CLINICAL PROTOCOL

A PHASE 1B/2 STUDY OF VIAGENPUMATUCEL-L (HS-110) IN COMBINATION WITH MULTIPLE TREATMENT REGIMENS IN PATIENTS WITH NON-SMALL CELL LUNG CANCER (THE "DURGA" TRIAL)

Protocol Number:	**HS110-102**
Version and Date:	**Amendment #6, 24 May 2019**
Previous Versions:	Amendment #5, 05 September 2018
	Amendment #4, 07 December 2017
	Amendment #3, 21 November 2016
	Amendment #2, 11 December 2015
	Amendment #1, 02 July 2015
	Initial Protocol, 30 December 2014
Investigational Product:	Viagenpumatucel-L (HS-110)
IND Number:	14814
Indication:	Non-Small Cell Lung Cancer (NSCLC)
Development Phase:	1b/2
Principal Investigator:	Daniel Morgensztern, MD
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1. INVESTIGATOR'S AGREEMENT

Protocol Number: HS110-102
Protocol Title: A Phase 1b/2 Study of Viagenpumatucel-L (HS-110) in Combination with Multiple Treatment Regimens in Patients with Non-Small Cell Lung Cancer (The "DURGA" Trial)

Amendment #: 6

Version Date: 24 May 2019

I have read and understood Protocol HS110-102 Amendment 6 (dated 24 May 2019) and agree to conduct the study as outlined and in accordance with the principles of Good Clinical Practice as described in the International Conference on Harmonization Guidelines (ICH E-6) and Form FDA 1572, including the archiving of essential documents. I agree to maintain the confidentiality of all information received or developed in connection with this protocol.

_____

Printed Name of Investigator

_____

Signature of Investigator

_____

Date

2. SPONSOR PROTOCOL APPROVAL PAGE

Protocol Number: HS110-102

Protocol Title: A Phase 1b/2 Study of Viagenpumatucel-L (HS-110) in Combination with Multiple Treatment Regimens in Patients with Non-Small Cell Lung Cancer (The "DURGA" Trial)

Amendment #: 6

Version Date: 24 May 2019

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

Lori McDermott

Lori McDermott, RN, MS
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24 May 2019
Approval Date

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24 May 2019
Approval Date

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Approval Date

3. SYNOPSIS

Name of Sponsor/Company:
Heat Biologics, Inc.

Name of Investigational Product:
Viagenpumatucel-L (HS-110)

Title of Study:
A Phase 1b/2 Study of Viagenpumatucel-L (HS-110) in Combination with Multiple Treatment Regimens in Patients with Non-Small Cell Lung Cancer (The "DURGA" Trial)

Study center(s): Up to 25 U.S. centers

Phase of development: 1b/2

Primary Objectives:

Phase 1b: To characterize the safety and tolerability of vaccination with HS-110 in combination with multiple immune modulating strategies in patients with non-small cell lung cancer (NSCLC).

Phase 2, Arm 5: To evaluate Objective Response Rate (ORR) by RECIST 1.1 (Response Evaluation Criteria in Solid Tumors).

Phase 2, Arm 6: To evaluate Progression Free Survival (PFS) by RECIST 1.1

Secondary Objectives:

- To evaluate overall survival (OS), objective response rate (ORR), progression free survival (PFS), duration of response (DOR), durable response rate (DRR) and disease control rate (DCR) per RECIST 1.1.
- Arm 5: To characterize the safety and tolerability of HS-110 in combination with nivolumab in patients with NSCLC.
- Arm 6: To characterize the safety and tolerability of HS-110 in combination with pembrolizumab ± pemetrexed in patients with NSCLC.

Exploratory Objectives:

- Efficacy parameters of ORR, PFS, DOR, DCR, and DRR will be analyzed using the principals of iRECIST to produce iORR, iPFS, iDOR, iDCR, and iDRR.
- To characterize the peripheral blood immunologic response (IR) via Enzyme-Linked ImmunoSpot (ELISPOT) analysis.
- To determine total peripheral blood mononuclear cell (PBMC) counts, including lymphocyte subsets.
- To evaluate archival and fresh biopsy tissue for presence of tumor-infiltrating lymphocytes (TIL), level of programmed cell death ligand (PD-L1) expression, correlation of pre- and post-treatment TIL and PD-L1 measurements with clinical outcomes, and expression of immune active cell subsets and molecules.
- To examine tumor mutation burden and other exploratory analysis of peripheral blood and tumor tissue to determine immune changes and response to treatment

Trial Design: This is a master protocol, intended to evaluate multiple immune modulation strategies in combination with HS-110; subsequent treatment arms will be added by amendment as supporting data as these combination therapies mature. Patients will be assigned to treatment arms based on the fit to eligibility criteria.

As of Amendment 4, the Phase 1b portion of the trial (consisting of the first 15 patients to receive HS-110 in combination with nivolumab) is complete. Subsequent patients and cohorts will be considered Phase 2. Treatment Arm 1 (HS-110 plus oxygen, n=1 patient) has been discontinued. Patients in previously designated Arms 2, 3, and 4 all received HS-110 + nivolumab but had different TIL status. Patients from these arms have now been reclassified as Arm 5, and further enrollment into this arm is ongoing.

As of Amendment 5, the patient population under study was expanded to include front line patients who have received immunotherapy (with or without chemotherapy), who have not progressed clinically or radiographically (per RECIST 1.1) at the most recent imaging assessment, and who will begin maintenance immunotherapy with SOC pembrolizumab ± pemetrexed. HS-110 will be added to their immunotherapy maintenance regimen, and must be initiated on or before maintenance cycle 3 (after completion of platinum chemotherapy), or no later than week 19 (if receiving front line pembrolizumab monotherapy).

Patients who meet all eligibility criteria will be enrolled to the below treatment arms and cohorts, until the total sample size for Phase 2 is met (n=105) in addition to the Phase 1b sample size (n=15) for a total study sample size of approximately 120 evaluable patients:

Arm 5: HS-110 plus SOC nivolumab (n=100, to include 15 phase 1b patients and 85 phase 2 patients)

Arm 6: HS-110 plus SOC pembrolizumab ± pemetrexed (n=up to 20 phase 2 patients).

Arm 5 patients will receive a combination of weekly HS-110 administered as 5 intradermal 0.1 mL injections at a dose of 1×10^7 viable cells/ 0.5 mL for 18 weeks and nivolumab infusions administered every two weeks. After 18 weeks of treatment, patients will continue on monotherapy SOC nivolumab until confirmed disease progression or unacceptable toxicity, whichever occurs first. After the completion of 18 weeks of combination therapy, patients may receive either nivolumab dosing schedule listed in the current approved package insert (every 2 weeks or every 4 weeks) per Investigator discretion.

Arm 5 patients will be scanned radiographically at Screening, Week 9, Week 18, and every 8 weeks thereafter until confirmed disease progression.

Arm 6 patients will receive a combination of weekly HS-110 administered as 5 intradermal 0.1 mL injections at a dose of 1×10^7 viable cells/0.5 mL for 13 weeks in combination with SOC pembrolizumab ± pemetrexed every 3 weeks. Following the 13-week priming period, HS-110 injections will be administered for boosting every 3 weeks in combination with SOC pembrolizumab ± pemetrexed until confirmed disease progression or unacceptable toxicity, whichever occurs first.

Arm 6 patients will be scanned radiographically at Screening and every 9 weeks thereafter until confirmed disease progression.

For all study patients, the scan schedule will continue until confirmed iCPD as defined by iRECIST, after which they will be followed for OS. Using the principles of iRECIST, patients with unconfirmed disease progression (iUPD) should continue on study treatment until confirmed progression (iCPD) unless clinical progression necessitates otherwise.

For all study patients, screening tumor samples (archival or fresh) and on-treatment biopsy tumor samples may be screened for expression of immune active cell subsets and molecules, expression of PD-L1 on tumor cells, and

evaluation for the presence of TILs. Pre- and post-treatment TIL and PD-L1 levels with be correlated with clinical outcomes.

Peripheral blood samples will be taken to evaluate tumor mutation burden and immune cell subsets for correlation with clinical outcomes.

Safety will be assessed by frequency of adverse events (AEs), evaluation of clinical laboratory parameters (hematology, liver function, electrolytes, troponin, and renal function), vital signs, electrocardiogram (ECG), and physical exams (PEs).

Efficacy will be assessed by measures of OS as well as ORR, DOR, DCR, DRR and PFS by RECIST 1.1.

Number of evaluable patients (planned): Up to 120

Phase 1b: 15 patients (completed in 2017)

Phase 2: Up to 105 patients

Inclusion criteria:

1. Age ≥18 years.
2. Histologically or cytologically confirmed non-small cell lung adenocarcinoma or squamous cell carcinoma. Patients with mixed histology other than adeno-squamous are not eligible.
3. At least one site of measurable disease by CT scan or MRI as defined by RECIST 1.1. [Note: criteria not applicable to Arm 6 patients who have achieved 100% reduction in target lesions.]
4. Arm 5: Received at least one prior line of therapy, but no more than 3 lines of therapy, for incurable (i.e. unresectable) or metastatic NSCLC, including cytotoxic chemotherapy, molecularly-targeted agents, or immunotherapy. One prior line of an FDA-approved checkpoint inhibitor (CPI) therapy is permitted, however a treatment period with CPI of at least 4 months is required.
   OR
   Arm 6: Received front line immunotherapy (with or without chemotherapy) for incurable (i.e. unresectable) or metastatic NSCLC and did not progress clinically or radiographically per RECIST 1.1 at most recent imaging assessment, and will begin maintenance immunotherapy with SOC pembrolizumab ± pemetrexed. [Note: HS-110 dosing to be initiated at/before the start of the 3rd maintenance treatment cycle, or within 19 weeks of front-line pembrolizumab monotherapy.]
5. Life expectancy of at least 18 weeks.
6. Arm 5: Documented disease progression at study entry
   OR
   Arm 6: Documented Stable Disease, Partial Response, Complete Response (SD/PR/CR) per RECIST 1.1 after a minimum of 9 to 12 weeks of front line immunotherapy (with or without chemotherapy).
7. Eastern Cooperative Oncology Group (ECOG) performance status (PS) of 0 or 1.
8. Central Nervous System (CNS) metastases may be permitted after discussion with the Medical Monitor and must meet the following conditions:

a. Patient must be treated and radiographically and neurologically stable. Stable CNS metastases are defined by the return of neurological symptoms to baseline, use of no more than 10 mg of prednisone or equivalent per day, and no evidence of new or active brain lesions in the repeated scan prior to study entry.
b. Brain lesions must have been previously irradiated, including whole brain radiation therapy or radiosurgery.
c. All radiation treatment (except for localized stereotactic palliative therapy) must be completed at least 4 weeks prior to enrollment.

9. Lab parameters:
   - 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.
10. Willing and able to comply with the protocol and sign informed consent, including office visits for weekly HS-110 injections for 18 weeks (Arm 5) or weekly HS-110 injections for 13 weeks followed by every 3 week boosting injections until disease progression (Arm 6).
11. Female patients who are of childbearing potential and fertile male patients must agree to use an effective form of contraception (e.g., abstinence, oral contraceptives, intrauterine device, barrier method with spermicide, or surgical sterilization) with their sexual partners throughout study participation. Female patients of childbearing potential must test negative for pregnancy prior to enrolling in the trial.
12. Willing and able to provide either archival or fresh biopsy sample at Screening, and fresh tumor biopsy at Week 10 when feasible. Archival tissue used at Screening must be representative of the patient's current disease state unless written authorization from the Sponsor is obtained. Note that the fresh biopsy at Week 10 may be waived with written authorization from the Sponsor.
13. Arm 5: Suitable for treatment with nivolumab per the current approved package insert.
    OR
    Arm 6: Suitable for front line maintenance treatment with pembrolizumab ± pemetrexed per the current approved package inserts.

Exclusion Criteria:

1. Arm 5: Received systemic anticancer therapy within 21 days prior to first dose of study drug.
2. Human immunodeficiency virus (HIV), hepatitis B or C, or severe/uncontrolled infections or concurrent illness, unrelated to the tumor, requiring active therapy. Testing is not required in the absence of history.
3. Any condition requiring concurrent systemic immunosuppressive therapy.
4. Known immunodeficiency disorders, either primary or acquired.
5. Known leptomeningeal disease.

6. Active malignancies within 12 months, with the exception of those with a negligible risk of metastasis or death, and treated with expected curative outcome.
7. Pregnant or breastfeeding.
8. Prior participation in a clinical study of HS-110.
9. Active, known, or suspected autoimmune disease at any time prior to study entry.
10. Received a live vaccine within 30 days prior to first dose of study drug.
11. Significant cardiovascular disease:
    a. Baseline Left Ventricular Ejection Fraction (LVEF) below lower limit of normal range per institutional standard by ECHO or MUGA to be obtained within 30 days prior to first dose of study drug
    b. History of myocardial infarction within 1 year of enrollment
    c. History of heart failure within 2 years of enrollment, or at any time if due to auto-immune causes or prior immunotherapy treatment, unless pre-approved by the medical monitor
    d. A clinically significant ECG abnormality, including PR interval of >260 ms, any evidence of heart block, or a baseline prolonged QTc interval (e.g., a repeated demonstration of a QTc interval >480 ms) to be obtained within 30 days prior to first dose of study drug
12. Refractory to immunotherapy (clinical or radiographic progression after 12 weeks or less of immunotherapy).

Investigational product, dosage and mode of administration:

HS-110 (viagenpumatucel-L) is provided as fully-diluted, frozen liquid not requiring additional dilution. The final drug product will consist of 10 million cells resuspended in buffered saline containing human serum albumin (HSA), dimethyl sulfoxide (DMSO) and pentastarch. Dosing will rotate injection site extremities at every time point: antero-lateral left thigh, antero-lateral right thigh, left shoulder, and right shoulder.

Arm 5:

HS-110

Patients will receive a dose of 1×10^7 HS-110 cells per 0.5 mL administered as 5 spatially divided intradermal injections (≤ 0.1 mL per injection) once weekly for 18 weeks, or until confirmed radiographic or clinical progression or unacceptable toxicity, whichever occurs first.

Nivolumab

Patients will receive SOC nivolumab every 2 weeks during the 18-week combination treatment period or until PD or unacceptable toxicity, whichever occurs first. After 18 weeks of combination treatment, SOC nivolumab may be administered per either dosing schedule in the current approved nivolumab package insert (every 2 weeks or every 4 weeks) per Investigator discretion.

Arm 6:

HS-110

Patients will receive a dose of 1×10^7 HS-110 cells per 0.5 mL administered as 5 spatially divided intradermal injections (≤ 0.1 mL per injection) once weekly for 13 weeks in combination with SOC pembrolizumab +/-

pemetrexed every 3 weeks. Following the 13-week priming period, HS-110 injections will be administered for boosting every 3 weeks in combination with pembrolizumab +/- pemetrexed until confirmed radiographic or clinical progression or unacceptable toxicity, whichever occurs first.

Pembrolizumab ± Pemetrexed

Patients in this group will receive SOC every 3 weeks per the pembrolizumab and pemetrexed package inserts for the treatment of NSCLC.

Safety Parameters:

Primary Endpoint:

Phase 1b: Safety and Tolerability: Measured by the frequency of treatment emergent adverse events (TEAEs)/serious adverse events (SAEs), including clinically significant (CS) abnormal laboratory parameters, ECGs, PEs, and vital signs in patients receiving at least 1 dose of HS-110.

Efficacy Parameters:

Primary Endpoints:

Phase 2: Arm 5- Objective Response Rate: Defined as the number of patients achieving a best overall response of complete response (CR) or partial response (PR) by RECIST 1.1, divided by the total number of enrolled patients. This will be calculated for each cohort. Note that ORR will be a secondary endpoint for Arm 6.

Phase 2: Arm 6- Progression-Free Survival: Calculated as the time between the date of first dose of HS-110 and the date of PD as defined by RECIST 1.1 or death, whichever occurs first. For patients with no recorded post-baseline tumor assessments, PFS will be censored at the day of first dose. For those who remain alive and have no PD, PFS will be censored on the date of last evaluable tumor assessment. This will be calculated for each cohort. Note that PFS will be a secondary endpoint for Arm 5.

Secondary Endpoints:

Overall Survival (OS): Calculated as the duration from date first dose of HS-110 to date of death from any cause or will be censored on the date the patient was last known to be alive.

Duration of Response (DOR): Calculated from the time of first response (CR or PR) until radiographic PD (per RECIST 1.1) or clinical deterioration requiring a change of treatment.

Disease Control Rate (DCR): Defined as the proportion of evaluable patients whose best overall response is PR, CR, or SD by RECIST 1.1.

Durable Response Rate (DRR/): Defined as the % of responders (CR or PR) with durable responses lasting at least 6 months from time of initial response. DRR will be calculated at 6 and 12 months.

OS Rate: Defined as the proportion of patients who are alive at 6, 12, and 24 months following first dose of HS-110.**PFS Rate:** Defined as the proportion of patients who have not progressed at 6 and 12 months following first dose of HS-110.

Safety and Tolerability: Measured by the frequency of TEAEs/SAEs including CS abnormal laboratory parameters, ECGs, PEs, and vital signs in patients receiving at least 1 dose of HS-110.

Exploratory Endpoints:

Efficacy parameters of ORR, PFS, DOR, DCR, and DRR will be analyzed using the principals of iRECIST to produce iORR, iPFS, iDOR, iDCR, and iDRR.

Peripheral blood IR will be measured by ELISPOT to detect an increase of 2-fold over baseline of IFNγ and/or granzyme B (gzB) positive T cells, as well as analysis of surface markers that define NK and T cell subsets of activation, memory and exhaustion by flow cytometry.

Evaluation of tumor tissue obtained for presence of TILs and correlation of pre- and post-treatment TIL levels with clinical outcomes.

Evaluation of tumor tissue obtained for expression of PD-L1 on tumor cells and correlation of pre- and post-treatment PD-L1 expression with clinical outcomes.

Evaluation of peripheral blood TMB to measure the number of mutations within the tumor genome and correlation of TMB levels with clinical outcomes.

Other exploratory analysis of peripheral blood and tumor tissue to determine immune changes and response to treatment may be conducted as new technology emerges.

Statistical methods:

Study populations are defined as follows:

Safety Population: all patients who receive at least 1 dose of HS-110.

Per-Protocol (PP) Population: all patients who have received at least 6 doses of HS-110, and who have a pre-treatment tumor assessment and at least one post-treatment tumor assessment.

Adenocarcinoma Population: all patients in the PP who have adenocarcinoma histology

The Phase 1b portion is an exploratory substudy with safety as a primary endpoint. In Phase 2, the results from each cohort in Arm 5 and Arm 6 will be tabulated separately.

Arm 5 will include 2 cohorts, with a primary endpoint of ORR for each cohort:

- Cohort A: CPI naïve patients (n=40)
- Cohort B: CPI progressor patients (n=60). Note that this Cohort will be permitted to over-enroll based on patient availability.

Arm 6 is an exploratory arm that will include up to 20 patients in 2 cohorts pending patient availability. The primary endpoint for each cohort will be PFS. The distribution of patients between these cohorts will not be controlled:

- Cohort C: Maintenance pembrolizumab
- Cohort D: Maintenance pembrolizumab + pemetrexed

Each cohort (A, B, C and D) will be analyzed including patients of all histology types, and then again including only adenocarcinoma patients.

Analyses will be performed within each of the cohorts to identify differences in strata for each of the following factors, provided sufficient data exists:

- Histology: adenocarcinoma and squamous cell carcinoma
- PD-L1 status: negative (<1%) and positive (≥1%) based on tumor cell expression

- TIL status: high (> 10%) and low (≤ 10%)
- Tumor Mutation Burden: high (10 or more mutations) and low (less than 10 mutations)

Additional factors, such as line of treatment or presence of injection site reactions, may be added to statistical models used for analyses; the method of pooling and testing for interaction among the different factors for the different cohorts will be described in detail in the SAP.

