A Phase I, first-in-human, dose-escalation study to evaluate the safety and immunologic response after administration of HS-130 in combination with HS-110 (viagenpumatucel-L) in patients with solid tumors refractory to standard care

Protocol No.:	HS130-001
IND No.:	19098
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Sponsor:	Heat Biologics 627 Davis Drive, Suite 400 Morrisville, NC 27560 (919) 240-7133
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Protocol Version:	2.0
Replaces:	1.2
Date:	11 February 2020

CONFIDENTIAL

INVESTIGATOR'S STATEMENT

1. I have carefully read this protocol entitled "A Phase I, first-in-human, dose-escalation study to evaluate the safety and immunologic response after administration of HS-130 in combination with HS-110 (viagenpumatucel-L) in patients with solid tumors refractory to standard care" and agree that it contains all the necessary information required to conduct the study. I agree to conduct this study as outlined in the protocol.
2. I understand that this study will not be initiated without approval of the appropriate Institutional Review Committee/Independent Ethics Committee (IRB/IEC), and that all administrative requirements of the governing body of the Institution will be complied with fully.
3. Informed written consent will be obtained from all participating patients in accordance with institutional guidelines, FDA requirements as specified in Title 21 CFR, Part 50, the European Union Directive 2001/20/EC and its associated Detailed Guidances, European Union GCP Directive 2005/28/EC, the ICH Guideline for Good Clinical Practice, Section 4.8, and the terms of the Declaration of Helsinki (2013).
4. I will enroll patients who meet the protocol criteria for entry.
5. I understand that my signature on each completed Case Report Form (CRF) indicates that I have carefully reviewed the complete set of CRFs and accept full responsibility for the contents thereof.
6. I understand that the information presented in this study protocol is confidential, and I hereby assure that no information based on the conduct of the study will be released without prior consent from the Sponsor unless this requirement is superseded by the Food and Drug Administration, a Competent Authority of the European Union or another Regulatory Authority.

Protocol Version 2.0: 11 February 2020

Investigator:

Name: _____ Telephone: _____

Address: _____

_____

Signature: _____ Date: _____

Heat Biologics:

Name: Lori McDermott, VP, Clinical Development & Regulatory Affairs

Signature: Lori McDermott Date: 11 Feb 2020

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CLINICAL STUDY SYNOPSIS

Name of Sponsor:
Heat Biologics
627 Davis Drive, Suite 400
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Name of finished product: HS-130/HS-110

Name of active ingredient: HS-130/HS-110

Title of the study: A Phase I, first-in-human, dose-escalation study to evaluate the safety and immunologic response after administration of HS-130 in combination with HS-110 (viagenpumatucel-L) in patients with solid tumors refractory to standard care

Protocol number: HS130-001

Investigator and study center: Rachel E. Sanborn, MD
Providence Cancer Institute,
Portland, OR, USA

Clinical phase: Phase I

Objectives:

Primary:

- To evaluate safety and tolerability of HS-130 in combination with HS-110 in patients with solid tumors refractory to Standard of Care (SOC)
- To determine the recommended phase 2 dose (RP2D) of the combination HS-130 and HS-110 in patients with solid tumors refractory to SOC

Secondary:

- To determine clinical response to combination treatment with HS-130 and HS-110

Exploratory:

- To study the immunological effect generated by HS-130 and HS-110 by evaluating proportions of natural killer (NK) and T cell subsets for levels of activation, memory and exhaustion using flow cytometry
- To evaluate patient archival tumor tissue for overexpressed Cancer Testis Antigens (CTAs) and shared antigen expression with HS-110
- To evaluate immune reactivation response to CTA expressed in HS-110 (e.g. by ELISPOT)
- To determine the presence of a specific cytokine/chemokine signature in response to combination treatment with HS-130 and HS-110, or any other unspecific inflammatory response
- Genomic, immunohistochemical and proteomic analyses of tumor tissue (pre-dose and on-treatment biopsy) to identify biomarkers predictive of response or resistance to HS-110/HS-130, for example by multiplex immunohistochemistry (mIHC)
- Assess immunologically active dose based on flow cytometry analysis of blood, using immune marker panels of activation and suppression as defined in Section 8.6.1

Study Overview:
This is an open-label, non-controlled, first-in-human, Phase I study of the combined intradermal administration of HS-130 and HS-110 to patients with advanced solid tumors refractory to SOC.

Escalating doses of the viable, replication-incompetent, human whole cell vaccines, HS-130 and HS-110, will be administered to patients via intradermal injections/re-injections (up to 10 total) on Day 1 of a two-week cycle. The length of each cycle is two weeks, and the DLT window of observation includes the safety data obtained from the first two treatment cycles, Cycle 1 and Cycle 2 (4 weeks).

Seven dose levels will be explored, and patients will receive separate escalating doses of HS-130 and HS-110 in alternating fixed 1:1 or 2:1 ratio based on the amount of secreted OX40L-Ig (HS-130) and gp96-Ig fusion protein (HS-110) per cell of the drug product. The starting dose of HS-130/HS-110 combination is based on the dose-ranging studies conducted in animal models of T cell expansion and tumor challenge, as well as established clinical experience from HS-110.

The first cohort will employ an accelerated design to evaluate the first 4 dose levels in single patients. There will be a staggered enrollment with a minimum 1-week delay between each patient in cohort 1. If any drug-related ≥ Grade 2 (other than Grade 2 injection site reaction with pain) event occurs during the first cycle of treatment, the study will revert to 3+3 design starting at that dose level.

Subsequent cohorts in the dose escalation phase will enroll patients following the standard 3+3 design. Three patients will be enrolled in each subsequent dose cohort, and enrolled with a (minimum) 1-week staggered delay (i.e. Patient 2 to be dosed ≥1-week after Patient 1 received the first dose, and Patient 3 to be dosed ≥1-week after Patient 2 received the first dose).

In the 3-patient cohorts (i.e. 3 patients treated at the same dose), if 1 out of 3 patients experience a DLT during the first two treatment cycles, the dose cohort will be expanded up to 6 patients. If ≥2 out of 6 patients experience DLTs, the MTD has been exceeded, and dose escalation will cease. Up to 3 additional patients will be enrolled at a lower dose if only 3 patients were treated at that dose level, to confirm safety of that dose. MTD will be defined as a dose where ≤1 out of 6 patients have DLTs.

Once all patients in a cohort have completed the first two cycles of dosing and received at least 2 doses of HS-130/HS-110, the safety and tolerability of the combination treatment administered will be reviewed by the safety review committee (SRC). If 0 out of 3 patients or 1 out of 6 patients experience a DLT, then the SRC may recommend enrollment at the next higher dose level.

Any patient who does not receive two doses of the study treatment during the DLT window of observation (first 2 cycles), for reasons other than study drug-related toxicity and did not experience a DLT will not be taken into account in the assessment of the overall DLT rate for the particular dose level cohort and will be replaced.

In the absence of progressive disease and intolerable toxicity after Cycle 2, the patient can continue the combination treatment of HS-130/HS-110 administered every 2-weeks until disease progression, death, patient's withdrawal of consent, Investigator decision to discontinue treatment, or intolerable toxicity, whichever occurs first.

Immune response may be a delayed effect, and in immuno-oncology, treatment beyond first progression is commonly used in situations where clinical progression is asymptomatic and/or is not likely to result in life-threatening complications with further progression. Therefore, at the discretion of the Investigator the treatment with the therapeutic vaccines HS-130/HS-110 may continue despite evidence of disease progression if the investigator considers this of a potential clinical benefit for the patient, and the following criteria are met:

- No other approved palliative or curative salvage therapy exists for the indication (e.g. resection of pulmonary metastases in osteosarcoma patients).

- The patient continues to meet all other study protocol eligibility criteria.
- No DLT has been observed, and all toxicities resolved to the baseline level, consistent with the study eligibility criteria.
- No deterioration of subject performance status.
- Does not delay imminent intervention to prevent serious complications of disease progression (e.g., CNS metastases).

Visits and study examinations will be performed per the Schedule of Assessments. Safety will be assessed by frequency of treatment-emergent adverse events (TEAEs), evaluation of clinical laboratory parameters (hematology, and biochemistry), weight, vital signs, electrocardiogram (ECG), performance status, physical exams (PEs), and recording of concurrent illness/therapy and adverse events. CTCAE version 5 will be used to grade all toxicities.

All patients will also be monitored for extensive safety assessment including serum cytokines/chemokines, immune reactivation response to HS-110 CTA and immune phenotype profiling of immune cell subsets. A post-treatment safety visit will be conducted approximately 30 days following the last dose. Response to treatment will be assessed according to RECIST 1.1[1] with planned evaluation performed every 8-weeks ± 1-week.

Number of patients: 13-30 patients will be enrolled in the study. Based on response observed in patients at different dose levels and/or in patients with a particular tumor type, the study protocol may be amended to allow for cohort expansion of patients with specific characteristics.

Diagnosis and main criteria for inclusion:

Inclusion Criteria:

Patients **must** meet all of the following inclusion criteria before they will be allowed to participate in the trial:

1. Patients with metastatic or advanced, unresectable solid tumor who have progressed, or recurred following standard-of-care (SOC) therapies or are ineligible for, or refuse, safe and effective SOC therapies and for whom, in the opinion of the Investigator, experimental therapy with HS-130/HS-110 may be beneficial.
2. Patients should have lesions that are safely accessible for biopsy and be willing to provide pre-treatment and on-treatment tissue biopsy. Fine-needle aspiration biopsy is not acceptable. Archival tumor tissue will be accepted in lieu of fresh biopsy at screening if sample was collected within 6-months from Cycle 1 Day 1, and the local pathologist confirms that an adequate amount of tissue/tumor cells exist to allow completion of all testing as outlined in the specimen collection manual.
3. Age ≥ 18 years.
4. Have an acceptable organ function:
    - Albumin ≥ 2.5 g/dL.
    - Total Bilirubin < 3.0 × upper limit of normal (ULN) unless patient has Gilbert's syndrome.
    - Alanine transaminase (ALT) and aspartate transaminase (AST) ≤ 3.0 × 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.
5. Have an Eastern Cooperative Oncology Group (ECOG) performance status of 0 or 1.
6. Life expectancy of at least three months.

7. Patients, both females and males, of childbearing/reproductive potential must agree to use adequate contraception while included in the trial and for six months after the last treatment with HS-130 and/or HS-110.
8. Patients must be willing and have the capacity to sign the informed consent form.

Exclusion Criteria:

If any of the following apply, the patient **MUST NOT** enter the trial:

1. Have clinically significant cardiac disease, including:
    - Onset of unstable angina within 6 months of signing the Informed Consent Form (ICF).
    - Acute myocardial infarction within 6 months of the signing the ICF.
    - Known congestive heart failure (Grade III or IV as classified by the New York Heart Association); and/ or a known decreased cardiac ejection fraction (LVEF) of < 45%.
    - Uncontrolled hypertension defined as systolic blood pressure ≥160 mmHg and/or diastolic blood pressure ≥ 100 mmHg, despite optimal medical management.
2. Known or clinically suspected leptomeningeal disease. Stable, previously treated metastases in the brain or spinal cord, are allowed as long as these are considered stable (by CT or MRI), and not requiring systemic corticosteroids.
3. History of ≥ grade 3 allergic reactions as well as known or suspected allergy or intolerance to any agent given in the course of this trial, live cell therapies, or live vaccines.
4. History of suspected cytokine release syndrome (CRS).
5. Known immunodeficiency disorders (testing not required).
6. Ongoing or current autoimmune disease. Permanent but stable and manageable immune related adverse events (irAE) from prior therapies are permissible, if prednisone equivalent corticosteroid use does not exceed 10 mg/day.
7. Any other condition requiring concurrent systemic immunosuppressive therapy (other than allowable exceptions which do not exceed 10mg/day of prednisone/corticosteroid use).
8. Major surgery (requiring general anesthesia or inpatient hospitalization) within four weeks before first IMP administration.
9. Any ongoing anticancer therapy including; small molecules, immunotherapy, chemotherapy, monoclonal antibodies, radiation (curative/treatment intent) or any other experimental drug. Prior therapy must be stopped within four weeks before first infusion in the study, or 5 half-lives, or twice the duration of the biological effect of the investigational product (whichever is shortest). Adjuvant anti-hormonal treatment(s) for previously treated breast cancer or prostate cancer are allowed. Bisphosphonates are allowed, Denosumab and other RANK ligand inhibitors are prohibited. Note that palliative radiation only requires a two week washout.
10. Known current malignancy other than inclusion diagnosis. Prior curable cancer with complete remission for >2 years is allowed.
11. Any other ongoing significant, uncontrolled medical condition as per Investigator discretion.
12. Received a live vaccine within 30 days prior to first dose of study drug.
13. Clinically significant active viral, bacterial or fungal infection requiring:
    a. Intravenous treatment with antimicrobial therapy completed less than two weeks prior to first dose, or
    b. Oral treatment with antimicrobial therapy completed less than one week prior to first dose.

    Prophylactic treatment with antibiotics (e.g. for dental extractions) is allowed.
14. Known positive serology for human immunodeficiency virus (HIV), hepatitis B, or hepatitis C (except in cases of immunity after cured infection). Testing not required.

15. Substance abuse, medical, psychological or social conditions that may interfere with the patient's participation in the trial or evaluation of the trial result in the opinion of the Investigator.
16. Women who are pregnant or breast feeding.

Test product, dose and mode of administration:
Each patient will be administered separate intradermal injections (at the same injection sites) of HS-130 (Lot HBI-HS-130-FP-001: OX40L-Ig concentration = 338 ng OX40L-Ig/10^6 cells/24-hr) and HS-110 (Lot 0000748931: gp96-Ig concentration = 104 ng gp96-Ig/10^6 cells/24-hr) based on the dose levels as defined in the dose escalation scheme (Section 6.1.1) on Day 1 of each cycle.

Dose-limiting toxicity (DLT):
Adverse events will be assessed per CTCAE version 5. Any toxicity that is at least possibly related to the study drug may be considered as a DLT, which is defined as non-acceptable (as defined below) treatment related toxicity (i.e., not attributable to the active disease, disease-related processes under investigation or intercurrent illness) observed during the first 4 weeks (or Cycle 1 and Cycle 2) of study treatment. Ongoing safety events beyond Cycle 2 will be reviewed across all cohorts during the study to help inform dose escalation decisions. Note, that all patients who enrolled in the study will be included in assessment of DLT.

DLT is defined as non-acceptable toxicity which includes:
1. Hematological toxicities ≥ Grade 3.
2. Non-hematological toxicity ≥ Grade 3.
3. Autoimmunity ≥ Grade 3
4. Any other toxicity (greater than at baseline), considered clinically significant and/or unacceptable, and that does not respond to supportive care and results in a disruption of the dosing schedule of more than 14 days.

DLT excludes:
1. Hematological and non-hematological ≤ Grade 2 unless considered non-acceptable.
2. Grade 3 self-limited or medically controllable toxicities (e.g., fever without ≥ Grade 3 neutropenia, nausea, vomiting, diarrhea, fatigue).
3. Electrolyte disturbances that are managed to Grade 1 or less with supplemental therapy.

