A Phase 2, Multicenter, Randomized Study to Evaluate the Safety and Efficacy of Viagenpumatucel-L (HS-110) in Combination with Low Dose (Metronomic) Cyclophosphamide Versus Chemotherapy Alone in Patients with Non-Small Cell Lung Adenocarcinoma after Failure of Two or Three Previous Treatment Regimens for Advanced Disease

Protocol HS110-201

Amendment History:

Date	Version	Amendment Number	Amendment Type
07 Mar 2014	1.0	Initial Protocol	Not applicable
18 April 2014	2.0	1	Non-substantial
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29 Oct 2014	4.0	3	Non-substantial

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SPONSOR PROTOCOL APPROVAL PAGE

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Amendment #: 3

Version #: 4.0

Version Date: 29 October 2014

I, the undersigned, have read this protocol and confirm that to the best of my knowledge it accurately describes the planned conduct of the study. I hereby approve this protocol for release to clinical trial sites.

Melissa Price, PhD
Vice President, Clinical and Regulatory Affairs
Heat Biologics

29-Oct-2014
Approval Date

INVESTIGATOR PROTOCOL AGREEMENT PAGE

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Version/Date: Version 4.0 (29 October 2014)

I understand that all documentation provided to me by Heat Biologics, Inc., or its designated representative(s) concerning this study that has not been published previously will be kept in the strictest confidence. This documentation includes the study protocol, investigator's brochure, case report forms, and other scientific data.

This study will not commence without the prior written approval of a properly constituted Institutional Review Board (IRB) or Ethics Committee (EC), and Institutional BioSafety Committee (IBC). No changes will be made to the study protocol without the prior written approval of Heat Biologics, Inc., and the IRB, EC, and/or IBC, except where necessary to eliminate an immediate hazard to the patient.

I have read and understand the clinical protocol and agree to conduct the clinical study in compliance with the protocol, Good Clinical Practice, and applicable local regulatory requirements.

Principal Investigator Name, printed: _____

Principal Investigator Signature: _____

Date: _____

CLINICAL PROTOCOL SYNOPSIS

Sponsor: Heat Biologics, Inc.		**Protocol No.** HS110-201
Name of Study Drug: Viagenpumatucel-L (HS-110)		**Phase of Development:** Phase 2
Trial title	A Phase 2, Multicenter, Randomized Study to Evaluate the Safety and Efficacy of Viagenpumatucel-L (HS-110) in Combination with Low Dose (Metronomic) Cyclophosphamide Versus Chemotherapy Alone in Patients with Non-Small Cell Lung Adenocarcinoma after Failure of Two or Three Previous Treatment Regimens for Advanced Disease	
Study Objective(s)	**Primary Objective:** • To evaluate overall survival **Secondary Objectives:** • To evaluate the safety of the combination of viagenpumatucel-L and low-dose cyclophosphamide (CY) • To evaluate immune-related overall response rate (irORR), (complete response and partial response) and also overall response rate (ORR) by RECIST • To evaluate immune-related disease control rate (irDCR) (complete response, partial response, and stable disease) and also disease control rate (DCR) by RECIST at 6 months following randomization and overall • To evaluate immune-related progression-free survival (irPFS) and also progression-free survival (PFS) by RECIST • To evaluate immune-related time to progression (irTTP) and also time to progression (TTP) by RECIST • To evaluate the proportion of patients who are alive at 6 months following randomization • To evaluate the proportion of patients who are alive at 12 months following randomization • To characterize the peripheral blood immunologic response via intracellular cytokine staining (ICS) by flow cytometry and/or ELISPOT on IFNγ-positive CD8+ cells following vaccination **Exploratory Objectives:** To evaluate exploratory endpoints, which may include: • Peripheral blood immunologic response by flow cytometry and ELISPOT • Total peripheral blood mononuclear cell (PBMC) counts by flow cytometry, including lymphocyte subsets • Evaluation of tumor tissue obtained from pre-treatment biopsy or archival biopsy tissue for shared tumor antigen expression, expression of major histocompatibility complex (MHC) class I, and expression of immunosuppressive molecules • Evaluation of tumor tissue obtained from post-treatment biopsy for presence of tumor-infiltrating T lymphocytes (TILs) • Evaluation of tumor tissue and PBMCs for T cell receptor (TCR) sequencing to determine correlation between clonally expanded T cell populations and other endpoints	
Trial centers	Up to 30 centers	
Total sample size	Approximately 123 patients will be randomized 2 to 1 into the experimental and control group, respectively.	

Trial design	Patients who have failed 2 or 3 prior lines of therapy for incurable or metastatic disease will be randomized 2:1 to 1 of the following treatment groups : **Experimental Group**: Viagenpumatucel-L plus metronomic CY (82 patients) **Control Group**: Physician's Choice (PC) (41 patients) • Vinorelbine • Erlotinib • Gemcitabine • Paclitaxel • Docetaxel • Pemetrexed Patients randomized to the experimental group will be treated during an induction phase with combination metronomic CY and viagenpumatucel-L weekly for 12 weeks followed by monotherapy viagenpumatucel-L in the maintenance phase once every 9 weeks for up to 12 months or until discontinuation from study treatment, at which time patients will be followed for overall survival. Patients randomized to the control group will be treated with a PC regimen until discontinuation from study treatment, at which time patients will be followed for overall survival. Patients with progressive disease by irRC at an assessment may continue on treatment until the next assessment if judged by the investigator to be in the patient's best interest. While treatment may continue beyond irPD, statistical analysis will still follow strict definitions as defined in section 6.5.1 Tumor Assessments. Blood samples will be taken to evaluate the CD8+ immune response in PBMCs and their correlation to overall survival. Patients will have samples drawn prior to the first study treatment, at Weeks 4, 10, 13, and 22, and at End of Treatment (EOT). Where considered appropriate by the investigator, patients randomized to the experimental group will be invited to consent for biopsies pre-treatment and at Week 13 (*i.e*. after completion of 12 weeks of treatment) for exploratory biomarker analysis. Patients will also be asked to consent to provide archival biopsy tissue if available. Examination of tumor samples will enable screening for expression of MHC class I (necessary for any immunologic response), expression of immunosuppressive molecules, including, for example, CTLA-4, PD-L1, and PD-1 (informative for future possible combination studies), expression of tumor antigens that are known to be expressed by viagenpumatucel-L, presence of TILs, and T-cell receptor (TCR) sequencing. Patients will be monitored for safety with adverse event (AE) reporting, clinical laboratory parameters (hematology, liver function, electrolytes, renal function, and urinalysis), 12-lead electrocardiogram (ECG) recording, vital signs, and physical exams. Efficacy assessments will include survival, tumor evaluation, and immune response. Tumor assessments will be done at screening, every 9 weeks until Week 28, and every 12 weeks thereafter until progression, unless clinical signs of progression necessitate earlier assessment.

Dosing regimen, form and route	**Experimental Group** • **Viagenpumatucel-L:** 1 x 10^7 cells weekly for 12 weeks followed by injections every 9 weeks for up to 12 months or until discontinuation from study treatment, whichever occurs first. Viagenpumatucel-L is provided as single-dose vials either 1) as concentrated frozen liquid, which will require dilution by the pharmacy with sterile saline, or 2) as fully-diluted frozen liquid not requiring additional dilution. In either case the final drug product will consist of 10 million cells resuspended in buffered saline containing human serum albumin (HSA), dimethyl sulfoxide (DMSO), and pentastarch. Each vaccine dose of 0.5 mL will be divided into 5 injections (0.1 mL per injection) and administered as 5 spatially divided intradermal injections in the same extremity to increase volume distribution and enhance antigen presentation to lymph node regions. Dosing will rotate injection site extremities every 4 timepoints: antero-lateral left thigh, antero-lateral right thigh, left shoulder and right shoulder. • **CY**: One 50mg tablet administered orally daily for 7 days on alternating weeks for a total of 6 weeks of therapy over 12 weeks **Control Group** Therapy to be given in nominal 21 day cycles with dose and route according to investigator's standard practice until progression • **Vinorelbine** • **Erlotinib** • **Gemcitabine** • **Paclitaxel** • **Docetaxel** • **Pemetrexed**

Eligibility criteria	**Inclusion Criteria:** 1. Histologically or cytologically confirmed non-small cell lung adenocarcinoma 2. Received at least 2 and no more than 3 prior lines of systemic therapy for Stage IV or recurrent incurable NSCLC, including cytotoxic chemotherapy, molecularly-targeted agents, or immunotherapy. Prior adjuvant or neoadjuvant chemotherapy or definitive chemoradiation for locally advanced disease does not count as a line of therapy as long as the last administration of the regimen occurred at least 12 months prior to enrollment. A repeat course of a prior line of systemic therapy does not count as an additional line of therapy. Maintenance systemic therapy or palliative radiotherapy to single sites of disease will not be considered an additional regimen. 3. Suitable, in the opinion of the investigator, for conventional single agent chemotherapy 4. Documented disease progression at study entry 5. Age $\geq$ 18 years 6. ECOG performance status (PS) $\leq$ 1; ECOG PS=2 patients may be considered after discussion with the Medical Monitor 7. CNS metastases may be permitted after discussion with the Medical Monitor but must be treated and neurologically stable. Patients must be on a stable or decreasing dose of corticosteroids and/or have no requirement for anticonvulsants for 14 days prior to screening. 8. Lab parameters: • Albumin $\geq$ 2.5 mg/dL • Total Bilirubin < 1.5 mg/dL unless known Gilbert's syndrome • Alanine transaminase (ALT), and aspartate transaminase (AST) $\leq$3.0 × upper limits of normal (ULN) or $\leq$5 × ULN in the case of liver metastases. • Calculated or measured creatinine clearance >35 mL/minute per the Cockcroft-Gault formula • Absolute neutrophil count $\geq$ 1,500/mm^3 • Hemoglobin $\geq$ 9 g/dL • Platelet count $\geq$ 100,000/mm^3 9. Willing and able to comply with the protocol and sign informed consent, including weekly clinic visits to receive injections for 12 weeks followed by every-3-week visits thereafter for up to 12 months if randomized to the experimental group. 10. Female patients who are of childbearing potential and fertile male patients must agree to use an effective form of contraception (e.g., abstinence, oral contraceptives, intrauterine device, barrier method with spermicide, or surgical sterilization) with their sexual partners throughout study participation. Female patients of childbearing potential must test negative for pregnancy prior to enrolling in the trial.

	Exclusion Criteria: 1. Received systemic anticancer therapy (including cytotoxic chemotherapy, monoclonal antibodies, immunotherapy, and tyrosine kinase inhibitors (TKIs)) or radiation therapy within the previous 14 days. 2. Received more than 3 lines of prior conventional therapy for advanced disease. 3. Human immunodeficiency virus (HIV), hepatitis B or C, or severe/uncontrolled infections or intercurrent illness, unrelated to the tumor, requiring active therapy. Testing is not required in the absence of history. 4. Any condition requiring concurrent systemic immunosuppressive therapy 5. Known immunodeficiency disorders, either primary or acquired 6. Known leptomeningeal disease 7. Other active malignancies 8. Prior treatment with a cancer vaccine for this indication 9. Pregnant or breastfeeding
Safety monitoring	All patients will be assessed for pre-existing symptoms during screening (from the date of signature of informed consent to immediately prior to first dose of study drug). Symptoms will be documented as AEs from the first dose of study drug until 4 weeks after the last dose of study drug or until death, whichever occurs first. Any AEs occurring after this time period will also be reported, if in the opinion of the investigator, the event is deemed related to study drug. All AEs will be followed until the event has subsided or, in the case of permanent impairment, until the condition stabilizes. The Data Monitoring Committee will assess safety of the vaccine on an ongoing basis during trial enrollment and dosing.

Statistical Methods	Patients will be randomized centrally using a stratified block design according to ECOG PS (strata: ECOG PS ≤ 1 vs. 2) and previous treatment with a checkpoint inhibitor (strata: yes vs. no) This sample size is based on the hypothesis that the combination of vaccine and CY versus physician's choice will result in a significant increase in overall survival. The sample size in this study will be 123 patients randomized in a 2 to 1 manner into the experimental and control groups (82 vs 41 randomized) to provide 59 events in the experimental group and 33 events in the control group. By assuming an alpha of 10% (one tailed), the study should have an 80% power to detect a 50% reduction in the risk of death (median overall survival (OS) of 10 months in the treatment group vs 5 months in the control group; HR = 0.50). The primary analysis will be conducted when 92 survival events have accrued. The primary endpoint will be overall survival. Survival curves will be generated by the method of Kaplan-Meier and compared with the log-rank test. In an exploratory analysis, the weighted log rank test will also be used. The weighted log rank test preserves the statistical power that is lost due to the potential lag time effect in efficacy with immunotherapeutic agents. In a supporting analysis, the hazard ratio for the risk of death between the experimental and control groups will be estimated using multivariate Cox Proportional Hazards regression. Independent variables with a $p<0.05$ will be retained in the final model. As a final exploratory analysis, restricted mean survival times will be generated. The secondary binary efficacy endpoints will be reported as odds ratios with 95% confidence intervals (CI). The additional exploratory endpoints will be evaluated descriptively as means, medians and proportions with appropriate measures of variance. Two interim analyses will be performed after approximately 14 and 41 patients randomized to the experimental group have had blood samples taken at Week 10 (*i.e.* after completion of 9 weeks of treatment). For the 41 patient analysis only, the trial will be discontinued, or modified as necessary, if fewer than 50% of patients in the experimental group experience a peripheral blood immunologic response (IR) via ICS of IFNγ-positive CD8+ cells greater than 2-fold over baseline unless there is evidence of clinical or immunologic activity in secondary endpoints. For example, if the overall response rate suggested clinical activity, the trial may still proceed as written. Neither of the interim analyses will examine overall survival.

Efficacy Parameters	Primary Endpoints: • **Overall Survival (OS):** OS will be calculated as the duration of survival from the date of randomization into the study to the date of death from any cause, or will be censored on the date the patient was last known to be alive Secondary Endpoints: • **Safety:** Safety is defined as the number of adverse events (AE)/serious adverse events (SAE) in patients receiving viagenpumatucel-L and low-dose CY. • **Immune-related overall disease control rate (irDCR):** irDCR is defined as the proportion of patients whose immune-related best overall response is immune-related partial response (irPR), immune-related complete response (irCR), or immune-related stable disease (irSD). irSD = does not meet criteria for irCR or irPR, in the absence of immune-related progressive disease (irPD). • **Overall Disease Control Rate (DCR):** DCR is defined as the proportion of patients whose best overall response using RECIST criteria is partial response (PR), complete response (CR), or stable disease (SD). SD = does not meet criteria for CR or PR, in the absence of progressive disease (PD). • **6-month immune-related disease control rate (6m-irDCR):** 6m-irDCR is defined as the proportion of patients whose immune-related best response is irPR, irCR, or irSD 6 months following randomization. • **6-month Disease Control Rate (6mDCR):** 6mDCR is defined as the proportion of patients whose best response using RECIST is PR, CR, or SD 6 months following randomization. • **Immune-related Overall Response Rate (irORR):** irORR is defined as the number of patients with irCR or irPR, divided by total participants in the data set. • **Overall Response Rate (ORR):** ORR is defined as the number of patients with CR or PR by RECIST, divided by total patients in the data set. • **Immune-related Progression-Free Survival (irPFS):** irPFS will be calculated as the time between randomization and the date of irPD or death, whichever occurs first. • **Progression-Free Survival (PFS):** PFS will be calculated as the time between randomization and the date of PD as defined by RECIST or death, whichever occurs first. • **Immune-related time to progression (irTTP):** irTTP is defined as the time between the date of randomization and the date of irPD. • **Time to progression (TTP):** TTP is defined as the time between the date of randomization and the date of RECIST documented PD. • **6-month overall survival (6mOS):** 6mOS will be calculated as the proportion of patients who are alive at 6 months following randomization • **12-month overall survival (12mOS):** 12mOS will be calculated as the proportion of patients who are alive at 12 months following randomization • **Immunologic response (IR):** Peripheral blood immunologic response via intracellular cytokine staining (ICS) by flow cytometry and/or ELISPOT of IFNγ-positive CD8+ cells greater than 2-fold over baseline

	Exploratory Endpoints: • Peripheral blood immunologic response (analysis of surface markers, CD3, CD4, CD8, CD19, CD25, CD45, CD56, FoxP3, and degranulation) and stimulation analysis via ICS of IFNγ and granzyme B (gzB). • Total PBMC counts by flow cytometry, including lymphocyte subsets (B cells, helper T cells, cytotoxic T cells, natural killer (NK) cells and regulatory T cells (T-regs)) • Evaluation of tumor tissue obtained from pre-treatment biopsy or archival biopsy tissue for shared tumor antigen expression (LAGE-1, NY-ESO-1, MAGE-[A1-10], CT7, CT10, GAGE, etc.), expression of MHC class I, and expression of immunosuppressive molecules, including, for example, CTLA-4, PD-L1 and PD-1, by mRNA expression and/or immunohistochemistry (IHC) analysis • Evaluation of tumor tissue obtained from post-treatment biopsy for presence of TILs • Evaluation of tumor tissue and PBMCs for TCR sequencing to determine correlation between clonally expanded T cell populations and other endpoints

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LIST OF ABBREVIATIONS

6mDCR	6-month Disease Control Rate
6m-irDCR	6-month Immune-Related Disease Control Rate
AE(s)	Adverse event(s)
ALT	Alanine aminotransferase
ANA	Antinuclear antibodies
AST	Aspartate aminotransferase
AT	As treated
CBC	Complete blood count
CFR	Code of Federal Regulations
cGMP	Current Good Manufacturing Practice
CI	Confidence interval
CRF	Case report form
CT	Computed tomography
CTCAE	Common Terminology Criteria for Adverse Events
CTL	Cytotoxic T lymphocytes
CTLA4	Cytotoxic T-lymphocyte associated antigen 4
CR	Complete response
CY	Cyclophosphamide
DC	Dendritic cells
DCR	Disease control rate
DMSO	Dimethyl sulfoxide
EC	Ethics Committee
ECG	Electrocardiograms
ECOG	Eastern Cooperative Oncology Group
ELISA	Enzyme-linked immunosorbent assay
ELISPOT	Enzyme-linked immunosorbent spot
EOT	End of Treatment
ER	Endoplasmic reticulum
ESR	Erythrocyte sedimentation rate
EX	Excluded Patients
FDA	Food and Drug Administration
FFPE	Formalin-fixed paraffin embedded
GCP	Good Clinical Practice
GLP	Good Laboratory Practice
G-CSF	Granulocyte colony-stimulating factor
gzB	Granzyme B
HIV	Human immunodeficiency virus
HLA	Human leukocyte antigen
HSA	Human serum albumin
IBC	Institutional Bioethics Committee
ICH	International Conference on Harmonization
ICS	Intracellular Cytokine Staining
IFNγ	Interferon gamma
IHC	Immunohistochemistry

IR	Immunologic Response
IRB	Institutional Review Board
irCR	Immune-Related Complete Response
irDCR	Immune-Related Overall Disease Control Rate
irORR	Immune-Related Overall Response
irPD	Immune-Related Progressive Disease
irPFS	Immune-Related Progression Free Survival
irPR	Immune-Related Partial Response
irRC	Immune-Related Response Criteria
irSD	Immune-Related Stable Disease
ISR	Injection Site Reaction
ITT	Intention to treat
i.v.	Intravenous
IXRS	Interactive Response System
LTFU	Long-term Follow-up
MedRA	Medical Dictionary for Regulatory Activities
MHC	Major histocompatibility complex
MRI	Magnetic resonance imaging
mRNA	Messenger Ribonucleic Acid
MSDS	Material safety data sheet
NCI	National Cancer Institute
NK	Natural killer
NSCLC	Non-small cell lung cancer
ORR	Overall Response Rate
OS	Overall Survival
PBMC	Peripheral blood mononuclear cell
PC	Physician's Choice
PCR	Polymerase Chain Reaction
PD	Progressive Disease
PD-1	Programmed death 1 receptor
PD-L1	Programmed death ligand 1
PFS	Progression-Free Survival
P.O.	Per os
PR	Partial Response
PS	Performance Status
RBC	Red blood cell
SAE	Serious adverse event
SAR	Suspected adverse reaction
SD	Stable Disease
SOA	Schedule of Assessments
T-reg	Regulatory T cell
TCR	T-cell Receptor
TEAE	Treatment emergent adverse event
TIL	Tumor Infiltrating Lymphocyte
TKI	Tyrosine Kinase Inhibitor

ULN	Upper limit of normal
US	United States
WBC	White blood cell

1.0 BACKGROUND

1.1 Non-Small Cell Lung Cancer

The annual incidence of non-small cell lung cancer (NSCLC) in the United States is the third highest of all malignancies, with ~200,000 cases being recorded in 2012.[1] More than 50% of patients have local or distant metastatic disease at diagnosis, and in stage IV the disease is almost uniformly fatal with a 5-year survival of <5%.[2] The overall annual mortality from lung cancer worldwide is 1.4 million, which is higher than that from colon, breast, and prostate carcinoma combined. Despite a number of therapeutic advances in the last decade, response to first line and subsequent therapy for advanced NSCLC remains suboptimal.