With a total enrollment into this hypothesis-generating clinical trial of up to 120 patients across the two treatment arms, this study should have sufficient patients to identify likely subgroups for whom the addition of HS-110 to SOC appears have a clinically meaningful benefit over SOC alone. No formal hypothesis testing will be performed.

Baseline demographic and clinical data (safety and efficacy) as well as all exploratory endpoints will be summarized using descriptive statistics (means, medians, proportions, standard deviations, minima, and maxima). Time-to-event endpoints (PFS/iPFS, OS) will be calculated using Kaplan-Meier methodology. All summaries of binary efficacy endpoints such as immune response, DCR/iDCR and ORR will be presented with exact 95% CI for each cohort.

4. TABLE OF CONTENTS

4.1. List of Tables

4.2. List of Figures

4.3. Abbreviations and Acronyms

Abbreviation	Definition
12mOS	12-month overall survival
6mOS	6-month overall survival
A2AR	A2A adenosine receptor
ADP	Adenosine diphosphate
AE	Adverse event
ALK	Anaplastic lymphoma kinase
ALT	Alanine aminotransferase
AMP	Adenosine monophosphate
ANA	Antinuclear antibodies
APC	Antigen presenting cell
AST	Aspartate aminotransferase
cAMP	Cyclic adenosine monophosphate
CBC	Complete blood count
CFR	Code of Federal Regulations
cGMP	Current good manufacturing practices
CI	Confidence interval
CNS	Central nervous system
CR	Complete response
CRF	Case report form
CT	Computed tomography
CTCAE	Common Terminology Criteria for Adverse Events
CTL	Cytotoxic T-lymphocyte
CTLA-4	Cytotoxic T-lymphocyte associated antigen 4
CPI	Checkpoint Inhibitor
DC	Dendritic cell
DCR	Disease control rate
DLT	Dose-limiting toxicity
DMC	Data monitoring committee
DMSO	Dimethyl sulfoxide
DRR	Durable Response Rate

Abbreviation	Definition
EC	Ethics committee
ECG	Electrocardiogram
ECHO	Echocardiogram
ECOG	Eastern Cooperative Oncology Group
EGFR	Epidermal growth factor receptor
ELISA	Enzyme-linked immunosorbent assay
ELISPOT	Enzyme-linked immunosorbent spot
EOT	End of treatment
ER	Endoplasmic reticulum
ESR	Erythrocyte sedimentation rate
FDA	Food and Drug Administration
FFPE	Formalin-fixed paraffin embedded
GCP	Good Clinical Practice
G-CSF	Granulocyte colony-stimulating factor
GLP	Good Laboratory Practice
gzB	Granzyme B
HIV	Human immunodeficiency virus
HLA	Human leukocyte antigen
HSA	Human serum albumin
IBC	Institutional Biosafety Committee
ICF	Informed consent form
IO	Immuno-oncology
i.v.	Intravenous
ICH	International Conference on Harmonisation
ICS	Intracellular cytokine staining
IDMC	Independent data monitoring committee
IDO	Indoleamine-2,3-dioxygenase
IEC	Independent Ethics Committee
IFNγ	Interferon-γ
IHC	Immunohistochemistry
IR	Immunologic response
IRB	Institutional Review Board

Abbreviation	Definition
iCPD	Confirmed Disease Progression based on immune responses assigned using iRECIST
iCR	Complete Response based on immune responses assigned using iRECIST
iUPD	Unconfirmed Disease Progression based on immune responses assigned using iRECIST
iPR	Partial Response based on immune responses assigned using iRECIST
iRECIST	Response Evaluation Criteria in Solid Tumors for use in trials testing immunotherapeutics
iSD	Stable Disease based on immune responses assigned using iRECIST
ISR	Injection site reaction
IST	Investigator-sponsored trial
LTFU	Long-term follow-up
LVEF	Left ventricular ejection fraction
mAbs	Monoclonal antibodies
MAGE-A1	Melanoma-associated antigen 1
Mcg	Microgram
MedDRA	Medical Dictionary for Regulatory Activities
MHC	Major histocompatibility complex
MRI	Magnetic resonance imaging
mRNA	Messenger ribonucleic acid
MSDS	Material safety data sheet
MUC1	Mucin-1 (tumor associated antigen)
MUGA	Multigated acquisition scan
NCCN	National Comprehensive Cancer Network
NCI	National Cancer Institute
NK	Natural killer
Non-iCR/non-iUPD	Neither criteria for iCR or iPD have been met
NOS	Not otherwise specified
NSCLC	Non-small cell lung cancer
ORR	Objective response rate
OS	Overall survival
PBMC	Peripheral blood mononuclear cells
PCR	Polymerase chain reaction

Abbreviation	Definition
PD	Progressive disease
PD-1	Programmed death receptor 1
PD-L1	Programmed death ligand 1
PET	Positron emission tomography
PFS	Progression-free survival
PI	Principal Investigator
PP	Protocol population
PR	Partial response
PS	Performance status
QoL	Quality of Life
RBC	Red blood cell
RECIST 1.1	Response Evaluation Criteria in Solid Tumors version 1.1
RR	Response rate
SAE	Serious adverse event
SAP	Statistical Analysis Plan
SAR	Serious adverse reaction
SD	Stable disease
SOA	Schedule of activities
SOC	Standard-of-care
TCR	T-cell receptor
TEAE	Treatment-emergent adverse event
TGF	Transforming growth factor
TIL	Tumor infiltrating lymphocytes
TKI	Tyrosine kinase inhibitor
TLR	Toll-like receptor
T-reg	Regulatory T-cell
TrPAL	Triple positive activated lymphocytes (CD16+CD56+CD69+)
ULN	Upper limit of normal
VEGF	Vascular endothelial growth factor
WBC	White blood cell

4.4. Statement of Compliance

This trial will be carried out in accordance with International Conference on Harmonisation Good Clinical Practice (ICH GCP) and the following the United States (US) Code of Federal Regulations (CFR) applicable to clinical studies (45 CFR Part 46, 21 CFR Part 11, 50, 54, 56, and Part 312).

The protocol, informed consent form (ICF), recruitment materials, and all participant materials will be submitted to the Institutional Review Board (IRB)/ Ethics Committee (EC) for review and approval. Approval of both the protocol and the consent form must be obtained before any participant is enrolled. Any amendment to the protocol and ICF will require review and approval by the IRB/EC prior to implementation. In addition, a determination will be made regarding whether a new ICF needs to be obtained from participants who already provided consent using a previously approved ICF.

5. INTRODUCTION

5.1. Non-Small Cell Lung Cancer

The annual incidence of non-small cell lung cancer (NSCLC) in the United States is estimated at ~222,500 cases in 2017 and remains the deadliest malignancy worldwide. Most NSCLC patients have local or distal metastatic lesions upon diagnosis (stage IV) and the disease has a poor 5-year survival rate of 5.2%.[1] Despite a number of therapeutic advances in the last decade, response to first-line and subsequent therapy for advanced NSCLC remains sub-optimal.

Treatment strategies include consideration regarding tumor histology, molecular pathology, age, and comorbidities. In patients without mutations of epidermal growth factor receptor (EGFR), anaplastic lymphoma kinase (ALK) or c-ros oncogene 1 (ROS1) rearrangements, first-line therapy generally includes platinum-based doublet chemotherapy, with or without the anti-vascular endothelial growth factor (VEGF) antibody, bevacizumab. Patients with mutations can significantly delay disease progression by treatment with molecularly targeted agents, therefore treatment with tyrosine kinase inhibitors (TKIs) should be considered a first line treatment in this patient population[2]. The programmed death-1 (PD-1) inhibitor pembrolizumab (KEYTRUDA®) has recently been approved by the FDA as a first line single agent therapy in patients with programmed cell death ligand-1 (PD-L1) expression more than 50% with negative or unknown results for EGFR mutations, ALK rearrangements, and ROS1 rearrangements. In addition, pembrolizumab is now used in combination with carboplatin/pemetrexed (PARAPLATIN® among others/ALIMTA®) as first-line therapy for patients with advanced non-squamous NSCLC or NSCLC not otherwise specified (NOS) based on the Keynote-021 results.[3]

The current standard of care (SOC) for second line therapy of NSCLC includes treatment with monoclonal antibody (mAB) immune checkpoint inhibitors (CPI) such as nivolumab (OPDIVO®), pembrolizumab and atezolizumab. These checkpoint inhibitors have delivered objective responses of ~20% in an unselected NSCLC population, with impressive clinical results in a subset of programmed death ligand 1 (PD-L1) positive patients. Specific subgroup analysis of single agent nivolumab found response rates in previously treated (second line) non-squamous patients to be 17 to 20%, and in squamous patients to be 14.5 to 20%[4,5]. PD-L1 expression is often associated with T-cell activation and patients with a low level of existing tumor-infiltrating lymphocytes (TIL) appear to be less likely to respond to checkpoint inhibition. In fact, 60-70% of NCSLC patients are TIL-negative, which may be a contributing factor in the low overall response rate to checkpoint therapy in this unselected patient population.

These observations support the hypothesis that tumor-specific T-cell activation enhances the clinical activity of checkpoint therapy. HS-110 represents a novel way to stimulate a CD8+ T-cell response toward tumor associated antigens to enhance checkpoint therapy in treating NSCLC. This trial will include both CPI naïve and CPI progressor patients. The relatively poor responses seen with second-line and subsequent treatments are due to a combination of progressive biological resistance of the underlying tumor arising from successive regimens of chemotherapy and a decline in the performance status of patients, due to treatment- and disease-related morbidities.

The large and increasing population of patients being delivered checkpoint inhibitor therapy to the post-first-line setting, opens an opportunity to combine an immunostimulatory vaccine, HS-110,

to create a potential synergist treatment. Since the historical objective response rate (ORR) for nivolumab as second line agent in NSCLC is 20%, this is a population that could derive benefit from the immunostimulating ability of HS-110 in combination with nivolumab. Immune CPI progressor patients have an unknown response rate to nivolumab as a single agent in the second-line setting. It is currently recommended for second-line therapy per National Comprehensive Cancer Network (NCCN) Clinical Practice Guidelines in Oncology™, but there is an insufficient quantity of data stating the exact ORR of nivolumab after a patient has progressed on first-line pembrolizumab. It can be understood logically to be a lower response, as the patient previously progressed while on the CPI in the first-line setting.

HS-110 in previous human trials in NSCLC was found to be safe and immunogenic. This mechanistically novel technology and inherent low toxicity profile in combination with nivolumab in the second-line setting has potential to fill an unmet need in this population.

5.2. Vaccine Monotherapy Approaches for NSCLC

Vaccines have the potential to trigger a durable antitumor response with minimal toxicity, thus presenting an attractive alternative for NSCLC treatments. Vaccine-based therapy utilizing an autologous or allogeneic antigenic stimulus to promote endogenous antitumor immune activation is currently being heavily investigated in the clinic. Melanoma-associated antigen 3 (MAGE-A3) and mucin 1 glycoprotein (MUC1) are antigens specifically associated with various solid tumors, including NSCLC. [6,7] Two vaccines, designed to target these antigens, have been unsuccessful in treating potentially curable, earlier stage NSCLC in recent phase 3 trials. The MAGE-A3 vaccine failed to extend disease-free survival in patients with MAGE-A3-positive tumors, and no gene-signature-defined patient subsets could be identified that may have experienced clinical benefit.[8,9] The L-BLP25 vaccine administered in combination with cyclophosphamide, failed to show an overall survival (OS) advantage against placebo in unresectable stage IIIB NSCLC after definitive chemoradiation.[7,10]

Although up to 50% of patient tumors may express either MAGE-A3 and/or MUC1, the expression of these antigens within an individual tumor is rarely uniform, reflecting the underlying genetic heterogeneity of tumors, and suggests that patients who may be positive for a particular molecular signature and/or antigen may also have a significant tumor burden that is negative for those same molecular targets, thus leading to ineffective treatment for single-agent therapies. Following treatment with a single-antigen vaccine, even in the presence of a robust immune response, MAGE-A3 or MUC1 negative tumor cells may be resistant to a tumor-specific immune response. Furthermore, these trials did not enrich their patient population through selection for specific biomarkers that may exist in certain patients who may have benefitted from either of these therapies.

5.3. Vaccine Combination Approaches to NSCLC

Tumor heterogeneity, as evidenced by the recurrence of tumors after single-agent chemotherapeutic interventions, strongly suggests that a multi-targeted approach may be more successful; however, combinations with traditional chemotherapeutic agents alone remains difficult due to the overt toxicity caused by those agents. Due to the lack of such toxicity with vaccine therapies, this is an attractive therapeutic option being investigated.

Recent phase 3 results of tumor cell vaccine, belagenpumatucel-L, showed that while the vaccine failed to improve OS across the entire study population, an additional subset analysis suggested that there was a survival benefit for belagenpumatucel-L treated patients who had recently completed front-line chemotherapy and in those who received front-line combination radiation chemotherapy.[11,12] Additionally, TG4010 (a recombinant viral vector genetically modified to express MUC1 and interleukin-2 [IL-2]), added to first-line chemotherapy, resulted in an increase in OS in NSCLC patients.[13] Furthermore, a better clinical outcome was observed in TG4010-treated patients with a normal percentage of triple positive activated lymphocytes (CD16+CD56+CD69+ [TrPAL]) when compared to patients with a high percentage of TrPAL.

The vaccine combination approaches of the current trial are predicated on an assumption that significant localized immunosuppression exists within the tumor microenvironment, mediated mainly by regulatory T-cells (T-regs), predominately driven by checkpoint pathway dysregulation, intra-tumor hypoxia, and extracellular adenosine. The consequent down-regulation of the CD4+CD8+ T-cell population results in a formidable degree of tumor immunodefense against tumor-directed vaccine strategies. A number of studies have consistently suggested elevated T-reg levels in NSCLC and a direct association with both an adverse prognostic outcome and response to therapy, findings of direct relevance to the currently proposed therapeutic strategy, predicated as it is on T-cell targeting.[14,15] T-regs in NSCLC also appear to exhibit particularly high levels of PD-L1 and CTLA-4, supporting their pivotal role in the control of the neoplastic immune milieu and further implicating them as suitable targets for therapeutic immuno-intervention.[15,16]

5.4. Description of Investigational Agent, 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 antigen-presenting cells that results in a specific CD8+ cytotoxic T-cell response.

Gp96 is a member of the heat-shock protein family and has evolved specific characteristics that are advantageous for a therapeutic cancer vaccine. Similar to other heat shock proteins, gp96 is an intracellular protein that functions as a protein chaperone to facilitate the proper folding of other cellular proteins. In contrast to other heat-shock proteins, endogenous gp96 is restricted to the endoplasmic reticulum (ER) via expression of a KDEL (target peptide sequence) ER retention sequence on its C-terminus. Within the ER, gp96 is exposed to a majority of proteins and antigens that eventually are displayed on MHC I. This property is likely to have influenced the evolution of a secondary role for gp96 as a molecular warning system for necrotic cell death.[17]

Endogenous gp96 is typically released from cells only upon physical destruction or necrotic cell death. Upon release from a dying cell, extracellular gp96 is able to interact with a series of receptors, including Toll-like receptors (TLR) -2 and TLR-4 on the surface of antigen presenting cells, and engagement of TLR-2 and -4 provides an adjuvant signal. Simultaneously, gp96 is able to bind to the endocytic scavenger receptor (CD91) to facilitate internalization of gp96 together with whatever protein cargo it bound within the dying cell. Any antigens brought into an antigen presenting cell by gp96 are then transferred to MHC I, through the cross-presentation pathway, for induction of a CD8+ T-cell-mediated cytotoxic T-cell response.[18]

Heat Biologics' *ImPACT* technology seeks to replicate this natural mechanism by engineering gp96 to become a secretable molecule through the replacement of the KDEL retention signal with a secretory sequence from an immunoglobulin molecule. The resulting gp96-Ig fusion protein can then be transfected into a tumor cell line that contains a profile of antigens that are specific for a given tumor type and used to stimulate a CD8+ T-cell response toward those antigens. In the case of HS-110, Heat Biologics has screened a series of NSCLC cell lines to prioritize antigens that are known to be shared amongst a high proportion of patients with NSCLC (including MAGE-A3, NY-ESO-1, etc.) and selected the AD100 cell line based on these shared antigen expression characteristics. Figure 1 illustrates that structure of HS-110.

Figure 1: Structure of *ImPACT*™ Vaccine, HS-110

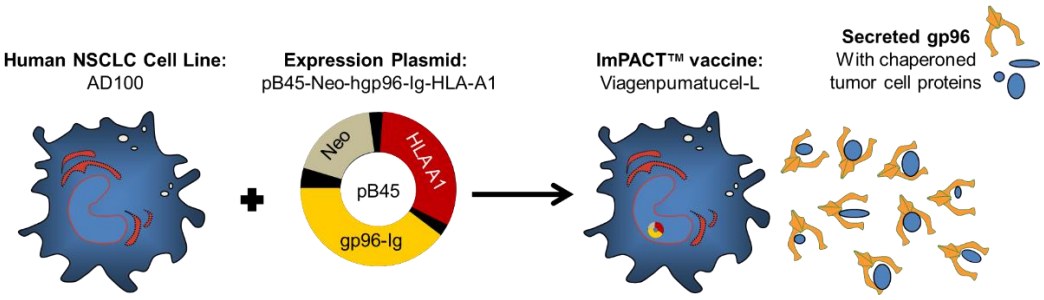


Figure 1: Schematic diagram showing the structure of HS-110. This vaccine has a cellular backbone (AD100 cell line) which has been modified with a gp96-Ig expression plasmid. Tumor cell antigen-gp96-Ig complexes are secreted by the cell in order to deliver a pan-antigenic antitumor response

5.5. Prior Human Experience with HS-110

A first-in-human Phase 1 investigator-initiated, single-center, open-label study to examine the safety and immunogenicity of HS-110 was conducted in patients with stage IV or recurrent NSCLC who failed at least one line of standard chemotherapy. The primary objective of this study was to evaluate the safety of HS-110 vaccine in patients with advanced NSCLC, and secondary objectives were to study the immune response to vaccination, monitor clinical responses, and recommend a dose-schedule (DS) combination for further testing in an initial clinical trial of vaccine efficacy.

A total of 36 patients were to be assigned to receive HS-110 administered as an intradermal injection following one of 3 DS regimens, designed to deliver equivalent numbers of cells for up to 18 weeks. Patients were treated with one of 3 dose-schedule (DS) combinations,

- DS-1: $>4\times10^7$ cells every other week for 6 weeks with up to 3 courses and 9 vaccinations.
- DS-2: $>2\times10^7$ cells weekly for 6 weeks with up to 3 courses and 18 vaccinations.
- DS-3: $>1\times10^7$ cells twice-weekly for 6 weeks with up to 3 courses and 36 vaccinations.

Nineteen (19) of the planned 36 patients enrolled in the study; 1 patient withdrew prior to receiving treatment and 18 received study treatment (n=11 patients in DS-1, n=4 patients in DS-2, and n=3 patients in DS-3). The first 7 patients were enrolled in the DS-1 cohort, and those enrolled subsequent were assigned to each of the DS cohorts in a 1:1:1 ratio. This study was closed to

enrollment at the mid-way point following a strategic decision to focus on further development under a commercial Investigational New Drug (IND) application. Data from this study have been published.[19]

Four patients died due to disease progression, and 4 patients reported a total of 6 serious adverse events (SAEs), none of which were considered by the Investigator to be treatment-related. Five SAEs were reported by 3 (16.7%) treated patients, which included rectal hemorrhage, dyspnea, chest pain, and lung infection (pneumonia), all of which were severe (Grade 3) in nature. One of these patients also reported a Grade 3 event of fatigue. The patient who did not receive treatment experienced a SAE of respiratory disorder, which resulted in study discontinuation.