A DLT will be considered related to HS-130/HS-110 treatment unless there is a clear, well-documented, alternative explanation for the AE. AEs that meet the above criteria but occur after the DLT window of observation will not be defined as DLTs, but will be reported as AEs/Serious Adverse Events (SAEs), as applicable, and will be reviewed across all cohorts during the study to help inform dose escalation decisions.

In case of suspicion of a DLT, the Investigator must inform the Medical Monitor/Sponsor immediately. The DLT will be confirmed by the Medical Monitor/Sponsor and a decision must be taken by the Sponsor regarding if an *ad hoc* SRC meeting is required.

Patients who are tolerating HS-130/HS-110 will not have to discontinue dosing prematurely due to the occurrence of DLTs in another patient in the same cohort, unless decided by the SRC. If requested by the Investigator, depending on the nature of the DLT and patient status, the SRC and the Sponsor may allow a patient to continue with study treatment at a reduced dose.

Safety Review Committee (SRC)

A Safety Review Committee (SRC) comprised of 3 members – one Investigator, a representative from Heat Biologics and the Medical Monitor, will evaluate the data obtained at each dose level and will recommend whether the dose should be escalated as per protocol, revised to a lower level or intermediate level, halted altogether or more patients are required at the same dose level to evaluate safety.

Duration of treatment:

Upon completion of the first two treatment cycles (i.e. 4-weeks with at least 2 doses of the combination treatment), in the absence of disease progression and unacceptable toxicity, patients may continue to be treated with the combination of HS-130/HS-110 at the same dose administered every 2-weeks until disease progression, death, patient's withdrawal of consent, Investigator decision to discontinue treatment, or intolerable toxicity, whichever occurs first.

At the discretion of the Investigator the treatment with the therapeutic vaccines HS-130/HS-110 may continue despite evidence of disease progression as per Section 4.1.

Criteria for evaluation:

Study assessments are summarized in the Schedule of Assessments. All screening procedures will be performed within 28 days prior to the first dose, unless otherwise specified.

Primary Endpoints

- Safety and Tolerability: number of patients with TEAEs, SAEs, DLTs.

Secondary Endpoints

- Best overall response (CR, PR, SD), overall survival, PFS per RECIST 1.11.

Exploratory Endpoints

- Immunological effect assessed by evaluating proportions of natural killer (NK) and T cell subsets for levels of activation, memory and exhaustion using flow cytometry
- Bioinformatics analysis of overexpressed CTAs and shared antigen expression with HS-110.
- Immune reactivation response to HS-110 CTA -induced secretion of cytokines (e.g. by ELISPOT).
- Changes in pro-inflammatory serum cytokines and chemokines, as well as non-specific inflammatory markers (e.g. C-reactive protein).
- Genomic, immunohistochemical and proteomic analysis of pre-treatment and on-treatment biopsy (collected from patients within 5-14 days after 2nd dose of HS-130/HS-110) for exploratory biomarker analysis.
- Immunologically active dose based on flow cytometry analysis of blood, using immune marker panels of activation and suppression as defined in Section 8.6.1.

Safety:

- Safety will be assessed throughout the study by means of physical examination, weight, vital signs, performance status, laboratory evaluations (hematology, biochemistry including cytokines and chemokines), electrocardiogram (ECG), and recording of concurrent illness/therapy and treatment-emergent adverse events. CTCAE version 5 will be used to grade all toxicities. Patients will also be monitored for any clinical symptoms associated with elevated cytokines levels. All related adverse events will be monitored until resolution or permanent outcome. Concomitant medications will be recorded throughout the study.

Efficacy:

- Response to treatment will be assessed according to RECIST 1.1[1]. Objective evaluation will be performed at baseline and then every 8-weeks ± 1-week.

Exploratory:

- Immune activation of peripheral blood mononuclear cells (PBMCs) for immunological effect will be determined from patient's blood samples collected on Day 1 (pre-dose) and Day 8 for Cycle 1 and Cycle 2, and on the 30-day safety follow-up visit.
- Serum cytokines and chemokines using an extensive panel of markers as described in Section 8.7, will be monitored at the time-points described below for Cycle 1 and Cycle 2. Samples should also be collected and

analyzed for patients that develop symptoms (i.e. flu-like symptoms, fever, or allergic reactions) at any time point for Cycle 3 and beyond.
  - Day 1: Pre-dose
  - Day 1: 2hr ± 10 minutes after last injection
- Immune reactivation in response to CTA expressed in HS-110 (Section 8.6.2) and the immunologically active dose (Section 8.6.1) will be assessed from patient's peripheral blood samples collected on Day 1 (pre-dose) and Day 8 for Cycle 1 and Cycle 2, and at 30-day safety follow-up visit.
- Pre-treatment tumor samples and an on-treatment biopsy (collected from patients within 5-14 days after 2nd dose of HS-130/HS-110) will be analyzed for exploratory biomarkers.

Statistical methods:
All analyses will be descriptive. Categorical variables will be presented with numbers and, if meaningful, percentages. Continuous variables will be presented by n, mean, median, standard deviation and range (min and max) as appropriate. Presentations will be by each dose cohort.

Safety Evaluable Population: All patients who received at least 1 dose of the study treatment.

Efficacy Evaluable Population: All patients with pre-treatment measurable disease by RECIST 1.1[1], who had at least one radiological assessment after pre-treatment or discontinued study treatment early due to disease progression.

ABBREVIATIONS

Abbreviation	Definition
AE	Adverse Event
ALT	Alanine Transaminase
APC	Antigen Presenting Cell
AST	Aspartate Transaminase
BUN	Blood Urea Nitrogen
CFR	Code of Federal Regulations
CR	Complete Response
CRF	Case Report Forms
CRO	Contract Research Organization
CRS	Cytokine Release Syndrome
CT	Computed Tomography
CTA	Cancer Testis Antigen
CTCAE	Common Terminology Criteria for Adverse Events
dL	Deciliter
DLT	Dose Limiting Toxicity
DMSO	Dimethyl Sulfoxide
EC	Ethics Committee
ECG	Electrocardiogram
ECOG	Eastern Cooperative Oncology Group
ELISPOT	Enzyme-Linked Immunosorbent Spot
FDA	Food and Drug Administration
fg	Femtogram
GCP	Good Clinical Practice
GITR	Glucocorticoid-Induced TNFR-Related Protein
GLP	Good Laboratory Practice
gzB	Granzyme B
HIV	Human Immunodeficiency Virus
HLA	Human Leukocyte Antigen
hr	Hour
HSA	Human Serum Albumin
ICF	Informed Consent Form
ICH	International Council for Harmonization
ICOS	Inducible T-Cell Costimulator
IEC	Independent Ethics Committee
IFN-α	Interferon-Alpha
IHC	Immunohistochemistry
IL	Interleukin
IMP	Investigational Medicinal Product
IND	Investigational New Drug (Application)
IP	Investigational Product
irAE	Immune Related Adverse Events
IRB	Institutional Review Board
kg	Kilogram

LD	Longest Diameter
LDH	Lactate Dehydrogenase
LVEF	Left Ventricular Ejection Fraction
MABEL	Minimum Anticipated Biological Effect Level
max	Maximum
MedDRA	Medical Dictionary for Regulatory Activities
mIHC	Multiplex Immunohistochemistry
min	Minimum
mL	Milliliter
MRI	Magnetic Resonance Imaging
MTD	Maximum Tolerated Dose
N/A	Not Applicable
NCI	National Cancer Institute
NE	Inevaluable
ng	Nanogram
NK	Natural Killer Cells
NOAEL	No Observed Adverse Effect Level
NOEL	No Observed Effect Level
NSCLC	Mon-Small Cell Lung Cancer
ºC	Degree Celsius
OS	Overall Survival
PBMC	Peripheral Blood Mononuclear Cell
PD	Progressive Disease
PET	Positron Emission Tomography
PFS	Progression-Free Survival
PR	Partial Response
RANK	Receptor Activator of Nuclear Factor Kappa-B
RECIST	Response Evaluation Criteria in Solid Tumors Version 1.1
RNA	Ribonucleic Acid
RP2D	Recommended Phase 2 Dose
RSI	Reference Safety Information
SAE	Serious Adverse Event
SARs	Serious Adverse Reactions
SD	Stable Disease
SGOT	Serum Glutamic-Oxaloacetic Transaminase
SGPT	Serum Glutamic-Pyruvic Transaminase
SOC	Standard of Care
SRC	Safety Review Committee
TBD	To Be Decided
TEAE	Treatment Emergent Adverse Events
TIL	Tumor-Infiltrating Lymphocytes
TLR	Toll-Like Receptor
TNF	Tumor Necrosis Factor
TNFRSF25	Tumor Necrosis Factor Receptor Superfamily Member 25.
Tregs	Regulatory T Cells
TSH	Thyroid-Stimulating Hormone

ULN	Upper Limit of Normal
US	Ultrasound
WBC	White Blood Cell
µg	Microgram

1.0 GENERAL INFORMATION

1.1 Protocol Number and Title of the Study

Protocol No.: HS130-001
Protocol Title: A Phase I, first-in-human, dose-escalation study to evaluate the safety and immunologic response after administration of HS-130 in combination with HS-110 (viagenpumatucel-L) in patients with solid tumors refractory to standard care

1.2 Sponsor

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1.3 Medical Monitor

Vance Y. Sohn MD
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1.4 Signature Authorization

Heat Biologics will sign the protocol.

1.5 Investigator and Institution

Rachel E. Sanborn, M.D.
Providence Cancer Institute
Portland, OR, USA

2.0 BACKGROUND INFORMATION

2.1 Introduction

The dramatic clinical success of cancer immunotherapies in a small percentage of patients has highlighted the need to identify combination approaches that increase the frequency of responders. Vaccination strategies using T cell costimulatory agents and/or blockade of immune inhibitory molecules (i.e. checkpoint inhibition) are being tested and developed as combination approaches in many ongoing clinical trials.

Agonist antibodies targeting T cell costimulatory receptors such as 4-1BB, OX40, TNFRSF25, GITR and ICOS are currently in clinical development based on their anti-tumor effects in a variety of pre-clinical model systems[2]. These agonist antibodies are typically delivered by intravenous infusion at target-saturating doses and achieve systemic bio-distribution within minutes, often resulting in global pathway activation[3]. This route of delivery for T cell costimulation is quite different than the physiological context in which the ligands for 4-1BB, OX40, TNFRSF25, GITR and ICOS, are expressed, which is localized to individual tissue

microenvironments wherein innate [commonly Toll-like receptor (TLR)] ligands stimulate antigen presenting cells to express these ligands[4,5,6]. In addition to being localized to tissue microenvironments, the kinetics of 4-1BB ligand (L), OX40L, TL1A, GITRL and ICOSL expression demonstrate rapid induction and subsequent down-regulation within a 2-5 day window[4,5]. Thus, the transient expression of costimulatory molecules is typically limited to individual tissue microenvironments wherein antigen-specific immune responses are being activated, but do not persist for more than a few days – a pattern that is not reproduced by systemic costimulation with monoclonal antibodies. Recently, it has been shown that micro-injection of monoclonal agonist antibodies into tumor lesions directly leads to anti-tumor benefits over systemic antibody administration, thus underscoring the benefit of employing localized co-stimulation versus systemic costimulation[7].

Heat Biologics, Inc. has developed viagenpumatucel-L, also known as HS-110, a novel allogeneic cellular immunotherapy designed to induce cell-mediated immunity for use in treatment of patients with refractory or metastatic non-small cell lung cancer (NSCLC). The active ingredients in viagenpumatucel-L are derived from a human lung adenocarcinoma cell line, AD100, episomally expressed HLA-A1 (the human histocompatibility surface antigen for identity) and gp96-Ig (transgene constructed from sequences encoding the human gp96 gene), and a robust repertoire of NSCLC associated overexpressed cancer testis antigens (CTAs). The secreted fusion protein (gp96-Ig) acts as a chaperone for these cancer antigens and an antigen presenting cell (APC) adjuvant (TLR activation) to induce CD8 biased cellular immune responses to these tumor antigens expressed by the AD100 host cell. To date, over 100 patients with non-small cell lung cancer have been treated with HS-110 with over 1000 doses of HS-110 administered intradermally (IND No. 14814).

To evaluate the additional therapeutic role of localized specific costimulation within the context of the HS-110 vaccine, Heat Biologics would like to explore the possibility of co-expression of a T cell costimulatory ligand fusion protein together with gp96-Ig to provide an efficacious combination immunotherapy, ultimately within a single cell-based product. On screening a panel of costimulatory molecules in murine animal models, OX40L co-stimulator was found to provide the most robust activation of antigen specific CD8 T cells with superior T cell expansion when secreted locally as a combination vaccine with gp96-Ig expression as compared to systemically administered OX40 agonist antibodies.

To study the effect of OX40L co-stimulator in combination with HS-110, Heat Biologics has developed HS-130, which is a viable, replication-incompetent (as final drug product) cell line genetically engineered from the same human lung adenocarcinoma cell line (AD100) as HS-110 but secreting OX40L-Ig fusion protein instead of gp96-Ig and HLA-A1. In the initial trial to be conducted under this IND, Heat Biologics would like to evaluate the safety and optimal immunologic dose of HS-130 in combination with HS-110 administered in a 1:1 or 2:1 ratio based on expression of OX40L-Ig and gp96-Ig (fg/24-hr/cell) respectively, in patients with solid tumors refractory to standard care.

Heat Biologics future development plan is to produce a combination therapy incorporating both T cell co-stimulation (OX40L-Ig) and vaccination (gp96-Ig) in one commercialized product using a single vector in a single cell line (AD100). After determining the optimal dose range of co-administered HS-110 and HS-130 from this clinical study, the combination will continue to be developed and evaluated in additional clinical trials of safety and efficacy after selection, manufacturing and clinical development of the combined product on a single vector/single cell line. The quantity of gp96-Ig and OX40L-Ig fusion proteins secreted by the combined product would be designed to mimic the same optimal dose level determined to be immunologically active from the initial studies conducted with HS-110 and HS-130. Heat Biologics understands that this development change constitutes a new drug product and will require a new IND

submission.

2.2 The Investigational Product

2.2.1 HS-130

The drug product HS-130 is a viable whole cell vaccine, made replication-incompetent by radiation, expressing the co-stimulatory fusion protein OX40L-Ig, which is the ligand for the OX40 receptor, a member of the TNF-receptor superfamily.

Similar to HS-110 (described below), HS-130 is derived from a human lung adenocarcinoma cell line established from a biopsy of a lung cancer patient and this cell line is designated as AD100. AD100 is transfected with a 7192 bp plasmid cDNA 'pcDNA3.4 OX40L-Ig' stably expressing the cDNA for OX40L-Ig to develop an irradiated drug product, HS-130.

The plasmid vector map for pcDNA3.4 OX40L-Ig is presented below in Figure 1.