Patients with metastatic or recurrent NSCLC who lack a relevant mutation are usually treated with platinum-containing doublet chemotherapy (with or without the anti-VEGF antibody bevacizumab [Avastin]).[3] Patients with EGFR or EML4-ALK mutations generally do better with appropriate molecularly targeted therapies, compared to wild type patients treated with doublet chemotherapy, but even these patients eventually progress and end up requiring conventional cytotoxic chemotherapy.[4,5]

With standard contemporary regimens, including maintenance therapy in the first line setting, median survival of patients with advanced NSCLC in 2013 was in the range of 12-16 months.[6,7] Despite improvements in the first line management of advanced NSCLC, all patients will eventually progress or remain refractory to initial therapy and at least 50 percent will then subsequently receive second line treatment, usually consisting of docetaxel, erlotinib or pemetrexed.[8]

An increasing proportion of these patients are also becoming candidates for third and fourth line interventions. However, despite a growing tendency toward more aggressive treatment of later stages of the disease, outcomes are limited as response to currently available therapies significantly diminishes at each successive stage of treatment. One large recent series of Western patients showed that response rates were reduced from a first line figure of 20.9% to a second line value of 16.3%, a third line one of 2.3% and a fourth line outcome of 0%. The disease control rate (response plus stable disease) also decreased dramatically from first- to fourth-line treatment.[9] A similar recent study in Japanese patients showed that 69.3%, 38.4%, 17.7%, and 6.0% of patients received second-, third-, fourth-, and fifth-line chemotherapy, respectively, with median survival times of 15.3 months, 12.8 months, 12.0 months and 9.9 months respectively. Overall response rates and disease control rates with third- and fourth-line chemotherapy were 17.0% and 34.4% and 11.3% and 24.5%, respectively.[10]

The relatively poor responses seen in the third and fourth line setting are due to a combination of progressive biological resistance of the underlying tumor arising from successive prior regimens of chemotherapy[11,12] and a decline in the performance status of patients, due to treatment and disease related morbidities.[13,14,15]

The increasing proportion of patients being delivered to the third line arena, combined with a lack of effective strategies with which to treat them, collectively create a significant clinical need for additional third line and beyond treatment interventions, which are mechanistically novel and of inherently low toxicity. Vaccine-based immunotherapy is one such candidate to meet the demands of this particular therapeutic challenge and is the subject of the current trial in patients with advanced NSCLC being treated in the third line setting.

1.2 Vaccine-based Immunotherapy for NSCLC

1.2.1 Background

While some types of tumors, such as renal carcinoma and melanoma, are traditionally thought to be immunogenic, as evidenced by documented spontaneous clinical regressions and durable responses to high-dose immunomodulatory agents, such as interleukin-2, evidence for an immune role in NSCLC has historically been less compelling, although substantial clinical evidence is now emerging to support this proposition.

In particular, the observation of objective responses following immunotherapy in patients with highly refractory NSCLC validates this approach in a preliminary manner suggesting that additional immunological strategies for tumor control, such as vaccines, are worth pursuing in the clinic.[16]

Vaccination approaches to immunotherapy focus on the induction of innate (natural killer [NK] cell) responses and tumor-specific T lymphocytes by various means. The first FDA-approved therapeutic cancer vaccine (Provenge, Dendreon Corp) consists of a patient autologous preparation of antigen presenting cells that have been pulsed with a single antigen (prostatic acid phosphatase) *in vitro*. These cells are then re-infused into patients and were shown to increase overall survival in patients with advanced prostate cancer. This approach is an example of an autologous vaccine and requires significant processing of patient material for each individualized treatment. This paradigm leads to increased cost of therapy, prolongs the period in which a patient may be off-treatment and is encumbered by the potential for manufacturing failure or shortfalls.

Another class of vaccine with a range of agents in various phases of clinical development includes allogeneic, cell-based therapy. One of the first in this class consisted of granulocyte-macrophage colony-stimulating factor (GM-CSF) transfected tumor cells used as vaccines through indirect presentation of tumor antigen to T cells by dendritic cells (DC).[17,18,19,20] Other examples include tumor cells transfected with B7.1 (CD80),[21,22,23,24,25,26] human leukocyte antigen (HLA) molecules,[27,28] or anti-sense transforming growth factor β2 (TGF-β2) DNA constructs or tumor cells decorated with bacterial sugar residues. What all of these approaches have in common, is that the transfer of tumor antigens from the injected vaccine construct to the patient immune system is an unregulated and random event.

Upon administration to patients, the allogeneic cells are destroyed by the patient's immune system and the resulting tumor cell fragments are endocytosed by tissue resident macrophages. Typically, antigens that are interpreted by the patient's immune system in this manner are subsequently displayed on major histocompatibility complex (MHC) class II, resulting predominantly in a CD4+ helper T cell-mediated (*not* CD8+ cytotoxic T cell-mediated) immune response. *This is a critical distinguishing characteristic between the current approach with viagenpumatucel-L, which exclusively leads to tumor antigen transfer to MHC I and activation of a CD8+ cytotoxic T cell-mediated response (discussed further below).*

1.2.2 Vaccines in development for NSCLC

There are two vaccines currently in clinical development for the treatment of potentially curable *earlier stage* NSCLC. The MAGE-A3 vaccine is being evaluated in the treatment of resectable stage I–IIIA NSCLC[29] and MUC 1 liposomal-BLP25 in unresectable stage IIIB NSCLC after definitive chemoradiation.[30,31,32] MAGE-A3 is an antigen specifically associated with various solid tumors, including NSCLC, while MUC1 is a membrane-bound glycoprotein that becomes overexpressed and undergoes aberrant glycosylation with malignant transformation of diverse tumor types, including NSCLC.

One of the common features of the MAGE-A3 and the MUC-1 vaccines is that they each target only a single antigen. Although up to 50 percent of patient tumors may express either MAGE-A3 and/or MUC-1, the expression of these antigens within an individual tumor is rarely uniform. This observation is representative of the underlying genetic heterogeneity of advanced cancer and predicts that even patients who are 'positive' for an individual antigen may have a significant tumor burden that is also antigen 'negative'. Following treatment with a single-antigen vaccine, it is reasonable to predict that, even in the presence of a robust immune response, MAGE-A3 or MUC-1 negative tumor cells will be resistant to the tumor-specific immune response.

Various strategies have therefore been devised to circumvent this limitation, including more diverse antigen targeting with allogeneic tumor cell vaccines, such as belagenpumatucel–L and viagenpumatucel-L.

Belagenpumatucel-L is a tumor cell vaccine made with four irradiated NSCLC cell lines (two adenocarcinoma lines, one squamous and one large-cell carcinoma line) modified with TGF-β2 antisense plasmid. Belagenpumatucel-L is currently being clinically evaluated in NCSLC in the *advanced* disease setting,[33] along with two other vaccine approaches. TG4010 is a recombinant viral vector genetically modified to express MUC1 and interleukin-2,[34,35,36] while the EGF vaccine (CIMAvax EGF) consists of human recombinant EGF combined with a Neisseria meningitis-derived carrier protein and an immunoadjuvant.[37,38]

Overall therefore, a variety of vaccine approaches is being evaluated in NSCLC in a range of clinical contexts, including adjuvant, maintenance and first line treatment settings. While none of these has yet received the validation of a successful phase III trial outcome, the promise of the results demonstrated in phase II trials attests to the growing clinical evidence supporting the utility of vaccine-based treatment strategies in this tumor type.

Viagenpumatucel-L is distinct from other competitive approaches in clinical testing as it is an allogeneic cell-based vaccine containing a broad range of NSCLC tumor antigens combined with a specific mechanism for the transport of these antigens to patient antigen presenting cells for the generation of a specific CD8+ cytotoxic T cell response (described below).

In this trial, viagenpumatucel-L is used in conjunction with metronomic low dose cyclophosphamide. Although it is anticipated that administration of viagenpumatucel-L alone will be associated with a substantial CD8+ response, one important mechanism that tumors use for defense against anti-tumor T cells is the recruitment of regulatory T cells (T-regs) to the tumor microenvironment. T-regs are the population of T cells that serves to protect from autoimmune disease and are frequently co-opted by tumors for their

own defense. Cyclophosphamide specifically inhibits T-reg function. In studies dating back to the 1970s, it has been shown that while treatment with high-dose cyclophosphamide leads to tumor cell killing through direct chemical cytotoxicity, treatment with low-dose cyclophosphamide (<200 mg/m^2) leads to tumor cell death via (amongst other mechanisms) inhibition of T-regs and subsequent facilitation of cytotoxic T cell-mediated killing.[39,40]

1.3 Description of Investigational Agent HS-110

Viagenpumatucel-L is a whole cell vaccine derived from a human lung adenocarcinoma cell line AD100, containing HLA-A1 and gp96-Ig that is both species (human) and indication (lung cancer)-specific, that has been irradiated to render cell replication incompetent while maintaining biological activity.

Gp96 is a member of the heat shock protein family and has evolved specific characteristics that are advantageous for a therapeutic cancer vaccine. Similar to other heat shock proteins, gp96 is an intracellular protein that functions as a protein chaperone to facilitate the proper folding of other cellular proteins. In contrast to other heat shock proteins, gp96 is restricted to the endoplasmic reticulum (ER) via expression of a KDEL ER retention sequence on its C-terminal end. Within the ER, gp96 has exposure to a majority of proteins and antigens that eventually are displayed on MHC I. This property is likely to have influenced the evolution of a secondary role for gp96 as a molecular warning system for necrotic cell death.

Because gp96 is an ER-restricted protein, it is typically released from cells only upon physical destruction or necrotic cell death. Upon release from a dying cell, extracellular gp96 is able to interact with a series of receptors, including Toll-like receptors (TLR) -2 and -4 on the surface of antigen presenting cells. Engagement of TLR-2 and -4 provides an adjuvant signal to a patient's antigen presenting cells. Simultaneously, gp96 is able to bind to the endocytic scavenger receptor, CD91, to facilitate internalization of gp96 together with whatever protein cargo it bound within the dying cell. Any antigens brought into an antigen presenting cell by gp96 are then transferred to MHC I, through the cross-presentation pathway, for induction of a CD8+ T cell-mediated cytotoxic T cell response.

Heat Biologic's *ImPACT* technology seeks to replicate this natural mechanism by engineering gp96 to become a secretable molecule through the replacement of the KDEL retention signal with a secretory sequence from an immunoglobulin molecule. The resulting gp96-Ig fusion protein can then be transfected into a tumor cell line that contains a profile of antigens that are specific for a given tumor type and used to stimulate a CD8+ T cell response toward those antigens. In the case of viagenpumatucel-L, Heat Biologics has screened a series of NSCLC cell lines to prioritize antigens that are known to be shared amongst a high proportion of patients with NSCLC (including MAGE−A3, NY−ESO−1, etc.) and selected the AD100 cell line based on these shared antigen expression characteristics.

1.4 Prior Human Experience

A first-in-humans Phase 1 study to examine the safety and immunogenicity of viagenpumatucel-L has been conducted in patients with stage IV, or recurrent NSCLC who had failed at least one line of standard chemotherapy.[41] The study was closed prematurely for administrative reasons. Follow-up continued through April 2011 for the 18 vaccinated patients across 3 different dose-schedule (DS) cohorts and is summarized here. All cohorts had up to 3 6-week courses of treatment. The DS-1 cohort (11 patients)

received > 4 x 10^7 cells (~ 5.7 x 10^5 cells/kg) every other week (up to 9 vaccinations), the DS-2 cohort (4 patients) received > 2 x 10^7 cells (~ 2.9 x 10^5 cells/kg) weekly (up to 18 vaccinations), and the DS-3 cohort (3 patients) received > 1 x 10^7 cells (~ 1.4 x 10^5 cells/kg) twice weekly (up to 36 vaccinations).

Two DS-3 patients completed the planned 3-course treatment. Five patients (2 DS-1 and 3 DS-2) completed 2 courses before being taken off treatment due to progressive disease, and 8 DS-1 patients completed 1 course before progression. Three patients, 1 in each cohort, died (2) or progressed (1) before completing the first course of vaccination.

Most adverse events were Grade 1 or Grade 2. Five adverse events among 3 treated patients were Grade 3 rectal hemorrhage, dyspnea, chest pain, pneumonia and fatigue.

By April 2011, 14 patients had died and 4 surviving patients had been followed for a median of 10.6 months (range 2.6 to 16.6). The Kaplan-Meier estimate of median survival was 8.0 months (95% confidence interval [CI]: 6.7 to 18.2), and the 6, 12, and 24-month overall survival (OS) rates were 77.8% (95% CI: 51.1 to 91.0%), 41.9% (95% CI: 19.1 to 63.3%), and 11.2% (95% CI: 0.8 to 37.3%), respectively. Although comparison is limited due to incomplete accrual to DS-2 and DS-3, 2 of 4 DS-2 patients and 2 of 3 DS-3 patients have survived longer than the median survival time of 7.1 months for the 11 DS-1 patients. Time to progression for DS-2 and DS-3 patients also appears to compare favorably with the median progression-free survival (PFS) of 1.3 months for DS-1 patients.

Patient immune responses were monitored in this trial using peripheral blood samples isolated from each patient before treatment and at 3 additional timepoints throughout the trial (6, 12 and 18 weeks). Using these samples, individual immune responses were measured by ELISPOT assays to determine the presence of an immune response characterized by production of IFNγ by patient CD8+ T cells. Of the 18 patients enrolled in the trial, at least 2 samples (baseline and either week 6, 12 and/or 18) were available for 15 of the 18 patients on the trial.

Of the 15 patients with samples that were able to be analyzed and compared to baseline, 11 of the 15 demonstrated a doubling or greater (in some cases upwards of 100-fold increases) of a CD8+ T cell-mediated, vaccine-specific immune response. Furthermore, there was no increase in CD4+ T cell-mediated immunity, confirming preclinical findings that the effect of the gp96-Ig approach is limited to CD8+ cytotoxic T cell responses.

When the survival of the immune responders (11/15 patients) was compared to that of the non-responders (4/15), it was observed that the immune responder overall survival was 16.5 months as compared to 4 months in the immune non-responder group. These data provide a possible link between increased vaccine-specific cytotoxic T cell responses and increased survival, which will be explored further in the current study.

2.0 RATIONALE

2.1 Background Rationale

As advanced NSCLC is an incurable condition all patients given first and second line therapy will eventually relapse, or remain refractory from the outset. Consequently, treatment in the third and fourth line arena is an important and expanding area of overall medical management, with approximately 40% of patients who receive initial therapy for advanced disease going on to third line or higher treatment.[42] Furthermore, patient perspectives are increasingly exceeding those of physicians, in favor of a greater preference for more prolonged treatment into the latest stages of the disease,[43,44] with almost 50% and 25% of patients undergoing active therapy within the last 4 and 2 weeks of their lives, respectively.[45]

Although objective response rates and PFS fall precipitously after second line therapy,[9] recently completed randomized trials with a placebo arm (MISSION and ZEPHYR), suggest that the median survival of patients in the post-second line setting is now as long as 8 months,[46,47] which compares highly favorably with previous estimates of just 3-4 months,[48] although there is as yet no clear evidence that survival is significantly improved by existing therapeutic interventions.[49]

The fact that a growing proportion of patients are reaching third, fourth and even fifth line settings[10] and the finding that over 50% of overall median survival may now reside in the post-second line context mean that the third line and beyond space is a significant and evolving area of therapeutic potential in the overall management of advanced NSCLC.

While current National Comprehensive Cancer Network (NCCN) guidelines recommend several options for first-line and second-line therapies, only erlotinib is endorsed as a third-line therapy in unselected patients.[50] Additionally crizotinib has been approved, essentially for any line of therapy, in patients with an EML4/ALK translocation.[51] However, recent clinical results have shown that, at least in the second line setting, erlotinib treatment leads to inferior outcomes, when compared to chemotherapy, in patients with wild type EGFR status.[52,53] Furthermore, crizotinib is only suitable for the 4-5% of NSCLC patients who actually have an EML4/ALK abnormality.[54] Therefore, for the vast majority of patients without mutated disease who lack corresponding molecularly targeted therapy, treatment options are significantly limited and substantially sub-optimal in the post- second line setting.

