approved or investigational)
- Systemically active steroids for more than 2 days or use of any systemic steroids during the treatment period or within 28 days before or after dosing
- Another investigational product

In addition, the following therapies should not be administered unless medically necessary, and approval must be obtained from the medical monitor for a subject to continue dosing if therapy is given concurrently with study participation:

- General anesthesia or deep sedation
- Aspirin >325 mg/d (chronic daily use of aspirin ≤325 mg/d and heparin flushes for central lines are allowed)
- More than 4 g/d of acetaminophen
- Systemic antibiotics

STUDY SYNOPSIS (continued)

Name of Sponsor Company: Aduro BioTech	**Individual Study Table Referring to Part of the Dossier**	***(For National Authority Use Only)***
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Test product, dose, and mode of administration:
CRS-207: 1×10^9 CFU reconstituted in 250 mL 0.9% sodium chloride and administered intravenously over 2 hours

Cyclophosphamide (Cytoxan): 200 mg/m^2 in 100 mL normal saline administered intravenously over 30 minutes

GVAX pancreas vaccine (Panc 6.03 and Panc 10.05 pancreatic tumor vaccine): intradermal injections of the allogeneic pancreatic tumor vaccine containing 5×10^8 cells (2.5×10^8 of each cell line)

Study duration:
The duration of one treatment cycle (i.e., six doses) will be 20 weeks. Subjects will be considered in the treatment period until 4 weeks after their final study dose, after which they will be in follow-up until death, early discontinuation, or completion of follow-up. Subjects will be followed for the duration of the study until all subjects have reached at least 24 months of follow-up or death. At the conclusion of the study, all remaining subjects will be offered enrollment in a long-term follow-up protocol.

Reference therapy, dose, and mode of administration:
There is no reference therapy or placebo administered in this study.

Criteria for Evaluation:
Efficacy: Overall survival will be measured from the first cyclophosphamide treatment until death or 24 months of follow-up (or death) of last subjects enrolled. The cellular and humoral immune responses directed against *Lm* and mesothelin will be assessed by using enzyme-linked immunosorbent spot, intracellular cytokine staining, and enzyme-linked immunosorbent assay. Overall response rate will be assessed by using RECIST and immune-related response criteria (irRC). Tumor marker kinetics will be measured through serum CA19-9 and carcinoembryonic antigen (CEA) levels, as applicable.

Safety: Safety will be assessed by collection of data on adverse events, vaccine-site reactions, vital signs, physical examination, clinical hematology, and serum chemistry.

Data analysis:
The data will be summarized in tables listing the mean, standard deviation, median, minimum, maximum, and number of subjects in a group for continuous data; in tables listing count and percentage for categorical data; and median and standard error for time-to-event data. Data will be listed for each subject. Statistical analyses will be performed and data appendices will be created by using SAS. The effects of noncompliance, dropouts, and covariates will be assessed to determine the impact on the general applicability of results from this study.

The efficacy analysis will be conducted on the full analysis set and per protocol analysis set. The full analysis set will consist of all randomized subjects who receive at least one dose of cyclophosphamide. The per protocol analysis set will consist of all subjects with metastatic pancreatic adenocarcinoma who receive at least three doses (at least one dose of CRS-207 in Treatment Arm A or three doses of cyclophosphamide/GVAX pancreas vaccine in Treatment Arm B). The primary efficacy parameter will be overall survival, which will be analyzed by log-rank test for the between arm comparison.

STUDY SYNOPSIS (continued)

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Data analysis, cont.:
For the full analysis set, if the true median survival for the sequential treatment is 8.1 months, and that for GVAX alone is 5 months, the sample size of N = 90 has approximately 80% power to yield a statistically significant difference (alpha = 0.15, 1-sided). Power is computed for a 2-stage group sequential design with a single interim analysis at half the total study "information" (i.e., 66 deaths total; interim analysis after 33 deaths) and with O'Brien-Fleming–like alpha spending function (gamma = −4). Details of the group sequential design and stopping criteria will be contained in the DMC charter or the statistical analysis plan (SAP).

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LIST OF APPENDICES

LIST OF ABBREVIATIONS

actA	*Listeria monocytogenes* protein encoded by *actA* gene and responsible for mediating host cell actin nucleation and actin-based motility
AE	adverse event
ALT	alanine aminotransferase
ANC	absolute neutrophil count
APTT	activated partial thromboplastin time
AST	aspartate aminotransferase
BP	blood pressure
BUN	blood urea nitrogen
CBC	complete blood count
CEA	carcinoembryonic antigen
CFR	Code of Federal Regulations
CFU	colony-forming unit
CRF	case report form
CT	computed tomography
CTCAE	Common Terminology Criteria for Adverse Events
CTM	clinical trial material
D	study day
DMC	data monitoring committee
ECOG	Eastern Cooperative Oncology Group
EDC	electronic data capture
ELISA	enzyme-linked immunosorbent assay
ELISPOT	enzyme-linked immunosorbent spot
FAS	full analysis set
GM-CSF	granulocyte-macrophage colony-stimulating factor
HLA	human leukocyte antigen
hMesothelin	human mesothelin
IB	Investigator's Brochure
ICF	informed consent form
ICH	International Conference on Harmonisation
inlB	internalin B
IRB	institutional review board
irRC	immune-related response criteria
LDH	lactate dehydrogenase
Lm	*Listeria monocytogenes*
MHC	major histocompatibility complex
MRI	magnetic resonance imaging
PBMC	peripheral blood mononuclear cells
PHI	protected health information
RECIST	Response Evaluation Criteria in Solid Tumors
SAE	serious adverse event
SAP	Statistical Analysis Plan
SOP	standard operating procedure
SPM	study procedures manual
UA	urinalysis
ULN	upper limit of normal
WBC	white blood cell

1.0 INTRODUCTION

1.1 BACKGROUND

Exocrine pancreatic cancers account for approximately 2% of new cancers diagnosed each year in the United States, and this disease is the fourth leading cause of cancer death for men and women.[1] Patients with local disease who undergo surgical resection (approximately 10% to 15% of all pancreatic carcinoma patients) have an estimated median survival of approximately 18 months, and approximately 20% of patients survive for 5 years.[2] Over 80% of pancreatic cancers are not diagnosed until regional or distant disease is present and patients are no longer amenable to surgical resection. Patients with metastatic disease have an estimated survival of only 3 to 6 months, and the 5-year survival rate after diagnosis in this cohort is less than 5%.[3]

1.1.1 Current Therapies for Pancreatic Cancer

Combination chemotherapy with gemcitabine provides a survival advantage for patients with advanced disease that is more favorable than treatment with 5-fluorouracil for improvement in pain, performance status, and weight gain.[4, 5] To date, the oral tyrosine kinase inhibitor erlotinib (Tarceva) is the only drug demonstrated to prolong survival when administered in combination with gemcitabine, although this combination regimen provides only a slight increase in median survival when compared with that for gemcitabine alone (6.24 months compared with 5.91 months, $p = 0.038$).[6] Further evaluations are continuing with gemcitabine and combinations for patients with resectable and locally advanced disease. However, the limited success of all modalities for treatment of pancreatic cancer indicates the critical need for novel therapies.[7-9] Recent progress in the understanding of immune surveillance and the requirements for successful cancer immunotherapy lends encouragement for continued evaluation of newer immunotherapy treatment methods.[10-12]

1.1.2 *Listeria monocytogenes*-Based Vaccine Therapy

Listeria monocytogenes (*Lm*) is an attractive platform for presentation of tumor-associated antigens and activation of immune response directed against cancer cells. *Lm* provides both a potent stimulation of innate immunity and also stimulates an adaptive immune response through recruitment and activation of

CD4+ and CD8+ T-cell immunity specific for encoded heterologous antigens.[13-16] Aduro BioTech developed a live-attenuated *Lm* platform strain (*Lm* Δ*actA*/Δ*inlB*), known as ANZ-100 (previously CRS-100), which has deletions of two genes, *actA* and *inlB*, that encode the virulence-determinant proteins ActA and Internalin B, respectively. These two proteins facilitate cell-to-cell spread and invasion of nonphagocytic cells, and deletion of *actA* and *inlB* in ANZ-100 results in 1,000-fold attenuation of these processes in mice as compared with wild-type *Lm*.[17] Uptake of ANZ-100 by macrophages and other phagocytic cells in the liver and spleen is still retained and results in a local inflammatory response as well as activation and recruitment of natural killer cells and T cells to the liver. ANZ-100 underwent clinical evaluation in a Phase 1 dose-escalation study after intravenous administration in adults with carcinoma and liver metastases and was found to be safe and well tolerated at doses up to 3×10^8 colony-forming units (CFU).

ANZ-100 has additionally been engineered to express mesothelin, and the resulting strain has been termed CRS-207. Mesothelin is a tumor-associated antigen with limited expression on the surface of normal tissues, but highly expressed by several human tumors, including pancreatic adenocarcinomas.[18-20] This feature makes mesothelin an attractive target for active tumor-specific immunotherapy. This assessment is confirmed by reports that positive clinical outcomes correlate with induction of mesothelin-specific cellular immunity in patients with pancreatic carcinoma after vaccination with an irradiated allogeneic whole-cell vaccine encoding granulocyte-macrophage colony-stimulating factor (GM-CSF), GVAX pancreas vaccine. A dose-dependent systemic antitumor response was reported in this Phase 1 clinical study, and progression-free and overall survival appeared to correlate with mesothelin-specific cell-mediated immune response.[21, 22]

CRS-207 was constructed by using the ANZ-100 strain by inserting a human mesothelin expression cassette integrated at the *inlB* locus. After uptake of CRS-207 by dendritic cells and macrophages, mesothelin is expressed and released into the cytosolic compartment and subsequently processed through the endogenous MHC Class I presentation pathway, resulting in activation of mesothelin-specific cell-mediated immunity. Other mechanisms to activate mesothelin-specific, cell-mediated immunity may include uptake and cross-presentation of antigens by dendritic cells and other cells after infection by CRS-207 and apoptosis.

Nonclinical studies have shown that CRS-207 elicits mesothelin-specific cellular immunity in mice and nonhuman primates and demonstrates therapeutic efficacy in tumor-bearing mice (refer to the Investigator's Brochure [IB] for details). Findings in a Good Laboratory Practice repeated-dose study in cynomolgus monkeys showed that treatment with up to 3×10^{10} CFU of CRS-207 resulted in no changes related to body weight, food consumption, or body temperature and in no findings related to ocular or functional cardiovascular evaluations. CRS-207 was detected in the blood at 24 hours after administration, but was undetectable at 72 hours. There were transient and dose-dependent decreases in red blood cell, platelet, and white blood cell counts. Hepatic and renal function changes were transient and generally less than twofold from that at baseline status. Overall, these safety and toxicology studies demonstrated an acceptable safety profile for CRS-207.

A Phase 1 study (VAC07001) has been completed with CRS-207 administered intravenously to determine the maximum tolerated dose and to explore the safety profile in subjects with mesothelioma, non–small-cell lung cancer, ovarian cancer, or pancreatic adenocarcinoma who had failed standard therapy. CRS-207 was found to be well tolerated at doses of 1×10^8 and 1×10^9 CFU. Adverse events (AEs) such as fevers, chills, and nausea reported as the most common, immediate, transient, mild, and temporally related to CRS-207 administration were self-correcting and were resolved by the time of the subjects' discharge. Lymphopenia was observed in all doses (1×10^8, 3×10^8, 1×10^9, and 1×10^{10} CFU), and transaminase elevations were observed at doses of 3×10^8, 1×10^9, and 1×10^{10} CFU. Both were dose dependent, although transient and not considered clinically significant. Two CRS-207-related serious adverse events (SAEs) were reported. One SAE of moderate constipation occurred in one subject after the second dose of CRS-207 at 1×10^8 CFU. The second SAE, a significant decrease in blood pressure (BP) after infusion, occurred in another subject after one dose of CRS-207 at 1×10^{10} CFU. This subject required aggressive fluid management and recovered to baseline status within 24 hours. No shedding of CRS-207 in the urine or stools was observed at any dose.

1.1.3 Cell-Based Immunotherapy

Immunotherapy is a novel therapeutic approach that has the ability to recruit and activate tumor-specific T cells and induce a cytotoxic response. The lethally irradiated allogeneic GVAX pancreas vaccine was developed from GM-CSF–

secreting pancreatic cancer lines Panc 10.05 and Panc 6.03 and has been shown to prime a systemic immune response in patients with resected pancreatic adenocarcinoma.[23] This approach is based on the concept that certain cytokines are required at the site of the tumor to effectively prime cancer-specific immunity. GM-CSF is the critical growth and differentiation factor for dendritic cells, the most potent professional antigen-presenting cell responsible for priming immune responses against infectious agents and tumor antigens.

Panc 10.05 and Panc 6.03 were originally developed from neoplastic tissue harvested from surgical specimens of patients undergoing pancreaticoduodenectomy at The Johns Hopkins Hospital and were genetically modified to secrete GM-CSF.[24, 25] These cells have been irradiated with 15,000 rads, and frozen in liquid nitrogen; upon thawing, they secrete GM-CSF at 80 to 90 ng/10^6 cells per 24 hours for up to 5 days in culture.[24, 26] Additionally, the cells express mesothelin, have undergone extensive regulatory testing, and maintain GM-CSF secretion, MHC class I levels, cytokeratin-positive staining, and the original K-ras mutation.[24] Safety and feasibility to produce and administer this vaccine have been demonstrated.[21, 23]

There are specific data to suggest that immune-modulating doses of the chemotherapy agent cyclophosphamide (Cytoxan) enhance vaccine-induced antitumor immune responses by inhibiting CD4+/CD25+ regulatory T-cell activity.[22, 27-29] In a previous Phase 2 clinical study (J0206) in subjects with advanced pancreatic cancer, a higher rate of induction of mesothelin-specific T-cell responses as well as longer overall survival were seen in subjects receiving GVAX pancreas vaccine given 24 hours after cyclophosphamide than in subjects receiving GVAX pancreas vaccine alone (median survival from first vaccinations: 129.5 days vs. 69 days, $p = 0.395$).[23] Treatment-related AEs were self-limiting (lasted up to 1 week) and included fever, rigors, rash, and pain at the injection sites. One subject experienced Grade 3/4 leukocytosis, dehydration, and fatigue. Overall, GVAX pancreas vaccine (5×10^8 cells) combined with cyclophosphamide (250 mg/m^2) was safe, had minimal toxicity, and was feasible to administer.

1.2 RATIONALE

Nonclinical studies in mice have shown a synergistic effect between GVAX and *Lm*-based vaccines in inducing immune response. Mice primed with GVAX

before a *Lm* vaccine boost 14 days later showed a significant increase in interferon gamma–secreting self-reactive CD8+ T cells than mice that received the *Lm* vaccine ($p = 0.0056$) or GVAX vaccine alone ($p = 0.0007$). Mice primed with GVAX pancreas vaccine before receiving the mouse version of CRS-207 (*Lm* Δ*actA*Δ*inlB* encoding the mouse homolog of mesothelin, *Lm* mMeso) also had significantly reduced tumor growth as compared with mice that received GVAX pancreas vaccine or *Lm* mMeso alone.

Preliminary clinical data suggest that sequential therapy with cyclophosphamide, GVAX pancreas vaccine, and CRS-207 has a positive effect on overall survival in patients with metastatic pancreatic cancer. In a Phase 2 study (J0501) investigating cyclophosphamide and GVAX pancreas vaccine in this population who had failed standard therapy, the median overall survival for the 13 subjects who received six doses of cyclophosphamide and GVAX pancreas vaccine was 9 months from the time of consent. Two of these subjects subsequently enrolled in the CRS-207 Phase 1 study (VAC07001) that included subjects with mesothelioma, non–small-cell lung cancer, ovarian cancer, or pancreatic adenocarcinoma who had failed standard therapy. Of the two subjects who received both GVAX pancreas vaccine (with cyclophosphamide) and CRS-207, one subject survived for 20 months after consent in the GVAX study, and one subject was still alive with ongoing survival since the GVAX study of 48 months (as of 01 March 2011). Median survival for the 11 subjects who did not receive CRS-207 after cyclophosphamide and GVAX pancreas vaccine was 8 months. In the CRS-207 Phase 1 study, 7 patients with pancreatic cancer were enrolled. Of these 7 subjects, 3 had received prior GVAX pancreas vaccine (2 discussed above in the J0501 study and 1 who received GVAX pancreas vaccine without cyclophosphamide in another study). The median survival from the first dose of CRS-207 for these 3 subjects was 17 months, whereas the median survival for subjects with pancreatic cancer who received CRS-207 but not prior GVAX pancreas vaccine therapy was 5 months. These results suggest that priming of the immune system with GVAX pancreas vaccine before CRS-207 boost enhances overall survival, possibly through induction of mesothelin-specific T-cell response.

The proposed routes of administration and doses of cyclophosphamide (200 mg/m^2) and GVAX pancreas vaccine (5×10^8 cells) for this study have been used previously and were well tolerated.[23, 30] The proposed dose level of CRS-207 (1×10^9 CFU) was well tolerated in the prior Phase 1 study

(VAC07001). Because cyclophosphamide, GVAX pancreas vaccine, and CRS-207 have each been previously shown to be safe at the proposed dose levels and the treatments will be administered sequentially (at least 3 weeks apart), no new significant AEs are expected with this treatment regimen. This study will be the first to investigate the efficacy, immunogenicity, and safety of cyclophosphamide and GVAX pancreas vaccine therapy given in sequence with CRS-207 in subjects with metastatic pancreatic adenocarcinoma.

2.0 OBJECTIVES

2.1 PRIMARY OBJECTIVE

The primary objective of this study is to compare overall survival in subjects receiving sequential administration of cyclophosphamide, GVAX pancreas vaccine and CRS-207 with overall survival in subjects receiving cyclophosphamide and GVAX vaccine alone.

2.2 SECONDARY OBJECTIVES

The secondary objectives of this study are as follows:

- To assess safety of the cyclophosphamide, GVAX pancreas vaccine, and CRS-207 treatment regimen

2.3 EXPLORATORY OBJECTIVES

The exploratory objectives are as follows:

- To assess the association of *Lm*- and mesothelin-specific T-cell and other immunological responses with overall survival in subjects receiving test treatments

- To evaluate overall response rate in subjects with measurable disease per RECIST receiving test treatments

- To measure tumor marker kinetics in subjects receiving test treatments

3.0 STUDY DESIGN

3.1 BASIC DESIGN CHARACTERISTICS

This is a Phase 2, randomized, multicenter, open-label study of cyclophosphamide and GVAX pancreas vaccine followed by CRS-207 in adults with metastatic pancreatic adenocarcinoma who have received or refused at least one prior chemotherapy treatment.

Eligible subjects will be randomized in a 2:1 ratio to receive either two doses of cyclophosphamide and GVAX pancreas vaccine and up to 4 doses of CRS-207 at 1×10^9 CFU (Treatment Arm A) or up to six doses of cyclophosphamide and GVAX pancreas vaccine (Treatment Arm B).

The study will consist of a screening period (within 28 days of the first administration of study drug), followed by administration of test treatments per Table 1. Both treatment arms will receive cycles of up to six doses of vaccine 3 weeks apart. Treatment Arm A will receive two doses of cyclophosphamide and GVAX pancreas vaccine and up to 4 doses of CRS-207. Treatment Arm B will receive up to six doses of cyclophosphamide and GVAX pancreas vaccine. Subjects will be contacted by phone on Day 4 (±1 day) of dosing weeks to evaluate injection-site reactions (after GVAX vaccinations) and AEs.

Table 1. Study Treatment Arms and Doses

Treatment Arm	Number of Subjects	Treatment and Dose	Treatment Cycle
A	60	Cyclophosphamide (200 mg/m^2), GVAX pancreas vaccine (5×10^8 cells), CRS-207 (1×10^9 CFU)	Weeks 1 and 4: • Cyclophosphamide (Day 1) • GVAX pancreas vaccine (Day 2) Weeks 7, 10, 13, and 16: • CRS-207 (Day 1)
B	30	Cyclophosphamide (200 mg/m^2), GVAX pancreas vaccine (5×10^8 cells)	Weeks 1, 4, 7, 10, 13, and 16: • Cyclophosphamide (Day 1) • GVAX pancreas vaccine (Day 2)

CFU = colony-forming unit.

To monitor initial safety of the sequential vaccine regimen, no more than one subject will be enrolled per week for the first six subjects. If any limiting toxicities are observed during the study (see Section 3.6), the data will be

reviewed with the Data Monitoring Committee (DMC) and the dose may be lowered to 1×10^8 CFU for all subsequent dosing with CRS-207.

All subjects will return to the study site during Week 20 for evaluation. To ensure eradication of CRS-207 before receiving additional therapies (or study treatment cycles), subjects in Treatment Arm A will receive a 10-day course of antibiotics 7 days after the last CRS-207 dose in each treatment cycle (or after their final dose if treatment is discontinued early). At the investigator's discretion, subjects may receive additional cycles of the assigned treatment regimen if they are clinically stable and meet dosing eligibility. After completion of treatment, subjects will continue to be followed by phone and optional clinic visits for subsequent cancer-related therapies, overall response rate, and blood draws for *Lm*- and mesothelin-specific immune responses (clinic visits only) for the duration of the study until all subjects have reached at least 24 months of follow-up or death. At the conclusion of the study, all remaining subjects will be offered enrollment in a long-term follow-up study.

Overall response rate will be assessed by using standard RECIST (see Appendix A) and immune-related response criteria (irRC), where new lesions in and by themselves do not qualify as progressive disease[31] (see Appendix B). Tumor marker kinetics will be measured through serum CA19-9 or carcinoembryonic antigen (CEA) levels, as applicable. The humoral and cellular immune responses directed against *Lm* and mesothelin will be evaluated by using enzyme-linked immunosorbent spot (ELISPOT), intracellular cytokine staining, and enzyme-linked immunosorbent assay (ELISA) for *Lm*- and mesothelin-specific antibodies. Safety will be assessed by collection of data on AEs, vaccine-site reactions, vital signs, physical examination, clinical hematology, and serum chemistry.

3.2 STUDY POPULATION

At least 90 subjects will be enrolled in a 2:1 randomization (60 subjects in Treatment Arm A; 30 subjects in Treatment Arm B). Study eligibility will be determined by the investigator on the basis of the inclusion and exclusion criteria.

3.2.1 Inclusion Criteria

To be considered eligible to participate in this study, subjects must meet the inclusion criteria listed below:

(1) Have histologically proven malignant adenocarcinoma of the pancreas; measurable disease is not required (Subjects with mixed histology will be included if the predominant component is adenocarcinoma. Subjects must have metastatic disease.)

(2) Have received or refused at least one chemotherapy regimen

(3) Be at least 18 years of age

(4) Have an Eastern Cooperative Oncology Group (ECOG) performance status of 0 or 1

(5) Have an anticipated life expectancy of greater than 12 weeks

(6) For women and men of childbearing potential, a medically acceptable method of highly effective contraception (oral hormonal contraceptive, condom plus spermicide, or hormone implants) must be used throughout the study period and for 28 days after their final vaccine administration (A barrier method of contraception must be employed by all subjects [male and female], regardless of other methods.)

(7) Be willing and able to give written informed consent, and be able to comply with all study procedures

(8) Have adequate organ function as defined by the laboratory values in Table 2

Table 2. Required Laboratory Values for Study Inclusion

Hematologic	Renal	Hepatic
WBC ≥3,500/μL ANC ≥1,500/μL Platelets ≥90 × 10^3/μL Hemoglobin ≥9 g/dL CD4 ≥0.2 × 10^9/L	Creatinine ≤2.0 × ULN	AST/ALT <2.0 × ULN Alkaline phosphatase ≤2.5 × ULN Bilirubin ≤ ULN

ALT = alanine aminotransferase; ANC = absolute neutrophil count; AST = aspartate aminotransferase; ULN = upper limit of normal; WBC = white blood cell.

3.2.2 Exclusion Criteria

To be eligible for entry into the study, subjects must not meet any of the exclusion criteria listed below:

(1) Have a known history or evidence of brain metastases

(2) Have a known allergy to both penicillin and sulfa

(3) Have an artificial (prosthetic) joint or other artificial implant or device that cannot be easily removed (Dental and breast implants are allowed if there is no history of infection of the implants and no clinically significant AEs associated with the implants. Biliary stents and mediports will be allowed; however, mediports cannot be used for infusion or blood draw from time of CRS-207 dosing through 4 days post-dose.)

(4) Have any evidence of hepatic cirrhosis or clinical or radiographic ascites

(5) Have had a pulmonary embolism or venous thromboembolism within 2 months of study enrollment

(6) Have radiographic or clinically significant pleural effusion

(7) Have known or suspected hypersensitivity to GM-CSF, hetastarch, pentastarch, corn, dimethyl sulfoxide, fetal bovine serum, trypsin (porcine origin), yeast, or any other component of GVAX pancreas vaccine or CRS-207 (e.g., glycerol)

(8) Have any immunodeficiency disease or immunocompromised state (e.g., use of immunosuppressive agents; chemotherapy or radiation therapy within 14 days of study treatment)

(9) Have received a diagnosis of HIV, hepatitis B, or hepatitis C (Subjects who are hepatitis C antibody positive may be enrolled if they are confirmed with negative viral load at screening.)

(10) Have active autoimmune disease or history of autoimmune disease requiring systemic steroids or other immunosuppressive treatment

(11) Have used any systemic steroids within 28 days of study treatment

(12) Use more than 3 g/d of acetaminophen

(13) Have received an investigational product within 28 days of study treatment or planned to receive within 28 days after vaccine administration

(14) Have had major surgery or significant traumatic injury occurring within 28 days before treatment administration or anticipated surgery or procedure requiring general anesthesia during the study participation (including 28 days after last dose of CRS-207) (Minor procedures [dental work, skin biopsy, etc.], celiac plexus block, and biliary stents are allowed.)

(15) Have an unhealed surgical wound

(16) Be a woman who is pregnant or breastfeeding

(17) Have clinically significant heart disease (such as uncontrolled angina, myocardial infarction within the last 3 months, congestive heart failure of New York Heart Association III or IV)

(18) Have valvular heart disease that requires antibiotic prophylaxis for prevention of endocarditis

(19) Have oxygen saturation <92% on room air, as measured by pulse oximeter

(20) Have an intercurrent illness that is either life-threatening or of clinical significance such that it might limit compliance with study requirements (Such illnesses include, but are not limited to, ongoing or active infection, metabolic or neurologic disease, peripheral vascular disease, or psychiatric illness.)

(21) Have insufficient peripheral venous access to permit completion of the study dosing and compliance with study phlebotomy regimen

(22) Be unwilling or unable to follow the study schedule for any reason

(23) Have a history of alcohol dependence or use of illicit drugs (e.g., opioids, cocaine, amphetamines, hallucinogens, etc.) that could potentially interfere with adherence to study procedures or requirements

(24) Is unable to avoid close contact with another individual known to be at high risk of listeriosis (e.g., newborn infant, pregnant woman, HIV-positive individual) during the course of CRS-207 treatment until completion of antibiotic regimen.

3.2.3 Dosing Eligibility

Subjects must have adequate organ function as defined by the laboratory values in Table 3 before dosing on Day 1 of dosing weeks. Laboratory tests may be done up to 72 hours before dosing on Day 1. Subjects who do not meet the dosing-eligibility requirements will be monitored. Doses may be delayed up to 2 weeks, after which time they will be considered missed (with the exception of Dose 2 in Treatment Arm A; see Section 4.2).

Table 3. Dosing-Eligibility Requirements

Hematologic	Renal	Hepatic
WBC ≥3,500/μL ANC ≥1,500/μL Platelets ≥90 × 10^3/μL Hemoglobin ≥9 g/dL	Creatinine ≤2.0 × ULN	AST/ALT ≤2.5 × ULN Bilirubin ≤1.5 × ULN

ALT = alanine aminotransferase; ANC = absolute neutrophil count; AST = aspartate aminotransferase; ULN = upper limit of normal; WBC = white blood cell.

3.3 ENDPOINTS

3.3.1 Primary Endpoint

The primary endpoint is overall survival, measured from first cyclophosphamide treatment until death or 24 months of follow-up (or death) of last subjects enrolled.

3.3.2 Secondary Endpoints

The secondary endpoints are as follows:

- Safety assessed by the following measures:
  - AEs
  - Injection-site reactions (after GVAX pancreas vaccine injections only)
  - Vital signs: BP, pulse, respiratory rate, temperature
  - Physical examination
  - Clinical hematology: complete blood count with differential absolute neutrophil count and platelet count
  - Clinical serum chemistry: sodium, potassium, chloride, bicarbonate, glucose, blood urea nitrogen, creatinine, lactate dehydrogenase, alanine aminotransferase (ALT), aspartate aminotransferase (AST), alkaline phosphatase, amylase, bilirubin (total, direct, indirect), total protein, albumin, calcium, magnesium, and phosphate

3.3.3 Exploratory Endpoints

Exploratory endpoints are as follows:

- Humoral and cellular immune responses directed against *Lm* and mesothelin assessed by using the following measures:
  - ELISPOT or intracellular cytokine staining assays of peripheral blood mononuclear cells (PBMC)
  - Induction of proinflammatory cytokines and chemokines in the serum
  - ELISA detection of mesothelin- and *Lm*-specific antibodies in the serum
- Overall response rate assessed by RECIST and irRC
- Tumor marker kinetics measured by change in serum CA19-9 or CEA concentrations from baseline

3.4 RANDOMIZATION AND BLINDING

This is an open-label study. Subjects meeting all inclusion and exclusion criteria will be randomized 2:1 to one of two treatment arms according to a randomization list generated for each site by an independent statistician.

3.5 REPLACEMENT OF DROPOUTS

Subjects who withdraw consent or are removed from the study before completing one cycle of treatment will be considered dropouts and may be replaced at the discretion of Aduro BioTech. The replacement subject will be enrolled in the same treatment arm as the dropout. Subjects who have disease progression may be allowed to continue in the study if the investigator believes they are deriving some benefit from the therapy.

3.6 LIMITING TOXICITIES

Limiting toxicities are defined as events that are determined by the investigator as related to CRS-207 and that meet one of the following criteria:

- A fever of >40°C that lasts for greater than 24 hours and does not respond to antipyretics
- Clinically significant hypotension unresponsive to intravenous fluids (systolic BP <90 mm Hg or mean arterial pressure <55 mm Hg as measured on two separate occasions at least 3 minutes apart)
- Grade 3 decreases in leukocytes, absolute neutrophil count, or platelets that persist for more than 4 days
- Hemoglobin $\leq$7.0 g/dL
- ALT, AST, or alkaline phosphatase elevations >5 times the upper limit of normal (Grade 3) that persist for more than 7 days
- Initiation of antibiotic therapy, coincident with simultaneous isolation of CRS-207 from a normally sterile body site, other than blood (e.g., cerebrospinal fluid, joint fluid)

- Grade 3 laboratory abnormalities lasting >48 hours

- Any other Grade 3 or greater event (except alopecia) according to National Cancer Institute's Common Terminology Criteria for Adverse Events (CTCAE) Version 4.03

To provide the appropriate safeguards, all unexpected Grade 3 events will be independently reviewed by the DMC. If the event is determined to be related to CRS-207 dosing and clinically meaningful, it will be considered a limiting toxicity. Unexpected Grade 3 laboratory abnormalities should be repeated within 24-72 hours.

The proportion of limiting toxicities will be continuously monitored. If the toxicity levels in the CRS-207 treatment arm are unacceptable (>33% of subjects), then CRS-207 dosing will suspended until further review and consideration by the sponsor, investigators, and DMC. If unacceptable toxicity occurs at the starting dose of 1×10^9 CFU, the dose may be lowered to 1×10^8 CFU for all subsequent dosing with CRS-207. Subjects currently on study in Treatment Arm A may continue to receive dosing at the lower dose. All subsequent subjects enrolled in Treatment Arm A will receive CRS-207 at the lower dose. Limiting toxicities will continue to be monitored by the DMC at the lower dose.

4.0 DRUGS AND DOSAGES

4.1 IDENTIFICATION AND DESCRIPTION OF CLINICAL TRIAL MATERIAL

4.1.1 Clinical Trial Material

CRS-207 is a formulated live-attenuated strain hMeso38 of *Lm*, derived by deletion of *actA* and *inlB* coding sequences from a Streptomycin-resistant, wild-type strain and insertion of the human mesothelin coding sequence. The CRS-207 drug product consists of attenuated *Lm* (1×10^9 CFU/mL) suspended in 1.5 mL of Dulbecco's phosphate buffered saline and 9% vol/vol glycerol, filled into a single-use 2-mL glass vial with a gray butyl stopper and aluminum crimp seal with a flip-off cap, and stored frozen at –60ºC or colder until intravenous administration. During the storage, preparation, and administration of individual study doses and for the disposal of materials used in the preparation and

administration of this product, the study will adhere to applicable institutional infection-control procedures for handling of *Lm*.

Cyclophosphamide (active ingredient cyclophosphamide monohydrate) is a synthetic antineoplastic drug chemically related to the nitrogen mustards. It is commercially available in a sterile powder formulation for use in intravenous administration. Cyclophosphamide will be reconstituted and administered per the package insert.

GVAX pancreas vaccine is an allogeneic pancreatic tumor vaccine consisting of two pancreatic cell lines (Panc 6.03 and Panc 10.05), each of which have been cultured and genetically modified with a plasmid vector encoding the complementary DNA for human GM-CSF. The vaccine cells are irradiated with 150 Gy by using a cesium-source irradiator and are stored at 1.25×10^8 cells per vial (two vials per cell line) in an injectable formulation of 6% hetastarch (or pentastarch) in 0.9% sodium chloride with 2% human serum albumin and 5% dimethyl sulfoxide filled into a sterile, single-use 1.8-mL polypropylene cryovial internally threaded with a silicone gasket and stored frozen in liquid nitrogen until the day of use. GVAX pancreas vaccine is administered by intradermal injection per the IB and study procedures manual (SPM).

4.1.2 Labeling

Because the study is not blinded, the labeling will be that used on commercial vials of cyclophosphamide. The vials for GVAX pancreas vaccine and CRS-207 will be labeled with the following: product name; volume; storage conditions; product lot number; concentration and passage number (for GVAX pancreas vaccine); sponsor name and address (for CRS-207); fill date; and a caution statement ("Caution: New drug limited by Federal law to investigational use"). CRS-207 drug product is packaged in kit boxes that are also labeled with product name, number of vials, concentration, storage condition, a caution statement, sponsor name and address, and kit lot number.

4.2 DOSING INSTRUCTIONS AND SCHEDULE

Cyclophosphamide will be administered to subjects by intravenous infusion at 200 mg/m^2 in 100 mL normal saline over 30 minutes on Day 1 of Weeks 1 and 4

for Treatment Arm A or Day 1 of Weeks, 1, 4, 7, 10, 13 and 16 for Treatment Arm B.

GVAX pancreas vaccine will be administered to subjects by intradermal injections on Day 2 of Weeks 1 and 4 for Treatment Arm A or Day 2 of Weeks 1, 4, 7, 10, 13 and 16 for Treatment Arm B. Equal numbers (2.5×10^8 each) of the Panc 6.03 and Panc 10.05 cells will be combined and divided into 6 injections. At the time of vaccination, two vials of each cell line are removed from the appropriate storage conditions and quickly thawed in a 37°C water bath. The thawed vials are transferred from the water bath to ice in a biosafety cabinet. Contents of all 4 vials are combined into a single sterile tube and drawn in approximately equal volumes from the tube with a 16-gauge needle into 6 1-cc Luer-Lok syringes. The 16-gauge Luer-Lok needles are replaced with 22-gauge needles for subject's administration. The syringes are then released to the appropriate medical personnel for intradermal injection and are kept on ice until the vaccine is administered. All injections much be given within 3 hours of thaw. The 3 hours start when the vials are placed in the water bath for thaw. Each vaccination will consist of six total intradermal injections of approximately 0.7 mL solution, two each in the upper right and left thighs, and two in the upper nondominant arm. . Vaccine sites will be premedicated with topical lidocaine-based anesthetic cream and covered with an occlusive dressing for at least 1 hour before vaccination (if subject is not allergic to lidocaine) to diminish discomfort associated with the intradermal injections. Subjects will be observed in the clinic for at least 60 minutes after the first vaccination and for at least 30 minutes after the last injection to ensure no immediate adverse reactions occur.

CRS-207 will be administered to subjects by intravenous infusion at 1×10^9 CFU in 250 mL 0.9% sodium chloride over 2 hours on Day 1 of Weeks 7, 10, 13, and 16 for Treatment Arm A. CRS-207 is prepared by thawing one 1.5 mL vial of drug product at room temperature. One (1) mL of product is drawn with a syringe and inserted into one bag of 250 mL 0.9% sodium chloride for intravenous injection.

CRS-207 must not be administered via central venous catheters or infusion ports. Before each CRS-207 infusion, subjects will be premedicated with 650 mg acetaminophen. Subjects will also receive a total of 1,000 mL of normal saline either immediately before or after CRS-207 infusion (or half of the volume may be given before CRS-207 and half after CRS-207 infusion). Subjects will be

observed in the clinic for at least 4 hours after each infusion. Subjects who are not stable to be released at 4 hours after infusion should continue to be monitored until stable. Hospital admissions for overnight monitoring will not be considered an SAE unless the event meets criteria for seriousness other than hospitalization.

All vaccine doses within a cycle are scheduled to be given approximately 3 weeks apart (Table 3). If necessary, a vaccine dose may be delayed for up to 2 weeks. In this case, subsequent doses should continue on a 3-week schedule. For example, if the Week 4 dose is delayed to Week 5, subsequent doses should be given on Weeks 8, 11, 14, and 17. If delayed more than 2 weeks between doses in a cycle, the dose will be considered missed and the subject should continue to receive the next dose as scheduled (i.e., 3 weeks from previous dose), with the exception that if the second dose of the first cycle in Treatment Arm A (second dose of cyclophosphamide and GVAX pancreas vaccine before receipt of the first dose of CRS-207) is delayed more than 2 weeks, the sponsor's medical monitor must be contacted for further instructions on continued dosing. Additional delays or modifications to the dosing schedule must be approved by the sponsor's medical monitor.

4.3 STORAGE AND HANDLING OF CLINICAL TRIAL MATERIAL

Cyclophosphamide powder should be kept at or below 25ºC. Cyclophosphamide reconstituted in normal saline is chemically and physically stable for 24 hours at room temperature and for 6 days when refrigerated. Guidelines outlining the procedures for proper handling and disposal of anticancer drugs should be followed when handling cyclophosphamide.[32] Protective gloves should be worn when handling cyclophosphamide in both powder and reconstituted forms.

GVAX pancreas vaccine cells must be stored in vapor-phase liquid nitrogen until the day of vaccination. CRS-207 must be stored at –60ºC or colder until just before use. The investigational sites, per institutional guidelines, will destroy used GVAX pancreas vaccine and CRS-207 vials after formulation for administration. The formulation of GVAX pancreas vaccine and CRS-207 for administration and the destruction of each used vial will be carefully documented in the study pharmacy manual. The study monitor will perform investigational agent accountability during on-site monitoring visits. Unused GVAX pancreas vaccine and CRS-207 will be destroyed at the study site after final investigational

product accountability and notification by Sponsor, unless otherwise directed by Sponsor.

Lm is classified by the Centers for Disease Control and Prevention for handling in the laboratory according to Biosafety Level 2 practices. Individuals who prepare CRS-207 for injection must take appropriate precautions (e.g., gloves, laboratory coat, face protection, needle stick or sharps precautions) to avoid contamination or direct contact with the agent. Once it is prepared for injection, the chance for direct exposure to CRS-207 by study personnel should be greatly diminished. However, study personnel and staff should continue to adhere to the institutional guidelines for standard precautions.

4.3.1 Environmental Precautions

Wild-type *Lm* is a common pathogen that is widely distributed in the environment and contaminates a variety of ready-to-eat foods. Despite the presence of *Lm* in diverse locations, clinically apparent human infection is not commonly reported in immunocompetent, normal individuals. Direct human-to-human spread of *Lm* is believed to be limited mainly to vertical transmission from mother to neonate. Standard isolation precautions are usually recommended for subjects infected with wild-type *Lm*. Precautions should therefore be exercised to avoid direct contact between subjects and individuals who are at high risk of listeriosis (e.g., newborn infants, pregnant women, HIV-positive individuals).

4.4 PRODUCT ACCOUNTABILITY

The investigator is responsible for the control of investigational agents under study. An investigational agent dispensing log must be kept current and should contain the following information:

- The study number and initials of each subject to whom the investigational agents are dispensed
- The date(s) and quantity of the investigational agent dispensed to the subject
- Documentation of proper disposal of used investigational drug vials

- Documentation of proper disposal (or return, at Sponsor's request) of unused investigational drug vials

All records and unused supplies of the investigational agents must be available for inspection at every monitoring visit.

4.5 PRIOR, CONCOMITANT, AND EXCLUDED THERAPY

During the course of the clinical study, subjects are anticipated to continue the use of prescribed medications identified during the screening procedures, consistent with study inclusion and exclusion criteria. Concomitant medications used in this study include the 10-day antibiotic regimen scheduled 7 days after completion of each cycle for Treatment Arm A (or each subject's final dose of CRS-207 if discontinued before end of cycle) and medications to treat any treatment-emergent AEs that may occur. Medications to treat treatment-emergent AEs should not interfere with the study and can be used at the investigator's discretion. Each subject should be premedicated with topical lidocaine-based anesthetic cream (if subject is not allergic to lidocaine) at the vaccine sites before GVAX pancreas vaccine administration and given 650 mg acetaminophen before CRS-207 administration. Antipyretics may be used to treat fever or to prevent recurrence of fever. The details of any concomitant medications must be recorded in the case report form (CRF). The generic name, dosage, duration, and reason for the concomitant medication should be included in this report.

The following therapies are not permitted during the treatment period (if administered, the subject may be removed from the study):

- Any anticancer chemotherapy or nonstudy immunotherapy (approved or investigational)

- Systemically active steroids for more than 2 days or any systemic steroids during the treatment period or within 28 days before or after dosing

- Another investigational product

In addition, the following therapies should not be administered during the treatment period unless medically necessary, and approval must be obtained from

the medical monitor for a subject to continue dosing if therapy is given concurrently with study participation:

- General anesthesia or deep sedation
- Aspirin >325 mg/d (chronic daily use of aspirin ≤325 mg/d and heparin flushes for central lines are allowed)
- More than 4 g/d of acetaminophen
- Systemic antibiotics

Subjects with clinical or laboratory signs or symptoms of infection who require initiation of antibiotics other than specified by protocol should have a clinically relevant evaluation, including appropriate bacterial cultures. Culture of cerebrospinal fluid should be obtained for subjects with suspected central nervous system infection. In such instances, analysis of cerebrospinal fluid should also include cell count, protein, glucose, and Gram stain. The preferred antibiotic regimen if CRS-207 infection is suspected or confirmed, is intravenous administration of ampicillin (or trimethoprim/sulfamethoxazole in penicillin-allergic subjects) plus gentamicin. For this purpose, initial doses of ampicillin should be approximately 12 g daily (divided doses every 3 to 4 hours), with gentamicin 3 mg/kg daily in divided doses every 8 hours (with adjustments according to renal function and serum levels of gentamicin). In penicillin-allergic subjects, initial intravenous doses of trimethoprim/sulfamethoxazole should be 15 to 20 mg/kg/d (based on trimethoprim component) divided four times per day, with gentamicin 3 mg/kg daily in divided doses every 8 hours (with adjustments according to renal function and serum levels of gentamicin). For those individuals who receive intravenous antibiotics, the course of therapy is anticipated to be greater than or equal to 14 days, depending on clinical course. Antibiotic treatment may be completed with use of oral antibiotics, if clinically indicated.

5.0 EXPERIMENTAL PROCEDURES

5.1 OVERVIEW: SCHEDULE OF TIME AND EVENTS

An overview of study time and events is presented in Table 4.

