USC Norris Comprehensive Cancer Center
Part of the Keck School of Medicine of USC

Local Protocol #: 0S-16-8

Protocol Title: A Phase IIa Trial of sEphB4-HSA in Combination with Anti PD-1 Antibody (Pembrolizumab, MK3475) in Patients with Non-Small Cell Lung and Head/Neck Cancer
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TITLE:	**A Phase IIa trial of sEphB4-HSA in combination with Anti PD-1 Antibody (Pembrolizumab, MK-3475) in patients with non-small cell lung and head/neck cancer**
IND NUMBER:	**131141**

Principal Investigator: **Jorge J. Nieva M.D.**
USC Norris Comprehensive Cancer Center
1441 Eastlake Ave, Suite 3440
Los Angeles, CA 90033
Phone: 323-865-0421
Fax: 323-865-0061
Email: jorge.nieva@med.usc.edu

Co-Investigators: **David Quinn**

Amir Goldkorn
Mitch Gross
James Hu

Statistics: **Denice Tsao-Wei**
USC Norris Comprehensive Cancer Center
1441 Eastlake Ave, Suite 4425
Los Angeles, CA 90033
Phone: 323-865-0370
Fax: 323-865-0061
Email: wei_d@med.usc.edu

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1.0 TRIAL SUMMARY

Abbreviated Title	Combination of MK-7435 and sEphB4-HSA in head neck cancer and NSCLC
Trial Phase	IIa
Clinical Indications	1) Patients diagnosed with locally advanced or metastatic non-small cell lung cancer that has progressed after at least 1 line of platinum based chemotherapy. 2) Patients diagnosed with squamous cell carcinoma of the head and neck whose disease has progressed after at least 1 line of platinum based chemotherapy
Trial Type	Phase IIa non-randomized, single arm
Type of control	None
Route of administration	IV infusion
Trial Blinding	No
Treatment Groups	Two parallel cohorts, grouped by indication
Number of trial subjects	25 each group
Estimated enrollment period	12 months
Estimated duration of trial	24 months
Duration of Participation	5 years
Estimated average length of treatment per patient	6 months

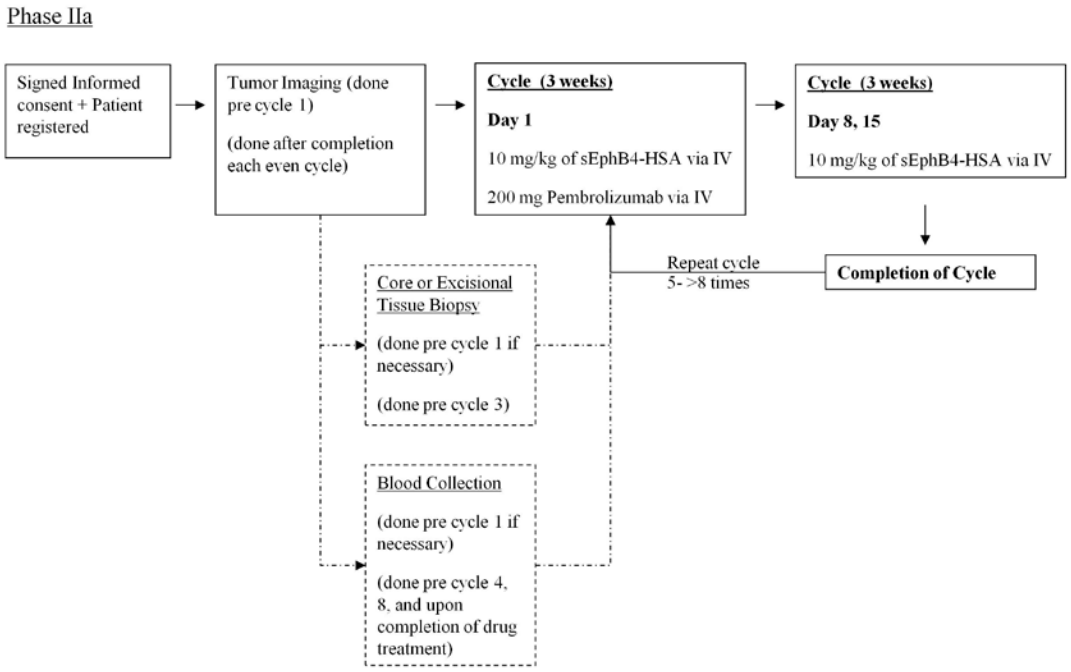
2.0 TRIAL DESIGN

2.1 Trial Design

An open label, single arm, phase IIa clinical trial of the combination of pembrolizumab with sEphB4-HSA in 2 parallel cohorts of patients with either advanced /metastatic non-small cell lung cancer (NSCLC) or relapsed/metastatic squamous cell carcinoma of the head and neck (SCCHN).

Note: As of the July 2018 Interim analysis, the NSCLC carcinoma cohort is closed

2.2 Trial Diagram



3.0 OBJECTIVES & HYPOTHESES

3.1 Primary Objective & Hypothesis

Objective: Determine the response rate of the combination of pembrolizumab and sEphB4-HSA as combination therapy

Hypothesis: combination of pembrolizumab and sEphB4-HSA will be more active than historical data on single agent pembrolizumab by activating T cell and promoting T cell NK cell trafficking into the tumor respectively

3.2 Secondary Objective & Hypothesis

Objective: Determine the biomarkers of response

Hypothesis: Pembrolizumab and sEphB4HSA combination induces T and NK cell activation and infiltration into tumor, and induces integrin expression in tumor vessels

3.3 Safety Objective:

Objective: Determine the unique toxicities of the combination of pembrolizumab and sEphB4-HSA.

Hypothesis: The combination will have a low rate of adverse events that will be characterized by the sum of the anticipated toxicity of the two agents, without unique toxicity.

4.0 BACKGROUND & RATIONALE

4.1 Pharmaceutical and Therapeutic Background

The importance of intact immune surveillance in controlling outgrowth of neoplastic transformation has been known for decades. Accumulating evidence shows a correlation between tumor-infiltrating lymphocytes (TILs) in cancer tissue and favorable prognosis in various malignancies. In particular, the presence of CD8+ T-cells and the ratio of CD8+ effector T-cells / FoxP3+ regulatory T-cells seems to correlate with improved prognosis and long-term survival in many solid tumors.

The PD-1 receptor-ligand interaction is a major pathway hijacked by tumors to suppress immune control. The normal function of PD-1, expressed on the cell surface of activated T-cells under healthy conditions, is to down-modulate unwanted or excessive immune responses, including autoimmune reactions. PD-1 (encoded by the gene Pdcd1) is an Ig superfamily member related to CD28 and CTLA-4 which has been shown to negatively regulate antigen receptor signaling upon engagement of its ligands (PD-L1 and/or PD-L2). The structure of murine PD-1 has been resolved. PD-1 and family members are type I transmembrane glycoproteins containing an Ig Variable-type (V-type) domain responsible for ligand binding and a cytoplasmic tail which is responsible for the binding of signaling molecules. The cytoplasmic tail of PD-1 contains 2 tyrosine-based signaling motifs, an immunoreceptor tyrosine-based inhibition motif (ITIM) and an immunoreceptor tyrosine-based switch motif (ITSM). Following T-cell stimulation, PD-1 recruits the tyrosine phosphatases SHP-1 and SHP-2 to the ITSM motif within its cytoplasmic tail, leading to the de-phosphorylation of effector molecules such as CD3ζ, PKCθ and ZAP70 which are involved in the CD3 T-cell signaling cascade. The mechanism by which PD-1 down modulates T-cell responses is similar to, but distinct from that of CTLA-4 as both molecules regulate an overlapping set of signaling proteins. PD-1 was shown to be expressed on activated lymphocytes including peripheral CD4+ and CD8+ T-cells, B-cells, T regs and Natural Killer cells. Expression has also been shown during thymic development on CD4-CD8- (double negative) T-cells as well as subsets of macrophages and dendritic cells. The ligands for PD-1 (PD-L1 and PD-L2) are constitutively expressed or can be induced in a variety of cell types, including non-

hematopoietic tissues as well as in various tumors. Both ligands are type I transmembrane receptors containing both IgV- and IgC-like domains in the extracellular region and contain short cytoplasmic regions with no known signaling motifs. Binding of either PD-1 ligand to PD-1 inhibits T-cell activation triggered through the T-cell receptor. PD-L1 is expressed at low levels on various non-hematopoietic tissues, most notably on vascular endothelium, whereas PD-L2 protein is only detectably expressed on antigen-presenting cells found in lymphoid tissue or chronic inflammatory environments. PD-L2 is thought to control immune T-cell activation in lymphoid organs, whereas PD-L1 serves to dampen unwarranted T-cell function in peripheral tissues. Although healthy organs express little (if any) PD-L1, a variety of cancers were demonstrated to express abundant levels of this T-cell inhibitor. PD-1 has been suggested to regulate tumor-specific T-cell expansion in subjects with melanoma (MEL). This suggests that the PD-1/PD-L1 pathway plays a critical role in tumor immune evasion and should be considered as an attractive target for therapeutic intervention.