A variety of molecularly target approaches[55] and chemotherapy strategies are currently employed empirically in the third and fourth line setting. Chemotherapy-based regimens include platin, or non-platin-based doublet therapy and also mono-therapy with agents, such as paclitaxel, docetaxel, vinorelbine, gemcitabine and pemetrexed.[56]

However, in practice the range of treatment choices actually available to patients is severely constrained by co-morbidities, often arising from prior first or second line therapy. For example, pemetrexed use may be complicated in patients with renal impairment[57] or uncontrolled effusions,[58] while docetaxel may be contra-indicated in patients with residual neuropathy from prior platin-based therapy.[59] Many patients also have a significantly high risk of febrile neutropenic complications from chemotherapy, a liability compounded by poor performance status and advanced age,[60] which are frequently characteristic features of patients in the more advanced stages of NSCLC.

Overall, therefore, the range of clinically useful agents is extremely limited in the third line and further setting. Although no agents have so far shown a survival advantage in the third line context, second line agents, such as docetaxel and pemetrexed, have shown improved survival despite achieving very low response rates, suggesting that most of the utility derived in the later stages of NSCLC is from disease stabilization,[9] an ideal mechanistic setting for a vaccine-based therapeutic approach. It is therefore anticipated that a vaccine, such as viagenpumatucel-L (HS-110), could offer superior efficacy to currently available third line strategies with a comparable or better safety profile.

The current trial will examine the clinical utility of a vaccine-based therapy compared to a range of widely used conventional third line agents.

2.2 Study-Specific Rationale

Summarizing the background information in the sections above, the rationale for this study of viagenpumatucel-L in combination with metronomic low-dose cyclophosphamide (CY) is as follows:

(1) Recent and paradigm-changing clinical data suggest that effective NSCLC immunotherapy is feasible and that under the right circumstances NSCLC cells may, in fact, become susceptible to attack by cytotoxic T lymphocytes (CTL).

(2) Secreted gp96-Ig from viagenpumatucel-L combines adjuvant activity with polyvalent peptide specificity and activates DC, NK cells, and CTL. As a result tumor cells can be killed by NK cell-specific mechanisms and by MHC-restricted CD8+ CTL activity. The activation of DC and NK cells by viagenpumatucel-L may also counteract the generation of immunosuppressive T-regs.

(3) Viagenpumatucel-L stimulates antigen cross presentation via the CD91 receptor, TLR2 and TRL4 on DC and macrophages (as described above). Allogeneic NSCLC cells are known to share public tumor antigens, including MAGE−A3, MUC1, NY-ESO-1 and others. Therefore allogeneic, gp96-secreting tumor cells used as a vaccine (such as viagenpumatucel-L) are expected to generate NK and CTL activity against the patient's autologous tumor through common expression of selected shared tumor antigens.

(4) The rationale for administering viagenpumatucel-L in combination with low-dose metronomic CY is based on the presumption that a majority of established tumors have developed an active mechanism of immune evasion. For some tumors this may include direct expression or recruitment of cells expressing CTLA-4 or PD-L1. In many cases, this immunosuppression may also be mediated by T-regs. The use of low-dose metronomic CY (50 mg, PO, QD, 1 week on/1 week off) has been demonstrated to provide prolonged suppression of both T-reg numbers and function without having direct cytotoxic effects on tumor cells.[61]

2.3 Justification of Study Drug Administration Strategy

2.3.1 Viagenpumatucel-L

The initial Phase 1 study in lung cancer examined 3 dosing schedules: twice weekly, weekly and once every 2 weeks. The twice weekly and weekly dosing schedules were determined to produce the most desirable immune response (at least a doubling of CD8+ numbers from baseline). The weekly dosing schedule was

selected for this trial as it represents the schedule with greatest patient acceptability for frequency of treatment visits.

The dose of 1x 10^7 cells was selected for this trial. The $1x10^7$ cells is half the dose that was used in the Phase 1 trial (DS-2 cohort). Murine data suggested that lower doses may produce sufficient immune response and may even result in superior clinical effects, and, therefore, the lower dose of $1x10^7$ cells was chosen. Additionally, this lower dose is prudent from a safety perspective as this trial is the first testing the combination with metronomic low-dose CY.

Vaccine will be administered weekly as 5 x 0.1mL intradermal injections (see Section 7.1). The selection of the route of administration is based on the hypothesis that split doses stimulate stronger immune responses by allowing vaccine antigens to reach more regional lymph nodes (where immune responses are generated). The vaccine will be administered intradermally to enhance stimulation of cellular immune responses as compared to subcutaneous or intramuscular immunization.

2.3.2 Cyclophosphamide (CY)

When administered at conventional cytotoxic doses (10-15 mg/kg intravenously), CY usage is associated with significant clinical toxicity, including myelosuppression (predominantly leukopenia and neutropenia and less frequently anemia or thrombocytopenia), hemorrhagic cystitis, nausea, vomiting, diarrhea, anorexia, alopecia, skin pigmentation and allergic reactions.[62]

However, at the dose proposed for the current study (50 mg daily on alternate weeks) the predominant toxicity is expected to be mild neutropenia or leukopenia, based upon extensive experience in the literature with the use of low-dose metronomic CY in a range of malignancies, including breast, prostate and lung cancer. Typically, grade 3 or higher hematological toxicities have been documented in less than 5% of patients in these studies and grade 3 or higher non-hematological toxicities in less than 2%, supporting the contention that low-dose CY, as proposed for the current study, is a safe and well tolerated intervention[63,64,65,66]

2.4 Rationale for Performing Tumor Biopsies

In order for an allogeneic cell-based vaccine to lead to a clinical response in a treated cancer patient, that vaccine must not just stimulate a tumor-antigen-specific immune response as detected by circulating lymphocytes in the peripheral blood, but those lymphocytes must infiltrate the tumor microenvironment in order to kill tumor cells. Patients who are predicted to respond to viagenpumatucel-L are those whose tumors express antigens that are known to overlap with the shared antigens contained within the AD100 cell backbone of viagenpumatucel-L. In addition, it is predicted that those patients whose tumors express a number of antigens that are shared with viagenpumatucel-L will have improved clinical responses as compared to those patients whose tumors only share 1 or 2 antigens with viagenpumatucel-L. Furthermore, it is possible that the likelihood of a patient having a clinical response to treatment with viagenpumatucel-L could be predicted by the presence and extent of tumor infiltration by CD8+ T cells, determined in turn by the degree of correlation found with shared individual antigens between patient tumors and viagenpumatucel-L. Consequently, acquisition of tumor tissue is essential to histologically examine tumor antigen expression and generate predictive information on which patients are most likely to have a clinical

response, and thus inform optimal patient selection for future trials. Archival biopsy tissue, if available, will be acceptable for the pre-treatment tumor antigen analysis.

3.0 OBJECTIVES

3.1 Primary Objective

To evaluate overall survival

3.2 Secondary Objectives

- To evaluate the safety of the combination of viagenpumatucel-L and low-dose CY
- To evaluate immune-related overall response rate (irORR), (complete response and partial response) and also overall response rate (ORR) by RECIST
- To evaluate immune-related disease control rate (irDCR) (complete response, partial response, and stable disease) and also disease control rate (DCR) by RECIST at 6 months following randomization and overall
- To evaluate immune-related progression free survival (irPFS) and also progression-free survival (PFS) by RECIST
- To evaluate immune-related time to progression (irTTP) and also time to progression (TTP) by RECIST
- To evaluate the proportion of patients who are alive at 6 months following randomization
- To evaluate the proportion of patients who are alive at 12 months following randomization
- To characterize the peripheral blood immunologic response via intracellular cytokine staining (ICS) by flow cytometry and/or ELISPOT on IFNγ-positive CD8+ cells following vaccination

3.3 Exploratory Objectives

- To evaluate exploratory endpoints, which may include:
    - Peripheral blood immunologic response by flow cytometry and ELISPOT
    - Total peripheral blood mononuclear cell (PBMC) counts by flow cytometry, including lymphocyte subsets
    - Evaluation of tumor tissue obtained from pre-treatment biopsy or archival biopsy tissue for shared tumor antigen expression, expression of MHC class I, and expression of immunosuppressive molecules
    - Evaluation of tumor tissue obtained from post-treatment biopsy for presence of tumor-infiltrating T lymphocytes (TIL)
    - Evaluation of tumor tissue and PBMCs for T cell receptor (TCR) sequencing to determine correlation between clonally expanded T cell populations and other endpoints

4.0 TRIAL DESIGN

Patients who have failed 2 or 3 prior lines of therapy for advanced disease will be randomized 2:1 to 1 of the following treatment groups:

Experimental Group: Viagenpumatucel-L plus metronomic CY (82 patients)
Control Group: Physician's Choice (PC) (41 patients)
Therapy to be given in nominal 21 day cycles with dose and schedule according to investigator's standard practice

- Vinorelbine
- Erlotinib
- Gemcitabine
- Paclitaxel
- Docetaxel
- Pemetrexed

Patients randomized to the experimental group will be treated during an induction phase with combination metronomic CY and viagenpumatucel-L weekly for 12 weeks followed by monotherapy viagenpumatucel-L in the maintenance phase once every 9 weeks for up to 12 months or until discontinuation from study treatment, at which time patients will be discontinued from treatment and followed for overall survival as defined by irRC, at which time patients will be discontinued from treatment and followed for overall survival. Patients randomized to the control group will be treated with a PC regimen until until discontinuation from study treatment, at which time patients will be followed for overall survival.

Patients with progressive disease by irRC at an assessment may continue on treatment until the next assessment if judged by the investigator to be in the patient's best interest. While treatment may continue beyond irPD, statistical analysis will still follow strict definitions as defined in section 6.5.1 Tumor Assessments.

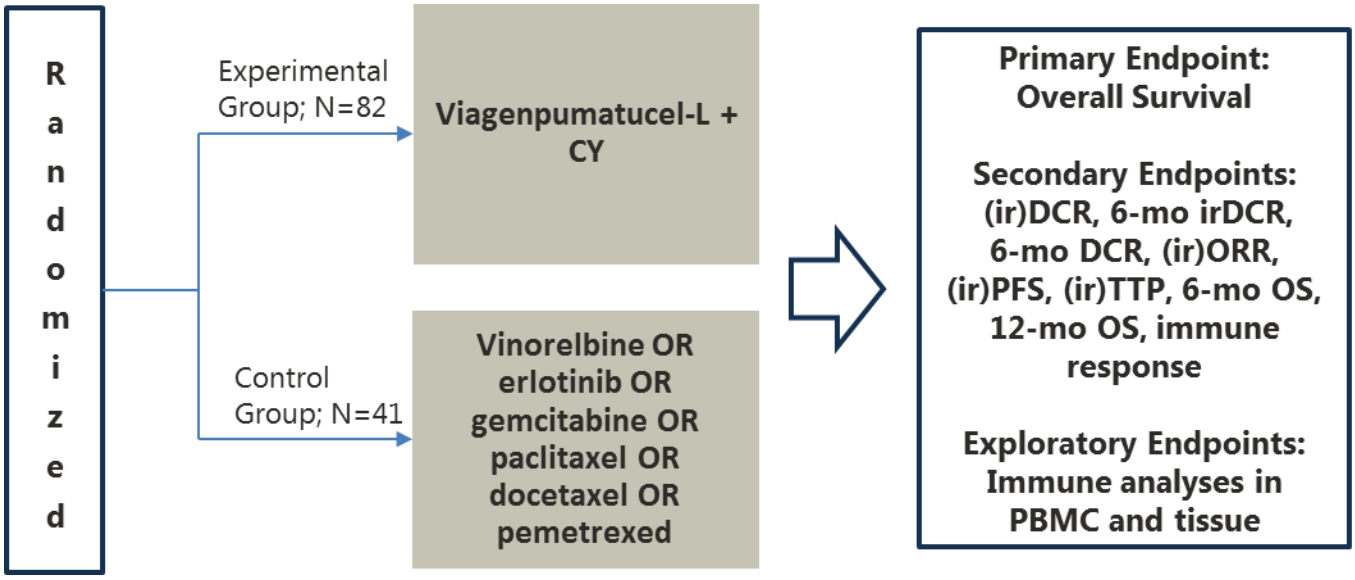
Blood samples will be taken to evaluate the CD8+ immune response in PBMCs and their correlation to overall survival. Patients will have samples drawn prior to first study treatment, at Weeks 4, 10, 13, and 22, and at End of Treatment (EOT).

Where considered appropriate by the investigator, patients randomized to the experimental group will be invited to consent for biopsies pre-treatment and at Week 13 for exploratory biomarker analysis. Patients will also be asked to consent to provide archival biopsy tissue if available. Examination of tumor samples will enable screening for expression of MHC class I (necessary for any immunologic response), expression of immunosuppressive molecules, including, for example, CTLA–4, PD-L1, and PD-1 (informative for future possible combination studies), expression of tumor antigens that are known to be expressed by viagenpumatucel-L, presence of TILs, and TCR sequencing.

Patients will be monitored for safety with adverse event (AE) reporting, clinical laboratory parameters (hematology, liver function, electrolytes, renal function, and urinalysis), 12-lead electrocardiogram (ECG) recording, vital signs, and physical exams. Efficacy assessments will include survival, tumor evaluation, and immune response. Tumor assessments will be done at screening, every 9 weeks until Week 28, and

every 12 weeks thereafter until progression, unless clinical signs of progression necessitate earlier assessment. The overall study design is summarized below in Figure 1.

Figure 1. Study Design



5.0 PARTICIPANT SELECTION

5.1 Inclusion Criteria

Patients must meet all of the following inclusion criteria to be enrolled into the study:

1. Histologically or cytologically confirmed non-small cell lung adenocarcinoma
2. Received at least 2 and no more than 3 prior lines of systemic therapy for Stage IV or recurrent incurable NSCLC, including cytotoxic chemotherapy, molecularly-targeted agents, or immunotherapy. Prior adjuvant or neoadjuvant chemotherapy or definitive chemoradiation for locally advanced disease does not count as a line of therapy as long as the last administration of the regimen occurred at least 12 months prior to enrollment. A repeat course of a prior line of systemic therapy does not count as an additional line of therapy. Maintenance systemic therapy or palliative radiotherapy to single sites of disease will not be considered an additional regimen.
3. Suitable, in the opinion of the investigator, for conventional single agent chemotherapy
4. Documented disease progression at study entry
5. Age $\geq$ 18 years
6. ECOG performance status (PS) $\leq$ 1; ECOG PS=2 patients may be considered after discussion with the Medical Monitor
7. CNS metastases may be permitted after discussion with the Medical Monitor but must be treated and neurologically stable. Patients must be on a stable or decreasing dose of corticosteroids and/or have no requirement for anticonvulsants for 14 days prior to screening.

8. Lab parameters:
   - Albumin ≥ 2.5 mg/dL
   - Total Bilirubin < 1.5 mg/dL unless known Gilbert's syndrome
   - Alanine transaminase (ALT), and aspartate transaminase (AST) ≤3.0 × upper limits of normal (ULN) or ≤5 × ULN in the case of liver metastases.
   - Calculated or measured creatinine clearance >35 mL/minute per the Cockcroft-Gault formula
   - Absolute neutrophil count ≥ 1,500/mm^3
   - Hemoglobin ≥ 9 g/dL
   - Platelet count ≥ 100,000/mm^3
9. Willing and able to comply with the protocol and sign informed consent, including weekly clinic visits to receive injections for 12 weeks followed by every-3-week visits thereafter for up to 12 months if randomized to the experimental group.
10. Female patients who are of childbearing potential and fertile male patients must agree to use an effective form of contraception (e.g., abstinence, oral contraceptives, intrauterine device, barrier method with spermicide, or surgical sterilization) with their sexual partners throughout study participation. Female patients of childbearing potential must test negative for pregnancy prior to enrolling in the trial.

5.2 Exclusion Criteria

Patients that meet <u>any</u> of the following exclusion criteria are not eligible to be enrolled into the study:

1. Received systemic anticancer therapy (including cytotoxic chemotherapy, monoclonal antibodies, immunotherapy, and tyrosine kinase inhibitors (TKIs)) or radiation therapy within the previous 14 days
2. Received more than 3 lines of prior conventional therapy for advanced disease.
3. Human immunodeficiency virus (HIV), hepatitis B or C, or severe/uncontrolled infections or intercurrent illness, unrelated to the tumor, requiring active therapy. Testing is not required in the absence of history.
4. Any condition requiring concurrent systemic immunosuppressive therapy
5. Known immunodeficiency disorders, either primary or acquired
6. Known leptomeningeal disease
7. Other active malignancies
8. Prior treatment with a cancer vaccine for this indication
9. Pregnant or breastfeeding

6.0 STUDY PROCEDURES

A signed, written informed consent form that is currently approved by an IRB/EC/IBC must be obtained from the potential patient before he/she can participate in any study-specific procedures, including study-specific screening procedures.

Patients will be enrolled and randomized once all screening procedures have been completed, and it is determined that the patient meets all eligibility criteria.

6.1 Schedule of Assessments (SOA)

In general, the schedule of assessments is divided into 3-week cycles with the first 12 weeks being the induction period and the remainder being the maintenance period. Patients in the experimental group may visit the clinic more frequently than patients in the control group during the induction period in order to permit the weekly treatment with viagenpumatucel-L and safety assessment of the combination with CY.

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Schedule of Assessments

			Induction												Maintenance											
			Cycle 1			Cycle 2			Cycle 3			Cycle 4			Cycle 5			Cycle 6		Cycle 7	Cycle 8	Cycle 9				
Procedure	**Screen**	**Baseline**[1]	**Wk 1**	Wk 2[2]	Wk 3[2]	**Wk 4**	Wk 5[2]	Wk 6[2]	**Wk 7**	Wk 8[2]	Wk 9[2]	**Wk 10**	Wk 11[2]	Wk 12[2]	**Wk 13**	**Wk 16**	**Wk 19**	**Wk 22**	**Wk 28**	**Wk 31**	**Wk 40**	**Wk 49**	**Wk 52**	**EOT**	**LTFU**		
Study Day	-28 to -1	-7 to 1	1	8±2	15±2	22±2	29±2	36±2	43±2	50±2	57±2	64±2	71±2	78±2	85±2	106±3	127±3	148±7	190±7	211±7	274±7	337±7	358±7	+28 ±7	Q3 mo		
Baseline Documentation																											
Informed Consent	X																										
Eligibility Assessment	X																										
Randomization		X																									
Medical History	X																										
ECOG PS	X	X																									
Pre-existing symptoms	X	X	X																								
Safety Assessments																											
Physical Exam inc. vital signs[3]	X					X			X			X			X									X			
12-lead ECG	X											X					X							X		
Laboratory Studies																											
Immunologic Response (mL)[4]			100			100						100			100			100						100			
Blood Hematology	X	X[5]		X	X	X	X	X	X	X	X	X	X	X	X			X		X	X	X		X			
Serum Chemistry	X	X[5]				X			X			X			X			X		X	X	X		X			
Urinalysis	X					X			X			X			X			X		X	X	X		X			
Pregnancy Test	X																							X			

NOTE: Visits marked in bold are mandatory for all patients.
[1] Baseline procedures may be combined with the Week 1 visit, so long as all procedures are performed prior to dosing.
[2] Patients randomized to the control group need not be seen in the clinic at these time points if standard practice dictates such. Patients randomized to the experimental group will still be seen.
[3] Full physical exam will be performed at screening and EOT. Exams at Weeks 4, 7, 10, and 13 are limited to vital signs and symptoms.
[4] Samples to be drawn prior to dosing. For patients randomized to the control group, if 100mL cannot be safely drawn due to cytopenia, 40mL of heparinized blood may be excluded.
[5] Hematology and Chemistry assessments need repeating at Baseline only if the Screening visit was performed >2 weeks prior to the first dose.