Table 4. Schedule of Time and Events

Assessments	Screening	Treatment																			Follow-up [c] (every 3 months)
		Week 1			Week 4[a]			Week 7[a]			Week 10[a]			Week 13[a]			Week 16[a]			Week 17	Week 20[b]	
Study Days	(D–28 to D0)	D1	D2	D4[d]	D1	D2	D4[d]	D1	D2	D4[d]	D1	D2	D4[d]	D1	D2	D4[d]	D1	D2	D4[d]	D1	D1	
Visit Windows (days)		-	-	±1	-	-	±1	-	-	±1	-	-	±1	-	-	±1	-	-	±1	-	±7	±7
Informed consent	X																					
Inclusion/exclusion	X																					
Medical history	X																					
Medication history	X																					
Cancer-related treatment	X																					X
Baseline signs/ symptoms	X																					
Virology screen[e]	X																					
Coagulation panel, UA[f]	X																					
Electrocardiogram	X																				X	
CT or MRI[g]	X										X										X	X
Physical examination[h]	X	X			X			X			X			X			X				X	
ECOG performance status	X	X			X			X			X			X			X				X	
Vital signs, weight[i]	X	X	X		X	X		X	X		X	X		X	X		X	X			X	
Pulse oximetry, height	X																					
Pregnancy test[j]	X	X			X			X			X			X			X					
CD4 count	X																					
Clinical hematology, serum chemistry[k]	X	X			X			X	X[l]		X	X[l]		X	X[l]		X	X[l]			X	
Tumor marker(s)[m]	X	X			X			X			X			X			X				X	
Vaccine-site reactions				X			X			X[n]			X[n]			X[n]			X[n]			
Concomitant medications, adverse events		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X		X	
PBMC for cellular immunity[o]		X						X			X			X			X				X	X
Serum for *Lm* and mesothelin immunity[p]		X			X			X	X[o]		X	X[o]		X	X[o]		X	X[o]			X	X
HLA-typing[q]		X																				
Antibiotics[r]																				X		
Dose Administration[s]	(Y = cyclophosphamide; G = GVAX pancreas vaccine; C = CRS-207)																					
Treatment Arm A		Y	G[t]		Y	G[t]		C[u]			C[u]			C[u]			C[u]					
Treatment Arm B		Y	G[t]		Y	G[t]		Y	G[t]		Y	G[t]		Y	G[t]		Y	G[t]				
Continuation eligibility[v]																					X	

Table 4. Schedule of Time and Events (continued)

ALT = alanine aminotransferase; ANC = absolute neutrophil count; APTT = activated partial thromboplastin time; AST = aspartate aminotransferase; BUN = blood urea nitrogen; CBC = complete blood count; CT = computed tomography; D = study day; ECOG = Eastern Cooperative Oncology Group; HLA = human leukocyte antigen; LDH = lactate dehydrogenase; *Lm* = *Listeria monocytogenes*; MRI = magnetic resonance imaging; PBMC = peripheral blood mononuclear cells; UA = urinalysis.

a Doses of cyclophosphamide and GVAX pancreas vaccine or CRS-207 on Weeks 4, 7, 10, 13, and 16 may be delayed up to 2 weeks (i.e., 5 weeks since previous dose). Subsequent doses should continue to be separated by 3-week intervals (e.g., if the second dose is delayed to Week 5, third dose should be given at Week 8). Doses delayed more than 2 weeks apart should be considered missed and the subject should continue to receive the next dose as scheduled with the exception that if the second dose of the first cycle in Treatment Arm A (2nd dose of cyclophosphamide and GVAX) is delayed more than 2 weeks, the sponsor's medical monitor must be contacted for further instructions. .

b Follow-up will occur 28 days after the final dose of one cycle (6 doses) or within 28 days after the final dose for subjects who do not complete all doses.

c Subjects will continue to be followed every 3 months by phone or optional clinic visit for the duration of the study until all subjects have reached at least 24 months of follow-up or death to document subsequent cancer-related therapies, request CT scans to assess overall response rate, and optional blood draws for *Lm* and mesothelin responses.

d Day 4 assessment will be conducted by phone.

e Virology screen: HIV antibody, hepatitis B surface antigen, and hepatitis C antibody; additional virology may also be evaluated. Subjects who are hepatitis C antibody positive and confirmed negative viral load at screening will be allowed to enroll.

f Coagulation panel: D-dimer, fibrinogen, international normalized ratio of prothrombin time, APTT; UA: bilirubin, blood, glucose, ketones, leukocytes, nitrite, pH, protein, specific gravity.

g Spiral CT of thorax, abdomen, and pelvis (and other imaging studies as clinically indicated to evaluate suspected sites of metastatic disease). If CT has been done within 14 days before screening, these results may be used for evaluation. If a subject cannot have a CT scan (e.g., allergy to contrast dye), an MRI should be performed. On-study CT scans may be done within 1 week prior to or after scheduled visit.

h Complete physical examinations will be conducted at baseline and Week 20; focused physical examinations to be conducted on Day 1 of dosing weeks.

i Blood pressure, pulse, respiratory rate, temperature are required as indicated. Weight will be taken on Day 1 of dosing weeks.

j Pregnancy tests will be administered only to women of childbearing potential: serum pregnancy test is required at screening, and urine pregnancy tests are required before doses on Day 1 of dosing weeks.

k Clinical hematology: CBC with differential ANC and platelet count; serum chemistry: sodium, potassium, chloride, bicarbonate, glucose, BUN, creatinine, LDH, ALT, AST, alkaline phosphatase, bilirubin (total, direct, and indirect), amylase, total protein, albumin, calcium, magnesium, and phosphate. Blood draws may be taken up to 72 hours before dosing. Blood draws must not be collected from a central line for at least 4 days after infusion of CRS-207.

l Required on Day 2 only after CRS-207 dosing; if liver function tests are Grade 2 or higher, subjects will have repeated testing on Day 7.

m CA 19-9 and CEA will be tested at screening, and only the applicable elevated tumor antigen will be followed.

n Injection-site reactions will be evaluated on Day 4 only after GVAX vaccinations.

o 90-200 mL of whole blood to be processed within 6 hours into peripheral blood mononuclear cells (PBMCs) and stored frozen in liquid nitrogen.

p For Treatment Arm A only (after CRS-207 dosing): 10 mL of serum for *Lm* and mesothelin immunity should be taken between 20 and 26 hours after start of dosing.

q HLA-typing to include type A and B, low resolution.

r 10-day course of antibiotics will be administered in Treatment Arm A 7 days after final dose of CRS-207 in each cycle (or after final dose if discontinued early) (see Section 5.2.2.4).

s Doses will be administered after all visit assessments and blood draws are completed.

t Subjects will be observed in the clinic for at least 60 minutes after first vaccination and at least 30 minutes after second vaccination.

u Vital signs (blood pressure, pulse, respiratory rate, temperature) will be obtained every 30 minutes during the CRS-207 infusion and every hour during postinfusion follow-up. Subjects will be observed for at least 4 hours after each infusion. Subjects who are not stable enough to be released at 4 hours after infusion should continue to be monitored until stable. Presence of fever alone does not indicate subject is not clinically stable.

v At investigator's discretion, subjects may be eligible for additional treatment cycles if they are clinically stable and meet dosing eligibility (see Section 5.2.4).

5.2 MEASUREMENTS AND EVALUATIONS

5.2.1 Screening Period (Day –28 to Day 0)

Before screening assessments are conducted, the subject must be given a complete explanation of the purpose and evaluations of the study. Subsequently, the subject must sign and receive a copy of an informed consent form (ICF) that was approved by the institutional review board (IRB) and an authorization for use and disclosure of protected health information (PHI) before any study-specific procedure is performed. An original signed consent form will be retained in the subject's source documentation at the site, and a copy will be provided for the subject to take home. Screening will occur within 28 days before treatment administration. Potential subjects will be evaluated for entry into the study according to the stated inclusion and exclusion criteria. Individuals who are identified during this screening as not eligible for study enrollment need not complete all screening procedures. The reason for ineligible status will be documented.

The following evaluations will be performed to assess the subject's eligibility for the study:

- Signed, written informed consent
- Inclusion and exclusion criteria
- Medical history, including history of carcinoma treatment
- Medication history over the past 28 days, including prescription and over-the-counter medications, herbs, vitamins, and minerals
- Baseline signs and symptoms
- Physical examination
- ECOG performance status

- Vital signs (BP, pulse, respiratory rate, temperature), height, weight, and pulse oxygen saturation

- Clinical assessment of tumor status

- Resting 12-lead electrocardiogram

- Clinical hematology: complete blood count with differential absolute neutrophil count and platelet count

- Serum chemistry: sodium, potassium, chloride, bicarbonate, glucose, blood urea nitrogen, creatinine, lactate dehydrogenase, ALT, AST, alkaline phosphatase, amylase, bilirubin (total, direct, indirect), total protein, albumin, calcium, magnesium, and phosphate

- Coagulation panel: D-dimer, fibrinogen, international normalized ratio of prothrombin time, and activated partial thromboplastin time (APTT)

- Virology screen: HIV antibody, hepatitis B surface antigen, and hepatitis C antibody (Additional virology screens may also be evaluated.)

- Urinalysis: bilirubin, blood, glucose, ketones, leukocytes, nitrite, pH, protein, and specific gravity

- CD4 count

- Tumor marker CA19-9 and CEA

- Serum pregnancy test (for women of childbearing potential only)

- Spiral CT scan of thorax, abdomen, and pelvis (and other imaging studies as clinically indicated to evaluate suspected sites of metastatic disease) if one has not been done within 14 days before screening (Tumor[s] should be measured according to RECIST and irRC [see Appendices D and E]. Measurable tumors are not required for study entry. If a subject cannot have a CT scan [e.g., allergy to contrast dye], a magnetic resonance imaging [MRI] should be performed.)

The investigator may use clinical judgment when determining the clinical significance of laboratory parameter findings throughout the study. The medical monitor may, depending on study criteria, be consulted before enrollment about a potential subject with abnormal laboratory values.

5.2.2 Treatment Period

5.2.2.1 Cyclophosphamide Administration (Day 1 of Weeks 1 and 4 for Treatment Arm A; Day 1 of Weeks 1, 4, 7, 10, 13, and 16 for Treatment Arm B)

Cyclophosphamide will be administered to subjects on Day 1 of Weeks 1 and 4 for Treatment Arm A and on Day 1 of Weeks 1, 4, 7, 10, 13, and 16 for Treatment Arm B by intravenous infusion at 200 mg/m^2 in 100 mL normal saline over 30 minutes after the following evaluations have been performed:

- ECOG performance status
- Vital signs (BP, pulse, respiratory rate, temperature) and weight
- Focused physical examination
- AEs and concomitant medications review
- Urine pregnancy test (for women of childbearing potential only)
- Blood draws for clinical hematology and serum chemistry
- Blood draw for tumor marker CA19-9 and/or CEA assessment, as applicable
- Blood draw for isolation of PBMC (90-200 mL), with the exception of no blood draw on Day 1, Week 4 (Samples must be processed by sponsor-qualified operators within 6 hours of collection and stored in liquid nitrogen.)
- Blood draw for *Lm*- and mesothelin-specific immunity assays (10 mL)
- Blood draw for HLA-typing (A and B, low resolution)

- For Week 10 only: spiral CT scan of thorax, abdomen, and pelvis (and other imaging studies as clinically indicated to evaluate suspected sites of metastatic disease) and measurement of tumor(s) according to RECIST and irRC (see Appendices A and B)

  Clinical assessment of tumor status should be recorded. If a subject cannot have a CT scan (e.g., allergy to contrast dye), an MRI should be performed. Subjects with progressive disease in the absence of clinical deterioration may continue treatment. CT scan may be done within 1 week prior to or after the scheduled visit.

Because results for clinical hematology and serum chemistry need to be obtained before each cyclophosphamide administration, subjects may have blood drawn for these evaluations up to 72 hours before dosing.

5.2.2.2 GVAX Pancreas Vaccine Administration (Day 2 of Weeks 1 and 4 for Treatment Arm A; Day 2 of Weeks 1, 4, 7, 10, 13, and 16 for Treatment Arm B)

GVAX pancreas vaccine will be administered on Day 2 of Weeks 1 and 4 for Treatment Arm A and on Day 2 of Weeks 1, 4, 7, 10, 13, and 16 for Treatment Arm B as detailed in Section 4.2. Subjects will be observed in the clinic for at least 60 minutes after first vaccination and at least 30 minutes after second vaccination.

The following evaluations will be performed before GVAX pancreas vaccine administration:

- Vital signs (BP, pulse, respiratory rate, temperature)

- AEs and concomitant medications review

On Day 4 (± 1 day), subjects will be contacted by phone to assess injection-site reactions, such as erythema, bruising (ecchymosis), induration, edema, nodule or vesicle formation, AEs, and concomitant medications.

5.2.2.3 CRS-207 Administration (Day 1 of Weeks 7, 10, 13, and 16 for Treatment Arm A)

CRS-207 will be administered to subjects in Treatment Arm A on Day 1 of Weeks 7, 10, 13, and 16 by intravenous infusion at 1×10^9 CFU in 250 mL 0.9% sodium chloride over 2 hours. Subjects will be premedicated with 650 mg of acetaminophen before drug administration. Either immediately before or immediately after infusion, subjects will receive a total of 1,000 mL of normal saline; half of the volume may be given before infusion and half after infusion. Investigators will not make dose adjustments or changes to administration schedule or rate without prior approval from Aduro BioTech. CRS-207 must not be administered via central venous catheter or infusion port. Vital signs (blood pressure, pulse, respiratory rate, temperature) will be obtained every 30 minutes during the CRS-207 infusion and every hour during post infusion follow-up. Subjects will be observed for at least 4 hours after each infusion. Subjects who are not stable enough to be released at 4 hours after infusion should continue to be monitored until stable. Presence of fever alone does not indicate subject is not clinically stable.

The following evaluations will be performed before CRS-207 administration:

- ECOG performance status
- Vital signs (BP, pulse, respiratory rate, temperature) and weight
- Focused physical examination
- AE and concomitant medications review
- Blood draws for clinical hematology and serum chemistry
- Blood draw for tumor marker CA19-9 and/or CEA assessment, as applicable
- Urine pregnancy test (for women of childbearing potential only)

- Blood draw for isolation of PBMCs (90-200 mL) (Samples must be processed by sponsor-qualified operators within 6 hours of collection and stored in liquid nitrogen.)

- Blood draw for *Lm*- and mesothelin-specific immunity assays (10 mL)

- For Week 10 only: spiral CT scan of thorax, abdomen, and pelvis (and other imaging studies as clinically indicated to evaluate suspected sites of metastatic disease) and measure tumor(s) according to RECIST and irRC (see Appendices A and B) (Clinical assessment of tumor status should be recorded. If a subject cannot have a CT scan [e.g., allergy to contrast dye], an MRI should be performed. Subjects with progressive disease in the absence of clinical deterioration may continue treatment. CT scan may be done within 1 week prior to or after the scheduled visit.)

Because results for clinical hematology and serum chemistry need to be obtained before each CRS-207 administration, subjects may have blood drawn for these evaluations up to 72 hours before dosing.

Subjects will return to the clinic 1 day after receiving CRS-207 (Day 2) to be evaluated for AEs, concomitant medications, vital signs, and to have blood drawn for clinical hematology, serum chemistry, and *Lm*- and mesothelin-specific immunity assays. Blood drawn for *Lm*- and mesothelin-specific immunity assays should be drawn within 20-26 hours after start of CRS-207 dosing. If liver function tests are Grade 2 or higher based on CTCAE (Version 4.03), subjects will repeat testing locally or at the research clinic on Day 7. Any unexpected Grade 3 laboratory abnormalities should be repeated within 24-72 hours. Blood samples must not be collected from a central line after infusion of CRS-207 for at least 4 days.

On Day 4 (± 1 day), subjects will be contacted by phone to assess AEs and concomitant medications.

5.2.2.4 Antibiotic Administration (7 Days after Last CRS-207 Dose in Each Treatment Cycle)

A 10-day course of oral amoxicillin (500 mg at 8-hour intervals) or trimethoprim/sulfamethoxazole in penicillin-allergic subjects (160 mg

trimethoprim/800 mg sulfamethoxazole at 12-hour intervals) will be initiated for each subject 7 days after the subject's last dose of CRS-207 for each treatment cycle (or after their final dose if discontinued early) to ensure clearance of CRS-207 before additional cycles or subsequent therapy. If the subject is withdrawn from the study more than 7 days after administration of CRS-207, then oral antibiotics will be administered as soon as possible after study withdrawal. In addition, intravenous ampicillin (or trimethoprim/sulfamethoxazole in penicillin-allergic subjects) plus gentamicin will be initiated earlier for possible infectious complications of CRS-207 for subjects who are suspected of having CRS-207 infection and meet the criteria listed below:

- Flu-like symptoms Grade 3 or greater lasting for ≥12 hours
- Fever Grade 4 or higher (>40.0ºC for >24 hours)
- Persistent fever >39ºC lasting for ≥48 hours
- Infection Grade 3 or higher (infection with interventional radiology or operative intervention indicated)
- Evidence of abscess
- Clinical signs or symptoms (e.g., neurologic signs or symptoms), which in the judgment of the investigator necessitate starting antibiotics

5.2.3 Treatment Follow-up (Day 1 of Week 20 ±7 days) or Within 28 Days after Final Dose)

Subjects will return at Week 20 or within 28 days of the final study dose for evaluation or to begin an additional treatment regimen. The following evaluations will be performed:

- Physical examination
- ECOG performance status
- Vital signs (BP, pulse, respiratory rate, temperature) and weight

- AE and concomitant medications review
- Blood draws for clinical hematology and serum chemistry
- Resting 12-lead electrocardiogram
- Blood draw for tumor marker CA19-9 or CEA assessment
- Blood draw for isolation of PBMCs (90-200 mL) (Samples must be processed by sponsor-qualified operators within 6 hours of collection and stored in liquid nitrogen.)
- Blood draw for *Lm*- and mesothelin-specific immunity assays (10 mL)
- Spiral CT scan of thorax, abdomen, and pelvis (and other imaging studies as clinically indicated to evaluate suspected sites of metastatic disease) and measure tumor(s) according to RECIST and irRC (see Appendices A and B) (Clinical assessment of tumor status should be recorded. If a subject cannot have a CT scan [e.g., allergy to contrast dye], an MRI should be performed. CT scan may be done within 1 week prior to or after the scheduled visit.)

5.2.4 Continuation of Additional Treatment Cycles

Subjects who are clinically stable and meet dosing requirements at the Week 20 follow-up may receive additional cycles of their assigned treatment based on investigator discretion and with sponsor approval. The additional cycle(s) may start as early as Week 20 (i.e., 4 weeks from last dose of previous cycle) and all assessments will be followed per the study schedule in Table 4, with the first dose of the additional cycle corresponding to Day 1, Week 1 of the study schedule.

5.2.5 Study Follow-up Period

When subjects complete all study treatment, they will continue to be followed every 3 months (± 7 days) by phone or optional clinic visit for the duration of the study until all subjects have reached at least 24 months of follow-up or death to document subsequent cancer-related therapies, request CT scans to assess overall response rate, and monitoring of immune responses to *Lm* and mesothelin (at

clinic visits only). At the conclusion of the study, all remaining subjects will be offered enrollment in a long-term follow-up study.

In accordance with good medical practice, any ongoing AE present at study termination, including a clinically significant laboratory test abnormality, which is determined by the investigator as possibly or probably related to the study investigational agents, will be followed until resolved, until the event stabilizes and the overall clinical outcome has been ascertained, or until the subject is lost to follow-up.

6.0 PROCEDURES FOR HANDLING ADVERSE EVENTS AND SERIOUS ADVERSE EVENTS

6.1 DEFINITION OF AN ADVERSE EVENT

The following definition of an AE will be used for this study:

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

Examples of AEs include the following:

- Significant or unexpected worsening or exacerbation of the indication under study
- Exacerbation of a chronic or intermittent preexisting condition, including an increase in frequency or intensity of the condition
- New conditions detected or diagnosed after investigational product administration, even if they were present before the start of the study
- Signs, symptoms, or the clinical sequelae of a suspected interaction with another medical product
- Signs, symptoms, or the clinical sequelae of a suspected overdose of either investigational product or a concurrent medication

An overdose should not be reported as an AE or SAE; instead the symptoms resulting from the overdose should be reported as the AE or SAE.

Examples of AEs do not include the following:

- Medical or surgical procedures (e.g., endoscopy, appendectomy) (Instead, the medical condition that led to the procedure is an AE.)

- Situations that are unwanted but in which an untoward medical occurrence did not occur, for example social inconvenience after admission to a hospital

- Anticipated day-to-day fluctuations of a preexisting disease or condition (present or detected before enrollment) that does not worsen overall

- Expected progression of the disease being studied, including signs or symptoms of the disease being studied, unless progression is more severe than expected for the subject's condition

It is the responsibility of the investigator to perform periodic and special assessments for AEs. The investigator and clinical staff will note all AEs offered by the subject at baseline, during administration of the clinical trial material (CTM), and at the follow-up visit. All clinical complaints volunteered by, or elicited from, the subject during the study will be recorded on the appropriate page of the CRF for the study period indicated. If any AE occurs, the subject will receive appropriate treatment and medical supervision.

All AEs judged to be clinically significant, including clinically significant laboratory abnormalities, will be followed until resolution. All AEs will be summarized in the annual report or more frequently, if requested by the regulatory agency. SAEs require special reporting in addition to documentation in the CRF as described below.

6.2 DEFINITION OF A SERIOUS ADVERSE EVENT

In this study, the definition of an SAE is an AE that meets any of the following criteria:

- Results in death

- Is life-threatening

  Note: The term *life-threatening* in the definition of *serious* refers to an event in which the subject was at risk of death at the time of the event. It does not refer to an event that hypothetically might have caused death if it were more severe.

- Requires hospitalization or prolongation of existing hospitalization

  Note: In general, hospitalization signifies that the subject has been detained at the hospital or emergency ward for observation or treatment that would not have been appropriate in the physician's office or out-patient setting. Complications that occur during hospitalization are AEs but not necessarily SAEs. An occurrence or complication that prolongs hospitalization is an SAE. When there is doubt as to whether hospitalization occurred or was necessary, the AE should be considered an SAE. Hospitalization for elective treatment of a preexisting condition that did not worsen from its original baseline severity is not considered an SAE.

  Hospital admissions for overnight monitoring following CRS-207 infusion will not be considered an SAE unless the event meets criteria for seriousness other than hospitalization.

- A persistent or significant disability or incapacity

  Note: The term *disability* means a substantial disruption of a person's ability to conduct normal life functions. This definition is not intended to include AEs of relatively minor medical significance, such as uncomplicated headache, nausea, vomiting, diarrhea, influenza, or accidental trauma (e.g., sprained ankle), that may interfere or prevent everyday life functions, but do not constitute a substantial disruption of a person's ability to conduct normal life functions.

- A congenital anomaly or birth defect

- Other important medical event

Note: Medical or scientific judgment should be exercised in deciding whether reporting is appropriate for other important medical events that may not result in death, be life-threatening, or require hospitalization but still may jeopardize the subject or may require medical intervention to prevent one of the outcomes listed in this definition. These events should also be considered serious.

An SAE requires additional detailed reports and follow-up. The content of these detailed reports must address the investigator's estimate of causality.

6.3 RECORDING ADVERSE EVENTS AND SERIOUS ADVERSE EVENTS

All preexisting medical conditions will be recorded on the baseline physical examination page of the CRF. Starting with the first administration of first investigational product, any new event or experience that was not present at screening, or worsening of an event present at screening, is considered to be an AE. Unchanged, chronic conditions are not AEs and should not be recorded on the AE page of the CRF.

When an AE or SAE occurs, it is the responsibility of the investigator to review all documentation (e.g., hospital progress notes, laboratory and diagnostic reports) relative to the event. The investigator is to record all relevant information about any AE (including SAEs) on the AE page of the CRF. It is not acceptable for the investigator to send photocopies of the subject's medical records in lieu of the proper completion of the appropriate AE (or SAE) CRF pages. However, there may be instances where copies of medical records for certain cases are requested. In such instances, all subject identifiers and PHI will be blinded on the copies of the medical records before submission to the appropriate authorities.

The investigator will also attempt to establish a diagnosis of the event on the basis of signs, symptoms, or other clinical information. In such cases, the diagnosis, not the individual signs and symptoms, should be documented on the appropriate CRF as the AE or SAE. In addition, SAEs need to be reported on the SAE report form provided in the SPM. The SPM provides additional guidelines.

6.4 ASSESSMENT OF GRADE

The investigator will make an assessment of grade for each AE and SAE reported during the study, which will be recorded in the CRF. The assessment will be based on the National Cancer Institute's Common Terminology Criteria for Adverse Events, Version 4.03, and graded as shown below:

- Grade 1: Mild; asymptomatic or mild symptoms; clinical or diagnostic observations only; intervention not indicated
- Grade 2: Moderate; minimal, local or noninvasive intervention indicated; limiting age-appropriate instrumental activities of daily living
- Grade 3: Severe or medically significant but not immediately life-threatening; hospitalization or prolongation of hospitalization indicated; disabling; limiting self-care activities of daily living
- Grade 4: Life-threatening consequences; urgent intervention indicated
- Grade 5: Death related to AE

Any AE that changes in grade during its course will be recorded in the CRF at the highest level experience by the subject.

6.5 ASSESSMENT OF CAUSALITY

The investigator is obligated to estimate the relationship between the investigational products and the occurrence of each AE or SAE by using his or her best clinical judgment. Other causes, such as the history of the underlying disease, concomitant therapy, other risk factors, and the temporal relationship of the event to the investigational products will be considered and investigated. The investigator will also consult the IB or product labeling information for marketed products in the determination of the assessment.

There may be situations when an SAE has occurred and the investigator has minimal information to include in the initial report. However, it is very important that the investigator always assess causality for every event before the

transmission of the SAE. The investigator may change his or her opinion of the causality in light of follow-up information, amending the SAE report. The causality assessment (Table 5) is one of the criteria used to determine regulatory reporting requirements and should not be left blank.

Table 5. Assessment of Causality/Relatedness of AEs

Term	Definition
Definitely related	The AE *is clearly related* to the investigational agent(s) or research intervention: the AE has a temporal relationship to the administration of the investigational agent(s) or research intervention, follows a known pattern of response, and no alternative cause is present.
Possibly related	The AE *may be related* to the investigational agent(s) or intervention: the AE has a temporal relationship to the administration of the investigational agent(s) or research intervention, follows a suspected pattern of response, but an alternative cause is present.
Probably related	The AE is *likely related* to the investigational agent(s) or intervention: the AE has a temporal relationship to the administration of the investigational agent(s) or research intervention and follows a known or suspected pattern of response, but an alternative cause may be present.
Unlikely to be related	The AE is *doubtfully related* to the investigational agent(s) or intervention: the AE has a temporal relationship to the administration of the investigational agent(s) or research intervention but follows no known or suspected pattern of response, and an alternative cause is present.
Unrelated (or not related)	The AE is *clearly NOT* related to the investigational agent(s) or intervention: the AE has no temporal relationship to the administration of the investigational agent(s) or research intervention and follows no known or suspected pattern of response, and an alternative cause is present.

AE = adverse event.

6.6 REPORTING OF SERIOUS ADVERSE EVENTS

Any SAE that occurred after starting experimental treatment will be reported to the sponsor by phone, fax, or e-mail within 24 hours of the time the investigator becomes aware of the event.

SAE Reporting Fax Number: 615-297-6539

The Medical Monitor may also be contacted to discuss a safety event:

John Grous, MD: 508-634-1344 / mobile: 774-287-9709

The urgency for reporting SAE(s) is fourfold:

1. To enable the safety department to fulfill the reporting requirements to the appropriate regulatory authority

2. To facilitate discussion (and implementation, if necessary) between the safety department and the investigator of appropriate follow-up measures in the event an expedited report is required

3. To facilitate Aduro BioTech's rapid dissemination of information about AEs to other investigators or sites in a multicenter study by using expediting reporting

4. To facilitate investigator reporting of unanticipated problems involving risk to human subjects to the IRB and institutional biosafety committee

In the event an SAE is observed, the SAE report will be completed as thoroughly as possible including the following:

- All available details about the event

- Signature of the investigator

The SAE report will be forwarded to the sponsor or designee within the designated time frames. If the investigator does not have all information about an SAE, the investigator will *not* wait to receive additional information before notifying the sponsor of the event and completing the form. The form will be updated when additional information is received.

Aduro BioTech will report all SAEs that are unexpected and considered possibly or probably related to the administration of the investigational agents to the Food and Drug Administration in the form of an expedited safety report within 15 calendar days after receiving information on the SAE. Aduro BioTech will also report to the United States Food and Drug Administration (FDA) and National Institutes of Health Office of Biotechnology Activities (NIH OBA) by fax or phone within 7 days of receiving the information, any unexpected life-threatening or fatal SAEs that are considered at least possibly associated with the

investigational agents. Aduro BioTech, or designee, will also notify all participating investigators of expedited safety reports within 15 calendar days after receiving information. The investigators will notify their reviewing IRB and institutional biosafety committee (IBC) as required by institutional policies.

6.7 FOLLOW-UP OF ADVERSE EVENTS AND SERIOUS ADVERSE EVENTS

After the initial AE or SAE report, the investigator is required to proactively follow each subject and provide further information to the safety department in regards to the subject's condition.

All AE(s) and SAE(s) will be followed until:

- Resolution
- The condition stabilizes
- The event is otherwise explained
- The subject is lost to follow-up

Once the event is resolved, the appropriate AE or SAE report page will be updated. The investigator will also ensure that the follow-up includes any supplemental information that may explain the causality of the event(s).

New or updated information will be recorded on the originally completed AE or SAE report, with all changes signed and dated by the investigator or designee. The updated AE or SAE report will then be signed by the investigator and resubmitted to the safety department.

7.0 STUDY OR STUDY SITE TERMINATION AND SUBJECT DISCONTINUATION

7.1 PREMATURE STUDY OR STUDY SITE TERMINATION

If Aduro BioTech, the investigator, the medical monitor, the study monitor, or appropriate regulatory officials discover conditions arising during the study that indicate that the study should be halted or that the study center should be terminated, this action may be taken after appropriate consultation among Aduro BioTech, the investigator, the medical monitor, and the study monitor. Conditions that may warrant termination of the study include, but are not limited to the following:

- The discovery of an unexpected, serious, or unacceptable risk to the subjects enrolled in the study

- A decision on the part of Aduro BioTech to suspend or discontinue testing, evaluation, or development of the product for any reason

A study conducted at a single study site in a multicenter study may also warrant termination under the following conditions:

- Failure of the investigator to enroll subjects into the study at an acceptable rate

- Failure of the investigator to comply with pertinent regulations of appropriate regulatory authorities

- Submission of knowingly false information from the research facility to Aduro BioTech, the study monitor, or appropriate regulatory authority

- Insufficient adherence to protocol requirements

Study termination and follow-up will be performed in compliance with the conditions set forth in the International Conference on Harmonisation (ICH) E6, Guideline for Good Clinical Practice, Sections 4.12, 4.13, 5.20, and 5.21.

7.2 SUBJECT DISCONTINUATION

Subjects will be encouraged to complete the study; however, they may voluntarily withdraw at any time. The investigator will provide a written explanation describing the reason for discontinuation in a source document, which will be transcribed to the appropriate CRF page. Subjects who wish to withdraw from the study will be encouraged to complete the planned administration of antibiotics and to complete assessments scheduled during the follow-up visit.

Subjects who withdraw from the study before receiving at least 3 doses in the first cycle (in either treatment arm) will be considered dropouts and may be replaced at the discretion of Aduro BioTech. Replacements will be enrolled in the same treatment arm as the dropout.

Subjects who experience disease progression may be allowed to continue in the study if the investigator believes they are deriving some benefit from the therapy. A subject may be removed from the study for the reasons listed in Sections 7.2.1 through 7.2.4.

7.2.1 Adverse Event

If a subject suffers an AE that, in the judgment of the investigator, Aduro BioTech, or the medical monitor, presents an unacceptable consequence or risk to the subject, the subject may be discontinued from further participation in the study.

7.2.2 Intercurrent Illness

A subject may be discontinued from the study if, in the judgment of the investigator, the subject develops an intercurrent illness or complication (including progressive disease) that, in any way, justifies withdrawal from the study.

7.2.3 Noncompliance

After consultation between the investigator, the medical monitor, or study monitor, and Aduro BioTech when appropriate, a subject may be discontinued from the study for the following administrative reasons:

- Failure to receive study medication or treatment as mandated by the protocol
- Failure to comply with protocol requirements
- Unauthorized, subject-initiated changes in dosing regimen

7.2.4 Refusal of Clinical Trial Material Administration

If, for any reason, the subject refuses CTM administration during the study, the subject may be discontinued from the study, and the reason(s) for refusal will be documented on the appropriate CRF page. Reasonable efforts should be made to monitor the subject for AEs and to complete follow-up assessments. These efforts should be documented on the appropriate CRF page.

8.0 DATA COLLECTION AND PROCESSING AND STATISTICAL ANALYSIS

8.1 DATA COLLECTION AND PROCESSING

CRFs will be used to capture study results and data. The study coordinator or other authorized study personnel will transcribe data from source documents onto paper or electronic CRFs. All CRFs will be reviewed and source verified by the study monitor during periodic site visits, and the study monitor will ensure that all data in the CRF are correct and complete. Before or between visits, the medical monitor or study monitor may request copies of the CRFs for preliminary medical review. Once the CRFs are complete and source-verified, the investigator must sign and date all required pages, verifying the accuracy of all data contained within the CRF. Training will be provided on proper completion of CRFs.

If electronic CRFs are used, training will be provided for the electronic data capture (EDC) system. All personnel using the EDC system must have appropriate education, training, and experience. The investigator will be provided with standard operating procedures (SOPs) (contained in the SPM or a vendor-specific SOP) on the use of the EDC system. The investigator will be responsible for documenting employee education, training, and previous experience that pertains to the EDC system.

The investigator must maintain adequate security of the EDC system, including documentation that all users have been trained on the appropriate SOPs and a list of authorized users. To ensure attributability, all personnel responsible for data entry must obtain a unique electronic signature before any data can be entered in the CRFs. The system must be configured to ensure that the signer cannot readily repudiate the signed record as not genuine. Authorized study personnel will be assigned a unique password and associated electronic signature after receiving SOP training.

If EDC systems other than those provided and maintained by the sponsor are used for documentation and data capture, the investigator must ensure that the systems are validated and ensure data backup as described in Section 9.2.

8.2 STATISTICAL ANALYSIS

8.2.1 General Overview

The data will be summarized in tables listing the mean, standard deviation, median, minimum, maximum and number of subjects in a group for continuous data; in tables listing count and percentage for categorical data; and median and standard error for time-to-event data. Data will be listed for each subject. All statistical analyses will be performed and data appendices will be created by using SAS. The effects of noncompliance, dropouts, and covariates will be assessed to determine the impact on the general applicability of results from this study. All hypothesis tests will be one-sided with alpha set to 0.15 for each test. There will be no adjustment for multiple comparisons.

Further details of the analysis, including the handling of missing data transformations, and further modifications to populations of analysis will be provided in a separate statistical analysis plan.

8.2.2 Populations of Interest

The full analysis set (FAS) follows an intention-to-treat principle and includes all randomized subjects who receive at least one dose of cyclophosphamide. All efficacy endpoints will be assessed for the FAS. FAS analyses will be conducted on the basis of the treatment actually received, since this is a Phase 2 study.

The per protocol population is defined as all subjects in the FAS who receive at least three doses (at least one dose of CRS-207 in Treatment Arm A or three doses of cyclophosphamide/GVAX pancreas vaccine in Treatment Arm B). Additional exploratory analyses will be conducted for those subjects who reach the time of the second CRS-207 dose, those who reach the time of the third, and those of the fourth.

Subjects with major protocol violations will be excluded from the per protocol population. The precise reasons for excluding subjects from the per protocol set will be fully defined and documented before database lock.

The safety population comprises all subjects randomized into the study who received any CTM. Safety analyses will be based on what CTM was actually administered.

8.2.3 Baseline Comparability

Demographics and baseline clinical variables for subjects in each treatment group will be summarized in tables, figures, and descriptive statistics to evaluate the balance achieved by randomization. All differences will be interpreted for their clinical significance and potential use as covariates in sensitivity analyses of efficacy endpoints.

8.2.4 Efficacy Analysis

Efficacy analysis will be conducted on full analysis and per protocol populations. Standard adjustments to analyses for prespecified or baseline-suggested clinical covariates will be performed; these covariate-adjusted analyses will be considered secondary analyses. Efficacy results will be declared statistically significant if the one-sided p-value is less than 0.15. Study success will be determined by the FAS; per protocol assessment is secondary.

The primary efficacy parameter is overall survival. The primary analysis of this parameter will consist of a log-rank test with one-sided overall (i.e., accounting for the interim analysis) $\alpha = 0.15$. As exploratory analyses, a Cox proportional hazards model will be used to evaluate the effect of covariates on overall survival.

Exploratory efficacy variables are tumor response, and relationship of response to *Lm*- and mesothelin-specific immunological responses, and tumor marker kinetics. Tumor response will be assessed descriptively.

8.2.5 Safety Analysis

AE data will be listed individually and incidence of AEs summarized by system organ class and preferred terms within a system organ class for each treatment group. When calculating the incidence of AEs, each AE (based on preferred terminology defined by Medical Dictionary for Regulatory Activities, Version 13.1, or the most current version) will be counted only once for a given subject. In analyses of grade and causality, if the same AE occurs on multiple

occasions, the highest grade and strongest relationship to study drug will be assumed. If two or more AEs are reported as a unit, the individual terms will be reported as separate experiences. Vaccine-site reactions will be listed and tabulated separately from the AEs.

Changes in vital signs, hematology, and clinical chemistry parameters from baseline to the end of the study will be examined. Treatment-emergent changes from normal to abnormal values in key laboratory parameters will be identified.

8.2.6 Pharmacokinetic Analysis

No formal pharmacokinetic or pharmacodynamic analyses are planned for the investigational agents used in this study.

8.2.7 Interim Analysis

Safety analyses will be performed throughout the study by a safety review committee composed of Aduro BioTech, the investigator, the medical monitor, and the DMC after every 20 subjects are enrolled.

An interim analysis for early stopping for efficacy or for futility will be performed after 33 deaths occur. The interim analysis will include stopping rules for overwhelming efficacy as well as for futility. If the analysis shows that the study has reached its efficacy stopping criteria or is highly unlikely to show a benefit based on interim data, the study may be stopped.

The primary analysis of overall survival for the FAS is according to a 2-stage group sequential design with a single interim analysis at half the total study "information" (i.e., 66 deaths total; interim analysis after 33 deaths), and with O'Brien-Fleming-like alpha and beta spending functions (gamma = –4). In order to stop the study at the interim analysis and conclude statistically significantly (alpha = 0.15, 1-sided) longer survival in the sequential treatment arm than in the control arm, a p-value less than 0.0225 is required. The cutoff for futility stopping is $p > 0.6824$. If the study is not stopped at the interim analysis, the p-value cutoff to support an efficacy conclusion at the final analysis is $p < 0.1464$. This preserves the overall alpha level for the primary endpoint analysis at 0.15. These computations and the power described below derive from the EAST5.4 software.

8.2.8 Data Monitoring Committee

This is an open-label Phase 2 study. An independent DMC will review AEs, clinical laboratory results, and other study safety data as requested by the sponsor and as described in Section 8.2.7. The DMC will also review the interim efficacy analysis data and provide recommendations on continuation of the study to the sponsor. Specific responsibilities and requirements will be detailed in the DMC charter.

8.2.9 Sample Size

At least 90 subjects will be enrolled during 18 months and followed 24 months from time of enrollment of the last subject. For the FAS, if the true median survival for the sequential treatment is 8.1 months, and that for GVAX alone is 5 months, the sample size of N = 90 has approximately 80% power to yield a statistically significant difference (alpha = 0.15, 1-sided). This is based on an assumed enrollment rate of five patients per month. Power is computed for a 2-stage group sequential design with a single interim analysis at half the total study "information" (i.e., 66 deaths total; interim analysis after 33 deaths), and with O'Brien-Fleming–like alpha spending function (gamma= –4). Details of the group sequential design and stopping criteria will be provided in the DMC charter or the statistical analysis plan, which will be written after protocol approval.

9.0 CLINICAL STUDY ADMINISTRATOIN

9.1 INFORMED CONSENT AND AUTHORIZATION FOR USE AND DISCLOSURE OF PROTECTED HEALTH INFORMATION

Written informed consent and authorization of use and disclosure of PHI must be obtained from each subject (or the subject's legally authorized representative) before performing any study-specific screening/baseline period evaluations. One copy of the signed ICF and authorization for use and disclosure of the PHI form will be given to the subject, and the investigator will retain the original. The ICF and authorization for use and disclosure of PHI, which is prepared by the investigator or the site, must be reviewed and approved by Aduro BioTech, the study monitor (if applicable), and the site's IRB before the initiation of the study. The ICF must contain the 20 elements of informed consent described in ICH E6, Section 4.8. The authorization for use and disclosure of PHI must contain the elements required by Title 45 of the Code of Federal Regulations (CFR), Section 164.508(b), for valid authorizations. Appendix C provides further details about the specific requirements for informed consent.

9.2 STUDY DOCUMENTATION

9.2.1 Investigator Information

Investigator information is included in the SPM, which is updated as needed.

9.2.2 Investigator Study Files

Documentation about the investigator and study staff, the IRB, and the institution, is required before study site initiation (Appendix D). Copies of these documents as well as supplemental information, such as the investigator's obligations, IB, clinical study protocol and amendments, safety information, CTM, biological samples, laboratory, SPM and study logs, monitoring activities, sponsor/investigator/study monitor correspondence, will be kept on-site in study site-specific binders.

Aduro BioTech will be responsible for maintaining backup of all CRF data. The investigator is responsible for maintaining backup of all electronic data systems used for primary documentation or source documentation. Backup of electronic

data will be performed periodically as described in the site-specific SOPs. Backup records must be stored at a secure location on site, and backup and recovery logs must be maintained to facilitate data recovery. Finally, if an electronic medical records system that is not supported by the sponsor (or is discontinued or decommissioned) is used, the investigator must maintain a system to retrieve these records or arrange for the transfer of these records to an alternate electronic format or to paper.

Changes to any electronic records requires an audit trail, in accordance with 21 CFR 11.10(e), and should include who made the changes and when and why the changes were made. An audit trail is defined as a secure, computer-generated, time-stamped electronic record that will allow reconstruction of the course of events relating to the creation, modification, and deletion of an electronic record. Audit trails must be created incrementally, in chronological order, and in a manner that does not allow new audit trail information to overwrite existing data. Finally, audit trails should be in a readable format and readily available at the study site and any other location where electronic study records are maintained.

Audit trails are generated automatically for electronic CRFs. The investigator is responsible for maintaining audit trails of all electronic data systems used for primary documentation or source documentation.

9.2.3 Case Report Forms and Source Documentation

The investigator must make study data accessible to the site monitor, to other authorized representatives of Aduro BioTech, and to the appropriate regulatory authority inspectors. The original CRF for each subject will be checked against source documents at the study site by the site monitor.

9.2.4 Retention of Study Documents

According to ICH E6, Section 4.9, all CRFs, as well as supporting paper and electronic documentation and administrative records, must be retained by the investigator for a minimum of 2 years after notification that the appropriate regulatory authority has approved the product for the indication under study, notification that the entire clinical investigation will not be used in support of a marketing application, or notification that the marketing application was not approved. No study documents will be destroyed or moved to a new location

without prior written approval from Aduro BioTech. If the investigator relocates, retires, or withdraws from the clinical study for any reason, all records required to be maintained for the study should be transferred to an agreed-upon designee, such as another investigator at the institution where the study was conducted.

Audit trails for electronic documents must be retained for a period at least as long as that required for the subject electronic records to which they pertain. The investigator must retain either the original or a certified copy of audit trails.

9.3 CONFIDENTIALITY

9.3.1 Data

All information about the nature of the proposed investigation provided by Aduro BioTech or the study monitor to the investigator (with the exception of information required by law or regulations to be disclosed to the IRB, the subject, or the appropriate regulatory authority) must be kept in confidence by the investigator.

9.3.2 Subject Anonymity

The anonymity of participating subjects must be maintained. Subjects will be identified by their initials and an assigned subject number on CRFs and other documents retrieved from the site or sent to the study monitor, Aduro BioTech, regulatory agencies, or central laboratories/reviewers. Documents that identify the subject (e.g., the signed ICF) must be maintained in strict confidence by the investigator, except to the extent necessary to allow auditing by the appropriate regulatory authority, the study monitor, or Aduro BioTech representatives.

9.4 PROTOCOL COMPLIANCE

Substantive changes in the protocol include changes that affect the safety of subjects or changes that alter the scope of the investigation, the scientific quality of the study, the experimental design, dosages, assessment variable(s), the number of subjects treated, or the subject selection criteria. Such changes must be prepared as a protocol amendment by Aduro BioTech only upon joint approval of the changes by Aduro BioTech and the investigator. A protocol amendment must receive IRB approval before implementation. In parallel with the IRB approval

process, the protocol amendment will be submitted to the appropriate regulatory authority as an amendment to the regulatory submission under which the study is being conducted. If a protocol amendment requires changes in the ICF, the revised ICF prepared by the investigator must also be approved by Aduro BioTech, the study monitor, and the IRB before implementation.

Emergency departures from the protocol that eliminate an apparent immediate hazard to a particular subject and that are deemed crucial for the safety and well-being of that subject may be instituted for that subject only. The investigator or the attending physician also will contact the medical monitor as soon as possible in the case of such a departure. These departures do not require preapproval by the IRB; however, the IRB and the medical monitor must be notified in writing as soon as possible after the departure has been made. In addition, the investigator will document in the subject's CRF the reasons for the protocol deviation and the ensuing events.

9.5 STUDY MONITOR FUNCTIONS AND RESPONSIBILITY

The study monitor, in accordance with Aduro BioTech's requirements, will ensure that the study is conducted and documented properly by carrying out the relevant activities outlined in ICH E6, Section 5.18.4.

9.6 GENERAL INFORMATION

The investigator should refer to the IB, product labels, and the SPM, any other information provided during the study initiation visit or by the study monitor, and the appendices of this protocol for further information about this investigational new product or details of the procedures to be followed during the course of this study.

10.0 REFERENCES

1. Evans, D.B., R.T. and J.L. Abbruzzese, Cancer of the Pancreas, J.B. Lippincott, Editor. 1997: Philadelphia, PA. p. 1054-1087.

2. Sener, S.F., et al., Pancreatic cancer: a report of treatment and survival trends for 100,313 patients diagnosed from 1985-1995, using the National Cancer Database. J Am Coll Surg, 1999. 189(1): p. 1-7.

3. Ferlay, J. and F. Bray, Cancer incidence, mortality and prevalence worldwide, Lyon, IARCPress: GLOBOCAN 2000. p. IARC CancerBase No. 5.

4. Burris III, H.A., et al., Improvements in survival and clinical benefit with gemcitabine as first-line therapy for patients with advanced pancreas cancer: a randomized trial. J Clin Oncol, 1997. 15(6): p. 2403-2413.

5. Friberg, G. and H.L. Kindler, Chemotherapy for advanced pancreatic cancer: past, present, and future. Curr Oncol Rep, 2005. 7(3): p. 186-195.

6. Moore, M.J., Brief communication: a new combination in the treatment of advanced pancreatic cancer. Semin Oncol, 2005. 32(6 Suppl 8): p. 5-6.

7. Freelove, R. and A.D. Walling, Pancreatic cancer: diagnosis and management. Am Fam Physician, 2006. 73(3): p. 485-492.

8. Eckel, F., G. Schneider, and R.M. Schmid, Pancreatic cancer: a review of recent advances. Expert Opin Investig Drugs, 2006. 15(11): p. 1395-1410.

9. Benson III, A.B., Adjuvant therapy for pancreatic cancer: one small step forward. JAMA, 2007. 297(3): p. 311-313.

10. Offringa, R., Cancer immunotherapy is more than a numbers game. Science, 2006. 314(5796): p. 68-69.

11. Koon, H. and M. Atkins, Autoimmunity and immunotherapy for cancer. N Engl J Med, 2006. 354(7): p. 758-760.

12. Laheru, D. and E.M. Jaffee, Immunotherapy for pancreatic cancer - science driving clinical progress. Nat Rev Cancer, 2005. 5(6): p. 459-467.