Figure 1: pcDNA3.4 OX40L-Ig Vector Map

The HS-130 intermediate drug product is supplied as a frozen product filled under aseptic conditions in 1.2 mL cryovials, containing 0.6 mL suspension of 2 x 10^7 viable cells/mL in a cryopreservative buffer, with a final formulation of 0.567% sodium chloride, 0.5% HSA, 0.007% sodium bicarbonate, 6% pentastarch, and 5% DMSO. These cryovials are irradiated at Steris to constitute final drug product and stored at Waisman Biomanufacturing prior to the initiation of clinical testing.

2.2.2 HS-110

HS-110 (viagenpumatucel-L) is an allogeneic, cell-based immunotherapy containing a broad range of NSCLC tumor antigens (up to 66 known cancer testis antigens) combined with a specific mechanism for the transport of these antigens to patient's antigen-presenting cells that results in a specific CD8+ cytotoxic T cell response.

Heat Biologics' HS-110 cell vaccine is engineered to produce a secretable gp96 fusion protein due to presence of a secretory sequence from an immunoglobulin constant region. The resulting gp96-Ig fusion protein plasmid is then transfected into a lung cancer cell line AD100 based on the shared antigen expression characteristics amongst a high proportion of patients with non-small cell lung cancer (NSCLC).

Figure 2 below illustrates the structure of HS-110 cell-based vaccine.

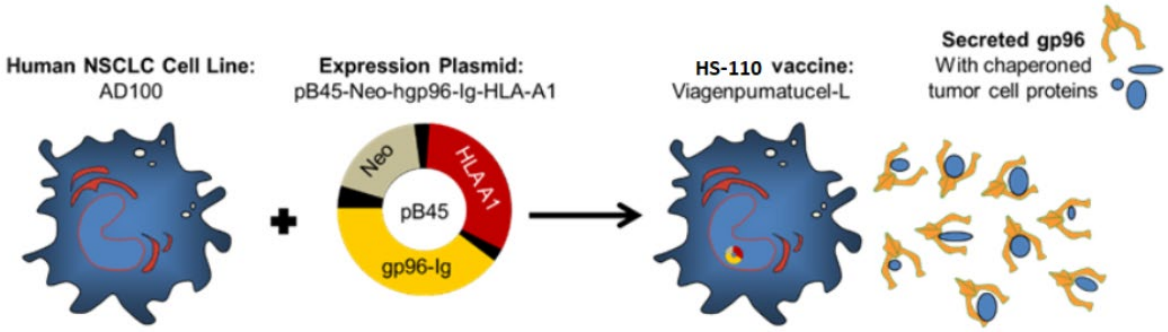

Figure 2: Schematic diagram showing the structure of HS-110. This vaccine has a cellular backbone (AD100 cell line) which has been modified with a gp96-Ig expression plasmid. Tumor cell antigen-gp96-Ig complexes are secreted by the cell in order to deliver a pan-antigenic antitumor response

HS-110 (viagenpumatucel-L) is packaged in single-dose vials as fully-diluted frozen liquid filled under aseptic conditions in 1.2 mL cryovials, containing 0.6 mL suspension of 2 x 10^7 cell/mL (targeted) in a cryopreservative buffer, with a final formulation of 0.567% sodium chloride, 0.5% HSA, 0.007% sodium bicarbonate, 6% pentastarch, and 5% DMSO.

2.3 Preclinical Studies

Key preclinical findings are summarized below. Please refer to the current Investigator's Brochure for details of these and other studies.

2.3.1 Pharmacodynamics studies

In the pre-clinical studies conducted by Heat Biologics in mouse animal models, species specific (mouse) surrogate vaccines (mHS-130 and mHS-110 secreting OX40-Ig and gp96-Ig respectively) were developed. Human HS-130 and HS-110 could not be administered to mice and vice versa due to their xenophilic nature leading to hyperacute xenograft rejection-mediated by innate and adaptive immune responses.[8,9,10] Similarly, mHS-130/mHS-110 was developed, which refers to the mouse version of the combination

vaccine secreting both OX40L-Ig and gp96-Ig in a cellular background specific for model species being tested.

In a study[11,12] to determine the T cell costimulatory activity of 3 agonist antibodies (OX40, ICOS and 4-1BB) when co-administered with mHS-110, OX40 agonist antibody showed the best synergy in promoting CD8+ T cell expansion, without the induction of CD4+ FoxP3+ T regulatory cell populations (Tregs). Comparatively, the addition of an ICOS agonist antibody did not increase CD8+ T cell expansion over mHS-110 alone, while the addition of a 4-1BB agonist antibody led to a significant increase in Tregs.

In an experiment[11,12] to explore a strategy to enable combination immunotherapy within a single vaccine product and to measure the efficacy of the gp96-Ig combination cellular vaccines, a cohort of mice was administered the combination vaccine mHS-130/mHS-110 and their immune response was recorded. The CD8+ T cell mediated immune response, via local OX40L-Ig expression, appeared to be superior to other fusion proteins (ICOSL-Ig, 4-1BBL-Ig) generating significant increases in both primary and boost immune responses evidenced by the expansion of antigen-specific CD8+ T cells.

In a preclinical study[11,12] to evaluate the memory and antigen specific response of mHS-130/mHS-110 combination vaccine, the combination vaccine resulted in superior activation and expansion of antigen-specific CD8+ and memory T cell subsets, along with antigen-specific CD8+ cytotoxic and CD4+ helper T cell responses without triggering a systemic induction of proinflammatory cytokines, which were associated with OX40 agonist antibody treatment.

The antitumor effect of mHS-130/mHS-110 was also studied in two preclinical mouse tumor models; B16-F10-melanoma and CT26-colon carcinoma. In both models mHS-110/mHS-130 generated potent antigen-specific T cell expansion and tumor infiltrating lymphocyte (TIL) counts were associated with delays in tumor growth[11,12]. This study repeated earlier findings that combination vaccination with mHS-130 (OX40L-Ig) and mHS-110 (gp96-Ig) could lead to increased frequency of complete tumor rejection, while concomitantly providing a potent memory response without increases in Treg numbers.

2.3.2 Immuno-toxicity Studies

Up until April 2019, over 100 patients with non-small cell lung cancer (NSCLC) have been treated, and over 1000 doses (up to 10 million cells/dose) of the HS-110 cellular vaccine have been administered (IND 14814), without any overt toxicity.

No formal GLP toxicology studies for HS-130 have been proposed or conducted to date. Since HS-130 and HS-110 are species (human)-specific, viable, replication-incompetent whole cell vaccines, that are administered intradermally, experimental experience suggests that safety pharmacology and toxicology studies with HS-130 and HS-110 in animals would be unlikely to predict similar effects in humans due to their nature as xenogeneic cellular entities. The mechanism for hyperacute xenograft rejection of discordant cellular entities (e.g., HS-130 in a mouse model) has been well characterized, involving responses from both innate and adaptive arms of the immune system.[8,9,10] These responses are rapidly induced and lead to overwhelming pro-inflammatory states that destroy the graft unless the recipient undergoes a conditioning regimen.[9,13,14] Such conditioning regimens are highly toxic and would modify

the host recipient in ways that would be too confounding for the purposes of studying the safety, pharmacology and toxicology of HS-130.

Based on the results from an *in-vitro* experiment[15] to compare the signaling strength of mouse, monkey and human OX40L-Ig in a human OX40 receptor signaling assay, the potency of OX40L from different species was found to be comparable in its magnitude to activate the human OX40 receptor in the Jurkat/OX40 cell based signaling system. It was observed that monkey (rhesus or cynomolgus) OX40L ligand is similar to human as well as compared to mouse OX40L in the human OX40 receptor assay. This suggests that all three species are compatible and share similar affinity for each receptor allowing for preclinical translation of mouse model results to human.

To study the mechanism of action of cancer vaccines, an intact and syngeneic immune system is required. There are no validated cancer cell line models for *in vivo* experiments in monkeys and the non-human primate tumor models are not validated or well characterized. Therefore, mouse surrogate cell lines in murine animal models were utilized to demonstrate *in vivo* proof-of-concept for activity and to study the toxicokinetics in order to estimate a safe clinical starting dose of HS-130 and HS-110.

To establish the acute effects in terms of cytokine and chemokine release, a non-GLP study[16] was conducted in mice to establish the differences between xenogeneic (HS-130) vs. same species (mHS-130) vs. a mouse OX40 agonist antibody. Five single escalating doses of HS-130, mHS-130, and an agonist OX40 antibody were administered to mice to determine a cell number threshold of HS-130, that can induce a robust xenogeneic rejection response in mice, as measured by systemic cytokine release. Significant responses were seen for the cytokines: IL-17A, ICL10, MCP-3/CCL7, MIP-1-beta/CCL4, TNF-alpha, Gro-alpha/KC/CXCL1, which could be partially attributed to an anti-human, xenotransplantation response and/or related to the expected innate immune response to foreign cellular matter, required to remove foreign protein particles. Significant response was only observed for the highest cellular dose tested. The No Observed Adverse Effect Level (NOAEL) was determined to be 400 µg (20 mg/kg) for agonist OX40 antibody, 219.5 ng/24-hr per animal (0.0109 mg/kg) and 387.2 ng/24-hr per animal (0.0193 mg/kg) for HS-130 and mHS-130, respectively.

2.3.3 Dose Range Finding Studies to Support Clinical Dosing

In the clinical study described in this protocol, HS-130 will be administered to the patients along with separate administration of HS-110 at the same injection sites.

To justify the selected clinical doses, the minimum anticipated biological effect level (MABEL) for dose combinations of mHS-130 (OX40L-Ig) and mHS-110 (gp96-Ig) in mice was determined using anti-tumor CD8+ T cell expansion and tumor growth inhibition as a measure of vaccine efficacy[17].

Mice were injected with three different dose ratios of mHS-130 to mHS-110, based on the secretion of OX40L-Ig to gp96-Ig (1.3:1, 2.5:1 and 5:1), in a dose-escalating manner. Based on this study, a ratio of 1.3-part OX40L-Ig to 1-part gp96-Ig provided the greatest expansion of anti-tumor CD8+ T cells, with the optimal expansion found to be 441 ng/24-hr of OX40L-Ig combined with 339 ng/24-hr of gp96-Ig. This dose and ratio combination also resulted in a higher proportion of activated, endogenous CD8+ T cells, marked as $CD44^{hi}$, and an increase in the percentage of short-lived effector cells (SLECs), which are responsible for early tumor cell killing. This dose combination also resulted in highly significant ($p<0.001$) tumor growth inhibition which accompanied an increase in CD4+ and CD8+ TIL accumulation in the tumor. The lowest dose combination provided a No Observed Effect Level (NOEL) of 50 ng/24-hr of OX40L-Ig to

38 ng/24-hr of gp96-Ig, at a ratio of 1.3 to 1, with a MABEL of 147 ng/24-hr of OX40L-Ig to 113 ng/24-hr of gp96-Ig.

2.4 Previous Clinical Studies

There are no previous clinical studies with HS-130.

HS-110 has been studied in humans and to date, over 100 patients with non-small cell lung cancer have been treated with HS-110 with over 1000 doses of HS-110 administered intradermally (IND No. 14814). The standard dose of HS-110 in the phase 1/2 study NCT02439450 is 1×10^7 viable cells/0.5 mL, administered as 5 (0.1 mL) intradermal injections weekly for 18 weeks (Arm 5), or weekly for 13 weeks followed by every 3 weeks boost dosing until progressive disease (Arm 6).

2.5 Rationale for Starting Dose and Dosing Schedule

Both HS-130 and HS-110 are viable allogenic tumor cell-based products, based on the human lung adenocarcinoma cell line AD100, which have been rendered replication-incompetent via irradiation. While the tolerability and safety to HS-110 is relatively well known (IND No. 14814), HS-130 has previously not been administered to humans and cannot be reliably studied in rodents due to hyperacute xenograft rejection. The starting dose rationale for this current study is based on the clinical experience for HS-110 and derived from non-clinical studies in mice using syngeneic cell lines as surrogates for HS-130 (mHS-130) and HS-110 (mHS-110) to calculate a MABEL. The use of MABEL is considered appropriate since the immunological (pharmacodynamic) response (CD8+ T cell clone and total CD8+ population) takes time to develop and is not related to plasma concentrations.

Based on the experimental outcome of the study conducted to determine CD8+ T cell expansion in mice when administered variable ratios of mHS-130 to mHS-110 with escalating doses of OX40L-Ig and gp96-Ig proteins within each ratio, a MABEL for selection of first human dose in clinical trials was determined, with no adjustments for weight or body surface area.

In this mouse study, a significant minimal effect was detected in a CD8+ T cell clone at an absolute dose of 50 ng/24-hr of OX40-Ig (mHS-130) to 38 ng/24-hr of gp96-Ig (mHS-110) at a 1.3 to 1 dose ratio respectively, compared to 38 ng/24-hr of gp96-Ig (mHS-110) alone (a dose without any measurable effect). For sub-populations of CD8+ T cells ($KLRG1^{hi}$, $CD127^{lo}$ and $CD44^{hi}$, short lived effector cells, SLEC), a significant increase was not detected until an absolute dose of 441 ng/24-hr of OX40L-Ig to 339 ng/24-hr of gp96-Ig at a 1.3:1 dose ratio. This also correlated with tumor growth inhibition and increased TIL numbers in tumors.

Thus, our suggested starting dose in patients is 150 ng/24-hr of HS-130 to 150 ng/24-hr of HS-110 (1:1 ratio) administered every 2-weeks. This dose:

- Represents the MABEL dose in mice for a specific clone of CD8+ T cells and the expansion of peripheral CD8+T cell populations (SELC and CD44 activated) using mHS-110 and mHS130 drug product surrogates. No adjustments for weight or BSA are suggested, which gives a safety factor to the human dose of >100-fold.
- Represents less than $1/10^{th}$ of the safe and effective current clinical dose for HS-110 (IND 14814). At the highest suggested dose in this study, HS-110 is given at approximately 0.8 of the documented HS-110 dose currently administered in patients.

- More than 2.5-fold below the absolute dose (ng per injection) NOAEL (no significant cytokine/chemokine release) of mHS-130 alone in mice.

To escalate the dose level, we propose the next dose at a 2:1 ratio of HS-130 to HS-110 (300 ng/24-hr OX40L-Ig to 150 ng/24-hr gp96-Ig) and so forth as described in the dose escalation scheme (Section 6.1.1). This approach is designed to bracket the HS-130 to HS-110 dose ratio findings in the mouse study.

2.6 Potential Risks and Benefits

As this is the first-in-man study of HS-130, no human data regarding the safety or potential benefit of HS-130 is available.

All currently available clinical data for HS-110 (viagenpumatucel-L) suggest that this allogeneic cell therapy is safe and well tolerated in adults with NSCLC. Mild to moderate injection site reactions, especially induration, erythema, pruritus, pain and rash are expected as they indicate the vaccine has an immunogenic effect, but these have been well-tolerated. No significant safety concerns or risks associated with this allogeneic cell therapy have been reported.