The majority of adverse events (AEs) were Grade 1 or Grade 2, the most frequent of which were induration (n=18, 100%), rash (n=16, 88.9%), pruritus and pain (n=5 each, 28%).

Overall, a total of 14 patients died and the 4 surviving patients have been followed for a median of 10.6 months (range 2.6 to 16.6). The Kaplan-Meier estimate of median survival was 8.0 months (95% confidence interval [CI]: 6.7 to 18.2), and the 6, 12, and 24-month OS rates were 77.8% (95% CI: 51.1 to 91.0%), 41.9% (95% CI: 19.1 to 63.3%), and 11.2% (95% CI: 0.8 to 37.3%), respectively. Although comparison is limited due to incomplete accrual, 2 (0.5%) patients who received weekly vaccines (DS-2) and 2 (66.7%) of those receiving vaccine 2 times per week (DS-3) have survived longer than the median survival time of 7.1 months for the 11 patients who were vaccinated every other week (DS-1). Time to progression for DS-2 and DS-3 patients also appears to compare favorably with the median progression-free survival (PFS) of 1.3 months for DS-1 patients. Although there were no objective responses by Response Evaluation Criteria in Solid Tumors (RECIST) 1.1, 7 of 15 evaluable patients exhibited stable disease (SD) after a single course of therapy; 3 of these patients had durable SD of greater than 3 years.

Of the 18 patients enrolled in the trial, at least 2 samples (baseline and either week 6, 12 and/or 18) were available for 15 of the 18 patients on the trial. Peripheral blood samples were collected from each patient prior to treatment and at 6-, 12-, and 18-week time points. Immune response was characterized by production of Interferon-gamma (IFNγ) by patient CD8+ T-cells and assayed by Enzyme-Linked ImmunoSpot (ELISPOT). Of the 15 evaluable patients, 11 (73.3%) demonstrated a doubling or greater (in some cases upwards of 100-fold increases) of a CD8+ T-cell-mediated, vaccine-specific immune response. Furthermore, there was no increase in CD4+ T-cell-mediated immunity by ELISPOT, confirming preclinical findings that the effect of the gp96-Ig approach is limited to CD8+ cytotoxic T-cell responses. When the survival of the immune responders (11/15 patients, 73.3%) was compared to that of the non-responders (4/15, 26.7%), it was observed that the immune responder OS was 16.5 months vs. 4 months in the immune non-responder group. These data provide a possible link between increased vaccine-specific cytotoxic T-cell responses and increased survival.

6. STUDY RATIONALE

6.1. Study Specific Rationale

The combination of HS-110 and nivolumab is hypothesized to evoke a synergistic effect, based on the theory that checkpoint inhibitors work best in PD-L1 positive tumors in the presence of TIL. Studies in mice have shown that the combination of PD-1 blockade and gp96-Ig vaccination results in a potent increase in the number of CD8+ cytotoxic T-cells.[20] Emerging data from the ongoing DURGA trial shows increased TIL after HS-110 vaccine. Thus, combining HS-110 with anti-PD-1 agents may enhance the vaccine's anti-tumor activity while prolonging or increasing the efficacy of the checkpoint inhibitor.

HS-110 is distinct from other competitive vaccine approaches in clinical testing as it is an allogeneic, cell-based immunotherapy containing a broad range of NSCLC tumor antigens combined with a specific mechanism for the transport of these antigens to patient antigen-presenting cells for the generation of a specific CD8+ cytotoxic T-cell response. It is, therefore, likely that HS-110 will represent a more effective antigenic stimulus than many other existing vaccine constructs.

HS-110 is based on Heat Biologics' *ImPACT*™ technology, a gp96-Ig fusion protein expression construct, which when expressed, leads to the secretion of gp96-bound cellular specific antigens. The backbone cell line for HS-110, AD100, was selected based on its antigenic profile which overlaps with the antigenic profiles in a large proportion of NSCLC patient tumor samples. Extracellular gp96 activates a CD8+ T-cell mediated immune response in 2 distinct manners: 1) by functioning as an adjuvant to activate dendritic cells (DC) via TLR-2 and TLR-4 and 2) by functioning as an antigen carrier for antigen cross presentation to CD8+ T-Cells via the endocytic scavenger receptor, CD91. These characteristics make gp96 unique because it can both activate and deliver chaperoned antigens by an antigen presenting cell (APC) to MHC I in order to elicit a CD8+ T-cell mediated immune response. A comparison of our *ImPACT* approach to other vaccine monotherapies is shown in Table 1 below.

Table 1: Comparison of *ImPACT* to Other Immunotherapies

Criteria	*ImPACT* Therapy	Other Allogeneic	Autologous Cell-based
Pan-antigen delivery	✓	Some	Some
Targeted delivery of antigens to APC in vivo	✓	×	Some
Exclusive cytotoxic CD8+ T-cell response	✓	×	Some
Dual antigen carrier/adjuvant	✓	×	×

Criteria	*ImPACT* Therapy	Other Allogeneic	Autologous Cell-based
Rapid and efficient new product development	✓	Some	×
Low manufacturing cost of goods sold	✓	Some	×

Thus, the rationale for the evaluation of HS-110 in combination with multiple immune modulating strategies is as follows:

- Recent and paradigm-changing clinical data support the feasibility of effective NSCLC immunotherapy when NSCLC cells become susceptible to attack by cytotoxic T lymphocytes (CTL).
- Secreted gp96-Ig from HS-110 combines immune adjuvant activity with polyvalent peptide specificity, activating DC, NK cells, and CTLs, and resulting in death of tumor cells by NK cell-specific mechanisms and by MHC-restricted CD8 + CTL activity. The activation of DC and NK cells by HS-110 may also counteract the generation of immunosuppressive T-regs.
- This master protocol design facilitates the testing of novel combinations of immunotherapies in a small number of patients in order to characterize the safety profile and immune response to advance promising new combination regimens into larger expansion cohorts.
- The combination of HS-110 with anti-PD-1 checkpoint inhibitors may enhance the efficacy of the vaccine by accelerating the immune system response with PD-L1, which is expressed on the surface of many tumor cells. Likewise, given that patients require TIL to respond to checkpoint inhibitor therapy, the combination may enhance or prolong their activity by inducing TIL presence in patients who do not have TIL at baseline. Though the exact TIL threshold is uncertain, for patients with baseline TIL, HS-110 may drive further activation and clonal expansion of antigen-specific and activated CD8 + T-cells, leading to a higher quality immune response of TIL.

6.2. Justification of HS-110 Dose Selection

As indicated in the initial phase 1 investigator-sponsored trial (IST), the weekly (2×10^7 cells) and twice weekly (1×10^7 cells) dosing schedules were determined to produce the most desirable immune response (at least a doubling of CD8+ numbers from baseline). The weekly dosing regimen was selected for this trial as a starting point, as it represents the schedule with greatest patient acceptability for frequency of treatment visits. Further, the choice of the lower dose is prudent from a safety perspective as this trial is the first testing HS-110 in combination with multiple treatment regimens that incorporate additional immunomodulation. Furthermore, murine and simian data suggest that lower doses may produce sufficient immune response with possibly superior clinical effects.[21] Specifically, the murine dose-ranging studies indicated that production

of approximately 400 ng gp96-Ig per million cells (15-20 micrograms [mcg] per kg on a weight basis) provided the optimal dose. Production of approximately 5-10 mcg gp96-Ig per million cells (1-2.5 mcg per kg on a weight basis) in a macaque dose-ranging study provided the optimal dose. Thus, there is not an expectation of a typical dose-escalation in larger mammals as is anticipated for most antibodies or small molecules where receptor saturation is predictive of efficacy. In the case of HS-110, no significant difference in immune response was detected between the 3 doses in the phase 1 IST and longer anecdotal survival was observed in 2 of 3 patients who received the 10 million cells per dose, twice-weekly treatment schedule. Finally, improvements in the cell-freezing protocol have increased the viability of the frozen cells. Thus, we concluded that the 10 million cells weekly dosing regimen was most appropriate for this phase 1b combination study.

The selection of the multi-injection intradermal route of administration for HS-110 is based on the hypothesis that split doses stimulate stronger immune responses by allowing vaccine antigens to reach more regional lymph nodes (where immune responses are generated). The vaccine will be administered intradermally to enhance stimulation of cellular immune responses as compared to subcutaneous or intramuscular immunization.

6.3. Rationale for Obtaining Archival Tissue and Performing Tumor Biopsies

In order for an allogeneic cell-based vaccine to elicit to a clinical response, it must not only stimulate a tumor-antigen-specific immune response as detected by circulating lymphocytes in the peripheral blood, but those lymphocytes must also infiltrate the tumor microenvironment. A response to HS-110 is expected in patients whose tumors express antigens that overlap with the antigens contained within the AD100 cell backbone of HS-110. In addition, the response of patients with tumors that express numerous antigens shared with HS-110 is expected to surpass the response of those with tumors that only share 1 or 2 antigens with HS-110. Furthermore, clinical response to HS-110 may be predicted by the presence and extent of tumor infiltration by CD8+ T-cells. Thus, archival or fresh biopsy tissue will be obtained for pre-treatment tumor analysis, and a fresh biopsy sample should be collected for post-treatment analysis when feasible (unless written authorization from the Sponsor is obtained).

6.4. Rationale for Inclusion of Squamous Cell Carcinoma Patients

While the AD100 line selected for HS-110 was derived from adenocarcinoma, an example of evaluating upregulated gene expression between NSCLC adenocarcinoma and squamous cell carcinoma has been depicted below (Figure 2) showing overlap of 14 antigens between adenocarcinoma tumor bank data and HS-110, and an overlap of 10 antigens between squamous cell carcinoma tumor bank antigen expression and HS-110. Thus, multiple shared antigens between HS-110 and squamous cell carcinoma support the rationale for inclusion of squamous cell carcinoma patients in this clinical trial.

Figure 2: Number of Common Antigens between HS-110, Squamous and Adenocarcinoma in NSCLC

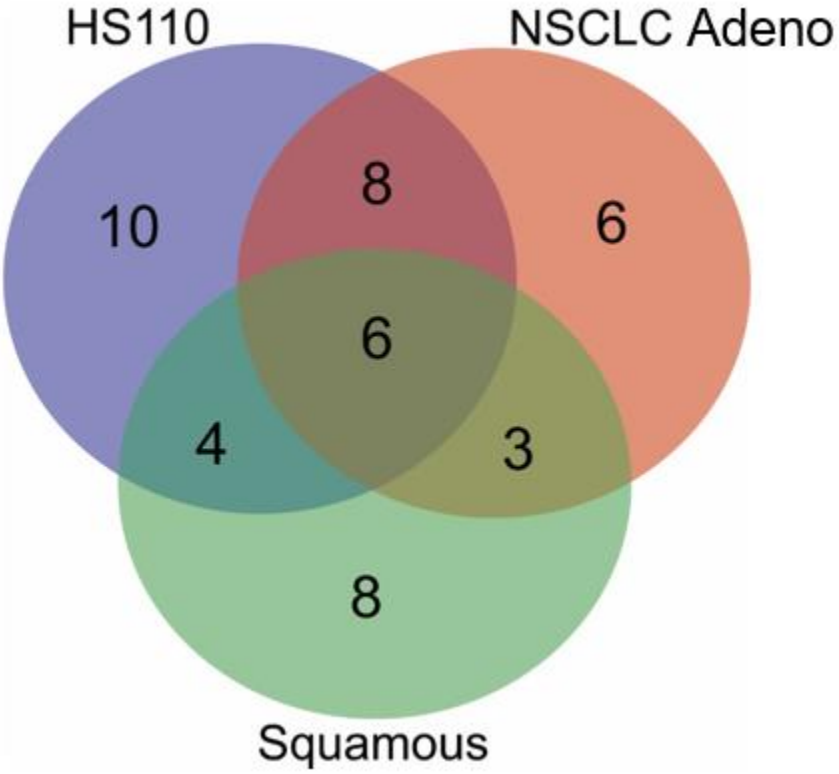


Figure 2: HS-110 was derived from AD100 cell line from adenocarcinoma; HS-110 has 14 antigens in common with adenocarcinoma and HS-110. In addition, HS-110 has 10 antigens in common with squamous NSCLC.

6.5. Rationale for Checkpoint Inhibitor Progressor Patients and First Line Maintenance Patients

Currently, pembrolizumab is the only checkpoint inhibitor approved for first-line treatment in NSCLC in patients with ≥ 50% PD-L1 expression. It has shown an improvement in ORR, but there are still patients that have PD. This is an area of unmet need and response rates to additional checkpoint inhibitors in the second and third line, specifically monoclonal antibodies (mAbs) such as nivolumab, pembrolizumab, and atezolizumab are unknown.

Combining HS-110 with anti-PD-1 agents may enhance the vaccine's anti-tumor activity while prolonging or increasing the efficacy of the checkpoint inhibitor. The combination of HS-110 and nivolumab is hypothesized to evoke a synergistic effect, based on the theory that checkpoint inhibitors work best in PD-L1 positive tumors in the presence of TIL. Studies in mice have shown that the combination of PD-1 blockade and gp96-Ig vaccination results in a potent increase in the number of CD8+ cytotoxic T-cells.[20] Emerging data from this ongoing DURGA trial shows increased TIL after HS-110 vaccine and increased tumor expression of PD-L1. Therefore,

combining this treatment for CPI progressor patients affords the opportunity to determine if HS-110 can stimulate PD-L1 expression on the tumor, and improve efficacy of nivolumab.

6.6. Rationale for First Line Maintenance Dosing

Patients in first line maintenance phase run the risk of disease progression, some of which can be attributed to the continuous generation of exhausted and inadequate numbers of tumor specific effector T cells. The goal of adding HS-110 along with PD-1/L1 blockade in the maintenance phase is to ensure a higher probability that tumor growth will be controlled by the continuous generation of antigen specific CD8+ T cells, and rescue of this activated CD8+ T cells from exhaustion. Many patients fail to receive second-line therapy due to rapid progression of disease, decrease in their performance status, or increase cancer-related symptoms. By treating patients with HS-110 along with PD-1 blockade in the maintenance phase of first line therapy, the window of opportunity for immune driven treatment benefit may be augmented and extended. Exhausted tumor specific T cells maybe refractory or resistant to complete rescue by PD-1 blockade therapy alone and require additional activation and expansion of new tumor specific sets of CD8+ T cells. It can therefore be surmised that concomitant dosage of HS-110 along with checkpoint blockade in the first line maintenance phase until progression can ensure an ongoing and expanded adaptive immune response as opposed to CPI treatment alone.

7. INVESTIGATIONAL PLAN

7.1. Overall Study Design

This is a master protocol, intended to evaluate multiple immune modulation strategies in combination with HS-110; subsequent treatment arms will be added by amendment as supporting data for these combination therapies mature. Patients will be assigned to treatment arms based on the fit to eligibility criteria.

As of Amendment 4, the Phase 1b portion of the trial (consisting of the first 15 patients to receive HS-110 in combination with nivolumab) is complete. Subsequent patients and cohorts will be considered Phase 2. Treatment Arm 1 (HS-110 plus oxygen, n=1 patient) has been discontinued. Patients in previously designated Arms 2, 3, and 4 all received HS-110 + nivolumab but had different TIL status. Patients from these arms have now been reclassified as Arm 5, and further enrollment into this arm is ongoing.

As of Amendment 5, the patient population under study will be expanded to include front line patients who have received immunotherapy (with or without chemotherapy), who have not progressed clinically or radiographically (per RECIST 1.1) at the most recent imaging assessment, and who will begin maintenance immunotherapy with SOC pembrolizumab ± pemetrexed. HS-110 will be added to their immunotherapy maintenance regimen, and must be initiated on or before maintenance cycle 3 (after completion of platinum chemotherapy), or no later than week 19 (if receiving front line pembrolizumab monotherapy).

Patients who meet all eligibility criteria will be enrolled to the below treatment arms and cohorts (n=120):

Arm 5 HS-110 plus SOC nivolumab (n=100, to include 15 phase 1b patients and 85 phase 2 patients).

Arm 6 HS-110 plus SOC pembrolizumab ± pemetrexed (n=up to 20 phase 2 patients).

Arm 5 patients will receive a combination of weekly HS-110 administered as 5 intradermal 0.1 mL injections at a dose of 1×10^7 viable cells/0.5 mL for 18 weeks and nivolumab infusions administered every two weeks. After 18 weeks of treatment, patients will continue on monotherapy SOC nivolumab until confirmed disease progression or unacceptable toxicity, whichever occurs first. After completion of 18 weeks of combination therapy, patients may receive either nivolumab dosing schedule listed in the package insert (every 2 weeks or every 4 weeks) per Investigator discretion.

Arm 5 patients will be scanned radiographically at Screening, Week 9, Week 18, and every 8 weeks thereafter until confirmed disease progression.

Arm 6 patients will receive a combination of weekly HS-110 administered as 5 intradermal 0.1 mL injections at a dose of 1×10^7 viable cells/0.5 mL for 13 weeks in combination with SOC pembrolizumab ± pemetrexed every 3 weeks. Following the 13-week priming period, HS-110 injections will be administered for boosting every 3 weeks in combination with SOC pembrolizumab or SOC pembrolizumab/pemetrexed until confirmed disease progression or unacceptable toxicity, whichever occurs first.

Arm 6 patients will be scanned radiographically at Screening and every 9 weeks thereafter until confirmed disease progression.

For all study patients, the scan schedule will continue until confirmed disease progression (iCPD) as defined by iRECIST, after which they will be followed for OS. Using the principles of iRECIST, patients with unconfirmed disease progression (iUPD) should continue on study treatment until confirmed progression (iCPD) unless clinical progression necessitates otherwise.

For all study patients, screening tumor samples (archival or fresh) and on-treatment biopsy tumor samples (when feasible to obtain) will be screened for expression of immune active cell subsets and molecules, expression of PD-L1 on tumor cells and evaluation for the presence of TILs. Pre- and post-treatment TIL and PD-L1 levels with be correlated with clinical outcomes.

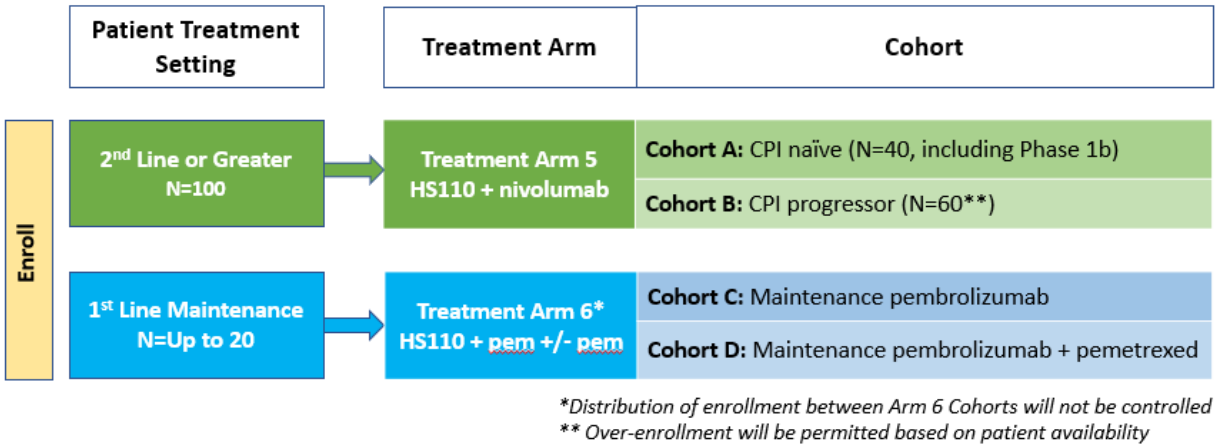
Peripheral blood samples will be taken to evaluate tumor mutation burden and immune cell subsets for correlation with clinical outcomes.