13. Slifka, M.K., et al., Antiviral cytotoxic T-cell memory by vaccination with recombinant Listeria monocytogenes. J Virol, 1996. 70(5): p. 2902-2910.

14. Shen, H., et al., Recombinant Listeria monocytogenes as a live vaccine vehicle for the induction of protective anti-viral cell-mediated immunity. Proc Natl Acad Sci U S A, 1995. 92(9): p. 3987-3991.

15. Portnoy, D.A., V. Auerbuch, and I.J. Glomski, The cell biology of Listeria monocytogenes infection: the intersection of bacterial pathogenesis and cell-mediated immunity. J Cell Biol, 2002. 158(3): p. 409-414.

16. Bahjat, K.S., et al., Cytosolic entry controls CD8+-T-cell potency during bacterial infection. Infect Immun, 2006. 74(11): p. 6387-6397.

17. Brockstedt, D.G., et al., Listeria-based cancer vaccines that segregate immunogenicity from toxicity. Proc Natl Acad Sci U S A, 2004. 101(38): p. 13832-13837.

18. Hassan, R., T. Bera, and I. Pastan, Mesothelin: a new target for immunotherapy. Clin Cancer Res, 2004. 10(12 Pt 1): p. 3937-3942.

19. Hassan, R., et al., Mesothelin is overexpressed in pancreaticobiliary adenocarcinomas but not in normal pancreas and chronic pancreatitis. Am J Clin Pathol, 2005. 124(6): p. 838-845.

20. Argani, P., et al., Mesothelin is overexpressed in the vast majority of ductal adenocarcinomas of the pancreas: identification of a new pancreatic cancer marker by serial analysis of gene expression (SAGE). Clin Cancer Res, 2001. 7(12): p. 3862-3868.

21. Jaffee, E.M., et al., Novel allogeneic granulocyte-macrophage colony-stimulating factor-secreting tumor vaccine for pancreatic cancer: a phase I trial of safety and immune activation. J Clin Oncol, 2001. 19(1): p. 145-156.

22. Thomas, A.M., et al., Mesothelin-specific CD8(+) T cell responses provide evidence of in vivo cross-priming by antigen-presenting cells in vaccinated pancreatic cancer patients. J Exp Med, 2004. 200(3): p. 297-306.

23. Laheru, D., et al., Allogeneic granulocyte macrophage colony-stimulating factor-secreting tumor immunotherapy alone or in sequence with cyclophosphamide for metastatic pancreatic cancer: a pilot study of safety, feasibility, and immune activation. Clin Cancer Res, 2008. 14(5): p. 1455-1463.

24. Jaffee, E.M., et al., Development and characterization of a cytokine-secreting pancreatic adenocarcinoma vaccine from primary tumors for use in clinical trials. Cancer J Sci Am, 1998. 4(3): p. 194-203.

25. Jaffee, E.M., et al., A phase I clinical trial of lethally irradiated allogeneic pancreatic tumor cells transfected with the GM-CSF gene for the treatment of pancreatic adenocarcinoma. Hum Gene Ther, 1998. 9(13): p. 1951-1971.

26. Jaffee, E.M., et al., High efficiency gene transfer into primary human tumor explants without cell selection. Cancer Res, 1993. 53(10 Suppl): p. 2221-2226.

27. Berd, D., H.C. Maguire Jr, and M.J. Mastrangelo, Induction of cell-mediated immunity to autologous melanoma cells and regression of metastases after treatment with a melanoma cell vaccine preceded by cyclophosphamide. Cancer Res, 1986. 46: p. 2572-2577.

28. Holmberg, L.A. and B.M. Sandmaier, Theratope vaccine (STn-KLH). Expert Opin Biol Ther, 2001. 1(5): p. 881-891.

29. Ercolini, A.M., et al., Recruitment of latent pools of high-avidity CD8(+) T cells to the antitumor immune response. J Exp Med, 2005. 201(10): p. 1591-1602.

30. Emens, L.A., et al., Timed sequential treatment with cyclophosphamide, doxorubicin, and an allogeneic granulocyte-macrophage colony-stimulating factor-secreting breast tumor vaccine: a chemotherapy dose-ranging factorial study of safety and immune activation. J Clin Oncol, 2009. 27(35): p. 5911-5918.

31. Wolchok, J.D., et al., Guidelines for the evaluation of immune therapy activity in solid tumors: immune-related response criteria. Clin Cancer Res, 2009. 15(23): p. 7412-7420.

32. Controlling occupational exposure to hazardous drugs. Occupational Safety and Health Administration. Am J Health Syst Pharm, 1996. 53(14): p. 1669-1685.

APPENDICES

APPENDIX A

RESPONSE EVALUATION CRITERIA IN SOLID TUMORS (RECIST) QUICK REFERENCE

Apply RECIST 1.1 criteria to tumor assessment and record on CRF.

	RECIST 1.1
Measurable Tumor Burden	A maximum of 5 target lesions in total (and up to 2 per organ) can be identified at baseline and measured through the course of therapy.
Minimum Size of Measurable Lesions	≥ 10 mm in longest diameter (LD) and 2X the slice thickness for extranodal lesions ≥ 15 mm in short axis diameter (SAD) for nodal lesions ≥ 10 mm in LD for clinical lesions (must be measured using electronic calipers) ≥ 20 mm in LD for chest X-ray (if clearly defined & surrounded by aerated lung); CT is preferable Ultrasound (US) cannot be used to measure lesions
Lymph Nodes	Lymph nodes are considered pathologically enlarged if >10 mm in SAD. To be measurable, nodal lesions must be ≥ 15 mm in SAD. Nodal lesions with SAD >10 mm and <15 mm are non-measurable. The sum of the diameters (LD for extranodal target lesions, SAD for nodal lesions) is followed through the course of therapy.
Bone Lesions	A lytic or mixed lytic-blastic bone lesion with a soft tissue component assessed on CT/MRI can be measurable if the minimum size criteria are met. Blastic bone lesions and bone lesions assessed on bone scan, positron emission therapy (PET) or plain films are non-measurable.
Cystic Lesions	Lesions that meet the criteria for radiographically defined simple cysts are not malignant. Cystic lesions thought to be metastases can be measurable if they meet the minimum size criteria. Non-cystic lesions are preferable.
Lesions with Prior Local Treatment	Lesions in previously irradiated areas (or areas treated with local therapy) are not measurable unless the lesion has progressed since therapy. Conditions should be defined in study protocols.
Too Small To Measure	If a target lesion becomes too small to measure, a default value of 5 mm is assigned. If the lesion disappears, the measurement is recorded as 0 mm.
Lesions which split or Coalesce	If extranodal target lesions fragment, the LDs of the fragmented portions are added to the sum. If target lesions coalesce and cannot be distinguished, the LD of the coalesced lesion is added to the sum.
Definition of Complete Response (CR)	CR requires the disappearance of all extranodal lesions, the regression of all nodal lesions to <10 mm SAD and the normalization of tumor marker level.

	RECIST 1.1
Definition of Progressive Disease (PD)	PD is assessed if the sum of the diameters has increased by ≥ 20% and ≥ 5 mm from nadir (including baseline if it is the smallest sum). Patients with measurable disease: for "unequivocal progression" based on non-target disease, there must be an overall level of substantial worsening that merits discontinuation of therapy (if target disease is SD/PR). Patients without measurable disease: for "unequivocal progression" of non-target disease, the increase in overall tumor burden must be comparable to the increase required for PD of measurable disease.
Assessment of New Lesions	New lesions should be unequivocal and not attributable to differences in scanning technique or findings which may not be tumor (i.e. 'new' bone lesions may be healing or flare of pre-existing lesions). If on is equivocal, repeat scans are needed to confirm. If confirmed, PD is assessed at the date of the initial scan. Lesions identified in anatomic locations not scanned at baseline are considered new. New lesions on US should be confirmed on CT/MRI.
FDG-PET	New lesions can be assessed using FDG-PET :(-) PET at baseline and (+) PET at follow-up is PD based on a new lesion. No PET at baseline and (+) PET at follow-up is PD if the new lesion is confirmed on CT. If a subsequent CT confirms the new lesion, the date of the PD is the date of the initial PET scan. No PET at baseline and (+) PET at follow-up corresponding to pre-existing lesion on CT that is not progressing; not PD.
Recurrence of lesions	For a patient with SD/PR, a lesion which disappears and then reappears will continue to be measured and added to the sum. Response will depend upon the status of the other lesions. For a patient with CR, reappearance of a lesion would be considered PD.
Overall Response	One overall response table integrates target, non-target and new lesions and another table integrates non-target and new lesions for the assessment of subjects without measurable disease.
Confirmation of Response	Confirmation of PR/CR is ONLY required for non-randomized trials where response is the primary endpoint. In these trials, subsequent confirmation of PR with one interim time point of SD is acceptable.

APPENDIX B

IMMUNE-RELATED RESPONSE CRITERIA (IRRC) QUICK REFERENCE

Comparison between WHO/RECIST 1.1 criteria and the irRC[31]

	WHO or RECIST 1.1	irRC RECIST 1.1
New, measurable lesions (i.e., ≥ 5 x 5 mm)	Always represent PD	Incorporated into tumor burden
New, non-measurable lesions (i.e., <5 x 5 mm)	Always represent PD	Does not define progression (but precludes irCR)
Non-index lesions	Changes contribute to defining best overall response (BOR) of CR, PR, SD, and PD	Contribute to defining irCR (complete disappearance required)
CR	Disappearance of all lesions in two consecutive observations not less than 4 week apart	Disappearance of all lesions in two consecutive observations not less than 4 week apart if single arm trial and primary endpoint only
PR	**WHO** ≥ 50% decrease in sum of the product of the two largest perpendicular diameters (SPD) of all index lesions compared with baseline in two observations at least 4 week apart, in absence of new lesions or unequivocal progression of non-index lesions **RECIST 1.1** > or = 30% decrease in the sum of the diameters of all index lesions compared with baseline in two observations at least 4 week apart, in absence of new lesions or unequivocal progression of non-index lesions	≥ 30% decrease in tumor burden compared with baseline in two observations at least 4 week apart if single arm trial and primary endpoint only

	WHO or RECIST 1.1	irRC RECIST 1.1
SD	**WHO** 50% decrease in SPD compared with baseline cannot be established nor 25% increase compared with nadir, in absence of new lesions or unequivocal progression of non-index lesions **RECIST 1.1** 30% decrease in sum of longest diameters of all index lesions compared with baseline cannot be established nor 20% increase compared with nadir, in the absence of new lesions or unequivocal progression of non-index lesions	30% decrease in tumor burden compared with baseline cannot be established nor 20% increase compared with nadir
PD	**WHO** At least 25% increase in SPD compared with nadir and/or unequivocal progression of non-index lesions and/or appearance of new lesions (at any single time point) **RECIST 1.1** At least 20% increase in the sum of the longest diameters of index lesions or unequivocal progression of non-index lesions	At least 20% increase in tumor burden compared with nadir (at any single time point) in two consecutive observations at least 4 week apart
Handling of lymph nodes	Not differentiated from other tumor measurements	Lymph nodes are considered pathologically enlarged if >10 mm in SAD. To be measurable, nodal lesions must be ≥ 15 mm in SAD. Nodal lesions with SAD >10 mm and <15 mm are non-measurable. The sum of the diameters (LD for extranodal target lesions, SAD for nodal lesions) is followed through the course of therapy

Derivation of irRC Overall Responses[31]
(Modified for RECIST 1.1. Criteria)

Measurable response	**Non-measureable response**		**Overall response**
Index and new, measurable lesions (tumor burden)* %	Non-index lesions	New, non-measurable lesions	Using irRC
↓ 100	Absent	Absent	irCR/\
↓ 100	Stable	Any	irPR/\
↓ 100	Unequivocal progression	Any	irPR/\
↓ ≥ 30	Absent/ Stable	Any	irPR/\
↓ ≥ 30	Unequivocal progression	Any	irPR/\
↓ <30 to <20↑	Absent/ Stable	Any	irSD
↓ <30 to <20↑	Unequivocal progression	Any	irSD
≥ 20?	Any	Any	irPD/\

*Decreases assessed relative to baseline, including measurable lesions only (>5 x 5 mm).

/\Assuming response (irCR or irPR) and progression (irPD) are confirmed by a second consecutive assessment at least 4 weeks apart.

Defining immune-related Response Criteria by RECIST 1.1 criteria at 20 weeks (irDCR at 20 weeks):

1. Any patient with stable disease or progressive disease at any time in the trial with "rapid clinical deterioration" felt to be related to disease progression is irPD

2. Any patient who meets the criteria for RECIST 1.1 CR at 20 weeks is irCR

3. Any patient who meets the criteria for RECIST 1.1 PR at 20 weeks is irPR

4. Any patient who meets the criteria for RECIST 1.1 SD at 20 weeks is irSD

5. A patient with RECIST 1.1 PD but no rapid clinical deterioration may stay on study if his/her next tumor measurement evaluation is stable disease or better.

6. If patient has first time PD by RECIST 1.1 criteria, call it unconfirmed PD for irRC RECIST 1.1.

7. A patient with unconfirmed irPD at 20 weeks whose next tumor measurement is SD or better will be considered to be included in the irDCR at 6 months.

8. A patient with unconfirmed irPD at 20 weeks who fails to qualify for RECIST 1.1 SD or unconfirmed CR or PR by next tumor measurement will be considered to have RECIST 1.1 PD and irPD at 20 weeks.

APPENDIX C

PROTECTION OF HUMAN SUBJECTS (ICH E6, SECTION 4.8)

PROTECTION OF HUMAN SUBJECTS (ICH E6, SECTION 4.8)

Informed consent must be obtained from every subject before he enters a study. It must be given freely and not under duress. Consent must be documented by the subject or the subject's legally authorized representative signing an IRB/IEC-approved consent form. When minors are involved, a parent or guardian should sign the consent form. If the minor is an adolescent (12 to 16-18 years of age, dependent on region, as specified in ICH E11, Clinical Investigation of Medicinal Products in the Pediatric Population), his signature should also be included. Subjects who do not speak English must be presented with a consent form written in a language that they understand. A copy of the signed consent form must be given and made available to the sponsor and representatives of the appropriate regulatory authority upon request. If, for any reason, subject risk is increased as the study progresses, a revised IRB/IEC-approved consent form must be signed by the subject.

Nothing in these regulations is intended to limit the authority of a physician to provide emergency medical care to the extent the physician is permitted to do so under applicable federal, state, or local laws. Only in the case of a life-threatening incident may an investigational agent be used without prior signed consent. In such an emergency situation, separate certifications must be written both by a physician not participating in the study and by the investigator. The certifications, along with the protocol and informed consent, must be sent to the IRB/IEC within 5 working days. In this situation, the investigator may not administer any subsequent product to that subject until informed consent and IRB/IEC approval are obtained.

1.0 BASIC ELEMENTS OF INFORMED CONSENT

Every consent form must include explanations of each of the following 20 elements:

- That the study involves research
- The purpose of the study
- The study treatment(s) and the probability for random assignment to each treatment
- The study procedures to be followed, including all invasive procedures
- The subject's responsibilities

- Those aspects of the study that are experimental

- The reasonably foreseeable risks or inconveniences to the subject and, when applicable, to an embryo, fetus, or nursing infant

- The reasonably expected benefits; and when there is no intended clinical benefit to the subject, the subject should be made aware of this

- The alternative procedure(s) or course(s) of treatment that may be available to the subject, and their important potential benefits and risks

- The compensation or treatment available to the subject in the event of a study-related injury

- The anticipated prorated payment, if any, to the subject for participating in the study

- The anticipated expenses, if any, to the subject for participating in the study

- That the subject's participation in the study is voluntary and that the subject may refuse to participate or withdraw from the study, at any time, without penalty or loss of benefits to which the subject is otherwise entitled

- That the monitor(s), the auditor(s), the IRB/IEC, and the regulatory authority(ies) will be granted direct access to the subject's original medical records for verification of clinical study procedures or data, without violating the confidentiality of the subject, to the extent permitted by applicable laws and regulations and that, by signing a written informed consent form, the subject or the subject's legally acceptable representative is authorizing such access

- That the records identifying the subject will be kept confidential and, to the extent permitted by the applicable laws or regulations, will not be made publicly available; and if the results of the study are published, the subject's identity will remain confidential

- That the subject or the subject's legally authorized representative will be informed in a timely manner if information becomes available that may be relevant to the subject's willingness to continue participation in the study

- The person(s) to contact for further information regarding the study and the rights of study subjects, and whom to contact in the event of a study-related injury

- The foreseeable circumstances or reasons under which the subject's participation in the study may be terminated

- The expected duration of the subject's participation in the study

- The approximate number of subjects involved in the study

Nothing in these regulations is intended to limit the authority of a physician to provide emergency medical care to the extent the physician is permitted to do so under applicable federal, state, or local laws.

The informed consent requirements in these regulations are not intended to preempt any applicable federal, state, or local laws that require additional information to be disclosed in order that informed consent be legally effective. Some states require further action on the investigator's part concerning subject consent.

APPENDIX D

REQUISITE DOCUMENTS FOR APPROVAL OF STUDY SITE

REQUISITE DOCUMENTS FOR APPROVAL OF STUDY SITE

Clinical trial material will be provided to the investigators after they have submitted the following documents to the sponsor or study monitor (if applicable):

- Signed protocol and amendment(s) if applicable
- Signed Statement of Investigator, e.g., 1572 (if required by the regulatory agency)
- Institutional review board/independent ethics committee (IRB/IEC) committee composition
- Document indicating IRB/IEC approval of the final protocol and amendment(s) if applicable (to include name, address, and chairperson of the IRB/IEC)
- Document indicating IRB/IEC approval of the final and revised informed consent document if applicable (to include name, address, and chairperson of the IRB/IEC)
- Blank copy of the IRB/IEC-approved final and revised informed consent document
- Document indicating IBC approval of the final protocol if applicable (to include name, address, and chairperson of the IBC)
- Signed Investigator's Clinical Study Agreement and Confidentiality Disclosure Agreement
- Laboratory Certification or Accreditation and normal ranges for tests that are performed in the laboratory for study assessments
- *Curricula vitae* for the investigator and subinvestigator(s)
- Financial disclosure for the investigator and subinvestigator(s)

APPENDIX E

RESPONSIBILITIES AND OBLIGATIONS OF INVESTIGATORS AND SPONSORS

RESPONSIBILITIES AND OBLIGATIONS OF INVESTIGATORS AND SPONSORS

1.0 SPONSOR

The sponsor or designee will:

1.1 Conduct a pre-investigation site selection visit or study initiation visit to:

- Establish the acceptability of the facility and record the visit in a written report (i.e., memorandum or form).

- Discuss with the investigator the proposed clinical trial and supply him with draft electronic case report forms (CRFs), the Investigator's Brochure, and the draft protocol for his review and approval.

- Discuss with the investigator the regulatory requirements with respect to informed consent, institutional review board/independent ethics committee (IRB/IEC) approval of the trial, the protocol, protocol amendments, and changes to the informed consent document.

- Discuss with the investigator the timing of interim and final reports to the study monitor and his obligation to supply the study monitor with copies of all study-related documents (including IRB/IEC approval, IRB/IEC charter or equivalent, membership and qualifications, protocol amendments, informed consent documents, and consent changes), CRFs, CRF changes, and all pertinent correspondence to and from the IRB/IEC.

1.2 Conduct periodic on-site visit(s) to:

- Assure adherence to the protocol.

- Review CRFs and source documents for accuracy and completeness of information.

- Examine pharmacy records for documentation of quantity and date of receipt of investigational drug, dispensation and accountability data for product administration to each subject, loss of materials, contamination, and unused supplies.

- Record and report (summarize) observations on the progress of the study and continued acceptability of the facilities, and prepare an on-site visit report.

- Review investigator files for required documents, (e.g., protocols; protocol amendments; Investigator's Brochure; Study Procedures Manual; IRB/IEC approval of protocols, amendments, and informed consent document; IRB/IEC charter and membership; and communications to and from the IRB/IEC and the study monitor).

2.0 INVESTIGATOR

2.1 Institutional Review Board/Independent Ethics Committee

The investigator must assure the study monitor that the IRB/IEC:

- Meets ICH guidelines as defined in ICH E63: Institutional Review Board/Independent Ethics Committee.

- Has the authority delegated by the parent institution and found in the IRB/IEC by-laws, operation guidelines, or charter to approve or disapprove clinical trials and protocols, including informed consent and other documents (e.g., protocol amendments and information to be supplied to subjects concerning informed consent).

- Complies with proper personnel make-up of the board.

- Convenes meetings using acceptable rules of order for making decisions, recording such decisions, and implementing them.

- Maintains files that contain (a) documentation of its decisions, such as are found in IRB/IEC minutes and correspondence, (b) written guidelines or by-laws governing IRB/IEC functions, (c) protocol, (d) protocol amendments, (e) approved informed consent document and information to be supplied to the subject, and (f) correspondence between the IRB/IEC and investigator (e.g., consent changes, protocol amendments).

2.2 Informed Consent Human Subjects

The investigator must assure the study monitor that the informed consent document for a subject:

- Meets ICH guidelines as defined in ICH E6 4.8: Informed Consent of Trial Subjects.
- Has been approved by the IRB/IEC, including (when required) information to be given to the subject regarding the study in which he is enrolled.
- Includes the basic elements and any additional elements of informed consent that are appropriate.
- Has been signed by the subject (or his legally authorized representative), the investigator, and a witness, and a copy has been given to the subject.
- May be provided to the subject in the "short form" (presented orally to the subject or the subject's legally authorized representative, with a witness listening) informed consent document with written information as an alternative.
- Assent has been obtained for minor children as required by the IRB.

2.3 Storage and Dispensing of Product Supplies

The investigator (or his pharmacist) must assure the study monitor that:

- Adequate and accurate written records show receipt and disposition of all product supplies, including dates, serial or lot numbers, quantities received, and each quantity dispensed, administered, or used, with identification of each subject.
- Purpose and reasons are given in written records for product disposal (e.g., the amount contaminated, broken, or lost) and the quantity that was returned to the sponsor.

2.4 Electronic Case Report Forms

The investigator must assure the study monitor that:

- The completed CRF accurately reflects the hospital records for each subject.
- The CRFs and hospital records will be accessible to the study monitor during on-site visits.

2.5 Files and Records

The investigator must assure the quality, integrity, and content of his files, which will be subject to audit by the study monitor and the appropriate regulatory authority inspectors. The files must contain, as minimum the following:

- Investigator's Brochure
- Investigator's Obligations including the following:

  21 CFR Part 312.50 General Responsibilities of Sponsors

  21 CFR Part 312.60 General Responsibilities of Investigators

  21 CFR Part 50 Protection of Human Subjects

  21 CFR Part 56 Institutional Review Boards

  International Conference on Harmonisation, Good Clinical Practice, Consolidated Guidelines
- IRB/IEC - approved protocol and protocol amendments
- Blank CRFs (and amendments to CRF)
- Study Procedures Manual and amended pages
- Statement of Investigator Forms (copy of signed Form FDA 1572 and a copy of each revised form if required by the regulatory agency) and current Curricula Vitae and Bibliography for each investigator and subinvestigator

- IRB document including the following:

  IRB/IEC charter membership and qualifications of each member

  IRB letter of approval of protocol and amendments

  IRB letter of approval of informed consent form and amendments

  Investigator's annual report to the IRB

  IRB annual reapproval of protocol

  Reports to IRB of deaths and SAEs

  Notification to IRB of study completion and investigator's final report

  IRB approval of advertisements for subject recruitment (if applicable)

  All additional correspondence with the IRB/IEC

- IRB/IEC-approved informed consent document (all versions) and information to be supplied to the subject

- Study staff signature log

- Subject Accountability Records including the following:

  Subject Screening Log

  Medical Exceptions Log

  Site Status Report

  Subject Identification code list

  Original signed Informed Consent Form

  A note stating the location of the CRFs and Data Clarification Requests (DCRs)

- Clinical trial material records including the following:

  Receipt, date and quantity, and batch or lot number

  Disposition dates and quantity administered to each subject

  Inventory records

  All correspondence related to clinical trial material

- SAE/Safety Reports

  Copies of signed SAE Reporting Forms

  All SAE correspondence, including MedWatch and Form FDA 3500A

- Biological Sample Inventory forms and correspondence with the analytical lab

- Monitoring Activities

  Monitoring Log (should include all visits [i.e., study site initiation, periodic, and termination visits])

  Telephone contact reports

  Site initiation visit reports

- General Correspondence

  All correspondence between the study monitor, sponsor, and the site

  All correspondence within the site concerning the protocol

Documents and records must be retained by the investigator:

- For a period of 2 years after the date a marketing application is approved for the product for the indication for which it is being investigated,

OR

- Until there are no pending or contemplated marketing applications,

OR

- For a minimum of 2 years after discontinuations of the clinical investigation.

CLINICAL PROTOCOL

TITLE OF STUDY:

A Phase 2, Randomized, Multicenter, Open-Label Study of the Efficacy and Immune Response of the Sequential Administration of GVAX Pancreas Vaccine (with Cyclophosphamide) Alone or Followed by CRS-207 in Adults with Metastatic Pancreatic Adenocarcinoma

Protocol ID:	**ADU-CL-01**
Sponsor:	**Aduro BioTech, Inc.** **626 Bancroft Way, #3C** **Berkeley, CA 94710-2224** **Phone: 510-848-4400** **Fax: 510-848-5614**
IND:	**14,678**
Date of Issue:	**06 November 2013, Version 8**

Signatures of Approval for Protocol (Version 8)

Affiliation	Name	Signature	Date:
Investigator:	Dung Le, MD		
Sponsor:	Dirk Brockstedt, Ph.D.		
Medical Monitor:	John Grous, M.D.		

CLINICAL PROTOCOL

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Signatures of Approval for Protocol (Version 8)

Affiliation	Name	Signature	Date:
Investigator:	Dung Le, MD		11/7/13
Sponsor:	Dirk Brockstedt, Ph.D.		
Medical Monitor:	John Grous, M.D.		

CLINICAL PROTOCOL

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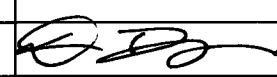
Signatures of Approval for Protocol (Version 8)

Affiliation	Name	Signature	Date:
Investigator:	Dung Le, MD		
Sponsor:	Dirk Brockstedt, Ph.D.		06 Nov 2013
Medical Monitor:	John Grous, M.D.		

CLINICAL PROTOCOL

TITLE OF STUDY:

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Date of Issue:	**06 November 2013, Version 8**

Signatures of Approval for Protocol (Version 8)

Affiliation	Name	Signature	Date:
Investigator:	Dung Le, MD		
Sponsor:	Dirk Brockstedt, Ph.D.		
Medical Monitor:	John Grous, M.D.		Nov 6, 2013

This study is to be performed in accordance with Good Clinical Practice, the ethical principles that have their origin in the Declaration of Helsinki: Title 21 of the Code of Federal Regulations Parts 50 (Protection of Human Subjects), 56 (Institutional Review Boards), and 312 (Investigational New Drug Application); and International Conference on Harmonisation E6 (Guideline for Good Clinical Practice).

Study Sponsor:	Aduro BioTech, Inc. 626 Bancroft Way, #3C Berkeley, CA 94710-2224 Phone: 510-848-4400 Fax: 510-848-5614
Sponsor Contacts:	Dirk Brockstedt, Ph.D., Senior Vice President of Research and Development 626 Bancroft Way, #3C Berkeley, CA 94710-2224 Phone: 510-809-4815 Fax: 510-848-5614 E-mail: dbrockstedt@adurobiotech.com Aimee Murphy, Director of Clinical Operations 626 Bancroft Way, #3C Berkeley, CA 94710-2224 Phone: 510-809-4806 Fax: 510-848-5614 E-mail: amurphy@adurobiotech.com
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Lead Investigator:	Dung Le, M.D. The Sidney Kimmel Comprehensive Cancer Center at Johns Hopkins The Bunting-Blaustein Cancer Research Building 1650 Orleans St. Room 407 Baltimore, MD 21231-1000 Phone: 443-287-0002 Fax: 410-614-8216 E-mail: dle@jhmi.edu

This study is to be performed in accordance with Good Clinical Practice, the ethical principles that have their origin in the Declaration of Helsinki: Title 21 of the Code of Federal Regulations Parts 50 (Protection of Human Subjects), 56 (Institutional Review Boards), and 312 (Investigational New Drug Application); and International Conference on Harmonisation E6 (Guideline for Good Clinical Practice).

Study Sponsor:	Aduro BioTech, Inc. 626 Bancroft Way, #3C Berkeley, CA 94710-2224 Phone: 510-848-4400 Fax: 510-848-5614
Sponsor Contacts:	Dirk Brockstedt, Ph.D., Senior Vice President of Research and Development 626 Bancroft Way, #3C Berkeley, CA 94710-2224 Phone: 510-809-4815 Fax: 510-848-5614 E-mail: dbrockstedt@adurobiotech.com Aimee Murphy, Director of Clinical Operations 626 Bancroft Way, #3C Berkeley, CA 94710-2224 Phone: 510-809-4806 Fax: 510-848-5614 E-mail: amurphy@adurobiotech.com
Contract Research Organization (CRO) Contacts:	Brad Phillips, Senior Clinical Project manager Medelis, Inc. 40 Burton Hills Blvd, Suite 370 Nashville, TN 37215 Phone: 615-297-6105 Fax: 615-385-7055 E-mail: Brad.Phillips@Medelis.com John Grous, M.D., Medical Monitor Medelis, Inc. 40 Burton Hills Blvd, Suite 370 Nashville, TN 37215 Phone: 508-634-1344 Cell: 774-287-9709 Fax: 615-385-7055 E-mail: DrHopedale@excite.com
Lead Investigator:	Dung Le, M.D. The Sidney Kimmel Comprehensive Cancer Center at Johns Hopkins The Bunting-Blaustein Cancer Research Building 1650 Orleans St. Room 407 Baltimore, MD 21231-1000 Phone: 443-287-0002 Fax: 410-614-8216 E-mail: dle@jhmi.edu

STUDY SYNOPSIS

Name of Sponsor Company: Aduro BioTech, Inc.	**Individual Study Table Referring to Part of the Dossier**	***(For National Authority Use Only)***
Name of Finished Product: Cytoxan; GVAX pancreas vaccine; CRS-207	**Volume:**	
Name of Active Ingredients: Cyclophosphamide; Panc 10.05 pcDNA1/GM-Neo, Panc 6.03 pcDNA1/GM-Neo; *Lm* Δ*actA*/Δ*inlB*/hMesothelin	**Page:**	

Title of Study: A Phase 2, Randomized, Multicenter, Open-Label Study of the Efficacy and Immune Response of the Sequential Administration of GVAX Pancreas Vaccine (with Cyclophosphamide) Alone or Followed by CRS-207 in Adults with Metastatic Pancreatic Adenocarcinoma

Primary Investigator: Dung Le, M.D.

Number of Sites: Up to 12

Phase of Development: Phase 2	**Treatment Period:** 5 months	**Study Duration:** 45 months

Objectives:

Primary:

- To compare overall survival in subjects receiving sequential administration of cyclophosphamide, GVAX pancreas vaccine and CRS-207 with overall survival in subjects receiving cyclophosphamide and GVAX vaccine alone

Secondary:

- To assess safety of the cyclophosphamide, GVAX pancreas vaccine, and CRS-207 treatment regimen

Exploratory:

- To assess the association of *Listeria monocytogenes (Lm)* and mesothelin-specific T-cell and other immunological responses with overall survival in subjects receiving test treatments
- To evaluate overall response rate in subjects with measureable disease per Response Evaluation Criteria in Solid Tumors (RECIST) receiving test treatments
- To measure tumor marker kinetics in subjects receiving test treatments

Methodology:

The study is an open-label, randomized, multicenter clinical study in adults with metastatic pancreatic adenocarcinoma who have received or refused at least one chemotherapy treatment.

At least 90 subjects will be enrolled and randomized in a 2:1 fashion into two treatment arms. Both treatment arms will receive up to six doses of vaccine 3 weeks apart (one cycle). Treatment Arm A will receive two doses of cyclophosphamide and GVAX pancreas vaccine and up to four doses of CRS-207. Treatment Arm B will receive up to six doses of cyclophosphamide and GVAX pancreas vaccine.

Treatment Arm	Number of Subjects	Treatment and Dose	Treatment Cycle
A	60	Cyclophosphamide (200 mg/m^2), GVAX pancreas vaccine (5×10^8 cells), CRS-207 (1×10^9 CFU)	Weeks 1 and 4: Cyclophosphamide (Day 1) GVAX pancreas vaccine (Day 2) Weeks 7, 10, 13, and 16: CRS-207 (Day 1)
B	30	Cyclophosphamide (200 mg/m^2), GVAX pancreas vaccine (5×10^8 cells)	Weeks 1, 4, 7, 10, 13, and 16: Cyclophosphamide (Day 1) GVAX pancreas vaccine (Day 2)

CFU = colony-forming unit.

STUDY SYNOPSIS (continued)

Name of Sponsor Company: Aduro BioTech, Inc. **Name of Finished Product:** Cytoxan; GVAX pancreas vaccine; CRS-207 **Name of Active Ingredients:** Cyclophosphamide; Panc 10.05 pcDNA1/GM-Neo, Panc 6.03 pcDNA1/GM-Neo; *Lm* Δ*actA*/Δ*inlB*/hMesothelin	**Individual Study Table Referring to Part of the Dossier** **Volume:** **Page:**	***(For National Authority Use Only)***

To monitor initial safety of the sequential vaccine regimen, no more than one subject will be enrolled per week for the first six subjects. If any limiting toxicities are observed during the study (see Section 3.6 of the Protocol), the data will be reviewed with the Data Monitoring Committee (DMC) and the dose may be lowered to 1×10^8 colony-forming units (CFU) for all subsequent dosing with CRS-207.

Subjects will return to the study site approximately 4 weeks after their final treatment for safety and immune response evaluations. They will continue to be followed by phone or optional clinic visit for subsequent cancer-related therapies, overall response rate, and *Lm*- and mesothelin-specific immune responses (at clinic visits only) until death or until study close, which occurs when all subjects have either died or completed 24 months on study (from time of randomization). At the investigator's discretion, subjects may receive additional treatment cycles of the assigned treatment regimen if they are clinically stable and meet dosing requirements.

During the trial, a planned interim analysis for early stopping for efficacy or for futility was performed per protocol after 41 deaths occurred. At this planned interim efficacy analysis, the study was determined by the DMC to meet the criteria for early stopping for efficacy (see Section 8.2.7) and subjects currently on treatment in Arm B will be offered CRS-207 treatment. Subjects on Arm A and in follow-up will continue with treatment and in follow-up per protocol. Additionally, subjects who receive at receive at least one dose of study treatment, discontinue from treatment and are in follow-up on protocol, may be eligible for re-treatment with cyclophosphamide, GVAX pancreas vaccine and CRS-207 (Arm A) regardless of their original treatment assignment or response to previous protocol therapy. At the time of study close, subjects will be offered enrollment into a long-term follow-up protocol. Subjects who are still receiving treatment at the time of study close, may complete the current treatment cycle (up to 6 doses) prior to transitioning to the long-term follow-up protocol.

Number of subjects (planned):
At least 90 subjects with metastatic pancreatic adenocarcinoma satisfying all eligibility criteria will be enrolled. With an expected enrollment rate of five patients per month, the accrual period would be 18 months, which, with the 24 months of follow-up of each subject, yields a maximum total study time of approximately 45 months (incorporating a treatment period between 1 day and 20 weeks in duration). An interim analysis will be conducted after 41 subjects have died. The study may be terminated after that interim analysis if results meet pre-specified stopping criteria or if the DMC recommends stopping on the basis of clinical judgment and guidelines in their charter and the sponsor accepts the recommendation. Details of the interim analysis and criteria are outlined in Section 8.2.7 and will be fully described in the DMC charter and statistical analysis plan (SAP).

STUDY SYNOPSIS (continued)

Name of Sponsor Company: Aduro BioTech, Inc.	**Individual Study Table Referring to Part of the Dossier**	***(For National Authority Use Only)***
Name of Finished Product: Cytoxan; GVAX pancreas vaccine; CRS-207	**Volume:**	
Name of Active Ingredients: Cyclophosphamide; Panc 10.05 pcDNA1/GM-Neo, Panc 6.03 pcDNA1/GM-Neo; *Lm* Δ*actA*/Δ*inlB*/hMesothelin	**Page:**	

Subject discontinuation:

A subject may be removed from the study for the following reasons:

(1) Occurrence of an adverse event that presents an unacceptable consequence or risk to the subject
(2) Development of an illness or complication (including progressive disease) that justifies withdrawal from the study, as determined by the investigator and medical monitor
(3) Noncompliance: failure to receive clinical study medication or treatment as mandated by the protocol, failure to comply with protocol requirements, or unauthorized subject-initiated changes in dosing regimen
(4) Refusal of clinical trial material administration by the subject
(5) Dose cohort, treatment arm, or study discontinued by the sponsor

Subjects who withdraw consent or are removed from the study before completing one treatment cycle may be replaced at the discretion of Aduro BioTech, Inc. (Aduro). Subjects who have disease progression may be allowed to continue in the study if the investigator believes they are deriving some benefit from the therapy.

Inclusion criteria:

(1) Have histologically proven malignant adenocarcinoma of the pancreas; measurable disease is not required (Subjects with mixed histology will be included if the predominant component is adenocarcinoma. Subjects must have metastatic disease.)
(2) Have received or refused at least one chemotherapy regimen
(3) Be at least 18 years of age
(4) Have an Eastern Cooperative Oncology Group performance status of 0 or 1
(5) Have an anticipated life expectancy of greater than 12 weeks
(6) For women and men of childbearing potential, a medically acceptable method of highly effective contraception (oral hormonal contraceptive, condom plus spermicide, or hormone implants) must be used throughout the study period and for 28 days after their final vaccine administration (A barrier method of contraception must be employed by all subjects [male and female], regardless of other methods.)
(7) Be willing and able to give written informed consent, and be able to comply with all study procedures
(8) Have adequate organ function, as defined by the laboratory values in Table 1

Table 1. Required Laboratory Values for Study Inclusion

Hematologic	Renal	Hepatic
WBC ≥3,500/μL ANC ≥1,500/μL Platelets ≥90 × 10^3/μL Hemoglobin ≥9 g/dL CD4 ≥0.2 × 10^9/L	Creatinine ≤2.0 × ULN	AST/ALT <2.0 × ULN Alkaline phosphatase <2.5 × ULN Bilirubin < ULN

ALT = alanine aminotransferase; ANC = absolute neutrophil count; AST = aspartate aminotransferase; ULN = upper limit of normal; WBC = white blood cell.

STUDY SYNOPSIS (continued)

Name of Sponsor Company: Aduro BioTech, Inc.	**Individual Study Table Referring to Part of the Dossier**	***(For National Authority Use Only)***
Name of Finished Product: Cytoxan; GVAX pancreas vaccine; CRS-207	**Volume:**	
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Exclusion criteria:

(1) Have a known history or evidence of brain metastases
(2) Have a known allergy to both penicillin and sulfa
(3) Have artificial (prosthetic) joint(s), orthopedic screw(s), metal plate(s) or other exogenous implant(s) or device(s) that cannot be easily removed (i.e., prosthetic heart values). Commonly used devices and prosthetics which are allowed include (other devices or implants not specified can be considered with approval of the medical monitor):
    - Dental and breast implants (providing no history of prior or current infection of the implants and no clinically significant adverse event(s) associated with the implants)
    - Radioactive prostatic seeds
    - Coronary artery stents (placed at least 3 months previously, with no signs or symptoms related to the stents or ischemic heart disease associated with the stents after placement)
    - Body wall meshes (for repair of body wall defects, i.e. hernias, or post-surgical repair)
    - Biliary stents, gastrointestinal stents, and ureteral stents
    - Venous access devices (VAD) such as Mediports (although these devices cannot be used for infusion of CRS-207 or for phlebotomy for 4 days inclusive after CRS-207 infusion).
(4) Have any evidence of hepatic cirrhosis or clinical or radiographic ascites
(5) Have had a pulmonary embolism or venous thromboembolism within 2 months of study enrollment
(6) Have clinically significant and/or malignant pleural effusion (Pleural effusions that are not clinically significant are allowed, defined as no more than 25% fluid level of the corresponding hemithorax and stable fluid level [non-progressive] over at least 6 weeks documented radiographically)
(7) Have known or suspected hypersensitivity to GM-CSF, hetastarch, pentastarch, corn, dimethyl sulfoxide, fetal bovine serum, trypsin (porcine origin), yeast, or any other component of GVAX pancreas vaccine or CRS-207 (e.g., glycerol)
(8) Have any immunodeficiency disease or immunocompromised state (e.g., use of immunosuppressive agents, chemotherapy or radiation therapy within 14 days of study treatment)
(9) Have received a diagnosis of HIV, hepatitis B, or hepatitis C (Subjects who are hepatitis C antibody positive may be enrolled if they are confirmed with negative viral load at screening.)
(10) Have active autoimmune disease or history of autoimmune disease requiring systemic steroids or other immunosuppressive treatment
(11) Have used any systemic steroids within 28 days of study treatment
(12) Use more than 3 g/d of acetaminophen
(13) Have received an investigational product within 28 days of study treatment or planned to receive within 28 days after vaccine administration
(14) Have had major surgery or significant traumatic injury occurring within 28 days before treatment administration or anticipated surgery or procedure requiring general anesthesia during the study participation (including 28 days after last dose of CRS-207) (Minor procedures [dental work, skin biopsy, etc.], celiac plexus block, and biliary stents are allowed.)
(15) Have an unhealed surgical wound
(16) Be a woman who is pregnant or breastfeeding
(17) Have clinically significant heart disease (such as uncontrolled angina, myocardial infarction within last 3 months, congestive heart failure of New York Heart Association III or IV)

STUDY SYNOPSIS (continued)

Name of Sponsor Company: Aduro BioTech, Inc.	**Individual Study Table Referring to Part of the Dossier**	***(For National Authority Use Only)***
Name of Finished Product: Cytoxan; GVAX pancreas vaccine; CRS-207	**Volume:**	
Name of Active Ingredients: Cyclophosphamide; Panc 10.05 pcDNA1/GM-Neo, Panc 6.03 pcDNA1/GM-Neo; *Lm* Δ*actA*/Δ*inlB*/hMesothelin	**Page:**	

Exclusion criteria, cont.:

(18) Have valvular heart disease that requires antibiotic prophylaxis for prevention of endocarditis
(19) Have oxygen saturation <92% on room air, as measured by pulse oximeter
(20) Have an intercurrent illness that is either life-threatening or of clinical significance such that it might limit compliance with study requirements (Such illnesses include, but are not limited to, ongoing or active infection, metabolic or neurologic disease, peripheral vascular disease, or psychiatric illness.)
(21) Have insufficient peripheral venous access to permit completion of the study dosing and compliance with study phlebotomy regimen
(22) Be unwilling or unable to follow the study schedule for any reason
(23) Have a history of alcohol dependence or use of illicit drugs (e.g., opioids, cocaine, amphetamines, hallucinogens, etc.) that could potentially interfere with adherence to study procedures or requirements
(24) Be unable to avoid close contact with another individual known to be at high risk of listeriosis (e.g., newborn infant, pregnant woman, HIV-positive individual) during the course of CRS-207 treatment until completion of antibiotic regimen
(25) Have received a prophylactic vaccine within 28 days of study treatment.

Dose eligibility:

Subjects must have adequate organ function as defined by the laboratory values in Table 2 before dosing on Day 1 of dosing weeks. Laboratory tests may be done up to 72 hours before dosing on Day 1.

Table 2. Dosing-Eligibility Requirements

Hematologic	Renal	Hepatic
WBC ≥3,500/μL ANC ≥1,500/μL Platelets ≥90 × 10^3/μL Hemoglobin ≥9 g/dL	Creatinine ≤2.0 × ULN	AST/ALT ≤5.0 × ULN Bilirubin ≤1.5 × ULN

ALT = alanine aminotransferase; ANC = absolute neutrophil count; AST = aspartate aminotransferase; ULN = upper limit of normal; WBC = white blood cell.

STUDY SYNOPSIS (continued)

Name of Sponsor Company: Aduro BioTech, Inc.	**Individual Study Table Referring to Part of the Dossier**	***(For National Authority Use Only)***
Name of Finished Product: Cytoxan; GVAX pancreas vaccine; CRS-207	**Volume:**	
Name of Active Ingredients: Cyclophosphamide; Panc 10.05 pcDNA1/GM-Neo, Panc 6.03 pcDNA1/GM-Neo; *Lm* Δ*actA*/Δ*inlB*/hMesothelin	**Page:**	

Prohibited medications:
The following therapies are not permitted during the study treatment period and may result in early termination of the subject from treatment:

- Anticancer chemotherapy or non-study immunotherapy (approved or investigational)
- Systemically active steroids for more than 2 days or use of any systemic steroids during the treatment period or within 28 days before or after dosing
- Another investigational product
- Filgrastim (Neupogen or G-CSF) or Saragrastim (Leukine or GM-CSF)
- Prophylactic vaccines (e.g., influenza, pneumococcal, Td/Tdap) within 1 week prior to or after study dosing. (Note: prophylactic vaccines are discouraged for the duration of the treatment period and should be avoided if possible.)

In addition, the following therapies should not be administered unless medically necessary, and approval must be obtained from the medical monitor for a subject to continue dosing if therapy is given concurrently with study participation:

- General anesthesia or deep sedation
- Aspirin >325 mg/d (chronic daily use of aspirin ≤325 mg/d and heparin flushes for central lines are allowed)
- More than 4 g/d of acetaminophen
- Systemic antibiotics

Test product, dose, and mode of administration:
CRS-207: 1×10^9 CFU reconstituted in 250 mL 0.9% sodium chloride and administered intravenously over 2 hours
Cyclophosphamide (Cytoxan): 200 mg/m^2 in 100 mL normal saline administered intravenously over 30 minutes
GVAX pancreas vaccine (Panc 6.03 and Panc 10.05 pancreatic tumor vaccine): intradermal injections of the allogeneic pancreatic tumor vaccine containing 5×10^8 cells (2.5×10^8 of each cell line)

Study duration:
The duration of one treatment cycle (i.e., six doses) will be 20 weeks. Subjects will be considered in the treatment period until 4 weeks after their final study dose, after which they will be in follow-up. Subjects will be followed until death, early discontinuation, or time of study close. Study close occurs when all subjects have either died or completed 24 months on study (from time of randomization). At the time of study close, subjects will be offered enrollment in a long-term follow-up protocol. Subjects who are still receiving treatment at the time of study close may complete the current treatment cycle (up to 6 doses) prior to transitioning to the long-term follow-up protocol.