To date, no clinically significant toxicities deemed by study Investigators as possibly, probably or definitely related to HS-110 (viagenpumatucel-L) have been reported, nor have there been any HS-110 related deaths or SARs in the development program.

Please see the current Investigator Brochure for further details about the potential risks and benefits associated with this study.

2.7 Characteristics of a Well-Conducted Trial

The following characteristics of an adequate and well-conducted trial will be implemented:

1. The Investigators will be well qualified by scientific training and experience.
2. Detailed Case Report Forms (CRFs) will be completed for every patient.
3. Requirements for institutional ethics review as set forth by the appropriate Institutional Review Board/Independent Ethics Committee (IRB/IEC), Title 21 Code of Federal Regulations (CFR) Part 56, the European Union Directive 2001/20/EC and its associated Detailed Guidances, European Union GCP Directive 2005/28/EC, the ICH Guideline for Good Clinical Practice, Sections 3 and 4, and the terms of the Declaration of Helsinki (2013), will be followed.
4. Requirements for informed consent in accordance with institutional guidelines, FDA requirements as specified in Title 21 CFR, Part 50, the European Union Directive 2001/20/EC and its associated Detailed Guidances, European Union GCP Directive 2005/28/EC, the ICH Guideline for Good Clinical Practice, Section 4.8, and the terms of the Declaration of Helsinki (2013), will be followed.
5. Safety data will be recorded and evaluated.
6. Routine monitoring visits will be conducted by the Sponsor's representative to ensure data accuracy.
7. Drug accountability will be strictly maintained.

8. This trial will be conducted according to Good Clinical Practice (GCP), the protocol and applicable regulatory requirements.

2.8 Patient Population

This study will enroll adult male and female patients of age ≥ 18 years with progressive or metastatic solid tumor types, who have failed standard treatment and/or for whom no other effective or safe treatment is available or appropriate.

3.0 TRIAL OBJECTIVES AND PURPOSE

Primary:

- To evaluate safety and tolerability of HS-130 in combination with HS-110 in patients with solid tumors refractory to Standard of Care (SOC)
- To determine the recommended phase 2 dose (RP2D) of the combination HS-130 and HS-110 in patients with solid tumors refractory to SOC

Secondary:

- To determine clinical response to combination treatment with HS-130 and HS-110

Exploratory:

- To study the immunological effect generated by HS-130 and HS-110 by evaluating proportions of natural killer (NK) and T cell subsets for levels of activation, memory and exhaustion using flow cytometry
- To evaluate patient archival tumor tissue for overexpressed Cancer Testis Antigens (CTAs) and shared antigen expression with HS-110
- To evaluate immune reactivation response to CTA expressed in HS-110 (e.g. by ELISPOT)
- To determine the presence of a specific cytokine/chemokine signature in response to combination treatment with HS-130 and HS-110, or any other unspecific inflammatory response
- Genomic, immunohistochemical and proteomic analyses of tumor tissue (pre-dose and on-treatment biopsy) to identify biomarkers predictive of response or resistance to HS-110/HS-130, for example by multiplex immunohistochemistry (mIHC)
- Assess immunologically active dose based on flow cytometry analysis of blood, using immune marker panels of activation and suppression as defined in section 8.6.1.

4.0 TRIAL DESIGN

4.1 Overview of Trial Design

This is an open-label, non-controlled, first-in-human, Phase I study of combined intradermal administration of HS-130 and HS-110 to patients with advanced solid tumors refractory to SOC.

Escalating doses of the viable, replication-incompetent, human whole cell vaccines, HS-130 and HS-110 will be administered to patients via intradermal injections/reinjections (up to 10 total) on Day 1 of a two-

week cycle. The length of each cycle is two weeks, and the DLT window of observation includes the safety data obtained from the first two treatment cycles, Cycle 1 and Cycle 2 (4 weeks).

Seven dose levels will be explored, and patients will receive separate escalating doses of HS-130 and HS-110 in alternating fixed 1:1 or 2:1 ratios based on the amount of secreted OX40L-Ig (HS-130) and gp96-Ig fusion protein (HS-110) per cell of the drug product (Section 6.1.1). The starting dose of HS-130/HS-110 combination is based on the dose-ranging studies conducted in animal models of T cell expansion and tumor challenge, as well as established clinical experience from HS-110.

In the absence of progressive disease and intolerable toxicity after Cycle 2, the patient can continue the combination treatment of HS-130/HS-110 administered every 2-weeks until disease progression, death, patient's withdrawal of consent, Investigator decision to discontinue treatment, or intolerable toxicity, whichever occurs first.

Immune response may be a delayed effect, and in immuno-oncology, treatment beyond first progression is commonly used in situations where clinical progression is asymptomatic and/or is not likely to result in life-threatening complications with further progression. Therefore, at the discretion of the Investigator the treatment with the therapeutic vaccines HS-130/HS-110 may continue despite evidence of disease progression, if the investigator considers this of a potential clinical benefit for the patient, and the following criteria are met:

- No other approved palliative or curative salvage therapy exists for the indication (e.g. resection of pulmonary metastases in osteosarcoma patients).
- The patient continues to meet all other study protocol eligibility criteria.
- No dose limiting toxicity (DLT) has been observed, and all toxicities resolved to the baseline level, consistent with the study eligibility criteria.
- No deterioration of subject performance status.
- Does not delay imminent intervention to prevent serious complications of disease progression (e.g., CNS metastases).

13-30 patients will be enrolled in the study. Based on response observed in patients at different dose levels and/or in patients with a particular tumor type, the study protocol may be amended to allow for cohort expansion of patients with specific characteristics.

4.2 End of Study

The end of the study is defined as the date of the last visit of the last patient participating in the trial.

4.3 Drug Product

HS-130 and HS-110 are viable allogenic tumor whole cell-vaccines, based on the human lung adenocarcinoma cell line AD100, which have been rendered replication-incompetent via irradiation.

HS-130 expresses the co-stimulatory fusion protein OX40L-Ig, which is the ligand for the OX40 receptor, a member of the TNF-receptor superfamily, while HS-110 expresses and secretes the heat shock protein gp96-Ig.

HS-110 has been evaluated in the NCT02439450 trial (IND No. 14814), while HS-130 has previously not been administered to humans.

4.4 Duration of Therapy

Upon completion of the first two treatment cycles (i.e. 4-weeks with at least 2 doses of the combination treatment), in the absence of disease progression and unacceptable toxicity, patients may continue to be treated with the combination of HS-130/HS-110 at the same dose administered every 2-weeks until disease progression, death, patient's withdrawal of consent, Investigator decision to discontinue treatment, or intolerable toxicity, whichever occurs first.

At the discretion of the Investigator the treatment with the therapeutic vaccines HS-130/HS-110 may continue despite evidence of disease progression as described in Section 4.1.

4.5 Trial Discontinuation

For reasonable cause, the Sponsor may terminate this study prematurely. Written notification of the termination is required. Conditions that may warrant termination include, but are not limited to:

- The discovery of an unexpected, significant, or unacceptable risk to the patients enrolled in the study.
- Failure of the Investigator to enter patients at an acceptable rate.
- Insufficient adherence to protocol requirements (non-compliance).
- Lack of evaluable and/or complete data.
- Decision to modify the developmental plan of the drug.
- A decision on the part of the Sponsor to suspend or discontinue development of the drug.

Section 5.5 Study Stopping Criteria lists events that warrants immediate stop of treatment until reviewed by the Safety Review Committee. This assessment may also result in trial discontinuation (equivalent to first bullet above).

4.6 Investigational Product Accountability/Disposition of Clinical Trial Supplies

Investigational Product (IP) accountability records will be maintained for all clinical trial supplies.

All unused clinical trial supplies will be destroyed per the institution's standard operating procedure. Destruction of IP and trial supplies must be documented, and the documentation will be reviewed by/sent to the Sponsor or their Designee.

5.0 SELECTION AND WITHDRAWAL OF SUBJECTS

5.1 Inclusion Criteria

Patients **must** meet all of the following inclusion criteria before they will be allowed to participate in the trial:

1. Patients with metastatic or advanced, unresectable solid tumor who have progressed, or recurred following standard-of-care (SOC) therapies or are ineligible for, or refuse, safe and effective SOC therapies and for whom, in the opinion of the Investigator, experimental therapy with HS-130/HS-110 may be beneficial.
2. Patients should have lesions that are safely accessible for biopsy and be willing to provide pre-treatment and on-treatment tissue biopsy. Fine-needle aspiration biopsy is not acceptable. Archival

tumor tissue will be accepted in lieu of fresh biopsy at screening if sample was collected within 6-months from Cycle 1 Day 1, and the local pathologist confirms that an adequate amount of tissue/tumor cells exist to allow completion of all testing as outlined in the specimen collection manual.

3. Age ≥ 18 years.
4. Have an acceptable organ function:
    - Albumin ≥ 2.5 g/dL.
    - Total Bilirubin < 3.0 × upper limit of normal (ULN) unless patient has Gilbert's syndrome.
    - Alanine transaminase (ALT) and aspartate transaminase (AST) ≤ 3.0 × 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.
5. Have an Eastern Cooperative Oncology Group (ECOG) performance status of 0 or 1.
6. Life expectancy of at least three months.
7. Patients, both females and males, of childbearing/reproductive potential must agree to use adequate contraception while included in the trial and for six months after the last treatment with HS-130 and/or HS-110.
8. Patients must be willing and have the capacity to sign the informed consent form.

5.2 Exclusion Criteria

Patients **MUST NOT** enter the trial if they meet any of the following exclusion criteria:

1. Have clinically significant cardiac disease, including:
    - Onset of unstable angina within 6 months of signing the Informed Consent Form (ICF).
    - Acute myocardial infarction within 6 months of the signing the ICF.
    - Known congestive heart failure (Grade III or IV as classified by the New York Heart Association); and/ or a known decreased cardiac ejection fraction (LVEF) of < 45%.
    - Uncontrolled hypertension defined as systolic blood pressure ≥160 mmHg and/or diastolic blood pressure ≥ 100 mmHg, despite optimal medical management.
2. Known or clinically suspected leptomeningeal disease. Stable, previously treated metastases in the brain or spinal cord, are allowed as long as these are considered stable (by CT or MRI), and not requiring systemic corticosteroids.

3. History of ≥ grade 3 allergic reactions as well as known or suspected allergy or intolerance to any agent given in the course of this trial, live cell therapies, or live vaccines.
4. History of suspected cytokine release syndrome (CRS).
5. Known immunodeficiency disorders (testing not required).
6. Ongoing or current autoimmune disease. Permanent but stable and manageable immune related adverse events (irAE) from prior therapies are permissible, if prednisone equivalent corticosteroid use does not exceed 10 mg/day.
7. Any other condition requiring concurrent systemic immunosuppressive therapy (other than allowable exceptions which do not exceed 10mg/day of prednisone/corticosteroid use).
8. Major surgery (requiring general anesthesia or inpatient hospitalization) within four weeks before first IMP administration.
9. Any ongoing anticancer therapy including; small molecules, immunotherapy, chemotherapy, monoclonal antibodies, radiation (curative/treatment intent) or any other experimental drug. Prior therapy must be stopped within four weeks before first infusion in the study, or 5 half-lives, or twice the duration of the biological effect of the investigational product (whichever is shortest). Adjuvant anti-hormonal treatment(s) for previously treated breast cancer or prostate cancer are allowed. Bisphosphonates are allowed, Denosumab and other RANK ligand inhibitors are prohibited. Note that palliative radiation only requires a two week washout.
10. Known current malignancy other than inclusion diagnosis. Prior curable cancer with complete remission for >2 years is allowed.
11. Any other ongoing significant, uncontrolled medical condition as per Investigator discretion.
12. Received a live vaccine within 30 days prior to first dose of study drug.
13. Clinically significant active viral, bacterial or fungal infection requiring:
    a. Intravenous treatment with antimicrobial therapy completed less than two weeks prior to first dose, or
    b. Oral treatment with antimicrobial therapy completed less than one week prior to first dose.

    Prophylactic treatment with antibiotics (e.g. for dental extractions) is allowed.
14. Known positive serology for human immunodeficiency virus (HIV), hepatitis B, or hepatitis C (except in cases of immunity after cured infection). Testing not required.
15. Substance abuse, medical, psychological or social conditions that may interfere with the patient's participation in the trial or evaluation of the trial result in the opinion of the Investigator.
16. Women who are pregnant or breast feeding.

5.3 Inclusion of Women, Minorities and Children

Both men and women and members of all races and ethnic groups are eligible for this study. Children are not eligible for this study because the safety and tolerability of the proposed dosing schedule has not been determined in adults.

5.4 Withdrawal Criteria

Protocol therapy will be discontinued at any time if any of the following situations occur:

1. Progressive disease (not including unconfirmed radiographic PD if Investigator opts to continue treatment as outlined in Section 8.2).
2. Adverse event.
   - The development of toxicity which, in the Investigator's judgment, precludes further therapy.
   - Unacceptable adverse event(s).
   - Intercurrent illness that prevents further administration of treatment.
3. Withdrawal by subject.
4. Lost to follow-up.
5. Non-compliance.
6. At the discretion of the Investigator/physician decision.
7. Death.
8. Pregnancy.
9. Study termination.

5.4.1 Withdrawn Subjects

When a patient is removed from the study, the Investigator will clearly document the reason in the medical record and complete the appropriate case report form describing the reason for discontinuation. In addition, every effort should be made to complete the appropriate assessments listed in Section 7.4.

Patients lost to follow-up will be withdrawn from the study. Patients will be declared "lost to follow-up" if the last contact date has exceeded two years, and/or the site has documented three attempts to contact the patient by telephone and/or certified letter to last known address.

5.4.2 Replacement of Subjects

Patients who discontinue due to toxicity (related to study drug) during the 4-week DLT window of observation of Cycle 1 and Cycle 2, or who do not receive all doses due to toxicity in Cycle 1 and Cycle 2, will not be replaced. Patients who discontinue or who do not receive at least two combination doses of HS-130/HS-110 for any reason other than toxicity during Cycle 1 and 2 will be replaced. Note, that all patients who enrolled in the study will be included in assessment of DLT per Section 6.1.2.

5.5 Study Stopping Criteria

If any of the following occur, administration of HS-130/HS-110 will be temporarily or permanently stopped, pending a review by the Safety Review Committee. During that time, no drug can be administered to any patient, until a decision is made.

- Any Death (other than progressive disease) that is at least possibly related to the study agent(s)
- Occurrence of two or more grade 4 events that are at least possibly related to the study agent(s)

Conditions that may warrant trial termination are listed in Section 4.5.

5.6 Noncompliance

All instances of protocol deviations will be recorded according to the study specific monitoring plan.

6.0 TREATMENT OF SUBJECTS

6.1 Drug Preparation and Administration

Both HS-130 and HS-110 drug products will be administered via intradermal injections/re-injections based on the dose levels as defined in the dose escalation scheme (Section 6.1.1) on Day 1 of each cycle.

If any serious adverse reaction occurs these may be treated per institutional practice, as noted in Section 6.4 Concomitant Medication.