Safety will be assessed by frequency of adverse events (AEs), evaluation of clinical laboratory parameters (hematology, liver function, electrolytes, troponin, and renal function), vital signs, electrocardiogram (ECG), and physical exams (PEs).

Efficacy will be assessed by measures of OS, ORR, DOR, DCR, DRR and PFS by RECIST 1.1.

The overall study design is summarized below in Figure 3.

Figure 3: Study Design



7.2. Study Treatments

Each patient will be assigned a unique patient identification number at screening; this unique identifier will be recorded on all CRFs and ancillary documents specific to the patient. Prospective patients will be considered enrolled in the study on the date of their first dose of HS-110.

Patients enrolled in Arm 5 will receive HS-110 administered concomitantly with nivolumab. HS-110 0.5 mL will be administered intradermally as weekly injections for 18 weeks. Standard of care nivolumab will be given intravenously every 2 weeks until the HS-110 administration period is

complete, after which nivolumab may be administered either every 2 weeks or every 4 weeks (per Investigator's discretion) in accordance with the current approved nivolumab Package Insert.

Patients enrolled in Arm 6 will receive HS-110 plus SOC pembrolizumab ± pemetrexed. HS-110 will be administered concomitantly with maintenance pembrolizumab +/- pemetrexed. HS-110 0.5 mL will be administered intradermally as weekly injections for 13 weeks, followed by 0.5 mL intradermal injections every 3 weeks. Treatment with HS-110 and pembrolizumab +/- pemetrexed will continue until confirmed disease progression or unacceptable toxicity, whichever occurs first.

Patients' participation in this study may continue 2 years or longer. The duration of the nivolumab, pembrolizumab, and pembrolizumab/pemetrexed treatments are standard of care (SOC) and will continue along with radiology scans until confirmed disease progression or unacceptable toxicity. Following confirmed disease progression, patients will be followed by telephone or office visit for survival approximately every 3 months.

8. STUDY OBJECTIVES AND PURPOSE

8.1. Primary Objectives

Phase 1b: To characterize the safety and tolerability of HS-110 in combination with multiple immune modulating strategies in patients with NSCLC.

Phase 2, Arm 5: To evaluate Objective Response Rate (ORR) by RECIST 1.1 in each cohort.

Phase 2, Arm 6: To evaluate progression free survival (PFS) by RECIST 1.1 in each cohort.

8.2. Secondary Objectives

- To evaluate overall survival (OS), objective response rate (ORR), progression free survival (PFS), duration of response (DOR), durable response rate (DRR) and disease control rate (DCR) per RECIST 1.1.
- Arm 5: To characterize the safety and tolerability of HS-110 in combination with nivolumab in patients with NSCLC.
- Arm 6: To characterize the safety and tolerability of HS-110 in combination with pembrolizumab ± pemetrexed in patients with NSCLC.

8.3. Exploratory Objectives

- Efficacy parameters of ORR, PFS, DOR, DCR, and DRR will be analyzed using the principals of iRECIST to produce iORR, iPFS, iDOR, iDCR, and iDRR.
- To characterize the peripheral blood immunologic response (IR) via Enzyme-Linked ImmunoSpot (ELISPOT) analysis.
- To determine total peripheral blood mononuclear cell (PBMC) counts, including leukocyte subsets that define NK and T cell subsets of activation, memory and exhaustion.
- To evaluate archival and fresh biopsy tissue for presence of tumor-infiltrating lymphocytes (TILs), level of PD-L1 expression, correlation of pre- and post-treatment TIL and PD-L1 measurements on tumor cells with clinical outcomes, and expression of immune active cells and molecules.
- To examine tumor mutation burden and other exploratory analysis of peripheral blood and tumor tissue to determine immune changes and response to treatment.

9. SELECTION AND WITHDRAWAL OF PATIENTS

The study population will consist of two distinct patient types. Arm 5 will include metastatic NSCLC patients that have failed first line therapy and are undergoing second line therapy or greater. The patients can have adenocarcinoma or squamous cell NSCLC and be checkpoint inhibitor (CPI) naïve or CPI progressor. Arm 6 will include metastatic NSCLC patients who have received immunotherapy (with or without chemotherapy) in the front line, who have not progressed clinically or radiographically (per RECIST 1.1) at the most recent imaging assessment, and who will begin initiation of maintenance immunotherapy with standard of care (SOC) pembrolizumab ± pemetrexed. [Note: HS-110 dosing to be initiated at/before the start of the 3rd maintenance treatment cycle, or within 19 weeks of front-line pembrolizumab monotherapy.]

The sections below list all of the inclusion and exclusion criteria patients must meet to proceed with enrollment, and they must voluntarily provide written consent to participate in the study.

9.1. Subject Inclusion Criteria

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

1. Age ≥18 years.
2. Histologically or cytologically confirmed diagnosis of non-small cell lung adenocarcinoma or squamous cell carcinoma. Patients with mixed histology other than adeno-squamous are not eligible.
3. At least one site of measurable disease by CT scan or MRI as defined by RECIST 1.1. [Note: criteria not applicable to Arm 6 patients who have achieved 100% reduction in Target Lesions.]
4. Arm 5: Received at least one prior line of therapy, but no more than three prior lines of therapy, for incurable (i.e. unresectable) or metastatic NSCLC, including cytotoxic chemotherapy, molecularly-targeted agents, or immunotherapy. One prior line of FDA-approved checkpoint inhibitor (CPI) therapy is permitted, however a treatment period with CPI of at least 4 months is required.

   OR

   Arm 6: Received front line immunotherapy (with or without chemotherapy) for incurable or metastatic NSCLC and did not progress clinically or radiographically per RECIST 1.1 at the most recent imaging assessment, and will begin maintenance immunotherapy with SOC pembrolizumab ± pemetrexed. [Note: HS-110 dosing to be initiated at/before the start of the 3rd maintenance treatment cycle, or within 19 weeks of front-line pembrolizumab monotherapy.]
5. Life expectancy of at least 18 weeks.
6. Arm 5: Documented disease progression at study entry.

   OR

Arm 6: Documented Stable Disease, Partial Response, Complete Response (SD/PR/CR) per RECIST 1.1 after a minimum of 9 to 12 weeks of front line immunotherapy (with or without chemotherapy).

7. Eastern Cooperative Oncology Group (ECOG) performance status (PS) of 0 or 1.
8. Central Nervous System (CNS) metastases may be permitted after discussion with the Medical Monitor and must meet the following conditions:
   a. Patient must be treated and radiographically and neurologically stable. Stable CNS metastases are defined by the return of neurological symptoms to baseline, use of no more than 10 mg of prednisone or equivalent per day, and no evidence of new or active brain lesions in the repeated scan prior to study entry.
   b. Brain lesions must have been previously irradiated, including whole brain radiation therapy or radiosurgery.
   c. All radiation treatment (except for localized stereotactic palliative therapy) must be completed at least 4 weeks prior to enrollment.
9. Lab parameters:
   - Albumin $\geq$2.5 g/dL.
   - Total Bilirubin $< 3.0 \times$ upper limit of normal (ULN) unless patient has Gilbert's syndrome.
   - Alanine transaminase (ALT) and aspartate transaminase (AST) $\leq 3.0 \times$ ULN or $\leq 5 \times$ ULN in the case of liver metastases.
   - Calculated or measured creatinine clearance > 35 mL/minute per the Cockcroft-Gault formula.
   - Absolute neutrophil count $\geq$1,500/mm^3.
   - Hemoglobin $\geq$9 g/dL.
   - Platelet count $\geq$100,000/mm^3.
10. Willing and able to comply with the protocol and sign informed consent, including office visits for weekly HS-110 injections for 18 weeks (Arm 5) or weekly HS-110 injections for 13 weeks followed by every 3 week boosting injections until disease progression (Arm 6).
11. Female patients who are of childbearing potential and fertile male patients must agree to use an effective form of contraception (e.g., abstinence, oral contraceptives, intrauterine device, barrier method with spermicide, or surgical sterilization) with their sexual partners throughout study participation. Female patients of childbearing potential must test negative for pregnancy prior to enrolling in the trial.
12. Willing to provide either archival or fresh biopsy sample at Screening, and fresh tumor biopsy at Week 10 when feasible. Archival tissue used at Screening must be representative of the patient's current disease state unless written authorization from the Sponsor is obtained. Fresh biopsy at Week 10 may be waived with written authorization from the Sponsor.

13. Arm 5: Suitable for treatment with nivolumab per the current approved package insert.

    OR

    Arm 6: Suitable for front line maintenance treatment with pembrolizumab ± pemetrexed per the current approved package inserts.

9.2. Subject Exclusion Criteria

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

1. Arm 5: Received systemic anticancer therapy within 21 days prior to first dose of study drug.
2. Human immunodeficiency virus (HIV), hepatitis B or C, or severe/uncontrolled infections or concurrent illness, unrelated to the tumor, requiring active therapy. Testing is not required in the absence of history.
3. Any condition requiring concurrent systemic immunosuppressive therapy.
4. Known immunodeficiency disorders, either primary or acquired.
5. Known leptomeningeal disease.
6. Active malignancies within 12 months, with the exception of those with a negligible risk of metastasis or death, and treated with expected curative outcome.
7. Pregnant or breastfeeding.
8. Prior participation in a clinical study of HS-110.
9. Active, known, or suspected autoimmune disease.
10. Received a live vaccine within 30 days prior to first dose of study drug.
11. Significant cardiovascular disease:
    a. Baseline Left Ventricular Ejection Fraction (LVEF) below lower limit of normal range per institutional standard by ECHO or MUGA within 30 days prior to first dose of study drug.
    b. History of myocardial infarction within 1 year of enrollment.
    c. History of heart failure within 2 years of enrollment, or at any time if due to auto-immune causes or prior immunotherapy treatment, unless pre-approved by the medical monitor.
    d. A clinically significant ECG abnormality, including PR interval of >260 ms, any evidence of heart block, or a baseline prolonged QTc interval (e.g., a repeated demonstration of a QTc interval >480 ms) within 30 days prior to first dose of study drug.
12. Refractory to prior immunotherapy (clinical or radiographic progression after 12 weeks or less of immunotherapy).

9.3. Patient Completion and Withdrawal

9.3.1. Patient Completion

Patients in Arm 5 will receive a combination of weekly injections of HS-110 and nivolumab infusions every two weeks for 18 weeks. After 18 weeks of treatment, patients will continue on monotherapy SOC nivolumab until disease progression or unacceptable toxicity, whichever occurs first. After 18 weeks of combination therapy, SOC nivolumab may be administered according to either dosing schedule in the nivolumab package insert (every 2 weeks or every 4 weeks) per Investigator discretion. Arm 5 patients will be scanned radiographically at Screening, Week 9, Week 18, and every 8 weeks thereafter until confirmed disease progression.

Patients in Arm 6 will receive weekly injections of HS-110 for 13 weeks in combination with SOC pembrolizumab ± pemetrexed infusions administered every 3 weeks. Following the 13-week priming treatment period, HS-110 injections will be administered for boosting every 3 weeks in combination with SOC pembrolizumab ± pemetrexed until confirmed disease progression or unacceptable toxicity, whichever occurs first. Arm 6 patients will be scanned radiographically at Screening and every 9 weeks thereafter until confirmed disease progression.

After confirmed disease progression, patients will be followed for collection of subsequent anti-cancer therapies and survival status every 3 months. This may be done via telephone or office visit.

9.3.2. Discontinuation from Study Treatments

Every effort must be made by study personnel to keep patients on study treatment(s); however, a patient **will** be discontinued prior to completion of HS-110 treatment for any of the following reasons:

- Grade 4 AE(s) considered by the Investigator to be related to study treatment (or Grade 3 AE(s) at the Investigator's discretion) assessed as related to treatment, except for "expected" AEs with nivolumab or pembrolizumab or pembrolizumab/pemetrexed treatment, as per the package inserts.
- Pregnancy.
- Termination of the study by the Sponsor.
- Intercurrent illness that prevents further administration of treatment.
- Patient withdrawal of consent.

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

- Progressive disease, according to iRECIST by a confirmed scan, or significant clinical progression at an earlier time point, if judged by the Investigator to be in the patient's best interests.

If a patient prematurely discontinues study treatment for any reason, the patient will continue to be followed for study endpoints, unless consent for this is specifically withdrawn.

A reason for discontinuation must be documented in the case report form (CRF). If the patient discontinues study treatment due to toxicity, "Adverse Event" will be recorded as the primary reason for withdrawal. If a patient is prematurely discontinued from the study at any time due to an AE or SAE, the patient must be followed until resolution, unless it is unlikely to improve because of underlying disease.

9.3.3. Patient Withdrawal from Study

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

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

If the patient does not have enough data to be considered evaluable (received at least 6 doses of HS-110 and had a pre-treatment tumor assessment and at least one post-treatment tumor assessment) an additional patient may be enrolled into the study.

10. STUDY PROCEDURES

This study will be conducted in compliance with the protocol, GCP, and applicable regulatory requirements. A current, signed and dated informed consent form (ICF) that has been approved by an IRB/IEC must be obtained from the potential patient before he/she can participate in any study-specific procedures, including study-specific screening procedures.

A patient will be considered enrolled on the date of the first dose of HS-110.

For Arm 5 patients, the study will generally be conducted in 4 periods, as follows: Screening, On Study (receiving HS-110 treatment), Post-HS-110 Follow-up (no longer receiving HS-110 treatment, but not yet progressed), and Survival Follow-up (after confirmed disease progression).

For Arm 6 patients, the study will generally be conducted in 3 periods, as follows: Screening, On Study (priming and boosting until progression), and Survival Follow-up (after confirmed disease progression).

10.1. Screening Procedures and Baseline (Day -28 to Day -1)

The following procedures and assessments must be conducted within approximately 4 weeks (Day -28 to Day -1) prior to the first dose of study medication.

For each potential patient, the following procedures and assessments will be performed by qualified study staff.

These procedures and assessments may occur on the same day as dosing, as long as the collection of biopsy tissue and blood samples occurs PRIOR to dosing with any study drug and recorded appropriately to verify. Qualified study personnel should obtain the following:

- A current IRB/IEC-approved ICF must be signed and dated before any study-related procedures are performed.
- Complete medical history including prior treatments and surgeries, prior medications, and pre-existing clinical signs and symptoms
- Patient demographics (age, sex, race and ethnicity)
- Eastern Cooperative Oncology Group (ECOG) performance status (PS) (Appendix 1)
- Full physical examination (PE) including height and weight, and an evaluation of all body systems (Section 13.1)
- Vital signs (blood pressure, heart rate, respiratory rate, and temperature)
- Draw blood for hematology, serum chemistry, and troponin I or T (Section 13.2)
- Blood draw for baseline immunological response (Section 14.2)
- Serum or urine pregnancy test for female patients of childbearing potential (Section 13.2)
- Tumor assessment, including CT scan or MRI, to document target and non-target lesions by RECIST 1.1 and iRECIST. (Section 14.1.1)

- Mandatory archival or fresh tissue collection. Note that sample must be obtained via incisional, excisional or core needle biopsy. A fine needle aspiration is not acceptable for archival or fresh biopsy. Additional tissue collection and preparation procedures are provided in a separate Biopsy Manual.
- Electrocardiogram (ECG)
- Echocardiogram (ECHO) or Multiple-Gated Acquisition (MUGA) Scan with left ventricular ejection fraction (LVEF) (Section 13.4)
- Verify eligibility criteria via inclusion and exclusion criteria per Section 9.1 and Section 9.2.

10.1.1. Baseline Assessments (Day -7 to Day 1)

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

- Reassessment of ECOG PS (Appendix 1)
- Record pre-existing symptoms as medical history and prior medications.
- Hematology and serum chemistry only if the Screening Visit was performed more than 2 weeks prior to the first dose (Section 13.2)
- Serum or urine pregnancy testing for females of child-bearing potential only if the Screening Visit was performed more than 2 weeks prior to the first dose (Section 13.2)
- Re-Verify eligibility criteria via inclusion and exclusion criteria per Section 9.1 and Section 9.2

10.2. Arm 5: On Study Treatment Procedures

Study-related procedures and assessments performed during treatment on study are detailed as follows and in the Schedule of Activities (SOA; Table 2). This period of the study is generally considered to be the combination treatment period from Day 1 through Week 18, but could be shorter in duration if HS-110 is prematurely discontinued.

10.2.1. Week 1 Assessments (Day 1)

The following procedures will be performed after all the previous Screening and Baseline procedures have been completed:

- Update of prior medications and pre-existing symptoms as medical history
- Reconfirm eligibility prior to dosing
- Blood draw for tumor mutation burden (TMB) obtained prior to dosing (Section 14.6). Note that Cohort B patients enrolled prior to Amendment 5 that did not have a week 1 TMB sample collected should have a one-time TMB lab drawn at the next feasible visit (i.e. Week 4, 10, 16 or post-HS110/survival follow-up).
- Blood draw for Troponin I or T levels obtained prior to dosing (Section 13.4)

- Administration of HS-110
- Monitor patients on site for potential acute reactions for 30 minutes after HS-110 administration (first dosing only)
- Administration of SOC nivolumab per package insert
- Record any AEs experienced by patient
- Record concomitant medications

10.2.2. **Week 2 Assessments**

The following procedures will be performed at Week 2 (Day 8±3):

- Blood draw for Troponin I or T levels obtained prior to dosing (Section 13.4)
- Vital signs, with abbreviated PE (Section 13.1) targeted to signs and symptoms
- Administration of HS-110
- Record AEs experienced by patient
- Record concomitant medications

10.2.3. **Week 3 Assessments**

The following procedures will be performed at Week 3 (Day 15±3):

- Blood draw for Troponin I or T levels obtained prior to dosing (Section 13.4)
- ECG conducted prior to dosing
- Vital signs, with abbreviated PE targeted to signs and symptoms
- Administration of HS-110
- Administration of SOC nivolumab, per package insert
- Record AEs experienced by patient
- Record concomitant medications

10.2.4. **Week 4 Assessments**

The following procedures will be performed at Week 4 (Day 22±3):

- Blood draw for Troponin I or T levels obtained prior to dosing (Section 13.4)
- Vital signs, with abbreviated PE targeted to signs and symptoms
- Blood draw for hematology and serum chemistry (Section 13.2)
- Administration of HS-110
- Record AEs experienced by the patient
- Record concomitant medications

10.2.5. **Week 5, 6, 8, and 11 Assessments**

The following procedures will be performed at Week 5 (Day 29±3), Week 6 (Day 36±3), Week 8 (Day 50±3), and Week 11 (Day 71±3).

- Vital signs, with abbreviated PE targeted to signs and symptoms (Weeks 5 and 11 only)
- Administration of HS-110
- Administration of SOC nivolumab (Weeks 5 and 11 only), per package insert
- Record AEs experienced by the patient
- Record concomitant medications

10.2.6. **Week 7 and 13 Assessments**

The following procedures will be performed at Week 7 (Day 43±3), and Week 13 (Day 85±3):

- Vital signs, with abbreviated PE targeted to signs and symptoms (Week 7 only).
- Blood draw for IR prior to dosing (Section 14.2)
- Blood draw for hematology and serum chemistry (Section 13.2)
- Administration of HS-110
- Administration of SOC nivolumab, per package insert
- Record AEs experienced by the patient
- Record concomitant medications

10.2.7. **Week 9 and 18 Assessments**

The following procedures will be performed at Weeks 9 (Day 57±3) and Week 18 (Day 120±3):

- Tumor assessment by CT scan or MRI and evaluation of tumor response using RECIST 1.1 and iRECIST (Section 14.1.1)
- Administration of HS-110
- Administration of SOC nivolumab (only on Week 9), per package insert
- Record AEs experienced by the patient
- Record concomitant medications

10.2.8. **Week 10 and 16 Assessments**

The following procedures will be performed at Week 10 (Day 64±3) and Week 16 (Day 106±3):

- Blood draw for hematology and serum chemistry (Section 13.2)
- Tumor biopsy (Week 10 only) to be obtained when feasible unless written authorization from the Sponsor is obtained. Note that sample must be obtained via incisional, excisional or core needle biopsy. A fine needle aspiration is not acceptable. Additional tissue collection and preparation procedures are provided in a separate Biopsy Manual.