Pembrolizumab, formerly designated as MK-3475, is a potent and highly selective humanized monoclonal antibody (mAb) of the IgG4/kappa isotype designed to directly block the interaction between PD-1 and its ligands, PD-L1 and PD-L2. Keytruda™ (pembrolizumab) has recently been approved in the United Stated for the treatment of patients with unresectable or metastatic melanoma and patients with metastatic NSCLC whose tumors express PD-L1 as determined by an FDA-approved test and who have disease progression on or after platinum-containing chemotherapy.

Bidirectional cell signaling between tumor cells and vasculature is mediated in part by type one receptor tyrosine kinase EphB4 and membrane-localized ligand EphrinB2. Signaling occurs forward in receptor expressing cells, and reverse signaling occurs in ligand expressing cells. EphB4 is over-expressed in head-neck cancers and EphB4 levels correlates with stage, grade and survival. EphB4 is also highly expressed in NSCLC. Inhibition of the EphrinB2-EphB4 interactions has a direct inhibitory effect on tumor cell proliferation in vitro and ex-vivo. EphrinB2 is also induced in tumor vessels and its activation promotes tumor angiogenesis. EphrinB2 in the tumor also prevents migration of immune cells into the tumor. soluble EphB4 fused on full length albumin (sEphB4-HSA) as a fusion protein inhibits this interaction and blocks bidirectional signaling, blocks PI3K signaling in the tumor itself and also promotes migration of immune cells into the tumor.

Pembrolizumab exhibits efficacy against tumors with high immune cell infiltration. Agents that promote immune cell migration into the tumor may thus have greater efficacy. Preliminary studies of sEphB4-HSA in tumor models show increase in T and NK cell migration into tumor. This is accompanied by the induction of ICAM-1 in the tumor vessels. ICAM-1 is an integrin that promotes attachment of T and NK cells to the endothelium followed by transmigration of cells into the tumor. sEphB4-HSA also shows downregulation of PI3K signaling by blocking EphB-EphrinB2 interactions in tumor cell and tumor vessels. EphrinB2, a transmembrane protein is induced in tumor vessels. EphrinB2 binds several members of EphB receptor tyrosine kinase family that are induced in tumor cells. EphrinB2- EphB induces bidirectional signaling. sEphB4HSA blocks the signaling and promotes immune cell trafficking into the tumor and inhibit survival signal in tumor cells by downregulating the PI3K pathway.

4.2 Rationale

4.2.1 Rationale for the Trial and Selected Subject Population

Pembrolizumab is active in SCCHN and NSCLC. In the Keynote-12 trial of 132 patients with recurrent or metastatic SCCHN the overall response rate was 25%. In the Keynote-001 trial of NSCLC patients, the overall response rate was 19%, though in patients who had high expression of PD-L1, the response rate was 45%. sEphB4-HSA also has activity in head neck cancer around 10% and has a limited experience in NSCLC, however, the in vitro and in vivo effects on immune cell infiltration into tumors suggests a potential for synergy of the combination. Both drugs have different mechanism of action and no overlapping toxicity. The current outcomes of patients with relapsed/metastatic disease with either histology are unsatisfactory. Combination of the drugs may thus be more active than each one alone without increase in toxicity. Both tumor types are incorporated into a single clinical trial to improve the opportunity to observe toxicities that may be unique to the combination in a larger number of patients.

4.2.2 Rationale for Dose Selection/Regimen/Modification

An open-label Phase I trial (Protocol 001) was being conducted to evaluate the safety and clinical activity of single agent MK-3475. The dose escalation portion of this trial evaluated three dose levels, 1 mg/kg, 3 mg/kg, and 10 mg/kg, administered every 2 weeks (Q2W) in subjects with advanced solid tumors. All three dose levels were well tolerated and no dose-limiting toxicities were observed. This first in human study of MK-3475 showed evidence of target engagement and objective evidence of tumor size reduction at all dose levels (1 mg/kg, 3 mg/kg and 10 mg/kg Q2W). No MTD has been identified to date. 10.0 mg/kg Q2W has been tested in PN001 with good tolerability. Recent data from other clinical studies within the MK-3475 program has shown that a lower dose of MK-3475 and a less frequent schedule may be sufficient for target engagement and clinical activity.

PK data analysis of MK-3475 administered Q2W and Q3W showed slow systemic clearance, limited volume of distribution, and a long half-life (refer to IB). Pharmacodynamic data (IL-2 release assay) suggested that peripheral target engagement is durable (>21 days).

A population pharmacokinetic analysis has been performed using serum concentration time data from 476 patients. Within the resulting population PK model, clearance and volume parameters of MK-3475 were found to be dependent on body weight. The relationship between clearance and body weight, with an allometric exponent of 0.59, is within the range observed for other antibodies and would support both body weight normalized dosing or a fixed dose across all body weights. MK-3475 has been found to have a wide therapeutic range based on the melanoma indication. The differences in exposure for a 200 mg fixed dose regimen relative to a 2 mg/kg Q3W body weight based regimen are anticipated to remain well within the established exposure margins of 0.5 – 5.0 for MK-3475 in the melanoma indication. The exposure margins are based on the notion of similar efficacy and safety in melanoma at 10 mg/kg Q3W vs. the proposed dose regimen of 2 mg/kg Q3W (i.e. 5-fold higher dose and exposure). The population PK evaluation revealed that there was no significant impact of tumor burden on exposure. In addition, exposure was similar between

the NSCLC and melanoma indications. Therefore, there are no anticipated changes in exposure between different indication settings.

The choice of the 200 mg Q3W as an appropriate dose for the switch to fixed dosing is based on simulations performed using the population PK model of pembrolizumab showing that the fixed dose of 200 mg every 3 weeks will provide exposures that 1) are optimally consistent with those obtained with the 2 mg/kg dose every 3 weeks, 2) will maintain individual patient exposures in the exposure range established in melanoma as associated with maximal efficacy response and 3) will maintain individual patients exposure in the exposure range established in melanoma that are well tolerated and safe.

A fixed dose regimen will simplify the dosing regimen to be more convenient for physicians and to reduce potential for dosing errors. A fixed dosing scheme will also reduce complexity in the logistical chain at treatment facilities and reduce wastage.

For sEphB4-HSA, an open-label Phase I trial was conducted. The dose escalation portion of this trial evaluated 2.5 mg/kg, 5 mg/kg, and 10 mg/kg every week and 10mg/kg, 15 mg/kg and 20 mg/kg every 2 weeks (Q2W) in subjects with advanced solid tumors. All dose levels were well tolerated and no dose-limiting toxicities were observed. This first in human study showed evidence of objective evidence with tumor size reduction at all dose levels above 2.5mg/kg (5 mg/kg and 10 mg/kg Q1W, 15, and 20 mg/kg Q2W). No MTD has been identified to date. 10.0 mg/kg Q1W will be the dose and schedule of this protocol to test for initial tumor activity.