			Induction												Maintenance											
			Cycle 1			Cycle 2			Cycle 3			Cycle 4			Cycle 5			Cycle 6		Cycle 7	Cycle 8	Cycle 9				
Procedure	**Screen**	**Baseline**[6]	**Wk 1**	Wk 2[7]	Wk 3[7]	**Wk 4**	Wk 5[7]	Wk 6[7]	**Wk 7**	Wk 8[7]	Wk 9[7]	**Wk 10**	Wk 11[7]	Wk 12[7]	**Wk 13**	**Wk 16**	**Wk 19**	**Wk 22**	**Wk 28**	**Wk 31**	**Wk 40**	**Wk 49**	**Wk 52**	**EOT**	**LTFU**	
Study Day	-28 to -1	-7 to 1	1	8±2	15±2	22±2	29±2	36±2	43±2	50±2	57±2	64±2	71±2	78±2	85±2	106±3	127±3	148±7	190±7	211±7	274±7	337±7	358±7	+28 ±7	Q3 mo	
Tumor Assessments																										
CT scan or MRI[8]	X											X					X		X		X		X		X[9]
Dosing																										
Vaccine[10]			X	X	X	X	X	X	X	X	X	X	X	X	X			X		X	X	X				
Metronomic CY			X*7		X*7		X*7		X*7		X*7		X*7													
Physician's Choice (Control Group)[11]			SOC	SOC	SOC	SOC	SOC	SOC	SOC	SOC	SOC	SOC	SOC	SOC	SOC	SOC	SOC	SOC	SOC	SOC	SOC	SOC	SOC			
Other Clinical Assessments																										
Tumor Biopsy[12]		X													X											
Adverse Events			X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X		
Concomitant Medications	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X[13]	
Survival																									X	

NOTE: Visits marked in bold are mandatory for all patients.
[6] Baseline procedures may be combined with the Week 1 visit, so long as all procedures are performed prior to dosing.
[7] Patients randomized to the control group need not be seen in the clinic at these timepoints if standard practice dictates such
[8] Scans will be performed every 9 weeks for the first 28 weeks and then every 12 weeks thereafter. irCR, irPR and irPD will be confirmed with a second tumor assessment after at least 4 weeks.
[9] Radiological assessments will continue, where possible, for patients withdrawing due to clinical progression but prior to irRC determined progression and for patients who remain on treatment after confirmed irPD.
[10] Patients are to be monitored on site for 30 minutes following each dose.
[11] Physician's Choice options should be given with dose and route according to investigator's standard practice until progression.
[12] Tumor biopsies will be obtained in consenting patients randomized to the experimental group at Baseline and Week 13. Archival biopsy tissue may be provided if available.
[13] Subsequent anticancer therapy will be collected.

6.2 Screening Procedures

The following procedures must be conducted <4 weeks prior to the first dose of study medication:

- Written informed consent
- Verify eligibility criteria
- Patient demographics
- ECOG PS – discuss with Medical Monitor any patients with ECOG = 2
- Clinically significant medical history, including prior treatments, concomitant medications, and pre-existing symptoms
- Physical examination (including weight, vital signs[heart rate, temperature, respiratory rate and blood pressure])
- 12-lead ECG
- Blood hematology, serum chemistry, and urinalysis
- Urine or serum pregnancy test for female patients of childbearing potential
- Tumor assessment, including CT scan or MRI, to document baseline index lesions for irRC and target and non-target lesions for RECIST

6.3 On-Study Procedures

Study-related procedures and assessments performed during treatment on study are detailed as follows and in the Schedule of Assessments table (see Section 6.1).

6.3.1 Baseline Assessments (Day -7 to 1)

The following procedures will be performed after all the previous screening procedures have been completed and prior to dosing. These assessments may occur on the same day as dosing, so long as the collection of biopsy tissue and blood samples occurs PRIOR to dosing.

Reassessment of ECOG PS (and discussion with Medical Monitor for patients whose ECOG PS has changed since Screening (see

- Appendix 1. ECOG Performance Status Scale))
- Record pre-existing symptoms and concomitant medications
- Blood hematology and serum chemistry only if the screening visit was performed >2 weeks prior to the first dose

Once the patient has met all of the eligibility requirements for the study, the patient will be randomized. Each patient will be assigned a unique study number and will be considered enrolled on the study at the time of randomization.

- Baseline tumor biopsy (where consent has been provided in patients randomized to the experimental group; archival biopsy tissue may be provided if available. *Note: Provide at least 4, non-stained, 10 micron sections for analysis of shared tumor antigen expression, expression of MHC class I, and expression of immunosuppressive molecules. If slides are not available, formalin-fixed paraffin embedded (FFPE) tissue (≥50 microns) is also acceptable.*)

6.3.2 Visit Assessments

6.3.2.1 Week 1 Assessments (Day 1)

The following procedures will be performed after all the previous screening and baseline procedures have been completed.

- Update of concomitant medications and pre-existing symptoms
- Blood draw for baseline immunologic response obtained prior to dosing
- Patients randomized to the experimental group
  - Administration of vaccine
  - Monitor patients on site for potential acute reactions for 30 minutes after vaccine administration
  - Metronomic CY administration (taken at home)
- Patients randomized to the control group
  - Physician's choice, depending on schedule (described in section 7.2)
- Record adverse events

6.3.2.2 Week 2, 6, 8 and 12 Assessments

The following procedures will be performed at Week 2 (Day 8 ± 2), Week 6 (Day 36 ± 2), Week 8 (Day 50 ± 2) and Week 12 (Day 78 ± 2). Note that patients in the control group need not be seen in the clinic if standard practice dictates such:

- Blood hematology
- Patients randomized to the experimental group
  - Administration of vaccine
  - Monitor patients on site for potential acute reactions for 30 minutes after vaccine administration
- Patients randomized to the control group

- Physician's choice, depending on schedule
- Record adverse events
- Record concomitant medications

6.3.2.3 Week 3, 5, 9 and 11 Assessments

The following procedures will be performed at Week 3 (Day 15 ± 2), Week 5 (Day 29 ± 2), Week 9 (Day 57 ± 2) and Week 11 (Day 71 ± 2). Note that patients in the control group need not be seen in the clinic if standard practice dictates such:

- Blood hematology
- Patients randomized to experimental group
  - Administration of vaccine
  - Monitor patients on site for potential acute reactions for 30 minutes after vaccine administration
  - Metronomic CY administration (taken at home)
- Patients randomized to the control group
  - Physician's choice, depending on schedule
- Record adverse events
- Record concomitant medications

6.3.2.4 Week 4 Assessments

The following procedures will be performed at Week 4 (Day 22 ± 2):

- Vital Signs, with physical exam targeted to signs and symptoms
- Blood draw for immunologic response obtained prior to dosing
- Blood hematology, serum chemistry, and urinalysis
- Patients in experimental group
  - Administration of vaccine
  - Monitor patient on site for potential acute reactions for 30 minutes after vaccine administration
- Patients in the control group
  - Physician's choice, depending on drug and schedule
- Record adverse events
- Record concomitant medications

6.3.2.5 Week 7 Assessments

The following procedures will be performed at Week 7 (Day 43 ± 2):

- Vital Signs, with physical exam targeted to signs and symptoms
- Blood hematology, serum chemistry, and urinalysis

- Patients in experimental group
  - Administration of vaccine
  - Monitor patient on site for potential acute reactions for 30 minutes after vaccine administration
  - Metronomic CY administration (taken at home)
- Patients in the control group
  - Physician's choice, depending on drug and schedule
- Record adverse events
- Record concomitant medications

6.3.2.6 Week 10 Assessments

The following procedures will be performed Week 10 (Day 64 ± 2):

- Vital Signs, with physical exam targeted to signs and symptoms
- 12-lead ECG
- Blood draw for immunologic response obtained prior to dosing
- Blood hematology, serum chemistry, and urinalysis
- Tumor Assessment by CT scan or MRI - irCR, irPR and irPD will be confirmed with a second tumor assessment at least 4 weeks later
- Patients in experimental group
  - Administration of vaccine
  - Monitor patient on site for potential acute reactions for 30 minutes after vaccine administration
- Patients in the control group
  - Physician's choice, depending on drug and schedule
- Record adverse events
- Record concomitant medications

6.3.2.7 Week 13 Assessments

The following procedures will be performed at Week 13 (Day 85 ± 2):

- Vital Signs, with physical exam targeted to signs and symptoms
- Blood draw for immunologic response obtained prior to dosing
- Blood hematology, serum chemistry, and urinalysis
- Patients in experimental group
  - Tumor biopsy (in consenting patients. *Note: Provide at least 4, non-stained, 10 micron sections for TCR sequencing and analysis of infiltrating T cells. If slides are not available, FFPE tissue (≥50 microns) is also acceptable.*)
  - Administration of vaccine
  - Monitor patient on site for potential acute reactions for 30 minutes after vaccine administration

- Patients in the control group
  - Physician's choice, depending on drug and schedule
- Record adverse events
- Record concomitant medications

6.3.2.8 Week 16 Assessments

The following procedures will be performed at Week 16 (Day 106 ± 3):

- Patients in experimental group
  - No experimental therapy
- Patients in the control group
  - Physician's choice, depending on drug and schedule
- Record adverse events
- Record concomitant medications

6.3.2.9 Week 19 Assessments

The following procedures will be performed Week 19 (Day 127 ± 3):

- 12-lead ECG
- Tumor Assessment by CT scan or MRI – irCR, irPR and irPD will be confirmed with a second tumor assessment at least 4 weeks later
- Patients in experimental group
  - No experimental therapy
- Patients in the control group
  - Physician's choice, depending on drug and schedule
- Record adverse events
- Record concomitant medications

6.3.2.10 Week 22 Assessments

The following procedures should be completed at Week 22 (Day 148 ± 7):

- Blood draw for immunologic response obtained prior to dosing
- Blood hematology, serum chemistry, and urinalysis
- Patients in experimental group
  - Administration of vaccine
  - Monitor patient on site for potential acute reactions for 30 minutes after vaccine administration
- Patients in the control group
  - Physician's choice, depending on drug and schedule
- Record concomitant medications

- Record adverse events

6.3.2.11Week 28 Assessments

The following procedures should be completed at Week 28 (Day 190 ± 7):

- Tumor Assessment by CT scan or MRI – irCR, irPR and irPD will be confirmed with a second tumor assessment at least 4 weeks later.
- Patients in experimental group
  - No experimental therapy
- Patients in the control group
  - Physician's choice, depending on drug and schedule
- Record adverse events
- Record concomitant medications

6.3.2.12Week 31 Assessments

The following procedures should be completed at Week 31 (Day 211 ± 7):

- Blood hematology, serum chemistry, and urinalysis
- Patients in experimental group
  - Administration of vaccine
  - Monitor patient on site for potential acute reactions for 30 minutes after vaccine administration
- Patients in the control group
  - Physician's choice, depending on drug and schedule
- Record concomitant medications
- Record adverse events

6.3.2.13Week 40 Assessments

The following procedures should be completed at Week 40 (Day 274 ± 7):

- Blood hematology, serum chemistry, and urinalysis
- Tumor Assessment by CT scan or MRI – irCR, irPR and irPD will be confirmed with a second tumor assessment at least 4 weeks later.
- Patients in experimental group
  - Administration of vaccine
  - Monitor patient on site for potential acute reactions for 30 minutes after vaccine administration
- Patients in the control group
  - Physician's choice, depending on drug and schedule
- Record concomitant medications
- Record adverse events

6.3.2.14Week 49 Assessments

The following procedures should be completed at Week 49 (Day 337 ± 7):

- Blood hematology, serum chemistry, and urinalysis
- Patients in experimental group
  - Administration of vaccine
  - Monitor patient on site for potential acute reactions for 30 minutes after vaccine administration
- Patients in the control group
  - Physician's choice, depending on schedule
- Record concomitant medications
- Record adverse events

6.3.2.15Week 52 Assessments

The following procedures should be completed at Week 52 (Day 358 ± 7):

- Tumor Assessment by CT scan or MRI – irCR, irPR and irPD will be confirmed with a second tumor assessment at least 4 weeks later.
- Patients in experimental group
  - No experimental therapy
- Patients in the control group
  - Physician's choice, depending on schedule
- Record adverse events
- Record concomitant medications

6.3.3 End of Treatment Visit (Day 28 ± 7 post last dose)

The following procedures should be completed approximately 4 weeks following last dose of vaccine, including patients who discontinue vaccine dosing prematurely.

- Physical examination (including weight, vital signs)
- 12-lead ECG
- Blood draw for immunologic response
- Blood hematology, serum chemistry, and urinalysis
- Urine or serum pregnancy test for female patients of childbearing potential
- Record adverse events
- Record concomitant medications

6.3.4 Long-term Follow-up Visits

All patients will be followed for survival until study termination or death, whichever occurs first. Radiological assessments will continue, where possible, for patients withdrawing due to clinical

progression but prior to irRC determined progression or for patients who continue on treatment beyond confirmed irPD. Survival data as well as information on any new anticancer therapy initiated after disease progression will be collected via phone call approximately every 3 months. Since OS is the primary endpoint of this study, follow-up continues even if subjects participate in other experimental studies or receive other treatment.

6.4 Safety Assessments

Safety will be assessed throughout the study by a qualified physician, physician assistant, or nursing staff. Measurements used to evaluate safety will include history, physical examination, vital signs, clinical laboratory tests, urinalysis, 12-lead ECG, and monitoring for AEs. AEs will be graded according to the National Cancer Institute Common Terminology Criteria for Adverse Events Version 4.03 (NCI-CTCAE v4.03) [NCI, 2010].

Laboratory measurements that deviate clinically significantly (as determined by the investigator) from previous measurements may be repeated. If warranted, additional or more frequent testing than is specified in the protocol should be done to provide adequate documentation of AEs and the resolution of AEs.

6.4.1 Physical Examination

Medical and physical examinations must be performed by a qualified physician, nurse practitioner, or physician assistant and should include a thorough review of all body systems at Screening and at the End of Treatment; exams at Weeks 4, 7, 10, and 13 are limited to vital signs and symptoms. Physical examinations will include vital signs. Blood pressure, heart rate, respiratory rate, and temperature will be measured after resting in a semi-supine or supine position.

6.4.2 Clinical Laboratory Evaluations

Patients will have blood samples collected for routine clinical laboratory testing. The clinical laboratory parameters will be analyzed at the site's local laboratory. Laboratory assessments to be completed will include hematology, serum chemistry and urine or serum pregnancy test (females of childbearing potential) and will be defined as following:

- **Serum Chemistry:** To include sodium, calcium, total protein, albumin, creatinine, blood urea nitrogen, total bilirubin, alkaline phosphatase, AST, ALT, potassium, chloride, bicarbonate, lactate dehydrogenase, and glucose.
- **Hematology**: To include white blood cell (WBC) with differential, platelet count, hemoglobin, and red blood cell (RBC) count.
- **Urine or serum pregnancy test**: See section 6.4.6 below for further details.
- Additional laboratory assessments may be conducted throughout the study as medically necessary.

6.4.3 Urinalysis

Patients will have urine samples collected for routine urinalysis. The urinalysis will include color, appearance, and dipstick for specific gravity, protein, white blood cell-esterase, glucose, ketones, urobilinogen, nitrite, WBC, RBC, and pH.

6.4.4 ECG

The following parameters from 12-lead electrocardiograms will be evaluated: heart rate, PR interval, QRS duration, QT interval, and QTcF interval.

6.4.5 Injection Site Reactions

The grading scale for injection site reactions (ISRs) used in this trial can be found in Appendix 4. Grade 1 ISRs consisting of mild redness, erythema and swelling around the injection site are anticipated. Grade 1 reactions should dissipate over several days to a week with no special treatment. All ISRs should be recorded on the Injection Site Reaction CRF page. If an unusual or Grade 3 or 4 ISR occurs, attempts to obtain photographs at the peak of severity and at follow-up visits that show resolution over time are encouraged. A ruler should be in the field of view to allow measurement of the size of the reaction. If the patient consents, the de-identified photograph(s) should be appended to the CRF.

6.4.6 Pregnancy

All female patients of childbearing potential will have a urine or serum pregnancy test performed at Screening and at the End of Treatment follow-up visit.

Female patients who become pregnant during the study should discontinue study medication immediately. The patient will receive counseling from the investigator or designee regarding the nature of the study medication and the potential risk on fetal development.

6.4.6.1 Time Period for Collecting Pregnancy Information

The time period for collecting information on whether a pregnancy occurs is from the Screening visit to 4 weeks after the last dose of study medication. Information on pregnancies identified prior to study drug administration does not need to be reported to Heat Biologics.

6.4.6.2 Action to be Taken if Pregnancy Occurs

The investigator will notify Heat Biologics, or designee, within 1 week of learning of a patient's pregnancy. The patient will also be followed to determine the outcome of the pregnancy. Information on the status of the mother and child will be forwarded to Heat Biologics, or designee. Generally, follow-up will be no longer than 6 to 8 weeks following the estimated delivery date. Any premature termination of the pregnancy will be reported.

While pregnancy itself is not considered to be an AE or serious adverse event (SAE), any pregnancy complication or elective termination of a pregnancy for medical reasons will be recorded as an AE or SAE (see AE/SAE section 8.1).

A spontaneous abortion after the first trimester will be reported as an SAE. Furthermore, any SAE occurring as a result of a post-study pregnancy and that is considered reasonably related to the investigational product by the investigator will be reported to Heat Biologics. While the investigator is not obligated to actively seek this information in former study participants, he or she may learn of an SAE through spontaneous reporting.

6.4.6.3 Action to be Taken if Pregnancy Occurs in a Female Partner of a Male Study Subject

The investigator will attempt to collect pregnancy information on any female partner of a male study patient who becomes pregnant while participating in this study. The investigator will record pregnancy information on the appropriate form and submit it to Heat Biologics, or designee, within 1 week of learning of the partner's pregnancy. The partner will also be followed to determine the outcome of the pregnancy. Information on the status of the mother and child will be forwarded to Heat Biologics, or designee. Generally, follow-up will be no longer than 6 to 8 weeks following the estimated delivery date. Any premature termination of the pregnancy after the first trimester will be reported.