Reference therapy, dose, and mode of administration:
There is no reference therapy or placebo administered in this study.

STUDY SYNOPSIS (continued)

Name of Sponsor Company: Aduro BioTech, Inc. **Name of Finished Product:** Cytoxan; GVAX pancreas vaccine; CRS-207 **Name of Active Ingredients:** Cyclophosphamide; Panc 10.05 pcDNA1/GM-Neo, Panc 6.03 pcDNA1/GM-Neo; *Lm* Δ*actA*/Δ*inlB*/hMesothelin	**Individual Study Table Referring to Part of the Dossier** **Volume:** **Page:**	***(For National Authority Use Only)***

Criteria for Evaluation:

Efficacy: Overall survival will be measured from the first cyclophosphamide treatment until death or end of follow-up. The cellular and humoral immune responses directed against *Lm* and mesothelin will be assessed by using enzyme-linked immunosorbent spot, intracellular cytokine staining, and enzyme-linked immunosorbent assay. Overall response rate will be assessed by using RECIST and immune-related response criteria (irRC). Tumor marker kinetics will be measured through serum CA19-9 and carcinoembryonic antigen (CEA) levels, as applicable. Other tumor markers may also be evaluated.

Safety: Safety will be assessed by collection of data on adverse events, vaccine-site reactions, vital signs, physical examination, clinical hematology, and serum chemistry.

Data analysis:

The data will be summarized in tables listing the mean, standard deviation, median, minimum, maximum, and number of subjects in a group for continuous data; in tables listing count and percentage for categorical data; and median and standard error for time-to-event data. Data will be listed for each subject. Statistical analyses will be performed and data appendices will be created by using SAS. The effects of noncompliance, dropouts, and covariates will be assessed to determine the impact on the general applicability of results from this study.

The efficacy analysis will be conducted on the full analysis set and per protocol analysis set. The full analysis set will consist of all randomized subjects who receive at least one dose of cyclophosphamide. The per protocol analysis set will consist of all subjects with metastatic pancreatic adenocarcinoma who receive at least three doses of the first cycle on the original treatment arm (at least one dose of CRS-207 in Treatment Arm A or three doses of cyclophosphamide/GVAX pancreas vaccine in Treatment Arm B). The primary efficacy parameter will be overall survival, which will be analyzed by log-rank test for the between arm comparison.

In the original design, for the full analysis set, if the true median survival for the sequential treatment is 8.1 months, and that for GVAX alone is 5 months, the sample size of N = 90 has approximately 85% power to yield a statistically significant difference (alpha = 0.15, 1-sided). Power was computed for a 2-stage group sequential design with a single interim analysis at half the total study "information" (i.e., 83 deaths total; interim analysis after 41 deaths) and with O'Brien-Fleming–like alpha spending function (gamma = −4). Details of the group sequential design and stopping criteria will be contained in the DMC charter or the statistical analysis plan (SAP).

During the trial, the timing of the final analysis was modified to be conducted after 70 events were observed in the primary analysis population (full analysis set). The justification for this change is that the overall study power would be preserved at an acceptable level (80% power) with a lower number of events (n = 70) compared to the number of events originally planned for (n=83, overall study power of approximately 85%). Further details on this modification to the originally planned analysis can be found in the SAP.

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LIST OF ABBREVIATIONS

actA	*Listeria monocytogenes* protein encoded by *actA* gene and responsible for mediating host cell actin nucleation and actin-based motility
AE	adverse event
ALT	alanine aminotransferase
ANC	absolute neutrophil count
APTT	activated partial thromboplastin time
AST	aspartate aminotransferase
BP	blood pressure
BUN	blood urea nitrogen
CBC	complete blood count
CEA	carcinoembryonic antigen
CFR	Code of Federal Regulations
CFU	colony-forming unit
CRF	case report form
CT	computed tomography
CTCAE	Common Terminology Criteria for Adverse Events
CTM	clinical trial material
D	study day
DMC	data monitoring committee
ECOG	Eastern Cooperative Oncology Group
EDC	electronic data capture
ELISA	enzyme-linked immunosorbent assay
ELISPOT	enzyme-linked immunosorbent spot
FAS	full analysis set
GM-CSF	granulocyte-macrophage colony-stimulating factor
HLA	human leukocyte antigen
hMesothelin	human mesothelin
IB	Investigator's Brochure
ICF	informed consent form
ICH	International Conference on Harmonisation
inlB	internalin B
IRB	institutional review board
irRC	immune-related response criteria
LDH	lactate dehydrogenase
Lm	*Listeria monocytogenes*
MHC	major histocompatibility complex
MRI	magnetic resonance imaging
PBMC	peripheral blood mononuclear cells
PHI	protected health information
RECIST	Response Evaluation Criteria in Solid Tumors
SAE	serious adverse event
SAP	Statistical Analysis Plan
SOP	standard operating procedure
SPM	study procedures manual
UA	urinalysis
ULN	upper limit of normal
WBC	white blood cell

1.0 INTRODUCTION

1.1 BACKGROUND

Exocrine pancreatic cancers account for approximately 2% of new cancers diagnosed each year in the United States, and this disease is the fourth leading cause of cancer death for men and women.[1] Patients with local disease who undergo surgical resection (approximately 10% to 15% of all pancreatic carcinoma patients) have an estimated median survival of approximately 18 months, and approximately 20% of patients survive for 5 years.[2] Over 80% of pancreatic cancers are not diagnosed until regional or distant disease is present and patients are no longer amenable to surgical resection. Patients with metastatic disease have an estimated survival of only 3 to 6 months, and the 5-year survival rate after diagnosis in this cohort is less than 5%.[3]

1.1.1 Current Therapies for Pancreatic Cancer

Combination chemotherapy with gemcitabine provides a survival advantage for patients with advanced disease that is more favorable than treatment with 5-fluorouracil for improvement in pain, performance status, and weight gain.[4, 5] To date, the oral tyrosine kinase inhibitor erlotinib (Tarceva) is the only drug demonstrated to prolong survival when administered in combination with gemcitabine, although this combination regimen provides only a slight increase in median survival when compared with that for gemcitabine alone (6.24 months compared with 5.91 months, $p = 0.038$).[6] Further evaluations are continuing with gemcitabine and combinations for patients with resectable and locally advanced disease. However, the limited success of all modalities for treatment of pancreatic cancer indicates the critical need for novel therapies.[7-9] Recent progress in the understanding of immune surveillance and the requirements for successful cancer immunotherapy lends encouragement for continued evaluation of newer immunotherapy treatment methods.[10-12]

1.1.2 *Listeria monocytogenes*-Based Vaccine Therapy

Listeria monocytogenes (*Lm*) is an attractive platform for presentation of tumor-associated antigens and activation of immune response directed against cancer cells. *Lm* provides both a potent stimulation of innate immunity and also stimulates an adaptive immune response through recruitment and activation of

CD4+ and CD8+ T-cell immunity specific for encoded heterologous antigens.[13-16] Aduro BioTech, Inc. (Aduro) developed a live-attenuated *Lm* platform strain (*Lm* Δ*actA*/Δ*inlB*), known as ANZ-100 (previously CRS-100), which has deletions of two genes, *actA* and *inlB*, that encode the virulence-determinant proteins ActA and Internalin B, respectively. These two proteins facilitate cell-to-cell spread and invasion of nonphagocytic cells, and deletion of *actA* and *inlB* in ANZ-100 results in 1,000-fold attenuation of these processes in mice as compared with wild-type *Lm*.[17] Uptake of ANZ-100 by macrophages and other phagocytic cells in the liver and spleen is still retained and results in a local inflammatory response as well as activation and recruitment of natural killer cells and T cells to the liver. ANZ-100 underwent clinical evaluation in a Phase 1 dose-escalation study after intravenous administration in adults with carcinoma and liver metastases and was found to be safe and well tolerated at doses up to 3×10^8 colony-forming units (CFU).

ANZ-100 has additionally been engineered to express mesothelin, and the resulting strain has been termed CRS-207. Mesothelin is a tumor-associated antigen with limited expression on the surface of normal tissues, but highly expressed by several human tumors, including pancreatic adenocarcinomas.[18-20] This feature makes mesothelin an attractive target for active tumor-specific immunotherapy. This assessment is confirmed by reports that positive clinical outcomes correlate with induction of mesothelin-specific cellular immunity in patients with pancreatic carcinoma after vaccination with an irradiated allogeneic whole-cell vaccine encoding granulocyte-macrophage colony-stimulating factor (GM-CSF), GVAX pancreas vaccine. A dose-dependent systemic antitumor response was reported in this Phase 1 clinical study, and progression-free and overall survival appeared to correlate with mesothelin-specific cell-mediated immune response.[21, 22]

CRS-207 was constructed by using the ANZ-100 strain by inserting a human mesothelin expression cassette integrated at the *inlB* locus. After uptake of CRS-207 by dendritic cells and macrophages, mesothelin is expressed and released into the cytosolic compartment and subsequently processed through the endogenous MHC Class I presentation pathway, resulting in activation of mesothelin-specific cell-mediated immunity. Other mechanisms to activate mesothelin-specific, cell-mediated immunity may include uptake and cross-presentation of antigens by dendritic cells and other cells after infection by CRS-207 and apoptosis.

Nonclinical studies have shown that CRS-207 elicits mesothelin-specific cellular immunity in mice and nonhuman primates and demonstrates therapeutic efficacy in tumor-bearing mice (refer to the Investigator's Brochure [IB] for details). Findings in a Good Laboratory Practice repeated-dose study in cynomolgus monkeys showed that treatment with up to 3×10^{10} CFU of CRS-207 resulted in no changes related to body weight, food consumption, or body temperature and in no findings related to ocular or functional cardiovascular evaluations. CRS-207 was detected in the blood at 24 hours after administration, but was undetectable at 72 hours. There were transient and dose-dependent decreases in red blood cell, platelet, and white blood cell counts. Hepatic and renal function changes were transient and generally less than twofold from that at baseline status. Overall, these safety and toxicology studies demonstrated an acceptable safety profile for CRS-207.

A Phase 1 study (VAC07001) has been completed with CRS-207 administered intravenously to determine the maximum tolerated dose and to explore the safety profile in subjects with mesothelioma, non–small-cell lung cancer, ovarian cancer, or pancreatic adenocarcinoma who had failed standard therapy. CRS-207 was found to be well tolerated at doses of 1×10^8 and 1×10^9 CFU. Adverse events (AEs) such as fevers, chills, and nausea reported as the most common, immediate, transient, mild, and temporally related to CRS-207 administration were self-correcting and were resolved by the time of the subjects' discharge. Lymphopenia was observed in all doses (1×10^8, 3×10^8, 1×10^9, and 1×10^{10} CFU), and transaminase elevations were observed at doses of 3×10^8, 1×10^9, and 1×10^{10} CFU. Both were dose dependent, although transient and not considered clinically significant. Two CRS-207-related serious adverse events (SAEs) were reported. One SAE of moderate constipation occurred in one subject after the second dose of CRS-207 at 1×10^8 CFU. The second SAE, a significant decrease in blood pressure (BP) after infusion, occurred in another subject after one dose of CRS-207 at 1×10^{10} CFU. This subject required aggressive fluid management and recovered to baseline status within 24 hours. No shedding of CRS-207 in the urine or stools was observed at any dose.

1.1.3 Cell-Based Immunotherapy

Immunotherapy is a novel therapeutic approach that has the ability to recruit and activate tumor-specific T cells and induce a cytotoxic response. The lethally irradiated allogeneic GVAX pancreas vaccine was developed from GM-CSF–

secreting pancreatic cancer lines Panc 10.05 and Panc 6.03 and has been shown to prime a systemic immune response in patients with resected pancreatic adenocarcinoma.[23] This approach is based on the concept that certain cytokines are required at the site of the tumor to effectively prime cancer-specific immunity. GM-CSF is the critical growth and differentiation factor for dendritic cells, the most potent professional antigen-presenting cell responsible for priming immune responses against infectious agents and tumor antigens.

Panc 10.05 and Panc 6.03 were originally developed from neoplastic tissue harvested from surgical specimens of patients undergoing pancreaticoduodenectomy at The Johns Hopkins Hospital and were genetically modified to secrete GM-CSF.[24, 25] These cells have been irradiated with 15,000 rads, and frozen in liquid nitrogen; upon thawing, they secrete GM-CSF at 80 to 90 ng/10^6 cells per 24 hours for up to 5 days in culture.[24, 26] Additionally, the cells express mesothelin, have undergone extensive regulatory testing, and maintain GM-CSF secretion, MHC class I levels, cytokeratin-positive staining, and the original K-ras mutation.[24] Safety and feasibility to produce and administer this vaccine have been demonstrated.[21, 23]

There are specific data to suggest that immune-modulating doses of the chemotherapy agent cyclophosphamide (Cytoxan) enhance vaccine-induced antitumor immune responses by inhibiting CD4+/CD25+ regulatory T-cell activity.[22, 27-29] In a previous Phase 2 clinical study (J0206) in subjects with advanced pancreatic cancer, a higher rate of induction of mesothelin-specific T-cell responses as well as longer overall survival were seen in subjects receiving GVAX pancreas vaccine given 24 hours after cyclophosphamide than in subjects receiving GVAX pancreas vaccine alone (median survival from first vaccinations: 129.5 days vs. 69 days, p = 0.395).[23] Treatment-related AEs were self-limiting (lasted up to 1 week) and included fever, rigors, rash, and pain at the injection sites. One subject experienced Grade 3/4 leukocytosis, dehydration, and fatigue. Overall, GVAX pancreas vaccine (5×10^8 cells) combined with cyclophosphamide (250 mg/m^2) was safe, had minimal toxicity, and was feasible to administer.

1.2 RATIONALE

Nonclinical studies in mice have shown a synergistic effect between GVAX and *Lm*-based vaccines in inducing immune response. Mice primed with GVAX before a *Lm* vaccine boost 14 days later showed a significant increase in interferon gamma–secreting self-reactive CD8+ T cells than mice that received the *Lm* vaccine ($p = 0.0056$) or GVAX vaccine alone ($p = 0.0007$). Mice primed with GVAX pancreas vaccine before receiving the mouse version of CRS-207 (*Lm* Δ*actA*Δ*inlB* encoding the mouse homolog of mesothelin, *Lm* mMeso) also had significantly reduced tumor growth as compared with mice that received GVAX pancreas vaccine or *Lm* mMeso alone.

Preliminary clinical data suggest that sequential therapy with cyclophosphamide, GVAX pancreas vaccine, and CRS-207 has a positive effect on overall survival in patients with metastatic pancreatic cancer. In a Phase 2 study (J0501) investigating cyclophosphamide and GVAX pancreas vaccine in this population who had failed standard therapy, the median overall survival for the 13 subjects who received six doses of cyclophosphamide and GVAX pancreas vaccine was 9 months from the time of consent. Two of these subjects subsequently enrolled in the CRS-207 Phase 1 study (VAC07001) that included subjects with mesothelioma, non–small-cell lung cancer, ovarian cancer, or pancreatic adenocarcinoma who had failed standard therapy. Of the two subjects who received both GVAX pancreas vaccine (with cyclophosphamide) and CRS-207, one subject survived for 20 months after consent in the GVAX study, and one subject was still alive with ongoing survival since the GVAX study of 60 months (as of 01 March 2012). Median survival for the 11 subjects who did not receive CRS-207 after cyclophosphamide and GVAX pancreas vaccine was 8 months. In the CRS-207 Phase 1 study, 7 patients with pancreatic cancer were enrolled. Of these 7 subjects, 3 had received prior GVAX pancreas vaccine (2 discussed above in the J0501 study and 1 who received GVAX pancreas vaccine without cyclophosphamide in another study). The median survival from the first dose of CRS-207 for these 3 subjects was 17 months, whereas the median survival for subjects with pancreatic cancer who received CRS-207 but not prior GVAX pancreas vaccine therapy was 5 months. These results suggest that priming of the immune system with GVAX pancreas vaccine before CRS-207 boost enhances overall survival, possibly through induction of mesothelin-specific T-cell response.

The proposed routes of administration and doses of cyclophosphamide (200 mg/m^2) and GVAX pancreas vaccine (5×10^8 cells) for this study have been used previously and were well tolerated.[23, 30] The proposed dose level of CRS-207 (1×10^9 CFU) was well tolerated in the prior Phase 1 study (VAC07001). Because cyclophosphamide, GVAX pancreas vaccine, and CRS-207 have each been previously shown to be safe at the proposed dose levels and the treatments will be administered sequentially (at least 3 weeks apart), no new significant AEs are expected with this treatment regimen. This study will be the first to investigate the efficacy, immunogenicity, and safety of cyclophosphamide and GVAX pancreas vaccine therapy given in sequence with CRS-207 in subjects with metastatic pancreatic adenocarcinoma.

2.0 OBJECTIVES

2.1 PRIMARY OBJECTIVE

The primary objective of this study is to compare overall survival in subjects receiving sequential administration of cyclophosphamide, GVAX pancreas vaccine and CRS-207 with overall survival in subjects receiving cyclophosphamide and GVAX vaccine alone.

2.2 SECONDARY OBJECTIVES

The secondary objectives of this study are as follows:

- To assess safety of the cyclophosphamide, GVAX pancreas vaccine, and CRS-207 treatment regimen

2.3 EXPLORATORY OBJECTIVES

The exploratory objectives are as follows:

- To assess the association of *Lm*- and mesothelin-specific T-cell and other immunological responses with overall survival in subjects receiving test treatments

- To evaluate overall response rate in subjects with measurable disease per RECIST receiving test treatments

- To measure tumor marker kinetics in subjects receiving test treatments

3.0 STUDY DESIGN

3.1 BASIC DESIGN CHARACTERISTICS

This is a Phase 2, randomized, multicenter, open-label study of cyclophosphamide and GVAX pancreas vaccine followed by CRS-207 in adults with metastatic pancreatic adenocarcinoma who have received or refused at least one prior chemotherapy treatment.

Eligible subjects will be randomized in a 2:1 ratio to receive either two doses of cyclophosphamide and GVAX pancreas vaccine and up to 4 doses of CRS-207 at 1×10^9 CFU (Treatment Arm A) or up to six doses of cyclophosphamide and GVAX pancreas vaccine (Treatment Arm B).

The study will consist of a screening period (within 28 days of the first administration of study drug), followed by administration of test treatments per Table 1. Both treatment arms will receive cycles of up to six doses of vaccine 3 weeks apart. Treatment Arm A will receive two doses of cyclophosphamide and GVAX pancreas vaccine and up to 4 doses of CRS-207. Treatment Arm B will receive up to six doses of cyclophosphamide and GVAX pancreas vaccine. Subjects will be contacted by phone on Day 4 (±1 day) of dosing weeks to evaluate injection-site reactions (after GVAX vaccinations) and AEs.

Table 1. Study Treatment Arms and Doses

Treatment Arm	Number of Subjects	Treatment and Dose	Treatment Cycle
A	60	Cyclophosphamide (200 mg/m^2), GVAX pancreas vaccine (5×10^8 cells), CRS-207 (1×10^9 CFU)	Weeks 1 and 4: • Cyclophosphamide (Day 1) • GVAX pancreas vaccine (Day 2) Weeks 7, 10, 13, and 16: • CRS-207 (Day 1)
B	30	Cyclophosphamide (200 mg/m^2), GVAX pancreas vaccine (5×10^8 cells)	Weeks 1, 4, 7, 10, 13, and 16: • Cyclophosphamide (Day 1) • GVAX pancreas vaccine (Day 2)

CFU = colony-forming unit.

To monitor initial safety of the sequential vaccine regimen, no more than one subject will be enrolled per week for the first six subjects. If any limiting toxicities are observed during the study (see Section 3.6), the data will be

reviewed with the Data Monitoring Committee (DMC) and the dose may be lowered to 1×10^8 CFU for all subsequent dosing with CRS-207.

All subjects will return to the study site during Week 20 for evaluation. To ensure eradication of CRS-207 before receiving additional therapies (or study treatment cycles), subjects in Treatment Arm A will receive a 10-day course of antibiotics 7 days after the last CRS-207 dose in each treatment cycle (or after their final dose if treatment is discontinued early). At the investigator's discretion, subjects may receive additional cycles of the assigned treatment regimen if they are clinically stable and meet dosing eligibility. After completion of treatment, subjects will continue to be followed by phone and optional clinic visits for subsequent cancer-related therapies, overall response rate, and blood draws for *Lm*- and mesothelin-specific immune responses (clinic visits only) until death or study close, which occurs after all subjects have died or been on study for at least 24 months (from time of randomization). During the trial, a planned interim analysis for early stopping for efficacy or for futility was performed per protocol after 41 deaths occurred. At this planned interim efficacy analysis, the study was determined by the DMC to meet the criteria for early stopping for efficacy (see Section 8.2.7) and subjects currently on treatment in Arm B will be offered CRS-207 treatment. Subjects on Arm A and in follow-up will continue with treatment and in follow-up per protocol. Additionally, subjects who receive at least one dose of study treatment, discontinue from treatment and are in follow-up on protocol, may be eligible for re-treatment with cyclophosphamide, GVAX pancreas vaccine and CRS-207 (Arm A) regardless of their original treatment assignment or response to previous protocol therapy. At the time of study close, subjects will be offered enrollment in a long-term follow-up study and continue to be evaluated for survival and clinical and immunological responses. Subjects who are still receiving treatment at the time of study close, may complete the current treatment cycle (up to 6 doses) prior to transitioning to the long-term follow-up protocol.

Overall response rate will be assessed by using standard RECIST (see Appendix A) and immune-related response criteria (irRC), where new lesions in and by themselves do not qualify as progressive disease[31] (see Appendix B). Tumor marker kinetics will be measured through serum CA19-9 or carcinoembryonic antigen (CEA) levels or other markers, as applicable. The humoral and cellular immune responses directed against *Lm* and mesothelin will be evaluated by using enzyme-linked immunosorbent spot (ELISPOT), intracellular cytokine staining,

and enzyme-linked immunosorbent assay (ELISA) for *Lm*- and mesothelin-specific antibodies. Safety will be assessed by collection of data on AEs, vaccine-site reactions, vital signs, physical examination, clinical hematology, and serum chemistry.

3.2 STUDY POPULATION

At least 90 subjects will be enrolled in a 2:1 randomization (60 subjects in Treatment Arm A; 30 subjects in Treatment Arm B). Study eligibility will be determined by the investigator on the basis of the inclusion and exclusion criteria.

3.2.1 Inclusion Criteria

To be considered eligible to participate in this study, subjects must meet the inclusion criteria listed below:

(1) Have histologically proven malignant adenocarcinoma of the pancreas; measurable disease is not required (Subjects with mixed histology will be included if the predominant component is adenocarcinoma. Subjects must have metastatic disease.)

(2) Have received or refused at least one chemotherapy regimen

(3) Be at least 18 years of age

(4) Have an Eastern Cooperative Oncology Group (ECOG) performance status of 0 or 1

(5) Have an anticipated life expectancy of greater than 12 weeks

(6) For women and men of childbearing potential, a medically acceptable method of highly effective contraception (oral hormonal contraceptive, condom plus spermicide, or hormone implants) must be used throughout the study period and for 28 days after their final vaccine administration (A barrier method of contraception must be employed by all subjects [male and female], regardless of other methods.)

(7) Be willing and able to give written informed consent, and be able to comply with all study procedures

(8) Have adequate organ function as defined by the laboratory values in Table 2

Table 2. Required Laboratory Values for Study Inclusion

Hematologic	Renal	Hepatic
WBC ≥3,500/μL ANC ≥1,500/μL Platelets ≥90 × 10^3/μL Hemoglobin ≥9 g/dL CD4 ≥0.2 × 10^9/L	Creatinine ≤2.0 × ULN	AST/ALT <2.0 × ULN Alkaline phosphatase ≤2.5 × ULN Bilirubin ≤ ULN

ALT = alanine aminotransferase; ANC = absolute neutrophil count; AST = aspartate aminotransferase; ULN = upper limit of normal; WBC = white blood cell.

3.2.2 Exclusion Criteria

To be eligible for entry into the study, subjects must not meet any of the exclusion criteria listed below:

(1) Have a known history or evidence of brain metastases

(2) Have a known allergy to both penicillin and sulfa

(3) Have artificial (prosthetic) joint(s), orthopedic screw(s), metal plate(s) or other exogenous implant(s) or device(s) that cannot be easily removed (i.e., prosthetic heart values). Commonly used devices and prosthetics which are allowed include (other devices or implants not specified can be considered with approval of the medical monitor):

- Dental and breast implants (providing no history of prior or current infection of the implants and no clinically significant adverse event(s) associated with the implants)
- Radioactive prostatic seeds
- Coronary artery stents (placed at least 3 months previously, with no signs or symptoms related to the stents or ischemic heart disease associated with the stents after placement)
- Body wall meshes (for repair of body wall defects, i.e. hernias, or post-surgical repair)

- Biliary stents, gastrointestinal stents, and ureteral stents
- Venous access devices (VAD) such as Mediports (although these devices cannot be used for infusion of CRS-207 or for phlebotomy for 4 days inclusive after CRS-207 infusion).

(4) Have any evidence of hepatic cirrhosis or clinical or radiographic ascites

(5) Have had a pulmonary embolism or venous thromboembolism within 2 months of study enrollment

(6) Have clinically significant and/or malignant pleural effusion (Pleural effusions that are not clinically significant are allowed, defined as no more than 25% fluid level of the corresponding hemithorax and stable fluid level [non-progressive] over at least 6 weeks documented radiographically)

(7) Have known or suspected hypersensitivity to GM-CSF, hetastarch, pentastarch, corn, dimethyl sulfoxide, fetal bovine serum, trypsin (porcine origin), yeast, or any other component of GVAX pancreas vaccine or CRS-207 (e.g., glycerol)

(8) Have any immunodeficiency disease or immunocompromised state (e.g., use of immunosuppressive agents; chemotherapy or radiation therapy within 14 days of study treatment)

(9) Have received a diagnosis of HIV, hepatitis B, or hepatitis C (Subjects who are hepatitis C antibody positive may be enrolled if they are confirmed with negative viral load at screening.)

(10) Have active autoimmune disease or history of autoimmune disease requiring systemic steroids or other immunosuppressive treatment

(11) Have used any systemic steroids within 28 days of study treatment

(12) Use more than 3 g/d of acetaminophen

(13) Have received an investigational product within 28 days of study treatment or planned to receive within 28 days after vaccine administration

(14) Have had major surgery or significant traumatic injury occurring within 28 days before treatment administration or anticipated surgery or procedure requiring general anesthesia during the study participation (including 28 days after last dose of CRS-207) (Minor procedures [dental work, skin biopsy, etc.], celiac plexus block, and biliary stents are allowed.)

(15) Have an unhealed surgical wound

(16) Be a woman who is pregnant or breastfeeding

(17) Have clinically significant heart disease (such as uncontrolled angina, myocardial infarction within the last 3 months, congestive heart failure of New York Heart Association III or IV)

(18) Have valvular heart disease that requires antibiotic prophylaxis for prevention of endocarditis

(19) Have oxygen saturation <92% on room air, as measured by pulse oximeter

(20) Have an intercurrent illness that is either life-threatening or of clinical significance such that it might limit compliance with study requirements (Such illnesses include, but are not limited to, ongoing or active infection, metabolic or neurologic disease, peripheral vascular disease, or psychiatric illness.)

(21) Have insufficient peripheral venous access to permit completion of the study dosing and compliance with study phlebotomy regimen

(22) Be unwilling or unable to follow the study schedule for any reason

(23) Have a history of alcohol dependence or use of illicit drugs (e.g., opioids, cocaine, amphetamines, hallucinogens, etc.) that could potentially interfere with adherence to study procedures or requirements

(24) Is unable to avoid close contact with another individual known to be at high risk of listeriosis (e.g., newborn infant, pregnant woman, HIV-positive individual) during the course of CRS-207 treatment until completion of antibiotic regimen.

(25) Have received a prophylactic vaccine (e.g., influenza, pneumococcal, dTP/dTAP) within 28 days of study treatment.

3.2.3 Dosing Eligibility

Subjects must have adequate organ function as defined by the laboratory values in Table 3 before dosing on Day 1 of dosing weeks. Laboratory tests may be done up to 72 hours before dosing on Day 1. Subjects who do not meet the dosing-eligibility requirements will be monitored. Doses may be delayed up to 2 weeks, after which time they will be considered missed (with the exception of Dose 2 in Treatment Arm A; see Section 4.2).

Table 3. Dosing-Eligibility Requirements

Hematologic	Renal	Hepatic
WBC ≥3,500/μL ANC ≥1,500/μL Platelets ≥90 × 10^3/μL Hemoglobin ≥9 g/dL	Creatinine ≤2.0 × ULN	AST/ALT ≤5.0 × ULN Bilirubin ≤1.5 × ULN

ALT = alanine aminotransferase; ANC = absolute neutrophil count; AST = aspartate aminotransferase; ULN = upper limit of normal; WBC = white blood cell.

3.3 ENDPOINTS

3.3.1 Primary Endpoint

The primary endpoint is overall survival, measured from first cyclophosphamide treatment until death or end of follow-up.

3.3.2 Secondary Endpoints

The secondary endpoints are as follows:

- Safety assessed by the following measures:
  - AEs
  - Injection-site reactions (after GVAX pancreas vaccine injections only)
  - Vital signs: BP, pulse, respiratory rate, temperature
  - Physical examination

- Clinical hematology: complete blood count with differential absolute neutrophil count and platelet count

- Clinical serum chemistry: sodium, potassium, chloride, bicarbonate, glucose, blood urea nitrogen, creatinine, lactate dehydrogenase, alanine aminotransferase (ALT), aspartate aminotransferase (AST), alkaline phosphatase, amylase, bilirubin (total, direct, indirect), total protein, albumin, calcium, magnesium, and phosphate

3.3.3 Exploratory Endpoints

Exploratory endpoints are as follows:

- Humoral and cellular immune responses directed against *Lm* and mesothelin assessed by using the following measures:
  - ELISPOT or intracellular cytokine staining assays of peripheral blood mononuclear cells (PBMC)
  - Induction of proinflammatory cytokines and chemokines in the serum
  - ELISA detection of mesothelin- and *Lm*-specific antibodies in the serum
- Overall response rate assessed by RECIST and irRC
- Tumor marker kinetics measured by change in serum CA19-9 or CEA concentrations from baseline

3.4 RANDOMIZATION AND BLINDING

This is an open-label study. Subjects meeting all inclusion and exclusion criteria will be randomized 2:1 to one of two treatment arms according to a randomization list generated for each site by an independent statistician.

3.5 REPLACEMENT OF DROPOUTS

Subjects who withdraw consent or are removed from the study before completing one cycle of treatment will be considered dropouts and may be replaced at the discretion of Aduro. Replacement subjects will be randomized in a 2:1 ratio of Treatment Arm A to Treatment Arm B. Subjects who have disease progression

may be allowed to continue in the study if the investigator believes they are deriving some benefit from the therapy.

3.6 LIMITING TOXICITIES

Limiting toxicities are defined as events that are determined by the investigator as related to CRS-207 and that meet one of the following criteria:

- A fever of >40°C that lasts for greater than 24 hours and does not respond to antipyretics
- Clinically significant hypotension unresponsive to intravenous fluids (systolic BP <90 mm Hg or mean arterial pressure <55 mm Hg as measured on two separate occasions at least 10 minutes apart)
- Grade 3 decreases in leukocytes, absolute neutrophil count, or platelets that persist for more than 4 days
- Hemoglobin $\leq$7.0 g/dL
- ALT, AST, or alkaline phosphatase elevations >5 times the upper limit of normal (Grade 3) that persist for more than 7 days
- Initiation of antibiotic therapy, coincident with simultaneous isolation of CRS-207 from a normally sterile body site, other than blood (e.g., cerebrospinal fluid, joint fluid)
- Unexpected Grade 3 laboratory abnormalities lasting >48 hours
- Any other Grade 3 or greater event (except alopecia, lymphopenia, and hypophosphatemia) according to National Cancer Institute's Common Terminology Criteria for Adverse Events (CTCAE) Version 4.03

To provide the appropriate safeguards, all unexpected Grade 3 events will be independently reviewed by the DMC. If the event is determined to be related to CRS-207 dosing and clinically meaningful, it will be considered a limiting toxicity. Unexpected Grade 3 laboratory abnormalities should be repeated within 24-72 hours if clinically indicated and monitored as necessary to determine if event meets DLT criteria.

The proportion of limiting toxicities will be continuously monitored. If the toxicity levels in the CRS-207 treatment arm are unacceptable (>33% of subjects), then CRS-207 dosing will suspended until further review and consideration by the sponsor, investigators, and DMC. If unacceptable toxicity occurs at the starting dose of 1×10^9 CFU, the dose may be lowered to 1×10^8 CFU for all subsequent dosing with CRS-207. Subjects currently on study in Treatment Arm A may continue to receive dosing at the lower dose. All subsequent subjects enrolled in Treatment Arm A will receive CRS-207 at the lower dose. Limiting toxicities will continue to be monitored by the DMC at the lower dose.

4.0 DRUGS AND DOSAGES

4.1 IDENTIFICATION AND DESCRIPTION OF CLINICAL TRIAL MATERIAL

4.1.1 Clinical Trial Material

CRS-207 is a formulated live-attenuated strain hMeso38 of *Lm*, derived by deletion of *actA* and *inlB* coding sequences from a Streptomycin-resistant, wild-type strain and insertion of the human mesothelin coding sequence. The CRS-207 drug product consists of attenuated *Lm* (1×10^9 CFU/mL) suspended in 1.5 mL of Dulbecco's phosphate buffered saline and 9% vol/vol glycerol, filled into a single-use 2-mL glass vial with a gray butyl stopper and aluminum crimp seal with a flip-off cap, and stored frozen at –60ºC or colder until intravenous administration. During the storage, preparation, and administration of individual study doses and for the disposal of materials used in the preparation and administration of this product, the study will adhere to applicable institutional infection-control procedures for handling of *Lm*.

Cyclophosphamide (active ingredient cyclophosphamide monohydrate) is a synthetic antineoplastic drug chemically related to the nitrogen mustards. It is commercially available in a sterile powder formulation for use in intravenous administration. Cyclophosphamide will be reconstituted and administered per the package insert.

GVAX pancreas vaccine is an allogeneic pancreatic tumor vaccine consisting of two pancreatic cell lines (Panc 6.03 and Panc 10.05), each of which have been cultured and genetically modified with a plasmid vector encoding the

complementary DNA for human GM-CSF. The vaccine cells are irradiated with 150 Gy by using a cesium-source irradiator and are stored at 1.25×10^8 cells per vial (two vials per cell line) in an injectable formulation of 6% hetastarch (or pentastarch) in 0.9% sodium chloride with 2% human serum albumin and 5% dimethyl sulfoxide filled into a sterile, single-use 1.8-mL polypropylene cryovial internally threaded with a silicone gasket and stored frozen in liquid nitrogen until the day of use. GVAX pancreas vaccine is administered by intradermal injection per the IB and study procedures manual (SPM).

4.1.2 Labeling

Because the study is not blinded, the labeling will be that used on commercial vials of cyclophosphamide. The vials for GVAX pancreas vaccine and CRS-207 will be labeled with the following: product name; volume; storage conditions; product lot number; concentration and passage number (for GVAX pancreas vaccine); sponsor name and address (for CRS-207); fill date; and a caution statement ("Caution: New drug limited by Federal law to investigational use"). CRS-207 drug product is packaged in kit boxes that are also labeled with product name, number of vials, concentration, storage condition, a caution statement, sponsor name and address, and kit lot number.

4.2 DOSING INSTRUCTIONS AND SCHEDULE

Cyclophosphamide will be administered to subjects by intravenous infusion at 200 mg/m^2 in 100 mL normal saline over 30 minutes on Day 1 of Weeks 1 and 4 for Treatment Arm A or Day 1 of Weeks, 1, 4, 7, 10, 13 and 16 for Treatment Arm B.

GVAX pancreas vaccine will be administered to subjects by intradermal injections on Day 2 of Weeks 1 and 4 for Treatment Arm A or Day 2 of Weeks 1, 4, 7, 10, 13 and 16 for Treatment Arm B. Equal numbers (2.5×10^8 each) of the Panc 6.03 and Panc 10.05 cells will be combined and divided into 6 injections. At the time of vaccination, two vials of each cell line are removed from the appropriate storage conditions and quickly thawed in a 37°C water bath. The thawed vials are transferred from the water bath to ice in a biosafety cabinet. Contents of all 4 vials are combined into a single sterile syringe and distributed in approximately equal volumes from the syringe with a 16-gauge needle into 6 1-cc Luer-Lok syringes. The 16-gauge Luer-Lok needles are replaced with 22-gauge

needles for administration. The syringes are then released to the appropriate medical personnel for intradermal injection and are kept on ice until the vaccine is administered. All injections much be given within 3 hours of thaw. The 3 hours start when the vials are placed in the water bath for thaw. Each vaccination will consist of six total intradermal injections of approximately 0.7 mL solution, two each in the upper right and left thighs, and two in the upper nondominant arm. Vaccine sites will be premedicated with topical lidocaine-based anesthetic cream and covered with an occlusive dressing for at least 1 hour before vaccination (if subject is not allergic to lidocaine) to diminish discomfort associated with the intradermal injections. Subjects will be observed in the clinic for at least 60 minutes after the first vaccination and for at least 30 minutes after the last injection to ensure no immediate adverse reactions occur. Detailed instructions on the preparation of GVAX pancreas vaccine for administration are provided in the pharmacy manual.

CRS-207 will be administered to subjects by intravenous infusion at 1×10^9 CFU in 250 mL 0.9% sodium chloride over 2 hours on Day 1 of Weeks 7, 10, 13, and 16 for Treatment Arm A. CRS-207 is prepared by thawing one 1.5 mL vial of drug product at room temperature. One (1) mL of product is drawn with a syringe and inserted into one bag of 250 mL 0.9% sodium chloride for intravenous injection. Detailed instructions on the preparation of CRS-207 for administration are provided in the pharmacy manual.

CRS-207 must not be administered via central venous catheters or infusion ports. Before each CRS-207 infusion, subjects will be premedicated with 650 mg acetaminophen. Subjects will also receive a total of 1,000 mL of normal saline either immediately before or after CRS-207 infusion (or a portion of the volume may be given before CRS-207 infusion and the remaining volume given after CRS-207 infusion). Subjects will be observed in the clinic for at least 4 hours after each infusion. Subjects who are not stable to be released at 4 hours after infusion should continue to be monitored until stable. Hospital admissions for overnight monitoring will not be considered an SAE unless the event meets criteria for seriousness other than hospitalization.

Accumulating subject experience during and after CRS-207 infusions at 1×10^9 CFU have further demonstrated the following clinical observations which are to be expected:

- **Fevers.** Despite the acetaminophen premedication, subjects can spike fevers up to 40°C starting at the end of the CRS-207 infusion generally through the next 24 hours. Oral Ibuprofen (400 to 800 mg) and acetaminophen (650 to 1000 mg) can be used in alternate sequence every 4 hours. Rarely, a cooling blanket has been used during the clinic stay. Fevers after 24 hours are uncommon, and rare after 36 hours.

- **Rigors**. Rigors (generally once or twice) have been observed starting during or at the end of the CRS-207 infusion through 24 hours. Intravenous narcotics such as morphine or meperidine can be administered per institutional policy.

- **Blood pressure**. Small drops in blood pressure have been observed necessitating additional IV fluids during the 4 hour observation period (up to 1 or 2 L). Reasons for this include the development of fever, compartmental shifts of fluid resulting from the CRS-207 infusion, and the use of narcotics. Some subjects have also been slightly hypotensive at 24 hours upon arrival to the clinic on Day 2. Subjects are encouraged to hydrate themselves liberally at home with oral fluids.

- **Appetite**. Appetite is generally suppressed during the 24 hours after CRS-207 infusion related to the factors listed above. Liberal intake of fluids is encouraged.

- **Nausea and vomiting**. Nausea and vomiting have been reported and observed infrequently within 24 hours after CRS-207 infusion.

All vaccine doses within a cycle are scheduled to be given approximately 3 weeks apart (Table 3). If necessary, a vaccine dose may be delayed for up to 2 weeks. In this case, subsequent doses should continue on a 3-week schedule. For example, if the Week 4 dose is delayed to Week 5, subsequent doses should be given on Weeks 8, 11, 14, and 17. If delayed more than 2 weeks between doses in a cycle, the dose will be considered missed and the subject should continue to receive the next dose as scheduled (i.e., 3 weeks from previous dose), with the exception that if the second dose of the first cycle in Treatment Arm A (second dose of cyclophosphamide and GVAX pancreas vaccine before receipt of the first dose of CRS-207) is delayed more than 2 weeks, the sponsor's medical monitor must be contacted for further instructions on continued dosing. Additional delays

or modifications to the dosing schedule must be approved by the sponsor's medical monitor.

4.3 STORAGE AND HANDLING OF CLINICAL TRIAL MATERIAL

Cyclophosphamide powder should be kept at or below 25ºC. Cyclophosphamide reconstituted in normal saline is chemically and physically stable for 24 hours at room temperature and for 6 days when refrigerated. Guidelines outlining the procedures for proper handling and disposal of anticancer drugs should be followed when handling cyclophosphamide.[32] Protective gloves should be worn when handling cyclophosphamide in both powder and reconstituted forms.

GVAX pancreas vaccine cells must be stored in vapor-phase liquid nitrogen until the day of vaccination. CRS-207 must be stored at –60ºC or colder until just before use. The investigational sites, per institutional guidelines, will destroy used GVAX pancreas vaccine and CRS-207 vials after formulation for administration. The formulation of GVAX pancreas vaccine and CRS-207 for administration and the destruction of each used vial will be carefully documented in the study pharmacy manual. The study monitor will perform investigational agent accountability during on-site monitoring visits. Unused GVAX pancreas vaccine and CRS-207 will be destroyed at the study site after final investigational product accountability and notification by Sponsor, unless otherwise directed by Sponsor.

Wild-type *Lm* is classified by the Centers for Disease Control and Prevention for handling in the laboratory according to Biosafety Level 2 practices. Individuals who prepare CRS-207 for injection must take appropriate precautions (e.g., gloves, laboratory coat, face protection, needle stick or sharps precautions) to avoid contamination or direct contact with the agent. Once it is prepared for injection, the chance for direct exposure to CRS-207 by study personnel should be greatly diminished. However, study personnel and staff should continue to adhere to the institutional guidelines for standard precautions.

4.3.1 Environmental Precautions

Wild-type *Lm* is a common pathogen that is widely distributed in the environment and contaminates a variety of ready-to-eat foods. Despite the presence of *Lm* in diverse locations, clinically apparent human infection is not commonly reported

in immunocompetent, normal individuals. Direct human-to-human spread of *Lm* is believed to be limited mainly to vertical transmission from mother to neonate. Standard isolation precautions are usually recommended for subjects infected with wild-type *Lm*. Precautions should therefore be exercised to avoid direct contact between subjects and individuals who are at high risk of listeriosis (e.g., newborn infants, pregnant women, HIV-positive individuals).

4.4 PRODUCT ACCOUNTABILITY

The investigator is responsible for the control of investigational agents under study. An investigational agent dispensing log must be kept current and should contain the following information:

- The study number and initials of each subject to whom the investigational agents are dispensed
- The date(s) and quantity of the investigational agent dispensed to the subject
- Documentation of proper disposal of used investigational drug vials
- Documentation of proper disposal (or return, at Sponsor's request) of unused investigational drug vials

All records and unused supplies of the investigational agents must be available for inspection at every monitoring visit.

4.5 PRIOR, CONCOMITANT, AND EXCLUDED THERAPY

During the course of the clinical study, subjects are anticipated to continue the use of prescribed medications identified during the screening procedures, consistent with study inclusion and exclusion criteria. Concomitant medications used in this study include the 10-day antibiotic regimen scheduled 7 days after completion of each cycle for Treatment Arm A (or each subject's final dose of CRS-207 if discontinued before end of cycle) and medications to treat any treatment-emergent AEs that may occur. Medications to treat treatment-emergent AEs should not interfere with the study and can be used at the investigator's discretion. Each subject should be premedicated with topical lidocaine-based anesthetic cream (if

subject is not allergic to lidocaine) at the vaccine sites before GVAX pancreas vaccine administration and given 650 mg acetaminophen before CRS-207 administration. Antipyretics may be used to treat fever or to prevent recurrence of fever. The details of any concomitant medications must be recorded in the case report form (CRF). The generic name, dosage, duration, and reason for the concomitant medication should be included in this report.

The following therapies are not permitted during the treatment period (if administered, the subject may be removed from the study):

- Any anticancer chemotherapy or non-study immunotherapy (approved or investigational)
- Systemically active steroids for more than 2 days or any systemic steroids during the treatment period or within 28 days before or after dosing
- Another investigational product
- Filgrastim (Neupogen or G-CSF) or Saragrastim (Leukine or GM-CSF)
- Prophylactic vaccines (e.g., influenza, pneumococcal, Td/Tdap) within 1 week prior to or after study dosing. (Note: prophylactic vaccines are discouraged for the duration of the treatment period and should be avoided if possible.)