PK data analysis of sEphB4-HSA administered Q1W and Q2W showed slow systemic clearance, limited volume of distribution, and a long half-life (refer to IB). Pharmacodynamic data suggested that the target engagement is durable (>21 days). This early PK and pharmacodynamic data provides scientific rationale for testing a Q1W and Q2W dosing schedule. sEphB4-HSA has been found to have a wide therapeutic range based on the early clinical experience. The differences in exposure for a 700 mg fixed dose regimen relative to a 10 mg/kg Q1W or Q2W body weight based regimen are anticipated to remain well within the established exposure margins of 0.5 – 5.0 for sEphB4-HSA. The exposure margins are based on the notion of similar efficacy and safety in in SCCHN at 10 mg/kg Q1W and Q2W. The population PK evaluation that there may be a significant impact of tumor burden on exposure remains to be determined. In addition, exposure was similar between different tumor types remains to be determined. There is no anticipated change in exposure between different indication settings.

The choice of the 10mg/kg Q1W as an appropriate dose will provide exposures that 1) are optimal, 2) will maintain individual patient exposures in the exposure range as associated with maximal efficacy response and 3) will maintain individual patients exposure in the exposure range established that are well tolerated and safe and 4) permits ease of scheduling with pembrolizumab on a Q3W schedule.

4.2.3 Rationale for Endpoints

The primary and secondary endpoints will be clinical (efficacy and safety) endpoints; descriptive/exploratory endpoints will include biomarker and correlative endpoints and will be used to better understand the joint effects of pembrolizumab and sEphB4-HSA on anti-tumor activity and immune cell infiltration.

4.2.3.1 Safety Endpoints

Safety and tolerability are secondary endpoints of this phase IIa clinical trial. This endpoint will be established by determining the rate of treatment related toxicity resulting in discontinuation of therapy and is intended to determine if the two drug combination can be reasonably combined in a clinical population where the primary goal is palliation. We anticipate that the rate of treatment discontinuation due to toxicity will be no higher than 25%.

4.2.3.2 Efficacy Endpoints

Overall response rate is the primary efficacy endpoint. In the Keynote-001 clinical trial, the overall response rate in previously treated patients was 19%, while the response rate in the PD-L1 positive population was 45%. We expect that the response rate for the combination of sEphB4-HSA will be higher than 20% in patients who are not pre-selected for PD-L1 positivity and approach 45% for the 2 drug combination in patients with no prior selection for PD-L1. Progression free survival, overall survival and duration of response will be secondary efficacy endpoints. All efficacy endpoints will be analyzed for each whole cohort as well as subgroups depending on pretreatment PD-L1 expression.

4.2.3.3 Biomarker Research

Archived tumor tissue will be obtained from all patients entering study, for central PD-1 and PD-L1 immunohistochemical testing by Merck, and will be repeated while on treatment after cycle #2 in order to understand the role that the combination therapy has on the expression levels of these markers. Patients will have research blood collections before initiating the treatment and before infusions on day 1 of every 4th cycle for quantitative peripheral blood T cell subset analysis using flow cytometry, CTCs will be assessed for PD-L1 expression along with analysis of the constituents of circulating tumor cell clusters.

5.0 METHODOLOGY

5.1 Entry Criteria

5.1.1 Diagnoses for entry into the trial

One of the following:

A) Locally advanced or metastatic non-small cell lung cancer that has progressed after at least 1 line of platinum based chemotherapy.

- Patients may have received up to 2 prior lines of chemotherapy

- Patients with actionable alterations in EGFR/ALK/ROS1/BRAF must also have progressed after treatment with a tyrosine kinase inhibitor appropriate for their genetic alteration.
- Untreated patients who refuse 1st line platinum based chemotherapy are also eligible

Note: As of the July 2018 Interim analysis, the NSCLC carcinoma cohort is closed

B) Squamous Cell Carcinoma of the head and neck whose disease has progressed after at least 1 line of platinum based chemotherapy

- Patients may have received up to 2 prior lines of chemotherapy.
- Untreated patients who refuse 1st line platinum based chemotherapy are also eligible
- Patients who relapse within 6 months of adjuvant cisplatin based concurrent chemo-radiation, or neoadjuvant cisplatin based therapy can be considered eligible without an additional course of platinum chemotherapy for relapsed disease.
- Patients may have either locally recurrent or distant metastatic disease.

5.1.2 Subject Inclusion Criteria

In order to be eligible for participation in this trial, the subject must:

1. Be willing and able to provide written informed consent/assent for the trial.

2. Be ≥ 18 years of age on day of signing informed consent.

3. Have measurable disease based on RECIST 1.1.

4. Be willing to provide tissue from a newly obtained core or excisional biopsy of a tumor lesion after 2 cycles of therapy

5. Have a performance status of 0 or 1 on the ECOG Performance Scale.

6. Demonstrate adequate organ function as defined in Table 1, all screening labs should be performed within 10 days of treatment initiation.

Table 1 Adequate Organ Function Laboratory Values

System	Laboratory Value
Hematological	
Absolute neutrophil count (ANC)	≥1,500 /mcL
Platelets	≥100,000 / mcL
Hemoglobin	≥9 g/dL or ≥5.6 mmol/L
Renal	
Serum creatinine **OR** Measured or calculated[a] creatinine clearance (GFR can also be used in place of creatinine or CrCl)	≤1.5 X upper limit of normal (ULN) **OR** ≥60 mL/min for subject with creatinine levels > 1.5 X institutional ULN
Hepatic	
Serum total bilirubin	≤ 1.5 X ULN **OR**

	Direct bilirubin ≤ ULN for subjects with total bilirubin levels > 1.5 ULN
AST (SGOT) and ALT (SGPT)	≤ 2.5 X ULN **OR** ≤ 5 X ULN for subjects with liver metastases
Albumin	≥2.5 g/dL
Coagulation	
International Normalized Ratio (INR) or Prothrombin Time (PT) Activated Partial Thromboplastin Time (aPTT)	≤1.5 X ULN unless subject is receiving anticoagulant therapy as long as PT or PTT is within therapeutic range of intended use of anticoagulants ≤1.5 X ULN unless subject is receiving anticoagulant therapy as long as PT or PTT is within therapeutic range of intended use of anticoagulants
[a]Creatinine clearance should be calculated per institutional standard.	

7. Female subject of childbearing potential should have a negative urine or serum pregnancy within 72 hours prior to receiving the first dose of study medication. If the urine test is positive or cannot be confirmed as negative, a serum pregnancy test will be required.

8. Female subjects of childbearing potential (Section 5.7.2) must be willing to use an adequate method of contraception as outlined in Section 5.7.2 – Contraception, for the course of the study through 120 days after the last dose of study medication.

Note: Abstinence is acceptable if this is the usual lifestyle and preferred contraception for the subject.

9. Male subjects of childbearing potential (Section 5.7.1) must agree to use an adequate method of contraception as outlined in Section 5.7.1- Contraception, starting with the first dose of study therapy through 120 days after the last dose of study therapy.

Note: Abstinence is acceptable if this is the usual lifestyle and preferred contraception for the subject.

5.1.3 Subject Exclusion Criteria

The subject must be excluded from participating in the trial if the subject:

1. Is currently participating and receiving study therapy or has participated in a study of an investigational agent and received study therapy or used an investigational device within 4 weeks of the first dose of treatment.

2. Has a diagnosis of immunodeficiency or is receiving systemic steroid therapy or any other form of immunosuppressive therapy within 7 days prior to the first dose of trial treatment.

3. Has a known history of active TB (Bacillus Tuberculosis)

4. Hypersensitivity to pembrolizumab or any of its excipients.

5. Has had a prior anti-cancer monoclonal antibody (mAb) within 4 weeks prior to study Day 1 or who has not recovered (i.e., ≤ Grade 1 or at baseline) from adverse events due to agents administered more than 4 weeks earlier.

6. Has had prior chemotherapy, targeted small molecule therapy, or radiation therapy within 2 weeks prior to study Day 1 or who has not recovered (i.e., ≤ Grade 1 or at baseline) from adverse events due to a previously administered agent.