6.5 Efficacy Assessments

6.5.1 Tumor Assessments

Tumor response assessments will incorporate results from radiographic tumor assessment (CT scans or MRI) and physical examination, where appropriate, and will follow both immune-related response criteria (irRC),[67] which have been previously defined to describe the unique response patterns observed with immunotherapeutic agents, and conventional RECIST 1.1 criteria.[68] All clinical decision-making (e.g. determination of progression) will follow definitions of irRC only.

The identification of index and new lesions (irRC) and target plus non-target lesions (RECIST criteria) will be documented at baseline, and repeat scans will be performed every 9 weeks until Week 28 and then every 12 weeks thereafter, unless clinical signs of progression necessitate earlier scanning.

The same method used at screening must be used throughout the study. Bone scans are NOT acceptable for determination of disease status, and suspected bone lesions must be confirmed by CT/MRI. PET scanning is strongly discouraged for the purposes of disease evaluation, and any proposed use should be discussed with the Medical Monitor prior to baseline scanning.

A centralized review of scans will be done during the course of this study. The data from the blinded independent review will be used for the response endpoints, rather than local reads. Further details are provided in the imaging charter.

6.5.1.1 Immune Criteria for Tumor Assessment

Whereas conventional RECIST criteria consider any new measurable lesion to indicate PD, irRC is based on changes in total tumor burden from the baseline (nadir, for irPD) tumor assessment, regardless of any initial increase in baseline lesions or the appearance of new lesions. This practice of determining next treatment steps based on the overall tumor burden is reasonably consistent with standard of care in the advanced clinical setting of the current study and is therefore suitable for application to both the experimental and control groups for clinical decision-making.

In accordance with immune criteria, at the baseline tumor assessment, the sum of the products of the two largest perpendicular diameters (SPD) of all index lesions (5 lesions per organ, up to 10 visceral lesions + 5 cutaneous index lesions) is calculated. At each subsequent tumor assessment, the SPD of the index lesions and of new, measurable lesions ($\geq 5 \times 5$ mm; up to 5 new lesions per organ, 10 visceral lesions) are added together to provide the total tumor burden:

Tumor Burden = SPDindex lesions + SPDnew, measurable lesions

Decreases in tumor burden must be assessed relative to baseline measurements (i.e., the SPD of all index lesions at screening).

Each investigator will assess disease response (complete response [irCR], partial response [irPR], stable disease [irSD], and progressive disease [irPD]) using irRC criteria outlined in Appendix 2. Patients determined to have irCR, irPR, or irPD will have an additional confirmatory scan performed at least 4 weeks after the initial scan. If a patient is classified as having irPD at a post-baseline tumor assessment, then confirmation of irPD by a second scan in the absence of rapid clinical deterioration is required. The definition of confirmation of progression represents an increase in tumor burden ≥25% compared with the nadir at 2 consecutive time points at least 4 weeks apart.

The disease response measures will allow for the calculation of the immune-related disease control rate and 6-month disease control rate (irDCR and 6m-irDCR), which includes irCR, irPR, and irSD; immune-related overall response rate (irORR), which includes irCR and irPR; immune-related progression-free survival (irPFS); and immune-related time to progression (irTTP).

6.5.1.2 RECIST Criteria for Tumor Assessment

At the baseline tumor assessment, tumor lesions/lymph nodes will be categorized as measurable or non-measurable with measurable tumor lesions recorded according to the longest diameter in the plane of measurement (except for pathological lymph nodes, which are measured in the shortest axis). When more than 1 measurable lesion is present at baseline, all lesions up to a maximum of 5 lesions total (and a maximum of 2 lesions per organ) representative of all involved organs should be identified as target lesions. For the purposes of this study, a maximum of *2* lymph nodes are permitted as target lesions, irrespective of the organ systems from which they originate. Target lesions should be selected on the basis of their size (lesions with the longest diameter). A sum of the diameters for all target lesions will be calculated and reported as the baseline sum diameters.

All other lesions (or sites of disease), including pathological lymph nodes, should be identified as non-target lesions and should also be recorded at baseline. Measurements are not required and these lesions should be followed as ‘present’, ‘absent’, or ‘unequivocal progression’.

Disease response (complete response (CR), partial response (PR), stable disease (SD), and progressive disease (PD)) will be assessed as outlined in Appendix 3.

The disease response measures will allow for the calculation of the disease control rate and 6-month disease control rate (DCR and 6mDCR), which includes CR, PR, and SD; the overall response rate (ORR), which includes CR and PR; progression-free survival (PFS); and time to progression (TTP).

6.5.2 Immunologic Response

Peripheral blood samples will be obtained prior to the first study treatment, at Weeks 4, 10, 13, and 22, and at EOT in all patients. All samples will be shipped to and processed by one or more central laboratories.

Ninety (90) mL heparinized blood and 10 mL of non-heparinized blood will be drawn at each time point and used for analysis as outlined below. Peripheral blood mononuclear cells (PBMCs) will be isolated from

heparinized blood samples by Ficoll separation. Isolated PBMCs will be utilized for immunophenotyping analysis using flow cytometry, DNA isolation and subsequent TCR sequencing, intracellular cytokine analysis, and for ELISPOT assays as described below. Serum collected from non-heparinized blood samples will be stored for batch analysis of antibody titers and serum cytokines/chemokines.

In addition to the analyses specified below, subsequent exploratory mechanistic analyses, the nature of which will be determined by emerging PBMC and tumor biopsy data on the immunological environment pre- and post-vaccine and/or CY administration, may also be performed.

6.5.2.1 Production of Interferon-gamma from CD8+ T Cells (ICS Assay)

The immune response will be evaluated by antigen-specific flow cytometry and/or ELISPOT analysis for IFNγ production by patient T cells. These ICS assays will be done under Good Laboratory Practice (GLP)-like conditions using standard operating procedures and validating assays with standardized negative and positive controls. Processing of all patient samples by a single facility in large batches will be performed to minimize assay variability between samples.

Thawed and isolated PBMCs will be challenged or restimulated with specific tumor vaccine antigens as follows:

- PBMCs alone (negative control)
- PBMCs + PMA + Ionomycin (positive control)
- PBMCs + viagenpumatucel-L whole cell lysates or AD100-HLA A1-gp96-Ig (vaccine)
- PBMC + a cocktail of known shared antigens, including MAGE-A3, CT7, XAGE-1b, XAGE-1d

A maximum of 4 stimulation conditions at each time point per blood sample will be set up.

For the flow cytometry assay, following in vitro stimulation, cells will be harvested and labeled with antibodies to cell surface markers, including CD4 and CD8, and then fixed and permeabilized and stained for the indicated intracellular markers, including IFNγ and gzB. Samples will be analyzed by flow cytometry immediately after staining.

For the ELISPOT assay, the frozen PBMCs will be thawed, antigen challenged, and plated for analysis of IFNγ and granzyme B (gzB) production by ELISPOT assay and analyzed in triplicate for each time point for each patient. If cells are limiting, IFNγ analysis will be prioritized. Following incubation, samples will be quantitated in an automated ELISPOT reader.

The frequency of IFNγ producing CD8+ cells is thought to mirror the frequency of cytotoxic CD8+ cells. However, cytotoxicity is primarily mediated by perforin and granzymes following granule exocytosis. In some instances IFNγ secretion and granule exocytosis are uncoupled. Therefore, the direct measurement of gzB secretion by ICS may provide a more direct readout for antigen-specific granule exocytosis and cytotoxicity. For clinical efficiency it may be important to detect both IFNγ secretion and gzB exocytosis. Antigen specificity of the ICS response will be evaluable by comparing responses generated using the various stimulator cell populations and specific NSCLC shared antigens as indicated. This will also enable separation of the ‘allo-antigen’ specific response with the potential parent cell line tumor-antigen-specific

response. Positive responses will be defined as a greater than 2-fold increase in the number of IFNγ-positive CD8+ T cells compared to baseline.

6.5.2.2 PBMC Counts

Total PBMC counts will be obtained from each patient from 2 sources. First, blood hematology will be performed for each patient according to the schedule of assessments in Section 6.1 at the clinical centers. Second, the peripheral blood phenotyping analysis (described below) will be performed quantitatively for each of the markers indicated, providing a secondary measure of PBMC subsets defined by expression of the individual markers indicated.

Total PBMC counts may be utilized as a surrogate endpoint for the overall health of a patient's immune system.

6.5.2.3 Phenotyping of Blood Lymphocyte Subsets

Following alkaline lysis of red blood cells using standard procedures, peripheral blood samples will be stained using antibodies specific for the following cell markers: CD3, CD4, CD8, CD19, CD25, CD45, CD56, and FoxP3. Samples will be analyzed by multicolor flow cytometry using standard procedures.

Flow cytometric analysis of patient peripheral blood samples will quantitatively determine the frequency and number of lymphocytes (CD45+), B cells (CD45+CD3-CD19+), helper T cells (CD45+CD3+CD4+), cytotoxic T cells (CD45+CD3+CD8+), T-regs (CD3+CD4+CD25+FoxP3+), and NK cells (CD45+CD56+) at baseline and over the course of therapy. In addition a T cell activation panel (CD4, CD8, Ki67, perforin, IFNγ) will be performed before and after in vitro stimulation with PMA/ionomycin, a T-reg panel (CD4, CD25, FoxP3, CD127, CD45-RA), a myeloid suppressor cell panel (CD39, CD11b, CD124, CD45, HLA-DR, CXCR4), and T cell suppression panel (CD4, CD8, CTLA-4, PD-1, Tim-3) will be performed on freshly isolated PBMC.

6.5.2.4 TCR Sequencing

ELISPOT and intracellular cytokine assays are frequently used to monitor patient immune response to immunotherapy, despite the knowledge that these assays have not previously been strongly predictive of clinical response. Thus, prognostic immune monitoring assays are highly desired. If TCR clones are present that recognize antigens introduced by viagenpumatucel-L, clonal expansion of these cells is indicative of effective vaccination and potentially predictive for the presence of patient tumor-antigen-specific T cells.

TCR genomic DNA extracted from tumor tissue and PBMCs will be amplified and sequenced using Adaptive Biotechnologies Corp. (www.adaptivebiotech.com) immunoSEQ assay.

The current study is designed to explore the feasibility of application of this approach to later phase studies. In addition, data generated using this approach during this study may later be compiled with a larger data set to investigate the prognostic significance of individual TCR sequences before and during treatment with viagenpumatucel-L.

Although this assay is potentially predictive of a clinical response, it remains an exploratory endpoint in this trial because this analysis can only be confirmed once expansion of individual T cell clones is found to correlate (or not) with improved patient survival. Thus, the TCR sequencing data will be analyzed both

before the survival data has matured in order to ascertain whether there are conserved sequences expanded for patients with similar HLA types but also to determine whether a clonal TCR signature emerges that has the potential to be used as a predictive biomarker for response in subsequent trials.

6.5.2.5 Analysis of Infiltrating T Cells (Post-Treatment Tumor Biopsy)

For the cohort of patients who undergo post-treatment biopsies, the tissue will be examined for the presence of TILs. Two-color fluorescence immunohistochemistry (IHC) and multicolor fluorescence-activated cell sorting analysis will be used for quantification of CD8+ T cells and measurement of their activation status (CD69-expression) and cytotoxic activity (CD107a-expression) *in situ.* These data will be correlated with clinical response.

6.5.2.6 Antigen Screening of Baseline or Archival Tumor Biopsy

A baseline or archival biopsy sample (all patients for whom this is available) containing at least 4, non-stained, 10 micron sections will be collected for the purpose of screening the tissue for representative antigen expression (LAGE-1, NY-ESO-1, MAGE-[A1-10], CT7, CT10, GAGE, etc.), expression of MHC class I, and expression of immunosuppressive molecules, including, for example, CTLA-4, PD-L1 and PD-1, by mRNA expression and/or IHC analysis. If slides are not available, FFPE tissue (≥50 microns) is also acceptable. These data will be retrospectively correlated with immune response to determine if a particular antigen expression profile may predict response to treatment.

The tumor arrays will be processed by IHC and PCR according to standard methods. Bound antibodies will be visualized by using the avidin-biotin complex method according to the recommendations of the supplier (Vectastatin Elite ABC Kit; Vector Laboratories Inc., Burlingame, CA). Diaminobenzidine will be used as chromogen. 57B staining will be classified as follows: no staining; "weak," indicating low-intensity staining regardless of positive cell percentages or medium-intensity staining of no more than 20% of cells; "moderate," indicating medium-intensity staining of more than 20% of cells or high-intensity staining of no more than 20% of cells; "strong," indicating high-intensity staining of more than 20% of cells. Only moderately and strongly positive cases will be considered positive. For PCR-based analysis, total RNA will be isolated from collected tissue samples and reverse transcribed to cDNA using standard methods. The expression of tumor antigens from cDNA samples will then be interrogated using real-time PCR and a variety of specific tumor antigen probes.

6.6 Patient Completion and Withdrawal

6.6.1 Patient Completion

Patients may continue to receive study drugs for 12 months, until death, or until they meet the criteria for treatment discontinuation. Patients will continue to be followed beyond discontinuation of treatment for subsequent therapies and survival.

6.6.2 Discontinuation from Study Treatment

Every effort must be made by study personnel to keep patients on study treatment. However, a patient **will** be discontinued prior to completion of the study treatment for any of the following reasons:

- Grade 4 adverse event (or Grade 3 adverse event at the Principal Investigator's discretion) assessed as definitely or probably related to therapy for patients in the experimental group
- Pregnancy
- Termination of the study by Heat Biologics
- Intercurrent illness that prevents further administration of treatment

Patients **may** also be discontinued prior to completion of the study treatment for any of the following reasons:

- Progressive disease, according to irRC by a confirmed scan or significant clinical progression at an earlier time point, if judged by the investigator to be in the patient's best interests. Patients who experience progressive disease in the absence of clinical deterioration may continue to receive study treatment.
- Significant deviation from protocol on the part of the patient (includes lack of compliance)
- Significant protocol violation on the part of the investigator

Patients may withdraw consent for participation in the study at any time. Additionally, the investigator may withdraw a patient at his/her discretion.

If a patient prematurely discontinues study treatment for any reason, the patient will continue to be followed for study endpoints, unless consent for this is withdrawn. If the patient withdraws consent for continued follow up, the investigator must make every effort to perform the EOT assessments 4 weeks following the last dose of vaccine, even if the patient has initiated other anticancer treatment.

The explanation of why the patient is discontinuing study treatment should be documented in the CRF. If the patient discontinues study treatment due to toxicity, "Adverse Event" will be recorded as the primary reason for withdrawal. If a patient is prematurely discontinued from the study at any time due to an AE or SAE, the patient must be followed until resolution to Grade 2 or less, unless it is unlikely to improve because of underlying disease.

If a patient fails to return for the necessary visits or discontinues prematurely from treatment, a genuine effort should be made to determine the reason why. For a patient lost to follow-up there should be at least 2 documented attempts to contact the patient.

6.6.3 Patient Withdrawal from Study

In accordance with International Conference on Harmonization (ICH) Good Clinical Practice (GCP) Guidelines, a patient has the right to withdraw from the study at any time for any reason without prejudice to his/her future medical care by the physician or at the institution. The investigator and sponsor also have the right to withdraw patients from the study treatment, as described below or for safety, behavioral, or

administrative reasons. Note that withdrawal of consent for treatment is not the same as withdrawal of consent for survival follow-up.

6.6.4 Replacement of Patients

Patients will not be replaced. An overage of patients has been included in the sample size to allow for patients who do not accrue an event for the primary efficacy analysis.

7.0 STUDY DRUG

All production, formulation, and packaging of the investigational agent will be in accordance with applicable current Good Manufacturing Practice (cGMP) and meet applicable criteria for use in humans.

7.1 Experimental Group

7.1.1 Viagenpumatucel-L (HS-110)

Viagenpumatucel-L is a cell line derived from a human lung adenocarcinoma biopsy of a lung cancer patient and that cell line is designated as AD100. The cell line derived from that patient has been kept in culture in standard medium and is free of contamination by mycoplasma, virus, or other adventitious agents. AD100 was transfected with the plasmid cDNA 'B45-neo-gp96Ig-HLA A1'.

Preparation of the drug product includes expansion of batches of cells with testing for presence of expression of HLA-A1 by fluorescent-activated cell sorter and gp96-Ig by enzyme-linked immunosorbent assay (ELISA). Cells are harvested, washed, resuspended in buffer, and irradiated at 12,000 rad to render cell replication incompetent while maintaining biological activity, i.e., expression of certain proteins. Samples are withdrawn for biological and safety analysis, and the remaining aliquots are frozen and stored at < -120°C.

Viagenpumatucel-L is provided as single-dose vials either 1) as concentrated frozen liquid, which will require dilution by the pharmacist with sterile saline, or 2) as fully-diluted frozen liquid not requiring additional dilution. In either case the final drug product will consist of 10 million cells resuspended in 0.6 mL buffered saline containing human serum albumin (HSA), dimethyl sulfoxide (DMSO), and pentastarch. Overfill of 0.1 mL is factored into each vial to allow extraction of the full 0.5 mL dose for patient administration. Additional detail can be found in the Pharmacy Manual.

Each viagenpumatucel-L dose of 0.5 mL will be divided into 5 injections (0.1 mL per injection) and administered as 5 spatially divided intradermal injections in the same extremity to increase volume distribution and enhance antigen presentation to lymph node regions. Vaccine dosing will rotate injection site extremities every 4 timepoints: antero-lateral left thigh, antero-lateral right thigh, left shoulder and right shoulder.

Viagenpumatucel-L will be given weekly for 12 weeks followed by every 9 weeks until progression or up to one year, whichever occurs first. Missed doses may be made up if the missed dose is given at least 4 days before the subsequent dose.

7.1.2 Cyclophosphamide

Cyclophosphamide (Cytoxan) is a synthetic antineoplastic alkylating agent chemically related to the nitrogen mustards. It interferes with the growth of susceptible rapidly proliferating malignant cells, via a mechanism of action involving cross-linking of tumor cell DNA. It is widely used in a range of hematological and solid malignancies (including lymphomas, multiple myeloma, mycosis fungoides, neuroblastoma, small cell lung carcinoma, ovary and breast adenocarcinoma), usually at doses of 10mg/kg or higher (600-750 mg/m^2). Cyclophosphamide tablets are white with blue flecks and will be supplied at a dosage of 50 mg cyclophosphamide (anhydrous). Additional information can be found in the package insert.[62] Cyclophosphamide should be taken once daily every other week for 12 weeks P.O. with food and a large glass of water in the morning. Missed doses will not be made up.