In addition, the following therapies should not be administered during the treatment period unless medically necessary, and approval must be obtained from the medical monitor for a subject to continue dosing if therapy is given concurrently with study participation:

- General anesthesia or deep sedation
- Aspirin >325 mg/d (chronic daily use of aspirin ≤325 mg/d and heparin flushes for central lines are allowed)
- More than 4 g/d of acetaminophen

- Systemic antibiotics

Subjects with clinical or laboratory signs or symptoms of infection who require initiation of antibiotics other than specified by protocol should have a clinically relevant evaluation, including appropriate bacterial cultures. Culture of cerebrospinal fluid should be obtained for subjects with suspected central nervous system infection. In such instances, analysis of cerebrospinal fluid should also include cell count, protein, glucose, and Gram stain. The preferred antibiotic regimen if CRS-207 infection is suspected or confirmed, is intravenous administration of ampicillin (or trimethoprim/sulfamethoxazole in penicillin-allergic subjects) plus gentamicin. For this purpose, initial doses of ampicillin should be approximately 12 g daily (divided doses every 3 to 4 hours), with gentamicin 3 mg/kg daily in divided doses every 8 hours (with adjustments according to renal function and serum levels of gentamicin). In penicillin-allergic subjects, initial intravenous doses of trimethoprim/sulfamethoxazole should be 15 to 20 mg/kg/d (based on trimethoprim component) divided four times per day, with gentamicin 3 mg/kg daily in divided doses every 8 hours (with adjustments according to renal function and serum levels of gentamicin). For those individuals who receive intravenous antibiotics, the course of therapy is anticipated to be greater than or equal to 14 days, depending on clinical course. Antibiotic treatment may be completed with use of oral antibiotics, if clinically indicated.

5.0 EXPERIMENTAL PROCEDURES

5.1 OVERVIEW: SCHEDULE OF TIME AND EVENTS

An overview of study time and events is presented in Table 4.

Table 4. Schedule of Time and Events

Assessments	Screen-ing	Treatment																				Follow-up [c] (every 3 months)
		Week 1			Week 4[a]			Week 7[a]			Week 10[a]			Week 13[a]			Week 16[a]			Week 17	Week 20[b]	
Study Days	(D–28 to D0)	D1	D2	D4[d]	D1	D2	D4[d]	D1	D2	D4[d]	D1	D2	D4[d]	D1	D2	D4[d]	D1	D2	D4[d]	D1	D1	D1
Visit Windows (days)		-	-	±1	-	-	±1	-	-	±1	-	-	±1	-	-	±1	-	-	±1	-	±7	±7
Informed consent	X																					
Inclusion/exclusion	X																					
Medical history	X																					
Medication history	X																					
Cancer-related treatment	X																					X
Baseline signs/ symptoms	X																					
Virology screen[e]	X																					
Coagulation panel, UA[f]	X																					
Electrocardiogram	X																				X	
CT or MRI[g]	X										X										X	X
Physical examination[h]	X	X			X			X			X			X			X				X	
ECOG performance status	X	X			X			X			X			X			X				X	
Vital signs, weight[i]	X	X	X		X	X		X	X		X	X		X	X		X	X			X	
Pulse oximetry, height	X																					
Pregnancy test[j]	X	X			X			X			X			X			X					
CD4 count	X																					
Clinical hematology, serum chemistry[k]	X	X			X			X	X[l]		X	X[l]		X	X[l]		X	X[l]			X	
Tumor marker(s)[m]	X	X			X			X			X			X			X				X	
Vaccine-site reactions				X			X			X[n]			X[n]			X[n]			X[n]			
Concomitant medications, adverse events		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X		X	
PBMC for cellular immunity[o]		X						X			X			X			X				X	X
Serum for *Lm* and mesothelin immunity[p]		X			X			X	X[p]		X	X[p]		X	X[p]		X	X[p]			X	X
HLA-typing[q]		X																				
Antibiotics[r]																				X		
Dose Administration[s]	(Y = cyclophosphamide; G = GVAX pancreas vaccine; C = CRS-207)																					
Treatment Arm A		Y	G[t]		Y	G[t]		C[u]			C[u]			C[u]			C[u]					
Treatment Arm B		Y	G[t]		Y	G[t]		Y	G[t]		Y	G[t]		Y	G[t]		Y	G[t]				
Continuation eligibility[v]																					X	

Table 4. Schedule of Time and Events (continued)

ALT = alanine aminotransferase; ANC = absolute neutrophil count; APTT = activated partial thromboplastin time; AST = aspartate aminotransferase; BUN = blood urea nitrogen; CBC = complete blood count; CT = computed tomography; D = study day; ECOG = Eastern Cooperative Oncology Group; HLA = human leukocyte antigen; LDH = lactate dehydrogenase; *Lm* = *Listeria monocytogenes*; MRI = magnetic resonance imaging; PBMC = peripheral blood mononuclear cells; UA = urinalysis.

a Doses of cyclophosphamide and GVAX pancreas vaccine or CRS-207 on Weeks 4, 7, 10, 13, and 16 may be delayed up to 2 weeks (i.e., 5 weeks since previous dose). Subsequent doses should continue to be separated by 3-week intervals (e.g., if the second dose is delayed to Week 5, third dose should be given at Week 8). Doses delayed more than 2 weeks apart should be considered missed and the subject should continue to receive the next dose as scheduled with the exception that if the second dose of the first cycle in Treatment Arm A (2nd dose of cyclophosphamide and GVAX) is delayed more than 2 weeks, the sponsor's medical monitor must be contacted for further instructions. .

b Follow-up will occur 28 days after the final dose of one cycle (6 doses) or within 28 days after the final dose for subjects who do not complete all doses. If the Week 20 visit occurs early (as protocol allows), a telephone assessment for adverse events should be made on day 28 (±1 day) after last study dose and documented.

c Subjects will continue to be followed every 3 months by phone or optional clinic visit for until death or study close to document subsequent cancer-related therapies, request CT scans to assess overall response rate and optional blood draws for *Lm* and mesothelin responses.

d Day 4 assessment will be conducted by phone.

e Virology screen: HIV antibody, hepatitis B surface antigen, and hepatitis C antibody; additional virology may also be evaluated. Subjects who are hepatitis C antibody positive and confirmed negative viral load at screening will be allowed to enroll.

f Coagulation panel: D-dimer, fibrinogen, international normalized ratio of prothrombin time, APTT; UA: bilirubin, blood, glucose, ketones, leukocytes, nitrite, pH, protein, specific gravity.

g Spiral CT of thorax, abdomen, and pelvis (and other imaging studies as clinically indicated to evaluate suspected sites of metastatic disease). If CT has been done within 14 days before screening, these results may be used for evaluation. If a subject cannot have a CT scan (e.g., allergy to contrast dye), an MRI should be performed. On-study CT scans may be done within 1 week prior to or after scheduled visit.

h Complete physical examinations will be conducted at baseline and Week 20; focused physical examinations to be conducted on Day 1 of dosing weeks.

i Blood pressure, pulse, respiratory rate, temperature are required as indicated. Weight will be taken on Day 1 of dosing weeks.

j Pregnancy tests will be administered only to women of childbearing potential: serum pregnancy test is required at screening, and urine pregnancy tests are required before doses on Day 1 of dosing weeks.

k Clinical hematology: CBC with differential ANC and platelet count; serum chemistry: sodium, potassium, chloride, bicarbonate, glucose, BUN, creatinine, LDH, ALT, AST, alkaline phosphatase, bilirubin (total, direct, and indirect), amylase, total protein, albumin, calcium, magnesium, and phosphate. Blood draws may be taken up to 72 hours before dosing. Blood draws must not be collected from a central line for at least 4 days after infusion of CRS-207.

l Required on Day 2 only after CRS-207 dosing; if liver function tests are Grade 2 or higher, subjects will have repeated testing on Day 7.

m CA 19-9 and CEA will be tested at screening, and only the applicable elevated tumor antigen will be followed. Other tumor markers may also be evaluated.

n Injection-site reactions will be evaluated on Day 4 only after GVAX vaccinations.

o 90-200 mL of whole blood to be processed within 6 hours into peripheral blood mononuclear cells (PBMCs) and stored frozen in liquid nitrogen.

p For Treatment Arm A only (after CRS-207 dosing): 10 mL of serum for *Lm* and mesothelin immunity should be taken between 20 and 26 hours after start of dosing.

q HLA-typing to include type A and B, low resolution.

r 10-day course of antibiotics will be administered in Treatment Arm A 7 days after final dose of CRS-207 in each cycle (or after final dose if discontinued early) (see Section 5.2.2.4).

s Doses will be administered after all visit assessments and blood draws are completed.

t Subjects will be observed in the clinic for at least 60 minutes after first vaccination and at least 30 minutes after second vaccination.

u Vital signs (blood pressure, pulse, respiratory rate, temperature) will be obtained every 30 minutes during the CRS-207 infusion and every hour during postinfusion follow-up. Subjects will be observed for at least 4 hours after each infusion. Subjects who are not stable enough to be released at 4 hours after infusion should continue to be monitored until stable. Presence of fever alone does not indicate subject is not clinically stable.

v At investigator's discretion, subjects may be eligible for additional treatment cycles if they are clinically stable and meet dosing eligibility (see Section 5.2.4).

5.2 MEASUREMENTS AND EVALUATIONS

5.2.1 Screening Period (Day –28 to Day 0)

Before screening assessments are conducted, the subject must be given a complete explanation of the purpose and evaluations of the study. Subsequently, the subject must sign and receive a copy of an informed consent form (ICF) that was approved by the institutional review board (IRB) and an authorization for use and disclosure of protected health information (PHI) before any study-specific procedure is performed. An original signed consent form will be retained in the subject's source documentation at the site, and a copy will be provided for the subject to take home. Screening will occur within 28 days before treatment administration. Potential subjects will be evaluated for entry into the study according to the stated inclusion and exclusion criteria. Individuals who are identified during this screening as not eligible for study enrollment need not complete all screening procedures. The reason for ineligible status will be documented.

The following evaluations will be performed to assess the subject's eligibility for the study:

- Signed, written informed consent
- Inclusion and exclusion criteria
- Medical history, including history of carcinoma treatment
- Medication history over the past 28 days, including prescription and over-the-counter medications, herbs, vitamins, and minerals
- Baseline signs and symptoms
- Physical examination
- ECOG performance status
- Vital signs (BP, pulse, respiratory rate, temperature), height, weight, and pulse oxygen saturation

- Clinical assessment of tumor status
- Resting 12-lead electrocardiogram
- Clinical hematology: complete blood count with differential absolute neutrophil count and platelet count
- Serum chemistry: sodium, potassium, chloride, bicarbonate, glucose, blood urea nitrogen, creatinine, lactate dehydrogenase, ALT, AST, alkaline phosphatase, amylase, bilirubin (total, direct, indirect), total protein, albumin, calcium, magnesium, and phosphate
- Coagulation panel: D-dimer, fibrinogen, international normalized ratio of prothrombin time, and activated partial thromboplastin time (APTT)
- Virology screen: HIV antibody, hepatitis B surface antigen, and hepatitis C antibody (Additional virology screens may also be evaluated.)
- Urinalysis: bilirubin, blood, glucose, ketones, leukocytes, nitrite, pH, protein, and specific gravity
- CD4 count
- Tumor marker CA19-9 and CEA (other tumor markers may also be evaluated)
- Serum pregnancy test (for women of childbearing potential only)
- Spiral CT scan of thorax, abdomen, and pelvis (and other imaging studies as clinically indicated to evaluate suspected sites of metastatic disease) if one has not been done within 14 days before screening (Tumor[s] should be measured according to RECIST and irRC [see Appendices A and B]. Measurable tumors are not required for study entry. If a subject cannot have a CT scan [e.g., allergy to contrast dye], a magnetic resonance imaging [MRI] should be performed.)

The investigator may use clinical judgment when determining the clinical significance of laboratory parameter findings throughout the study. The medical monitor may, depending on study criteria, be consulted before enrollment about a potential subject with abnormal laboratory values.

5.2.2 Treatment Period

5.2.2.1 Cyclophosphamide Administration (Day 1 of Weeks 1 and 4 for Treatment Arm A; Day 1 of Weeks 1, 4, 7, 10, 13, and 16 for Treatment Arm B)

Cyclophosphamide will be administered to subjects on Day 1 of Weeks 1 and 4 for Treatment Arm A and on Day 1 of Weeks 1, 4, 7, 10, 13, and 16 for Treatment Arm B by intravenous infusion at 200 mg/m^2 in 100 mL normal saline over 30 minutes after the following evaluations have been performed:

- ECOG performance status
- Vital signs (BP, pulse, respiratory rate, temperature) and weight
- Focused physical examination
- AEs and concomitant medications review
- Urine pregnancy test (for women of childbearing potential only)
- Blood draws for clinical hematology and serum chemistry; samples may be drawn up to 72 hours prior to dosing. If screening assessments were done within 72 hours of dosing, samples do not need to be repeated for Week 1, Day 1.
- Blood draw for tumor marker CA19-9 and/or CEA assessment, as applicable (other tumor markers may also be evaluated); samples may be drawn up to 72 hours prior to dosing
- Blood draw for isolation of PBMCs (90-200 mL), with the exception of no blood draw on Day 1, Week 4 (Samples may be drawn up to 72 hours prior

to dosing and must be processed by sponsor-qualified operators within 6 hours of collection and stored in liquid nitrogen.)

- Blood draw for *Lm*- and mesothelin-specific immunity assays (10 mL); samples may be drawn up to 72 hours prior to dosing

- For Week 1, Day 1 only: Blood draw for HLA-typing (A and B, low resolution); sample may be drawn up to 72 hours prior to dosing

- For Week 10 only: spiral CT scan of thorax, abdomen, and pelvis (and other imaging studies as clinically indicated to evaluate suspected sites of metastatic disease) and measurement of tumor(s) according to RECIST and irRC (see Appendices A and B). (Clinical assessment of tumor status should be recorded. If a subject cannot have a CT scan (e.g., allergy to contrast dye), an MRI should be performed. Subjects with progressive disease in the absence of clinical deterioration may continue treatment. CT scan may be done within 1 week prior to or after the scheduled visit.)

5.2.2.2 GVAX Pancreas Vaccine Administration (Day 2 of Weeks 1 and 4 for Treatment Arm A; Day 2 of Weeks 1, 4, 7, 10, 13, and 16 for Treatment Arm B)

GVAX pancreas vaccine will be administered on Day 2 of Weeks 1 and 4 for Treatment Arm A and on Day 2 of Weeks 1, 4, 7, 10, 13, and 16 for Treatment Arm B as detailed in Section 4.2. Subjects will be observed in the clinic for at least 60 minutes after first vaccination and at least 30 minutes after second vaccination.

The following evaluations will be performed before GVAX pancreas vaccine administration:

- Vital signs (BP, pulse, respiratory rate, temperature)

- AEs and concomitant medications review

On Day 4 (± 1 day), subjects will be contacted by phone to assess injection-site reactions (such as erythema, bruising [ecchymosis], induration, edema, nodule or vesicle formation, pruritis, and tenderness), AEs, and concomitant medications.

5.2.2.3 CRS-207 Administration (Day 1 of Weeks 7, 10, 13, and 16 for Treatment Arm A)

CRS-207 will be administered to subjects in Treatment Arm A on Day 1 of Weeks 7, 10, 13, and 16 by intravenous infusion at 1×10^9 CFU in 250 mL 0.9% sodium chloride over 2 hours. Subjects will be premedicated with 650 mg of acetaminophen before drug administration. Either immediately before or immediately after infusion, subjects will receive a total of 1,000 mL of normal saline; half of the volume may be given before infusion and half after infusion. Investigators will not make dose adjustments or changes to administration schedule or rate without prior approval from Aduro. CRS-207 must not be administered via central venous catheter or infusion port. Vital signs (blood pressure, pulse, respiratory rate, temperature) will be obtained every 30 minutes during the CRS-207 infusion and every hour during post infusion follow-up. Subjects will be observed for at least 4 hours after each infusion. Subjects who are not stable enough to be released at 4 hours after infusion should continue to be monitored until stable. Presence of fever alone does not indicate subject is not clinically stable.

The following evaluations will be performed before CRS-207 administration:

- ECOG performance status
- Vital signs (BP, pulse, respiratory rate, temperature) and weight
- Focused physical examination
- AE and concomitant medications review
- Blood draws for clinical hematology and serum chemistry; samples may be drawn up to 72 hours prior to dosing

- Blood draw for tumor marker CA19-9 and/or CEA assessment, as applicable (other tumor markers may also be evaluated); samples may be drawn up to 72 hours prior to dosing

- Urine pregnancy test (for women of childbearing potential only)

- Blood draw for isolation of PBMCs (90-200 mL) (Samples may be drawn up to 72 hours prior to dosing and must be processed by sponsor-qualified operators within 6 hours of collection and stored in liquid nitrogen.)

- Blood draw for *Lm*- and mesothelin-specific immunity assays (10 mL); samples may be drawn up to 72 hours prior to dosing

- For Week 10 only: spiral CT scan of thorax, abdomen, and pelvis (and other imaging studies as clinically indicated to evaluate suspected sites of metastatic disease) and measure tumor(s) according to RECIST and irRC (see Appendices A and B) (Clinical assessment of tumor status should be recorded. If a subject cannot have a CT scan [e.g., allergy to contrast dye], an MRI should be performed. Subjects with progressive disease in the absence of clinical deterioration may continue treatment. CT scan may be done within 1 week prior to or after the scheduled visit.)

Subjects will return to the clinic 1 day after receiving CRS-207 (Day 2) to be evaluated for AEs, concomitant medications, vital signs, and to have blood drawn for clinical hematology, serum chemistry, and *Lm*- and mesothelin-specific immunity assays. Blood drawn for *Lm*- and mesothelin-specific immunity assays should be drawn within 20-26 hours after start of CRS-207 dosing. If liver function tests are Grade 2 or higher based on CTCAE (Version 4.03), subjects will repeat testing locally or at the research clinic on Day 7. Any unexpected Grade 3 laboratory abnormalities should be repeated within 24-72 hours. Blood samples must not be collected from a central line after infusion of CRS-207 for at least 4 days.

On Day 4 (± 1 day), subjects will be contacted by phone to assess AEs and concomitant medications.

5.2.2.4 Antibiotic Administration (7 Days after Last CRS-207 Dose in Each Treatment Cycle)

A 10-day course of oral amoxicillin (500 mg at 8-hour intervals) or trimethoprim/sulfamethoxazole in penicillin-allergic subjects (160 mg trimethoprim/800 mg sulfamethoxazole at 12-hour intervals) will be initiated for each subject 7 days after the subject's last dose of CRS-207 for each treatment cycle (or after their final dose if discontinued early) to ensure clearance of CRS-207 before additional cycles or subsequent therapy. If the subject is withdrawn from the study more than 7 days after administration of CRS-207, then oral antibiotics will be administered as soon as possible after study withdrawal. In addition, intravenous ampicillin (or trimethoprim/sulfamethoxazole in penicillin-allergic subjects) plus gentamicin will be initiated earlier for possible infectious complications of CRS-207 for subjects who are suspected of having CRS-207 infection and meet the criteria listed below:

- Flu-like symptoms Grade 3 or greater lasting for ≥12 hours
- Fever Grade 4 or higher (>40.0ºC for >24 hours)
- Persistent fever >39ºC lasting for ≥48 hours
- Infection Grade 3 or higher (infection with interventional radiology or operative intervention indicated)
- Evidence of abscess
- Clinical signs or symptoms (e.g., neurologic signs or symptoms), which in the judgment of the investigator necessitate starting antibiotics

5.2.3 Treatment Follow-up (Day 1 of Week 20 ±7 days) or Within 28 Days after Final Dose)

Subjects will return at Week 20 or within 28 days of the final study dose for evaluation or to begin an additional treatment regimen. If the Week 20 visit occurs early (as protocol allows), a telephone assessment for adverse events should be made on day 28 (±1 day) after last study dose and documented.

The following evaluations will be performed:

- Physical examination
- ECOG performance status
- Vital signs (BP, pulse, respiratory rate, temperature) and weight
- AE and concomitant medications review
- Blood draws for clinical hematology and serum chemistry
- Resting 12-lead electrocardiogram
- Blood draw for tumor marker CA19-9 or CEA assessment (other tumor markers may also be evaluated)
- Blood draw for isolation of PBMCs (90-200 mL) (Samples must be processed by sponsor-qualified operators within 6 hours of collection and stored in liquid nitrogen.)
- Blood draw for *Lm*- and mesothelin-specific immunity assays (10 mL)
- Spiral CT scan of thorax, abdomen, and pelvis (and other imaging studies as clinically indicated to evaluate suspected sites of metastatic disease) and measure tumor(s) according to RECIST and irRC (see Appendices A and B) (Clinical assessment of tumor status should be recorded. If a subject cannot have a CT scan [e.g., allergy to contrast dye], an MRI should be performed. CT scan may be done within 1 week prior to or after the scheduled visit.)

5.2.4 Continuation of Additional Treatment Cycles

Subjects who are clinically stable and meet dosing requirements at the Week 20 follow-up may receive additional cycles of their assigned treatment based on investigator discretion and with sponsor approval. The additional cycle(s) may start as early as Week 20 (i.e., 4 weeks from last dose of previous cycle) and all

assessments will be followed per the study schedule in Table 4, with the first dose of the additional cycle corresponding to Day 1, Week 1 of the study schedule.

Modifications to the assessments for additional cycles are as follows:

- Assessments done at Week 20 which are required at Day 1, Week 1 of the treatment cycle do not need to be repeated in duplicate if Day 1, Week 1 of the next cycle is started with 14 days of the Week 20 visit assessments.

- HLA-typing does not need to be repeated at Day 1, Week 1 of additional cycles.

- For sites that have the option of conducting a leukopheresis procedure under this study (or a related substudy), subjects who consent to leukopheresis during an additional cycle, are not required to provide the scheduled PBMC blood collections for that cycle.

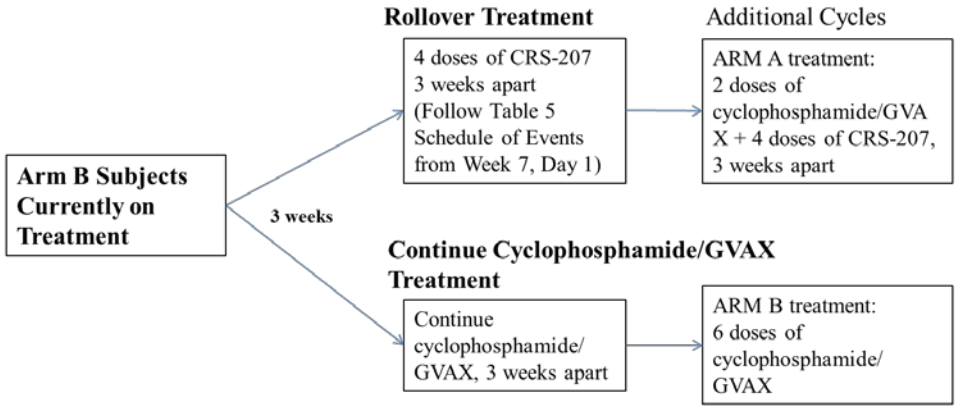
Schedule modifications to allow for longer intervals between vaccine doses (i.e., greater than 3 weeks between cyclophosphamide/GVAX pancreas dosing and/or CRS-207 dosing) will be considered for subjects on additional cycles. In any case, cyclophosphamide must be administered with 1 day prior to GVAX pancreas vaccine and vaccine doses should not be given less than 3 weeks or more than 8 weeks apart. Schedule modifications must be approved by the sponsor and medical monitor.

5.2.5 Rollover Treatment for Arm B Subjects

During the trial, a planned interim analysis for early stopping for efficacy or for futility was performed per protocol after 41 deaths occurred. At this planned interim efficacy analysis, the study was determined by the DMC to meet the criteria for early stopping for efficacy (see Section 8.2.7) and subjects currently on treatment in Arm B will be offered CRS-207 treatment. Subjects on Arm A and in follow-up will continue with treatment and in follow-up per protocol. Arm B subjects currently on treatment will have the option to either continue to receive cyclophosphamide/GVAX pancreas vaccine doses on the protocol schedule or to receive up to 4 doses of CRS-207 (see Figure 1). Subjects may choose to rollover to CRS-207 followed by combination cyclophosphamide/GVAX pancreas vaccine and CRS-207 (Arm A) treatment at any time during their Arm B

treatment. The first dose of CRS-207 will be given at least 3 weeks after their last dose of cyclophosphamide/GVAX pancreas vaccine. The requirements, procedures and schedule for the CRS-207 dosing and follow-up will follow the Arm A protocol schedule starting with Week 7, Day 1. At the investigator's discretion, after 4 doses of CRS-207, subjects may continue to receive additional cycles of the Arm A treatment regimen starting with Week 1, Day 1 if they are clinically stable and meet dosing eligibility.

Figure 1. Rollover Treatment Option for Arm B Subjects



5.2.6 Study Follow-up Period

When subjects complete all study treatment, they will continue to be followed every 3 months (± 7 days) by phone or optional clinic visit for the duration of the study until death or study close to document subsequent cancer-related therapies, request CT scans to assess overall response rate, and monitoring of immune responses to *Lm* and mesothelin (at clinic visits only). At the time of study close, which occurs after all subjects have died or completed 24 months on study (from time of randomization), subjects will be offered enrollment in a long-term follow-up study and continue to be evaluated for survival and clinical and immunological responses. Subjects who are still receiving treatment at the time of study close may complete the current treatment cycle (up to 6 doses) prior to transitioning to the long-term follow-up protocol.

In accordance with good medical practice, any ongoing AE present at study termination, including a clinically significant laboratory test abnormality, which is determined by the investigator as possibly or probably related to the study investigational agents, will be followed until resolved, until the event stabilizes

and the overall clinical outcome has been ascertained, or until the subject is lost to follow-up.

5.2.7 Re-treatment of Subjects Previously on Treatment

Subjects who received at least one dose of investigational product, discontinued treatment and are still in follow-up on protocol, may be eligible for re-treatment with cyclophosphamide, GVAX pancreas vaccine and CRS-207 if the investigator believes that the subject may benefit from receiving treatment. Subjects being considered for re-treatment must meet study eligibility criteria (Section 3.2) and must be approved by the sponsor, medical monitor and lead investigator. Subjects must have all screening assessments repeated (with the exception of height, demographics and baseline cancer history) within 4 weeks of start of re-treatment to confirm eligibility. All subjects offered re-treatment will receive Arm A treatment of cyclophosphamide, GVAX pancreas vaccine and CRS-207 at the same dose and schedule in this protocol regardless of their original treatment assignment or response to previous protocol therapy. Subjects will follow all procedures for Treatment Arm A dosing and follow-up visits per protocol (Table 4 and Section 5.2.2, with the exception that HLA-typing is not required to be repeated on Day 1). Subjects may receive a minimum of one cycle of treatment and may be eligible for additional treatments if they are clinically stable and meet dosing requirements for additional cycles (Section 5.2.4). The window for initiation of re-dosing subjects will close approximately 6 months before study close.). Details of data collection and CRF completion will be provided separately.

6.0 PROCEDURES FOR HANDLING ADVERSE EVENTS AND SERIOUS ADVERSE EVENTS

6.1 DEFINITION OF AN ADVERSE EVENT

The following definition of an AE will be used for this study:

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

Examples of AEs include the following:

- Significant or unexpected worsening or exacerbation of the indication under study
- Exacerbation of a chronic or intermittent preexisting condition, including an increase in frequency or intensity of the condition
- New conditions detected or diagnosed after investigational product administration, even if they were present before the start of the study
- Signs, symptoms, or the clinical sequelae of a suspected interaction with another medical product
- Signs, symptoms, or the clinical sequelae of a suspected overdose of either investigational product or a concurrent medication

An overdose should not be reported as an AE or SAE; instead the symptoms resulting from the overdose should be reported as the AE or SAE.

Examples of AEs do not include the following:

- Medical or surgical procedures (e.g., endoscopy, appendectomy) (Instead, the medical condition that led to the procedure is an AE.)

- Situations that are unwanted but in which an untoward medical occurrence did not occur, for example social inconvenience after admission to a hospital

- Anticipated day-to-day fluctuations of a preexisting disease or condition (present or detected before enrollment) that does not worsen overall

- Expected progression of the disease being studied, including signs or symptoms of the disease being studied, unless progression is more severe than expected for the subject's condition

It is the responsibility of the investigator to perform periodic and special assessments for AEs. The investigator and clinical staff will record all AEs offered by the subject at baseline after first clinical trial material (CTM) administration, during administration of the CTM, and at the follow-up visits. All clinical complaints volunteered by, or elicited from, the subject during the study will be recorded on the appropriate page of the CRF for the study period indicated. If any AE occurs, the subject will receive appropriate treatment and medical supervision.

All AEs judged to be clinically significant, including clinically significant laboratory abnormalities, will be followed until resolution. All AEs will be summarized in the annual report or more frequently, if requested by the regulatory agency. SAEs require special reporting in addition to documentation in the CRF as described below.

6.2 DEFINITION OF A SERIOUS ADVERSE EVENT

In this study, the definition of an SAE is an AE that meets any of the following criteria:

- Results in death

- Is life-threatening

  Note: The term *life-threatening* in the definition of *serious* refers to an event in which the subject was at risk of death at the time of the event. It does not refer to an event that hypothetically might have caused death if it were more severe.

- Requires hospitalization or prolongation of existing hospitalization

  Note: In general, hospitalization signifies that the subject has been detained at the hospital or emergency ward for observation or treatment that would not have been appropriate in the physician's office or out-patient setting. Complications that occur during hospitalization are AEs but not necessarily SAEs. An occurrence or complication that prolongs hospitalization is an SAE. When there is doubt as to whether hospitalization occurred or was necessary, the AE should be considered an SAE. Hospitalization for elective treatment of a preexisting condition that did not worsen from its original baseline severity is not considered an SAE.

  Hospital admissions for overnight monitoring following CRS-207 infusion will not be considered an SAE unless the event meets criteria for seriousness other than hospitalization.

- A persistent or significant disability or incapacity

  Note: The term *disability* means a substantial disruption of a person's ability to conduct normal life functions. This definition is not intended to include AEs of relatively minor medical significance, such as uncomplicated headache, nausea, vomiting, diarrhea, influenza, or accidental trauma (e.g., sprained ankle), that may interfere or prevent everyday life functions, but do not constitute a substantial disruption of a person's ability to conduct normal life functions.

- A congenital anomaly or birth defect

- Other important medical event

Note: Medical or scientific judgment should be exercised in deciding whether reporting is appropriate for other important medical events that may not result in death, be life-threatening, or require hospitalization but still may jeopardize the subject or may require medical intervention to prevent one of the outcomes listed in this definition. These events should also be considered serious.

An SAE requires additional detailed reports and follow-up. The content of these detailed reports must address the investigator's estimate of causality.

6.3 RECORDING ADVERSE EVENTS AND SERIOUS ADVERSE EVENTS

All preexisting medical conditions will be recorded on the baseline physical examination page of the CRF. Starting with the first administration of first investigational product, any new event or experience that was not present at screening, or worsening of an event present at screening, is considered to be an AE. Unchanged, chronic conditions are not AEs and should not be recorded on the AE page of the CRF.

When an AE or SAE occurs, it is the responsibility of the investigator to review all documentation (e.g., hospital progress notes, laboratory and diagnostic reports) relative to the event. The investigator is to record all relevant information about any AE (including SAEs) on the AE page of the CRF. It is not acceptable for the investigator to send photocopies of the subject's medical records in lieu of the proper completion of the appropriate AE (or SAE) CRF pages. However, there may be instances where copies of medical records for certain cases are requested. In such instances, all subject identifiers and PHI will be blinded on the copies of the medical records before submission to the appropriate authorities.

The investigator will also attempt to establish a diagnosis of the event on the basis of signs, symptoms, or other clinical information. In such cases, the diagnosis, not the individual signs and symptoms, should be documented on the appropriate CRF as the AE or SAE. In addition, SAEs need to be reported on the SAE report form provided in the SPM. The SPM provides additional guidelines.

All AEs and SAEs regardless of causality will be recorded through 28 days after final study treatment. During the study follow-up period, only SAEs (including

deaths) considered possibly, probably or definitely related to investigational product will be reported.

6.4 ASSESSMENT OF GRADE

The investigator will make an assessment of grade for each AE and SAE reported during the study, which will be recorded in the CRF. The assessment will be based on the National Cancer Institute's Common Terminology Criteria for Adverse Events, Version 4.03, and graded as shown below:

- Grade 1: Mild; asymptomatic or mild symptoms; clinical or diagnostic observations only; intervention not indicated
- Grade 2: Moderate; minimal, local or noninvasive intervention indicated; limiting age-appropriate instrumental activities of daily living
- Grade 3: Severe or medically significant but not immediately life-threatening; hospitalization or prolongation of hospitalization indicated; disabling; limiting self-care activities of daily living
- Grade 4: Life-threatening consequences; urgent intervention indicated
- Grade 5: Death related to AE

Any AE that changes in grade during its course will be recorded in the CRF at the highest level experience by the subject.

6.5 ASSESSMENT OF CAUSALITY

The investigator is obligated to estimate the relationship between the investigational products and the occurrence of each AE or SAE by using his or her best clinical judgment. Other causes, such as the history of the underlying disease, concomitant therapy, other risk factors, and the temporal relationship of the event to the investigational products will be considered and investigated. The investigator will also consult the IB or product labeling information for marketed products in the determination of the assessment.

There may be situations when an SAE has occurred and the investigator has minimal information to include in the initial report. However, it is very important that the investigator always assess causality for every event before the transmission of the SAE. The investigator may change his or her opinion of the causality in light of follow-up information, amending the SAE report. The causality assessment (Table 5) is one of the criteria used to determine regulatory reporting requirements and should not be left blank.

Table 5. Assessment of Causality/Relatedness of AEs

Term	Definition
Definitely related	The AE *is clearly related* to the investigational agent(s) or research intervention: the AE has a temporal relationship to the administration of the investigational agent(s) or research intervention, follows a known pattern of response, and no alternative cause is present.
Probably related	The AE is *likely related* to the investigational agent(s) or intervention: the AE has a temporal relationship to the administration of the investigational agent(s) or research intervention and follows a known or suspected pattern of response, but an alternative cause may be present.
Possibly related	The AE *may be related* to the investigational agent(s) or intervention: the AE has a temporal relationship to the administration of the investigational agent(s) or research intervention, follows a suspected pattern of response, but an alternative cause is present.
Unlikely to be related	The AE is *doubtfully related* to the investigational agent(s) or intervention: the AE has a temporal relationship to the administration of the investigational agent(s) or research intervention but follows no known or suspected pattern of response, and an alternative cause is present.
Unrelated (or not related)	The AE is *clearly NOT* related to the investigational agent(s) or intervention: the AE has no temporal relationship to the administration of the investigational agent(s) or research intervention and follows no known or suspected pattern of response, and an alternative cause is present.

AE = adverse event.

6.6 REPORTING OF SERIOUS ADVERSE EVENTS

Any SAE that occurred after starting experimental treatment will be reported to the sponsor by phone, fax, or e-mail within 24 hours of the time the investigator becomes aware of the event.

SAE Reporting Fax Number: 615-297-6539

The medical monitor may also be contacted to discuss a safety event:

John Grous, MD: 508-634-1344 / mobile: 774-287-9709

The urgency for reporting SAE(s) is fourfold:

1. To enable the safety department to fulfill the reporting requirements to the appropriate regulatory authority

2. To facilitate discussion (and implementation, if necessary) between the safety department and the investigator of appropriate follow-up measures in the event an expedited report is required

3. To facilitate Aduro's rapid dissemination of information about AEs to other investigators or sites in a multicenter study by using expediting reporting

4. To facilitate investigator reporting of unanticipated problems involving risk to human subjects to the IRB and institutional biosafety committee

In the event an SAE is observed, the SAE report will be completed as thoroughly as possible including the following:

- All available details about the event

- Signature of the investigator

The SAE report will be forwarded to the sponsor or designee within the designated time frames. If the investigator does not have all information about an SAE, the investigator will *not* wait to receive additional information before notifying the sponsor of the event and completing the form. The form will be updated when additional information is received.

Aduro will report all SAEs that are unexpected and considered possibly or probably related to the administration of the investigational agents to the Food and Drug Administration in the form of an expedited safety report within 15 calendar days after receiving information on the SAE. Aduro will also report to the United States Food and Drug Administration (FDA) and National Institutes of Health Office of Biotechnology Activities (NIH OBA) by fax or phone within 7 days of receiving the information, any unexpected life-threatening or fatal SAEs that are considered at least possibly associated with the investigational agents. Aduro, or designee, will also notify all participating investigators of expedited

safety reports within 15 calendar days after receiving information. The investigators will notify their reviewing IRB and institutional biosafety committee (IBC) as required by institutional policies.

6.7 FOLLOW-UP OF ADVERSE EVENTS AND SERIOUS ADVERSE EVENTS

After the initial AE or SAE report, the investigator is required to proactively follow each subject and provide further information to the safety department in regards to the subject's condition.

All AE(s) and SAE(s) will be followed until:

- Resolution
- The condition stabilizes
- The event is otherwise explained
- The subject is lost to follow-up

Once the event is resolved, the appropriate AE or SAE report page will be updated. The investigator will also ensure that the follow-up includes any supplemental information that may explain the causality of the event(s).

New or updated information will be recorded on the originally completed AE or SAE report, with all changes signed and dated by the investigator or designee. The updated AE or SAE report will then be signed by the investigator and resubmitted to the safety department.

7.0 STUDY OR STUDY SITE TERMINATION AND SUBJECT DISCONTINUATION

7.1 PREMATURE STUDY OR STUDY SITE TERMINATION

If Aduro, the investigator, the medical monitor, the study monitor, or appropriate regulatory officials discover conditions arising during the study that indicate that the study should be halted or that the study center should be terminated, this action may be taken after appropriate consultation among Aduro, the investigator, the medical monitor, and the study monitor. Conditions that may warrant termination of the study include, but are not limited to the following:

- The discovery of an unexpected, serious, or unacceptable risk to the subjects enrolled in the study
- A decision on the part of Aduro to suspend or discontinue testing, evaluation, or development of the product for any reason

A study conducted at a single study site in a multicenter study may also warrant termination under the following conditions:

- Failure of the investigator to enroll subjects into the study at an acceptable rate
- Failure of the investigator to comply with pertinent regulations of appropriate regulatory authorities
- Submission of knowingly false information from the research facility to Aduro, the study monitor, or appropriate regulatory authority
- Insufficient adherence to protocol requirements

Study termination and follow-up will be performed in compliance with the conditions set forth in the International Conference on Harmonisation (ICH) E6, Guideline for Good Clinical Practice, Sections 4.12, 4.13, 5.20, and 5.21.

7.2 SUBJECT DISCONTINUATION

Subjects will be encouraged to complete the study; however, they may voluntarily withdraw at any time. The investigator will provide a written explanation describing the reason for discontinuation in a source document, which will be transcribed to the appropriate CRF page. Subjects who wish to withdraw from the study will be encouraged to complete the planned administration of antibiotics and to complete assessments scheduled during the follow-up visit.

Subjects who withdraw from the study before receiving at least 3 doses in the first cycle (in either treatment arm) will be considered dropouts and may be replaced at the discretion of Aduro. Replacement subjects will be randomized in a 2:1 ratio of Treatment Arm A to Treatment Arm B, according to a replacement randomization list generated by an independent statistician.

Subjects who experience disease progression may be allowed to continue in the study if the investigator believes they are deriving some benefit from the therapy. A subject may be removed from the study for the reasons listed in Sections 7.2.1 through 7.2.4.

7.2.1 Adverse Event

If a subject suffers an AE that, in the judgment of the investigator, Aduro, or the medical monitor, presents an unacceptable consequence or risk to the subject, the subject may be discontinued from further participation in the study.

7.2.2 Intercurrent Illness

A subject may be discontinued from the study if, in the judgment of the investigator, the subject develops an intercurrent illness or complication (including progressive disease) that, in any way, justifies withdrawal from the study.

7.2.3 Noncompliance

After consultation between the investigator, the medical monitor, or study monitor, and Aduro when appropriate, a subject may be discontinued from the study for the following administrative reasons:

- Failure to receive study medication or treatment as mandated by the protocol
- Failure to comply with protocol requirements
- Unauthorized, subject-initiated changes in dosing regimen

7.2.4 Refusal of Clinical Trial Material Administration

If, for any reason, the subject refuses CTM administration during the study, the subject may be discontinued from the study, and the reason(s) for refusal will be documented on the appropriate CRF page. Reasonable efforts should be made to monitor the subject for AEs and to complete follow-up assessments. These efforts should be documented on the appropriate CRF page.

8.0 DATA COLLECTION AND PROCESSING AND STATISTICAL ANALYSIS

8.1 DATA COLLECTION AND PROCESSING

CRFs will be used to capture study results and data. The study coordinator or other authorized study personnel will transcribe data from source documents onto paper or electronic CRFs. All CRFs will be reviewed and source verified by the study monitor during periodic site visits, and the study monitor will ensure that all data in the CRF are correct and complete. Before or between visits, the medical monitor or study monitor may request copies of the CRFs for preliminary medical review. Once the CRFs are complete and source-verified, the investigator must sign and date all required pages, verifying the accuracy of all data contained within the CRF. Training will be provided on proper completion of CRFs.

If electronic CRFs are used, training will be provided for the electronic data capture (EDC) system. All personnel using the EDC system must have appropriate education, training, and experience. The investigator will be provided with standard operating procedures (SOPs) (contained in the SPM or a vendor-specific SOP) on the use of the EDC system. The investigator will be responsible for documenting employee education, training, and previous experience that pertains to the EDC system.

The investigator must maintain adequate security of the EDC system, including documentation that all users have been trained on the appropriate SOPs and a list of authorized users. To ensure attributability, all personnel responsible for data entry must obtain a unique electronic signature before any data can be entered in the CRFs. The system must be configured to ensure that the signer cannot readily repudiate the signed record as not genuine. Authorized study personnel will be assigned a unique password and associated electronic signature after receiving SOP training.

If EDC systems other than those provided and maintained by the sponsor are used for documentation and data capture, the investigator must ensure that the systems are validated and ensure data backup as described in Section 9.2.

8.2 STATISTICAL ANALYSIS

8.2.1 General Overview

The data will be summarized in tables listing the mean, standard deviation, median, minimum, maximum and number of subjects in a group for continuous data; in tables listing count and percentage for categorical data; and median and standard error for time-to-event data. Data will be listed for each subject. All statistical analyses will be performed and data appendices will be created by using SAS. The effects of noncompliance, dropouts, and covariates will be assessed to determine the impact on the general applicability of results from this study. All hypothesis tests will be one-sided with alpha set to 0.15 for each test. There will be no adjustment for multiple comparisons.

The primary analysis of the study will be performed using data collected prior to the roll-over of Arm B patients to Arm A. The final study analysis will be performed upon study completion. Further details of the analysis, including the handling of missing data transformations, further modifications to populations of analysis, and data handling procedures for roll-over and re-treated subjets will be provided in separate SAPs.

8.2.2 Populations of Interest

The full analysis set (FAS) follows an intention-to-treat principle and includes all randomized subjects who receive at least one dose of cyclophosphamide. All efficacy endpoints will be assessed for the FAS. FAS analyses will be conducted on the basis of the treatment actually received for the primary analysis, since this is a Phase 2 study. The final study analysis SAP will describe the analytic strategy used to summarize efficacy data by treatment for roll-over and re-treated subjects.

The per protocol population is defined as all subjects in the FAS who receive at least three doses of the first cycle on the original treatment arm (at least one dose of CRS-207 in Treatment Arm A or three doses of cyclophosphamide/GVAX pancreas vaccine in Treatment Arm B). Additional exploratory analyses will be conducted for those subjects who reach the time of the second CRS-207 dose, those who reach the time of the third, and those of the fourth.

Subjects with major protocol violations will be excluded from the per protocol population. The precise reasons for excluding subjects from the per protocol set will be fully defined and documented before database lock.

The safety population comprises all subjects randomized into the study who received any CTM. Safety analyses will be based on what CTM was actually administered for the primary analysis. The final study analysis SAP will describe the analytic strategy used to summarize safety data by treatment for roll-over and re-treated subjects.

8.2.3 Baseline Comparability

Demographics and baseline clinical variables for subjects in each treatment group will be summarized in tables, figures, and descriptive statistics to evaluate the balance achieved by randomization. All differences will be interpreted for their clinical significance and potential use as covariates in sensitivity analyses of efficacy endpoints.

8.2.4 Efficacy Analysis

Efficacy analysis will be conducted on full analysis and per protocol populations. Standard adjustments to analyses for pre-specified or baseline clinical covariates will be performed; these covariate-adjusted analyses will be considered secondary analyses. Efficacy results will be declared statistically significant if the one-sided p-value is less than 0.15. Study success will be determined by the FAS; per protocol assessment is secondary.

The primary efficacy parameter is overall survival. The primary analysis of this parameter will consist of a log-rank test with one-sided overall (i.e., accounting for the interim analysis) $\alpha = 0.15$. As exploratory analyses, a Cox proportional hazards model will be used to evaluate the effect of covariates on overall survival.

Exploratory efficacy variables are tumor response, and relationship of response to *Lm*- and mesothelin-specific immunological responses, and tumor marker kinetics. Tumor response will be assessed descriptively.

8.2.5 Safety Analysis

AE data will be listed individually and incidence of AEs summarized by system organ class and preferred terms within a system organ class for each treatment group. When calculating the incidence of AEs, each AE (based on preferred terminology defined by Medical Dictionary for Regulatory Activities, Version 13.1, or the most current version) will be counted only once for a given subject. In analyses of grade and causality, if the same AE occurs on multiple occasions, the highest grade and strongest relationship to study drug will be assumed. If two or more AEs are reported as a unit, the individual terms will be reported as separate experiences. Vaccine-site reactions will be listed and tabulated separately from the AEs.

Changes in vital signs, hematology, and clinical chemistry parameters from baseline to the end of the study will be examined. Treatment-emergent changes from normal to abnormal values in key laboratory parameters will be identified.

8.2.6 Pharmacokinetic Analysis

No formal pharmacokinetic or pharmacodynamic analyses are planned for the investigational agents used in this study.

8.2.7 Interim Analysis

Safety analyses will be performed throughout the study by a safety review committee composed of Aduro, the investigator, the medical monitor, and the DMC after the first 10, 20, 40, 60, and 90 subjects are enrolled.