- Administration of HS-110
- Record AEs experienced by the patient
- Record concomitant medications

10.2.9. Week 12, 14, 15, and 17 Assessments

The following procedures will be performed at Week 12 (Day 78±3), Week 14 (Day 92±3), Week 15 (Day 99±3), and Week 17 (Day 113±3).

- Vital signs, with abbreviated PE targeted to signs and symptoms (Week 15 only)
- Administration of HS-110
- Administration of SOC nivolumab, per package insert (Weeks 15 and 17 only)
- Record AEs experienced by the patient
- Record concomitant medications

10.3. Arm 5: End of Treatment (EOT) Visit

The following procedures should be completed approximately 3 to 4 weeks following last dose of HS-110, including patients who discontinue dosing prematurely. If patient completes all 18 weeks of HS-110 treatment, the EOT Visit should occur at Week 21 or 22.

- Full PE (including height and weight)
- Vital signs (blood pressure, heart rate, respiratory rate, and temperature)
- Blood draw for IR (Section 14.2)
- Blood draw for hematology and serum chemistry (Section 13.2)
- Record AEs experienced by the patient
- Record concomitant medications

10.4. Arm 5: Follow-up Procedures

10.4.1. Post-HS-110 Follow Up (After HS-110 treatment until disease progression)

The off-treatment follow-up period for Arm 5 is defined as the time when patients have discontinued or completed HS-110 treatment and are receiving SOC treatment with nivolumab monotherapy, which is administered per Investigator discretion according to the package insert dosing regimens of either every 2 weeks or every 4 weeks. During this time, radiological assessments will continue every 8 weeks until confirmation of iCPD by iRECIST. Any AEs deemed related to study drug will also be recorded.

10.4.2. Survival Follow-Up (Progressive Disease until Death)

The survival follow-up period refers to the time between the confirmation of PD and patient death. Patients will be followed for OS. Survival status and subsequent anti-cancer therapy will be

collected approximately every 3 months in a clinic visit or by telephone if the patient is no longer attending clinic visits at the investigative site.

10.5. Arm 6: On Study Treatment Procedures

10.5.1. Week 1 Assessments (Day 1)

The following procedures will be performed after all the previous Screening and Baseline procedures have been completed, with HS-110 dosing beginning no later than the start of the 3rd maintenance treatment cycle, or more than 19 weeks from the start of front-line treatment for patients receiving pembrolizumab monotherapy:

- Update of prior medications and pre-existing symptoms as medical history
- Reconfirm eligibility prior to dosing
- Blood draw for tumor mutation burden obtained prior to dosing (Section 14.6)
- Blood draw for Troponin I or T levels obtained prior to dosing (Section 13.4)
- Administration of HS-110
- Monitor patients on site for potential acute reactions for 30 minutes after HS-110 administration (first dose only)
- Administration of SOC pembrolizumab ± pemetrexed per package inserts
- Record any AEs experienced by patient.
- Record concomitant medications.

10.5.2. Week 2 Assessments

The following procedures will be performed at Week 2 (Day 8 ± 3):

- Blood draw for Troponin I or T levels obtained prior to dosing (Section 13.4)
- Vital signs, with abbreviated PE (Section 13.1) targeted to signs and symptoms
- Administration of HS-110
- Record AEs experienced by patient
- Record concomitant medications

10.5.3. Week 3 Assessments

The following procedures will be performed at Week 3 (Day 15 ± 3):

- Blood draw for Troponin I or T levels obtained prior to dosing (Section 13.4)
- ECG conducted prior to dosing
- Vital signs, with abbreviated PE targeted to signs and symptoms
- Administration of HS-110

- Record AEs experienced by patient
- Record concomitant medications

10.5.4. **Week 4 Assessments**

The following procedures will be performed at Week 4 (Day 22 ± 3):

- Blood draw for Troponin I or T levels obtained prior to dosing (Section 13.4)
- Blood draw for hematology and serum chemistry (Section 13.2)
- Vital signs, with abbreviated PE targeted to signs and symptoms
- Administration of HS-110
- Administration of SOC pembrolizumab ± pemetrexed per package inserts
- Record AEs experienced by patient
- Record concomitant medications

10.5.5. **Week 5, 6, 8, 9, 11 and 12 Assessments**

The following procedures will be performed at Week 5 (Day 29 ±3),Week 6 (Day 36 ± 3), Week 8 (Day 50 ± 3), Week 9 (Day 57 ± 3), Week 11 (Day 71 ±3) and at Week 12 (Day 78 ± 3):

- Administration of HS-110
- Record AEs experienced by patient
- Record concomitant medications
- Week 9 only: Tumor assessment by CT scan or MRI and evaluation of tumor response using RECIST 1.1 and iRECIST (Section 14.1.1)

10.5.6. **Week 7 and 13 Assessments**

The following procedures will be performed at Week 7 (Day 43 ± 3) and Week 13 (Day 85 ± 3):

- Blood draw for immunological response obtained prior to dosing (Section 14.2)
- Blood draw for hematology and serum chemistry (Section 13.2)
- Vital signs, with abbreviated PE targeted to signs and symptoms (Week 7 only)
- Administration of HS-110
- Administration of SOC pembrolizumab ± pemetrexed per package insert
- Record AEs experienced by patient
- Record concomitant medications

10.5.7. **Week 10 Assessments**

The following procedures will be performed at Week 10 (Day 64 ± 3):

- Vital signs, with abbreviated PE targeted to signs and symptoms
- Blood draw for hematology and serum chemistry (Section 13.2)
- Administration of HS-110
- Administration of SOC pembrolizumab ± pemetrexed per package insert
- Record AEs experienced by patient
- Record concomitant medications
- Tumor biopsy collected when feasible unless written authorization from the Sponsor is obtained. Note that sample must be obtained via incisional, excisional or core needle biopsy. A fine needle aspiration is not acceptable. Additional tissue collection and preparation procedures are provided in a separate Biopsy Manual.

10.5.8. **Boosting Visits and Assessments (Week 14 to EOT)**

Following the 13-week priming period, HS-110 injections will be administered for boosting every 3 weeks (±3 days) in combination with SOC pembrolizumab ± pemetrexed until confirmed disease progression. During this time, radiological assessments will continue every 9 weeks until confirmation of iCPD per iRECIST. Concomitant medications and AE/SAEs will also be recorded.

10.6. Arm 6: End of Treatment

The following procedures should be completed approximately 3 to 4 weeks following last dose of HS-110, including patients who discontinue dosing prematurely.

- Full PE (including height and weight)
- Vital signs (blood pressure, heart rate, respiratory rate, and temperature)
- Blood draw for IR (Section 14.2)
- Blood draw for hematology and serum chemistry (Section 13.2)
- Record AEs experienced by the patient
- Record concomitant medications

10.7. Arm 6: Survival Follow-Up (Progressive Disease until Death)

The survival follow-up period refers to the time between the confirmation of PD and patient death. Patients will be followed for OS. Survival status and subsequent anti-cancer therapy will be collected approximately every 3 months in a clinic visit or by telephone if the patient is no longer attending clinic visits at the investigative site.

10.8. Schedule of Activities (SOA)

Table 2 outlines the clinical assessments and treatments by week for Arm 5 receiving HS-110 in combination with nivolumab and Table 3 outlines the clinical assessments and treatments by week for Arm 6 receiving HS-110 in combination with pembrolizumab ± pemetrexed.

Table 2: Schedule of Activities (Arm 5: HS-110+ Nivolumab)

Activity	Screening		Week																		EOT[1]	Post-HS-110 FU	Survival FU
	D-28 to D-1		1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18			
Study Day		Baseline[2] D-7 to D1		8 ±2	15 ±3	22 ±3	29 ±3	36 ±3	43 ±3	50 ±3	57 ±3	64 ±3	71 ±3	78 ±3	85 ±3	92 ±3	99 ±3	106 ±3	113 ±3	120 ±3	+21 to 28	Q8 weeks	Q3 months
Informed Consent	X																						
Medical History	X	X																					
Demographics	X																						
ECOG PS	X	X																					
PE with vitals	X[3]			X	X	X	X		X				X				X				X[3]		
Hematology[4] and serum chemistry[4]	X	X[5]				X			X			X			X			X			X		
Troponin I or T[6]	X		X	X	X	X																	
Pregnancy Test[7]	X	X[5]																					
Tumor Mutation Burden Lab[8]			X[9]																				
Immunologic Response Lab[10]	X								X						X						X		
Tissue Sample Collection[11]	X											X											

[1] EOT should be completed approximately 3 to 4 weeks following last dose of HS-110, including for patients who discontinue dosing prematurely.

[2] Baseline procedures may be combined with Week 1 visit, as long as they are performed prior to dosing.

[3] Full physical exam will be performed at Screening and EOT and includes obtaining the patient's height and weight, and an assessment of the following body systems: HEENT, Pulmonary, Cardiovascular, Musculoskeletal, Abdominal/Gastrointestinal, Lymphatic, Neurological, Dermatologic, and Genito-urinary systems. Abbreviated physical exams will be conducted at Weeks 2, 3, 4, 5, 7, 11, and 15 and are limited to vital signs and symptoms unless otherwise clinically indicated.

[4] Blood draw for hematology requires 5 mL and serum chemistry requires 5 mL; hematology assessments include white blood cell (WBC) with differential, platelet count, hemoglobin, red blood cell (RBC) count and absolute neutrophils; serum chemistry includes assessment of sodium, calcium, total protein, albumin, creatinine, blood urea nitrogen (BUN), total bilirubin, alkaline phosphatase, AST, ALT, potassium, chloride, sodium bicarbonate, lactate dehydrogenase, and glucose.

[5] Repeat assessment at Baseline only if Screening Visit was performed > 2 weeks prior to dosing.

[6] Blood draw for Troponin I or T requires 5 mL (performed at Screening and Weeks 1 through 4).

[7] Urine or serum pregnancy test. Blood draw for serum pregnancy test for women of childbearing potential requires 1 mL (performed at Screening and Baseline prior to dosing).

[8] Blood draw for TMB requires 20 ml of blood at Week 1 prior to dosing.

[9] Cohort B Patients who enrolled prior to Amendment 5 and did not have a week 1 TMB sample drawn should have this sample collected at the next feasible visit..

[10] Blood draw for IR requires 50 mL of blood (performed at Screening and at Weeks 7, 13 and EOT).

[11] Tissue biopsy sample collection may be archival or fresh at screening, and fresh tissue collected at Week 10 when feasible.

Activity	**Screening**		**Week**																		**EOT[1]**	**Post-HS-110 FU**	**Survival FU**
	D-28 to D-1		**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**10**	**11**	**12**	**13**	**14**	**15**	**16**	**17**	**18**			
Study Day		Baseline[2] D-7 to D1		8 ±2	15 ±3	22 ±3	29 ±3	36 ±3	43 ±3	50 ±3	57 ±3	64 ±3	71 ±3	78 ±3	85 ±3	92 ±3	99 ±3	106 ±3	113 ±3	120 ±3	+21 to 28	Q8 weeks	Q3 months
Tumor Assessment by CT or MRI[12]	X										X									X		Q8 weeks from wk 18	
ECG	X				X																		
ECHO or MUGA with LVEF	X																						
Verify eligibility criteria	X	X	X																				
Prior and Concomitant Medications	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X[11]	X[13]
HS-110 Administration			X[14]	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X			
SOC Nivolumab administration[15]			X		X		X		X		X		X		X		X		X			Q2 or Q4 weeks[16]	
Record AEs/SAEs[17]			X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X[18]	
Survival Status																							X

[12] Tumor assessment will be evaluated by RECIST 1.1 and iRECIST
[13] Only subsequent anti-cancer therapy will be recorded
[14] 30 minute observation after first dose only
[15] Nivolumab will be administered every 2 weeks while receiving HS-110 treatment
[16] Nivolumab dosing schedule during Post-HS-110 Follow Up determined per Investigator discretion
[17] AEs/SAEs to be recorded up to 4 weeks after the last administration of HS-110, and followed until resolution (unless not resolvable due to underlying disease)
[18] Only AEs deemed related to study drug will be recorded

Table 3: Schedule of Activities (Arm 6: HS-110 + Pembrolizumab +/- Pemetrexed)

Activity	Screening		Week													Boosting	EOT[19]	Survival FU
	D-28 to D-1		1	2	3	4	5	6	7	8	9	10	11	12	13			
Study Day		Baseline[20] D-7 to D1		8 ±2	15 ±3	22 ±3	29 ±3	36 ±3	43 ±3	50 ±3	57 ±3	64 ±3	71 ±3	78 ±3	85 ±3	Q3 weeks ±3	+21 to 28	Q3 months
Informed Consent	X																	
Medical History	X	X																
Demographics	X																	
ECOG PS	X	X																
PE with vital signs	X[21]			X	X	X			X			X					X[19]	
Hematology[22] and serum chemistry[22]	X	X[23]				X			X			X			X		X	
Troponin I or T[24]	X		X	X	X	X												
Pregnancy Test[25] (serum or urine)	X	X[23]																
Tumor Mutation Burden Lab[26]			X															
Immunologic Response Lab[27]	X								X						X		X	
Tissue Collection[28]	X											X						

[19] EOT should be completed approximately 3 to 4 weeks following last dose of HS-110, including premature/early termination of HS-110 treatment.

[20] Baseline procedures may be combined with Week 1 visit, as long as they are performed prior to dosing.

[21] Full physical exam will be performed at Screening and EOT and includes obtaining the patient's height and weight, and an assessment of the following body systems: HEENT, Pulmonary, Cardiovascular, Musculoskeletal, Abdominal/Gastrointestinal, Lymphatic, Neurological, Dermatologic, and Genito-urinary systems. Abbreviated physical exams will be conducted at Weeks 2, 3, 4, , 7, and 10 are limited to vital signs and symptoms unless otherwise clinically indicated.

[22] Blood draw for hematology requires 5 mL and serum chemistry requires 5 mL; hematology assessments include white blood cell (WBC) with differential, platelet count, hemoglobin, red blood cell (RBC) count and absolute neutrophils; serum chemistry includes assessment of sodium, calcium, total protein, albumin, creatinine, blood urea nitrogen (BUN), total bilirubin, alkaline phosphatase, AST, ALT, potassium, chloride, sodium bicarbonate, lactate dehydrogenase, and glucose.

[23] Repeat assessment at Baseline only if Screening Visit was performed > 2 weeks prior to dosing.

[24] Blood draw for Troponin I or T requires 5 mL (performed at Screening and Weeks 1 through 4).

[25] Blood draw for serum pregnancy test for women of childbearing potential requires 1 mL (performed at Screening and Baseline prior to dosing).

[26] Blood draw for TMB requires 20 ml of blood at Week 1 prior to dosing.

[27] Blood draw for IR requires 50 mL of blood (performed at Screening and at Weeks 7, 13 and EOT).

[28] Tissue biopsy sample collection may be archival or fresh at screening, and fresh tissue collected at Week 10 when feasible.

Activity	Screening		Week													Boosting	EOT[29]	Survival FU
	Day -28 to D-1		1	2	3	4	5	6	7	8	9	10	11	12	13			
Study Day		Baseline D-7 to D1		8 ±2	15 ±3	22 ±3	29 ±3	36 ±3	43 ±3	50 ±3	57 ±3	64 ±3	71 ±3	78 ±3	85 ±3	Q3 weeks ±3	+21 to 28	Q3 months
Tumor Assessment by CT or MRI[30]	X										X					Q9 weeks from week 9		
ECG	X				X													
ECHO or MUGA with LVEF	X																	
Verify eligibility criteria	X	X	X															
Prior and Concomitant Medications	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X[31]
HS-110 vaccination			X[32]	X	X	X	X	X	X	X	X	X	X	X	X	X		
SOC Pembrolizumab +/- pemetrexed administration[33]			X			X			X			X			X	X		
Record AEs/SAEs[34]			X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	
Survival Status																		X

[29] EOT should be completed approximately 3 to 4 weeks following last dose of HS-110, including premature/early termination of HS-110 treatment.
[30] Tumor assessment will be evaluated by RECIST 1.1 and iRECIST. Qualifying imaging assessment for Arm 6 may be completed up to 6 weeks prior to first HS-110 administration.
[31] Only subsequent anti-cancer therapy will be recorded.
[32] 30 minute observation after first dose only.
[33] Pembrolizumab +/- pemetrexed will be administered every 3 weeks per package insert.
[34] AEs/SAEs to be recorded up to 4 weeks after the last administration of HS-110, and followed until resolution (unless not resolvable due to underlying disease).

11. TREATMENT OF PATIENTS

11.1. Description of Study Drug

Table 4: Investigational Product

PARAMETER	PRODUCT INFORMATION
INN/USAN name	Viagenpumatucel-L
Code Name	HS-110
Dosage Form	Suspension for Injection (ready-to-use or concentrated)
Strength / Dose	1×10^7 viable cells/ 0.5 mL
Route of Administration	Intradermal
Dosing Regimen	Arm 5: Weekly, 5 intradermal 0.1 mL injections for 18 weeks Arm 6: Weekly, 5 intradermal 0.1 mL injections for 13 weeks followed by 5 intradermal 0.1mL injections every 3 weeks until disease progression or unacceptable toxicity (whichever occurs first)
How Supplied	Ready-to-use single-dose vial: 0.6 mL (includes 0.5 mL dose plus 0.1 mL overage)
Storage Conditions	$\leq$-120^{0}C Stored in liquid nitrogen vapor phase

11.2. Prior and Concomitant Medications

All prior and concomitant medications, including prescription and over-the-counter medications taken during the 14 days before the date of first dose, during the study treatment, and through 4 weeks post the last dose of study drug, will be documented. Subsequent anti-cancer therapy will also be collected during off-treatment follow up and survival follow up. Any concomitant medication(s), including herbal or vitamin preparations, taken during the study will be recorded in the CRF. At a minimum, the drug name, dose, and the dates of administration will be recorded.

11.3. Permitted Medications

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.

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

11.3.1. Prohibited Medications

In principle, steroid therapy is not permitted, but use of steroids for TEAEs may be considered after consultation with the Medical Monitor. Patients receiving replacement doses of corticosteroids for adrenal insufficiency should not have their replacement dose withheld. Arm 6 patients receiving SOC pemetrexed may receive steroids as recommended per Package Insert.

Topical and inhaled steroids will be permitted. Other than protocol-defined agents, no concomitant chemotherapy, immunotherapy, immunosuppressive or other anticancer therapy will be permitted while receiving study treatments.

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

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

11.3.2. Supportive Care

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

11.4. Treatment of Investigational Product Overdose

There have been no cases of overdose with HS-110. Treatment of any suspected or confirmed overdose with HS-110 should be symptomatic, and supportive care is recommended in cases where overdose is suspected. As described in the Investigator's Brochure (IB) for HS-110, the Sponsor does not recommend specific treatment for overdose or toxicity; however, the Investigator should use appropriate clinical judgment in treating the overdose. For the purposes of this study, an overdose of HS-110 is defined as any dose 50% greater than the intended dose for that patient. Appropriate supportive care measures may need to be provided to address these potential toxicities in the event of an overdose.

11.5. Dose Adjustment Criteria

Any Grade 3 or higher AE determined to be treatment-related (HS-110 and/or nivolumab and/or pembrolizumab ± pemetrexed) will be discussed with the Medical Monitor before continuing with dosing, with the following exceptions:

- Local injection site reactions lasting <72 hours, including pain, redness, swelling, induration, or pruritus
- Systemic injection reactions lasting <72 hours of fever, myalgia, headache, or fatigue
- For patients in Treatment Arm 5: known and manageable reactions considered "expected" with nivolumab per the package insert
- For patients in Treatment Arm 6: known and manageable reactions considered "expected" with pembrolizumab and/or pemetrexed per the package inserts.