The HS-130 final drug product is packaged in single-dose vials as fully-diluted frozen liquid filled under aseptic conditions in 1.2 mL cryovials, containing 0.6 mL suspension of 2 x 10^7 cells/mL (targeted) in a cryopreservative buffer, with a final formulation of 0.567% sodium chloride, 0.5% human serum albumin (HSA), 0.007% sodium bicarbonate, 6% pentastarch, and 5% dimethyl sulfoxide (DMSO).

HS-110 (viagenpumatucel-L) is packaged in single-dose vials as fully-diluted frozen liquid filled under aseptic conditions in 1.2 mL cryovials, containing 0.6 mL suspension of 2 x 10^7 cell/mL (targeted) in a cryopreservative buffer, with a final formulation of 0.567% sodium chloride, 0.5% HSA, 0.007% sodium bicarbonate, 6% pentastarch, and 5% DMSO.

Each patient will be administered up to a total of 10 spatially divided intradermal injections/re-injections of ≤ 0.14 mL per injection, depending on the required HS-130 and HS-110 dose levels. HS-130 will be injected first, and a period of no less than 2 minutes, but no more than 5 minutes, should elapse before administering HS-110. HS-110 must be injected into the same exact location as the HS-130 injections (re-injected sites). There are some dose levels (3, 5, 6, and 7) where the number of HS-110 injections will exceed the number of HS-130 injections. In these cases, after all HS-130 sites have been re-injected, the HS-110 may be administered in a new spatially divided injection site.

At each cycle, the injection region will alternate between the left shoulder and right shoulder. The HS-130 and HS-110 injections will all be administered into the designated injection region for that cycle (left shoulder or right shoulder) to increase volume distribution and enhance antigen presentation to lymph node regions.

Table 1: HS-130/HS-110 Dose Administration Guidelines

			Volume (mL) per Injection						
Dose Level	**Study Drug**	**Total mL**	**Injection #1**	**Injection #2**	**Injection #3**	**Injection #4**	**Injection #5**	**Injection #6**	**Injection #7**
-1	HS-130	**0.02**	0.02						
	HS-110	**0.06**	0.06						
1	HS-130	**0.04**	0.04						
	HS-110	**0.10**	0.10						
2	HS-130	**0.10**	0.10						
	HS-110	**0.10**	0.10						
3	HS-130	**0.10**	0.10						
	HS-110	**0.22**	0.12	0.10					
4	HS-130	**0.18**	0.10	0.08					
	HS-110	**0.22**	0.12	0.10					
5	HS-130	**0.18**	0.10	0.08					
	HS-110	**0.44**	0.12	0.12	0.10	0.10			
6	HS-130	**0.36**	0.12	0.12	0.12				
	HS-110	**0.44**	0.12	0.12	0.10	0.10			
7	HS-130	**0.36**	0.12	0.12	0.12				
	HS-110	**0.86**	0.14	0.12	0.12	0.12	0.12	0.12	0.12

Drug products will be supplied to clinical sites via shipments in liquid nitrogen dry-shipper units, which will be validated to maintain cryogenic temperatures for up to 10 days. Upon arrival, the products will be transferred to controlled liquid nitrogen storage at the clinical site in the liquid nitrogen vapor phase until ready for preparation. Study staff must take care to minimize temperature excursions during transfer of the product from shipping containers to controlled liquid nitrogen storage on site.

Drug products will not be retrieved from cryogenic storage until the study subject is present and available for dosing. When removing a product carton from storage to retrieve a vial for dosing, any doses remaining in the carton will be returned to cryogenic storage immediately. Study drugs must be administered within 2 hours of retrieval from the dewar (cryogenic storage).

Stability studies for HS-130 are currently ongoing and clinical sites will be notified of storage information and/or shelf life change. The instructions for preparation, administration, stability and storage of HS-110 to be used in combination with HS-130 will reference instructions per the Investigational Product Manual.

6.1.1 Dose Escalation Scheme

Escalating doses of the viable, replication-incompetent, human whole cell vaccines, HS-130 and HS-110 will be administered to patients via intradermal injections/re-injections (up to 10 total) on Day 1 of a two-

week cycle. The length of each cycle is two weeks, and the DLT window of observation includes the safety data obtained from the first two treatment cycles, Cycle 1 and Cycle 2 (4 weeks).

Seven dose levels will be explored, and patients will receive separate escalating doses of HS-130 and HS-110 in alternating fixed 1:1 or 2:1 ratio based on the amount of secreted OX40L-Ig (HS-130) and gp96-Ig fusion protein (HS-110) per cell of the drug product. The starting dose of HS-130/HS-110 combination is based on the dose-ranging studies conducted in animal models of T cell expansion and tumor challenge, as well as established clinical experience from HS-110.

Table 2: HS-130/HS-110 Dose Levels

Cohort	Dose level	HS-130 dose* (ng/24-hr OX40L-Ig)	HS-110 dose* (ng/24-hr gp96-Ig)	HS-130: HS-110 Ratio	Total number of AD100 cells (Q2W)#	Minimum number of patients
1	-1	75 ng/24-hr	75 ng/24-hr	1:1	1.0 million	1
	1	150 ng/24-hr	150 ng/24-hr	1:1	1.9 million	1
	2	300 ng/24-hr	150 ng/24-hr	2:1	2.3 million	1
	3	300 ng/24-hr	300 ng/24-hr	1:1	3.8 million	1
	4	600 ng/24-hr	300 ng/24-hr	2:1	4.7 million	1
2	5	600 ng/24-hr	600 ng/24-hr	1:1	7.6 million	3
3	6	1,200 ng/24-hr	600 ng/24-hr	2:1	9.3 million	3
4	7	1,200 ng/24-hr	1,200 ng/24-hr	1:1	15.1 million	3

*The number of cells administered to achieve the HS-130 (ng/24-hr of OX40L-Ig protein) and HS-110 (ng/24-hr of gp96-Ig protein) dose will be determined based on the specifications for that batch of the drug product. For HS-130: Lot HBI-HS-130-FP-001 = 241 fg/cell/24-hr and HS-110: Lot 0000748931 = 104 fg/cell/24-hr. The productivity per cell will be determined using the same assay format and standards for pre-clinical and clinical derived material.

The suggested total number of allogeneic tumor cells (AD100) administered every second week at the highest dose level is similar to or less than the weekly dose of 10 million HS-110 cells that has been established safe and immunologically effective in the HS-110 study (NCT02439450, IND No. 14814).

The first cohort will employ an accelerated design to evaluate the first 4 dose levels in single patients. There will be a staggered enrollment with a minimum 1-week delay between each patient in cohort 1. If any drug-related ≥ Grade 2 (other than Grade 2 injection site reaction with pain) event occurs during the first cycle of treatment, the study will revert to 3+3 design starting at that dose level.

Subsequent cohorts in the dose escalation phase will enroll patients following the standard 3+3 design. Three patients will be enrolled in each subsequent dose cohort and enrolled with a (minimum) 1-week staggered delay (i.e. Patient 2 to be dosed ≥1-week after Patient 1 received the first dose, and Patient 3 to be dosed ≥1-week after Patient 2 received the first dose).

In the 3-patient cohorts (i.e. 3 patients treated at the same dose), if 1 out of 3 patients experience a DLT during the first two treatment cycles, the dose cohort will be expanded up to 6 patients. If ≥2 out of 6 patients experience DLTs, the MTD has been exceeded, and dose escalation will cease. Up to 3 additional patients will be enrolled at the next lowest dose if only 3 patients were treated at that dose level, to confirm safety of that dose. If a DLT is observed already with the first patient in Cohort 1, the Safety Review

Committee (Section 8.1.2.8.1) may suggest and approve a dose de-escalation cohort with at least 50 % reduction of HS-110 and HS-130 (dose level -1).

Once all patients in a cohort have completed the first two cycles of dosing and received at least 2 doses of HS-130/HS-110, the safety and tolerability of the combination treatment administered will be reviewed by the safety review committee (SRC). If 0 out of 3 patients or 1 out of 6 patients experience a DLT, then the SRC may recommend enrollment at the next higher dose level.

Any patient who does not receive two doses of the study treatment during the DLT window of observation (first 2 cycles/4 weeks), for reasons other than study drug-related toxicity and did not experience a DLT will not be taken into account in the assessment of the overall DLT rate for the particular dose level cohort and will be replaced.

6.1.2 Dose-Limiting Toxicity

Adverse events will be assessed per CTCAE version 5. Any toxicity that is at least possibly related to the study drug may be considered as a DLT, which is defined as non-acceptable (as defined below) treatment related toxicity (i.e., not attributable to the active disease, disease-related processes under investigation or intercurrent illness) observed during the first 4 weeks (or Cycle 1 and Cycle 2) of study treatment. Ongoing safety events beyond Cycle 2 will be reviewed across all cohorts during the study to help inform dose escalation decisions. Note, that all patients who enrolled in the study will be included in assessment of DLT.

<u>DLT is defined as non-acceptable toxicity which includes:</u>

1. Hematological toxicities ≥ Grade 3.
2. Non-hematological toxicity ≥ Grade 3.
3. Autoimmunity ≥ Grade 3
4. Any other toxicity (greater than at baseline), considered clinically significant and/or unacceptable, and that does not respond to supportive care and results in a disruption of the dosing schedule of more than 14 days.

<u>DLT excludes:</u>

1. Hematological and non-hematological ≤ Grade 2 unless considered non-acceptable.
2. Grade 3 self-limited or medically controllable toxicities (e.g., fever without ≥ Grade 3 neutropenia, nausea, vomiting, diarrhea, fatigue).
3. Electrolyte disturbances that are managed to Grade 1 or less with supplemental therapy.

A DLT will be considered related to HS-130/HS-110 treatment unless there is a clear, well-documented, alternative explanation for the AE. AEs that meet the above criteria, but occur after the DLT window of observation will not be defined as DLTs, but will be reported as AEs/Serious Adverse Events (SAEs), as applicable, and will be reviewed across all cohorts during the study to help inform dose escalation decisions.

In case of suspicion of a DLT, the Investigator must inform the Medical Monitor/Sponsor immediately. The DLT will be confirmed by the Medical Monitor/Sponsor and a decision must be taken by the Sponsor regarding if an *ad hoc* SRC meeting is required.

Patients who are tolerating HS-130/HS-110 will not have to discontinue dosing prematurely due to the

occurrence of DLTs in another patient in the same cohort, unless decided by the SRC. If requested by the Investigator, depending on the nature of the DLT and patient status, the SRC and the Sponsor may allow a patient to continue with study treatment at a reduced dose.

6.1.3 Maximum Tolerated Dose (MTD) and Recommended Phase 2 Dose (RP2D)

The definition of MTD will be based upon review of safety data and DLTs corresponding to the first two cycles of therapy in at least 6 evaluable patients. MTD will be defined as a dose where 0 or 1 out of 6 patients have DLTs. The RP2D may be equivalent to MTD OR the maximum feasible dose. The dose that is selected after this study for phase 2 evaluation may also be an immunologically active dose (assessed based on flow cytometry analysis of blood, using immune marker panels of activation and suppression as defined in Section 8.6.1).

6.2 Dose Interruptions/Withholding

Study drug may be withheld from a patient based on the Investigator‘s decision in the event of intercurrent illness, adverse event, administrative reasons, or other reasons. If the patient‘s condition subsequently improves, or the situation that resulted in withholding study drug rectifies itself, the Investigator may resume dosing as soon as possible, unless the delay is more than 2-weeks. Doses should not be skipped.

Dosing should be delayed for any DLT-equivalent toxicity and possible >Grade 2 adverse events considered related to study medication. At the Investigator’s discretion, dosing may recommence when the toxicity has resolved to Grade 2 or less. Immune related reactions or allergy should resolve to Grade 1 or less.

Treatment will be discontinued if the next cycle cannot be initiated if a TEAE has not resolved (to acceptable grade) after ≤2 weeks.

Patients who miss a dose during Cycle 1 and Cycle 2 may be replaced in the study per Section 5.4.2. The interruption and/or missed dose(s) should be recorded.

6.3 Dose Modification

One level dose reduction per the dose escalation scheme, for toxicity is allowed. If the toxicity is equivalent to a DLT (see Section 6.1.2) then continued treatment at a lower dose level needs approval by the sponsor and/or SRC.

6.4 Concomitant Treatment

Patients must not receive any other concurrent anti-cancer therapy, including investigational agents while on study treatment.

Unexpected serious adverse reactions, including severe allergic reactions, may be treated according to standard-of-care and institutional practice without limitations, including antihistamines, corticosteroids, cytokine antagonists, antipyretics and analgesics.

Supportive treatment may include anti-emetic, anti-diarrheal, anti-pyretic, anti-histamines, analgesics, antibiotics, and blood products. At the discretion of the treating physician, patients may receive anti-histamine prophylaxis according to the standard of care in clinical practice.

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

For patients with bone metastases requiring medication for treatment and/or prevention of skeletal-related events bisphosphonates are permissible but RANK-ligand inhibitors are prohibited throughout the trial.

While on treatment in the study, use of the type of medications specified below should be avoided. HS-130 and HS-110 will be temporarily stopped for the period of time these medications are used.

- Immunosuppressive agents, except to treat a drug-related adverse event
- Systemic corticosteroids > 10 mg daily prednisone equivalent

Ocular, intra-articular, intranasal, and inhalational corticosteroids are allowed.

6.5 Monitoring Subject Compliance

This study will be monitored by Heat Biologics or its CRO according to ICH E6 guidelines of GCP. The study site monitor will regularly visit the study sites to ensure that the study is conducted according to the protocol and GCP principles.

7.0 STUDY EVALUATIONS

7.1 Schedule of Study Evaluations

Study evaluations are summarized in Table 3 and described in Sections 1.1 through 7.6.