7.2 Control Group

7.2.1 Physician's Choices

Investigators may choose from the following restricted list of treatment options: vinorelbine, erlotinib, gemcitabine, paclitaxel, docetaxel, or pemetrexed if the patient has not previously received it. The treatment regimens will be given in nominal 21 day cycles with dose and route according to investigator's standard practice until progression.

Additional information can be found in the respective package inserts.

7.3 Treatment Assignment and Stratification

Patients will be randomized centrally using a stratified block design into the experimental group or the control group. Patients will be stratified according to their ECOG PS: either PS $\leq$ 1 or PS=2 and previous treatment with a checkpoint inhibitor (strata: yes vs. no). Patients will then be placed into blocks of 6 and randomized 2 to 1.

Each patient will be assigned a unique study number at screening and will be considered enrolled in the study at the time of randomization through IXRS.

7.4 Study Drug Handling and Accountability

Physician's choice regimens will not be supplied by the sponsor and will be sourced at each institution individually according to its standard procedure. The following subsections apply to the experimental group only.

7.4.1 Preparation

Viagenpumatucel-L must be thawed and labeled prior to injection. Preparation of the product and labeling procedures will be described in the Pharmacy Manual.

7.4.2 Labeling

Study drug vials/bottles will be labeled with the product name, the dose identification number, storage requirements, and the statement "Caution: New Drug--Limited by Federal (or United States) law to investigational use." Additional country-level requirements may be included on the carton label.

7.4.3 Storage

Viagenpumatucel-L must be stored at ≤ -120°C in liquid nitrogen storage (a Dewar unit). If liquid nitrogen storage is not available at the investigative site, a unit will be supplied by the study sponsor. The sponsor will also arrange for replacement of the liquid nitrogen at regular intervals to ensure that the proper storage temperature is maintained throughout the study.

Cyclophosphamide will be stored at room temperature.

7.4.4 Product Accountability

The investigator or designee, where applicable, will be responsible for investigational product accountability, reconciliation, and record maintenance. In accordance with all applicable regulatory requirements, the investigator or designated site staff (e.g., investigational drug pharmacist) must maintain current investigational product accountability records throughout the course of the study. These records will contain the following information:

- Date, quantity, and vial/bottle number(s) received from and returned to the sponsor (if applicable)
- Patient Study ID number, date, quantity, and vial/bottle number(s) of agent dispensed
- Date, quantity, and vial/bottle number(s) of accidental loss of study agent (if applicable)
- Date, quantity, and vial/bottle number(s) investigational product destroyed per institutional guidelines (if applicable)
- Documentation of storage conditions

These inventories must be made available for inspection by the study monitor. The investigator will be responsible for ensuring that all used and unused trial supplies are accounted for. At the end of the trial the study monitor will also collect the original investigational agent dispensing record. A copy of the dispensing record should be kept at the site and maintained with the study records.

7.4.5 Occupational Safety

Precautions should be taken to avoid direct contact with the investigational product. A Material Safety Data Sheet (MSDS) describing occupational hazards and recommended handling precautions will be available to the investigator for viagenpumatucel-L.

7.5 Concomitant Medications

All concomitant medications, including prescription and over-the-counter medications taken during the 14 days before the date of first dose, during the study treatment, and through 4 weeks post the last dose of study drug, will be documented. Any concomitant medication(s), including herbal or vitamin preparations, taken during the study will be recorded in the CRF. At a minimum, the drug name, dose, and the dates of administration will be recorded. Caffeine consumption and supplemental oxygen use will also be collected.

7.5.1 Permitted Medications

Local and/or systemic injection reactions may be treated with anti-allergics, antipyretics and/or analgesics in accordance with standard local practice and investigator's clinical judgment.

Pre-treatment of the vaccine injection site with anesthetic cream is allowed only after the Week 1 vaccine administration has been performed without it and injection pain has been documented as an adverse event.

For patients randomized to the control group, granulocyte colony-stimulating factor (G-CSF) is allowed at the investigator's discretion according to local institutional guidelines. For patients randomized to the experimental group, G-CSF should be given only after a patient experiences Grade 3 neutropenia.

7.5.2 Prohibited Medications

In principle, steroid therapy is not permitted, but patients who are on a stable low dose of steroids (e.g. those with brain metastases; low dose is defined as daily steroid ≤ prednisone 10mg) may be considered on an individual basis after consultation with the Medical Monitor. Topical and inhalation steroids will be permitted. No concomitant chemotherapy, immunotherapy, immunosuppressive or other anticancer therapy will be permitted prior to discontinuation from treatment in the study.

Erlotinib, vinorelbine, paclitaxel, and docetaxel are all substrates for the CYP3A4 cytochrome p450 isozyme. Caution should be exercised when using any of these agents with strong inhibitors (e.g. ketoconazole, indinavir, nelfinavir, ritonavir, saquinavir, clarithromycin, erythromycin, telithromycin, itraconazole, and nefazadone) or inducers (e.g. carbamazepine, rifampin, phenytoin, and St. John's Wort) of the CYP3A4 pathway.

Administration of other concomitant investigational agents, for any indication, is not permitted while on this study.

During long-term follow-up there are no prohibited medications, and patients may enroll in any investigational study for which they are eligible.

7.5.3 Supportive Care

Patients should receive full supportive care during the study, including transfusions of blood and blood products, and treatment with antibiotics, antiemetics, antidiarrheals, and analgesics, and other care as deemed appropriate and in accordance with their institutional guidelines.

7.6 Treatment of Investigational Product Overdose

There have been no cases of overdose with viagenpumatucel-L. Treatment of any suspected or confirmed overdose with viagenpumatucel-L should be symptomatic, and supportive care is recommended in cases where overdose is suspected. As described in the Investigator's Brochure for viagenpumatucel-L, Heat Biologics does not recommend specific treatment for overdose or toxicity; however, the investigator should use appropriate clinical judgment in treating the overdose. For the purposes of this study, an overdose of viagenpumatucel-L is defined as any dose 50% greater than the intended dose for that patient. Appropriate

supportive care measures may need to be provided to address these potential toxicities in the event of an overdose.

7.7 Dose Modifications

Any AE ≥ Grade 3 possible, probably, or definitely related to one or more study drugs will be discussed with the Medical Monitor before continuing with dosing, with the following exceptions, for which no discussion with the Medical Monitor will be required:

- Local injection site reactions lasting < 72 hours including pain, redness, swelling, induration, or pruritus
- Systemic injection reactions lasting < 72 hours of fever, myalgia, headache, or fatigue

No dose modifications of viagenpumatucel-L will be permitted.

It is not anticipated that any significant toxicity is likely to arise in patients who receive CY. However, should any Grade 3 adverse events occur, which are considered by the investigator to be related to CY, then the dose of CY will be delayed until the toxicity has resolved to at least Grade 1 (any concurrent viagenpumatucel-L therapy will continue uninterrupted). If the dose of CY has to be delayed for more than 2 consecutive weeks of dosing (i.e a 4 week period overall), then CY dosing will be discontinued in that patient (although viagenpumatucel-L therapy will continue, in accordance with the provisions of the protocol). There is no provision in the protocol for a dose reduction with CY.

Control group regimens will be given at full strength with dose reductions as needed for management of toxicity according to the investigator's standard of care.

8.0 SAFETY MONITORING

All patients will be assessed for pre-existing symptoms during screening (from the date of signature of informed consent to immediately prior to first dose of study drug). Symptoms will be documented as AEs from the first dose of study drug until 4 weeks after the last dose of study drug or until death, whichever occurs first. Any AEs occurring after this time period will also be reported, if in the opinion of the investigator, the event is deemed related to study drug. All AEs will be followed until the event has subsided or, in the case of permanent impairment, until the condition stabilizes.

8.1 Adverse Events (AE) and Serious Adverse Events (SAE)

The investigator is responsible for the detection and documentation of events meeting the criteria and definition of an AE or SAE, as provided in this protocol. During the study when there is a safety evaluation, the investigator or site staff will be responsible for detecting, documenting and reporting AEs and SAEs, as detailed in both this section of the protocol and in the AE/SAE section of the study procedures manual. AEs should only be recorded for up to 4 weeks following the last dose of study medication, unless the AE is considered definitely, probably, or possibly related to the study medication, which requires that the AE be reported regardless of the amount of time that has passed since receiving the last dose of study medication.

8.1.1 Definition of an AE

An adverse event is any untoward medical occurrence associated with the use of a medicinal product in humans, whether or not considered related to the medicinal product (21 CFR 312.32 (a)). Note: an AE can therefore be any unfavorable and unintended sign (including an abnormal laboratory finding), symptom or disease (new or exacerbated) temporally associated with the use of a medicinal product. For marketed medicinal products, this also includes failure to produce expected benefits (*i.e.,* lack of efficacy), abuse, or misuse.

A suspected adverse reaction (SAR) is defined as any AE for which there is reasonable possibility that the drug caused the AE (21 CFR 312.32 (a)).

An AE or SAR is considered unexpected if it is not listed in the Investigator's Brochure or is not listed at the specificity or severity that has been observed or, if an Investigator's Brochure is not required or available, is not consistent with the risk information described in the general investigational plan or elsewhere in the current application (21 CFR 312.32 (a)).

8.1.2 Definition of an SAE

The Code of Federal Regulations (CFR) Title 21 part 312.32 and ICH Guideline for Industry: Clinical Safety Data Management: Definitions and Standards for Expedited Reporting, ICH-E2a March 1995, as implemented by the US FDA, defines a SAE or serious adverse drug experience as any untoward medical occurrence that at any dose:

- Results in death (i.e., the AE actually causes or leads to death)
- Is life-threatening (with regards to determining if an AE is serious, "life-threatening" is defined as an AE for which the patient was at risk of death at the time of the event. It does not refer to an event which hypothetically might have caused death if it were more severe. If either the investigator or the sponsor believes that an AE meets the definition of life-threatening, it will be considered life-threatening)
- Requires inpatient hospitalization or prolongation of existing hospitalization
- Results in persistent or significant incapacity or substantial disruption of the ability to conduct normal life functions
- Results in a congenital anomaly/birth defect
- Results in any "other" important medical event. Medical or scientific judgment should be exercised in deciding whether reporting is appropriate in other situations, such as important medical events that may not be immediately life-threatening or result in death or hospitalization but may jeopardize the patient or may require medical or surgical intervention to prevent one of the other outcomes listed in the above definition. Examples of such events are intensive treatment in an emergency room or at home for allergic bronchospasm, blood dyscrasias, or convulsions that do not result in hospitalization, or development of drug dependency or drug abuse.

8.1.3 Disease-Related Events or Outcomes Not Qualifying as SAEs

An event that is part of the natural course of the disease under study (i.e., disease progression) should not be reported as an SAE. Death due to disease progression is to be recorded on the Death CRF page and not as a SAE. However, if the progression of the underlying disease is greater than what would normally be expected for the patient, or if the investigator considers that there was a causal relationship between treatment with viagenpumatucel-L or protocol design/procedures and the disease progression, then it must be reported as an SAE. Any new primary cancer must be reported as an SAE.

8.1.4 Clinical Laboratory Abnormalities and Other Abnormal Assessments as AEs and SAEs

Abnormal laboratory findings (e.g., clinical chemistry, hematology, and urinalysis) or other abnormal assessments (e.g., ECGs or vital signs) that are judged by the investigator as **clinically significant** will be recorded as AEs and SAEs if they meet the definition of an AE or SAE. Clinically significant abnormal laboratory findings or other abnormal assessments that are detected during the study or are present at baseline and significantly worsen following the start of the study will be reported as AEs or SAEs. However, clinically significant abnormal laboratory findings or other abnormal assessments that are associated with the disease being studied, unless judged by the investigator as more severe than expected for the patient's condition, or that are present or detected at the start of the study and do not worsen, will **not** be reported as AEs or SAEs.

The investigator will exercise his or her medical and scientific judgment in deciding whether an abnormal laboratory finding or other abnormal assessment is clinically significant.

8.1.5 Reporting Adverse Events

The investigator will record all directly observed AEs and all AEs spontaneously reported by the study patient on the *Adverse Event* CRF. In addition, each study patient will be questioned about AEs.

Each AE should be described in detail on the *Adverse Event* CRF and SAEs on a *Serious Adverse Event* form and include the following information: start and stop dates, CTCAE v. 4.03 grading, relationship to study medication, action taken, and outcome. AEs should be recorded from time of first dose up to 4 weeks following the last dose of study medication regardless of the causal relationship to the study medication. AEs considered possibly, probably, or definitely related to study medication should be recorded at any time regardless of when they occurred.

The investigator will also assess the possible relationship between the AE and any of the study medications as well as any concomitant medications according to the following criteria:

- Definitely related: AE and administration of 1 or more study products are related in time, and a direct association can be demonstrated.
- Probably related: AE and administration of 1 or more study products are reasonably related in time, and AE is more likely explained by study product than other reasons.
- Possibly related: AE and administration of 1 or more study products are reasonably related in time, and AE can be explained equally well by causes other than study product.

- Unlikely related: Potential relationship between AE and 1 or more study products could exist (i.e., the possibility cannot be excluded), but AE is most likely explained by causes other than study product
- Not related: AE is clearly explained by another cause not related to any study product.

Event outcome will be recorded using the following categories:

- Recovered/resolved
- Recovering/resolving
- Not recovered/not resolved
- Recovered/resolved with sequelae
- Fatal
- Unknown

8.1.6 Prompt Reporting of SAEs

All SAEs, whether or not considered related to study drug, must be reported by telephone within 24 hours to the Medical Monitor listed on page 2 of this protocol. During the initial phone call, the Medical Monitor will require the following patient information:

- Patient identification, including patient study number, initials, and sex
- Date of first study drug dose
- Total dose and number of doses administered
- Date and amount of last study drug dose
- Whether the patient was taking study drug at the time of the AE
- Date, duration, and description of AE
- Events and/or symptoms leading up to the AE
- Action taken, including whether patient was withdrawn from study
- Concomitant therapy, including doses, routes, and regimens
- Pertinent laboratory data
- Medical history, including time on study prior to AE and history that might be related to the AE
- Study drug status (e.g., interrupted, discontinued, dose changed)

In addition to the above information, the Medical Monitor will require the investigator's assessment of the following:

- Severity of the AE
- Investigator's assessment of the relationship of the AE to study treatment
- Outcome of the AE

Any oral report of SAEs must be followed within 48 hours by a detailed, written report signed by the investigator. Any necessary follow-up must be submitted within a reasonable time thereafter. The sponsor will promptly report SAEs related to viagenpumatucel-L or CY to the FDA and other applicable regulatory agencies in accordance with Title 21 of the CFR, Part 312.32 (21 CFR 312.32) and local regulatory requirements. The investigator should also comply with any applicable requirements related to the reporting of SAEs to the IRB/EC.

The investigator will provide an SAE follow-up report to the sponsor. In this report, the investigator is to assess and record the SAE in detail, including the date and time of onset, description, intensity, duration, outcome, etiology, relationship to study drug, and action taken. Any SAEs that continue at the patient's last study visit must be followed until the event resolves or follow-up is agreed to be adequate by the investigator, Medical Monitor, and sponsor.

The clinical site investigator and the Medical Monitor will review each SAE report and evaluate the relationship of the SAE to study treatment and to underlying disease. Based on the investigator's and sponsor's assessment of the SAE, a decision will be made concerning the need for further action. The primary consideration governing further action is whether new findings affect the safety of patients participating in the clinical study. If the discovery of a new SAE related to viagenpumatucel-L and/or CY raises concern over the safety of continued administration of study drug to patients, the sponsor will take immediate steps to notify the FDA and all investigators participating in clinical studies of viagenpumatucel-L.

Further action that may be required includes the following:

- Modification of the protocol
- Discontinuation or suspension of the study
- Modification of the existing consent form and informing current study participants of new findings
- Addition of any newly identified viagenpumatucel-L related AEs to the list of expected AEs to the Investigator's Brochure

8.2 Data Monitoring Committee

The Data Monitoring Committee will be responsible for review of data from the interim analyses as well as ongoing safety evaluation. This team will meet regularly to review continuing safety data, and a description of the membership, roles and responsibilities, and data to be reviewed will be outlined in a separate charter.

8.3 Trial Stopping Rules

Under any of the following circumstances, dosing for all patients randomized to the experimental group will halt immediately until a thorough investigation has been conducted by the Data Monitoring Committee, and the team agrees that it is safe to continue. At the discretion of the team, the FDA or other Health Regulatory Agencies may be consulted.

- In the event of a death within 24 hours of vaccination that cannot be clearly attributed to another cause

- If at any time during the study 3 or more subjects randomized to the treatment group experience any anaphylactic reactions, a full-thickness ulceration/necrosis, or any AE ≥ Grade 3 possibly, probably, or definitely related to study drug with the following exceptions:
    - Local injection site reactions lasting < 72 hours, including pain, redness, swelling, induration, or pruritus
    - Systemic reactions lasting < 72 hours of fever, myalgia, headache, or fatigue
- In the event of any unexpected Grade 4 toxicities, assessed as possibly, probably, or definitely related to viagenpumatucel-L

9.0 STATISTICAL CONSIDERATIONS

9.1 General Statistical Considerations

Baseline demographic data as well as all exploratory endpoints will be presented descriptively as means, medians, or proportions with appropriate measures of variance. All efficacy analyses will be based on the intention to treat (ITT) population unless otherwise specified. Survival curves for the primary endpoint of OS (and others where appropriate, including PFS and TTP) will be generated by the method of Kaplan-Meier and compared with the log-rank test. In an exploratory analysis, the weighted log rank test will also be used. The weighted log rank test preserves the statistical power that is lost due to a potential lag time effect in efficacy with immunotherapeutic agents.[69] In a supporting analysis, the hazard ratio with appropriate 95% CI for the risk of death between the experimental and control group will be estimated using multivariate Cox Proportional Hazard regression. To identify the set of baseline factors with the greatest potential for association with OS, those with a p-value of ≤ 0.25 in a simple univariate Cox regression with the dependent variable, will be retained for further consideration. This is a recommended approach for removing weak prognostic covariates so that a more manageable set of variables can be analyzed via multivariate techniques.[70] After this univariate screening process, the final independent variables with a $p < 0.05$ will be retained in the final model through a backwards elimination process. As a final exploratory analysis, restricted mean survival times will be generated as described by Royston and Parmer.[71] Restricted mean survival time estimation is recommended in cases where the proportional hazards assumption is in doubt.

The binary secondary endpoints (i.e. survival at 6 months and 12 months) will be presented as odds ratios with appropriate 95% CI.

The overall analysis will include a univariate comparison of prespecified baseline features (including age and PS). All of the analyses will be performed using SAS® Version 9.1 (or later).