An interim analysis for early stopping for efficacy or for futility will be performed after 41 deaths occur. The interim analysis will include stopping rules for overwhelming efficacy as well as for futility. If the analysis shows that the study has reached its efficacy stopping criteria or is highly unlikely to show a benefit based on interim data, the study may be stopped.

The original statistical design is based on primary analysis of overall survival for the FAS is according to a 2-stage group sequential design with a single interim analysis at half the total study "information" (i.e., 83 deaths total; interim analysis after 41 deaths), and with O'Brien-Fleming-like alpha and beta spending

functions (gamma = –4). In order to stop the study at the interim analysis and conclude statistically significantly (alpha = 0.15, 1-sided) longer survival in the sequential treatment arm than in the control arm, a p-value less than 0.0179 is required. The cutoff for futility stopping is $p > 0.7329$. If the study is not stopped at the interim analysis, the p-value cutoff to support an efficacy conclusion at the final analysis is $p < 0.1468$. This preserves the overall alpha level for the primary endpoint analysis at 0.15. These computations and the power described below derive from the EAST5.4 software.

During the trial, the timing of the final analysis was modified to be conducted after 70 events were observed in the primary analysis population (FAS). The justification for this change is that the overall study power will be preserved at an acceptable level (80% power) with a lower number of events (n = 70) compared to the number of events originally planned for (n=83, overall study power of approximately 85%). Further details on this modification to the originally planned analysis can be found in the statistical analysis plan.

8.2.8 Data Monitoring Committee

This is an open-label Phase 2 study. An independent DMC will review AEs, clinical laboratory results, and other study safety data as requested by the sponsor and as described in Section 8.2.7. The DMC will also review the interim efficacy analysis data and provide recommendations on continuation of the study to the sponsor. Specific responsibilities and requirements will be detailed in the DMC charter.

8.2.9 Sample Size

At least 90 subjects will be enrolled during 18 months and followed for approximately 27 months (this includes a treatment period between 1 day and 20 weeks in duration and a 24 month post-treatment follow-up period). For the FAS, if the true median survival for the sequential treatment is 8.1 months, and that for GVAX alone is 5 months, the sample size of N = 90 has approximately 85% power to yield a statistically significant difference (alpha = 0.15, 1-sided). This is based on an assumed enrollment rate of five patients per month. Power is computed for a 2-stage group sequential design with a single interim analysis at half the total study "information" (i.e., 83 deaths total; interim analysis after 41 deaths), and with O'Brien-Fleming–like alpha spending function (gamma= –4).

Details of the group sequential design and stopping criteria will be provided in the DMC charter or the statistical analysis plan, which will be written after protocol approval.

As noted in Section 8.2.7, the timing of the final analysis has been modified to be conducted after 70 events. Therefore, for the FAS, if the true median survival for the sequential treatment is 8.1 months, and that for GVAX alone is 5 months, the sample size of N = 70 has approximately 80% power to yield a statistically significant difference (alpha = 0.15, 1-sided). Further details on this modification to the originally planned analysis can be found in the statistical analysis plan.

9.0 CLINICAL STUDY ADMINISTRATION

9.1 INFORMED CONSENT AND AUTHORIZATION FOR USE AND DISCLOSURE OF PROTECTED HEALTH INFORMATION

Written informed consent and authorization of use and disclosure of PHI must be obtained from each subject (or the subject's legally authorized representative) before performing any study-specific screening/baseline period evaluations. One copy of the signed ICF and authorization for use and disclosure of the PHI form will be given to the subject, and the investigator will retain the original. The ICF and authorization for use and disclosure of PHI, which is prepared by the investigator or the site, must be reviewed and approved by Aduro, the study monitor (if applicable), and the site's IRB before the initiation of the study. The ICF must contain the 20 elements of informed consent described in ICH E6, Section 4.8. The authorization for use and disclosure of PHI must contain the elements required by Title 45 of the Code of Federal Regulations (CFR), Section 164.508(b), for valid authorizations. Appendix C provides further details about the specific requirements for informed consent.

9.2 STUDY DOCUMENTATION

9.2.1 Investigator Information

Investigator information is included in the SPM, which is updated as needed.

9.2.2 Investigator Study Files

Documentation about the investigator and study staff, the IRB, and the institution, is required before study site initiation (Appendix D). Copies of these documents as well as supplemental information, such as the investigator's obligations, IB, clinical study protocol and amendments, safety information, CTM, biological samples, laboratory, SPM and study logs, monitoring activities, sponsor/investigator/study monitor correspondence, will be kept on-site in study site-specific binders.

Aduro will be responsible for maintaining backup of all CRF data. The investigator is responsible for maintaining backup of all electronic data systems used for primary documentation or source documentation. Backup of electronic

data will be performed periodically as described in the site-specific SOPs. Backup records must be stored at a secure location on site, and backup and recovery logs must be maintained to facilitate data recovery. Finally, if an electronic medical records system that is not supported by the sponsor (or is discontinued or decommissioned) is used, the investigator must maintain a system to retrieve these records or arrange for the transfer of these records to an alternate electronic format or to paper.

Changes to any electronic records requires an audit trail, in accordance with 21 CFR 11.10(e), and should include who made the changes and when and why the changes were made. An audit trail is defined as a secure, computer-generated, time-stamped electronic record that will allow reconstruction of the course of events relating to the creation, modification, and deletion of an electronic record. Audit trails must be created incrementally, in chronological order, and in a manner that does not allow new audit trail information to overwrite existing data. Finally, audit trails should be in a readable format and readily available at the study site and any other location where electronic study records are maintained.

Audit trails are generated automatically for electronic CRFs. The investigator is responsible for maintaining audit trails of all electronic data systems used for primary documentation or source documentation.

9.2.3 Case Report Forms and Source Documentation

The investigator must make study data accessible to the site monitor, to other authorized representatives of Aduro, and to the appropriate regulatory authority inspectors. The original CRF for each subject will be checked against source documents at the study site by the site monitor.

9.2.4 Retention of Study Documents

According to ICH E6, Section 4.9, all CRFs, as well as supporting paper and electronic documentation and administrative records, must be retained by the investigator for a minimum of 2 years after notification that the appropriate regulatory authority has approved the product for the indication under study, notification that the entire clinical investigation will not be used in support of a marketing application, or notification that the marketing application was not approved. No study documents will be destroyed or moved to a new location

without prior written approval from Aduro. If the investigator relocates, retires, or withdraws from the clinical study for any reason, all records required to be maintained for the study should be transferred to an agreed-upon designee, such as another investigator at the institution where the study was conducted.

Audit trails for electronic documents must be retained for a period at least as long as that required for the subject electronic records to which they pertain. The investigator must retain either the original or a certified copy of audit trails.

9.3 CONFIDENTIALITY

9.3.1 Data

All information about the nature of the proposed investigation provided by Aduro or the study monitor to the investigator (with the exception of information required by law or regulations to be disclosed to the IRB, the subject, or the appropriate regulatory authority) must be kept in confidence by the investigator.

9.3.2 Subject Anonymity

The anonymity of participating subjects must be maintained. Subjects will be identified by their initials and an assigned subject number on CRFs and other documents retrieved from the site or sent to the study monitor, Aduro, regulatory agencies, or central laboratories/reviewers. Documents that identify the subject (e.g., the signed ICF) must be maintained in strict confidence by the investigator, except to the extent necessary to allow auditing by the appropriate regulatory authority, the study monitor, or Aduro representatives.

9.4 PROTOCOL COMPLIANCE

Substantive changes in the protocol include changes that affect the safety of subjects or changes that alter the scope of the investigation, the scientific quality of the study, the experimental design, dosages, assessment variable(s), the number of subjects treated, or the subject selection criteria. Such changes must be prepared as a protocol amendment by Aduro only upon joint approval of the changes by Aduro and the investigator. A protocol amendment must receive IRB approval before implementation. In parallel with the IRB approval process, the protocol amendment will be submitted to the appropriate regulatory authority as

an amendment to the regulatory submission under which the study is being conducted. If a protocol amendment requires changes in the ICF, the revised ICF prepared by the investigator must also be approved by Aduro, the study monitor, and the IRB before implementation.

Emergency departures from the protocol that eliminate an apparent immediate hazard to a particular subject and that are deemed crucial for the safety and well-being of that subject may be instituted for that subject only. The investigator or the attending physician also will contact the medical monitor as soon as possible in the case of such a departure. These departures do not require preapproval by the IRB; however, the IRB and the medical monitor must be notified in writing as soon as possible after the departure has been made. In addition, the investigator will document in the subject's CRF the reasons for the protocol deviation and the ensuing events.

9.5 STUDY MONITOR FUNCTIONS AND RESPONSIBILITY

The study monitor, in accordance with Aduro's requirements, will ensure that the study is conducted and documented properly by carrying out the relevant activities outlined in ICH E6, Section 5.18.4.

9.6 GENERAL INFORMATION

The investigator should refer to the IB, product labels, and the SPM, any other information provided during the study initiation visit or by the study monitor, and the appendices of this protocol for further information about this investigational new product or details of the procedures to be followed during the course of this study.

10.0 REFERENCES

1. Evans, D.B., R.T. and J.L. Abbruzzese, Cancer of the Pancreas, J.B. Lippincott, Editor. 1997: Philadelphia, PA. p. 1054-1087.

2. Sener, S.F., et al., Pancreatic cancer: a report of treatment and survival trends for 100,313 patients diagnosed from 1985-1995, using the National Cancer Database. J Am Coll Surg, 1999. 189(1): p. 1-7.

3. Ferlay, J. and F. Bray, Cancer incidence, mortality and prevalence worldwide, Lyon, IARCPress: GLOBOCAN 2000. p. IARC CancerBase No. 5.

4. Burris III, H.A., et al., Improvements in survival and clinical benefit with gemcitabine as first-line therapy for patients with advanced pancreas cancer: a randomized trial. J Clin Oncol, 1997. 15(6): p. 2403-2413.

5. Friberg, G. and H.L. Kindler, Chemotherapy for advanced pancreatic cancer: past, present, and future. Curr Oncol Rep, 2005. 7(3): p. 186-195.

6. Moore, M.J., Brief communication: a new combination in the treatment of advanced pancreatic cancer. Semin Oncol, 2005. 32(6 Suppl 8): p. 5-6.

7. Freelove, R. and A.D. Walling, Pancreatic cancer: diagnosis and management. Am Fam Physician, 2006. 73(3): p. 485-492.

8. Eckel, F., G. Schneider, and R.M. Schmid, Pancreatic cancer: a review of recent advances. Expert Opin Investig Drugs, 2006. 15(11): p. 1395-1410.

9. Benson III, A.B., Adjuvant therapy for pancreatic cancer: one small step forward. JAMA, 2007. 297(3): p. 311-313.

10. Offringa, R., Cancer immunotherapy is more than a numbers game. Science, 2006. 314(5796): p. 68-69.

11. Koon, H. and M. Atkins, Autoimmunity and immunotherapy for cancer. N Engl J Med, 2006. 354(7): p. 758-760.

12. Laheru, D. and E.M. Jaffee, Immunotherapy for pancreatic cancer - science driving clinical progress. Nat Rev Cancer, 2005. 5(6): p. 459-467.

13. Slifka, M.K., et al., Antiviral cytotoxic T-cell memory by vaccination with recombinant Listeria monocytogenes. J Virol, 1996. 70(5): p. 2902-2910.

14. Shen, H., et al., Recombinant Listeria monocytogenes as a live vaccine vehicle for the induction of protective anti-viral cell-mediated immunity. Proc Natl Acad Sci U S A, 1995. 92(9): p. 3987-3991.

15. Portnoy, D.A., V. Auerbuch, and I.J. Glomski, The cell biology of Listeria monocytogenes infection: the intersection of bacterial pathogenesis and cell-mediated immunity. J Cell Biol, 2002. 158(3): p. 409-414.

16. Bahjat, K.S., et al., Cytosolic entry controls CD8+-T-cell potency during bacterial infection. Infect Immun, 2006. 74(11): p. 6387-6397.

17. Brockstedt, D.G., et al., Listeria-based cancer vaccines that segregate immunogenicity from toxicity. Proc Natl Acad Sci U S A, 2004. 101(38): p. 13832-13837.

18. Hassan, R., T. Bera, and I. Pastan, Mesothelin: a new target for immunotherapy. Clin Cancer Res, 2004. 10(12 Pt 1): p. 3937-3942.

19. Hassan, R., et al., Mesothelin is overexpressed in pancreaticobiliary adenocarcinomas but not in normal pancreas and chronic pancreatitis. Am J Clin Pathol, 2005. 124(6): p. 838-845.

20. Argani, P., et al., Mesothelin is overexpressed in the vast majority of ductal adenocarcinomas of the pancreas: identification of a new pancreatic cancer marker by serial analysis of gene expression (SAGE). Clin Cancer Res, 2001. 7(12): p. 3862-3868.

21. Jaffee, E.M., et al., Novel allogeneic granulocyte-macrophage colony-stimulating factor-secreting tumor vaccine for pancreatic cancer: a phase I trial of safety and immune activation. J Clin Oncol, 2001. 19(1): p. 145-156.

22. Thomas, A.M., et al., Mesothelin-specific CD8(+) T cell responses provide evidence of in vivo cross-priming by antigen-presenting cells in vaccinated pancreatic cancer patients. J Exp Med, 2004. 200(3): p. 297-306.

23. Laheru, D., et al., Allogeneic granulocyte macrophage colony-stimulating factor-secreting tumor immunotherapy alone or in sequence with cyclophosphamide for metastatic pancreatic cancer: a pilot study of safety, feasibility, and immune activation. Clin Cancer Res, 2008. 14(5): p. 1455-1463.

24. Jaffee, E.M., et al., Development and characterization of a cytokine-secreting pancreatic adenocarcinoma vaccine from primary tumors for use in clinical trials. Cancer J Sci Am, 1998. 4(3): p. 194-203.

25. Jaffee, E.M., et al., A phase I clinical trial of lethally irradiated allogeneic pancreatic tumor cells transfected with the GM-CSF gene for the treatment of pancreatic adenocarcinoma. Hum Gene Ther, 1998. 9(13): p. 1951-1971.

26. Jaffee, E.M., et al., High efficiency gene transfer into primary human tumor explants without cell selection. Cancer Res, 1993. 53(10 Suppl): p. 2221-2226.

27. Berd, D., H.C. Maguire Jr, and M.J. Mastrangelo, Induction of cell-mediated immunity to autologous melanoma cells and regression of metastases after treatment with a melanoma cell vaccine preceded by cyclophosphamide. Cancer Res, 1986. 46: p. 2572-2577.

28. Holmberg, L.A. and B.M. Sandmaier, Theratope vaccine (STn-KLH). Expert Opin Biol Ther, 2001. 1(5): p. 881-891.

29. Ercolini, A.M., et al., Recruitment of latent pools of high-avidity CD8(+) T cells to the antitumor immune response. J Exp Med, 2005. 201(10): p. 1591-1602.

30. Emens, L.A., et al., Timed sequential treatment with cyclophosphamide, doxorubicin, and an allogeneic granulocyte-macrophage colony-stimulating factor-secreting breast tumor vaccine: a chemotherapy dose-ranging factorial study of safety and immune activation. J Clin Oncol, 2009. 27(35): p. 5911-5918.

31. Wolchok, J.D., et al., Guidelines for the evaluation of immune therapy activity in solid tumors: immune-related response criteria. Clin Cancer Res, 2009. 15(23): p. 7412-7420.

32. Controlling occupational exposure to hazardous drugs. Occupational Safety and Health Administration. Am J Health Syst Pharm, 1996. 53(14): p. 1669-1685.

APPENDICES

APPENDIX A

RESPONSE EVALUATION CRITERIA IN SOLID TUMORS (RECIST) QUICK REFERENCE

Apply RECIST 1.1 criteria to tumor assessment and record on CRF.

	RECIST 1.1
Measurable Tumor Burden	A maximum of 5 target lesions in total (and up to 2 per organ) can be identified at baseline and measured through the course of therapy.
Minimum Size of Measurable Lesions	≥ 10 mm in longest diameter (LD) and 2X the slice thickness for extranodal lesions ≥ 15 mm in short axis diameter (SAD) for nodal lesions ≥ 10 mm in LD for clinical lesions (must be measured using electronic calipers) ≥ 20 mm in LD for chest X-ray (if clearly defined & surrounded by aerated lung); CT is preferable Ultrasound (US) cannot be used to measure lesions
Lymph Nodes	Lymph nodes are considered pathologically enlarged if >10 mm in SAD. To be measurable, nodal lesions must be ≥ 15 mm in SAD. Nodal lesions with SAD >10 mm and <15 mm are non-measurable. The sum of the diameters (LD for extranodal target lesions, SAD for nodal lesions) is followed through the course of therapy.
Bone Lesions	A lytic or mixed lytic-blastic bone lesion with a soft tissue component assessed on CT/MRI can be measurable if the minimum size criteria are met. Blastic bone lesions and bone lesions assessed on bone scan, positron emission therapy (PET) or plain films are non-measurable.
Cystic Lesions	Lesions that meet the criteria for radiographically defined simple cysts are not malignant. Cystic lesions thought to be metastases can be measurable if they meet the minimum size criteria. Non-cystic lesions are preferable.
Lesions with Prior Local Treatment	Lesions in previously irradiated areas (or areas treated with local therapy) are not measurable unless the lesion has progressed since therapy. Conditions should be defined in study protocols.
Too Small To Measure	If a target lesion becomes too small to measure, a default value of 5 mm is assigned. If the lesion disappears, the measurement is recorded as 0 mm.
Lesions which split or Coalesce	If extranodal target lesions fragment, the LDs of the fragmented portions are added to the sum. If target lesions coalesce and cannot be distinguished, the LD of the coalesced lesion is added to the sum.
Definition of Complete Response (CR)	CR requires the disappearance of all extranodal lesions, the regression of all nodal lesions to <10 mm SAD and the normalization of tumor marker level.

	RECIST 1.1
Definition of Progressive Disease (PD)	PD is assessed if the sum of the diameters has increased by ≥ 20% and ≥ 5 mm from nadir (including baseline if it is the smallest sum). Patients with measurable disease: for "unequivocal progression" based on non-target disease, there must be an overall level of substantial worsening that merits discontinuation of therapy (if target disease is SD/PR). Patients without measurable disease: for "unequivocal progression" of non-target disease, the increase in overall tumor burden must be comparable to the increase required for PD of measurable disease.
Assessment of New Lesions	New lesions should be unequivocal and not attributable to differences in scanning technique or findings which may not be tumor (i.e. 'new' bone lesions may be healing or flare of pre-existing lesions). If on is equivocal, repeat scans are needed to confirm. If confirmed, PD is assessed at the date of the initial scan. Lesions identified in anatomic locations not scanned at baseline are considered new. New lesions on US should be confirmed on CT/MRI.
FDG-PET	New lesions can be assessed using FDG-PET :(-) PET at baseline and (+) PET at follow-up is PD based on a new lesion. No PET at baseline and (+) PET at follow-up is PD if the new lesion is confirmed on CT. If a subsequent CT confirms the new lesion, the date of the PD is the date of the initial PET scan. No PET at baseline and (+) PET at follow-up corresponding to pre-existing lesion on CT that is not progressing; not PD.
Recurrence of lesions	For a patient with SD/PR, a lesion which disappears and then reappears will continue to be measured and added to the sum. Response will depend upon the status of the other lesions. For a patient with CR, reappearance of a lesion would be considered PD.
Overall Response	One overall response table integrates target, non-target and new lesions and another table integrates non-target and new lesions for the assessment of subjects without measurable disease.
Confirmation of Response	Confirmation of PR/CR is ONLY required for non-randomized trials where response is the primary endpoint. In these trials, subsequent confirmation of PR with one interim time point of SD is acceptable.

APPENDIX B

IMMUNE-RELATED RESPONSE CRITERIA (IRRC) QUICK REFERENCE

Comparison between RECIST 1.1 criteria and the irRC[31]

	RECIST 1.1	irRC RECIST 1.1
New, measurable lesions (i.e., ≥ 5mm)	Always represent PD	Incorporated into tumor burden
New, non-measurable lesions (i.e., < 5mm)	Always represent PD	Does not define progression (but precludes irCR)
Non-index lesions	Changes contribute to defining best overall response (BOR) of CR, PR, SD, and PD	Contribute to defining irCR (complete disappearance required)
CR	Disappearance of all lesions in two consecutive observations not less than 4 week apart	Disappearance of all lesions in two consecutive observations not less than 4 week apart if single arm trial and primary endpoint only
PR	> or = 30% decrease in the sum of the diameters of all index lesions compared with baseline in two observations at least 4 week apart, in absence of new lesions or unequivocal progression of non-index lesions	≥ 30% decrease in tumor burden compared with baseline in two observations at least 4 week apart if single arm trial and primary endpoint only
SD	< 30% decrease in sum of longest diameters of all index lesions compared with baseline cannot be established nor < 20% increase compared with nadir, in the absence of new lesions or unequivocal progression of non-index lesions	< 30% decrease in tumor burden compared with baseline cannot be established nor < 20% increase compared with nadir
PD	At least 20% increase in the sum of the longest diameters of index lesions and/or unequivocal progression of non-index lesions	At least 20% increase in tumor burden compared with nadir (at any single time point) in two consecutive observations at least 4 week apart

	RECIST 1.1	irRC RECIST 1.1
Handling of lymph nodes	Lymph nodes are considered pathologically enlarged if > 10 mm in SAD. To be measurable, nodal lesions must be ≥ 15 mm in SAD. Nodal lesions with SAD > 10 mm and < 15 mm are non- measurable. The sum of the diameters (LD for extranodal target lesions, SAD for nodal lesions) is followed through the course of therapy	Not differentiated from other tumor measurements

Derivation of irRC Overall Responses[31]
(Modified for RECIST 1.1. Criteria)

Measurable response	**Non-measureable response**		**Overall response**
Index and new, measurable lesions (tumor burden)* %	Non-index lesions	New, non-measurable lesions	Using irRC
↓ 100	Absent	Absent	irCR/\
↓ 100	Stable	Any	irPR/\
↓ 100	Unequivocal progression	Any	irPR/\
↓ ≥ 30	Absent/ Stable	Any	irPR/\
↓ ≥ 30	Unequivocal progression	Any	irPR/\
↓ <30 to <20↑	Absent/ Stable	Any	irSD
↓ <30 to <20↑	Unequivocal progression	Any	irSD
≥ 20?	Any	Any	irPD/\

*Decreases assessed relative to baseline, including measurable lesions only (>5 x 5 mm).
/\Assuming response (irCR or irPR) and progression (irPD) are confirmed by a second consecutive assessment at least 4 weeks apart.

Defining immune-related Response Criteria by RECIST 1.1 criteria at 20 weeks (irDCR at 20 weeks):

1. Any patient with stable disease or progressive disease at any time in the trial with "rapid clinical deterioration" felt to be related to disease progression is irPD

2. Any patient who meets the criteria for RECIST 1.1 CR at 20 weeks is irCR

3. Any patient who meets the criteria for RECIST 1.1 PR at 20 weeks is irPR

4. Any patient who meets the criteria for RECIST 1.1 SD at 20 weeks is irSD

5. A patient with RECIST 1.1 PD but no rapid clinical deterioration may stay on study if his/her next tumor measurement evaluation is stable disease or better.

6. If patient has first time PD by RECIST 1.1 criteria, call it unconfirmed PD for irRC RECIST 1.1.

7. A patient with unconfirmed irPD at 20 weeks whose next tumor measurement is SD or better will be considered to be included in the irDCR at 6 months.

8. A patient with unconfirmed irPD at 20 weeks who fails to qualify for RECIST 1.1 SD or unconfirmed CR or PR by next tumor measurement will be considered to have RECIST 1.1 PD and irPD at 20 weeks.

APPENDIX C

PROTECTION OF HUMAN SUBJECTS (ICH E6, SECTION 4.8)

PROTECTION OF HUMAN SUBJECTS (ICH E6, SECTION 4.8)

Informed consent must be obtained from every subject before he enters a study. It must be given freely and not under duress. Consent must be documented by the subject or the subject's legally authorized representative signing an IRB/IEC-approved consent form. When minors are involved, a parent or guardian should sign the consent form. If the minor is an adolescent (12 to 16-18 years of age, dependent on region, as specified in ICH E11, Clinical Investigation of Medicinal Products in the Pediatric Population), his signature should also be included. Subjects who do not speak English must be presented with a consent form written in a language that they understand. A copy of the signed consent form must be given and made available to the sponsor and representatives of the appropriate regulatory authority upon request. If, for any reason, subject risk is increased as the study progresses, a revised IRB/IEC-approved consent form must be signed by the subject.

Nothing in these regulations is intended to limit the authority of a physician to provide emergency medical care to the extent the physician is permitted to do so under applicable federal, state, or local laws. Only in the case of a life-threatening incident may an investigational agent be used without prior signed consent. In such an emergency situation, separate certifications must be written both by a physician not participating in the study and by the investigator. The certifications, along with the protocol and informed consent, must be sent to the IRB/IEC within 5 working days. In this situation, the investigator may not administer any subsequent product to that subject until informed consent and IRB/IEC approval are obtained.

1.0 BASIC ELEMENTS OF INFORMED CONSENT

Every consent form must include explanations of each of the following 20 elements:

- That the study involves research
- The purpose of the study
- The study treatment(s) and the probability for random assignment to each treatment
- The study procedures to be followed, including all invasive procedures
- The subject's responsibilities

- Those aspects of the study that are experimental

- The reasonably foreseeable risks or inconveniences to the subject and, when applicable, to an embryo, fetus, or nursing infant

- The reasonably expected benefits; and when there is no intended clinical benefit to the subject, the subject should be made aware of this

- The alternative procedure(s) or course(s) of treatment that may be available to the subject, and their important potential benefits and risks

- The compensation or treatment available to the subject in the event of a study-related injury

- The anticipated prorated payment, if any, to the subject for participating in the study

- The anticipated expenses, if any, to the subject for participating in the study

- That the subject's participation in the study is voluntary and that the subject may refuse to participate or withdraw from the study, at any time, without penalty or loss of benefits to which the subject is otherwise entitled

- That the monitor(s), the auditor(s), the IRB/IEC, and the regulatory authority(ies) will be granted direct access to the subject's original medical records for verification of clinical study procedures or data, without violating the confidentiality of the subject, to the extent permitted by applicable laws and regulations and that, by signing a written informed consent form, the subject or the subject's legally acceptable representative is authorizing such access

- That the records identifying the subject will be kept confidential and, to the extent permitted by the applicable laws or regulations, will not be made publicly available; and if the results of the study are published, the subject's identity will remain confidential

- That the subject or the subject's legally authorized representative will be informed in a timely manner if information becomes available that may be relevant to the subject's willingness to continue participation in the study

- The person(s) to contact for further information regarding the study and the rights of study subjects, and whom to contact in the event of a study-related injury

- The foreseeable circumstances or reasons under which the subject's participation in the study may be terminated

- The expected duration of the subject's participation in the study

- The approximate number of subjects involved in the study

Nothing in these regulations is intended to limit the authority of a physician to provide emergency medical care to the extent the physician is permitted to do so under applicable federal, state, or local laws.

The informed consent requirements in these regulations are not intended to preempt any applicable federal, state, or local laws that require additional information to be disclosed in order that informed consent be legally effective. Some states require further action on the investigator's part concerning subject consent.

APPENDIX D

REQUISITE DOCUMENTS FOR APPROVAL OF STUDY SITE

REQUISITE DOCUMENTS FOR APPROVAL OF STUDY SITE

Clinical trial material will be provided to the investigators after they have submitted the following documents to the sponsor or study monitor (if applicable):

- Signed protocol and amendment(s) if applicable
- Signed Statement of Investigator, e.g., 1572 (if required by the regulatory agency)
- Institutional review board/independent ethics committee (IRB/IEC) committee composition
- Document indicating IRB/IEC approval of the final protocol and amendment(s) if applicable (to include name, address, and chairperson of the IRB/IEC)
- Document indicating IRB/IEC approval of the final and revised informed consent document if applicable (to include name, address, and chairperson of the IRB/IEC)
- Blank copy of the IRB/IEC-approved final and revised informed consent document
- Document indicating IBC approval of the final protocol if applicable (to include name, address, and chairperson of the IBC)
- Signed Investigator's Clinical Study Agreement and Confidentiality Disclosure Agreement
- Laboratory Certification or Accreditation and normal ranges for tests that are performed in the laboratory for study assessments
- *Curricula vitae* for the investigator and subinvestigator(s)
- Financial disclosure for the investigator and subinvestigator(s)

APPENDIX E

RESPONSIBILITIES AND OBLIGATIONS OF INVESTIGATORS AND SPONSORS

RESPONSIBILITIES AND OBLIGATIONS OF INVESTIGATORS AND SPONSORS

1.0 SPONSOR

The sponsor or designee will:

1.1 Conduct a pre-investigation site selection visit or study initiation visit to:

- Establish the acceptability of the facility and record the visit in a written report (i.e., memorandum or form).

- Discuss with the investigator the proposed clinical trial and supply him with draft electronic case report forms (CRFs), the Investigator's Brochure, and the draft protocol for his review and approval.

- Discuss with the investigator the regulatory requirements with respect to informed consent, institutional review board/independent ethics committee (IRB/IEC) approval of the trial, the protocol, protocol amendments, and changes to the informed consent document.

- Discuss with the investigator the timing of interim and final reports to the study monitor and his obligation to supply the study monitor with copies of all study-related documents (including IRB/IEC approval, IRB/IEC charter or equivalent, membership and qualifications, protocol amendments, informed consent documents, and consent changes), CRFs, CRF changes, and all pertinent correspondence to and from the IRB/IEC.

1.2 Conduct periodic on-site visit(s) to:

- Assure adherence to the protocol.

- Review CRFs and source documents for accuracy and completeness of information.

- Examine pharmacy records for documentation of quantity and date of receipt of investigational drug, dispensation and accountability data for product administration to each subject, loss of materials, contamination, and unused supplies.

- Record and report (summarize) observations on the progress of the study and continued acceptability of the facilities, and prepare an on-site visit report.

- Review investigator files for required documents, (e.g., protocols; protocol amendments; Investigator's Brochure; Study Procedures Manual; IRB/IEC approval of protocols, amendments, and informed consent document; IRB/IEC charter and membership; and communications to and from the IRB/IEC and the study monitor).

2.0 INVESTIGATOR

2.1 Institutional Review Board/Independent Ethics Committee

The investigator must assure the study monitor that the IRB/IEC:

- Meets ICH guidelines as defined in ICH E63: Institutional Review Board/Independent Ethics Committee.

- Has the authority delegated by the parent institution and found in the IRB/IEC by-laws, operation guidelines, or charter to approve or disapprove clinical trials and protocols, including informed consent and other documents (e.g., protocol amendments and information to be supplied to subjects concerning informed consent).

- Complies with proper personnel make-up of the board.

- Convenes meetings using acceptable rules of order for making decisions, recording such decisions, and implementing them.

- Maintains files that contain (a) documentation of its decisions, such as are found in IRB/IEC minutes and correspondence, (b) written guidelines or by-laws governing IRB/IEC functions, (c) protocol, (d) protocol amendments, (e) approved informed consent document and information to be supplied to the subject, and (f) correspondence between the IRB/IEC and investigator (e.g., consent changes, protocol amendments).

2.2 Informed Consent Human Subjects

The investigator must assure the study monitor that the informed consent document for a subject:

- Meets ICH guidelines as defined in ICH E6 4.8: Informed Consent of Trial Subjects.
- Has been approved by the IRB/IEC, including (when required) information to be given to the subject regarding the study in which he is enrolled.
- Includes the basic elements and any additional elements of informed consent that are appropriate.
- Has been signed by the subject (or his legally authorized representative), the investigator, and a witness, and a copy has been given to the subject.
- May be provided to the subject in the "short form" (presented orally to the subject or the subject's legally authorized representative, with a witness listening) informed consent document with written information as an alternative.
- Assent has been obtained for minor children as required by the IRB.

2.3 Storage and Dispensing of Product Supplies

The investigator (or his pharmacist) must assure the study monitor that:

- Adequate and accurate written records show receipt and disposition of all product supplies, including dates, serial or lot numbers, quantities received, and each quantity dispensed, administered, or used, with identification of each subject.
- Purpose and reasons are given in written records for product disposal (e.g., the amount contaminated, broken, or lost) and the quantity that was returned to the sponsor.

2.4 Electronic Case Report Forms

The investigator must assure the study monitor that:

- The completed CRF accurately reflects the hospital records for each subject.
- The CRFs and hospital records will be accessible to the study monitor during on-site visits.

2.5 Files and Records

The investigator must assure the quality, integrity, and content of his files, which will be subject to audit by the study monitor and the appropriate regulatory authority inspectors. The files must contain, as minimum the following:

- Investigator's Brochure
- Investigator's Obligations including the following:

  21 CFR Part 312.50 General Responsibilities of Sponsors

  21 CFR Part 312.60 General Responsibilities of Investigators

  21 CFR Part 50 Protection of Human Subjects

  21 CFR Part 56 Institutional Review Boards

  International Conference on Harmonisation, Good Clinical Practice, Consolidated Guidelines
- IRB/IEC - approved protocol and protocol amendments
- Blank CRFs (and amendments to CRF)
- Study Procedures Manual and amended pages
- Statement of Investigator Forms (copy of signed Form FDA 1572 and a copy of each revised form if required by the regulatory agency) and current Curricula Vitae and Bibliography for each investigator and subinvestigator

- IRB document including the following:

  IRB/IEC charter membership and qualifications of each member

  IRB letter of approval of protocol and amendments

  IRB letter of approval of informed consent form and amendments

  Investigator's annual report to the IRB

  IRB annual reapproval of protocol

  Reports to IRB of deaths and SAEs

  Notification to IRB of study completion and investigator's final report

  IRB approval of advertisements for subject recruitment (if applicable)

  All additional correspondence with the IRB/IEC

- IRB/IEC-approved informed consent document (all versions) and information to be supplied to the subject

- Study staff signature log

- Subject Accountability Records including the following:

  Subject Screening Log

  Medical Exceptions Log

  Site Status Report

  Subject Identification code list

  Original signed Informed Consent Form

  A note stating the location of the CRFs and Data Clarification Requests (DCRs)

- Clinical trial material records including the following:

  Receipt, date and quantity, and batch or lot number

  Disposition dates and quantity administered to each subject

  Inventory records

  All correspondence related to clinical trial material

- SAE/Safety Reports

  Copies of signed SAE Reporting Forms

  All SAE correspondence, including MedWatch and Form FDA 3500A

- Biological Sample Inventory forms and correspondence with the analytical lab

- Monitoring Activities

  Monitoring Log (should include all visits [i.e., study site initiation, periodic, and termination visits])

  Telephone contact reports

  Site initiation visit reports

- General Correspondence

  All correspondence between the study monitor, sponsor, and the site

  All correspondence within the site concerning the protocol

Documents and records must be retained by the investigator:

- For a period of 2 years after the date a marketing application is approved for the product for the indication for which it is being investigated,

OR

- Until there are no pending or contemplated marketing applications,

OR

- For a minimum of 2 years after discontinuations of the clinical investigation.

Summary of Protocol Changes
ADU-CL-01: Version 3 to Version 4

#	Protocol Section Title	Summary of Changes	Version 3 (06 July 2011)		Version 4 (10 April 2012)	
			Section #	Page #(s)	Section #	Page #(s)
1	General	• Changed name of Sponsor from Aduro BioTech to Aduro BioTech, Inc. (Aduro). • Minor updates to Sponsor Contact information were made. • Applicable changes were made to the Synopsis section to correspond with the modifications made in the text; however these changes are not listed separately in this Summary. • Minor editorial and typographical errors were corrected and not listed individually in this Summary.	N/A	N/A	N/A	N/A
2	Rationale	• Updated survival data on patients from the Phase 1 study.	1.2	5	1.2	5
3	Basic Design Characteristics	• Clarified follow-up period for subjects is every 3 months until death or up to 24 months. • Clarified that other tumor markers in addition to CA19-9 and CEA may be measured and followed.	3.1	9	3.1	9
4	Exclusion Criteria	• Exclusion Criterion (3) revised as follows: "Have artificial (prosthetic) joint(s), orthopedic screw(s), metal plate(s) or other exogenous implant(s) or device(s) that cannot be easily removed (i.e, prosthetic heart values). Commonly used devices and prosthetics which are allowed include (other devices or implants not specified can be considered with approval of the medical monitor): – Dental and breast implants (providing no history of prior or current infection of the implants and no clinically significant adverse event(s) associated with the implants) – Radioactive prostatic seeds – Coronary artery stents (placed at least 3 months previously, with no signs or symptoms related to the stents or ischemic heart disease associated with the stents after placement) – Body wall meshes (for repair of body wall defects, i.e. hernias, or post-surgical repair) – Biliary stents, gastrointestinal stents, and ureteral stents – Venous access devices (VAD) such as Mediports (although these devices cannot be used for infusion of CRS-207 or for phlebotomy for 4 days inclusive after CRS-207 infusion)." • Exclusion Criterion (6) revised from "Have radiographic or clinically significant pleural effusion" to : "Have clinically significant and/or malignant pleural effusion (Pleural effusions that are not clinically significant are allowed, defined as no more than 25% fluid level of the corresponding hemithorax and stable fluid level [non-progressive] over at least 6 weeks documented radiographically)"	3.2.2	11	3.2.2	11-12

#	Protocol Section Title	Summary of Changes	Version 3 (06 July 2011)		Version 4 (10 April 2012)	
			Section #	Page #(s)	Section #	Page #(s)
5	Dosing Eligibility	• Modified the dosing eligibility for AST and ALT to be up to 5.0 times the upper limit of normal within 72 hours prior to dosing on Day 1 of dosing weeks.	3.2.3	13	3.2.3	14
6	Primary Endpoints	• Clarified that the primary endpoint is overall survival, measured from first cyclophosphamide treatment until death or up to 24 months of follow-up for each subject.	3.3.1	13	3.3.1	14
7	Limiting Toxicities	• Revised criteria for clinically significant hypotension unresponsive to intravenous fluids from "…systolic BP <90 mm Hg or mean arterial pressure <55 mm Hg as measured on two separate occasions at least 3 minutes apart..." to ""…systolic BP <90 mm Hg or mean arterial pressure <55 mm Hg as measured on two separate occasions at least 10 minutes apart…" • Revised criteria for "Grade 3 laboratory abnormalities lasting >48 hours" to "Unexpected Grade 3 laboratory abnormalities lasting >48 hours" • Revised criteria for "Any other Grade 3 or greater event (except alopecia) according to National Cancer Institute's Common Terminology Criteria for Adverse Events (CTCAE) Version 4.03" to include lymphopenia and hypophosphatemia as exceptions to limiting toxicity criteria. • Added that unexpected Grade 3 laboratory abnormalities should be repeated within 24-72 hours "if clinically indicated and monitored as necessary to determine if event meets DLT criteria."	3.6	15-16	3.6	16
8	Dosing Instructions and Schedule	• Provided minor clarifications and additional details of preparation and administration of GVAX pancreas vaccine and CRS-207. • Specified that detailed instructions on the preparation of GVAX pancreas vaccine and CRS-207 for administration are provided in the pharmacy manual. • Added detailed descriptions of clinical observations that are to be expected following CRS-207 dosing.	4.2	18	4.2	18-20
9	Prior, Concomitant, and Excluded Therapy	• Added "Filgrastim (Neupogen or G-CSF) or Saragrastim (Leukine or GM-CSF)" to therapies not permitted during the treatment period.	4.5	21	4.5	23

#	Protocol Section Title	Summary of Changes	Version 3 (06 July 2011)		Version 4 (10 April 2012)	
			Section #	Page #(s)	Section #	Page #(s)
10	Overview: Schedule of Time and Events	• Notations for "Serum for Lm and mesothelin immunity" were corrected in the table to refer to footnote (p). • Footnote (b): added "If the Week 20 visit occurs early (as protocol allows), a telephone assessment for adverse events should be made on a day 28 (±1day) after the last study dose and documented." • Footnote (c): Clarified that all subjects will be followed every 3 months until death or up to 24 months. • Footnote (m): Added that "Other tumor markers may also be evaluated."	5.1	24-25	5.1	26-27
11	Screening Period	• Clarified that other tumor markers in addition to CA19-9 and CEA may be evaluated.	5.2.1	27	5.2.1	29

12	Cyclophosphamide Administration…	• Clarified that other tumor markers in addition to CA19-9 and CEA may be evaluated.
		• Modified to allow subjects to have blood drawn up to 72 hours before dosing for the following laboratory evaluations:
		  • Tumor marker CA19-9 and/or CEA (or other) assessment
		  • Blood draw for isolation of PBMCs
		  • Blood draw for L*m*- and mesothelin-specific immunity assays
		  • Blood draw for HL**A**-typing (Week 1, Day 1 only)
			5.2.2.1	28	5.2.2.1	30-31

13	GVAX Pancreas Vaccine Administration…	• Added pruritis and tenderness to list of injection-site reactions to be evaluated on Day 4 post-GVAX injection.	5.2.2.2	29	5.2.2.2	32

14	CRS-207 Administration…	• Clarified that other tumor markers in addition to CA19-9 and CEA may be evaluated.
		• Modified to allow subjects to have blood drawn up to 72 hours before dosing for the following laboratory evaluations:
		  • Tumor marker CA19-9 and/or CEA (or other) assessment
		  • Blood draw for isolation of PBMCs
		  • Blood draw for L*m*- and mesothelin-specific immunity assays
			5.2.2.3	30-31	5.2.2.3	32-33

15	Treatment Follow-up	• Added "If the Week 20 visit occurs early (as protocol allows), a telephone assessment for adverse events should be made on day 28 (±1 day) after last study dose and documented." • Clarified that other tumor markers in addition to CA19-9 and CEA may be evaluated.	5.2.3	32-33	5.2.3	34-35

#	Protocol Section Title	Summary of Changes	Version 3 (06 July 2011)		Version 4 (10 April 2012)	
			Section #	Page #(s)	Section #	Page #(s)
16	Study Follow-up Period	• Clarified follow-up period for subjects is every 3 months until death or up to 24 months.	5.2.5	33	5.2.5	36
17	Definition of an Adverse Event	• Clarified that "The investigator and clinical staff will record all AEs offered by the subject at baseline after first clinical trial material (CTM) administration, during administration of the CTM, and at the follow-up visits."	6.1	36	6.1	38
18	Recording Adverse Events and Serious Adverse Events	• Clarified that "All AEs and SAEs regardless of causality will be recorded through 28 days after final study treatment. During the study follow-up period, only serious adverse events (including deaths) considered possibly, probably or definitely related to investigational product will be reported."	6.3	38	6.3	40-41

19	Interim Analysis	• Modified to include a safety analysis by a safety review committee after the first 10 subjects are enrolled, in addition to the safety analyses performed after the first 20 subjects are enrolled and every 20 subjects thereafter.
		• Due to clarifications in the study follow-up period, the following statistical modifications were made:
		  • Revised number of required events (i.e., deaths) for interim analysis and final analysis to 41 and 83, respectively.
		  • Changed the p-value cut-off for stopping the study at the interim analysis and conclude statistically significantly longer survival in the sequential treatment arm than the control arm from $p<0.0225$ to $p<0.0179$
		  • Changed the p-value cut-off for futility stopping from $p>0.6824$ to $p>0.7336$.
		  • Changed the p-value cut-off to support an efficacy conclusion at the final analysis if the study is not stopped at the interim analysis from $p<0.1464$ to $p<0.1468$.
			8.2.7	49	8.2.7	52

20	Sample Size	• Study follow-up period, statistical power and number of required events for the interim and final analyses were updated.	8.2.9	50	8.2.9	53
21	Appendix B	• Removed references to WHO criteria	N/A	64-65	N/A	67-68

Summary of Protocol Changes
ADU-CL-01: Version 4 to Version 5

#	Protocol Section Title	Summary of Changes	Version 4 (10 April 2012)		Version 5 (16 Oct 2012)	
			Section #	Page # (s)	Section #	Page # (s)
1	General	• Minor editorial and typographical errors were corrected and not listed individually in this Summary. • Applicable changes were made to the Synopsis section to correspond with the modifications made in the text; however these changes are not listed separately in this Summary.	N/A	N/A	N/A	N/A
2	Exclusion Criteria	• Add criterion to exclude subjects that have received a prophylactic vaccine (e.g., influenza, pneumococcal, dTP/dTAP) within 28 days of study treatment.	3.2.2	10-13	3.2.2	10-13
3	Replacement of Dropouts	• Clarified that replacement subjects will be randomized in 2:1 ratio of Treatment Arm A to Treatment Arm B.	3.5	15	3.5	15
4	Prior, Concomitant and Excluded Therapy	• Added the following therapy not permitted during the treatment period: • Prophylactic vaccines (e.g., influenza, pneumococcal, Td/Tdap) within 1 week prior to or after study dosing (Note: prophylactic vaccines are discouraged for the duration of the treatment period and should be avoided if possible.)	4.5	22-24	4.5	22-24
5	Interim Analysis	• Clarified that safety analyses will be performed throughout the study by a safety review committee after the first 10, 20, 40, 60 and 90 subjects are enrolled.	8.2.7	51	8.2.7	51