Table 3: Schedule of Assessments

	Pre-treatment	Cycle 1 (± 2 days)[p]		Cycle 2 (± 2 days)[p]		Cycle 3 and beyond (± 2 days)[p]	30-day safety follow up visit (±3 days)[m]	Post-treatment Follow-up (±1 week)[n]	Survival Follow-up (±2 week)[o]
		Day 1	Day 8	Day 1	Day 8	Day 1			
Informed consent	X[a]								
Medical history	X[a]								
Physical exam	X[b]	X[b]	X	X	X	X	X		
Weight	X[b]	X[b]	X	X	X	X	X		
Vital signs[c]	X[b]	X	X	X	X	X	X		
ECG[d]	X[a]	X		X		X	X		
ECOG performance status	X[b]	X[b]	X	X	X	X	X		
Tumor measurement[e]	X[a]					X[e]		X[n]	
Hematology[f]	X[b]	X[b]		X		X	X		
Blood chemistry[g]	X[b]	X[b]		X		X	X		
Pregnancy test [h]	X[b]								
Blood Sample for Immune Response Labs[i]		X[i]	X[i]	X[i]	X[i]		X		
Blood sample for cytokines/chemokines[j]		X[j]		X[j]		X[j]			
Biopsy[k]	X[a]					X[k]			
HS-130 and HS-110 administration[l]		X		X		X			
Concomitant medications/Treatment	X[a]	← Throughout Study →					X	X	X[o]
Adverse events		← Throughout Study →					X	X	
Survival Status									X[o]

a: Within 28 days prior to treatment.
b: Within 7 days prior to treatment. For Cycle 1 Day 1, these tests may be performed within 3 days. Tests done within 3 days of Cycle 1 Day 1 do not need to be repeated unless clinically indicated.
c: Vital signs, including blood pressure, heart rate, respiratory rate, and temperature. During Cycle 1 and Cycle 2 on Day 1: Before HS130/HS110 treatment; after treatment at 30 mins (±5min), 1hr (±5min). Other Cycles on Day 1: only Pre-dose.
d: Standard 12-lead ECG (in triplicate) while patient is in semi-recumbent position pre-dose on Day 1 of each cycle.
e: Tumor measurement per RECIST 1.1[1]. Patients will be evaluated at screening and then after every 8-weeks ± 1 week from C1D1 until disease progression.
f: Hematology, including hemoglobin, WBC with differential, and platelet count (Approximately 5 mL blood per draw).
g: Blood chemistry, including sodium, potassium, BUN, glucose, SGOT/SGPT (ALT/AST), alkaline phosphatase, total protein, total bilirubin, albumin, lactate dehydrogenase (LDH), TSH, creatinine, C-reactive protein and calcium. (Approximately 5 mL blood per draw).
h: Pregnancy test; for women of childbearing potential, a negative pregnancy test (urine or serum) must be documented.
i: Approximately 23 mL blood per draw Day 1 (pre-dose) and Day 8 for C1 and C2, and at 30-day safety follow-up visit for immune response labs (See Section 8.6).
j: Cytokines and chemokines sample collection on Day 1 for C1 and C2 at time-points: Before HS130/HS110 treatment, and 2 hr ± 10 minutes after treatment. For C3 and beyond only if the patient is symptomatic i.e. flu-like symptoms, fever, or allergic reactions. (Approximately 3 mL blood per draw).
k: Pre-treatment biopsy (archival tissue may be submitted if collected less than 6-months prior to C1D1 and the local pathologist confirms that an adequate amount of tissue/tumor cells exist to allow completion of all testing as outlined in the Specimen Collection Manual) and on-treatment biopsy collected within 5-14 days after patient completes 2nd dose of HS-130/HS-110 for genomic and proteomic analysis of exploratory biomarkers (e.g. mIHC). Biopsy should be collected for patients with accessible tumor lesions, incl. metastases (e.g. lymph node metastases) where it is considered feasible without a risk of complications for the patient. Coagulation parameters and blood cells should be assessed and reviewed per institutional standard prior to any biopsy.
l: HS-130 and HS-110 will be administered via intradermal injections/re-injections (up to 10 total) on Day 1 of each cycle, depending on the assigned dose level. (See section 6.1 Drug preparation and administration)
m: All assessments should be performed at 30 days ± 3 days after the last treatment, during the 30-day safety follow-up visit.
n: If a patient stops treatment for any other reason than progressive disease, radiological assessments will continue every 12 weeks starting from the date of patient's last dose until disease progression or initiation of new anti-cancer treatment.
o: Survival status and subsequent anti-cancer therapy information will be collected approximately every 12 weeks in a clinic visit, or by telephone from the time of disease progression or initiation of new anti-cancer treatment until death.
p: Each cycle is 14 days.

7.2 Pre-treatment

Within 28 days from C1D1:

- Sign informed consent
- ECG in triplicate (a standard 12-lead ECG is taken while patient is in a semi-recumbent position)
- Medical history including prior treatments and surgeries, prior medications, and pre-existing clinical signs and symptoms
- Imaging for tumor measurements by RECIST 1.1[1]
- Fresh Biopsy (archival tissue may be submitted if collected less than 6-months prior to C1D1 and the local pathologist confirms that an adequate amount of tissue/tumor cells exist to allow completion of all testing as outlined in the Tumor Biopsy Collection Manual). Note that coagulation tests should be reviewed prior to procedure per institutional standards.

Within 7 days from C1D1:

- Physical exam
- Weight
- Vital signs (blood pressure, heart rate, respiratory rate, and temperature)
- ECOG performance status (APPENDIX I)
- Pregnancy test for women of childbearing potential (i.e. not surgically sterile or post-menopausal > 1 year)
- Blood draw for Hematology, Blood chemistry

7.3 During Treatment

Each cycle will be 14-days.

7.3.1 Cycle 1

7.3.1.1 Cycle 1 Day 1 ± 2 days (Week 1)

- Physical Exam (may be done within 3 days prior)
- Weight (may be done within 3 days prior)
- Vital signs (blood pressure, heart rate, respiratory rate, and temperature: Before HS130/HS110 treatment; after HS130/HS110 treatment at 30 mins (±5m), and 1hr (±5m))
- ECG in triplicate (a standard 12-lead ECG is taken while patient is in a semi-recumbent position; pre-dose)
- ECOG performance status (may be done within 3 days prior) (APPENDIX I)
- Blood draw for Hematology (may be done within 3 days prior)
- Blood draw for Blood chemistry tests (may be done within 3 days prior)
- HS-130/HS-110 administration
- Blood draw for immune response labs (Immunological Effect/Immune re-activation) (Pre-dose)
- Blood draw for Cytokines/Chemokines (Pre-dose, and 2 hr ± 10 minutes after completion of HS130/HS110 treatment)
- Record Concomitant medications (Update prior medications if applicable)
- Record Adverse events

7.3.1.2 Cycle 1 Day 8 ± 2 days (Week 2)

- Physical Exam

- Weight
- Vital signs (blood pressure, heart rate, respiratory rate, and temperature)
- ECOG Performance status (APPENDIX I)
- Blood draw for immune response labs (Immunological Effect/Immune re-activation)
- Record Concomitant medications
- Record Adverse events

7.3.2 Cycle 2

7.3.2.1 Cycle 2 Day 1 ± 2 days (Week 3)

- Physical Exam
- Weight
- Vital signs (blood pressure, heart rate, respiratory rate, and temperature: Before HS130/HS110 treatment; after HS130/HS110 treatment at 30 mins (±5m), and 1hr (±5m))
- ECG in triplicate (a standard 12-lead ECG is taken while patient is in a semi-recumbent position; pre-dose)
- ECOG Performance status (APPENDIX I)
- Blood draw for Hematology
- Blood draw for Blood chemistry tests
- Blood draw for immune response labs (Immunological Effect/immune re-activation) (Pre-dose)
- Blood draw for Cytokines/Chemokines (Pre-dose, and 2 hr ± 10 minutes after completion of HS130/HS110 treatment)
- Record Concomitant medications
- Record Adverse events
- HS-130/HS-110 administration

7.3.2.2 Cycle 2 Day 8 ± 2 days (Week 4)

- Physical Exam
- Weight
- Vital signs (blood pressure, heart rate, respiratory rate, and temperature)
- ECOG Performance status (APPENDIX I)
- Blood draw for immune response labs (Immunological Effect/Immune re-activation)
- Record Concomitant medications
- Record Adverse events

7.3.3 Cycle 3 and Beyond (Day 1± 2 days)

- Physical Exam
- Weight
- Vital signs (blood pressure, heart rate, respiratory rate, and temperature only before HS130/HS110 treatment)
- ECG in triplicate (a standard 12-lead ECG is taken while patient is in a semi-recumbent position) (pre-dose)
- ECOG Performance status (APPENDIX I)
- Blood draw for Hematology

- Blood draw for Blood chemistry tests
- Blood draw for Cytokines/Chemokines (Only if patient is symptomatic)
- Record Concomitant medications
- Record Adverse events
- HS-130/HS-110 administration
- On-treatment Biopsy (within 5-14 days after patient completes 2nd dose of HS-130/HS-110). Note that coagulation tests should be reviewed prior to procedure per institutional standards.
- Imaging for tumor measurements by RECIST 1.1[1] (every 8-weeks ± 1 week from C1D1 until disease progression)

7.4 30-Day Safety Follow up Visit from Last Dose (±3 days)

The following assessments will be performed at 30 days ± 3 days of the last treatment for all patients who have discontinued treatment with HS-130/HS-110:

- Physical Exam
- Weight
- Vital signs (blood pressure, heart rate, respiratory rate, and temperature)
- ECG in triplicate (a standard 12-lead ECG is taken while patient is in a semi-recumbent position)
- ECOG Performance status (APPENDIX I)
- Blood draw for Hematology
- Blood draw for Blood chemistry tests
- Blood draw for immune response labs (Immunological Effect/Immune re-activation)
- Record Concomitant medications
- Record Adverse events

7.5 Post-treatment Follow-up (± 1 week)

The following assessments will be performed every 12-weeks starting from the date of last dose for any patient that stops treatment for any reason other than progressive disease until disease progression or if the patient starts a new treatment. Any AEs deemed related to study drug will also be recorded.

- Record concomitant medications and/or treatments
- Record Adverse events
- Imaging for tumor measurements (CT scan or MRI)

7.6 Survival Follow-up (± 2 weeks)

The survival follow-up period refers to the time between disease progression (or confirmed disease progression in cases where Investigator treats beyond initial progression as outlined in section 8.2) and patient death. Survival status and subsequent anti-cancer therapy will be collected approximately every 12 weeks in a clinic visit, or by telephone. Patients who withdraw consent for study procedures should still be followed for survival and/or public records searched as per FDA guidance issued October 2008 entitled “Guidance for Sponsors, Clinical Investigators, and IRBs: Data Retention When Subjects Withdraw from FDA-Regulated Clinical Trials”.

8.0 STUDY ASSESSMENTS

8.1 Safety Assessments

8.1.1 Safety Analysis

Safety data will be tabulated for all patients and include vital signs, laboratory parameters, and adverse events.

8.1.2 Reporting of Adverse Events

8.1.2.1 Adverse Events

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

The AE reporting period starts on Cycle 1 Day 1; if an AE occurs before the first dose of study treatment it will be captured as baseline and considered a part of the medical history; however, if the AE is directly attributed to a study procedure prior to C1D1, it may be reported as an AE At each evaluation, patients should be interviewed in a non-directed manner to elicit potential adverse reactions from the patient. The occurrence of an adverse event will be based on changes in the patient's physical examination, laboratory results, and/or signs and symptoms.

All adverse events (except Grade 1 and 2 laboratory abnormalities that do not require an intervention), regardless of causal relationship, are to be recorded in the case report form and source documentation. The Investigator must determine the intensity of any adverse events according to the NCI Common Terminology Criteria for Adverse Events (CTCAE) Version 5.0 (APPENDIX II) and their causal relationship. Those AEs not covered by these criteria will be graded as follows:

1. Mild: Discomfort noticed, but no disruption of normal daily activity. Prescription drug not ordinarily needed for relief of symptom but may be given because of personality of patient.

2. Moderate: Discomfort sufficient to reduce or affect normal daily activity. Patient is able to continue in study; treatment for symptom may be needed.

3. Severe: Incapacitating, severe discomfort with inability to work or to perform normal daily activity. Severity may cause cessation of treatment with test drug; treatment for symptom may be given and/or patient hospitalized.

4. Life-Threatening: Symptom(s) place the patient at immediate risk of death from the reaction as it occurred; it does not include a reaction that, had it occurred in a more serious from, might have caused death.

5. Fatal: Event caused the death of the patient.

Adverse events will be followed until resolution or stabilization while the patient remains on-study. Once the patient is removed from study, events thought to be related to the study medication will be followed until resolution or stabilization, unless, in the Investigator's opinion the event is unlikely to resolve due to the patient's underlying disease, or until the patient starts a new treatment regimen or the patient is lost to follow-up.

8.1.2.2 Attribution Definitions

An adverse event is considered to be associated with the use of the Investigational Product if the attribution is determined as possible or definite. Attribution of AEs will be recorded in the CRF as:

- Unrelated: The AE is clearly NOT related to the study treatment.
- Possible: The AE may be related to the study treatment.
- Definite: The AE is clearly related to the study treatment.

8.1.2.3 Definition of an Unexpected Adverse Event

An unexpected adverse event is defined as any adverse drug experience, the specificity or severity of which is not consistent with the current Investigator Brochure; or, if an Investigator Brochure is not required or available, the specificity or severity of which is not consistent with the risk information described in this protocol or in the regulatory agency study authorization application.

Unexpected, as used in this definition, refers to an adverse drug experience that has not been previously observed (e.g., included in the Investigator Brochure) rather than from the perspective of such experience not being anticipated from the pharmacological properties of the pharmaceutical product.

8.1.2.4 Serious Adverse Event (SAE)

A serious adverse event is defined as any untoward medical occurrence that at any dose:

1. Results in death,

2. Is life-threatening (i.e., 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 was more severe),

3. Requires in-patient hospitalization or prolongation of existing hospitalization excluding that for pain management, disease staging/re-staging procedures, or catheter placement unless associated with other serious events,

4. Results in persistent or significant disability/incapacity, or

5. Is a congenital anomaly/birth defect.

Important medical events that may not result in death, be life-threatening, or require hospitalization may be considered serious adverse drug events when, based on appropriate medical judgment, they may jeopardize the patient or subject and may require medical or surgical intervention to prevent one of the outcomes listed above.

Disease Progression, or death as a result of disease progression, **are not considered to be SAEs**. However, if the progression of the underlying disease is greater than what would normally be expected as part of the natural course of the disease under study for the patient, or if the Investigator considers that there was a causal relationship between treatment with study drug or protocol design/procedures and the disease progression, then it must be reported as an SAE.

8.1.2.5 Reference Safety Information

The Reference Safety Information (RSI), in the current, approved Investigator's Brochure, is a list of expected Serious Adverse Reactions which are classified using Preferred Terms (PTs) according to the Medical Dictionary for Regulatory Activities (MedDRA). The RSI section will be used for assessing the expectedness of the study medication.

8.1.2.6 Pregnancy

Any pregnancy detected during the study, or that occurs within 30 days after stopping study medication, must be reported immediately to the Investigator. Pregnancy, in and of itself, is not regarded as an adverse event, unless there is suspicion that study medication may have interfered with the effectiveness of a contraceptive medication. If the patient becomes pregnant while on-study, the study drug should be immediately discontinued. Pregnancy information about a female patient or a female partner of a male patient should be reported immediately from the time the Investigator first becomes aware of a pregnancy or its outcome. This will be performed by the Investigator per instructions from the Sponsor, or its designee.

Any pregnancy complication, spontaneous abortion, elective termination of a pregnancy for medical reasons, outcome of stillbirth, congenital anomaly/birth defect, or serious adverse event in the mother will be recorded as an SAE and will be reported as described in Section 8.1.2.7.

8.1.2.7 Reporting of Serious Adverse Events

Adverse events classified as serious require expeditious handling and reporting to Sponsor’s monitoring CRO to comply with regulatory requirements. In general, reporting of Serious Adverse Events (SAEs) will begin at the time of first dosing on Cycle Day 1; however, SAEs occurring prior to first dosing may be reported if directly attributable to a study procedure.