Prospective subset analyses will include the following:

1) Evaluation of the difference in treatment outcomes in the per-protocol population, as defined below, who had an immune response defined as an increase of IFNγ-positive CD8+ cells greater than 2-fold over baseline compared to those who did not.
2) Evaluation of the difference in treatment outcomes in the per-protocol population, as defined below, who were previously treated with a checkpoint inhibitor versus checkpoint-naïve patients.

9.2 Sample Size

Approximately 123 patients will be randomized in a 2:1 ratio to the experimental or the control group. Approximately 20-30 centers will enroll patients.

Simulation studies have suggested that a 2 to 3 month delay in the separation of survival curves with experimental immunotherapeutic drugs can reduce the available statistical power of 15 to 20%.[72] Therefore, the statistical power in the current study was adjusted for this anticipated loss. This sample size was based on the hypothesis that the combination of viagenpumatucel-L and CY versus the control group will result in a significant increase in OS. The overall sample size in this study is expected to be 123 patients, randomized in a 2 to 1 manner into the experimental and control groups (82 vs 41 randomized to provide 59 events in the experimental group and 33 events in the control group). By assuming an alpha of 10% (one tailed), the study should have a final 80% power (assuming a 15% initial loss) to detect a 50% reduction (*i.e.* HR = 0.50) in the risk of death between the experimental and control groups (median OS in the experimental group of 10 months vs. 5 months in the control group) over a 3.5 year trial period.

9.3 Analysis Populations

Study populations are defined as follows:

Per-protocol population: defined as all randomized patients who have not had a major protocol deviation as defined in section 10.3.

Intention to Treat (ITT): defined as all randomized patients summarized by randomized treatment.

As Treated (AT): defined as all randomized patients who receive at least 1 dose of randomized treatment, and summarized by treatment received.

Other sub-populations of patients for secondary and exploratory analyses may be defined at the time of statistical analysis and will be identified in any reporting of results.

9.4 Accountability, Demographics, and Baseline Characteristics

Accountability information will be summarized, including the number of enrolled patients, dosed patients, and patients withdrawn by reason.

Descriptive information on demographics and baseline data, including age, sex, weight, height, physical examination, and medical history, will be provided in a summary table. Summaries will be provided by treatment group and overall for the AT and ITT population classifications.

9.5 Interim Analyses

Two exploratory interim analyses will be performed after approximately 14 and 41 patients randomized to the experimental group have had blood samples taken at Week 10. For the 41 patient analysis only, the trial may be discontinued, or modified as necessary, if fewer than 50% of patients in the experimental group experience a peripheral blood immunologic response (IR) via intracellular cytokine staining (ICS) of IFNγ-positive CD8+ cells greater than 2-fold over baseline unless there is evidence of clinical or immunologic

activity in secondary endpoints. For example, if the overall response rate suggested clinical activity, the trial may still proceed as written. Neither of the interim analyses will examine overall survival.

9.6 Primary Efficacy Endpoints and Analyses

9.6.1 Overall Survival (OS)

The primary efficacy parameter is OS, calculated as the duration of survival from the date of randomization into the study to the date of death from any cause, or will be censored on the date the patient was last known to be alive. The primary analysis will be conducted when 92 survival events have occurred. Analysis details are provided in Section 9.1.

9.7 Secondary Efficacy Endpoints and Analyses

9.7.1 Safety

Safety is defined as the proportion of AE/SAE in patients receiving viagenpumatucel-L and low-dose CY compared to the proportion of AE/SAE in patients receiving Physician's Choice.

9.7.2 Immune-related overall disease control rate (irDCR)

irDCR is defined as the proportion of participants whose immune-related best overall response is immune-related partial response (irPR), immune-related complete response (irCR), or immune-related stable disease (irSD), as defined by irRC. Differences in irDCR between the experimental and control groups will be presented as odds ratios with 95% CI.

9.7.3 Overall disease control rate (DCR)

DCR is defined as the proportion of participants whose best overall response is partial response (PR), complete response (CR), or stable disease (SD) by RECIST criteria. Differences in DCR between the experimental and control groups will be presented as odds ratios with 95% CI.

9.7.4 6-month immune-related disease control rate (6m-irDCR)

6m-irDCR is defined as the proportion of participants whose immune-related best response is irPR, irCR, or irSD 6 months following randomization. Differences in 6m-irDCR between the experimental and control groups will be presented as odds ratios with 95% CI.

9.7.5 6-month disease control rate (6mDCR)

6mDCR is defined as the proportion of participants whose best response using RECIST criteria is PR, CR, or SD 6 months following randomization. Differences in 6mDCR between the experimental and control groups will be presented as odds ratios with 95% CI.

9.7.6 Immune-related overall response rate (irORR)

irORR is defined as the number of participants with irCR or irPR, divided by total participants in the data set. Differences in irORR between the experimental and control groups will be presented as odds ratios with 95% CI.

9.7.7 Overall response rate (ORR)

ORR is defined as the number of participants with CR or PR, divided by total participants in the data set. Differences in ORR between the experimental and control groups will be presented as odds ratios with 95% CI.

9.7.8 Immune-related Progression-Free Survival (irPFS)

irPFS will be calculated as the time between randomization and date of immune-related progressive disease (irPD) as defined by irRC or death, whichever occurs first. For patients with no recorded post baseline tumor assessments, irPFS will be censored at randomization. For those who remain alive and have no irPD, irPFS will be censored on the date of last evaluable tumor assessment. Kaplan-Meier curves will be produced separately for each treatment group along with the estimated rate of patients without disease progression or death at each time point. Analysis details are provided in Section 9.1.

9.7.9 Progression-Free Survival (PFS)

PFS will be calculated as the time between randomization and the date of progressive disease (PD), as defined by RECIST 1.1 or death, whichever occurs first. For patients with no recorded post-baseline tumor assessments, PFS will be censored at randomization. For those who remain alive and have no PD, PFS will be censored on the date of last evaluable tumor assessment. Kaplan-Meier curves will be produced separately for each treatment group along with the estimated rate of patients without disease progression or death at each time point. Analysis details are provided in Section 9.1.

9.7.10 Immune-related Time to Progression (irTTP)

irTTP is defined as the time between the date of randomization and the date of irPD. Kaplan-Meier curves will be produced separately in an exploratory analysis for each treatment group along with the estimated rate of patients without disease progression at each time point.

9.7.11 Time to Progression (TTP)

TTP is defined as the time between the date of randomization and the date of RECIST documented PD. Kaplan-Meier curves will be produced separately in an exploratory analysis for each treatment group along with the estimated rate of patients without disease progression at each time point.

9.7.12 6-month overall survival (6mOS)

6mOS will be calculated as the proportion of patients who are alive at 6 months after randomization and presented as an odds ratio with 95% CI in the ITT population.

9.7.13 12-month overall survival (12mOS)

12mOS will be calculated as the proportion of patients who are alive at 12 months after randomization and presented as an odds ratio with 95% CI in the ITT population.

9.7.14 Immunologic Response (IR)

IR is defined as the peripheral blood immunologic response via flow cytometry and/or ELISPOT of IFNγ-positive CD8+ cells greater than 2-fold over baseline. The exploratory parameters associated with IR will

be presented descriptively as means, medians, or proportions with appropriate measures of variance. Appropriate transformations will be undertaken in cases where the data are not normally distributed. These analyses will be completed using the per-protocol population.

9.8 Exploratory Endpoints and Analysis

The following endpoints will be evaluated in patients completing at least 9 weeks of study medication:

- Peripheral blood immunologic response (analysis of surface markers, CD3, CD4, CD8, CD19, CD25, CD45, CD56, FoxP3, and degranulation) and stimulation analysis via ICS of IFNγ and gzB.
- Total PBMC counts by flow cytometry, including lymphocyte subsets (B cells, helper T-cells, cytotoxic T-cells, NK cells and T-regs)
- Evaluation of tumor tissue obtained from pre-treatment biopsy or archival biopsy tissue for shared tumor antigen expression (LAGE-1, NY-ESO-1, MAGE-[A1-10], CT7, CT10, GAGE, etc.), expression of MHC class I, and expression of immunosuppressive molecules, including, for example, CTLA-4, PD-L1 and PD-1, by mRNA expression and/or IHC analysis
- Evaluation of tumor tissue obtained from post-treatment biopsy for presence of TILs
- Evaluation of tumor tissue and PBMCs for T cell receptor sequencing to determine correlation between clonally expanded T cell populations and other endpoints

Particular attention will be paid to determining the presence of an association between individual TCR clones as determined by deep sequencing of patient TCR and OS. Because clinical responses to viagenpumatucel-L are expected to be driven by the stimulation of antigen-specific CD8+ T cell clones that recognize antigens introduced by viagenpumatucel-L that are commonly expressed by an individual patient tumor, this analysis may provide a more specific surrogate for IR than traditional ELISPOT or ICS assays.

In addition, other recent vaccine trials have demonstrated a relationship between the frequency and activation status of patient NK cells and OS (TG4010, Transgene/Novartis). Thus, this relationship will also be analyzed for viagenpumatucel-L in the current study using Cox Proportional Hazard regression in an exploratory manner.

Exploratory endpoints will be summarized descriptively by time point of collection as described in preceding sections. Appropriate transformations will be undertaken in cases were the data are not normally distributed.

9.9 Safety Analysis

The analysis will be completed for the As Treated population.

9.9.1 Adverse Events

Treatment emergent adverse events (TEAEs) will be defined as events that occur on or after the first dose of study medication. The Medical Dictionary for Regulatory Activities (MedDRA) coding dictionary will be used for the coding of AEs. TEAEs, serious or CTCAE Grade 3 or 4 TEAEs, and TEAEs related to therapy will be summarized overall and by system organ class and preferred term by treatment group. These will summarize the number of events and the number and percent of patients with a given event. In addition,

the number and percent of patients with TEAEs will be provided by maximum severity. A summary of all TEAEs by system organ class and preferred term occurring in at least 5% of patients in either treatment group will be provided.

9.9.2 Laboratory Assessments

All laboratory-based data will be presented as listings of all values as well as abnormal results judged to be clinically significant, which will also be reported as AEs. Numeric summaries of all observed and change from baseline laboratory evaluations will be provided by visit and treatment group, including chemistry, hematology, and urinalysis results. No inferential comparisons are planned.

9.9.3 Vital Signs

Numeric summaries of all observed and change from baseline vital signs will be provided by time point and treatment group, including blood pressure, heart rate, respiratory rate, and temperature. No inferential analyses are planned for vital signs.

9.9.4 ECGs and Physical Examination

Physical examination data and changes will be presented as listings. ECG results will be presented as listings and summarized by treatment group and visit based on incidence of clinically significant abnormalities. No inferential comparisons across treatment groups are planned.

9.9.5 Other Assessments

Other collected data not specifically mentioned, including physical examinations and protocol deviations, will be presented in patient listings.

10.0 STUDY CONDUCT CONSIDERATIONS

10.1 Regulatory and Ethical Considerations

The study will be conducted in accordance with all applicable regulatory requirements, including a US IND, and Heat Biologics will obtain favorable opinion/approval to conduct the study from the appropriate regulatory agency in accordance with applicable country-specific regulatory requirements or local regulations, where applicable, prior to a site initiating the study in that country.

The study will also be conducted in accordance with GCP, all applicable patient privacy requirements, and the guiding principles of the Declaration of Helsinki. This includes, but is not limited to, the following:

- IRB/EC/IBC review and favorable opinion/approval to conduct the study and of any subsequent relevant amending documents
- Patient informed consent
- Investigator reporting requirements

A copy of the site-specific proposed informed consent document should be submitted to the sponsor for review and comment before submission to the IRB/EC. The study should not begin until the document has been reviewed by the sponsor and until the document has been approved by the IRB/EC. The informed

consent document shall contain all the elements of informed consent specified in the regulations. Written informed consent will be obtained for each patient before he or she can participate in the study.

10.2 Quality Control (Study Monitoring)

In accordance with applicable regulations and GCP, Heat Biologics will perform quality control and assurance checks. Before enrolling any patient into this study, sponsor personnel (or designees) and the investigator will review the protocol, the brochure for clinical investigators, the CRFs and instructions for their completion, the procedure for obtaining informed consent, and the procedure for reporting AEs and SAEs. A qualified representative of the sponsor will monitor the conduct of the study by visiting the site and by contacting the site by telephone.

The investigator agrees that qualified representatives of the sponsor and regulatory agencies will have, both during and after this study, direct access to review medical records pertinent to the clinical study as permitted by regulations. Patients will not be identified by name in documents that leave the study site, and confidentiality of information in medical records will be preserved unless disclosure is required by regulations.

Heat Biologics will monitor the study consistent with the demands of the study and site activity to verify that the:

- Data are authentic, accurate and complete;
- Safety and rights of patients are being protected;
- Study is conducted in accordance with the currently approved protocol and any other study agreements, GCP, and all applicable regulatory requirements.

10.3 Protocol Deviations

In general, a protocol deviation is an inadvertent excursion to, or non-compliance with, the IRB/EC approved protocol. The investigator is responsible for ensuring the study is conducted in accordance with the procedures described in this protocol and should not implement any changes to the protocol unless it is required to eliminate an immediate hazard to the patient.

If the deviation affects the safety of the patient, the sponsor must be notified immediately. Other deviations outside of these categories will be reported to the IRB/EC in accordance with local requirements, as applicable. Deviations that fall into the following categories will be captured on the CRFs.

- Entered into the study without meeting eligibility criteria
- Developed withdrawal criteria during the study and was not withdrawn
- Received wrong treatment or incorrect dose
- Received excluded concomitant treatment
- Failed to collect data necessary to interpret primary endpoints

10.4 Quality Assurance

To ensure compliance with GCP and all applicable regulatory requirements, Heat Biologics may conduct 1 or more quality assurance audits. Regulatory agencies may also conduct regulatory inspection of this study. Such audits/inspections can occur at any time during or after completion of the study. If an audit or inspection occurs, the investigator and institution agree to allow the auditor/inspector direct access to all relevant documents and to allocate his/her time and the time of his/her staff to the auditor/inspector to discuss findings and any relevant issues.

10.5 Study and Site Closure

Upon completion or premature discontinuation of the study, the Site Monitor will conduct site closure activities with the investigator or site staff, as appropriate, in accordance with applicable regulations, GCP, and Heat Biologics procedures.

In addition, Heat Biologics reserves the right to temporarily suspend or prematurely discontinue this study at any time for reasons, including, but not limited to, safety or ethical issues or severe non-compliance. For this multicenter study, this can occur at 1 or more sites. If Heat Biologics determines such action is needed, Heat Biologics will discuss this with the investigator or the head of the medical institution, where applicable, including the reasons for taking such action, at that time. When feasible, Heat Biologics will provide advance notification to the investigator or the head of the medical institution, where applicable, of the impending action prior to its taking effect.

Heat Biologics will promptly inform all other investigators or the head of the medical institution, where applicable, and/or institutions conducting the study if the study is suspended or prematurely discontinued for safety reasons. Heat Biologics will also promptly inform the regulatory authorities of the suspension or premature discontinuation of the study and the reason(s) for the action. If required by applicable regulations, the investigator or the head of the medical institution, where applicable, must inform the IRB/EC promptly and provide the reason for the suspension or premature discontinuation.

10.6 Records Retention

Following closure of the study, the investigator or the head of the medical institution, where applicable, must maintain all site study records, except for those required by local regulations to be maintained by someone else, in a safe and secure location. The records must be maintained to allow easy and timely retrieval, when needed (e.g., audit or inspection), and, whenever feasible, to allow any subsequent review of data in conjunction with assessment of the facility, supporting systems, and staff. Where permitted by local laws/regulations or institutional policy, some or all of these records can be maintained in a format other than hard copy (e.g., microfiche, scanned, electronic); however, caution needs to be exercised before such action is taken. The investigator must assure that all reproductions are legible and are a true and accurate copy of the original and meet accessibility and retrieval standards, including regenerating a hard copy, if required. Furthermore, the investigator must ensure there is an acceptable back up of these reproductions and that an acceptable quality control process exists for making these reproductions.

These records should be retained for not less than 2 years after the last approval of a marketing application in an ICH region and until there are no pending or contemplated marketing applications in an ICH region or at least 2 years have elapsed since the formal discontinuation of clinical development of the

investigational product. These documents should be retained for a longer period, however, if required by applicable regulatory requirements or by an agreement with the sponsor. Thereafter, records will not be destroyed without giving the sponsor prior written notice and the opportunity to further store such records.

The investigator must notify Heat Biologics of any changes in the archival arrangements, including, but not limited to, the following: archival at an off-site facility, transfer of ownership of the records in the event the investigator leaves the site.

10.7 Provision of Study Results and Information to Investigators

When required by applicable regulations, the investigator signatory for the clinical study report will be determined at the time the report is written. When the clinical study report is completed, Heat Biologics will provide the investigator with a full summary of the study results. The investigator is encouraged to share the summary results with the patients, as appropriate. In addition the investigator will be given reasonable access to review the relevant statistical tables, figures, and reports and will be able to review the results for the entire study at the Heat Biologics site or other mutually agreeable location.

10.8 Data Management

The data collection tool for this study will be Heat Biologics-defined CRFs. Patient data necessary for analysis and reporting will be entered/transmitted into a validated database or data system.

After the sponsor receives the CRFs, the sponsor's Medical Monitor (or designee) will review the data for safety information, and the sponsor's clinical data associates (or designees) will review them for logical consistency and will use automated programs to help identify missing data, selected protocol violations, out-of-range data, and other inconsistencies. Requests for data clarification or correction will be forwarded to the investigative site for timely resolution.

Appendix 1. ECOG Performance Status Scale

ECOG PERFORMANCE STATUS[73]

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

Credit: the Eastern Cooperative Oncology Group, Robert Comis M.D., Group Chair

Appendix 2: Immune-related Response Criteria

The overall response according to irRC is derived from time point response assessments based on tumor burden as follows below:[67]

- irCR, complete disappearance of all lesions (whether measurable or not, and no new lesions) confirmed by a repeat, consecutive assessment at least 4 weeks from the date first documented. New non-measurable lesions do not indicate progression, but preclude irCR.
- irPR, decrease in tumor burden $\geq$ 50% relative to baseline confirmed by a consecutive assessment at least 4 weeks after first documentation
- irSD, not meeting criteria for irCR or irPR, in absence of irPD
- irPD, increase in tumor burden $\geq$ 25% relative to nadir (minimum recorded tumor burden) confirmed by a repeat, consecutive assessment at least 4 weeks from the date first documented. New measurable lesions do not automatically define disease progression but are incorporated into the total tumor burden.