Where judged appropriate by the Investigator (after discussion with the Medical Monitor) a dose delay may be necessary for ≥Grade 3 AEs until resolution of the toxicity (to Grade 1 or less).

HS-110: No dose modifications of HS-110 will be permitted.

Nivolumab, pembrolizumab and pemetrexed: Dose modifications are permitted according to their package inserts. If nivolumab, pembrolizumab and/or pemetrexed is discontinued due to toxicity, patients may continue to receive HS-110. This approach is consistent with results showing clinical benefit in patients even after toxicity-related treatment discontinuation.

12. STUDY DRUG MATERIALS AND MANAGEMENT

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

12.1. HS-110

HS-110 is provided as single-dose vials containing fully-diluted frozen liquid not requiring additional dilution. The final drug consists of 10 million cells resuspended in buffered saline containing human serum albumin (HSA), dimethyl sulfoxide (DMSO), and pentastarch. Overfill of 0.1 mL is factored into each vial to allow extraction of the full 0.5 mL dose for patient administration. Additional detail can be found in the Pharmacy Manual.

Each HS-110 dose totaling 1×10^7 cells per dose will be administered as 5 spatially divided intradermal injections (≤0.1 mL per injection) in the same extremity to increase volume distribution and enhance antigen presentation to lymph node regions. Vaccine dosing will rotate injection site extremities at every time point: antero-lateral left thigh, antero-lateral right thigh, left shoulder, and right shoulder. Missed doses may be made up if the missed dose is given at least 4 days before the subsequent dose. All doses will be administered at the Investigator site.

In Arm 5, HS-110 will be administered weekly for 18 weeks.

In Arm 6, HS-110 will be administered weekly for 13 weeks. Following the 13-week priming period, HS-110 injections will be administered for boosting every 3 weeks in combination with SOC pembrolizumab ± pemetrexed until confirmed disease progression or unacceptable toxicity (whichever occurs first).

12.2. Study Drug Storage

The activity of HS-110 is critically dependent on the viability of the cells in the preparation and vials must be stored at cryogenic temperature (≤ - 120º C) in liquid nitrogen vapor phase. The product is supplied to the clinical site from the clinical supply depot via shipments in liquid nitrogen dry-shipper units which are validated to maintain temperature for 10 days. Upon arrival, the product must be transferred to controlled liquid nitrogen storage at the clinical site for continued storage. If liquid nitrogen storage is not available at the investigative site, a unit will be supplied by the Sponsor. The Sponsor will also arrange for replacement of the liquid nitrogen at regular intervals to ensure that the proper storage temperature is maintained throughout the study. Study staff must take care to minimize temperature excursions during transfer of the product from shipping containers to controlled ultralow temperature storage on site. The product should 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 must be returned to ≤ - 120ºC immediately.

Additional study drugs (nivolumab, pembrolizumab, pemetrexed) will be commercially supplied and stored according to instructions in their current approved package inserts.

12.3. Study Drug Preparation

HS-110 must be thawed and the syringes labeled prior to injection. Preparation of the product and syringe labeling procedures is described in the Pharmacy Manual. Note that HS-110 must be administered within 2 hours of removing from liquid nitrogen dewar.

12.4. Labeling

HS-110 is labeled with the product name, the dose identification number, storage requirements, and the statement "Caution: New Drug — Limited by Federal (or United States) law to investigational use." Additional country-level requirements may be included on the carton label. Additional study drugs (nivolumab, pembrolizumab, and pemetrexed) are used as commercially supplied; labelling is not applicable.

12.5. Study Drug Accountability

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

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

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

12.6. Occupational Safety

Precautions should be taken to avoid direct contact with the study drug. A Material Safety Data Sheet (MSDS) describing occupational hazards and recommended handling precautions will be provided to the Investigator.

13. ASSESSMENT OF SAFETY

Safety data will be collected throughout the study by a qualified physician, physician assistant, or nursing staff. Measurements used to evaluate safety will include medical history, physical examination, vital signs, clinical laboratory tests, ECGs, and evaluation of AEs. AEs will be graded according to the National Cancer Institute Common Terminology Criteria for Adverse Events Version 4.03 (NCI CTCAE v4.03).[22]

Clinically significant abnormal laboratory parameters (as determined by the Investigator) may be repeated. If warranted, additional or more frequent testing than is specified in the protocol if warranted by the physician to monitor and treat AEs and should be documented in the study record until resolution.

13.1. Physical Examination

PEs must be performed by a qualified physician, nurse practitioner, or physician assistant and should include a thorough review of all body systems at Screening (Day -28 to Day -1) and at the EOT Visit. Body systems to be evaluated include Head, Eyes, Ears, Nose and Throat (HEENT), Pulmonary, Cardiovascular, Musculoskeletal, Abdominal/Gastrointestinal, Lymphatic, Neurological, Dermatologic, and Genito-urinary systems. In addition, the full PE will include obtaining the patient's height and weight.

Abbreviated PEs will be conducted at Weeks 2, 3, 4, 5, 7, 11, 15 for arm 5, and at Weeks 2, 3, 4, 7, and 10 for arm 6. Abbreviated PEs are limited to vital signs and physical symptoms unless otherwise clinically indicated. Vital signs include blood pressure, heart rate, respiratory rate, and temperature, and will be measured after resting in a semi-supine or supine position.

13.2. Clinical Laboratory Evaluations

Blood samples will be collected for routine clinical laboratory testing and cardiovascular monitoring. The clinical laboratory parameters will be analyzed at the site's local laboratory. Laboratory assessments to be completed will include serum chemistry, hematology, Troponin I or T, and urine or serum pregnancy test (females of childbearing potential), and are defined as follows:

- **Serum Chemistry (5 mL):** To include sodium, calcium, total protein, albumin, creatinine, blood urea nitrogen (BUN), total bilirubin, alkaline phosphatase, AST, ALT, potassium, chloride, sodium bicarbonate, lactate dehydrogenase, and glucose.
- **Hematology (5 mL)**: To include white blood cell (WBC) with differential, platelet count, hemoglobin, red blood cell (RBC) count and absolute neutrophils.
- **Troponin I or T (5 mL)**: See Section 13.4 for further details.
- **Urine or serum (1 mL) pregnancy test**: See Section 13.5 for further details.
- Additional laboratory assessments may be conducted throughout the study as medically necessary.

13.3. Injection Site Reactions

The grading scale for injection site reactions (ISRs) used in this trial can be found in Appendix 2. Grade 1 ISRs consisting of mild redness, erythema, and swelling around the injection site are anticipated. Grade 1 reactions should dissipate over several days to a week with no special treatment. All ISRs, regardless of grade, should be recorded on the Injection Site Reaction CRF page, including a photograph of each reaction where feasible. If an unusual, Grade 3, or Grade 4 ISR occurs, attempts to obtain photographs at initial report and at follow-up visits, which show resolution over time, are encouraged. A ruler should be in the field of view to allow measurement of the size of the reaction. De-identified photograph(s) should be appended to the CRF.

13.4. Cardiac Monitoring

Troponin I or T and ECGs will be used in the first month of the study to monitor for signs of immune-related cardiotoxicity as per Table 2. The following actions should be taken in the event of changes in cardiac monitoring tests:

- **Isolated Troponin I or T elevation:**
    - Delay HS-110 and additional study drug treatment (nivolumab, pembrolizumab, or pembrolizumab/pemetrexed).
    - Assess patient for new onset of chest pain, shortness of breath, orthopnea (shortness of breath when lying down), or syncope.
    - Perform ECG and ECHO to evaluate for new evidence of heart block, reduction in LVEF, pericardial effusion, or other abnormalities.
    - Repeat Troponin I or T in 2-3 days.
    - If new symptoms have developed and/or repeat troponin remains elevated (above upper limit of normal per institution), consider discontinuation of therapy and cardiology consultation. In this event contact Medical Monitor to discuss the case.
    - If Troponin decreases with no other clinically significant findings, treatment can be restarted after discussion and approval by Medical Monitor.
- **ECG evidence of heart block:**
    - Delay HS-110 and additional study drug treatment (nivolumab, pembrolizumab, or pembrolizumab/pemetrexed).
    - Assess patient for new onset of chest pain, shortness of breath, orthopnea (shortness of breath when lying down), and syncope.
    - Perform ECHO to evaluate for reduction (> 10% reduction from baseline or below lower limit of normal per institution) in LVEF, pericardial effusion, or other abnormalities.
    - Repeat ECG in 2-3 days.
    - If new symptoms have developed and/or repeat ECG remains abnormal consider discontinuation of therapy and cardiology consultation. In this event contact Medical Monitor to discuss the case.

- Treatment must be permanently discontinued in confirmed cases of acute onset heart block. All cases must be discussed with Medical Monitor.

13.5. Pregnancy

All female patients of childbearing potential will have a urine or serum pregnancy test performed at the Screening and Baseline Visits.

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

13.5.1. Time Period for Collecting Pregnancy Information

All pregnancy information should be collected from the time of Screening Visit (up to Day -28 prior to study drug administration) to 4 weeks after the last dose of study medication. Patients with pregnancies identified during screening will be recorded as screen failures.

13.5.2. Action to be Taken if Pregnancy Occurs

The Investigator will notify the Sponsor, or designee, within 24 hours of learning of a patient's pregnancy. The patient will also be followed to determine the outcome of the pregnancy. Information on the status of the mother and child will be forwarded to the Sponsor, or designee. Generally, follow-up will be no longer than 6 to 8 weeks following the estimated delivery date. Any premature termination of the pregnancy will be reported.

While pregnancy itself is not considered to be an AE or SAE, any pregnancy complication or elective termination of a pregnancy for medical reasons will be recorded as an AE or SAE (see AE and SAE Section 15.1).

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

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

The Investigator will attempt to collect pregnancy information on any male study patient's female partner who becomes pregnant while participating in this study. The Investigator will record pregnancy information on the appropriate form and submit it to the Sponsor, or designee, within 24 hours of learning of the partner's pregnancy. The partner will also be followed to determine the outcome of the pregnancy. Information on the status of the mother and child will be forwarded to the Sponsor or designee. Generally, follow-up will be no longer than 6 to 8 weeks following the estimated delivery date. Any premature termination of the pregnancy will be reported.

14. ASSESSMENT OF EFFICACY

14.1. Tumor Assessments

Tumor response assessments will incorporate results from radiographic tumor assessment (CT scans or MRI) of the chest, abdomen, and pelvis as well as physical examination, where appropriate, and will follow RECIST 1.1 and iRECIST criteria. PET scans will also be collected if obtained but are not required per protocol.

The identification of target plus non-target lesions by CT or MRI will be documented at Screening, and repeat scans will be performed at Week 9, Week 18 and then every 8 weeks thereafter (Arm 5), or at Screening and every 9 weeks (Arm 6) until confirmed iCPD per iRECIST, unless clinical signs of progression necessitate earlier scanning.

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

14.1.1. RECIST 1.1 and iRECIST for Tumor Assessment

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

Radiographic assessment (CT scan or MRI) will be performed as follows:

Arm 5: Screening, Week 9, Week 18, and every 8 weeks thereafter until confirmed disease progression;

Arm 6: Screening and every 9 weeks until confirmed disease progression

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

Disease response via RECIST 1.1 and iRECIST will be assessed as outlined in Appendix 3.

The determination of iRECIST response uses the same guidelines to determine measurable or non-measurable lesions. The concept change for iRECIST is the resetting of the bar if RECIST 1.1 progression is followed at the next assessment by tumor shrinkage. This approach allows atypical responses, such as delayed responses that occur after pseudoprogression, to be identified, further understood, and better characterized. Refer to Appendix 3 for further details.

The disease response measures will allow for the calculation of the ORR, PFS, and DCR. The ORR includes CR/iCR, and PR/iPR. PFS is the time between treatment assignment and the date of PD/iPD or death, whichever comes first. The DCR includes responses of PR/iPR, CR/iCR or SD/iSD.

14.2. Immunologic Response (IR)

Peripheral blood samples (50 mL) will be collected at Screening,Week 7, Week 13, and EOT. All samples will be shipped to and processed by Heat Biologics, Inc. or its designee.

Forty (40) mL heparinized blood and 10 mL of non-heparinized blood will be drawn at each of the above time points and used for analysis as outlined below. PBMCs will be isolated from heparinized blood samples by Ficoll separation. Isolated PBMCs will be utilized for immunophenotyping and functional analysis using fluorescence activated cell sorting (FACS) and ELISPOT assays as described below. A subset of isolated PBMCs will by lysed in nucleic acid preservative buffers for downstream analysis of molecular signatures. Serum collected from non-heparinized blood samples will be stored for batch analysis of antibody titers to HLA-A1, in non-HLA-A1 positive patients and serum cytokines/chemokines.

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

14.3. Production of Interferon-gamma and Granzyme B from PBMCs (ELISPOT)

The immune response will be evaluated by antigen-specific ELISPOT analysis for IFNγ and Granzyme B production by patient cells. These ELISPOT assays will be conducted in our research facility.

Previously cryopreserved and thawed PBMCs will be challenged or restimulated with specific tumor vaccine antigens as follows:

- PBMCs+PMA+Ionomycin (positive control).
- PBMCs+HS-110 whole cell lysates
- PBMCs+an overlapping cocktail of known shared antigens, which may include Survivin, TTK, NY-ESO-1, CEP55, MAGEA1, MAGEA3, MAGEA6, MAGEA12, MAGEB1, MAGEC1, MAGEC2, CXORF61, GAGE1, BAGE1, CTCFL, DDX43, SSX1, SSX4, and HORMAD 1.

For the ELISPOT assay, the frozen PBMCs will be thawed, antigen challenged, and plated for analysis of IFNγ and GzB production by two color enzymatic ELISPOT assay and analyzed in duplicate per time point for each patient. Following incubation, samples will be quantitated in an automated ELISPOT reader.

The frequency of IFNγ producing PBMC is thought to mirror the frequency of cytotoxic CD8+ cells; however, cytotoxicity is primarily mediated by perforin and granzymes following granule exocytosis. In some instances, IFNγ secretion and granule exocytosis are uncoupled. Therefore, the direct measurement of gzB secretion by ELISPOT may provide a more direct readout for

antigen-specific granule exocytosis and cytotoxicity. Antigen specificity of the ELISPOT response will be evaluated by comparing responses generated using the various stimulator cell populations and specific NSCLC shared antigens as indicated. This will also enable separation of the 'allo-antigen' specific response with the potential parent cell line tumor antigen-specific response. Positive responses will be defined as a greater than two-fold increase in the number of IFNγ-positive PBMC compared to baseline.

14.4. Phenotyping Phenotypic Analysis of Blood Lymphocyte Subsets by FACS

Flow cytometric analysis of patient peripheral blood samples will quantitatively determine the frequency and number of lymphocytes (CD45+), B-cells (CD45+,CD3-,CD19+), helper T-cells (CD45+,CD3+,CD4+), T-cells (CD45+,CD3+,CD8+), regulatory T-cells (CD3+, CD4+, CD25+, FoxP3+), and NK cells (CD45+, CD56+, CD3-) at baseline and over the course of therapy. In addition, a NK/T-cell activation panel (Ki67, CD137, CD27, CD28), memory panel (CD27, Cd28, CD45 RA, CD197, CD57) and exhaustion panel (CTLA4, PD-1, Tim3, TIGIT) will be performed.

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

Post-treatment biopsies will be collected at week 10, when feasible, and the tissue will be examined for the presence of TILs. Multicolor fluorescence immunohistochemistry (IHC) will be used for quantification of infiltrating CD3+, CD4+ and FOXP3+ T-cells and measurement of their activation status, Ki67 and PD-1 expression, and cytotoxic activity (gzB expression) *in situ.* These data will be correlated with clinical response.

14.6. Tumor Mutation Burden Analysis

Tumor Mutation Burden (TMB) is the number of coding somatic base substitution and indel mutations occurring in a tumor specimen, per megabase (Mb) of coding genome assessed. Approximately 20 mLs of whole blood will be collected using cell free DNA collection tubes at the Week 1 visit prior to dosing. Samples will be shipped to, and analyzed by, Foundation Medicine using their FoundationACT® circulating tumor DNA (ctDNA) assay. Note that Cohort B patients enrolled prior to Amendment 5 that did not have a week 1 TMB sample collected should have this one-time lab drawn at the next feasible visit (i.e. Week 4, 10, 16 or post-HS110/survival follow-up).

15. SAFETY MONITORING

15.1. Adverse and Serious Adverse Events

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

The Investigator is responsible for the detection and documentation of events meeting the criteria and definition of an AE or SAE, as provided in this protocol. During the study when there is a safety evaluation, the Investigator or site staff will be responsible for detecting, documenting, and reporting AEs and SAEs.

15.1.1. **Adverse Event (AE)**

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

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

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

15.1.2. **Serious Adverse Event (SAE)**

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

- Results in death (i.e., the AE actually causes or leads to death).
- Is life-threatening (with regards to determining if an AE is serious, "life-threatening" is defined as an AE for which the patient was at risk of death at the time of the event. It does not refer to an event which hypothetically might have caused death if it were more severe. If either the investigator or the Sponsor believes that an AE meets the definition of life-threatening, it will be considered life-threatening).
- Requires inpatient hospitalization or prolongation of existing hospitalization.

- Results in persistent or significant incapacity or substantial disruption of the ability to conduct normal life functions.
- Results in a congenital anomaly/birth defect.
- Results in any "other" important medical event. Medical or scientific judgment should be exercised in deciding whether reporting is appropriate in other situations, such as important medical events that may not be immediately life-threatening or result in death or hospitalization but may jeopardize the patient or may require medical or surgical intervention to prevent one of the other outcomes listed in the above definition. Examples of such events are intensive treatment in an emergency room or at home for allergic bronchospasm, blood dyscrasias, or convulsions that do not result in hospitalization, or development of drug dependency or drug abuse.

15.1.3. Disease-Related Events or Outcomes not Qualifying as SAEs

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

15.1.4. Clinical Laboratory Abnormalities and Other Abnormal Assessments as AEs and SAEs

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

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

15.2. Relationship to Study Drug

The Investigator, or other qualified physician designee, will assess the possible relationship between the AE/SAE and any of the study medications, as well as any concomitant medications according to the following criteria:

- Related: AE and administration of one or more study products are related in time, and AE is explained by one or more study products.
- Not related: AE is explained by another cause not related to any study product.

Event outcome will be recorded using the following categories:

- Recovered/resolved.
- Not recovered/not resolved.
- Recovered/resolved with sequelae.
- Fatal.
- Unknown.

15.3. Reporting Adverse Events

The Investigator will record all directly observed AEs and all AEs spontaneously reported by the study patient. In addition, each study patient will be questioned about any AEs they have experienced during each study visit.

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

15.4. Prompt Reporting of SAEs

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

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

- In addition to the above information, the Medical Monitor will require the Investigator's assessment of the following:
  - Severity of the AE.
  - Relationship of the AE to study treatment.
  - Outcome of the AE.

Any oral report of SAEs must be followed within 48 hours by a detailed, written report signed by the Investigator. Any necessary follow-up must be submitted as soon as reasonably possible. The Sponsor will promptly report SAEs related to HS-110 or additional study drug to the FDA and other applicable regulatory agencies in accordance with 21 CFR 312.32 and local regulatory requirements. The Investigator should also comply with any applicable requirements related to the reporting of SAEs to the IRB/EC.

The Medical Monitor will review each SAE report and evaluate the relationship of the SAE to study treatment and to underlying disease. Based on the Investigator's and Medical Monitor's (Sponsor's) assessment of the SAE, a decision will be made concerning the need for further action. The primary consideration governing further action is whether new findings affect the safety of patients participating in the clinical study. If the discovery of a new SAE related to HS-110 and/or additional study drug raises concern over the safety of continued administration of study drug to patients, the Sponsor will take immediate steps to notify the FDA and all Investigators participating in clinical studies of HS-110.