    - Note: Subjects with ≤ Grade 2 neuropathy are an exception to this criterion and may qualify for the study.

    - Note: If subject received major surgery, they must have recovered adequately from the toxicity and/or complications from the intervention prior to starting therapy.

7. Has a known additional malignancy that is progressing or requires active treatment. Exceptions include basal cell carcinoma of the skin or squamous cell carcinoma of the skin that has undergone potentially curative therapy or in situ cervical cancer.

8. Has known active central nervous system (CNS) metastases and/or carcinomatous meningitis. Subjects with previously treated brain metastases may participate provided they are not active . This exception does not include carcinomatous meningitis which is excluded regardless of clinical stability. Known brain metastases are considered active, if any of the following criteria is applicable:

    a. Brain imaging during screening demonstrates progression of existing metastases and/or appearance of new lesions compared to brain imaging performed at least 4 weeks earlier

    b. Neurological symptoms attributed to brain metastases have not returned to baseline

    c. Steroids were used for brain metastases within 28 days of randomization

9. Has active autoimmune disease that has required immune suppressing systemic treatment in the past 2 years (i.e. with use of disease modifying agents, corticosteroids or immunosuppressive drugs). Replacement therapy (eg., thyroxine, insulin, or physiologic corticosteroid replacement therapy for adrenal or pituitary insufficiency, etc.) is not considered a form of systemic treatment.

10. Has known history of, or any evidence of active, non-infectious pneumonitis.

11. Has an active infection requiring systemic therapy.

12. Has a history or current evidence of any condition, therapy, or laboratory abnormality that might confound the results of the trial, interfere with the subject's participation for the full duration of the trial, or is not in the best interest of the subject to participate, in the opinion of the treating investigator.

13. Has known psychiatric or substance abuse disorders that would interfere with cooperation with the requirements of the trial.

14. Is pregnant or breastfeeding, or expecting to conceive or father children within the projected duration of the trial, starting with the pre-screening or screening visit through 120 days after the last dose of trial treatment.

15. Has received prior therapy with an anti-PD-1, anti-PD-L1, anti-PD-L2, or anti cytotoxic T-lymphocyte-associated antigen-4 (CTLA-4) antibody including ipilimumab or any other antibody or drug specifically targeting T-cell co-stimulation or checkpoint pathways.

16. Has a known history of Human Immunodeficiency Virus (HIV) (HIV 1/2 antibodies).

17. Has known active Hepatitis B (e.g., HBsAg reactive) or Hepatitis C (e.g., HCV RNA [qualitative] is detected).

18. Has received a live vaccine within 30 days of planned start of study therapy.

    Note: Seasonal influenza vaccines for injection are generally inactivated flu vaccines and are allowed; however intranasal influenza vaccines (e.g., Flu-Mist®) are live attenuated vaccines, and are not allowed.

5.2 Trial Treatments

The treatment to be used in this trial is outlined below in Table 2

Table 2 Trial Treatment

Drug	Dose/Potency	Dose Frequency	Route of Administration	Regimen/Treatment Period	Use
Pembrolizumab	200 mg IV	Q3W	IV infusion	Day 1 of each 3 week cycle	Experimental
sEphB4-HSA	10 mg/kg	Q1W	IV infusion	Day 1, 8,15 of each 3 week cycle	Experimental

Trial treatment should begin on the day of randomization or as close as possible to the date on which treatment is allocated/assigned. Trial therapy will continue up to 24 months, until disease progression, unacceptable toxicity, withdrawal of consent, investigator discretion, or sponsor decision to terminate the trial. Patients who stop therapy after 24 months and experience subsequent disease progression, may resume therapy for another 24 months.

5.2.1 Dose Selection/Modification

5.2.1.1 Dose Selection

The rationale for selection of doses to be used in this trial is provided in Section 4.0 – Background and Rationale.

Details on preparation and administration of pembrolizumab (MK-3475) are provided in the Pharmacy Manual.

5.2.1.2 Dose Modification for Pembrolizumab

Adverse events (both non-serious and serious) associated with pembrolizumab exposure may represent an immunologic etiology. These adverse events may occur shortly after the first dose or several months after the last dose of treatment. Pembrolizumab must be withheld for drug-related toxicities and severe or life-threatening AEs as per 3 below. See Section 5.6 for supportive care guidelines, including use of corticosteroids.

Table 3 Dose Modification Guidelines for Drug-Related Adverse Events

Toxicity	Hold Treatment For Grade	Timing for Restarting Treatment	Treatment Discontinuation
Diarrhea/Colitis	2-3	Toxicity resolves to Grade 0-1	Toxicity does not resolve within 12 weeks of last dose or inability to reduce corticosteroid to 10 mg or less of prednisone or equivalent per day within 12 weeks
	4	Permanently discontinue	Permanently discontinue
AST, ALT, or Increased Bilirubin	2	Toxicity resolves to Grade 0-1	Toxicity does not resolve within 12 weeks of last dose
	3-4	Permanently discontinue (see exception below)[a]	Permanently discontinue
Type 1 diabetes mellitus (if new onset) or Hyperglycemia	T1DM or 3-4	Hold pembrolizumab for new onset Type 1 diabetes mellitus or Grade 3-4 hyperglycemia associated with evidence of beta cell failure	Resume pembrolizumab when patients are clinically and metabolically stable
Hypophysitis	2-4	Toxicity resolves to Grade 0-1. Therapy with pembrolizumab can be continued while endocrine replacement therapy is instituted	Toxicity does not resolve within 12 weeks of last dose or inability to reduce corticosteroid to 10 mg or less of prednisone or equivalent per day within 12 weeks
Hyperthyroidism	3	Toxicity resolves to Grade 0-1	Toxicity does not resolve within 12 weeks of last dose or inability to reduce corticosteroid to 10 mg or less of prednisone or equivalent per day within 12 weeks
	4	Permanently discontinue	Permanently discontinue
Hypothyroidism		Therapy with pembrolizumab can be continued while thyroid replacement therapy is instituted	Therapy with pembrolizumab can be continued while thyroid replacement therapy is instituted
Infusion Reaction	2[b]	Toxicity resolves to Grade 0-1	Permanently discontinue if toxicity develops despite adequate premedication
	3-4	Permanently discontinue	Permanently discontinue
Pneumonitis	2	Toxicity resolves to Grade 0-1	Toxicity does not resolve within 12 weeks of last dose or inability to reduce corticosteroid to 10 mg or less of prednisone or equivalent per day within 12 weeks
	3-4	Permanently discontinue	Permanently discontinue

Toxicity	Hold Treatment For Grade	Timing for Restarting Treatment	Treatment Discontinuation
Renal Failure or Nephritis	2	Toxicity resolves to Grade 0-1	Toxicity does not resolve within 12 weeks of last dose or inability to reduce corticosteroid to 10 mg or less of prednisone or equivalent per day within 12 weeks
	3-4	Permanently discontinue	Permanently discontinue
All Other Drug-Related Toxicity[c]	3 or Severe	Toxicity resolves to Grade 0-1	Toxicity does not resolve within 12 weeks of last dose or inability to reduce corticosteroid to 10 mg or less of prednisone or equivalent per day within 12 weeks
	4	Permanently discontinue	Permanently discontinue

Note: Permanently discontinue for any severe or Grade 3 drug-related AE that recurs or any life-threatening event.

[a] For patients with liver metastasis who begin treatment with Grade 2 AST or ALT, if AST or ALT increases by greater than or equal to 50% relative to baseline and lasts for at least 1 week then patients should be discontinued.

[b] If symptoms resolve within one hour of stopping drug infusion, the infusion may be restarted at 50% of the original infusion rate (e.g., from 100 mL/hr to 50 mL/hr). Otherwise dosing will be held until symptoms resolve and the subject should be premedicated for the next scheduled dose; Refer to Table 2 – Infusion Treatment Guidelines for further management details.

[c] Patients with intolerable or persistent Grade 2 drug-related AE may hold study medication at physician discretion. Permanently discontinue study drug for persistent Grade 2 adverse reactions for which treatment with study drug has been held, that do not recover to Grade 0-1 within 12 weeks of the last dose.