Summary of Protocol Changes
ADU-CL-01: Version 5 to Version 6

#	Protocol Section Title	Summary of Changes	Version 5 (16 Oct 2012)		Version 6 (14 Dec 2012)	
			Section #	Page # (s)	Section #	Page # (s)
1	General	• Applicable changes were made to the Synopsis section to correspond with the modifications made in the text; however these changes are not listed separately in this Summary.	N/A	N/A	N/A	N/A
2	Basic Design Characteristics	• Clarified that subjects will be evaluated for survival and clinical and immunological responses in the long-term follow-up study. • Add the following language regarding treatment options at the conclusion of the study: "Subjects who are still receiving treatment at the time of study close, may complete the current treatment cycle (up to 6 doses) prior to transitioning to long-term follow-up."	3.1	9	3.1	9
3	Continuation of Additional Treatment Cycles	Specified the following modifications to the assessments for additional cycles: • Assessments done at Week 20 which are required at Day 1, Week 1 of the treatment cycle do not need to be repeated in duplicate if Day 1, Week 1 of the next cycle is started with 14 days of the Week 20 visit assessments. • HLA-typing does not need to be repeated at Day 1, Week 1 of additional cycles. • For sites that have the option of conducting a leukopheresis procedure under this study (or a related substudy), subjects who consent to leukopheresis during an additional cycle, are not required to provide the scheduled PBMC blood collections for that cycle.	5.2.4	35-36	5.2.4	35-36
5	Study Follow-up Period	• Clarified that subjects will be evaluated for survival and clinical and immunological responses in the long-term follow-up study. • Add the following language regarding treatment options at the conclusion of the study: "Subjects who are still receiving treatment at the time of study close, may complete the current treatment cycle (up to 6 doses) prior to transitioning to long-term follow-up."	5.2.5	36	5.2.5	36
6	Subject Discontinuation	• Clarified that replacement subjects will be randomized in a 2:1 ratio of Treatment Arm A to Treatment Arm B, according to a replacement randomization list generated by an independent statistician per Amendment #3 (version 5).	7.2	46	7.2	46

#	Protocol Section Title	Summary of Changes	Version 5 (16 Oct 2012)		Version 6 (14 Dec 2012)	
			Section #	Page # (s)	Section #	Page # (s)
7	Interim Analysis	• Added the following language to modify the timing of the final analysis: "During the trial, the timing of the final analysis was modified to be conducted after 70 events were observed in the primary analysis population (FAS). The justification for this change is that the overall study power will be preserved at an acceptable level (80% power) with a lower number of events (n = 70) compared to the number of events originally planned for (n=83, overall study power of approximately 85%). Further details on this modification to the originally planned analysis can be found in the statistical analysis plan."	8.2.7	51	8.2.7	51-52
8	Sample Size	• Added the following language to modify the timing of the final analysis: "As noted in Section 8.2.7, the timing of the final analysis has been modified to be conducted after 70 events. Therefore, for the FAS, if the true median survival for the sequential treatment is 8.1 months, and that for GVAX alone is 5 months, the sample size of N = 70 has approximately 80% power to yield a statistically significant difference (alpha = 0.15, 1-sided). Further details on this modification to the originally planned analysis can be found in the statistical analysis plan."	8.2.8	52	8.2.8	52-53

Summary of Protocol Changes
ADU-CL-01: Version 6 to Version 7

#	Protocol Section Title	Summary of Changes	Version 6 (14 Dec 2012)		Version 7 (28 Feb 2013)	
			Section #	Page # (s)	Section #	Page # (s)
1	General	• Applicable changes were made to the Synopsis section to correspond with the modifications made in the text; however these changes are not listed separately in this Summary.	N/A	N/A	N/A	N/A
2	Basic Design Characteristics	The following text was added: • "During the trial, a planned interim analysis for early stopping for efficacy or for futility was performed per protocol after 41 deaths occurred. At this planned interim efficacy analysis, the study was determined by the DMC to meet the criteria for early stopping for efficacy (see Section 8.2.7) and subjects currently on treatment in Arm B will be offered CRS-207 treatment. Subjects on Arm A and in follow-up will continue with treatment and in follow-up per protocol."	3.1	8	3.1	9
3	Rollover Treatment for Arm B Subjects	The following section was added: • "During the trial, a planned interim analysis for early stopping for efficacy or for futility was performed per protocol after 41 deaths occurred. At this planned interim efficacy analysis, the study was determined by the DMC to meet the criteria for early stopping for efficacy (see Section 8.2.7) and subjects currently on treatment in Arm B will be offered CRS-207 treatment. Subjects on Arm A and in follow-up will continue with treatment and in follow-up per protocol. Arm B subjects currently on treatment will have the option to either continue to receive cyclophosphamide/GVAX pancreas vaccine doses on the protocol schedule or to receive up to 4 doses of CRS-207 (see Figure 1). Subjects may choose to rollover to CRS-207 followed by combination cyclophosphamide/GVAX pancreas vaccine and CRS-207 (Arm A) treatment at any time during their Arm B treatment. The first dose of CRS-207 will be given at least 3 weeks after their last dose of cyclophosphamide/GVAX pancreas vaccine. The requirements, procedures and schedule for the CRS-207 dosing and follow-up will follow the Arm A protocol schedule starting with Week 7, Day 1. At the investigator's discretion, after 4 doses of CRS-207, subjects may continue to receive additional cycles of the Arm A treatment regimen starting with Week 1, Day 1 if they are clinically stable and meet dosing eligibility."	N/A	N/A	5.2.5	36

Summary of Protocol Changes
ADU-CL-01: Version 7 to Version 8

#	Protocol Section Title	Summary of Changes	Version 7 (28 Feb 2013)		Version 8 (06 Nov 2013)	
			Section #	Page # (s)	Section #	Page # (s)
1	General	• Applicable changes were made to the Synopsis section to correspond with the modifications made in the text; however these changes are not listed separately in this Summary.	N/A	N/A	N/A	N/A
2	Basic Design Characteristics	• Modified the follow-up period on study to have all subjects followed until "…study close, which occurs after all subjects have died or been on study for at least 24 months (from time of randomization)." • Added the following text to allow for re-treatment of subjects who have discontinued treatment but are currently in follow-up: "Additionally, subjects who receive at least one dose of study treatment, discontinue from treatment and are in follow-up on protocol, may be eligible for re-treatment with cyclophosphamide, GVAX pancreas vaccine and CRS-207 (Arm A) regardless of their original treatment assignment or response to previous protocol therapy. " • Modified text: "Subjects who are still receiving treatment <u>at the time of study close</u>, may complete the current treatment cycle (up to 6 doses) prior to transitioning to the long-term follow-up protocol."	3.1	9	3.1	9
3	Primary Endpoint	• Clarified that the "…primary endpoint is overall survival, measured from first cyclophosphamide treatment until death or <u>end of follow-up</u>."	3.3.1	14	3.3.1	14
4	Continuation of Additional Treatment Cycles	Added the following text: • "Schedule modifications to allow for longer intervals between vaccine doses (i.e., greater than 3 weeks between cyclophosphamide/GVAX pancreas dosing and/or CRS-207 dosing) will be considered for subjects on additional cycles. In any case, cyclophosphamide must be administered with 1 day prior to GVAX pancreas vaccine and vaccine doses should not be given less than 3 weeks or more than 8 weeks apart. Schedule modifications must be approved by the sponsor and medical monitor."	5.2.4	35	5.2.4	35

#	Protocol Section Title	Summary of Changes	Version 7 (28 Feb 2013)		Version 8 (06 Nov 2013)	
			Section #	Page # (s)	Section #	Page # (s)
5	Study Follow-up Period	Modified text to reflect changes in the study follow-up period: • "When subjects complete all study treatment, they will continue to be followed every 3 months (± 7 days) by phone or optional clinic visit for the duration of the study until death or study close to document subsequent cancer-related therapies, request CT scans to assess overall response rate, and monitoring of immune responses to *Lm* and mesothelin (at clinic visits only). At the time of study close, which occurs after all subjects have died or completed 24 months on study (from time of randomization), subjects will be offered enrollment in a long-term follow-up study and continue to be evaluated for survival and clinical and immunological responses. Subjects who are still receiving treatment at the time of study close may complete the current treatment cycle (up to 6 doses) prior to transitioning to the long-term follow-up protocol."	5.2.6	37	5.2.6	37
6	Re-treatment of Subjects Previously on Treatment	Added section regarding re-treatment of subjects previously on treatment: • "Subjects who received at least one dose of investigational product, discontinued treatment and are still in follow-up on protocol, may be eligible for re-treatment with cyclophosphamide, GVAX pancreas vaccine and CRS-207 if the investigator believes that the subject may benefit from receiving treatment. Subjects being considered for re-treatment must meet study eligibility criteria (Section 3.2) and must be approved by the sponsor, medical monitor and lead investigator. Subjects must have all screening assessments repeated (with the exception of height, demographics and baseline cancer history) within 4 weeks of start of re-treatment to confirm eligibility. All subjects offered re-treatment will receive Arm A treatment of cyclophosphamide, GVAX pancreas vaccine and CRS-207 at the same dose and schedule in this protocol regardless of their original treatment assignment or response to previous protocol therapy. Subjects will follow all procedures for Treatment Arm A dosing and follow-up visits per protocol (Table 4 and Section 5.2.2, with the exception that HLA-typing is not required to be repeated on Day 1). Subjects may receive a minimum of one cycle of treatment and may be eligible for additional treatments if they are clinically stable and meet dosing requirements for additional cycles (Section 5.2.4). The window for initiation of re-dosing subjects will close approximately 6 months before study close. Details of data collection and CRF completion will be provided separately."	5.2.7	N/A	5.2.7	38

#	Protocol Section Title	Summary of Changes	Version 7 (28 Feb 2013)		Version 8 (06 Nov 2013)	
			Section #	Page # (s)	Section #	Page # (s)
7	General Overview	• Added text: "The primary analysis of the study will be performed using data collected prior to the roll-over of Arm B patients to Arm A. The final study analysis will be performed upon study completion. Further details of the analysis, including the handling of missing data transformations, further modifications to populations of analysis, and data handling procedures for roll-over and re-treated subjets will be provided in separate SAPs." • Deleted text: "Further details of the analysis, including the handling of missing data transformations, and further modifications to populations of analysis will be provided in a separate statistical analysis plan."	8.2.1	50	8.2.1	51
8	Populations of Interest	• Modified text as follows: "FAS analyses will be conducted on the basis of the treatment actually received <u>for the primary analysis, since this is a Phase 2 study. The final study analysis SAP will describe the analytic strategy used to summarize efficacy data by treatment for roll-over and re-treated subjects</u>. • Clarified definition of per protocol population as: "The per protocol population is defined as all subjects in the FAS who receive at least three doses <u>of the first cycle on the original treatment arm</u>…" • Modified text as follows: "Safety analyses will be based on what CTM was actually administered <u>for the primary analysis. The final study analysis SAP will describe the analytic strategy used to summarize safety data by treatment for roll-over and re-treated subjects</u>."	8.2.2	50	8.2.2	51

INTERIM STATISTICAL ANALYSIS PLAN

Protocol ADU-CL-01

A Phase 2, Randomized, Multicenter, Open-Label Study of the Efficacy and Immune Response of the Sequential Administration of GVAX Pancreas Vaccine (with Cyclophosphamide) Alone or Followed by CRS-207 in Adults with Metastatic Pancreatic Adenocarcinoma

Protocol Number: **(Version Date)**	ADU-CL-01 14 December 2012, Version 6
Name of Test Drug(s):	CRS-207, GVAX Pancreas Vaccine
Phase:	2
Methodology:	The study is an open-label, randomized, multicenter clinical study in adults with metastatic pancreatic adenocarcinoma who have received or refused at least one chemotherapy treatment. At least 90 subjects will be enrolled and randomized in a 2:1 fashion into two treatment arms. Both treatment arms will receive up to six doses of vaccine 3 weeks apart (one cycle). Treatment Arm A will receive two doses of cyclophosphamide and GVAX pancreas vaccine and up to four doses of CRS-207. Treatment Arm B will receive up to six doses of cyclophosphamide and GVAX pancreas vaccine.
Sponsor:	Aduro BioTech, Inc. 626 Bancroft Way, #3C Berkeley, CA 94710-2224 USA
Sponsor Representative:	Aimee Murphy, Director of Clinical Operations 626 Bancroft Way, #3C Berkeley, CA 94710-2224 Phone: 510-848-4400 x106 Fax: 510-848-5614 E-mail: amurphy@adurobiotech.com
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Document Date: 20 December 2012

Document Version: 2.0

SIGNATURE PAGE

Protocol Title:	A Phase 2, Randomized, Multicenter, Open-Label Study of the Efficacy and Immune Response of the Sequential Administration of GVAX Pancreas Vaccine (with Cyclophosphamide) Alone or Followed by CRS-207 in Adults with Metastatic Pancreatic Adenocarcinoma
Sponsor:	Aduro BioTech, Inc. 626 Bancroft Way, #3C Berkeley, CA 94710-2224 USA
Protocol Number:	ADU-CL-01
Document Date/Version:	20 December 2012/v2.0

Cytel, Inc. Author:
Seth Zuckerman, M.S.
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955 Chesterbrook Blvd., Suite 113
Chesterbrook, PA 19087

Signature:_____

Date:_____

Sponsor Approval

By signing this document, I acknowledge that I have read the document and approve of the planned statistical analyses described herein. I agree that the planned statistical analyses are appropriate for this study, are in accordance with the study objectives, and are consistent with the statistical methodology described in the protocol, clinical development plan, and all applicable regulatory guidance's and guidelines.

I have discussed any questions I have regarding the contents of this document with the biostatistical author.

I also understand that any subsequent changes to the planned statistical analyses, as described herein, may have a regulatory impact and/or result in timeline adjustments. All changes to the planned analyses will be described in the clinical study report (CSR).

Sponsor Signatory:
Aimee Murphy
Director of Clinical Operations
626 Bancroft Way, #3C
Berkeley, CA 94710-2224

Signature:_____

Date:_____

SIGNATURE PAGE

Protocol Title: A Phase 2, Randomized, Multicenter, Open-Label Study of the Efficacy and Immune Response of the Sequential Administration of GVAX Pancreas Vaccine (with Cyclophosphamide) Alone or Followed by CRS-207 in Adults with Metastatic Pancreatic Adenocarcinoma

Sponsor: Aduro BioTech, Inc.
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Protocol Number: ADU-CL-01

Document Date/Version: 20 December 2012/v2.0

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Chesterbrook, PA 19087

Signature: Seth Zuckerman
Date: 21 Dec 2012

Sponsor Approval

By signing this document, I acknowledge that I have read the document and approve of the planned statistical analyses described herein. I agree that the planned statistical analyses are appropriate for this study, are in accordance with the study objectives, and are consistent with the statistical methodology described in the protocol, clinical development plan, and all applicable regulatory guidance's and guidelines.

I have discussed any questions I have regarding the contents of this document with the biostatistical author.

I also understand that any subsequent changes to the planned statistical analyses, as described herein, may have a regulatory impact and/or result in timeline adjustments. All changes to the planned analyses will be described in the clinical study report (CSR).

Sponsor Signatory:
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Signature: Aimee Murphy
Date: 21 Dec 2012

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ABBREVIATIONS

Abbreviation	Definition
AE	Adverse events
CSR	Clinical study report
CR	Complete Response
DMC	Data Monitoring Committee
ECG	Electrocardiogram
FAS	Full Analysis Set
FDA	Food and Drug Administration
ICH	International Conference on Harmonisation
ISP	Independent Statistical Provider
iSAP	Statistical Interim Analysis Plan
MedDRA	Medical Dictionary for Regulatory Activities
OS	Overall Survival
PR	Partial Response
PT	Preferred Term
SAE	Serious Adverse Event
SI	International System of Units
SOC	System Organ Class
TEAE	Treatment-emergent Adverse Event
TESAE	Treatment-emergent Serious Adverse Events
WHO	World Health Organization

1. INTRODUCTION AND OBJECTIVES OF ANALYSIS

1.1. Introduction

ADU-CL-01 is a phase 2, randomized, multicenter, open-label study of the efficacy and immune response of the sequential administration of GVAX pancreas vaccine (with cyclophosphamide) alone or followed by CRS-207 in adults with metastatic pancreatic adenocarcinoma. The study, as described in the protocol, has a single, pre-planned interim efficacy analysis by a Data Monitoring Committee (DMC). The sponsor has no involvement in the data analysis, interpretation, or recommendation.

1.2. Objectives of Statistical Analysis

This interim statistical interim analysis plan (iSAP) is designed to outline the methods to be used in the analysis of study data at the interim time point. Populations for analysis, data handling rules, statistical methods, and formats for data presentation are provided.

Unless otherwise noted, this document describes how the analyses will be handled for the interim analysis only. Documentation for the final analysis will be maintained in a separate statistical analysis plan.

The statistical analyses and summary tabulations described in this iSAP will provide the basis for the reporting of the results from the planned interim analysis for this trial.

Recommendations from ICH-E9[1] Guideline on Statistical Principals for Clinical Trials will be followed.

This iSAP also will outline any differences in the currently planned analytical objectives relative to those planned in the study protocol.

1.2.1. Primary Objective

The primary objective of this study is to evaluate overall survival (OS).

1.2.2. Secondary Objective

The secondary objective is to assess the safety of the cyclophosphamide, GVAX pancreas vaccine, and CRS-207 treatment regimen.

1.2.3. Exploratory Objectives

The exploratory objectives are:

- To assess the association of Listeria monocytogenes (*Lm*) and mesothelin-specific T-cell and other immunological responses with overall survival
- To evaluate overall response rate in subjects with measureable disease per Response Evaluation Criteria in Solid Tumors (RECIST) and immune-related response criteria (irRC)
- To measure tumor marker kinetics

2. STUDY DESIGN

2.1. Synopsis of Study Design

At least 90 subjects with metastatic pancreatic adenocarcinoma satisfying all eligibility criteria will be enrolled and randomized in a 2:1 fashion into the two treatment arms. Both treatment arms will receive up to six doses of vaccine 3 weeks apart (one cycle). Treatment Arm A will receive two doses of cyclophosphamide and GVAX pancreas vaccine and up to four doses of CRS-207. Treatment Arm B will receive up to six doses of cyclophosphamide and GVAX pancreas vaccine.

To monitor initial safety of the sequential vaccine regimen, no more than one subject will be enrolled per week for the first six subjects. If any limiting toxicities are observed during the study, the data will be reviewed with the Data Monitoring Committee (DMC) and the dose may be lowered to 1×10^8 colony-forming units (CFU) for all subsequent dosing with CRS-207.

Subjects will return to the study site approximately 4 weeks after their final treatment for safety and immune response evaluations. They will continue to be followed by phone or optional clinic visit for subsequent cancer-related therapies, overall response rate, and *Lm*- and mesothelin-specific immune responses (at clinic visits only) for the duration of the study until all subjects have reached at least 24 months of follow-up or death.

At the investigator's discretion, subjects may receive additional treatment cycles of the assigned treatment regimen if they are clinically stable and meet dosing requirements.

With an expected enrollment rate of five subjects per month, the accrual period would be 18 months, which, with the 24 months of follow-up of each subject, yields a maximum total study time of 42 months.

An interim analysis will be conducted after 41 subjects have died. The study may be terminated after that interim analysis if results meet pre-specified stopping criteria or if the DMC recommends stopping on the basis of clinical judgment and guidelines in the DMC charter and the sponsor accepts the recommendation.

The interim analysis will be conducted by an Independent Statistics Provider (ISP) and reviewed by the DMC.

2.2. Randomization Methodology

This is an open-label study. Subjects meeting all inclusion and exclusion criteria will be randomized 2:1 to one of two treatment arms according to a randomization list generated for each site by an independent statistician.

2.2.1. Unblinding

Not Applicable.

2.3. Stopping Rules and Unblinding

The interim analysis will be conducted after 41 subjects have died. After the targeted number of events have been observed, a "snap-shot" of the database will be cleaned and locked for the purposes of the interim analysis. After the interim database has been cleaned and locked, the independent statistician will produce the results to be presented to the DMC.

The DMC will be responsible for making a recommendation to the Sponsor to either continue with the study, to stop the study if unacceptable safety and/or efficacy have been observed, or to stop the study if overwhelming efficacy has been observed.

2.4. Study Procedures

The schedule of assessments is outlined in section 5.1 of the study protocol.

2.5. Interim Analysis Endpoints

2.5.1. Primary Efficacy Endpoint

The primary endpoint is overall survival, defined as the time between the date of randomization and the date of death. The primary analysis of this endpoint will consist of a log-rank test.

The primary efficacy interim analysis will be conducted after the required number of deaths have occurred (41 events). The 41st event is expected to occur approximately 21 months after randomization of the 1st subject.

2.5.2. Exploratory Efficacy Endpoints

2.5.2.1. Overall Response Rate

The secondary endpoint is the overall response rate, defined as the percentage of subjects whose response is CR or PR based on the Response Evaluation Criteria in Solid Tumors (RECIST) and the immune-related response criteria (irRC) (See Appendices A and B of the study protocol for full details on response criteria). Separate summaries of the overall response rate will be provided according to both sets of criteria.

2.5.2.2. Tumor Marker Kinetics

Assessments for tumor markers CA19-9 and CEA were conducted during the study and will be summarized in subject data listings. Other tumor markers may also be evaluated and will be provided in subject data listings.

2.5.3. Safety Variables

Safety assessments included physical examinations, measurement of vital signs, 12-lead electrocardiograms (ECGs), clinical laboratory evaluations including hematology and serum chemistry, concomitant medication usage, assessment of weight, pregnancy testing, and monitoring of adverse events.

The only physical exam data that will be collected will be abnormalities recorded as medical history or adverse events.

3. SUBJECT POPULATIONS

3.1. Population Definitions

The following subject populations will be evaluated and used for presentation and analysis of the data:

- Full Analysis Set (FAS): all randomized subjects who received at least 1 dose of cyclophosphamide.
- Safety Population: all randomized subjects who received any clinical trial material.
- Per-Protocol Population (PP): all subjects in the FAS who received at least 3 doses (at least one dose of CRS-207 in Treatment Arm A or three doses of cyclophosphamide/GVAX pancreas vaccine in Treatment Arm B).

A review of the treatment exposure data will be completed to determine if there were any subjects that did not receive clinical trial material. Any subjects not receiving clinical trial material will be fully documented in the final study report.

If all subjects are treated per the randomization schedule and receive at least 1 dose of cyclophosphamide, the Safety Population will be equivalent to the FAS population. In this scenario, the FAS population would be used for all analyses..

A distinct Safety Population will only exist if there are subjects that did not receive at least 1 dose of cyclophosphamide, but did receive other clinical trial material (i.e., GVAX or CRS-207).

The FAS Population is the primary population for the analysis of all efficacy parameters. If a distinct Safety Population exists, it will only be used for the analysis of safety parameters (unless otherwise requested by the DMC).

4. STATISTICAL METHODS

4.1. Sample Size Justification

At least 90 subjects will be enrolled during 18 months and followed for approximately 27 months (this includes a treatment period between 1 day and 20 weeks in duration and a 24 month post-treatment follow-up period). For the FAS, if the true median survival for the sequential treatment is 8.1 months, and that for GVAX alone is 5 months, the sample size of N = 90 has approximately 85% power to yield a statistically significant difference (alpha = 0.15, 1-sided). This is based on an assumed enrollment rate of five subjects per month. For the original statistical design, power was computed for a 2-stage group sequential design with a single interim analysis at approximately half the total study "information" (i.e., 83 deaths total; interim analysis after 41 deaths), and with an O'Brien-Fleming–like alpha spending function (gamma= –4)[2,3].

During the trial, the timing of the final analysis was modified to be conducted after 70 events were observed in the primary analysis population (FAS). The justification for this change is that the overall study power will be preserved at an acceptable level (80% power) with a lower number of events (n = 70) compared to the number of events originally planned for (n=83). Therefore, for the FAS, if the true median survival for the sequential treatment is 8.1 months, and that for GVAX alone is 5 months, the sample size of N = 70 has approximately 80% power to yield a statistically significant difference (alpha = 0.15, 1-sided).

4.2. General Statistical Methods and Data Handling

4.2.1. General Method

Tabulations will be produced for appropriate demographic, baseline, primary efficacy and safety parameters. For categorical variables, summary tabulations of the number and percentage within each category (with a category for missing data) of the parameter will be presented. For continuous variables, the N, mean, median, standard deviation, minimum and maximum values will be presented.

Formal statistical hypothesis testing will be performed on the primary endpoint with all tests conducted at the 1-sided, 0.15 level of significance. Summary statistics will be presented, as well as confidence intervals on selected parameters, as described in the sections below.

4.2.2. Computing Environment

All descriptive statistical analyses will be performed using SAS statistical software (Version 9.2 or higher). Adverse events will be coding using MedDRA version 12.0. Concomitant medications will be coded using World Health Organization (WHO) Drug version March 2010.

4.2.3. Methods of Pooling Data

Not applicable to the present study.

4.2.4. Adjustments for Covariates

No adjustments for covariates are planned for during the interim analysis.

4.2.5. Multiple Comparisons/Multiplicity

No adjustments for multiple comparisons will be applied for the interim analysis.

4.2.6. Subpopulations

No analyses of subgroups of subjects are planned for the interim analysis.

4.2.7. Withdrawals, Discontinuations, Lost to Follow-up

Subjects who withdraw consent or are removed from the study before completing one cycle of treatment will be considered dropouts and may be replaced at the discretion of Aduro BioTech, Inc. Subjects who have disease progression may be allowed to continue in the study if the investigator believes they are deriving some benefit from the therapy.

4.2.8. Missing and Unused Data

For safety data, there will be no substitutions made to accommodate missing data points. All data recorded on the Case Report Form (CRF) will be included in data listings.

4.2.9. Definition of Baseline and Dose 1 Date Values

For all assessments, Baseline is defined as the last non-missing measurement prior to randomization. Baseline assessments should be collected prior to dosing.

For most subjects dose 1 is assumed to be the same as the first drug administration date. A review of the data will be conducted to confirm that the dose 1 date is the same as the first drug administration date.

4.2.10. Change in Value from X to Y

Change in Value from X date to Y date = Value on Y date – Value on X date

4.3. Interim Analyses

The primary endpoint analysis will be performed per Section 4.8.1.

The interim analysis for early stopping for efficacy or for futility will be performed after 41 deaths occur. The interim analysis will include stopping rules for overwhelming efficacy as well as for futility. If the analysis shows that the study has reached its efficacy stopping criteria or is highly unlikely to show a benefit based on interim data, the study may be stopped.

The original statistical design was based on a primary analysis of overall survival for the FAS according to a 2-stage group sequential design with a single interim analysis at approximately half the total study "information" (i.e., 83 deaths total; interim analysis after 41 deaths), and with O'Brien-Fleming-like alpha and beta spending functions (gamma = –4). In order to stop the study at the interim analysis and conclude statistically significantly (alpha = 0.15, 1-sided) longer survival in the sequential treatment arm than in the control arm, a p-value less than 0.0179 was required. The cutoff for futility stopping was $p > 0.7329$. If the study was not stopped at the interim analysis, the p-value cutoff to support an efficacy conclusion at the final analysis was $p < 0.1468$. This preserved the overall alpha level for the primary endpoint analysis at 0.15. These computations were derived from EAST software (Version 5.4).

As noted in Section 4.1, the timing of the final analysis has been modified to be conducted after 70 events. Therefore, in order to stop the study at the interim analysis and conclude statistically significantly (alpha = 0.15, 1-sided) longer survival in the sequential treatment arm than in the control arm, a p-value less than 0.0263 is required. The cutoff for futility stopping is $p > 0.6395$. If the study is not stopped at the interim analysis, the p-value cutoff to support an efficacy conclusion at the final analysis is $p < 0.1461$. This preserves the overall alpha level for the primary endpoint analysis at 0.15. These computations were also derived from EAST software (Version 5.4).

4.4. Subject Disposition

Subject disposition will be tabulated by treatment group, including the number screened, the number in each subject population for analysis, reasons for subjects not being randomized, the number that received at least one dose of clinical trial material, the number who withdrew prior to completing the study, and reasons for withdrawal.

A by-subject listing of study completion information, including the reason for premature study withdrawal, if applicable, will be presented.

4.5. Demographic and Baseline Characteristics

Age at randomization, gender and race will be summarized by treatment group for each subject population using descriptive statistics. No formal statistical comparisons will be performed.

Demographic and Baseline data will also be provided in data listings.

4.6. Medical History

Medical/Surgical history will be displayed in tables and listings. These summaries will be provided for the final study analysis. If necessary, summaries can be provided for the interim analysis upon request.

4.7. Treatment Exposure

The following treatment exposure parameters will be summarized for cyclophosphamide, GVAX and CRS-207 separately by treatment group:

- The cumulative dose of cyclophosphamide (mg), GVAX (cells) and CRS-207 (colony forming units) will be summarized by cycle and administration with descriptive statistics: n, mean, standard deviation, median, and range.
- The frequency and percentage of subjects experiencing any interruptions in treatment during a cycle.
- The distribution (frequency and percentage) of administrations during a cycle.
- Treatment duration defined as: Last dose date – First dose date (defined in Section 4.2.9) + 1. This will provided with the results for the final analysis.

4.8. Efficacy Evaluation

The primary efficacy analysis for the interim analysis will be conducted after the required number of deaths have occurred (41 events). The 41st death is expected to occur approximately 21 months after randomization of the 1st subject. The FAS Population will be used for the primary analysis of the efficacy endpoint. If appropriate, similar analyses may be performed using the Per-Protocol population, the Safety Population, or both.

4.8.1. Primary Efficacy Endpoint

The primary efficacy endpoint analysis will be based on the log-rank test.

Kaplan-Meier methods will be used to estimate OS for each treatment group. Estimates of median survival will be provided along with 95% confidence intervals. Hazard ratio estimates will also be presented.

Overall survival will be censored at the earlier of the cutoff date for interim analysis and the last date known to be alive for subjects not known to have died.

Sensitivity analyses may be performed to assess the effect of other covariates on OS.

In addition, an exploratory Cox proportional hazards regression analysis may be performed to assess the effects of other covariates on OS if adequate baseline data are available. The model will include terms for treatment group, the covariate(s) of interest, along with the term for treatment by covariate interaction.

4.8.2. Exploratory Efficacy Endpoint

4.8.2.1. Overall Response Rate

Point estimates of the overall response rate will be calculated for each treatment group as the percentage of subjects with CR or PR based on the Response Evaluation Criteria in Solid Tumors (RECIST) and the immune-related response criteria (irRC) response criteria (See Appendix Appendices A and B of the study protocol for full details on response criteria). Separate summaries of the overall response rate will be provided according to both sets of criteria. In addition to the overall response rates, the frequency and percentage of subjects in each response category (CR, PR, SD, PD and Not Evaluable) as well as the frequency and percentage of subjects with CR, PR or SD will be summarized.

A 95% CI for the overall response rate will be calculated for each treatment group using the Clopper-Pearson method.

The overall response rate will be compared between treatment groups using a chi-square test. A 95% CI for the difference in overall response rates between treatment groups will be calculated using the normal approximation to the binomial distribution.

4.8.2.2. Tumor Marker Kinetics

Assessments for tumor markers CA19-9 and CEA were conducted during the study and will be summarized by treatment group using subject data listings. Other tumor markers evaluated during the study will also be summarized with subject data listings.

Additional efficacy analyses will be provided if requested by the DMC.

4.9. Safety Analyses

Safety analyses will be conducted using the Safety Population.

4.9.1. Adverse Events

Adverse Events (AEs) are collected from the time of first clinical trial material administration until the end of the follow-up period. Treatment-emergent AEs (TEAEs) are defined as new events occurring on or after dose 1, having been absent prior to dose 1 or worsening from pre to post treatment. All AEs collected on or after dose 1 of the study will be considered post treatment, even if they occur after the last dose of therapy. TEAEs will be summarized by system organ class and preferred term using the Medical Dictionary for Regulatory Activities (MedDRA) Version 12.0 dictionary. Subjects will be counted only once for each preferred term, once for each body system, and by the highest event severity, regardless of how many events the subject experienced. All AEs that occurred for subjects who were never treated will be presented in a separate listing.

Tabular summaries will include the incidence overall [number and percentage of subjects with treatment-emergent adverse events classified by System Organ Class (SOC) and preferred term]; incidence by intensity [graded according to the National Cancer Institute Common Toxicity Criteria for Adverse Events (NCI CTCAE) version 4.03 or newer], causality, seriousness, and outcome (e.g., leading to discontinuation of study treatment); and other presentations as appropriate.

No formal hypothesis-testing analysis of adverse events incidence rates will be performed.

All adverse events occurring on study will be listed in subject data listings. All SAEs that are recorded on the CRF will be contained in data listings.

4.9.2. Laboratory Data

Laboratory samples are collected according to the study flow chart in Section 5.1 of the study protocol. For labs that are summarized per visit, the first value will be taken per visit per subject. The only exception to this will be at Baseline where the last value collected prior to treatment will represent Baseline. For lab values that are comprised of a character and numeric value (e.g., <1.5), only the numeric value will be used for the summaries in the tables. Both the numeric and character values will be presented in the listing. If any laboratory parameter has data available for less than 10 subjects, that parameter will only be presented in a listing and not a table. Descriptive statistics for blood chemistry, urinalysis, and hematology parameters will be provided by treatment group. The actual values of labs will be presented by visit as well as change scores from Baseline defined in Section 4.2.10.

For women of childbearing potential a urine pregnancy test will be administered at Screening and must be negative for study eligibility. The test will be repeated at Day 1 of each dosing week. Pregnancy test results will be provided in subject data listings for the final analysis.

Laboratory abnormalities occurring from the start of study drug administration through the end of follow-up will be collected. Shift tables from low, normal, high, and 3 times the normal value will be presented. Clinical laboratory values will be expressed using International System of Units (SI) units as appropriate.

Graphical representations of laboratory data over time will also be provided.

All laboratory data will also be provided in data listings.

4.9.3. Vital Signs and Physical Examinations

Complete physical examinations will be performed at Screening and at the end of treatment (Week 20). Focused physical examination will be performed on Day 1 of dosing weeks. Any abnormal findings are entered in medical history or as an adverse event.

Vital signs (blood pressure, pulse rate, respiratory rate, and oral body temperature) will be recorded at all study visits.

Height will be measured at screening. Body weight will be measured at screening and on Day 1 of each dosing week.

The actual value and change from Baseline (defined in Section 4.2.10) to each on study evaluation will be summarized for vital signs.

Graphical representations of vital sign data over time will also be provided.

By-subject listings of vital sign measurements will also be presented in a data listing.

4.9.4. Electrocardiogram

A 12-lead ECG will be conducted at screening and at Week 20. ECG results will be summarized descriptively, including the number and percent of subjects with normal, not clinically significant abnormal and clinically significant abnormal results by visit. Shift tables will be presented to show how results changed from Screening over time.

All ECG data for each subject will also be provided in a data listing for the final analysis.

4.9.5. Concomitant Medications

Each subject's use of concomitant medications will be reviewed and recorded at each visit. At screening, prospective subjects will be asked about the medications (prescription and non-prescription, including vitamins and supplements) they have taken prior to screening. Once randomized, subjects will be asked about the medications they have taken since the prior study visit.

The investigator will record all medications used by the subject, including the name of the medication, the dose, route of administration, regimen, dates when the medication was started and stopped, and the indication for use.

Concomitant medications will be coded using the WHO Drug dictionary (March 2010). Results will be tabulated by Anatomic Therapeutic Class (ATC) and preferred term for subjects overall as well as within treatment group.

The use of concomitant medications will also be included in a by-subject data listing.

5. CHANGES TO PLANNED ANALYSES

Protocol Amendment #4 (version 6, dated 14 December 2012) modified the final analysis as follows:

During the trial, the timing of the final analysis was modified to be conducted after 70 events were observed in the primary analysis population (FAS). The justification for this change was that the overall study power would be preserved at an acceptable level (80% power) with a lower number of events (n = 70) compared to the number of events originally planned for (n=83, overall study power of approximately 85%).

6. REFERENCES

1. ICH-E9 Statistical Principals for Clinical Trials, September 1998
2. O'Brien PC, Fleming TR. A multiple testing procedure for clinical trials. Biometrics. 1979 Sep;35(3):549-56.
3. Lan KK, DeMets DL. Discrete sequential boundaries for clinical trials. Biometrika. 1983;70(3):659-63.
4. ICH-E3 Struture and Content of Clinical Study Report, July 1996

7. LIST OF DATA TABLES, FIGURES AND LISTINGS FOR DMC SAFETY REVIEW MEETINGS AND INTERIM ANALYSIS

All tables, listings and figures will be numbered according to the ICH-E3 Guideline[4].

7.1. Statistical Tables and Figures to be Generated

Table of contents for suggested summaries for periodic safety review meetings.

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TABLES		
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STATISTICAL ANALYSIS PLAN

Protocol ADU-CL-01

A Phase 2, Randomized, Multicenter, Open-Label Study of the Efficacy and Immune Response of the Sequential Administration of GVAX Pancreas Vaccine (with Cyclophosphamide) Alone or Followed by CRS-207 in Adults with Metastatic Pancreatic Adenocarcinoma

Protocol Number: **(Version Date)**	ADU-CL-01 28 February 2013, Version 7
Name of Test Drug(s):	CRS-207, GVAX Pancreas Vaccine
Phase:	2
Methodology:	The study is an open-label, randomized, multicenter clinical study in adults with metastatic pancreatic adenocarcinoma who have received or refused at least one chemotherapy treatment. At least 90 subjects will be enrolled and randomized in a 2:1 fashion into two treatment arms. Both treatment arms will receive up to six doses of vaccine 3 weeks apart (one cycle). Treatment Arm A will receive two doses of cyclophosphamide and GVAX pancreas vaccine and up to four doses of CRS-207. Treatment Arm B will receive up to six doses of cyclophosphamide and GVAX pancreas vaccine. At the planned interim analysis, the study met the pre-defined criteria for stopping and subjects in Arm B were offered Arm A treatment.
Sponsor:	Aduro BioTech, Inc. 626 Bancroft Way, #3C Berkeley, CA 94710-2224 USA
Sponsor Representative:	Aimee Murphy, Director of Clinical Operations 626 Bancroft Way, #3C Berkeley, CA 94710-2224 Phone: 510-848-4400 x106 Fax: 510-848-5614 E-mail: amurphy@adurobiotech.com

SIGNATURE PAGE

Protocol Title: A Phase 2, Randomized, Multicenter, Open-Label Study of the Efficacy and Immune Response of the Sequential Administration of GVAX Pancreas Vaccine (with Cyclophosphamide) Alone or Followed by CRS-207 in Adults with Metastatic Pancreatic Adenocarcinoma

Sponsor: Aduro BioTech, Inc.
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Protocol Number: ADU-CL-01

Document Date/Version: 25 September 2013/v1.0

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Signature: Seth Zuckerman
Date: 04 OCT 2013

Sponsor Approval

By signing this document, I acknowledge that I have read the document and approve of the planned statistical analyses described herein. I agree that the planned statistical analyses are appropriate for this study, are in accordance with the study objectives, and are consistent with the statistical methodology described in the protocol, clinical development plan, and all applicable regulatory guidance's and guidelines.

I have discussed any questions I have regarding the contents of this document with the biostatistical author.

I also understand that any subsequent changes to the planned statistical analyses, as described herein, may have a regulatory impact and/or result in timeline adjustments. All changes to the planned analyses will be described in the clinical study report (CSR).

Sponsor Signatory:
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Signature: [signature]
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ABBREVIATIONS

Abbreviation	Definition
AE	Adverse Events
CSR	Clinical Study Report
CR	Complete Response
DMC	Data Monitoring Committee
ECG	Electrocardiogram
FAS	Full Analysis Set
FDA	Food and Drug Administration
ICH	International Conference on Harmonisation
irRC	Immune-Related Response Criteria
ISP	Independent Statistical Provider
ITT	Intent-to-Treat Set
MedDRA	Medical Dictionary for Regulatory Activities
NCI CTCAE	National Cancer Institute Common Toxicity Criteria for Adverse Events
OS	Overall Survival
PD	Progressive Disease
PFS	Progression-Free Survival
PP	Per-Protocol Set
PR	Partial Response
PT	Preferred Term
RECIST	Response Evaluation Criteria in Solid Tumors
SAE	Serious Adverse Event
SAP	Statistical Analysis Plan
SD	Stable Disease
SI	International System of Units
SOC	System Organ Class
TEAE	Treatment-emergent Adverse Event
TESAE	Treatment-emergent Serious Adverse Events
TTP	Time to Progression
WHO	World Health Organization

1. INTRODUCTION AND OBJECTIVES OF ANALYSIS

1.1. Introduction

ADU-CL-01 is a phase 2, randomized, multicenter, open-label study of the efficacy and immune response of the sequential administration of GVAX pancreas vaccine (with cyclophosphamide) alone or followed by CRS-207 in adults with metastatic pancreatic adenocarcinoma. The study, as described in the protocol, has a single, pre-planned interim efficacy analysis by an independent Data Monitoring Committee (DMC). The planned interim safety and efficacy analysis was conducted in February 2013 based on the Interim Statistical Analysis Plan (version 2.0, dated 20 December 2012). At this interim analysis, the study met the primary endpoint criteria for stopping the study for efficacy and the study was stopped based on DMC recommendation. Subjects will continue to be treated and followed on protocol until death or up to 24 months of follow-up after which they will be offered enrollment into a long-term follow-up study for survival.

1.2. Objectives of Statistical Analysis

This statistical analysis plan (SAP) is designed to outline the methods to be used in the analysis of study data for the primary study analysis. An additional analysis will also be performed when all subjects complete the study, which will be referred to as the final follow-up study analysis.

Unless otherwise noted, this document describes how the analyses will be handled for the primary study analysis only. The interim analysis was documented in a separate SAP and the final follow-up study analysis will be documented in a separate SAP.

The statistical analyses and summary tabulations described in this SAP will provide the basis for the reporting of the results from the planned primary study analysis for this trial. Populations for analysis, data handling rules, statistical methods, changes from the study protocol and formats for data presentation are provided.

Recommendations from ICH-E9[1] Guideline on Statistical Principals for Clinical Trials will be followed.

1.2.1. Primary Objective

The primary objective of this study is to compare overall survival (OS) in subjects receiving sequential administration of cyclophosphamide, GVAX pancreas vaccine and CRS-207 with OS in subjects receiving cyclophosphamide and GVAX vaccine alone.

1.2.2. Secondary Objective

The secondary objective is to assess the safety of the cyclophosphamide, GVAX pancreas vaccine and CRS-207 treatment regimen.

1.2.3. Exploratory Objectives

The exploratory objectives are:

- To assess the association of Listeria monocytogenes (*Lm*) and mesothelin-specific T cell and other immunological responses with OS
- To evaluate overall response rate in subjects with measureable disease per Response Evaluation Criteria in Solid Tumors (RECIST) and immune-related response criteria (irRC)
- To measure tumor marker kinetics

2. STUDY DESIGN

2.1. Synopsis of Study Design

At least 90 subjects with metastatic pancreatic adenocarcinoma satisfying all eligibility criteria will be enrolled and randomized in a 2:1 fashion into the two treatment arms. Both treatment arms will receive up to six doses of vaccine 3 weeks apart (one cycle). Treatment Arm A will receive two doses of cyclophosphamide and GVAX pancreas vaccine and up to four doses of CRS-207. Treatment Arm B will receive up to six doses of cyclophosphamide and GVAX pancreas vaccine.

To monitor initial safety of the sequential vaccine regimen, no more than one subject will be enrolled per week for the first six subjects. If any limiting toxicities are observed during the study, the data will be reviewed with the DMC and the dose may be lowered to 1×10^8 colony-forming units (CFU) for all subsequent dosing with CRS-207.

Subjects will return to the study site approximately 4 weeks after their final treatment for safety and immune response evaluations. They will continue to be followed by phone or optional clinic visits for subsequent cancer-related therapies, overall response rate, and *Lm*- and mesothelin-specific immune responses (at clinic visits only) for the duration of the study until all subjects have reached at least 24 months of follow-up or death.

At the investigator's discretion, subjects may receive additional treatment cycles of the assigned treatment regimen if they are clinically stable and meet dosing requirements.

With an expected enrollment rate of five subjects per month, the accrual period would be 18 months, which, with the 24 months of follow-up of each subject, yields a maximum total study time of 42 months.

A planned interim analysis will be conducted as described in Section 4.3. The interim analysis will be conducted by an Independent Statistics Provider (ISP) and reviewed by the DMC.

2.2. Randomization Methodology

This is an open-label study. Subjects meeting all inclusion and exclusion criteria will be randomized 2:1 to one of two treatment arms according to a randomization list generated for each site by an independent statistician.

2.3. Study Procedures

The schedule of assessments is outlined in Section 5.1 of the study protocol.

2.4. Analysis Endpoints

2.4.1. Primary Efficacy Endpoint

The primary endpoint is OS, defined as the time between the date of first dose and the date of death (date of death minus date of first dose +1).

2.4.2. Exploratory Endpoints

2.4.2.1. Tumor Responses Assessed Based on RECIST and irRC

Overall response rate, disease control rate, best overall objective disease response and response by cycle and visit will be defined and summarized as described in Section 4.8.2.1 (see Appendices A and B of the study protocol for full details on response criteria).

2.4.2.2. Tumor Marker Kinetics

Assessments for tumor markers CA19-9 and CEA will be measured through serum levels prior to and post-treatment. Other tumor markers may also be evaluated and will be provided in subject data listings.

2.4.2.3. Humoral and Cellular Immune Responses

Humoral and cellular immune responses directed against *Lm* and mesothelin assessed will be measured by enzyme-linked immunosorbent spot (ELISPOT) or intracellular cytokine staining assays of peripheral blood mononuclear cells (PBMC), induction of proinflammatory cytokines and chemokines in the serum and enzyme-linked immunosorbent assay (ELISA) detection of mesothelin- and *Lm*-specific antibodies in the serum. Analyses for these data will be perfomed as part of the follow-up final study analysis and will not be included with the primary study analysis.

2.4.2.4. Additional Efficacy endpoints

The following additional efficacy endpoints will also be analyzed using RECIST and irRC responses:

- Time to Progression (TTP)
- Progression-free Survival (PFS)

Full details regarding these endpoints can be found in Section 4.8.2.

2.4.3. Safety Variables

Safety assessments included physical examinations, measurement of vital signs, 12-lead electrocardiograms (ECGs), clinical laboratory evaluations including hematology and serum chemistry, concomitant medication usage, assessment of weight, pregnancy testing, monitoring of adverse events and monitoring of vaccine site reactions.

The only physical exam data that will be collected will be abnormalities recorded as medical history or adverse events.