For any serious adverse event (SAE) that occurs while a patient is on-study; within 30 days of the last study drug administration, regardless of any opinion as to the relationship of the SAE to the study drug; or if any SAE that the Investigator feels is related to the study drug occurs later than 30 days after the last study drug administration, the Sponsor or it’s designee must be notified immediately (within 24 hours of becoming aware of the event).

8.1.2.8 Safety Data Review

8.1.2.8.1 Safety Review Committee

A Safety Review Committee (SRC) comprises of 3 members – one Investigator, a representative from Heat Biologics and the Medical Monitor will evaluate the data obtained at each dose level including a review of all adverse events (serious and non-serious adverse events) as they are reported by the study site. The SRC will recommend whether the dose should be escalated as per protocol, revised to a lower level or

intermediate level, halted altogether or more patients are required at the same dose level to evaluate safety. If a DLT is observed already with the first patient treated in Cohort 1, the SRC may suggest and approve dose de-escalation with at least 50% reduction of HS-130 and HS-110 (dose level -1), depending on the nature of the reaction.

Ad-hoc SRC meetings may be called for by both the SRC and Sponsor any time during the study if DLTs are observed and/or new safety data warrants immediate action to the conduct of the trial (including events defined by the Study Stopping Criteria in Section 5.5).

The conclusion of the SRC meeting will be documented in meeting minutes. The outcome of the SRC meeting will be communicated to all Investigators.

8.2 Efficacy Assessments

Patient's disease status will be monitored by clinical and radiological assessment (CT scans or MRI) as per RECIST 1.1[1] criteria (Section 8.2.1). Patient response per RECIST 1.1[1] will be evaluated as complete response, partial response, stable disease, or progressive disease.

For the purpose of this study, patients will be evaluated after every 8-weeks ± 1-week from C1D1. In the event objective response (PR or CR) is noted, changes in tumor measurements must be confirmed by repeat assessments that should be performed at least 4 weeks after the criteria for response are first met. For stable disease (SD), follow-up measurements must meet the SD criteria at least 6 weeks after study entry.

Response to immune therapies may occur after conventional determination of disease progression based on RECIST 1.1[1]; therefore, at the Investigator's discretion patients may continue to receive the HS-130/HS-110 combination treatment after progressive disease is first observed.

8.2.1 RECIST 1.1 Criteria

8.2.1.1 Definitions

Response and progression will be evaluated in this study using the international criteria (version 1.1) proposed by the Response Evaluation Criteria in Solid Tumors (RECIST) Committee[1]. Changes in only the largest diameter (unidimensional measurement) of the tumor lesions are used in the RECIST 1.1[1] criteria. Note: Lesions are either measurable or non-measurable using the criteria provided below. The term "evaluable" in reference to measurability will not be used because it does not provide additional meaning or accuracy.

8.2.1.2 Measurable Disease

Measurable disease is defined by the presence of at least one measurable lesion. Measurable lesions are defined as those that can be accurately measured in at least one dimension [longest diameter (LD) in the plane of measurement to be recorded] with a minimum size of:

- 10 mm by CT scan (CT scan slice thickness no greater than 5 mm)
- 10 mm caliper measurement by clinical exam (lesions which cannot be accurately measured with calipers should be recorded as non-measurable)
- 20 mm by chest x-ray

Malignant lymph nodes: To be considered pathologically enlarged and measurable, a lymph node must be ≥ 15 mm in short axis when assessed by CT scan (CT scan slice thickness no greater than 5 mm).

8.2.1.3 Non-measurable Disease

All other lesions (or sites of disease), including small lesions (longest diameter < 10 mm or pathological lymph nodes with ≥ 10 to < 15 mm short axis) are considered non-measurable disease. Lesions considered truly non-measurable include: leptomeningeal disease, ascites, pleural/pericardial effusions, lymphangitis cutis/pulmonis, inflammatory breast disease, abdominal masses/abdominal organomegaly identified by physical exam and not followed by CT or MRI.

Bone lesions, cystic lesions and lesions previously treated with local therapy must be considered as follows:

Bone lesions:

- Bone scan, PET scan or plain films are not considered adequate imaging techniques to measure bone lesions. However, these techniques can be used to confirm the presence or disappearance of bone lesions.
- Lytic bone lesions or mixed lytic-blastic lesions, with identifiable soft tissue components, that can be evaluated by cross sectional imaging techniques (i.e., CT or MRI) can be considered as measurable lesions if the soft tissue component meets the definition of measurability described above.
- Blastic bone lesions are non-measurable.

Cystic lesions:

- Lesions that meet the criteria for radiographically defined simple cysts should not be considered malignant lesions (neither measurable nor non-measurable) since they are, by definition, simple cysts.
- 'Cystic lesions' thought to represent cystic metastases can be considered measurable lesions, if they meet the definition of measurability described above. However, if non-cystic lesions are present in the same patient, these are preferred for selection as target lesions.

Lesions with prior local treatment:

- Tumor lesions situated in a previously irradiated area, or in an area subjected to other loco-regional therapy, are usually not considered measurable unless there has been demonstrated progression in the lesion.

8.2.1.4 Target Lesions

All measurable lesions up to a maximum of two lesions per organ and five lesions in total, representative of all involved organs, should be identified as target lesions and recorded and measured at baseline. Target lesions should be selected on the basis of their size (lesions with the longest diameter) and their suitability for accurate repeated measurements (either by imaging techniques or clinically). A sum of the diameters (longest for non-nodal lesions, short axis for nodal lesions) for all target lesions will be calculated and reported as the baseline sum diameters. The baseline sum diameters will be used as reference by which to characterize the objective tumor response.

8.2.1.5 Lymph Node Assessment

For lymph nodes, measurements should be made of the short axis, which is defined as perpendicular to the LD of node assessed in the plane of measurement:

- Target lesion if short axis ≥ 15 mm
- Non-target lesion if short axis is ≥ 10 but < 15 mm
- Normal if short axis < 10 mm

For baseline, add the actual short axis measurement to the sum of LD of non-nodal lesions.

8.2.1.6 Non-target Lesions

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 of these lesions are not required and these lesions should be followed as "present," "absent," or in rare cases "unequivocal progression." In addition, it is possible to record multiple non-target lesions involving the same organ as a single item on the case report form (e.g., 'multiple enlarged pelvic lymph nodes' or 'multiple liver metastases').

8.2.1.7 Guidelines for Evaluation of Measurable Disease

All measurements should be taken and recorded in metric notation using a ruler or calipers. All baseline evaluations should be performed as closely as possible to the beginning of treatment and never more than 4 weeks before the beginning of the treatment.

Target lesions located in a previously irradiated areas should if possible be avoided, but such lesions may be designated as target lesions if clearly progressing (by RECIST 1.1[1] definition) at the latest evaluation prior to screening.

The same method of assessment and the same technique should be used to characterize each identified and reported lesion at baseline and during follow-up. Imaging-based evaluation is preferred to evaluation by clinical examination when both methods have been used to assess the antitumor effect of a treatment.

Clinical lesions. Clinical lesions will only be considered measurable when they are superficial and ≥ 10 mm diameter as assessed using calipers (e.g., skin nodules). In the case of skin lesions, documentation by color photography, including a ruler to estimate the size of the lesion, is recommended. When lesions can be evaluated by both clinical exam and imaging, imaging evaluation should be undertaken since it is more objective and may be reviewed at the end of the study.

Chest x-ray. Chest CT is preferred over chest x-ray, particularly when progression is an important endpoint. Lesions on chest x-ray may be considered measurable if they are clearly defined and surrounded by aerated lung.

Conventional CT and MRI. This guideline has defined measurability of lesions on CT scan based on the assumption that CT slice thickness is 5 mm or less. When CT scans have slice thickness > 5 mm, the minimum size for a measurable lesion should be twice the slice thickness. MRI is acceptable in certain situations (e.g., for body scans).

Ultrasound (US). US should not be used to measure tumor lesions. US examinations cannot be reproduced in their entirety for independent review at a later date because they are operator dependent. If new

lesions are identified by US, confirmation by CT or MRI is advised. If there is concern about radiation exposure at CT, MRI may be used instead of CT.

8.2.1.8 Response Criteria

8.2.1.8.1 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). In addition to the relative increase of 20%, the sum must also demonstrate an absolute increase of at least 5 mm. The appearance of one 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.

8.2.1.8.2 Assessment of Target Lymph Nodes

Lymph nodes identified as target lesions should always have the actual short axis measurement recorded (measured in the same anatomical plane as the baseline exam), even if the nodes regress to below 10 mm on study. In order to qualify for CR, each node must achieve a short axis < 10 mm. For PR, SD and PD, the actual short axis measurement of the nodes is to be included in the sum of target lesions.

8.2.1.8.3 Target Lesions that Become "too small to measure"

All lesions (nodal and non-nodal) recorded at baseline should have their actual measurements recorded at each subsequent evaluation, even when very small (e.g., 2 mm). If it is the opinion of the radiologist that the lesion has disappeared, the measurement should be recorded as 0 mm. If the lesion is believed to be present and is faintly seen but too small to measure, a default value of 5 mm should be assigned.

8.2.1.8.4 Lesions that Split or Coalesce on Treatment

When non-nodal lesions fragment, the longest diameters of the fragmented portions should be added together to calculate the target lesion sum. Similarly, as lesions coalesce, a plane between them may be maintained that would aid in obtaining diameter measurements of each individual lesion. If the lesions have truly coalesced such that they are no longer separable, the vector of the longest diameter should be the maximal longest diameter for the 'coalesced lesion.'

8.2.1.8.5 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 (< 10 mm 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. (The appearance of one or more new lesions is also considered progression.) To achieve 'unequivocal progression' on the basis of the non-target disease, there must be an overall level of substantial worsening in non-target disease such that, even in the presence of SD or PR in target disease, the overall tumor burden has increased sufficiently to merit discontinuation.

8.2.1.8.6 New Lesions

The finding of a new lesion should be unequivocal (i.e., not attributed to differences in scanning technique, change in imaging modality, or findings thought to represent something other than tumor, such as a 'new' healing bone lesion). A lesion identified on a follow-up study in an anatomical location that was not scanned at baseline is considered a new lesion and will indicate disease progression. If a new lesion is equivocal, continued therapy and follow-up evaluation will clarify if it represents truly new disease. If repeat scans confirm this is definitely a new lesion, then progression should be declared using the date of the initial scan.

8.2.1.9 Evaluation of Best Overall Response

The best overall response is the best response recorded from the start of the treatment until disease progression/recurrence (taking as reference for progressive disease the smallest measurements recorded since the treatment started). The patient's best overall response assignment will depend on findings of both target and non-target disease and will also take into consideration the appearance of new lesions. Furthermore, depending on the nature of the study, it may also require confirmatory measurement. Specifically, in non-randomized trials where response is the primary endpoint, confirmation of PR or CR is needed to deem either one the "best overall response."

It is assumed that at each protocol-specified time point, a response assessment occurs (Table 4) provides a summary of the overall response status calculation at each time point for patients who have measurable disease at baseline. When patients have non-measurable disease, (Table 5) should be used.

Table 4: Time point response: Patients with target (+/- non-target) disease

Target Lesions	Non-target Lesions	New Lesions	Overall Response
CR	CR	No	CR
CR	Non-CR / non-PD	No	PR
CR	Not evaluated	No	PR
PR	Non-PD or not all evaluated	No	PR
SD	Non-PD or not all evaluated	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			

Table 5: Time point response: Patients with non-target disease only

Non-target Lesions	New Lesions	Overall Response
CR	No	CR
Non-CR / non-PD	No	Non-CR / non-PD*
Not all evaluated	No	NE
Unequivocal PD	Yes or No	PD
Any	Yes	PD
CR=complete response; PD=progressive disease; NE=inevaluable * Non-CR/non-PD is preferred over SD for non-target disease		

Best response determination for studies where confirmation of CR or PR is required:
Complete or partial responses may be claimed only if the criteria for each are confirmed by a repeat assessment at least 4-weeks later. In this circumstance, the best overall response can be interpreted as in (Table 6).

Table 6: Best overall response when confirmation of CR and PR required

Overall response First time point	Overall response Subsequent time point	BEST overall response
CR	CR	CR
CR	PR	SD, PD or PR*
CR	SD	SD provided minimum criteria for SD duration met, otherwise PD
CR	PD	SD provided minimum criteria for SD duration met, otherwise PD
CR	NE	SD provided minimum criteria for SD duration met, otherwise NE
PR	CR	PR
PR	PR	PR
PR	SD	SD
PR	PD	SD provided minimum criteria for SD duration met, otherwise PD
PR	NE	SD provided minimum criteria for SD duration met, otherwise NE
NE	NE	NE
CR=complete response; PR=partial response; SD=stable disease; PD=progressive disease; NE=inevaluable * If CR is truly met at first time point, then any disease seen at a subsequent time point, even disease meeting PR criteria relative to baseline, makes the disease PD at that point (since disease must have reappeared after CR). Best response would depend on whether minimum duration for SD was met. However, sometimes 'CR' may be claimed when subsequent scans suggest small lesions were likely still present and in the fact patient had PR, not CR, at the first time point. Under these circumstances, the original CR should be changed to PR and the best response is PR.		

8.2.1.10 Confirmatory Measurement/Duration of Response

8.2.1.10.1 Confirmation

To be assigned a status of PR or CR, changes in tumor measurements must be confirmed by repeat assessments that should be performed at least 4 weeks after the criteria for response are first met. In the case of SD, follow-up measurements must have met the SD criteria at least once after study entry at a minimum interval of 6-weeks.

8.2.1.10.2 Duration of Overall Response

The duration of overall response is measured from the time measurement criteria are met for CR or PR (whichever is first recorded) until the first date that recurrent or progressive disease is objectively documented (taking as reference for progressive disease the smallest measurements recorded since the treatment started).

The duration of overall CR is measured from the time measurement criteria are first met for CR until the first date that recurrent disease is objectively documented.

8.2.1.10.3 Duration of Stable Disease

Stable disease is measured from the start of the treatment until the criteria for progression are met, taking as reference the smallest measurements recorded since the treatment started.

8.3 Best Overall Response

The best overall response is the best response (CR, PR, SD) recorded from the start of the study treatment until disease progression/recurrence, taking into account any requirement for confirmation.

8.4 Overall Survival (OS)

OS will be calculated as the duration of survival from the date of first HS-130/HS-110 combination treatment until the date of death from any cause. If the date of death is not available, OS will be censored at the date the patient was last known to be alive.

8.5 Progression-free Survival (PFS)

Progression-free survival (PFS) is defined for each patient as the time from date of first HS-130/HS-110 combination treatment to the date of the first documented tumor progression (per RECIST 1.1[1]) or death due to any cause. Patients who die without a reported prior progression will be considered to have progressed on the date of their death. Patients who did not progress or die will be censored on the date of their last evaluable tumor assessment. Patients who started any subsequent anticancer therapy without a prior reported progression will be censored at the last evaluable tumor assessment prior to the initiation of the subsequent anticancer therapy.