Further action that may be required includes the following:

- Modification of the protocol.
- Discontinuation or suspension of the study.
- Modification of the existing consent form and informing current study participants of new findings.
- Addition of any newly identified HS-110 related AEs to the list of expected AEs to the Investigator's Brochure.

15.5. Study Review Committee and Data Monitoring Committee

In the phase 1b portion of the study, a Study Review Committee provided ongoing safety evaluations and recommendation for advancement into phase 2. Moving forward, a fully constituted and independent Data Monitoring Committee (DMC) will review ongoing safety and efficacy of phase 2 patients. A full description of the membership, roles, and responsibilities of the DMC will be outlined in a separate charter.

Ad-hoc meetings will also occur if the Sponsor, Medical Monitor, or Investigator believes a safety issue has arisen during the course of the trial that may warrant further review or trial alteration.

16. STATISTICS

16.1. General Statistical Considerations

Patients will be analyzed according to the following cohorts for Arm 5:

- Cohort A, composed of all CPI naïve patients (n=40, including 15 phase 1b patients).
- Cohort B, composed of all CPI progressor patients (n=60). Note that this cohort will be permitted to over-enroll.

Patients will be analyzed according the following cohorts for Arm 6. Distribution will not be controlled within the two cohorts (n=up to 20 based on patient availability):

- Cohort C, composed of all patients receiving maintenance pembrolizumab
- Cohort D, composed of all patients receiving maintenance pembrolizumab + pemetrexed

Each cohort (A, B, C and D) will be analyzed including patients of all histology types, and then again including only adenocarcinoma patients.

Analyses will be performed within each of the cohorts to identify differences in strata for each of the following factors if sufficient data exists:

- Histology: adenocarcinoma and squamous cell carcinoma
- PD-L1 status: negative (<1%) and positive (≥1%) based on tumor cell expression
- TIL status: high (> 10%) and low (≤ 10%)
- Tumor Mutation Burden: high (10 or more mutations) and low (less than 10 mutations)

Additional factors, such as line of treatment or presence of injection site reactions, may be added to statistical models used for analyses; the method of pooling and testing for interaction among the different factors will be described in detail in the SAP.

The intent of this clinical investigation is to establish the ORR and quantify the duration of PFS across the various subsets in NSCLC patients who receive HS-110.

Categorical variables will be summarized by frequency distributions (number and percentage of patients), while continuous variables will be summarized by descriptive statistics (mean, standard deviation, median, minimum and maximum). All binary clinical endpoints such as immune response, DCR and ORR will be presented as point estimates with 95% CI for each cohort. Time-to-event endpoints (PFS, OS) will be calculated using Kaplan-Meier methodology.

TEAEs will be summarized in an overall summary of treatment-emergent adverse events (TEAEs), as well as tables summarized all TEAEs (by SOC and PT), TEAEs related to HS-110, TEAEs related to the combination therapy (nivolumab, pembrolizumab, or pembrolizumab/pemetrexed, serious TEAEs, serious TEAEs related to the combination therapy, and grade 3+ TEAEs. Listings of all TEAEs, serious TEAEs, and TEAEs leading to discontinuation will also be presented.

16.2. Sample Size

Within Arm 5, Cohorts A and B are planned to enroll 40 and 60 patients, respectively. Note that Cohort B will be permitted to over-enroll based on patient availability. The phase 1b patients

(n=15) will be included in the sample size for Cohort A. The distribution of patients, relative to enrollment, will not be controlled within Arm 6 (Cohorts C and D) but is planned to be up to 20 total based on patient availability. Response will be summarized for various combinations of factors in an exploratory manner. With a total enrollment into this clinical investigation of up to 120 patients, this study should provide sufficient precision to provide a characterization of the likely efficacy subsets to be used in a larger study.

16.3. Analysis Populations

Study populations are defined as follows:

Safety Population: defined as all patients who receive at least 1 dose of HS-110.

Per-Protocol (PP): defined as all patients who have received at least 6 weekly doses of HS-110 in combination with either nivolumab (given with every other HS-110 dose) or pembrolizumab (given with every third HS-110 dose during priming), and who have a pre-treatment tumor assessment and at least one post-treatment tumor assessment.

Adenocarcinoma Population: defined as all patients in the PP who had adenocarcinoma histology.

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

16.4. Disposition, Demographics, and Baseline Characteristics

Disposition information will be summarized, including the numbers of dosed patients, and patients withdrawn by reason, as well as the reason for discontinuation from treatment.

Descriptive information on demographics and baseline characteristics, including age, sex, weight, height, physical examination, and baseline ECOG score will be provided in a summary table. Summaries will be provided by treatment group and overall for the Safety and Per Protocol populations.

16.5. Primary Efficacy Endpoint and Analysis

Safety/tolerability is the primary endpoint for the phase 1b portion of this study. For the phase 2 portion of this study, the primary endpoint for Arm 5 cohorts is ORR and the primary endpoint for Arm 6 cohorts is PFS.

16.5.1. **Phase 1b: Safety and Tolerability**

Safety will be measured by the frequency of treatment emergent adverse events (TEAEs)/serious adverse events (SAEs), including clinically significant (CS) abnormal laboratory parameters, ECGs, PEs, and vitals in patients receiving at least one dose of HS-110.

16.5.2. **Phase 2: Objective Response Rate (Arm 5 Cohorts A/B) and Progression Free Survival (Arm 6 Cohorts C/D)**

For Arm 5 Cohorts A and B, ORR will be defined as the proportion of patients achieving a best overall response of complete response (CR) or partial response (PR) by RECIST 1.1. These response rates will be summarized for each cohort using counts and percentages. 95% exact confidence intervals will also be presented.

For Arm 6 Cohorts C and D, PFS will be calculated as the time between first dose of HS-110 and the date of PD, as defined by RECIST 1.1 or death, whichever occurs first. For patients with no recorded post-baseline tumor assessments, PFS will be censored at day 1. For those who remain alive and have no PD, PFS will be censored on the date of last evaluable tumor assessment. Kaplan-Meier curves will be produced separately for each Cohort in Arms 5 and 6. Analysis details are provided in the SAP.

These analyses will be conducted on the ITT population. A secondary examination of response will be performed using the Per Protocol population and the Adenocarcinoma population.

16.6. Secondary Efficacy Endpoints and Analyses

16.6.1. Objective Response Rate

Defined as the proportion of patients achieving a best overall response of complete response (CR) or partial response (PR) by RECIST 1.1.These response rates will be summarized for each cohort using counts and percentages. 95% exact confidence intervals will also be presented. A second, exploratory measure of ORR, iORR, will be calculated using the principles of iRECIST. For Arm 6, the rate of improvement in RECIST 1.1 response from SD to CR/PR will also be presented.

This analysis will be conducted on the Safety population. A secondary examination of response will be performed using the Per Protocol population and the Adenocarcinoma population.

16.6.2. Overall Survival

OS will be calculated as the duration of survival from the date of first HS-110 dosing into the study to the date of death from any cause or will be censored on the date the patient was last known to be alive.

16.6.3. Progression-Free Survival

PFS will be calculated as the time between the date of first dose of HS-110 and the date of PD, as defined by RECIST 1.1 or death, whichever occurs first. A second, exploratory measure of PFS, iPFS, will be calculated as the time between the date of first dose of HS-110 and the date of iCPD as defined by iRECIST or death, whichever occurs first. For patients with no recorded post-baseline tumor assessments, PFS/iPFS will be censored at the day of first dose. For those who remain alive and have no PD, PFS/iPFS will be censored on the date of last evaluable tumor assessment. Kaplan-Meier curves will be produced separately for each Cohort in Arms 5 and 6. Analysis details are provided in the SAP.

16.6.4. Duration of Response

DOR will be calculated from the time of first confirmed response (CR or PR) until radiographic PD by RECIST 1.1. A second, exploratory DOR measure, iDOR, will be calculated as the time of first confirmed response (iCR or iPR) until iCPD as defined by iRECIST.

16.6.5. Disease Control Rate

DCR is defined as the proportion of patients whose best overall response is PR, CR, or SD, as defined by RECIST 1.1. A second, exploratory DCR rate, iDCR, is defined as the proportion of patients whose best overall response is iPR, iCR, or iSD, as defined by iRECIST.

16.6.6. 6-month Durable Response Rate

6 mo DRR is defined as the percentage of responders with durable responses lasting at least 6 months from time of initial response by RECIST 1.1. A second, exploratory DRR measure, 6 mo iDRR, is defined as the percentage of responders with durable responses lasting at least 6 months from the time of initial response by iRECIST.

16.6.7. 12-month Durable Response Rate

12 mo DRR is defined as the percentage of responders with durable responses lasting at least 12 months from the time of initial response by RECIST 1.1. A second, exploratory DRR measure, 12 mo iDRR, is defined as the percentage of responders with durable responses lasting at least 12 months from the time of initial response by iRECIST.

16.6.8. 6-month Overall Survival

6m OS will be calculated as the proportion of patients who are alive at 6 months following the date of first dose of HS-110 and will be presented as a median with exact 95% CI.

16.6.9. 12-month Overall Survival

12m OS will be calculated as the proportion of patients who are alive at 12 months following the date of first dose of HS-110 and will be presented as a median with exact 95% CI.

16.6.10. 6-month Progression Free Survival

6m PFS will be calculated as the proportion of patients who have not progressed at 6 months following the date of first dose of HS-110 and will be presented as a median with exact 95% CI.

16.6.11. 12-month Progression Free Survival

12m PFS will be calculated as the proportion of patients who have not progressed at 12 months following the date of first dose of HS-110 and will be presented as a median with exact 95% CI.

16.6.12. Safety and Tolerability

Safety will be measured as the frequency of TEAEs/SAEs, including CS abnormal laboratory parameters, ECGs, PEs, and vitals in patients receiving at least one dose of HS-110.

16.7. Exploratory Endpoints and Analyses

The following endpoints will be evaluated:

- As outlined in section 16.6, efficacy parameters of ORR, PFS, DOR, DCR, and DRR will be analyzed using the principals of iRECIST to produce iORR, iPFS, iDOR, iDCR, and iDRR.
- Peripheral blood IR will be measured by ELISPOT to detect an increase of 2-fold over baseline of IFNγ and/or granzyme B (gzB) positive T cells, as well as analysis of surface markers that define NK and T cell subsets of activation, memory and exhaustion by flow cytometry.

- Evaluation of tumor tissue obtained for presence of TILs (%) and correlation of pre- and post-treatment TIL levels with clinical outcomes.
- Evaluation of tumor tissue obtained for percent expression of PD-L1 on tumor cells and correlation of pre- and post-treatment PD-L1 expression with clinical outcomes.
- Evaluation of peripheral blood TMB to measure the number of mutations within the tumor genome and correlation of TMB levels with clinical outcomes.

Other exploratory analyses of peripheral blood and tumor tissue to determine immune changes and response to treatment may be conducted as new technology emerges.

Exploratory endpoints will be summarized descriptively at each scheduled sampling time point. Appropriate transformations may be undertaken in cases were the data are not Normally distributed.

16.8. Safety Analyses

The analyses will be completed for the Safety population.

16.8.1. **Adverse Events**

Treatment emergent AEs are AE which occur on or after the first dose of study medication. The Medical Dictionary for Regulatory Activities (MedDRA) will be used for the coding of AEs. TEAEs, serious or CTCAE Grade 3 or 4 TEAEs, and TEAEs related to HS-100 will be summarized overall and by system organ class and preferred term by treatment group. These will summarize the number of events and the number and percent of patients with a given event. In addition, the number and percent of patients with TEAEs will be tabulated by maximum severity. A summary of all TEAEs by system organ class and preferred term occurring in at least 5% of patients in each Arm will be tabulated.

16.8.2. **Laboratory Assessments**

All laboratory-based data will be presented as listings of all values as well as abnormal results judged to be clinically significant, which will also be reported as AEs. Numeric summaries of all observed and change from baseline laboratory evaluations will be provided (e.g., by visit and treatment arm), including chemistry, hematology, and Troponin I or Troponin T results.

16.8.3. **Vital Signs**

Numeric summaries of all observed and change from baseline vital signs will be provided by time point and treatment group, including blood pressure, heart rate, respiratory rate, and temperature.

16.8.4. **ECGs**

Numeric summaries of all observed and change from baseline in ECG parameters will be provided by time point and treatment arm, including heartrate, QRS duration (msec), QT interval (msec), QTcF interval (msec), and PR interval (msec) and the overall assessment of normal, abnormal, not clinically significant, and abnormal, clinically significant.

16.8.5. **Other Assessments**

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

17. DESCRIPTION OF ETHICAL CONSIDERATIONS RELATED TO THE TRIAL.

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

The study will also be conducted in accordance with 21 CFR parts 50, 54, 56, and 312, ICH GCP, all local, regional and federal regulatory requirements, all applicable patient privacy requirements, and the guiding principles of the Declaration of Helsinki. This includes, but is not limited to, the following:

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

A copy of the site-specific proposed ICF should be submitted to the Sponsor for review and comment before submission to the IRB/EC. The study should not begin until the ICF has been reviewed and approved by the Sponsor and until the document has been approved by the IRB/EC of record. The ICF shall contain all the elements of informed consent specified in the above regulations and guidance. Written informed consent will be obtained for each patient before he or she can participate in the study.

18. DIRECT ACCESS TO SOURCE DATA/DOCUMENTS

18.1. Study Monitoring

In accordance with applicable regulations and GCP, the Sponsor will perform quality control and assurance checks. Before enrolling any patient into this study, the Sponsor (or designees) will review the protocol, the IB, draft CRFs and instructions for their completion, and significant protocol sections (i.e. reporting AEs and SAEs) with the Investigator. A qualified designee of the Sponsor will monitor the conduct of the study at reasonable intervals by visiting the site and/or by contacting the site by telephone and e-mail.

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

The Sponsor will monitor the study consistent with the demands of the study and site activity to ensure that the:

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

18.2. Protocol Deviations

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

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

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

19. QUALITY CONTROL AND QUALITY ASSURANCE

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

20. DATA HANDLING AND RECORDKEEPING

20.1. Retention of Records

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

These records should be retained for not less than 2 years after the last approval of a marketing application in an ICH region and until there are no pending or contemplated marketing applications in an ICH region or at least 2 years have elapsed since the formal discontinuation of clinical development of the investigational product. These documents should be retained for a longer period; however, if required by applicable regulatory requirements or by an agreement with the Sponsor. Thereafter, records will not be destroyed without giving the Sponsor prior written notice and the opportunity to further store such records.

The Investigator must notify Sponsor of any changes in the archival arrangements, including, but not limited to, the following: archive at an off-site facility, change in office and archive location, transfer of ownership of the records in the event the Investigator leaves the site.

20.2. Provision of Study Results and Information to Investigators

When required by applicable regulations, the Investigator signatory for the clinical study report (CSR) will be determined at the time the report is written. When the CSR is completed, Sponsor will provide the Investigator with a summary of the study results.

20.3. Data Management

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

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

20.4. Study and Site Closure

Upon completion or premature discontinuation of the study, the Sponsor (or designee(s) will conduct site closure activities with the Investigator or site staff, as appropriate, in accordance with applicable regulations, GCP, and Sponsor procedures.

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

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

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APPENDIX 1: ECOG PERFORMANCE STATUS SCALE

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

Credit: The Eastern Cooperative Oncology Group, Robert Comis, MD, Group Chair

APPENDIX 2: GRADING SCALE FOR INJECTION SITE REACTIONS

Local Reaction to Injectable Product	Grade 1 Mild	Grade 2 Moderate	Grade 3 Severe	Grade 4 Potentially Life Threatening
Pain	Does not interfere with activity	Repeated use of non-narcotic pain reliever >24 hours or interferes with activity	Any use of narcotic pain reliever or prevents daily activity	Emergency room visit or hospitalization
Tenderness	Mild discomfort to touch	Discomfort with movement	Significant discomfort at rest	Emergency room visit or hospitalization
Erythema/Redness	0.5-5 cm	5.1-10 cm	>10 cm	Necrosis or exfoliative dermatitis
Induration/Swelling*	0.5-5 cm and does not interfere with activity	5.1-10 cm or interferes with activity	>10 cm or prevents daily activity	Necrosis

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

APPENDIX 3: THE RESPONSE EVALUATION CRITERIA IN SOLID TUMORS (RECIST 1.1) GUIDELINES AND GUIDLELINES FOR RESPONSE CRITERIA FOR USE IN TRIALS TESTING IMMUNOTHERAPEUTICS (IRECIST)

RECIST 1.1

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

Evaluation of target lesions:

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

Evaluation of non-target lesions:

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

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

Target Lesions	Non-target Lesions	New Lesions	Overall Response
CR	CR	No	CR
CR	Non-CR/Non-PD	No	PR
CR	NE	No	PR

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

CR=Complete Response, PR=Partial Response, SD=Stable Disease, PD=Progressive Disease, NE=Not Evaluable

When target lesions show SD/PR and some subset of non-target lesions are considered not evaluable, a careful decision must be made whether to call the overall response at this time point SD/PR or NE. This is based on whether the lesions that are not evaluable, if they showed growth, could cause an overall response of PD in the context of the other lesion responses seen. If the non-target lesions that are not evaluable comprise a significant proportion of the overall disease burden, the appropriate time point response is NE.

** Please refer to the complete New response evaluation criteria in solid tumours: Revised RECIST guidelines – version 1.1 for further details*[23].

iRECIST

The guidelines continue to recommend use of RECIST 1.1 to define whether tumor lesions are measurable or non-measurable and the principles used to determine objective tumor response are largely unchanged from RECIST 1.1. The concept change for iRECIST is the resetting the bar if RECIST 1.1 progression is followed at the next assessment by tumor shrinkage.

iRECIST defines unconfirmed progress (iUPD) on the basis of RECIST 1.1 principles; however, iUPD requires confirmation on repeat imaging no less than 4 weeks later, which is done on the basis of observing either a further increase in size (or in the number of new lesions) in the lesion category in which progression was first identified in (i.e., target or non-target disease), or progression (defined by RECIST 1.1) in lesion categories that had not previously met RECIST 1.1 progression criteria. However, if progression is not confirmed, but instead tumor shrinkage occurs (compared with baseline), which meets the criteria of iCR, iPR, or iSD, then the bar is reset so that iUPD needs to occur again (compared with nadir values) and then be confirmed (by further growth) at the next assessment for iCPD to be assigned. If no change in tumor size or extent from iUPD occurs, then the time point response would again be iUPD. This approach allows atypical responses, such as delayed responses that occur after pseudoprogression, to be identified, further understood, and better characterized.

However, many aspects of new lesion assessment are unique to iRECIST. If a new lesion is identified (thus meeting the criteria for iUPD) and the patient is clinically stable, treatment should be continued. New lesions should be assessed and categorized as measurable or non-measurable using RECIST 1.1 principles.

The algorithm for patients with no previous iUPD is identical to RECIST 1.1. For patients with iUPD at the last time point response, the next time point response is dependent on the status of all lesions, including target, non-target, new lesion target, and new lesion non-target; on whether any increase in size has occurred (either a further increase in size or a sufficient increase to assign a new iUPD if the criteria were not previously met); or the appearance of additional new lesions.