Dosing interruptions are permitted in the case of medical / surgical events or logistical reasons not related to study therapy (e.g., elective surgery, unrelated medical events, patient vacation, and/or holidays). Subjects should be placed back on study therapy within 3 weeks of the scheduled interruption, unless otherwise discussed with the Sponsor. The reason for interruption should be documented in the patient's study record. Patients who permanently discontinue pembrolizumab may continue treatment with single agent sEphB4-HSA at the discretion of the treating physician.

5.2.1.3 Dose Modification for sEphB4-HSA

sEphB4-HSA must be withheld for drug-related toxicities and severe or life-threatening AEs as per Table 3b below.

Dose modification scheme is as follows:

(1) Dose level 0: 10 mg/Kg q week

(2) Dose level -1: 5 mg/Kg q week

(3) Dose level -2: 2.5 mg/Kg q week

Patients can have a maximum of 2 dose reductions for drug-related toxicity beyond which they will be removed from the study. If patient requires more than 2 dose reductions, they will be treated with single agent pembrolizumab or be removed from study treatment at the discretion of the treating physician.

Dose Modification Guidelines for sEphB4-HSA-Related Adverse Event

Toxicity	Hold Treatment For Grade	Timing for Restarting Treatment	Discontinue Subject
Unmanageable[1] non-hematologic toxicity other than alopecia	3-4	Toxicity resolves to Grade 0-1 or baseline, one dose level reduction. Patients with toxicities that are manageable with supportive therapy may not require dose reductions (for example, patients with Grade 3-4 nausea, vomiting or diarrhea must have persistent toxicity despite having received optimal supportive therapy in order to require a dose reduction). Patients with ≥ Grade 3 electrolyte abnormalities, if easily managed medically (return to Grade 2 or less within 72 hours), do not require a dose reduction.	*Treatment can be continued with supportive management as described in 5.6.1*
AST, ALT	2	Subjects who experience a grade 2 AST and or ALT will have subsequent doing held until the AST/ALT return to grade 0/1 and then can resume the prior dose, however, if the return to grade 0/1 takes longer than 7 days, the subject will be treated at a 1 level dose reduction Grade 3 AST and/or ALT that represents at least a two grade increase from baseline or AST/ALT ≥ 10XULN –hold therapy, recheck weekly, initiate retreatment when resolved to baseline with one dose level reduction.	Toxicity does not resolve within 12 weeks of last dose.
	3-4	Permanently discontinue (see exception below)[2]	Permanently discontinue
Hypertension[3]	2	Initiate antihypertensive drugs	Treatment can continue while antihypertensive drugs are initiated

Toxicity	Hold Treatment For Grade	Timing for Restarting Treatment	Discontinue Subject
	3	First occurrence, if asymptomatic and on antihypertensive therapy, may continue treatment, and optimize antihypertensive therapy. Second occurrence, despite antihypertensive therapy, hold until grade < 3, one dose level reduction	Treatment can continue while antihypertensive drugs are initiated
	4	Permanently discontinue sEphB4-HSA	Permanently discontinue sEphB4-HSA
Thrombocytopenia	3-4	Toxicity resolves to Grade 0-1, one dose level reduction	Toxicity does not resolve within 12 weeks of last dose.
Neutropenia	4	Toxicity resolves to Grade 0-1, one dose level reduction	Treatment can continue with GCSF support

5.2.2 Timing of Dose Administration

Trial treatment should be administered on Day 1 of each cycle after all procedures/assessments have been completed as detailed on the Trial Flow Chart (Section 6.0). Trial treatment may be administered up to 3 days before or after the scheduled Day 1 of each cycle due to administrative reasons.

All trial treatments will be administered on an outpatient basis.

Pembrolizumab 200 mg will be administered as a 30 minute IV infusion every 3 weeks. Sites should make every effort to target infusion timing to be as close to 30 minutes as possible. However, given the variability of infusion pumps from site to site, a window of -5 minutes and +10 minutes is permitted (i.e., infusion time is 30 minutes: -5 min/+10 min).

sEphB4-HSA will be administered as a 60 minute +/- 10 min infusion every week. The infusion will be initiated after completion of the pembrolizumab infusion.

The Each Pharmacy Manual contains specific instructions for the preparation of the pembrolizumab sEphB4-HSA and infusion fluid and administration of infusion solution.

5.2.3 Trial Blinding/Masking

This is a single arm, non-randomized, open-label trial; therefore, the Sponsor, investigator and subject will know the treatment administered.

5.3 Concomitant Medications/Vaccinations (allowed & prohibited)

Medications or vaccinations specifically prohibited in the exclusion criteria are not allowed during the ongoing trial. If there is a clinical indication for one of these or other medications or vaccinations specifically prohibited during the trial, discontinuation from trial therapy or vaccination may be required. The investigator should discuss any questions regarding this with the Merck Clinical team. The final decision on any supportive therapy or vaccination rests with the investigator and/or the subject's primary physician.

5.3.1 Acceptable Concomitant Medications

All treatments that the investigator considers necessary for a subject's welfare may be administered at the discretion of the investigator in keeping with the community standards of medical care. All concomitant medication will be recorded on the case report form (CRF) including all prescription, over-the-counter (OTC), herbal supplements, and IV medications and fluids. If changes occur during the trial period, documentation of drug dosage, frequency, route, and date may also be included on the CRF.

All concomitant medications received within 28 days before the first dose of trial treatment and 30 days after the last dose of trial treatment should be recorded. Concomitant medications administered after 30 days after the last dose of trial treatment should be recorded for SAEs and ECIs as defined in Section 7.2.

5.3.2 Prohibited Concomitant Medications

Subjects are prohibited from receiving the following therapies during the Screening and Treatment Phase (including retreatment for post-complete response relapse) of this trial:

- Antineoplastic systemic chemotherapy or biological therapy
- Immunotherapy not specified in this protocol
- Chemotherapy not specified in this protocol
- Investigational agents other than pembrolizumab
- Radiation therapy
    - Note: Radiation therapy to a symptomatic solitary lesion or to the brain may be allowed at the investigator's discretion.
- Live vaccines within 30 days prior to the first dose of trial treatment and while participating in the trial. Examples of live vaccines include, but are not limited to, the following: measles, mumps, rubella, varicella/zoster, yellow fever, rabies, BCG, and typhoid vaccine.
- Systemic glucocorticoids for any purpose other than to modulate symptoms from an event of clinical interest of suspected immunologic etiology. The use of physiologic doses of corticosteroids may be approved after consultation with the Sponsor.

Subjects who, in the assessment by the investigator, require the use of any of the aforementioned treatments for clinical management should be removed from the trial. Subjects may receive other medications that the investigator deems to be medically necessary.

The Exclusion Criteria describes other medications which are prohibited in this trial.

There are no prohibited therapies during the Post-Treatment Follow-up Phase.

5.4 Rescue Medications & Supportive Care

5.4.1 Supportive Care Guidelines

Subjects should receive appropriate supportive care measures as deemed necessary by the treating investigator. Suggested supportive care measures for the management of adverse events with potential immunologic etiology are outlined below. Where appropriate, these guidelines include the use of oral or intravenous treatment with corticosteroids as well as additional anti-inflammatory agents if symptoms do not improve with administration of corticosteroids. Note that several courses of steroid tapering may be necessary as symptoms may worsen when the steroid dose is decreased. For each disorder, attempts should be made to rule out other causes such as metastatic disease or bacterial or viral infection, which might require additional supportive care. The treatment guidelines are intended to be applied when the investigator determines the events to be related to pembrolizumab.

Note: if after the evaluation the event is determined not to be related, the investigator does not need to follow the treatment guidance (as outlined below). Refer to Section 5.2.1 for dose modification.

It may be necessary to perform conditional procedures such as bronchoscopy, endoscopy, or skin photography as part of evaluation of the event.