3. SUBJECT POPULATIONS

3.1. Population Definitions

The following subject populations will be evaluated and used for presentation and analysis of the data:

- Full Analysis Set (FAS): all randomized subjects who received at least 1 dose of cyclophosphamide.
- Safety Population: all randomized subjects who received any clinical trial material.
- Per-Protocol Population (PP): all subjects in the FAS who received at least 3 doses (at least one dose of CRS-207 in Treatment Arm A or three doses of cyclophosphamide/GVAX pancreas vaccine in Treatment Arm B).
- Intent-to-Treat (ITT): all randomized subjects

A review of the treatment exposure data will be completed to determine if there were any subjects that did not receive clinical trial material. Any subjects not receiving clinical trial material will be fully documented in the primary analysis study report.

All subject populations will be analyzed on the basis of the actual treatment received.

The FAS Population is the primary population for the analysis of all efficacy parameters. A distinct Safety Population will only exist if there are subjects that did not receive at least 1 dose of cyclophosphamide, but did receive other clinical trial material (i.e., GVAX or CRS-207). If a distinct Safety Population exists, it will only be used for the analysis of safety parameters.

The ITT Population will only be utilized as part of a sensitivity analysis of the primary efficacy endpoint of OS.

4. STATISTICAL METHODS

4.1. Sample Size Justification

The original protocol had been designed to enroll at least 90 subjects during 18 months and followed for approximately 27 months (this includes a treatment period between 1 day and 20 weeks in duration and a 24 month post-treatment follow-up period). For the FAS, if the true median survival for the sequential treatment is 8.1 months, and that for GVAX alone is 5 months, the sample size of N = 90 has approximately 85% power to yield a statistically significant difference (overall alpha = 0.15, 1-sided). This is based on an assumed enrollment rate of five subjects per month. For the original statistical design, power was computed for a 2-stage group sequential design with a single interim analysis at approximately half the total study "information" (i.e., 83 deaths total; interim analysis after 41 deaths) and with an O'Brien-Fleming-like alpha spending function (gamma= –4)[2,3].

During the trial, and prior to the interim analysis, a protocol amendment dated 14DEC2012 was implemented such that the timing of the interim and final analyses were to be conducted after 41 and 70 events, respectively, were observed in the primary analysis population (FAS). The justification for this change is that the overall study power will be preserved at an acceptable level (80% power) with a lower number of events (n = 70) compared to the number of events originally planned for (n=83). Therefore, for the FAS, if the true median survival for the sequential treatment is 8.1 months, and that for GVAX alone is 5 months, the sample size of N = 70 deaths has approximately 80% power to yield a statistically significant difference (overall alpha = 0.15, 1-sided). See Section 4.3 for additional details on the interim analysis and sequential stopping rules.

The primary objective of the study was met at the time of the planned interim analysis. All subjects had been enrolled by that time and Arm B subjects were offered and initiated rollover treatment as of 29APR2013. Therefore, the primary study analysis will be conducted using a data cut-off date of 29APR2013. See Section 4.2.2 for full details regarding how the data will be filtered for this primary analysis.

4.2. General Statistical Methods and Data Handling

4.2.1. General Method

Tabulations will be produced for appropriate demographic, baseline, efficacy, exploratory and safety parameters. For categorical variables, summary tabulations of the number and percentage within each category (with a category for missing data) of the parameter will be presented. For continuous variables, the N, mean, median, standard deviation, minimum and maximum values will be presented.

Formal statistical hypothesis testing will be performed on the primary endpoint with all tests conducted at the 1-sided, overall 0.15 level of significance. Summary statistics will be presented, as well as 95% confidence intervals on selected parameters, as described in the sections below.

4.2.2. Raw Data Set Filtering

As a result of the interim analysis, a decision was made to allow subjects on treatment on treatment Arm B to "rollover" to treatment Arm A. Therefore, the data cut-off for the primary study analysis will be 29APR2013 which is one day prior to the first subject receiving "rollover treatment (i.e., a switch from treatment Arm B to treatment Arm A). As such, all raw data sets will be filtered to include information obtained from all clinical study visits up to and including 29APR2013.

The following rules were applied in the creation of this data snap-shot:

- For raw data sets where more than one visit date variable is available, the DOV (Date of Visit) variable will be used.
- For Adverse Events (AEs), the AE onset date will be used.
- For Laboratory data, the assessment date will be used.
- For Concomitant Medications, the start date will be used.
- In general, for AEs, laboratory tests and concomitant medications, if the non-missing parts of a partial date clearly determine that the data point is after 29APR2013, the data point will be excluded. For example, if the year=2013 and the month is May, the record would be excluded during the filtering process.

Appendix 2 includes complete details of how the data sets were created including which specific variables will be used for the filtering of each raw data set.

For the primary efficacy analysis, the following additional censoring rules were applied on the data sets:

- Events up to and including 29APR2013 are counted as events.
- Events occurring after 29APR2013 will be censored as of 29APR2013. These events will be included in a listing of subject deaths and flagged to identify that the death occurred after 29APR2013. For example, if the last follow-up visit for a subject was 01MAY2013 and the subject's status was "Not Alive" at this visit, the subject would be counted as a censored observation with an analysis date of 29APR2013.
- If a subject has a last known date of follow-up after 29APR2013 and the subject's status is "Alive", the subject will be censored as of 29APR2013.

Any modifications to the data handling rules mentioned in this section will be documented in the clinical study report.

4.2.3. Data Handling

Treatment period data for all subjects will be extracted from the INFORM eCRF database system. Follow-up data on all subjects will be extracted from a separate follow-up database where the data from the paper follow-up case report forms [CRFs] was manually entered. The following data will be manually derived (based on clinical review) and then merged with other Analysis Data Sets for the purpose of analysis:

- Number of prior treatments for metastatic disease
- Disease status at entry (i.e., progressive disease [PD] or stable disease [SD])

4.2.4. Computing Environment

All descriptive statistical analyses will be performed using SAS statistical software (Version 9.2 or higher). AEs will be coding using the Medical Dictionary for Regulatory Activities (MedDRA), version 12.0. Concomitant medications will be coded using World Health Organization (WHO) Drug version March 2010.

4.2.5. Methods of Pooling Data

Not applicable to the present study.

4.2.6. Adjustments for Covariates

No adjustments for covariates are planned for the primary analysis. Exploratory analyses and sensitivity analyses may be performed with adjustments for covariates as necessary.

4.2.7. Multiple Comparisons/Multiplicity

No adjustments for multiple comparisons will be applied for the primary analysis.

4.2.8. Subpopulations

Subgroup analyses of the primary efficacy endpoint will be provided for the following sub-populations:

- Number of prior treatments for metastatic disease (e.g., no prior treatment, 1 prior treatment [2^{nd}-line subjects] or 2 or more prior treatments [3^{rd}+ line subjects])

4.2.9. Withdrawals, Discontinuations, Lost to Follow-up

Subjects who withdrew consent or were removed from study treatment before completing one cycle of treatment were considered dropouts and could be replaced at the discretion of Aduro BioTech, Inc. Subjects who had disease progression were allowed to continue on treatment if the investigator believed they were deriving some benefit from the therapy.

After completion of treatment or early discontinuation from treatment, subjects were followed by phone and optional clinic visits for subsequent cancer-related therapies, overall response rate and blood draws for *Lm*- and mesothelin-specific immune responses (clinic visits only) until death or up to 24 months of follow-up.

4.2.10. Missing, Unused and Incomplete Data

In general, for safety data, there will be no substitutions made to accommodate missing data points.

As described in Section 4.2.2, as part of the raw data set filtering process, the following rule will be applied. For AEs, laboratory tests and concomitant medications, if the non-missing parts of a partial date clearly determine that the data point is after 29APR2013, the data point will be excluded. For example, if the year=2013 and the month is May, the record would be excluded during the filtering process.

All data recorded on the CRF will be included in data listings.

4.2.11. Definition of Baseline and Dose 1 Date Values

For all assessments, Baseline is defined as the last non-missing measurement prior to randomization.

For all subjects, the dose 1 date is equivalent to the first study drug administration date.

4.2.12. Definition of Nadir

For summarizing laboratory data (including tumor marker data), the nadir will be defined as the lowest value recorded through the current visit including the Baseline assessment.

4.2.13. Change in Value from X to Y

Change in Value from X date to Y date = Value on Y date – Value on X date

4.3. Interim Analyses

The primary endpoint analysis will be performed per Section 4.8.1.

The interim analysis for early stopping for efficacy or for futility was planned to be performed after 41 deaths occurred. The interim analysis included stopping rules for efficacy as well as for futility. If the analysis showed that the study had reached its efficacy stopping criteria or was highly unlikely to show a benefit based on interim data, the study could be stopped.

After the targeted number of events are observed, a "snap-shot" of the database will be transferred to an ISP to produce the result for the DMC review.

The original statistical design was based on a primary analysis of OS for the FAS according to a 2-stage group sequential design with a single interim analysis at approximately half the total study "information" (i.e., 83 deaths total; interim analysis after 41 deaths), and with O'Brien-Fleming-like alpha and beta spending functions (gamma = –4). In order to stop the study at the interim analysis and conclude statistically significantly (overall alpha = 0.15, 1-sided) longer survival in the sequential treatment arm than in the control arm, a p-value less than 0.0179 was required and the cutoff for futility stopping was $p > 0.7329$[5]. If the study was not stopped at the interim analysis, the p-value cutoff to support an efficacy conclusion at the final analysis was $p < 0.1468$. This preserved the overall alpha level for the primary endpoint analysis at 0.15. These computations were derived from EAST software (Version 5.4).

During the trial, and prior to the interim analysis, a protocol amendment was implemented such that the timing of the final analysis was to be conducted after 70 events were observed in the primary analysis population (FAS). The justification for this change was that the overall study power would be preserved at an acceptable level (80% power) with a lower number of events (n = 70) compared to the number of events originally planned for (n=83). Therefore, in order to stop the study at the interim analysis (41 deaths) and conclude statistically significantly (overall alpha = 0.15, 1-sided) longer survival in the sequential treatment arm than in the control arm, a p-value less than 0.0263 was required. The cutoff for futility stopping is $p > 0.6395$. If the study was not stopped at the interim analysis, the p-value cutoff to support an efficacy conclusion at the final analysis (70 deaths) was $p < 0.1461$. This preserved the overall alpha level for the primary endpoint analysis at 0.15. These computations were also derived from EAST software (Version 5.4).

After reviewing the results of the interim analysis, the DMC made a recommendation to the sponsor to stop the trial for evidence of efficacy based on the pre-specified criteria in favor of treatment Arm A. The study was fully enrolled at the time of the interim analysis. Based on the recommendation of the DMC, the subjects in treatment Arm B were given the option to receive treatment with CRS-207 or continue to receive cyclophosphamide/ GVAX pancreas vaccine doses on the protocol schedule. Given that the primary objective of the study was met and subjects were offered and initiated rollover treatment as of 29APR2013, the primary study analysis will be conducted using a data cut-off date of 29APR2013. Data prior to and after the data cut-off will be handled as described in Section 4.2.2. See Section 5.2.5 of the study protocol for full details on the rollover procedures.

The primary study objective was met at the interim analysis when the pre-defined stopping criteria for evidence of efficacy was met. For completeness, the primary efficacy analysis will be repeated using the 29APR2013 data cut-off and p-values for the primary efficacy endpoint will be reported but no additional hypothesis testing will be performed.

4.4. Subject Disposition

Subject disposition will be tabulated by treatment group, including the number in each subject population for analysis, the number that received at least one dose of clinical trial material, the number who withdrew prior to completing the study and reasons for withdrawal.

A by-subject listing of study completion information, including the reason for premature study withdrawal, if applicable, will be presented.

4.5. Demographic and Baseline Characteristics

Age at randomization, gender, ethnicity and race will be summarized by treatment group for each subject population using descriptive statistics. No formal statistical comparisons will be performed.

Demographic and Baseline data will also be provided in data listings.

4.6. Medical History

Medical/surgical history will be displayed in tables and listings.

4.7. Treatment Exposure

The following treatment exposure parameters will be summarized for cyclophosphamide, GVAX and CRS-207 separately by treatment group:

- The cumulative dose of cyclophosphamide (mg), GVAX (cells) and CRS-207 (colony-forming units [CFU]) will be summarized by cycle and administration with descriptive statistics: n, mean, standard deviation, median, and range.
- The frequency and percentage of subjects experiencing any interruptions in treatment during a cycle.
- The distribution (frequency and percentage) of administrations during a cycle.

  Treatment duration defined as: Last dose date – First dose date (defined in Section 4.2.11) + 1.

4.8. Efficacy Evaluation

The FAS Population will be used for the primary analysis of the primary efficacy endpoint. Similar analyses will be performed using the PP population.

4.8.1. Primary Efficacy Endpoint

The primary endpoint is OS, defined as the time between the date of first dose and the date of death or censoring. The primary analysis of this endpoint will consist of a one-sided log-rank test.

OS will be censored at the earlier of the cutoff date for the primary analysis and the last date known to be alive for subjects not known to have died at the time of the primary analysis with the data filtering rules described in Section 4.2.2.

Kaplan-Meier methods will be used to estimate OS for each treatment group. Estimates of median survival will be provided along with 95% confidence intervals. In addition, hazard ratio estimates will also be presented based on a Cox proportional hazards regression analysis that includes treatment as a factor.

Analysis of OS will be repeated for the PP and ITT sets. For the ITT set, OS is defined as the time between the date of randomization and the date of death or censoring for untreated subjects and the time between the date of first dose and the date of death or censoring for treated subjects.

An exploratory Cox proportional hazards regression analysis may be performed to assess the effects of other covariates on OS if adequate Baseline data are available. Additional sensitivity analyses may be performed to assess the effect of other covariates on OS.

4.8.2. Exploratory Endpoints

4.8.2.1. Overall Response Rate and Objective Disease Response

For an individual subject, the "Best Overall Response" is defined as the best response across all assessments from all cycles on study treatment. All available assessments are included in the derivation of "Best Overall Response", except for the situation where another anti-cancer therapy has been introduced. In these cases, additional assessments after the additional therapy has been introduced will not be included. This logic is applied only for the derivation of "Best Overall Response" and will not be applied in the summary of responses by cycle and visit.

Point estimates of the overall response rate and disease control rate will be calculated for each treatment group based on RECIST 1.1 and the irRC (see Appendices A and B of the study protocol for full details on response criteria). The overall response rate is defined as subjects with a "Best Overall Response" of complete response (CR) or partial response (PR). The disease control rate is defined as subjects with a "Best Overall Response" of CR, PR or SD. The duration of a response and confirmation of the response at a subsequent visit are not part of the requirements for "Disease Control". Additional analyses may be conducted where the status of these patients is modified due to the change in clinical condition. Separate summaries of the overall response rate will be provided according to both sets of criteria.

In addition to the overall response and disease control rates, the frequency and percentage of subjects in each "Best Overall Response" response category (CR, PR, SD, PD and Not Evaluable, Missing) will be summarized according to both sets of criteria. Summaries of response by cycle and visit will also be summarized according to both sets of criteria.

The denominator for the tumor response summaries across all treatment cycles is all subjects in the relevant analysis population. A row will also be included to account for subjects with missing assessments.

A 95% CI for the overall response rate will be calculated for each treatment group using the Clopper-Pearson method.

The overall response rate will be compared between treatment groups using a chi-square test. A 95% CI for the difference in overall response rates between treatment groups will be calculated using the normal approximation to the binomial distribution.

4.8.2.2. Tumor Marker Kinetics

Assessments for tumor markers CA19-9 and CEA were conducted during the study and will be presented using subject data listings. Other tumor markers evaluated during the study will also be presented with subject data listings.

Figures may be used to display the "absolute change from nadir" for the last assessment across all treatment cycles.

4.8.2.3. Time to Progression

TTP is defined as the number of months from the start of treatment (date of first documented dose of clinical trial material) to the date of documented disease progression (PD or relapse from CR as assessed using RECIST 1.1 criteria). TTP will be estimated using the Kaplan-Meier method and the median TTP will be summarized for each treatment group. The tables on the following page display the censoring rules that will be applied for the primary method as well as for an initial sensitivity analysis:

Time to Progression

Primary Method (censor for new anti-cancer therapy but not for treatment withdrawals)

Situation	Date of Progression or Censoring	Outcome
No Baseline tumor assessments	Day 1	Censored
Progression after more than one missed assessment visit prior to switch to other anti-cancer therapy	Date of last radiological assessment of measured lesions	Censored
Progression documented prior to switch to other anti-cancer therapy	Earliest of the following prior to switch to other anti-cancer therapy - Date of radiological assessment showing new lesion (if progression is based on new lesion); or - Date of last radiological assessment of measured lesions (if progression is based on increase in sum of measured lesions)	Progressed
Death prior to switch to other anti-cancer therapy	Date of death	Censored
Switch to other anti-cancer therapy.	Date of last radiological assessment of measured lesions prior other anti-cancer therapy	Censored
No progression prior to switch to other anti-cancer therapy	Date of last radiological assessment of measured lesions prior to switch to other anti-cancer therapy	Censored

Sensitivity Method (censor for new anti-cancer therapy and treatment withdrawals)

Situation	Date of Progression or Censoring	Outcome
No Baseline tumor assessments	Day 1	Censored
Progression after more than one missed visit during treatment period	Date of last radiological assessment of measured lesions	Censored
Progression documented during treatment period	Earliest of the following assessed prior to treatment withdrawal and switch to other anti-cancer therapy: - Date of radiological assessment showing new lesion (if progression is based on new lesion); or - Date of last radiological assessment of measured lesions (if progression is based on increase in sum of measured lesions)	Progressed
Treatment discontinuation for any reason and/or switch to other anti-cancer therapy.	Date of last radiological assessment of measured lesions prior to withdrawal and switch to other anti-cancer therapy	Censored
Death	Date of death	Censored
No progression during the treatment period	Date of last radiological assessment of measured lesions prior to withdrawal and switch to other anti-cancer therapy	Censored

4.8.2.4. Progression-free survival

Progression-free survival (PFS) is defined as the number of months from the start of the treatment (date of first documented dose of clinical trial material) to disease progression (PD or relapse from CR as assessed using RECIST 1.1 criteria) or death due to any cause. PFS will be estimated using the Kaplan-Meier method and the median PFS time will be summarized for each treatment group. The tables on the following pages display the censoring rules that will be applied for the primary method as well as for an initial sensitivity analysis:

Progression-Free Survival

Primary Method (censor for new anti-cancer therapy but not for treatment withdrawals)

Situation	Date of Progression or Censoring	Outcome
Death before first assessment visit	Date of death	Progressed
No Baseline tumor assessments	Day 1	Censored
Death or progression after more than one missed assessment visit prior to switch to other anti-cancer therapy	Date of last radiological assessment of measured lesions	Censored
Progression documented prior to switch to other anti-cancer therapy	Earliest of the following assessed prior to switch to other anti-cancer therapy: - Date of radiological assessment showing new lesion (if progression is based on new lesion); or - Date of last radiological assessment of measured lesions (if progression is based on increase in sum of measured lesions)	Progressed
Death between adequate assessment visits prior to switch to other anti-cancer therapy	Date of death	Progressed
Switch to other anti-cancer therapy.	Date of last radiological assessment of measured lesions prior other anti-cancer therapy	Censored
No progression prior to switch to other anti-cancer therapy	Date of last radiological assessment of measured lesions	Censored

Progression-Free Survival

Sensitivity Method (censor for new anti-cancer therapy and treatment withdrawals)

Situation	Date of Progression or Censoring	Outcome
Death before first assessment visit	Date of death	Progressed
No Baseline tumor assessments	Day 1	Censored
Death or progression after more than one missed visit during treatment period	Date of last radiological assessment of measured lesions	Censored
Progression documented during treatment period	Earliest of the following assessed prior to treatment withdrawal and switch to other anti-cancer therapy: - Date of radiological assessment showing new lesion (if progression is based on new lesion); or - Date of last radiological assessment of measured lesions (if progression is based on increase in sum of measured lesions)	Progressed
Death between adequate assessment visits during the treatment period	Date of death	Progressed
Treatment discontinuation for any reason and/or switch to other anti-cancer therapy.	Date of last radiological assessment of measured lesions prior to withdrawal and switch to other anti-cancer therapy	Censored
No progression during the treatment period	Date of last radiological assessment of measured lesions prior to withdrawal and switch to other anti-cancer therapy	Censored

4.8.2.5. Radiological Tumor Response

A waterfall plot may be used to display the maximum decrease in "percent change from Baseline" in the "sum of diameters for all target lesions" across all assessments. The "sum of diameters for all target lesions" is obtained from the Tumor Assessment Target Lesion Panel in the eCRF (the corresponding raw data variable from the form is: LSSUM_T_SCR). The plot will display vertical bars for each patient with the maximum decrease in "percent change from Baseline" across all assessments. The x-axis will sort the patients from left to right, displaying patients with an "increase" from Baseline first and the patients with a "decrease" from Baseline last. Separate Plots will be created for each treatment arm and subject data will be color coded to display the "Best Overall Response" across all treatment cycles as defined in Section 4.8.2.1.

4.9. Safety Analyses

Safety analyses will be conducted using the Safety Population.

4.9.1. Adverse Events

AEs were collected from the time of first clinical trial material administration until 28 days after the final study treatment. During the study follow-up period, only SAEs (including deaths) considered possibly, probably or definitely related to investigational product were reported.

Treatment-emergent AEs (TEAEs) are defined as new events occurring on or after dose 1, having been absent prior to dose 1 or worsening from pre to post treatment. All AEs collected on or after dose 1 of the study up to 28 days after the final study treatment will be considered treatment-emergent. AEs with missing or partial onset dates will be considered as TEAEs unless the partial date indicates that AE began prior to initiation of dose 1. TEAEs will be summarized by system organ class (SOC) and preferred term using the MedDRA, Version 12.0 dictionary. Subjects will be counted only once for each preferred term, once for each body system and by the highest event severity, regardless of how many events the subject experienced. All AEs that occurred for subjects who were never treated will be presented in a separate listing.

Tabular summaries will include the incidence overall [number and percentage of subjects with TEAEs classified by SOC and preferred term]; incidence by intensity [graded according to the National Cancer Institute Common Toxicity Criteria for Adverse Events (NCI CTCAE) version 4.03 or later], causality, seriousness and outcome (e.g., leading to discontinuation of study treatment); and other presentations as appropriate.

For AE summaries that display data by study drug administration period, the following logic will be applied in assigning events to a specific administration period:

If based on the timing of the event, the event falls into an administration period where the subject was not dosed, the event will be attributed to the last administration period where the subject actually received dosing. For example, if subject ADU-CL-01-XXX-XXX had "Erosive Esophagitis" which based on dates, is assigned to Cycle 1, Administration Period 2, but the subject did not actually receive dosing during administration period 2, the event will be assigned to Cycle 1, Administration Period 1.

This logic will also be applied to the AE summaries that combine administration periods “1 and 2” and periods “3 through 6”. For example, if an event falls into administration period 3, but the subject did not receive clinical trial material during this administration period, the event will be attributed to administration period 2 or the last administration period where the subject actually received dosing.

No formal hypothesis-testing analysis of adverse events incidence rates will be performed.

All AEs occurring on study will be listed in subject data listings. All SAEs that are recorded on the CRF will be contained in data listings.

4.9.2. Laboratory Data

Laboratory samples are collected according to the study flow chart in Section 5.1 of the study protocol. For labs that are summarized per visit, the first value will be taken per visit per subject. The only exception to this will be at Baseline where the last value collected prior to treatment will represent Baseline. Baseline is defined in Section 4.2.11.

For lab values that are comprised of a character and numeric value (e.g., "<1.5"), only the numeric value will be used for the summaries in the tables. Both the numeric and character values will be presented in the listing.

If any laboratory parameter has data available for less than 10 subjects, that parameter will only be presented in a listing and not a table.

Descriptive statistics of the observed value and change from Baseline for blood chemistry, urinalysis and hematology parameters will be provided by treatment cycle and visit for each treatment group.

Laboratory toxicities occurring from the start of study drug administration until 28 days after the final study treatment will be collected and summarized for each laboratory parameter overall and by treatment cycle and visit.

Shift tables displaying the shift from Baseline to the Worst Value by NCI CTCAE grade will be presented by treatment cycle and visit as well as across all treatment cycles. The "Worst Value" is defined as the maximum NCI CTCAE grade based upon the worst observation during active study participation. "Worst" can defined as "high" or "low" (or bilaterally) and will be specified within the parameter being summarized.

Clinical laboratory values will be expressed using International System of Units (SI) units as appropriate.

Graphical representations of laboratory data over time will also be provided.

All laboratory data, including pregnancy test results for females of child-bearing potential, will also be provided in data listings.

4.9.3. Vital Signs and Physical Examinations

Complete physical examinations will be performed at screening and at the end of treatment (Week 20). Focused physical examination will be performed on Day 1 of dosing weeks. Any abnormal findings are entered in medical history or as an AE.

Vital signs (blood pressure, pulse rate, respiratory rate and oral body temperature) will be recorded at all study visits.

Height and pulse oximetry will be measured at screening. Body weight will be measured at screening and on Day 1 of each dosing week.

The actual value and change from Baseline (defined in Section 4.2.10) to each on study evaluation will be summarized for vital signs.

Graphical representations of vital sign data over time will also be provided.

By-subject listings of vital sign measurements will also be presented in a data listing.

4.9.4. Electrocardiogram (ECG)

A 12-lead ECG was conducted at screening and at Week 20. ECG results will be summarized descriptively, including the number and percent of subjects with normal, not clinically significant abnormal and clinically significant abnormal results by visit. Shift tables will be presented to show how results changed from Screening over time.

All ECG data for each subject will also be provided in a data listing for the primary analysis.

4.9.5. Concomitant Medications

Each subject's use of medications was reviewed and recorded at each visit. At screening, prospective subjects were asked about the medications (prescription and non-prescription, including vitamins and supplements) they have taken prior to screening. Once randomized, subjects were asked about the medications they have taken since the prior study visit.

All medications used by the subject were recorded including the name of the medication, the dose, route of administration, regimen, dates when the medication was started and stopped and the indication for use.

Medications will be coded using the WHO Drug dictionary (March 2010). All medications captured in the database will be considered a concomitant medication, unless the medication ended prior to the first dose of study medication, or if the medication was started more than 28 days after the last dose of study treatment. Medications with missing or partial dates will be considered concomitant unless the partial date indicates that the medication ended prior to first dose of study medication or started more than 28 days after last dose of study medication. Concomitant medications will be tabulated by Anatomic Therapeutic Class and preferred term for subjects overall as well as within treatment group.

All medications will also be presented in a by-subject data listing. Those that are considered concomitant medications will be flagged.

5. CHANGES TO PLANNED ANALYSES

Protocol Amendment #4 (version 6, dated 14 December 2012) modified the final analysis as follows:

During the trial, and prior to the interim analysis, a protocol amendment dated 14DEC2012 was implemented such that the timing of the interim analysis and final analysis (if the stopping rule for efficacy or futility was not met) was modified to be conducted after 41 and 70 events, respectively, were observed in the primary analysis population (FAS). The justification for this change was that the overall study power would be preserved at an acceptable level (80% power) with a lower number of events (n = 70) compared to the number of events originally planned for (n=83, overall study power of approximately 85%).

In addition, as a result of the pre-specified interim analysis on 04FEB2013, the DMC recommended that the trial should be stopped early for efficacy. All subjects had been enrolled by that time and Arm B subjects were offered and initiated rollover treatment as of 29APR2013. Therefore, this primary analysis is based on a data cut-off date of 29APR2013 (using the data filtering rules described in Section 4.2.2).

Although not included in the original study protocol, an ITT Population will be included as part of this primary study analysis. The ITT population will only be utilized as part of a sensitivity analysis of the primary efficacy endpoint of OS. For the ITT population, the primary endpoint of OS is defined as the time between the date of randomization and the date of death or censoring for untreated subjects and the time between the date of first dose and the date of death for treated subjects (Event Date - Reference Date + 1).

6. REFERENCES

1. ICH-E9 Statistical Principals for Clinical Trials, September 1998
2. O'Brien PC, Fleming TR. A multiple testing procedure for clinical trials. Biometrics. 1979 Sep;35(3):549-56.
3. Lan KK, DeMets DL. Discrete sequential boundaries for clinical trials. Biometrika. 1983;70(3):659-63.
4. ICH-E3 Struture and Content of Clinical Study Report, July 1996
5. Hwang IK, Shih WJ, and DeCani JS (1990). Group sequential designs using a family of type I error probability spending functions. Statist.Med.,, 9, 1439-1445.

7. LIST OF DATA TABLES, FIGURES AND LISTINGS FOR FINAL ANALYSIS

All tables, listings and figures will be numbered according to the ICH-E3 Guideline[4].

The complete table of contents of data tables, figures and listings can be found in the Microsoft Excel spreadsheet provided in Appendix 1.

8. APPENDIX 1 – TABLE OF CONTENTS FOR TABLES FIGURES AND LISTINGS

9. APPENDIX 2 – DETAILS FOR RAW DATA FILTERING PROCESS

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4	14.1.2.1	Summary of Subject Disposition	FAS
5	14.1.2.2	Summary of Treatment Status	FAS
6	14.1.3	Summary of Subject Demographics	FAS
7	14.1.4	Summary of Subject Baseline Characteristics	FAS
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10	14.2.2.1	Summary of Overall Response Rate (based on Recist 1.1) by Treatment	FAS
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18	14.3.2.11	Overall AE Summary By Cycle	Safety
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20	14.3.2.1b	Summary of Incidence of Treatment- Emergent Adverse Events by Cycle, Treatment and Administration - Administrations 1 and 2 Only	Safety
21	14.3.2.1c	Summary of Incidence of Treatment- Emergent Adverse Events by Cycle, Treatment and Administration - Administrations 3 to 6 Only	Safety
22	14.3.2.2a	Summary of Incidence of Treatment- Emergent Adverse Events by Cycle, Treatment, Administration and Grade (Grade 3 or higher)	Safety
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30	14.3.2.3c	Summary of Incidence of Treatment-Emergent and Treatment-Related Adverse Events by Cycle, Treatment and Administration - Administrations 3 to 6 Only	Safety
31	14.3.2.4a	Summary of Incidence of Treatment- Emergent Serious Adverse Events by Cycle, Treatment and Administration	Safety
32	14.3.2.4b	Summary of Incidence of Treatment- Emergent Serious Adverse Events by Cycle, Treatment and Administration - Administrations 1 and 2 Only	Safety

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33	14.3.2.4c	Summary of Incidence of Treatment- Emergent Serious Adverse Events by Cycle, Treatment and Administration - Administrations 3 to 6 Only	Safety
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48	14.4.8.2	Laboratory Tests - Chemistry - LDH - Change from Baseline by Treatment Group and Study Visit
51	14.5.1.1	Vital Signs - Systolic and Diastolic Blood Pressure - Individual Patient Plots for CY + G + C Treatment Group by Study Visit
52	14.5.1.2	Vital Signs - Systolic and Diastolic Blood Pressure - Individual Patient Plots for CY + G Treatment Group by Study Visit
53	14.5.2.1	Vital Signs - Oral Body Temperature - Individual Patient Plots for CY + G + C Treatment Group by Study Visit
54	14.5.2.2	Vital Signs - Oral Body Temperature - Individual Patient Plots for CY + G + C Treatment Group by Study Visit
55	14.2.1	Overall Survival by Treatment
56	14.2.2	Overall Survival by Treatment - Per-Protocol Population

	A	B
1		
2	**Number**	**Titles**
3	16.2.1	Subject Disposition
4	16.2.4.1	Subject Demographics
5	16.2.4.2	Baseline Characteristics
6	16.2.5.1	Study Drug Administration - Cyclophosphamide
7	16.2.5.2	Study Drug Administration - GVAX
8	16.2.5.3	Study Drug Administration - CRS-207
9	16.2.6.1	Survival Analysis Parameters - Full Analysis Set
10	16.2.6.2	Overall Response Parameters - Full Analysis Set
11	16.2.6.3	Tumor Marker Kinetics - Full Analysis Set
12	16.2.7.1.1	Adverse Events
13	16.2.7.1.2	Seriuos Adverse Events
14	16.2.7.2	Injection Site Reaction
15	16.2.8.1.1	Laboratory Tests – Hematology
16	16.2.8.1.2	Grade 3 and above Lab toxicity Laborotory Tests - Hematology
17	16.2.8.2.1	Laboratory Tests – Chemistry
18	16.2.8.2.2	Grade 3 and above Lab toxicity Laborotory Tests - Chemistry
19	16.2.8.3.1	Laboratory Tests – CD4
20	16.2.8.3.2	Grade 3 and above Lab toxicity Laboratory Tests – CD4

	A	B
1		
21	16.2.8.4.1	Laboratory Tests – Coagulation
22	16.2.8.4.2	Grade 3 and above Lab toxicity Laboratory Tests – Coagulation
23	16.2.8.5.1	Laboratory Tests – Urinalysis
24	16.2.8.6	Pregnancy Test
25	16.2.9.1	Vital Sign
26	16.2.9.2	Concomitant Medications
27	16.3.1	Deaths

	A	B	C
1	**Raw Data**		
2	RD_AE	AESTDT	Date ~ Date of onset
3	RD_AE_ACTIVE	AESTDT	Date ~ Date of onset
4	RD_AE_DELETE	AESTDT	Date ~ Date of onset
5	RD_AE_PR	DOV	Date of Visit
6	RD_CCVRL	LBDTTM_1	Date ~ Date and Time Sample Collected ~ CD4
7		LBDTTM_2	Date ~ Date and Time Sample
8		SAMPDT_1	Date ~ Date sample collected ~ Was a sample collected for Virology
9		DOV	Date of Visit
10	RD_CCVRL_SCTVIROL_OTH_1	SAMPDT_2	Date ~ Date sample collected
11	RD_CCVRL_SCTVIROL_OTH_ACTIVE	SAMPDT_2	Date ~ Date sample collected
12	RD_CCVRL_SCTVIROL_OTH_DELETED	SAMPDT_2	Date ~ Date sample collected
13	RD_CM	CMSTDT_1	Date ~ Start Date
14	RD_CM_ACTIVE	CMSTDT_1	Date ~ Start Date
15	RD_CM_DELETED	CMSTDT_1	Date ~ Start Date
16	RD_CM_PR	DOV	Date of Visit
17	RD_COLUMNLABELS		
18	RD_CONTELIG	DOV	Date of Visit
19	RD_CPE	CPEDT	Date ~ YesIf yes specify date of examination ~ Has a complete physical examination been done
20	RD_CPPR	DOV	Date of Visit
21	RD_CP_SCTCP	CPDT	Date ~ Date of Procedure
22	RD_CP_SCTCP_ACTIVE	CPDT	Date ~ Date of Procedure
23	RD_CP_SCTCP_DELETED	CPDT	Date ~ Date of Procedure
24	RD_CTSCAN	SCTHRDT	Date ~ DoneDate of procedure ~ Scan performed
25		SCTHRDT_1	Date ~ DoneDate of procedure ~ Scan performed
26		SCTHRDT_2	Date ~ DoneDate of procedure ~ Scan performed
27		DOV	Date of Visit
28	Rd_CTSCAN_SCTCTSCAN_3	SCTHRDT_3	Date ~ Date of procedure
29	Rd_CTSCAN_SCTCTSCAN_ACTIVE	SCTHRDT_3	Date ~ Date of procedure
30	Rd_CTSCAN_SCTCTSCAN_DELETED	SCTHRDT_3	Date ~ Date of procedure
31	RD_CYCLO	EXSTDTTM_1Date ~ YesStart Date and Time of Administration ~ Was dose administered	
32	RD_DATADICTIONARY		
33	RD_DEMOG_1	DOV	Date of Visit
34	RD_DIAG_C	DGIDGDT	Date ~ Date of Initial Diag
35	RD_DOV	DOV_1	Date ~ Date of visit assessment
36	RD_DOV_1	DOV_1	Date ~ Date of visit assessment
37	RD_ECG	ECGDT	Date ~ YesDate Performed ~ Was an ECG performed
38	RD_ECG_SCR	ECGDT	Date ~ YesDate Performed ~ Was an ECG performed
39	RD_ECOG	ECOGDT	Date ~ YesDate of Assessment ~ Was ECOG Performance Assessment performed
40	RD_ELIG	DTMCNSDT	Date ~ Consent Date
41	RD_ENROL		
42	RD_FPE	FPEDT	Date ~ YesIf yes specify date of examination ~ Has a focused physical examination been done
43	RD_FPE_SCTCPE_1	DOV	Date of Visit
44	RD_FPE_SCTCPE_ACTIVE	DOV	Date of Visit
45	RD_FPE_SCTCPE_DELETED	DOV	Date of Visit
46	RD_GVAX	EXINJDT	Date ~ YesDate of Injection ~ Was dose administered
47	RD_HLA	HLADT	Date ~ YesIf Yes specify date collected ~ Was a sample collected for HLA typing
48	RD_LB_C	LBDTTM	Date ~ Date and Time Sample
49	RD_LB_COAG	LBDTTM	Date ~ Date and Time Sample
50	RD_LB_C_SCTLB_C1	LBDTTM	Date ~ Date and Time Sample
51	RD_LB_C_SCTLB_C1_ACTIVE	LBDTTM	Date ~ Date and Time Sample
52	RD_LB_C_SCTLB_C1_DELETED	LBDTTM	Date ~ Date and Time Sample
53	RD_LB_H	LBDTTM	Date ~ Date and Time Sample
54	RD_LB_C_SCTLB_H1	LBDTTM	Date ~ Date and Time Sample
55	RD_LB_C_SCTLB_H1_ACTIVE	LBDTTM	Date ~ Date and Time Sample
56	RD_LB_C_SCTLB_H1_DELETED	LBDTTM	Date ~ Date and Time Sample
57	RD_LB_PREG	DTMLBDTTM_2_1	Date ~ YesDate performed ~ Pregnancy test
58	RD_LB_PREG_S	DTMLBDTTM_2	Date ~ YesDate performed ~ Pregnancy test
59	RD_LB_U	LBDTTM	Date ~ Date and Time Sample
60	RD_LESION	RESP_NEWDT	Date ~ Evaluation Date
61	RD_LESION_ACTIVE	RESP_NEWDT	Date ~ Evaluation Date
62	RD_LESION_DELETED	RESP_NEWDT	Date ~ Evaluation Date
63	RD_LESION_NT	LSDT_N_1	Date ~ Evaluation Date
64		LSDT_N_2	Date ~ Evaluation Date
65		LSDT_N_3	Date ~ Evaluation Date
66		LSDT_N_4	Date ~ Evaluation Date
67		LSDT_N_5	Date ~ Evaluation Date
68		LSDT_N_6	Date ~ Evaluation Date
69		LSDT_N_7	Date ~ Evaluation Date
70		LSDT_N_8	Date ~ Evaluation Date
71		LSDT_N_9	Date ~ Evaluation Date
72		LSDT_N_10	Date ~ Evaluation Date
73		DOV	Date of Visit
74	RD_LESION_NTPR	DOV	Date of Visit
75	RD_LESION_NT_SCR	LSDT_N_SCR_1	Date ~ Evaluation Date
76		LSDT_N_SCR_2	Date ~ Evaluation Date
77		LSDT_N_SCR_3	Date ~ Evaluation Date
78		LSDT_N_SCR_4	Date ~ Evaluation Date
79		LSDT_N_SCR_5	Date ~ Evaluation Date
80		LSDT_N_SCR_6	Date ~ Evaluation Date
81		LSDT_N_SCR_7	Date ~ Evaluation Date
82		LSDT_N_SCR_8	Date ~ Evaluation Date
83		LSDT_N_SCR_9	Date ~ Evaluation Date
84		LSDT_N_SCR_10	Date ~ Evaluation Date

	A	B	C
1	**Raw Data**		
85		DOV	Date of Visit
86	RD_LESION_T	LSDTA_1	Date ~ Evaluation Date
87		LSDTA_2	Date ~ Evaluation Date
88		LSDTA_3	Date ~ Evaluation Date
89		LSDTA_4	Date ~ Evaluation Date
90		LSDTA_5	Date ~ Evaluation Date
91		DOV	Date of Visit
92	RD_LESION_TPR	DOV	Date of Visit
93	RD_LWAION_T_SCR	LSDT_1	Date ~ Evaluation Date
94		LSDT_2	Date ~ Evaluation Date
95		LSDT_3	Date ~ Evaluation Date
96		LSDT_4	Date ~ Evaluation Date
97		LSDT_5	Date ~ Evaluation Date
98		DOV	Date of Visit
99	RD_LM_MESO	LMDT	Date ~ YesIf Yes specify date collected ~ Was a sample collected for Lm and Mesothelin specific immunity assays
100	RD_MHX	MHSTDT	Date ~ Onset date
101	RD_MHX_ACTIVE	MHSTDT	Date ~ Onset date
102	RD_MHX_DELETED	MHSTDT	Date ~ Onset date
103	RD_MHXPR	DOV	Date of Visit
104	RD_PBMC	PBDT_1	Date ~ YesIf Yes specify date and time collected ~ Was a sample collected for PBMC
105	RD_PRCA_SCTPRCA	CMSTDT	Date ~ Start Date
106	RD_PRCA_SCTPRCA_ACTIVE	CMSTDT	Date ~ Start Date
107	RD_PRCA_SCTPRCA_DELETED	CMSTDT	Date ~ Start Date
108	RD_RADPR	DOV	Date of Visit
109	RD_RAD_SCTRAD	RDFRDSDT	Date ~ Start Date
110	RD_RAD_SCTRAD_ACTIVE	RDFRDSDT	Date ~ Start Date
111	RD_RAD_SCTRAD_DELETED	RDFRDSDT	Date ~ Start Date
112	RD_RAND_1	DTMRANDDTTM	Date ~ YesDate of Randomization ~ Will subject be randomized
113	RD_REGDOCS		
114	RD_RESP	RESPDT	Date ~ Date of Assessment
115	RD_RESP_IR	RESPDT	Date ~ Date of Assessment
116	RD_SCREEN	DOV	Date of Visit
117	RD_STDRG	EXSTDTTM_1_1	Date ~ YesStart Date and Time of Administration ~ Was infusion administered
118	RD_SURG_SCTSURG	SUDT	Date ~ Date of Surgery
119	RD_SURG_SCTSURG_ACTIVE	SUDT	Date ~ Date of Surgery
120	RD_SURG_SCTSURG_DELETED	SUDT	Date ~ Date of Surgery
121	RD_TM	TMDT_TMSMPYN	Date ~ YesIf Yes specify date collected ~ Was a sample collected for CA19 9 assessment as applicable
122		TMDT_TMSMPYN_1	Date ~ YesIf Yes specify date collected ~ Was a sample collected for CEA assessment as applicable
123		DOV	Date of Visit
124	RD_TM_SCTTM_2_1	TMDT_1	Date ~ YesIf Yes specify date collected
125	RD_TM_SCTTM_2_1_ACTIVE	TMDT_1	Date ~ YesIf Yes specify date collected
126	RD_TM_SCTTM_2_1_DELETED	TMDT_1	Date ~ YesIf Yes specify date collected
127	RD_TRTARM	DOV	Date of Visit
128	RD_TRTCOMP	DOV	Date of Visit
129	RD_UNSPR		
130	RD_VIROL	SAMPDT	Date ~ YesDate sample collected ~ Was a sample collected for Virology
131	RD_VIROL_SCTVIROL_OTH	SAMPDT	Date ~ Date sample collected
132	RD_VIROL_SCTVIROL_OTH_ACTIVE	SAMPDT	Date ~ Date sample collected
133	RD_VIROL_SCTVIROL_OTH_DELETED	SAMPDT	Date ~ Date sample collected
134	RD_VISITREPORT		
135	RD_VS	VSDT	Date ~ Date of Assessment
136	RD_VS1	VSDT_1	Date ~ Date of Assessment
137		VSDT_2	Date ~ Date of Assessment
138		VSDT_3	Date ~ Date of Assessment
139		VSDT_4	Date ~ Date of Assessment
140		VSDT_5	Date ~ Date of Assessment
141		VSDT_6	Date ~ Date of Assessment
142		VSDT_7	Date ~ Date of Assessment
143		VSDT_8	Date ~ Date of Assessment
144		VSDT_9	Date ~ Date of Assessment
145		DOV	Date of Visit
146	RD_VS1_SCTVS10	VSDT_1	Date ~ Date of Assessment
147	RD_VS1_SCTVS10_ACTIVE	VSDT_1	Date ~ Date of Assessment
148	RD_VS1_SCTVS10_DELETED	VSDT_1	Date ~ Date of Assessment
149	RD_VS2	VSDT	Date ~ Date of Assessment
150	RD_VS3	VSDT	Date ~ Date of Assessment
151	RD_VSR	DOV	Date of Visit
152			
153			
154	**Follow-up Data**		
155	CT_OTH_tab	VISITDT_A1_1	
156		VISITDT_A1_2	
157		VISITDT_A1_3	
158	CT_SCN_tab	VISITDT_A2_1	
159		VISITDT_A2_2	
160		VISITDT_A2_3	
161	CT_SCN_TAB_tab	SCTHRDT_A1_1	
162		SCTHRDT_A1_2	
163	LESION_NEW_Tab	VISITDT_A1_1	
164		VISITDT_A1_2	
165		VISITDT_A1_3	
166	LS_NT_C_tab	VISITDT_A1_1	

	A	B	C
1	**Raw Data**		
167		VISITDT_A1_2	
168		VISITDT_A1_3	
169	LS_NT_tab	VISITDT_A1_1	
170		VISITDT_A1_2	
171		VISITDT_A1_3	
172	LS_T_tab	VISITDT_A1_1	
173		VISITDT_A1_2	
174		VISITDT_A1_3	
175	PBMC_tab	VISITDT_A2_1	
176		VISITDT_A2_2	
177		VISITDT_A2_3	
178	PRCA_tab	VISITDT_A1_1	
179		VISITDT_A1_2	
180		VISITDT_A1_3	
181	RAD_tab	VISITDT_A1_1	
182		VISITDT_A1_2	
183		VISITDT_A1_3	
184	RESP_tab	VISITDT_A2_1	
185		VISITDT_A2_2	
186		VISITDT_A2_3	
187	RESPirRC_tab	VISITDT_A1_1	
188		VISITDT_A1_2	
189		VISITDT_A1_3	
190	SF_DISC_tab	DSCONTDT_A1	
191	SF_Tab	VISITDT_A1_1	
192		VISITDT_A1_2	
193		VISITDT_A1_3	