Derivation of irRC Overall Responses

Measurable Response	**Nonmeasurable response**		**Overall response**
Index and new, measurable lesions (tumor burden),* %	**Non-index lesions**	**New, nonmeasurable lesions**	**Using irRC**
↓100	Absent	Absent	irCR†
↓100	Stable	Any	irPR†
↓100	Unequivocal progression	Any	irPR†
↓≥50	Absent/Stable	Any	irPR†
↓≥50	Unequivocal progression	Any	irPR†
↓<50 to <25↑	Absent/Stable	Any	irSD
↓<50 to <25↑	Unequivocal progression	Any	irPD†
≥25↑	Any		

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

†Assuming complete and partial response (irCR and irPR) and progression (irPD) are confirmed by a second, consecutive assessment at least 4 wk apart.

Appendix 3. The Response Evaluation Criteria in Solid Tumors (RECIST) Guidelines

The overall response according to RECIST 1.1 is derived from time-point response assessments based on tumor burden as follows below.[68]

Evaluation of target lesions:

- Complete Response (CR): Disappearance of all target lesions. Any pathological lymph nodes (whether target or non-target) must have reduction in short axis to <10 mm.
- Partial Response (PR): At least a 30% decrease in the sum of diameters of target lesions, taking as reference the baseline sum diameters.
- Progressive Disease (PD): At least a 20% increase in the sum of diameters of target lesions, taking as reference the smallest sum on study (this includes the baseline sum if that is the smallest on study). In addition to the relative increase of 20%, the sum must also demonstrate an absolute increase of at least 5 mm. (Note: the appearance of 1 or more new lesions is also considered progression).
- Stable Disease (SD): Neither sufficient shrinkage to qualify for PR nor sufficient increase to qualify for PD, taking as reference the smallest sum diameters while on study.

Evaluation of non-target lesions:

- Complete Response (CR): Disappearance of all non-target lesions and normalization of tumor marker level. All lymph nodes must be non-pathological in size (<10mm short axis).
- Non-CR/Non-PD: Persistence of one or more non-target lesion(s) and/or maintenance of tumor marker level above the normal limits.
- Progressive Disease (PD): Unequivocal progression of existing non-target lesions. (Note: the appearance of 1 or more new lesions is also considered progression).

Evaluation of Overall Time Point Response for Patients with Measurable Disease at Baseline

Target Lesions	Non-target Lesions	New Lesions	Overall Response
CR	CR	No	CR
CR	Non-CR/Non-PD	No	PR
CR	NE	No	PR
PR	Non-PD or NE	No	PR
SD	Non-PD or NE	No	SD
Not all evaluated	Non-PD	No	NE
PD	Any	Yes or No	PD
Any	PD	Yes or No	PD
Any	Any	Yes	PD

CR = Complete Response, PR = Partial Response, SD = Stable Disease, PD = Progressive Disease, NE = Inevaluable

*When target lesions show SD/PR and some subset of non-target lesions is inevaluable, a careful decision must be made whether to call the overall response at this time point SD/PR or NE. This is based on whether the inevaluable lesions, if they showed growth, could cause an overall response of PD in the context of the

other lesion responses seen. If the inevaluable non-target lesions comprise a significant proportion of the overall disease burden, the appropriate time point response is NE.

Appendix 4. Grading Scale for Injection Site Reactions

The grading scale is derived from the FDA Guidance for Industry (http://www.fda.gov/biologicsbloodvaccines/guidancecomplianceregulatoryinformation/guidances/vaccines/ucm074775.htm#TOXICITYGRADINGSCALETABLES)

	Grade 1 **Mild**	**Grade 2** **Moderate**	**Grade 3** **Severe**	**Grade 4** **Potentially Life Threatening**
Pain	Does not interfere with activity	Repeated use of non-narcotic pain reliever > 24 hours or interferes with activity	Any use of narcotic pain reliever or prevents daily activity	Emergency room visit or hospitalization
Tenderness	Mild discomfort to touch	Discomfort with movement	Significant discomfort at rest	Emergency room visit or hospitalization
Erythema/Redness	2.5-5 cm	5.1-10 cm	> 10 cm	Necrosis or exfoliative dermatitis
Induration/Swelling*	2.5-5 cm and does not interfere with activity	5.1-10 cm or interferes with activity	> 10 cm or prevents daily activity	Necrosis

* Induration/Swelling should be evaluated and graded using the functional scale as well as the actual measurement.

Appendix 5. Amendment Change Log

Protocol Change	Section Affected	Version Where Implemented
Added amendment history	Title page	Version 2.0, Amendment 1
Added pregnancy assessments	Protocol synopsis (Eligibility criteria), 5.1 Inclusion Criteria, 6.1.1 SOA Stage A, 6.1.2 SOA Stage B, 6.2 Screening Procedures, 6.3.4 End of Treatment Visit, 6.5.2 Clinical Laboratory Evaluations, 6.5.6 Pregnancy (including 6.5.6.1-6.5.6.3), 6.7.3 Discontinuation	Version 2.0, Amendment 1
Added respiratory rate to vital signs	6.2 Screening Procedures, 6.5.1 Physical Examinations, 9.8.3 Vital Signs	Version 2.0, Amendment 1
Added docetaxel as a physician's choice regimen	Protocol synopsis (Trial design; Dosing regimen, form and route), 4.0 Trial Design, 6.1.1 SOA Stage A, 6.1.2 SOA Stage B, 7.2.1 Physican's Choices, 7.5.2 Prohibited Medications	Version 2.0, Amendment 1
Eliminate immune monitoring and blood banking after Week 22 in Stage A and Week 19 in Stage B	6.1.1 SOA Stage A, 6.1.2 SOA Stage B, 6.3.2.13 Week A31 Assessments and every 9 weeks thereafter, 6.3.3.10 Week B28 Assessments and every 9 weeks thereafter, 6.6.2 Immunological Response	Version 2.0, Amendment 1
Updated treatment period to 1 year; previously listed as 2 years	Protocol synopsis (Trial design; Dosing regimen, form and route; Eligibility criteria), 4.0 Trial Design, 5.1 Inclusion Criteria, 6.3.2.11 Week A25 Assessments and every 9 weeks thereafter, 6.3.3.9 Week B25 Assessments and every 9 weeks thereafter, 6.3.3.10 Week B28 Assessments and every 9 weeks thereafter, 6.7.1 Patient Completion	Version 2.0, Amendment 1
Updated eligibility requirement from two lines of conventional therapy to two lines of therapy, including conventional therapy, targeted therapy, immunotherapy, or investigational therapy administered through a clinical trial	Protocol synopsis (Trial design), 4.0 Trial Design	Version 2.0, Amendment 1
Added abstinence as an acceptable form of contraception	Protocol synopsis (Eligibility criteria), 5.1 Inclusion Criteria	Version 2.0, Amendment 1
Remove Stage B for patients randomized to the control group	Protocol synopsis (Trial design), 4.0 Trial Design, 6.1.2 Schedule of Assessments; 6.3.3 Stage B Assessments; 6.7.3 Study Discontinuation	Version 2.0, Amendment 1

Protocol Change	Section Affected	Version Where Implemented
Remove blood banking for patients randomized to the control group	6.1.1, 6.1.2 Schedule of Assessments; 6.3 On-study Procedures	Version 2.0, Amendment 1
Remove Blood for exploratory analysis from Stage B table - duplicate entry to "Immunologic Response" entry	6.1.2 Schedule of Assessments;	Version 2.0, Amendment 1
Add Hematology and Chemistry to BL procedures if screening labs done >2 weeks prior to first dose	6.1.1 Schedule of Assessments; 6.3.1 Baseline Assessments	Version 2.0, Amendment 1
Add language that pre-medication with anesthetic cream is allowed	7.5.1 Permitted Medications	Version 2.0, Amendment 1
Updated the Schedule of Events descriptions to match the tables	6.3 On Study Procedures	Version 2.0, Amendment 1
Remove Weeks B4, B5, B8 and B9 visits to be consistent with text indicating weekly clinic visits for 12 weeks followed by every 3 weeks thereafter	6.1.2 SOA – After First Progression; 6.3 On Study Procedures	Version 2.0, Amendment 1
Modification of schedule of Vital Signs and targeted Physical Exam in Stage B to align with the ECGs	6.1.2 SOA – After First Progression; 6.3 On Study Procedures; 6.5.1 Physical Examination	Version 2.0, Amendment 1
Update title	Cover page, Sponsor Protocol Approval page, Investigator Protocol Agreement page, Synopsis	Version 3.0, Amendment 2
Expanded on reference to serum collected for immunologic response	6.5.2 Immunologic Response	Version 3.0, Amendment 2
Note that cyclophosphamide is administered every other week for 12 weeks	7.1.2 Cyclophosphamide	Version 3.0, Amendment 2
Prohibit dose modifications of viagenpumatucel-L but allowed dose reductions of Physician's Choice drugs as needed for management of toxicity according to the investigator's standard of care	7.7 Dose Modifications (formerly Dose Delays)	Version 3.0, Amendment 2
Remove radiotherapy as a prior regimen for eligibility	Synopsis, 5.1 Inclusion Criteria	Version 3.0, Amendment 2

Protocol Change	Section Affected	Version Where Implemented
Reduce viagenpumatucel-L dosing in the maintenance period from every 3 week s to every 9 weeks	Synopsis; 4.0 Trial Design; 6.1 SOA; 6.3.2.8-12 Assessments at Weeks 16, 19, 22+9x, 25+9x, and 28+9x	Version 3.0, Amendment 2
Do not treat any patients after progression	Synopsis, 2.1 Background Rationale, 2.2 Study-Specific Rationale, 3.2 Secondary Objectives, 4.0 Trial Design (including Figure 1), 6.1 SOA, 6.3.4 LTFU Visits, 6.4.1 Physical Examination, 6.5.1 Tumor Assessments, 6.6.3 Discontinuation from Study Treatment, 7.2.1 Physician's Choices, 9.6 Secondary Efficacy Endpoints and Analyses	Version 3.0, Amendment 2
Add 6-month immune-related disease control rate and 6-month disease control rate as study endpoints	Synopsis; 3.2 Secondary Objectives; Figure 1; 9.6.2-5 irDCR, DCR, 6m-irDCR,and 6mDCR	Version 3.0, Amendment 2
Remove known allergy to soy or egg products as an exclusion criteria	Synopsis, 5.2 Exclusion Criteria	Version 3.0, Amendment 2
Biopsy only collected in patients randomized to viagenpumatucel-L	Synopsis, 4.0 Trial Design, 6.1 SOA, 6.3.1 Baseline Assessments	Version 3.0, Amendment 2
Move post-treatment biopsy to Week 13	Synopsis, 4.0 Trial Design, 6.1 Schedule of Assessments, 6.3.2.6-7 Assessments at Weeks 10 and 13	Version 3.0, Amendment 2
Stop immune response testing in patients receiving physician's choice regimens after Week 1	Synopsis; 4.0 Trial Design; 6.1 SOA; 6.3.2.4-7 Assessments at Weeks 4, 7, 10, and 13; 6.3.2.10 Assessments Week22+9x, 6.3.3 EOT, 6.5.2 Immunologic Response	Version 3.0, Amendment 2
Remove dose and route requirements for physician's choice regimens	Synopsis, 6.1 SOA, 7.2.1 Physician's Choices	Version 3.0, Amendment 2
Update Sponsor address	Contact Page	Version 3.0, Amendment 2
Allow patients on stable low dose steroids after consulting Medical Monitor	7.5.2 Prohibited Medications	Version 3.0, Amendment 2

Protocol Change	Section Affected	Version Where Implemented
Add pemetrexed as a physician's choice	Synopsis, 4.0 Trial Design, 7.2.1 Physician's Choices	Version 3.0, Amendment 2
Add interim analysis	Synopsis, 4.0 Trial Design, 8.3 Trial Stopping Rules	Version 3.0, Amendment 2
Allow patients who have received 3 prior lines of therapy	Synopsis, 5.1 Inclusion Criteria	Version 3.0, Amendment 2
Allow patients to provide archival biopsy tissue	Synopsis, 2.4 Rationale for Performing Tumor Biopsies, 3.3 Exploratory Objectives, 4.0 Trial Design, 6.1 SOA, 6.5.2.5 Antigen Screening of Baseline or Archival Tumor Biopsy, 9.7 Exploratory Endpoints and Analysis	Version 3.0, Amendment 2
Moved exploratory objectives to a separate section (rather than a subset of secondary endpoints)	Synopsis, 3.3 Exploratory Objectives	Version 3.0, Amendment 2
Added grading scale for injection site reactions	Appendix 4. Grading Scale for Injection Site Reactions	Version 3.0, Amendment 2
Added Data Monitoring Committee	Synopsis, 8.2 Data Monitoring Committee, 8.3 Trial Stopping Rules	Version 3.0, Amendment 2
Allow G-CSF	7.5.1 Permitted Medications	Version 3.0, Amendment 2
Indicated where randomization will occur (at baseline)	6.1 Schedule of Assessments, 6.3.1 Baseline Assessments	Version 3.0, Amendment 2
Updated and expanded the maintenance visit	6.1 Schedule of Assessments, 6.3.2.10-15 Assessments at Weeks 22, 28, 31, 40, 49, and 52	Version 3.0, Amendment 2
Added concomitant medication assessment	6.3.1 Baseline Assessments	Version 3.0, Amendment 2
Removed volumes of samples collected	6.3.2 Visit Assessments (throughout)	Version 3.0, Amendment 2
Specified CT and MRI for tumor assessments	6.3.2 Visit Assessments (throughout)	Version 3.0, Amendment 2

Protocol Change	Section Affected	Version Where Implemented
Take immune response samples from all patients	Synopsis, 4.0 Trial Design, 6.1 SOA, 6.3.2.4 Week 4 Assessments, 6.3.2.6 Week 10 Assessments, 6.3.2.7 Week 13 Assessments, 6.3.2.10 Week 22 Assessments, 6.3.3 End of Treatment Visit, 6.5.2 Immunologic Response	Version 4.0, Amendment 3
Eliminate immune response and blood banking at Weeks 7 and 40	Synopsis, 4.0 Trial Design, 6.1 SOA, 6.3.2.5 Week 7 Assessments, 6.5.2 Immunologic Response	Version 4.0, Amendment 3
Combine immune response and blood banking into a single category	Former section 6.5.3, Schedule of Assessments, 6.5.2 Immunologic Response,	Version 4.0, Amendment 3
Update immunologic response methodology and endpoints	Synopsis, 6.5.2 Immunologic Response, 9.7 Exploratory Endpoints and Analysis	Version 4.0, Amendment 3
Indicate preference for tissue sections rather than FFPE	6.3.1 Baseline Assessments, 6.3.2.7 Week 13 Assessments, 6.5.2.5 Antigen Screening of Baseline or Archival Tumor Biopsy	Version 4.0, Amendment 3
Describe make up doses of vaccine and CY	7.1.1 Viagenpumatucel-L (HS-110), 7.1.2 Cyclophosphamide	Version 4.0, Amendment 3
Clarify steroid therapy use and define low-dose steroid therapy	7.5.2 Prohibited Medications	Version 4.0, Amendment 3
Indicate that patients in the experimental arm should receive G-CSF only after a Grade 3 neutropenia	7.5.1 Permitted Medications	Version 4.0, Amendment 3
Indicate that patients may not receive other investigative therapies	7.5.2 Prohibited Medications	Version 4.0, Amendment 3
Not require patients with progressive disease to discontinue study treatment	6.6.3 Discontinuation from Study Treatment	Version 4.0, Amendment 3
Indicate that dose should be taken with food and water in the morning	7.1.2 Cyclophosphamide	Version 4.0, Amendment 3

Protocol Change	Section Affected	Version Where Implemented
Indicate that only patients in the experimental group should discontinue study treatment for a Grade 4 event definitely or probably related to therapy	6.6.3 Discontinuation from Study Treatment	Version 4.0, Amendment 3
Indicate in that Grade 3 or greater adverse events or unexpected Grade 4 toxicities should be assessed as possibly, probably, or definitely related to study drug to stop the trial	8.3 Trial Stopping Rules	Version 4.0, Amendment 3
Indicate that patients in the control group can have a reduced volume of blood collected for immune response	6.1 SOA	Version 4.0, Amendment 3
Exclude patient with any condition requiring active steroid or other immunosuppressive therapy	Synopsis, 5.2 Exclusion Criteria	Version 4.0, Amendment 3
Exclude patients with prior treatment with a cancer vaccine	Synopsis, 5.2 Exclusion Criteria	Version 4.0, Amendment 3
Include patients with no more than 3 lines of prior therapy	Synopsis, 5.1 Inclusion Criteria	Version 4.0, Amendment 3
Collect information on caffeine consumption and supplemental oxygen use	7.5 Concomitant Medications	Version 4.0, Amendment 3
Interim analysis for trial stopping will occur after 41 patients in the experimental group have had blood samples taken at Week 10	Synopsis, 4.0 Trial Design	Version 4.0 Amendment 3
Added exploratory analysis after 14 patients in the experimental group have had blood samples taken at Week 10.	Synopsis, 4.0 Trial Design	Version 4.0, Amendment 3
Specify that cyclophosphamide should be taken by mouth	7.1.2 Cyclophosphamide	Version 4.0, Amendment 3

Protocol Change	Section Affected	Version Where Implemented
Long-term follow-up will be until study termination or death, whichever occurs first	6.3.4 Long-term Follow-up Visits	Version 4.0, Amendment 3
Stress that follow-up needs to continue even if patients initiate other therapy	6.3.4 Long-term Follow-up Visits	Version 4.0, Amendment 3
Changed the order of Patient Withdrawal from Study and Discontinuation from Study Treatment	6.6.2 Discontinuation from Study Treatment, 6.6.3 Patient Withdrawal from Study	Version 4.0, Amendment 3
Point out that withdrawal of consent for treatment is not the same as withdrawal of consent for follow-up	6.6.3 Patient Withdrawal from Study	Version 4.0, Amendment 3
Removed "other than viagenpumatucel-L" from the sentence on concomitant investigational agents	7.5.2 Prohibited Medications	Version 4.0, Amendment 3
Noted that during follow-up there are no prohibited medications and patients may enroll in any appropriate investigational study	7.5.2 Prohibited Medications	Version 4.0, Amendment 3
Updated safety from number of AE/SAE to proportion of AE/SAE	9.6.1 Safety	Version 4.0, Amendment 3
Prior adjuvant or neoadjuvant chemotherapy or definitive chemoradiation with curative intent, or a repeat course of a prior line of systemic therapy does not count as a prior line of therapy if last administration occurred at least 12 months prior to enrollment	Synopsis, 5.1 Inclusion Criteria	Version 4.0, Amendment 3
State when the primary analysis will be conducted	Synopsis, 4.0 Trial Design, 9.5.1 Overall Survival	Version 4.0, Amendment 3

Protocol Change	**Section Affected**	**Version Where Implemented**
Added Heat Biologics logo	Cover page	Version 4.0, Amendment 3
Defined AEs to be recorded as possibly, probably, or definitely related to study medication	8.1.5 Reporting Adverse Events	Version 4.0, Amendment 3

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