- **Pneumonitis**:
    - For **Grade 2 events**, treat with systemic corticosteroids. When symptoms improve to Grade 1 or less, steroid taper should be started and continued over no less than 4 weeks.
    - For **Grade 3-4 events**, immediately treat with intravenous steroids. Administer additional anti-inflammatory measures, as needed.
    - Add prophylactic antibiotics for opportunistic infections in the case of prolonged steroid administration.
    - If there is recurrence of grade 2 pneumonitis, pembrolizumab will be permanently discontinued.
- **Diarrhea/Colitis**:

  Subjects should be carefully monitored for signs and symptoms of enterocolitis (such as diarrhea, abdominal pain, blood or mucus in stool, with or without fever) and of bowel perforation (such as peritoneal signs and ileus).

- All subjects who experience diarrhea/colitis should be advised to drink liberal quantities of clear fluids. If sufficient oral fluid intake is not feasible, fluid and electrolytes should be substituted via IV infusion. For Grade 2 or higher diarrhea, consider GI consultation and endoscopy to confirm or rule out colitis.
- For **Grade 2 diarrhea/colitis,** administer oral corticosteroids.
- For **Grade 3 or 4 diarrhea/colitis,** treat with intravenous steroids followed by high dose oral steroids.
- When symptoms improve to Grade 1 or less, steroid taper should be started and continued over no less than 4 weeks.

- **Type 1 diabetes mellitus (if new onset, including diabetic ketoacidosis [DKA]) or ≥ Grade 3 Hyperglycemia, if associated with ketosis (ketonuria) or metabolic acidosis (DKA)**
  - For **T1DM** or **Grade 3-4** Hyperglycemia
    - Insulin replacement therapy is recommended for Type I diabetes mellitus and for Grade 3-4 hyperglycemia associated with metabolic acidosis or ketonuria.
    - Evaluate patients with serum glucose and a metabolic panel, urine ketones, glycosylated hemoglobin, and C-peptide.
- **Hypophysitis**:
  - For **Grade 2** events, treat with corticosteroids. When symptoms improve to Grade 1 or less, steroid taper should be started and continued over no less than 4 weeks. Replacement of appropriate hormones may be required as the steroid dose is tapered.
  - For **Grade 3-4** events, treat with an initial dose of IV corticosteroids followed by oral corticosteroids. When symptoms improve to Grade 1 or less, steroid taper should be started and continued over no less than 4 weeks. Replacement of appropriate hormones may be required as the steroid dose is tapered.
- **Hyperthyroidism or Hypothyroidism**:

  Thyroid disorders can occur at any time during treatment. Monitor patients for changes in thyroid function (at the start of treatment, periodically during treatment, and as indicated based on clinical evaluation) and for clinical signs and symptoms of thyroid disorders.

  - **Grade 2** hyperthyroidism events (and **Grade 2-4** hypothyroidism):
    - In hyperthyroidism, non-selective beta-blockers (e.g. propranolol) are suggested as initial therapy.
    - In hypothyroidism, thyroid hormone replacement therapy, with levothyroxine or liothyroinine, is indicated per standard of care.
  - **Grade 3-4** hyperthyroidism

- Treat with an initial dose of IV corticosteroid followed by oral corticosteroids. When symptoms improve to Grade 1 or less, steroid taper should be started and continued over no less than 4 weeks. Replacement of appropriate hormones may be required as the steroid dose is tapered.

- **Hepatic**:
  - For **Grade 2** events, monitor liver function tests more frequently until returned to baseline values (consider weekly).
    - Treat with IV or oral corticosteroids
  - For **Grade 3-4** events, treat with intravenous corticosteroids for 24 to 48 hours.
  - When symptoms improve to Grade 1 or less, a steroid taper should be started and continued over no less than 4 weeks.
- **Renal Failure or Nephritis**:
  - For **Grade 2** events, treat with corticosteroids.
  - For **Grade 3-4** events, treat with systemic corticosteroids.
  - When symptoms improve to Grade 1 or less, steroid taper should be started and continued over no less than 4 weeks.
- **Management of Infusion Reactions**: Signs and symptoms usually develop during or shortly after drug infusion and generally resolve completely within 24 hours of completion of infusion.

  Table 2 below shows treatment guidelines for subjects who experience an infusion reaction associated with administration of pembrolizumab (MK-3475).

Table 3 Infusion Reaction Treatment Guidelines

NCI CTCAE Grade	Treatment	Premedication at subsequent dosing
Grade 1 Mild reaction; infusion interruption not indicated; intervention not indicated	Increase monitoring of vital signs as medically indicated until the subject is deemed medically stable in the opinion of the investigator.	None
Grade 2 Requires infusion interruption but responds promptly to symptomatic treatment (e.g., antihistamines, NSAIDS, narcotics, IV fluids); prophylactic medications indicated for < =24 hrs	**Stop Infusion and monitor symptoms.** Additional appropriate medical therapy may include but is not limited to: IV fluids Antihistamines NSAIDS Acetaminophen Narcotics Increase monitoring of vital signs as medically indicated until the subject is deemed medically stable in the opinion of the investigator. If symptoms resolve within one hour of stopping drug infusion, the infusion may be restarted at 50% of the original infusion rate (e.g., from 100 mL/hr to 50 mL/hr). Otherwise dosing will be held until symptoms resolve and the subject should be premedicated for the next scheduled dose.	Subject may be premedicated 1.5h (± 30 minutes) prior to infusion of pembrolizumab (MK-3475) with: Diphenhydramine 50 mg po (or equivalent dose of antihistamine). Acetaminophen 500-1000 mg po (or equivalent dose of antipyretic).

NCI CTCAE Grade	Treatment	Premedication at subsequent dosing
	Subjects who develop Grade 2 toxicity despite adequate premedication should be permanently discontinued from further trial treatment administration.	
Grades 3 or 4 Grade 3: Prolonged (i.e., not rapidly responsive to symptomatic medication and/or brief interruption of infusion); recurrence of symptoms following initial improvement; hospitalization indicated for other clinical sequelae (e.g., renal impairment, pulmonary infiltrates) Grade 4: Life-threatening; pressor or ventilatory support indicated	**Stop Infusion.** Additional appropriate medical therapy may include but is not limited to: IV fluids Antihistamines NSAIDS Acetaminophen Narcotics Oxygen Pressors Corticosteroids Epinephrine Increase monitoring of vital signs as medically indicated until the subject is deemed medically stable in the opinion of the investigator. Hospitalization may be indicated. **Subject is permanently discontinued from further trial treatment administration.**	No subsequent dosing
Appropriate resuscitation equipment should be available in the room and a physician readily available during the period of drug administration.		

5.4.2 Supportive Care Guidelines specific to sEphB4-HSA

sEphB4-HSA is associated with hypertension which can be properly managed medically and as such would not require treatment delays or discontinuation. The following guidelines are provided for supportive care.

- **Hypertension**

  This is an expected class effect adverse event. All blood pressure measurements should be made after the patient has been in a supine position for 10 minutes or longer.

  - Patients with grade 2 hypertension as evidenced by two or more different measurements that are at least one our apart should be initiated on antihypertensive therapy per the treating physician.

  - In the case of a first occurrence of grade 3 asymptomatic hypertension, patients may continue on treatment while their antihypertensive therapy is optimized. A second occurrence of grade 3 hypertension despite antihypertensive therapy would require holding treatment with sEphB4-HSA until hypertension returns to ≤ grade 2 at which point treatment can be resumed with one dose reduction.

5.5 Diet/Activity/Other Considerations

5.5.1 Diet

Subjects should maintain a normal diet unless modifications are required to manage an AE such as diarrhea, nausea or vomiting.

5.5.2 Contraception

Pembrolizumab may have adverse effects on a fetus in utero. Furthermore, it is not known if pembrolizumab has transient adverse effects on the composition of sperm.

For this trial, male subjects will be considered to be of non-reproductive potential if they have azoospermia (whether due to having had a vasectomy or due to an underlying medical condition).