Assignment of time point response using iRECIST

	Time point response with no previous iUPD in any category	**Time point response with previous iUPD in any category ***
Target lesions: iCR; non-target lesions: iCR; new lesions: no	iCR	iCR
Target lesions: iCR; non-target lesions: non-iCR/non-iUPD; new lesions: no	iPR	iPR
Target lesions: iPR; non-target lesions: non-iCR/non-iUPD; new lesions: no	iPR	iPR
Target lesions: iSD; non-target lesions: non-iCR/non-iUPD; new lesions: no	iSD	iSD
Target lesions: iUPD with no change, or with a decrease from last time point; non-target lesions: iUPD with no change, or decrease from last time point; new lesions: yes	Not Applicable	New lesions confirm iCPD if new lesions were previously identified and they have increased in size (≥5 mm in sum of measures for new lesion target or any increase for new lesion non-target) or number; if no change is seen in new lesions (size or number) from last time point, assignment remains iUPD
Target lesions: iSD, iPR, iCR; non-target lesions: iUPD; new lesions: no	iUPD	Remains iUPD unless iCPD is confirmed on the basis of a further increase in the size of non-target disease (does not need to meet RECIST 1.1 criteria for unequivocal progression)
Target lesions: iUPD; non-target lesions: non-iCR/non-iUPD, or iCR; new lesions: no	iUPD	Remains iUPD unless iCPD is confirmed on the basis of a further increase in sum of measures ≥5 mm; otherwise, assignment remains iUPD
Target lesions: iUPD; non-target lesions: iUPD; new lesions: no	iUPD	Remains iUPD unless iCPD is confirmed based on a further increase in previously identified target lesion iUPD in sum of measures ≥5 mm or non-target lesion iUPD (previous assessment need not have shown unequivocal progression)
Target lesions: iUPD; non-target lesions: iUPD; new lesions: yes	iUPD	Remains iUPD unless iCPD is confirmed on the basis of a further increase in previously identified target lesion iUPD sum of measures ≥5 mm, previously identified non-target lesion iUPD (does not need to be

	Time point response with no previous iUPD in any category	**Time point response with previous iUPD in any category ***
		unequivocal), or an increase in the size or number of new lesions previously identified
Target lesions: non-iUPD or progression; non-target lesions: non-iUPD or progression; new lesions: yes	iUPD	Remains iUPD unless iCPD is confirmed on the basis of an increase in the size or number of new lesions previously identified
Target lesions, non-target lesions, and new lesions defined according to RECIST 1.1 principles; if no pseudoprogression occurs, RECIST 1.1 and iRECIST categories for complete response, partial response, and stable disease would be the same. *Previously identified in assessment immediately before this time point. "i" indicates immune responses assigned using iRECIST. iCR=complete response. iPR=partial response. iSD=stable disease. iUPD=unconfirmed progression. non-iCR/non-iUPD=criteria for neither CR nor PD have been met. iCPD=confirmed progression. RECIST=Response Evaluation Criteria in Solid Tumors.		

Please refer to the complete Guidelines for iRECIST[24].

APPENDIX 4: AMENDMENT JUSTIFICATION AND CHANGE LOG

Amendment 6 Justification

Amendment 6 is designed to provide clarification and improve ease of operationalization of Amendment 5 across multiple sites with differing practices of front-line patient management. In general, the timing to initiate additive HS-110 to front line maintenance will be restricted by weeks and/or cycles rather than be tethered to the timing of imaging scans. Amendment 6 also clarifies that the primary endpoint of PFS added in Amendment 5 only applies to the newly added Arm 6 cohorts in front-line maintenance; original Arm 5 patients (Cohorts A & B) will retain the same primary endpoint (ORR) which has been in place since the inception of the trial. Additionally, Amendment 6 modifies the allocation of patients to Cohorts B, C, and D due to operational considerations but does not affect the total sample size for the trial. Lastly, Amendment 6 offers clarification around frequently asked questions with regard to eligibility criteria, allows for retro-active collection of TMB samples for Cohort B patients enrolled prior to Amendment 5, as well as modifies the Arm 6 PE schedule to better align with physician visits.

Amendment 5 Justification:

Amendment 5 expands the patient population to include patients receiving front line pembrolizumab ± pemetrexed, as well as relaxes the eligibility criteria for CPI Progressors. Per Investigator feedback, the minimum CPI treatment duration requirement for Arm 5 CPI progressor patients is lowered from 6 months to 4 months. Additionally, the term CPI relapsed is being corrected to CPI progressor, which is more clinically relevant.

To enhance compliance with protocol procedures, the Week 10 tumor biopsy may be waived with written authorization from the Sponsor.

To further characterize the patient population, Tumor Mutation Burden (TMB) testing will be performed for exploratory analysis. TMB is a biomarker which has been associated with response to immunotherapy in multiple disease types. TMB measures the number of mutations within a tumor genome, and tumors which harbor more mutations have been shown to have a greater likelihood of response to immunotherapy.

Amendment 4 Justification:

Amendment 4 corrects the study design by taking the current 4-arm trial and combining the 3 TIL classified arms into one treatment arm receiving HS-110 and nivolumab. This design contains treatment arm cohorts based on previous immune checkpoint inhibitor exposure. The TIL status and response to treatment will still be analyzed as an exploratory endpoint and the statistical plan was amended to support the change in trial design. This amendment also broadens the histological type of NSCLC to include squamous cell in addition to adenocarcinoma. While the AD-100 line selected for HS-110 was derived from adenocarcinoma, an evaluation of upregulated gene expression between NSCLC adenocarcinoma and squamous cell carcinoma have multiple shared antigens between HS-110 and squamous cell carcinoma, thus supporting the rationale for inclusion of squamous cell carcinoma patients in this clinical trial. In addition, the long-term follow-up scans were defined to every 8 weeks and iRECIST evaluation criteria was added. Visit windows were expanded to allow for weekends and holidays, and the text throughout has been streamlined and rearranged for compliance with the ICH E6 guidelines and NIH-FDA protocol template.

Amendment 3 Justification:

Amendment 3 addresses the exclusion criteria and safety monitoring secondary to the recent publication of myocarditis with combination immunotherapy treatment.[25] It also realigns the physical exam schedule for consistency with nivolumab dosing days.

Amendment 2 Justification:

Amendment 2 changes address the issue of biopsies that are not evaluable in the ongoing cohorts. Recent experience suggests 25-40% of biopsies will not be evaluable. Patients without an evaluable pre-treatment biopsy are currently being balanced between the two arms in a "next man up" fashion without knowing their TIL status. Arm 4 will allow these patients to continue to receive while maintaining the appropriate sample size of Arms 2 and 3. This Arm also acts as an overflow for patients who consent to study participation and meet the eligibility criteria for a cohort that is filled. Finally, Amendment 2 will allow prospective revision of the expansion cohort selection criteria based on emerging response data from the trial.

Amendment 1 Justification:

In the period since the HS110-102 protocol was initiated, the treatment paradigm for this population has undergone a substantial change with the approval of checkpoint inhibitors for treatment of NSCLC. The main change in Amendment 1 is in response to that changing landscape: addition of study arms to assess the combination of viagenpumatucel with nivolumab (administered per current, approved labeling). Because nivolumab is an approved therapy for this indication and theophylline is not, the option for combination with theophylline is being discontinued (no patients were enrolled in the theophylline arm of the study.) Amendment 1 also introduces mandatory biopsies for the study arms prescribing the 2-drug combination of viagenpumatucel with nivolumab; this requirement is implemented to define the characteristics of the enrolled population and to allow comparison to emerging literature on patients who typically respond to checkpoint inhibitors (see Section 2.3 for more information). Finally, Amendment 1 allows for expansion (of up to 30 patients) for any combination treatments that show efficacy signals.

DURGA Amendment Change Log

Protocol Change	Affected Section(s) Numbers	Section Titles
Amendment 2		
Updated protocol template; moved information to a new template; moved sections to fit content of new template	All Sections	
Closed oxygen + HS-110 arm	6.1	Overall Study Design
Converted expansion cohorts to official Phase 2 study	6.1 6.3 and 14	Overall Study Design, Treatment Assignment, and Statistics
Updated background information. Excluded discussion of hypoxia and adenosine pathway	3	Synopsis

Protocol Change	Affected Section(s) Numbers	Section Titles
Removed oxygen as a combination drug; removed oxygen-related assessments	4.1,4.2.2, 5.3, 6, 8.2, 9.4, 10.2, 10.4, 11.3, 12.8, and 14.8	Study Specific Rationale, Oxygen (former), Exploratory Objectives, Investigational Plan, Subject Exclusion Criteria; Dose Modifications (former); Oxygen (former), Study Drug Storage, ABG Panel (former), Antigen Screening of Baseline or Archival Tumor Biopsy (former), Exploratory Endpoints (former) and Analyses (former)
Updated schedule of assessments to reflect removal of oxygen endpoints and change in frequency of CT/MRI scans	7	Study Procedures
Added Cohort C for patients who cannot be entered into Cohort A or B	6.1	Overall Study Design
Added rationale for Cohort C	4.4	Rationale for Arm 4
Added the possibility of using archival tissue for the pre-treatment biopsy	6.1 and8.1	Overall Study Design and Subject Inclusion Criteria
Added TCR repertoire characterization by sequencing as an exploratory endpoint	5.3, 6.1, 12.1.2, and 14.7	Exploratory Objectives, Overall Study Design, Characterization of TCR Repertoire, and Exploratory Endpoints and Analyses
Added correlation of pre- and post-treatment TIL levels with clinical outcomes to exploratory objectives	5.3, 6.1, and 14.7	Exploratory Objectives, Overall Study Design, and Exploratory Endpoints and Analyses
Removed references to irRC for tumor assessments	12.1, 12.2, 14.7.2, and Appendix 2 (former)	Tumor Assessments, Immune Criteria for Tumor Assessment (former), and Progression Free Survival (former),
Added references for RECIST 1.1 for tumor assessments	12.1, 12.1.1, 14.6.5, 14.7, and Appendix 3	Tumor Assessments; RECIST 1.1 for Tumor Assessment; Progression-Free Survival, and Exploratory Endpoints
Updated amendment change log	Appendix 4	
Revised language to allow prospective revision of the expansion cohort selection criteria	6.3	Treatment Assignment
Updated study drug information	9.1 and 10.1	Description of Study Drug and HS-110 (HS-110)

Protocol Change	Affected Section(s) Numbers	Section Titles
Updated information for study drug storage	10.2	Study Drug Storage
Added objective response rate as the primary endpoint for Phase 2	5.1 and 14.5.2	Primary Objective and Phase 2: Objective Response Rate
Updated statistical considerations relative to planned analyses	14	Statistics
Periodic editorial changes, including, updating Synopsis	Multiple sections	Throughout document
Amendment 3		
Revised cardiac exclusion criteria secondary to recent publications of myocarditis with combination immunotherapy treatment	8.2	Subject Exclusion Criteria
Added cardiac safety monitoring secondary to recent publications of myocarditis with combination immunotherapy treatment	7.2, 7.4, and 11.5	On-study Procedures, Schedule of Assessments, and Cardiac Monitoring
Revised Physical Exam schedule to be consistent with nivolumab dosing days.	7.2, 7.4, and 11.1	On-study Procedures, Schedule of Assessments, and Physical Examination
Amendment 4		
Corrected study design with the correct use of 'treatment arms' by combining the previous TIL-defined treatment arms (#2, 3, and 4) into one single treatment arm of nivolumab plus HS-110 (arm #5), and correlating TIL status to clinical outcomes by statistical analysis.	6 and 14	Investigational Plan and Statistics
Modified the eligibility criteria by removing exclusion criteria #12 which prohibited the entry of patients who received prior treatment with immune checkpoint inhibitors, and replacing with criteria to exclude patients who are refractory to checkpoint inhibitors.	8.2	Subject Exclusion Criteria
Modified the eligibility criteria by amending inclusion criteria #1 to allow squamous cell histology in addition to adenocarcinoma.	8.1	Subject Inclusion Criteria
Corrected study design by removing references to 'cycles'.	Multiple Sections	Throughout document

Protocol Change	Affected Section(s) Numbers	Section Titles
Updated cardiac monitoring testing to allow Troponin T in lieu of Troponin I as per facility standard of care.	7.2, 7.4, and 11.5	On-study Procedures, Schedule of Assessments, and Cardiac Monitoring
Updated the frequency of follow-up assessments and post-HS-110 radiological scans to every 8 weeks rather than every 9 to 12 weeks.	Multiple sections including 7.2 and 7.4	On-study Procedures and Schedule of Assessments
Clarified the difference in follow up between 'post-HS-110' as off-treatment follow up, and 'post-nivolumab' as survival follow up.	Multiple sections including 7.2 and 7.4	On-study Procedures and Schedule of Assessments
Updated study endpoints to include Duration of Response and updated statistical plan based on amended study design.	5, 14, and 16	Trial Objectives and Purpose and Statistics
iRECIST analysis criteria added.	Multiple sections and Appendix 3	Throughout the document iRECIST was added in addition to RECIST 1.1 evaluations. Defined criteria for RECIST and iRECIST were added to Appendix 3.
Streamlining of text throughout document for clarity and adding/re-arranging text for compliance with ICH E6 guideline and NIH-FDA protocol template.	Multiple sections	Throughout the document
Expansion of visit windows, including EOT, to allow for weekends and holidays. Added text/assessments to ensure completeness and consistency between SOA and other sections of protocol.	10 and Table 2	Study Procedures and Schedule of Activities
Removal of option to conduct study visits at home with qualified home health personnel.	10 and 12.1	Study Procedures and HS-110
Removal of intradermal testing.	10 and Table 2	Study Procedures and Schedule of Activities
Removal of immune response lab draw at Week 4 and replacement at Week 1 prior to dosing.	10 and Table 2	Study Procedures and Schedule of Activities
Removal of pregnancy test at EOT visit and replacement at Baseline visit.	10 and Table 2	Study Procedures and Schedule of Activities

Protocol Change	Affected Section(s) Numbers	Section Titles
Addition of enrollment flowsheet	Appendix 5	Appendix 5
Amendment 5		
Expansion of patient population to include front line patients who have received immunotherapy with or without chemotherapy, who did not progress at the first imaging assessment and who will begin maintenance immunotherapy with pembrolizumab ± pemetrexed (Arm 6).	Synopsis, 7.1, Figure 3, 7.2, 9, 9.1, 9.2	Trial Design, Overall Study Design, Study Treatments, Selection and Withdrawal of Patients, Subject Inclusion Criteria, Subject Exclusion Criteria
Addition of study procedures (including treatment) and follow-up for Arm 6.	9.3.1, 10.5, 10.6, 10.7, 11.5, 12, 12.4, 13.4, 14.1, 14.1.1, 15.6, Table 3	Patient Completion, Arm 6: Treatment and Follow-up Procedures, Dose Adjustment Criteria, Study Drug Materials and Management, Labeling, Tumor Assessments, RECIST 1.1 and iRECIST for Tumor Assessment, Stopping Rules, Schedule of Activities (Arm 6: HS-110 + Pembrolizumab ±Pemetrexed),
Changed the primary endpoint to PFS, and assigned ORR as a secondary endpoint.	Synopsis, 7.1, 8.1, 8.2, 16.5, 16.6	Trial Design, Overall Study Design, Primary Objectives, Secondary Objectives, Primary Efficacy Endpoints and Analysis, Secondary Efficacy Endpoints and Analysis
Addition of option for Sponsor waiver for collection of Week 10 biopsy.	Synopsis, 6.3, 7.1, 9.1, 10.2.8, 14.6, 16.7, Table 2	Trial Design, Rationale for Obtaining Archival Tissue and Performing Tumor Biopsies, Overall Study Design, Inclusion Criteria, Week 10 and 16 Assessments, Analysis of Infiltrating T Cells (Optional Post Treatment Tumor Biopsy), Exploratory Endpoints and Analyses, Schedule of Activities (Arm 5: Treatment and Follow-up Procedures)
Tumor Mutation Burden (TMB) testing added as exploratory analysis.	Synopsis, 14.9, 16.7	Exploratory Endpoints, Tumor Mutation Burden Testing, Exploratory Endpoints and Analysis
Modified and streamlined statistical methodology without formal hypothesis testing.	Synopsis, 16.1, 16.2, 16.3, 16.4, 16.5, 16.6, 16.7, 16.8	Overall Study Design, General Statistical Considerations, Sample Size, Analysis Populations, Disposition, Demography and Baseline Characteristics, Primary Efficacy Endpoints and Analysis, Secondary Efficacy Endpoints and Analysis, Exploratory Endpoints and Analysis, Safety Analysis

Protocol Change	Affected Section(s) Numbers	Section Titles
Separation of efficacy endpoints between RECIST 1.1 and iRECIST.	Synopsis, 8.1, 8.2, 16.5, 16.6	Trial Design, Primary Objectives, Secondary Objectives, Primary Efficacy and Endpoints and Analysis, Secondary Efficacy Endpoints and Analysis
Removal of Appendix 5.	Appendix 5	Level 2 Flowchart / Minimum Enrollment Requirements for the Initial Examination of Response by the DMC (version 1.0)
Removal of histology-based cohorts in Arm 5, and addition of enrollment caps for Treatment Arm 5 cohorts and Arm 6.	Synopsis, 7.1, 16.1	Trial Design, Overall Study Design, General Statistical Considerations
Change in terminology from 'subjects' to 'patients'.	N/A	Various throughout document
Change in terminology from 'relapsed' to 'progressor'.	N/A	Various throughout document
Modification of existing eligibility criteria from a 6-month CPI requirement to a 4 month CPI requirement.	Synopsis, 9.1	Subject Inclusion Criteria
Removal of Week 19 visit for Arm 5.	10.2, SOA	Arm 5: On Study Treatment Procedures
Removal of exploratory testing involving TCR repertoire, major histocompatibility (MHC) class I expression, and characterization of neo-antigens.	Synopsis, 7.1, 8.3, 14.4, 16.7	Trial Design, Overall Study design, Exploratory Endpoints, Exploratory Endpoints and Analysis, Phenotyping Phenotypic Analysis of Blood Lymphocyte Subsets by FACS
Reference to Investigational Product as 'HS-110' from 'Viagenpumatucel-L'	N/A	Various throughout document
Change in terminology from 'Off-Treatment Follow-Up' to 'Post-HS-110 Follow-Up' period.	N/A	Various throughout document
Revised nivolumab dosing schedule in Arm 5 Post-HS-110 Follow-Up period.	7.1, 7.2, 9.3.1,	Overall Study design, Study Treatments, Patient Completion,
Removal of immune response lab draw at Week 1 prior to dosing and replacement with TMB.	10.2.1, Table 2	Week 1 Assessments (Day 1), Schedule of Activities (Arm 5: Treatment and Follow-up Procedures)
Amendment 6		
Clarification of timing for addition of HS-110 to front-line maintenance treatment.	9.0, 9.1.9, 10.1, 10.5.1	Synopsis, Selection and Withdraw of Patients, Subject Inclusion Criteria, Screening Procedures and Baseline, Week 1 Assessments
Clarification that original primary endpoint of ORR will still apply to Arm 5 Cohorts A & B, and the recently	8.1, 16.5.2, 16.6	Synopsis, Primary Objectives, Primary Efficacy Endpoints; Secondary Efficacy Endpoints

Protocol Change	Affected Section(s) Numbers	Section Titles
added PFS will only the primary endpoint for the new Arm 6 Cohorts C & D. Also corrected the omission of 6 and 12 month PFS endpoints.		
Increase in Cohort B Sample Size from 40 to 60 with option for over-enrollment based on patient availability; Decrease in Cohort C/D Sample Size from 40 to up to 20 based on patient availability. Total trial sample size remains unchanged.	7.1, Figure 3,	Synopsis, Overall Study Design, Study Design
Clarifying remarks inserted to eligibility criteria.	9.1, 9.2	Synopsis, Subject Inclusion Criteria, Subject Exclusion Criteria
Modified Injection Site Reaction Grading Scale to capture more ISRs.	Appendix 2	Injection Site Reaction Grading Scale
Added exclusion criteria for patients who have received more than 3 lines of treatment for metastatic NSCLC.	9.2	Synopsis, Subject Exclusion Criteria
Clarification on TMB collection when not obtained at Week 1.	10.2.1, Table 2, 14.6	Week 1 Assessments, Arm 5 Schedule of Assessments, Tumor Mutation Burden
Alignment of Arm 6 PE with physician visits.	10.5.5, 10.5.8, Table 3	Week 5 & 11 Assessments, Week 10 Assessments; Arm 6 Schedule of Assessments