8.6 Analysis of Immune Response

Approximately 23 mL of blood will be collected on Day 1 (prior to administration of HS130/HS110) and Day 8 of Cycle 1 and Cycle 2, and at 30-day safety follow-up visit for the following immune response assessments.

8.6.1 Analysis of Immunological Effect

Immune-phenotyping of patient's peripheral blood sample will be performed by flow cytometry, which may include but is not limited to surface and intracellular markers that define naïve T cells (CD4 and CD8), central memory T cells (CD4 and CD8), effector T cells (CD4 and CD8), memory T cells (CD4 and CD8), senescent T cells (cytotoxic and helper), terminal differentiated senescent T cells (cytotoxic and helper), natural killer (NK) cells, natural killer T cells (NKT), T regulatory cells, proliferative T regulatory cells, activated T cells (helper and cytotoxic), proliferative T cells (helper and cytotoxic), T cell markers of exhaustion (helper and cytotoxic; CTLA-4, PD-1, TIGIT, TIM3).

Immune phenotype profiling to determine proportions of NK and T cell subsets for levels of activation, memory and exhaustion will be performed from blood samples collected on Day 1 (prior to administration of HS130/HS110) and Day 8 for Cycle 1 and Cycle 2, and at 30-day safety follow-up visit. The goal of this analysis will be to establish an immunologically active clinical dose for the combination of HS-130 and HS-110.

8.6.2 Immune Reactivation Response

Immune reactivation response to CTA expressed in HS-110 will be evaluated by determining antigen-induced secretion of cytokines IFNγ, granzyme B (gzB) from patients PBMCs via ELISPOT from blood samples collected Day 1 (pre-dose) and Day 8 for Cycle 1 and Cycle 2 and at 30-day safety follow-up visit. Number of cells responding over the course of treatment after subtraction of appropriate patient controls will be calculated.

8.7 Analysis of Pro-inflammatory Cytokines and Chemokines

Approximately 3 mL of blood samples will be collected at the following time-points during Day 1 of Cycle 1 and Cycle 2 for determination of serum cytokines and chemokines using an extensive panel of markers that may include but is not limited to, G-CSF, GM-CSF, IFN-gamma, IFN-alpha, IL-1alpha, IL-1beta, IL-2, IL-3, IL-4, IL-5, IL-6, IL-7, IL-8, IL-9, IL-10, IL-12p40, IL-13, IL-15/15R, IL-17A, IL-18, IL-22, IL-23, IL-27, IL-28, IL-31, IP-10/CXCL10, LIF, MCP-3/CCL7, M-CSF, MIP-1alpha/CCL3, MIP-1beta/CCL4, MIP-2/CXCL2, RANTES/CCL5, TNFalpha, ENA78/CXCL5, and Eotaxin-1/CCL11.

- Day 1: Prior to administration of HS130/HS110
- Day 1: 2hr ± 10 minutes after completion of HS130/HS110 treatment

For Cycle 3 and beyond cytokine/chemokine testing will only be performed if the patient is symptomatic (i.e. flu-like symptoms, fever, or allergic reactions).

8.8 Bioinformatics Analysis of CTAs and Shared Antigen Expression

Archival tissue from patients will be sent for bioinformatics analysis (e.g. RNA sequencing) of overexpressed CTAs and to study shared antigen expression with HS-110.

8.9 Exploratory Biomarkers

Biopsy samples will be collected from patients during screening/baseline and within 5-14 days after patients have completed second dose of treatment with the HS-130/HS-110 combination drug product. Archival tissue may be substituted for fresh biopsy during screening/baseline, if collected less than 6-

months prior to Cycle 1 Day 1 and the local pathologist confirms that an adequate amount of tissue/tumor cells exist to allow completion of all testing as outlined in the Tumor Biopsy Collection Manual.

Biopsies should only be collected from lesions considered safely accessible, either image-guided or palpable cutaneous or sub-cutaneous lesions. For patients on continuous anticoagulant therapy, study-specific biopsies should not be done unless local guidelines to mitigate the risk of hemorrhage are followed and the procedure can be done with minimal risk for the patient.

Genomic, immunohistochemistry and proteomic analyses of the collected tumor tissue may be performed to identify biomarkers predictive of response or resistance to HS-110/HS-130, for example by multiplex immunohistochemistry (mIHC). Immunohistochemistry analysis using multiplexed immune markers on the collected on-treatment biopsy and could be compared to baseline biopsy to study effect of HS-110/HS-130 combination treatment on patient tumors and could be correlated with clinical response. This exploratory analysis could change in line with scientific understanding and technical development as the clinical study progresses. Please note that pre-treatment and/or post-treatment tissue samples will only be collected if it poses limited risk to the patient.

9.0 STATISTICS

Demographic data and disease-related characteristics will be summarized using descriptive statistics (count and percent, mean, median, standard deviation, minimum, maximum). Continuous variables will be presented by n, mean, median, standard deviation and range (min and max) as appropriate. Data will be presented by each dose cohort. All patient data, efficacy and safety data will be summarized.

9.1 Analysis Populations

Safety Evaluable Population: All patients who received at least 1 dose of the study treatment.

Efficacy Evaluable Population: All patients with pre-treatment measurable disease by RECIST 1.1[1], who had at least one radiological assessment after pre-treatment or discontinued study treatment early due to disease progression.

9.2 Endpoints

9.2.1 Primary

- Safety and Tolerability: number of patients with TEAEs, SAEs, DLTs.

9.2.2 Secondary

- Best overall response (CR, PR, SD), overall survival, PFS per RECIST 1.1[1].

9.2.3 Exploratory

- Immunological effect assessed by evaluating proportions of natural killer (NK) and T cell subsets for levels of activation, memory and exhaustion using flow cytometry.
- Bioinformatics analysis of overexpressed CTAs and shared antigen expression with HS-110.
- Immune reactivation response to HS-110 CTA -induced secretion of cytokines (e.g. by ELISPOT).

- Changes in pro-inflammatory serum cytokines and chemokines, as well as non-specific inflammatory markers (e.g. C-reactive protein).
- Genomic, immunohistochemical and proteomic analysis of pre-treatment and on-treatment biopsy (collected from patients within 5-14 days after 2nd dose of HS-130/HS-110) for exploratory biomarker analysis.
- Immunologically active dose based on flow cytometry analysis of blood, using immune marker panels of activation and suppression as defined in Section 8.6.1.

9.3 Safety

Safety will be assessed by means of physical examination, weight, vital signs, performance status, laboratory evaluations (hematology, biochemistry, cytokines and chemokines), electrocardiogram (ECG), and recording of concurrent illness/therapy and treatment-emergent adverse events. CTCAE version 5 will be used to grade all toxicities. Patients will also be monitored for any clinical symptoms associated with elevated cytokines levels. All related adverse events will be monitored until resolution. Patients will be monitored for safety and concomitant medications throughout the study.

Safety data will be summarized for the safety evaluable population. These data will include AEs and laboratory parameters. Adverse event terms will be coded using the most current version of Medical Dictionary for Drug Regulatory Activities (MedDRA®).

9.4 Efficacy

Assessment of tumor response will be performed according to RECIST 1.1[1]. Patients will be evaluated after every 8-weeks ± 1-week for tumor response. Best overall response (CR, PR, SD), OS and PFS will be determined for each patient.

9.5 Exploratory/Other Studies

Separate reports will be generated for the bioinformatics analysis of archived/fresh tissue samples, immune reactivation, changes in pro-inflammatory cytokines/chemokines, and exploratory biomarker analysis of patient pre-treatment and on-treatment tumor tissue samples.

9.6 Sample Size

This is an exploratory trial and therefore no sample size calculations have been performed. The number of patients (13 - 30 patients) is based on the planned number of dose escalation cohorts required to identify the RP2D (defined as MTD or the highest feasible dose). Based on response observed in patients at different dose levels and/or in patients with a particular tumor type, the study protocol may be amended to allow for cohort expansion of patients with specific characteristics.

10.0 QUALITY CONTROL AND QUALITY ASSURANCE PROCEDURES

10.1 Monitoring of the Study and Regulatory Compliance

The Sponsor, or designee, will make an initiation site visit to each institution to review the protocol and its requirements with the Investigator(s), inspect the drug storage area, fully inform the Investigator of his/her responsibilities and the procedures for assuring adequate and correct documentation. During the

initiation site visit, the case report forms (CRFs) will be reviewed. Other pertinent study materials will also be reviewed with the Investigator's research staff. During the course of the study, the monitor will make regular site visits in order to review protocol compliance, examine CRFs and individual subject's medical records and assure that the study is being conducted according to pertinent regulatory requirements. All CRF entries will be verified with source documentation according to the study monitoring plan. The review of medical records will be done in a manner to assure that patient confidentiality is maintained.

10.2 Curricula Vitae and Financial Disclosure of Investigators

All Principal Investigators will be required to provide a current signed and dated curriculum vitae, a completed FDA Form 1572 and a financial disclosure statement to Sponsor, or designee. All Sub-Investigators will be required to provide a current curriculum vitae and a financial disclosure statement to Sponsor or designee.

10.3 Protocol Modifications

No modification of the protocol should be implemented without the prior written approval of the Sponsor or the Sponsor's representative. Any such changes which may affect a patient's treatment or informed consent, especially those increasing potential risks, must receive prior approval by the IRB/IEC. The exception to this is where modifications are necessary to eliminate an immediate hazard to trial subjects, or when the change involves only logistical or administrative aspects of the trial (e.g., change in monitor, change in telephone number). Other administrative revisions which may impact the clinical portion of a study will be duly reported to the IRB/IEC by the Principal Investigator.

10.4 Publication Policy

The publication of the results of the study will be subject to the terms and conditions of the clinical trial agreement between the Sponsor and Investigators. Sponsor approval is required for publication of any data from this trial.

11.0 ETHICAL CONSIDERATIONS

11.1 Informed Consent

The Investigator will obtain written informed consent from each patient, or their authorized representative, participating in the study. The form must be signed, witnessed and dated. The informed consent form will contain all the Essential Elements of Informed Consent set forth in 21 CFR, Part 50, the European Union Directive 2001/20/EC and its associated Detailed Guidances, European Union GCP Directive 2005/28/EC, the ICH Guideline for Good Clinical Practice, Section 4.8, and the terms of the Declaration of Helsinki (2013). Copies of the signed document should be given to the patient and filed in the Investigator's study file, as well as the patient's medical record if in conformance with the institution's Standard Operating Procedures.

11.2 Institutional Review Board/Independent Ethics Committee

The study will not be initiated without approval of the appropriate Institutional Review Board/Independent Ethics Committee (IRB/IEC) and compliance with all administrative requirements of the governing body of the institution. This protocol, consent procedures, and any amendments must be

approved by the IRB/IEC in compliance with current regulations of the FDA and the European Union as applicable and in accordance with ICH/GCPs. A letter of approval will be sent to the Sponsor prior to initiation of the study and when any subsequent modifications are made. The IRB/IEC will be kept informed by the Investigator, Sponsor's monitoring CRO or the Sponsor, as required by national regulations, as to the progress of the study as well as to any serious and unexpected adverse events.

11.3 Patient Privacy

In order to maintain patient confidentiality, all case report forms, study reports and communications relating to the study will identify patients by initials and assigned patient numbers; patients should not be identified by name. In accordance with local, national or federal regulations, the Investigator will allow the Sponsor or designee personnel access to all pertinent medical records in order to verify the data gathered on the case report forms and to audit the data collection process. Regulatory agencies such as the US Food and Drug Administration (FDA) may also request access to all study records, including source documentation for inspection. Clinical information will not be released without the written permission of the patient as outlined in the patient consent form.

12.0 DATA HANDLING AND RECORD KEEPING

12.1 Data to be Entered Directly in the Case Report Form

The CRF will be the source record.

12.2 Recording of Data

Data collected during the study will be entered in the patient's Case Report Form (CRF) by the investigational site staff. The staff will keep records of the patient's visit in the files considered as source documents for the site, e.g., hospital chart, research chart. The Investigator will be responsible for the recording of all data on the CRF and for submitting the data to the Sponsor or their designee in a timely manner. Should any value be significantly different from normal, the Investigator will comment in the appropriate sections provided in the CRF.

The Investigator will provide access to his/her original records to permit a representative from the Sponsor to verify the proper transcription of data. To facilitate photocopying, entries must be recorded legibly in black ink only. Erroneous entries will be crossed out with a single line, so as to remain legible. The correct value will be entered above the error and then initialed and dated by the person authorized to make the correction.

12.3 Study Records

U.S. Federal laws require that an Investigator maintain all study records for the indication under investigation for two years following the date a Product Licensing Application is approved or, if no application is to be filed or if the application is not approved for such indication, until two years after the investigation is discontinued and the FDA is notified.

13.0 REFERENCES

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APPENDIX I - ECOG Performance Status

Grade	
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 housework, 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.

APPENDIX II - Common Terminology Criteria for Adverse Events (CTCAE) v5.0

Available from the Cancer Therapy Evaluation Program website:
https: //ctep.cancer.gov/protocolDevelopment/electronic_applications/ctc.htm

APPENDIX III - Summary of Changes

Protocol Change	Affected Section(s) Numbers	Section Titles
Version 2.0, dated 11 February 2020		
Update to Sponsor address.	Title Page, Synopsis, Section 1.2	Title Page, Synopsis, Sponsor
Update to Medical Monitor email address.	Section 1.3	Title Page, Medical Monitor
'Immunological effect' changed from secondary endpoint to exploratory endpoint	Synopsis, Sections 3.0, 9.2.2, 9.2.3	Synopsis, Trial Objectives and Purpose, Secondary Endpoints, Exploratory Endpoints
Clarification that the DLT observation period is four weeks.	Synopsis, 6.1.2	Synopsis, Dose-Limiting Toxicity
Clarification that patients who refuse standard of care may be eligible	Synopsis, 5.1	Synopsis, Inclusion Criteria
Clarification of eligibility regarding washout of radiation for curative/treatment (4 weeks) and palliative radiation (2 weeks)	Synopsis, 5.2	Synopsis, Exclusion Criteria
Updated Study 'withdraw criteria' categories to align with CDISC reporting categories	5.4	Withdraw Criteria
Clarification of when patients will be declared "lost to follow-up"	5.4.1	Withdrawn Subjects
Clarification of verbiage regarding dose reductions	6.1.1	Dose Escalation Scheme
Clarification that AEs occurring prior to C1D1 may be reportable if directly related to a study procedure	8.1.2.1	Adverse Events
Clarification that, in general, Disease Progression and/or Deaths related to Disease Progression are not considered to be Serious Adverse Events	8.1.2.4	Serious Adverse Events
Clarification that SAEs occurring prior to dosing on Day 1 may be reportable if directly related to a study procedure	8.1.2.7	Reporting of Serious Adverse Events
Removed Pain Assessment as part of the safety section	9.3	Safety
Added a summary of protocol changes from previous versions	Appendix III	Summary of Changes