Female subjects will be considered of non-reproductive potential if they are either:

(1) postmenopausal (defined as at least 12 months with no menses without an alternative medical cause; in women < 45 years of age a high follicle stimulating hormone (FSH) level in the postmenopausal range may be used to confirm a post-menopausal state in women not using hormonal contraception or hormonal replacement therapy. In the absence of 12 months of amenorrhea, a single FSH measurement is insufficient.);

OR

(2) have had a hysterectomy and/or bilateral oophorectomy, bilateral salpingectomy or bilateral tubal ligation/occlusion, at least 6 weeks prior to screening;

OR

(3) has a congenital or acquired condition that prevents childbearing.

Female and male subjects of reproductive potential must agree to avoid becoming pregnant or impregnating a partner, respectively, while receiving study drug and for 120 days after the last dose of study drug by complying with one of the following:

(1) practice abstinence[†] from heterosexual activity;

OR

(2) use (or have their partner use) acceptable contraception during heterosexual activity.

Acceptable methods of contraception are[‡]:

Single method (one of the following is acceptable):

- intrauterine device (IUD)

- vasectomy of a female subject's male partner
- contraceptive rod implanted into the skin

Combination method (requires use of two of the following):

- diaphragm with spermicide (cannot be used in conjunction with cervical cap/spermicide)
- cervical cap with spermicide (nulliparous women only)
- contraceptive sponge (nulliparous women only)
- male condom or female condom (cannot be used together)
- hormonal contraceptive: oral contraceptive pill (estrogen/progestin pill or progestin-only pill), contraceptive skin patch, vaginal contraceptive ring, or subcutaneous contraceptive injection

†Abstinence (relative to heterosexual activity) can be used as the sole method of contraception if it is consistently employed as the subject's preferred and usual lifestyle and if considered acceptable by local regulatory agencies and ERCs/IRBs. Periodic abstinence (e.g., calendar, ovulation, sympto-thermal, post-ovulation methods, etc.) and withdrawal are not acceptable methods of contraception.

‡If a contraceptive method listed above is restricted by local regulations/guidelines, then it does not qualify as an acceptable method of contraception for subjects participating at sites in this country/region.

Subjects should be informed that taking the study medication may involve unknown risks to the fetus (unborn baby) if pregnancy were to occur during the study. In order to participate in the study subjects of childbearing potential must adhere to the contraception requirement (described above) from the day of study medication initiation (or 14 days prior to the initiation of study medication for oral contraception) throughout the study period up to 120 days after the last dose of trial therapy. If there is any question that a subject of childbearing potential will not reliably comply with the requirements for contraception, that subject should not be entered into the study.

5.5.3 Use in Pregnancy

If a subject inadvertently becomes pregnant while on treatment with pembrolizumab, the subject will immediately be removed from the study. The site will contact the subject at least monthly and document the subject's status until the pregnancy has been completed or terminated. The outcome of the pregnancy will be reported to the Sponsor, Vasgene Therapeutics and to Merck without delay and within 24 hours to the Sponsor and within 2 working days to Merck and Vasgene Therapeutics if the outcome is a serious adverse experience (e.g., death, abortion, congenital anomaly, or other disabling or life-threatening complication to the mother or newborn).

The study investigator will make every effort to obtain permission to follow the outcome of the pregnancy and report the condition of the fetus or newborn to the Sponsor. If a male subject impregnates his female partner the study personnel at the site must be informed immediately and the pregnancy reported to the Sponsor, Vasgene Therapeutics and to Merck and followed as described above and in Section 7.2.2.

5.5.4 Use in Nursing Women

It is unknown whether pembrolizumab and sEphB4-HSA is excreted in human milk. Since many drugs are excreted in human milk, and because of the potential for serious adverse reactions in the nursing infant, subjects who are breast-feeding are not eligible for enrollment.

5.6 Subject Withdrawal/Discontinuation Criteria

Subjects may withdraw consent at any time for any reason or be dropped from the trial at the discretion of the investigator should any untoward effect occur. In addition, a subject may be withdrawn by the investigator or the Sponsor if enrollment into the trial is inappropriate, the trial plan is violated, or for administrative and/or other safety reasons. Specific details regarding discontinuation or withdrawal are provided in Section 7.1.4 – Other Procedures.

A subject must be discontinued from the trial for any of the following reasons:

- The subject or legal representative (such as a parent or legal guardian) withdraws consent.
- Confirmed radiographic disease progression

  Note: For unconfirmed radiographic disease progression, imaging should be repeated after 2 additional cycles of study treatments in order to confirm progressive disease.

  Note: A subject may be granted an exception to continue on treatment with confirmed radiographic progression if clinically stable or clinically improved,
- Unacceptable adverse experiences as described in Section 5.2.1.2
- Intercurrent illness that prevents further administration of treatment
- Investigator's decision to withdraw the subject
- The subject has a confirmed positive serum pregnancy test
- Noncompliance with trial treatment or procedure requirements
- The subject is lost to follow-up
- Completed 24 months of uninterrupted treatment with pembrolizumab or 35 administrations of study medication, whichever is later.

Note: 24 months of study medication is calculated from the date of first dose. Subjects who stop pembrolizumab after 24 months may be eligible for up to one year of additional study treatment if they progress after stopping study treatment provided they meet the requirements detailed in Section 7.1.5.5

- Administrative reasons

The End of Treatment and Follow-up visit procedures are listed in Section 6 (Protocol Flow Chart) and Section 7.1.5 (Visit Requirements). After the end of treatment, each subject will be followed for 30 days for adverse event monitoring (serious adverse events will be collected for 90 days after the end of treatment as described in Section 7.2.3.1). Subjects who discontinue for reasons other than progressive disease will have post-treatment follow-up for disease status until disease progression, initiating a non-study cancer treatment, withdrawing consent or becoming lost to follow-up. After documented disease progression each subject will be followed by telephone for overall survival until death, withdrawal of consent, or the end of the study, whichever occurs first.

5.6.1 Discontinuation of Study Therapy after CR

Discontinuation of treatment may be considered for subjects who have attained a confirmed CR that have been treated for at least 24 weeks with pembrolizumab and had at least two treatments with pembrolizumab beyond the date when the initial CR was declared. Subjects who then experience radiographic disease progression may be eligible for up to one year of additional treatment with pembrolizumab via the Second Course Phase at the discretion of the investigator if no cancer treatment was administered since the last dose of pembrolizumab, the subject meets the safety parameters listed in the Inclusion/Exclusion criteria, and the trial is open. Subjects will resume therapy at the same dose and schedule at the time of initial discontinuation. Additional details are provided in Section 7.1.5.5.

5.7 Subject Replacement Strategy

Patients who are deemed not evaluable for response will be replaced

5.8 Clinical Criteria for Early Trial Termination

Early trial termination will be the result of the criteria specified below:

1. Quality or quantity of data recording is inaccurate or incomplete

2. Poor adherence to protocol and regulatory requirements

3. Incidence or severity of adverse drug reaction in this or other studies indicates a potential health hazard to subjects

4. Plans to modify or discontinue the development of the study drug

In the event of Merck decision to no longer supply study drug, ample notification will be provided so that appropriate adjustments to subject treatment can be made.

6.0 TRIAL FLOW CHART

6.1 Study Flow Chart

Trial Period:	**Screening Phase**		**Treatment Cycles[a]**								**End of Treatment**	**Post-Treatment**	
							To be repeated beyond 8 cycles						
Treatment Cycle/Title:	Pre-screening (Visit 1)	Main Study Screening (Visit 2)	1	2	3	4	5	6	7	8	Discon	Safety Follow-up	Survival Follow-Up
Scheduling Window (Days):		-28 to -1		± 3	± 3	± 3	± 3	± 3	± 3	± 3	At time of Discon	30 days post discon	Every 12 weeks
Administrative Procedures													
Pre-screening Consent	X												
Informed Consent		X											
Inclusion/Exclusion Criteria		X											
Demographics and Medical History	X												
Prior and Concomitant Medication Review	X												
Trial Treatment Administration			X	X	X	X	X	X	X	X			
Post-study anticancer therapy status												X	X
Survival Status						X				X	X	X	X
Clinical Procedures/Assessments													
Review Adverse Events	X	X	X	X	X	X	X	X	X	X	X	X	X
Full Physical Examination		X											
Directed Physical Examination	X		X	X	X	X	X	X	X	X			
Vital Signs and Weight	X	X	X	X	X	X	X	X	X	X			
ECOG Performance Status	X	X	X	X	X	X	X	X	X	X			
Laboratory Procedures/Assessments: analysis performed by LOCAL laboratory													
Pregnancy Test – Urine or Serum β-HCG[1]	X	X	X	X	X	X	X	X	X	X			
PT/INR and aPTT		X				X				X			
CBC with Differential		X	X	X	X	X	X	X	X	X			

Trial Period:	**Screening Phase**		**Treatment Cycles[a]**								**End of Treatment**	**Post-Treatment**	
Treatment Cycle/Title:	Pre-screening (Visit 1)	Main Study Screening (Visit 2)	1	2	3	4	To be repeated beyond 8 cycles 5	6	7	8	Discon	Safety Follow-up	Survival Follow-Up
Scheduling Window (Days):		-28 to -1		± 3	± 3	± 3	± 3	± 3	± 3	± 3	At time of Discon	30 days post discon	Every 12 weeks
Comprehensive Serum Chemistry Panel		X	X	X	X	X	X	X	X	X			
Urinalysis		X				X				X			
T3, FT4 and TSH		X				X				X			
Efficacy Measurements													
Tumor Imaging		X		X		X		X		X			
Tumor Biopsies/Archival Tissue Collection/Correlative Studies Blood													
Archival or Newly Obtained Tissue Collection		X			X								
Exploratory Biomarker Blood Collection		X				X				X	X		
Anti-Drug Antibodies and Serum Banking		X	X	X						X			

[1] only in women of child bearing potential

7.0 TRIAL PROCEDURES

7.1 Trial Procedures

The Trial Flow Chart - Section 6.0 summarizes the trial procedures to be performed at each visit. Individual trial procedures are described in detail below. It may be necessary to perform these procedures at unscheduled time points if deemed clinically necessary by the investigator.

Furthermore, additional evaluations/testing may be deemed necessary by the Sponsor and/or Merck for reasons related to subject safety. In some cases, such evaluation/testing may be potentially sensitive in nature (e.g., HIV, Hepatitis C, etc.), and thus local regulations may require that additional informed consent be obtained from the subject. In these cases, such evaluations/testing will be performed in accordance with those regulations.

7.1.1 Administrative Procedures

7.1.1.1 Informed Consent

The Investigator must obtain documented consent from each potential subject prior to participating in a clinical trial.

7.1.1.1.1 General Informed Consent

Consent must be documented by the subject's dated signature or by the subject's legally acceptable representative's dated signature on a consent form along with the dated signature of the person conducting the consent discussion.

A copy of the signed and dated consent form should be given to the subject before participation in the trial.

The initial informed consent form, any subsequent revised written informed consent form and any written information provided to the subject must receive the IRB/ERC's approval/favorable opinion in advance of use. The subject or his/her legally acceptable representative should be informed in a timely manner if new information becomes available that may be relevant to the subject's willingness to continue participation in the trial. The communication of this information will be provided and documented via a revised consent form or addendum to the original consent form that captures the subject's dated signature or by the subject's legally acceptable representative's dated signature.

Specifics about a trial and the trial population will be added to the consent form template at the protocol level.

The informed consent will adhere to IRB/ERC requirements, applicable laws and regulations and Sponsor requirements.

7.1.1.2 Inclusion/Exclusion Criteria

All inclusion and exclusion criteria will be reviewed by the investigator or qualified designee to ensure that the subject qualifies for the trial.

7.1.1.3 Medical History

A medical history will be obtained by the investigator or qualified designee. Medical history will include all active conditions, and any condition diagnosed within the prior 10 years that are considered to be clinically significant by the Investigator. Details regarding the disease for which the subject has enrolled in this study will be recorded separately and not listed as medical history.

7.1.1.4 Prior and Concomitant Medications Review

7.1.1.4.1 Prior Medications

The investigator or qualified designee will review prior medication use, including any protocol-specified washout requirement, and record prior medication taken by the subject within 28 days before starting the trial. Treatment for the disease for which the subject has enrolled in this study will be recorded separately and not listed as a prior medication.

7.1.1.4.2 Concomitant Medications

The investigator or qualified designee will record medication, if any, taken by the subject during the trial. All medications related to reportable SAEs and ECIs should be recorded as defined in Section 7.2.

7.1.1.5 Disease Details and Treatments

7.1.1.5.1 Disease Details

The investigator or qualified designee will obtain prior and current details regarding disease status.

7.1.1.5.2 Prior Treatment Details

The investigator or qualified designee will review all prior cancer treatments including systemic treatments, radiation and surgeries.

7.1.1.5.3 Subsequent Anti-Cancer Therapy Status

The investigator or qualified designee will review all new anti-neoplastic therapy initiated after the last dose of trial treatment. If a subject initiates a new anti-cancer therapy within 30 days after the last dose of trial treatment, the 30day Safety Follow-up visit must occur before the first dose of the new therapy. Once new anti-cancer therapy has been initiated the subject will move into survival follow-up.

7.1.1.6 Assignment of Screening Number

All patients will be assigned a study identification number (sequential number based on when first screened for participation in the trial, which will become the study ID once the patient is registered and starts treatment) and a random database number.

7.1.1.7 Trial Compliance (Medication/Diet/Activity/Other)

Drugs will be administered intravenously in the infusion rooms; doses and date and timing will be abstracted from the Pharmacy records and nursing notes

7.1.2 Clinical Procedures/Assessments

7.1.2.1 Adverse Event (AE) Monitoring

The investigator or qualified designee will assess each subject to evaluate for potential new or worsening AEs as specified in the Trial Flow Chart and more frequently if clinically indicated. Adverse experiences will be graded and recorded throughout the study and during the follow-up period according to NCI CTCAE Version 4.0 (see Section 11.2). Toxicities will be characterized in terms regarding seriousness, causality, toxicity grading, and action taken with regard to trial treatment.

For subjects receiving treatment with pembrolizumab all AEs of unknown etiology associated with pembrolizumab exposure should be evaluated to determine if it is possibly an event of clinical interest (ECI) of a potentially immunologic etiology (termed immune-related adverse events, or irAEs); see the separate ECI guidance document in Appendix 4 regarding the identification, evaluation and management of potential irAEs.

Please refer to section 7.2 for detailed information regarding the assessment and recording of AEs.

7.1.2.2 Full Physical Exam

The investigator or qualified designee will perform a complete physical exam during the screening period. Clinically significant abnormal findings should be recorded as medical history. A full physical exam should be performed during screening,

7.1.2.3 Directed Physical Exam

For cycles that do not require a full physical exam per the Trial Flow Chart, the investigator or qualified designee will perform a directed physical exam as clinically indicated prior to trial treatment administration.

7.1.2.4 Vital Signs

The investigator or qualified designee will take vital signs at screening, prior to the administration of each dose of trial treatment and at treatment discontinuation as specified in

the Trial Flow Chart (Section 6.0). Vital signs should include temperature, pulse, respiratory rate, weight and blood pressure. Height will be measured at screening only.

7.1.2.5 Eastern Cooperative Oncology Group (ECOG) Performance Scale

The investigator or qualified designee will assess ECOG status (see Section 11.1) at screening, prior to the administration of each dose of trial treatment and discontinuation of trial treatment as specified in the Trial Flow Chart.

7.1.2.6 Tumor Imaging and Assessment of Disease

Contrast computed tomography covering the chest, abdomen and pelvis per study calendar every 2 cycles is the modality of choice for assessment of response using RECIST 1.1 criteria. For patients in the head and neck cancer cohort, a neck soft tissue CT scan will be included. Patients in the non-small cell lung cohort will have soft tissue neck imaging included only if there was known measurable disease in that location at baseline. Patients who have no disease in the pelvis at baseline, and no pelvic symptoms may have the pelvic portion of the CT omitted.

7.1.2.7 Tumor Tissue Collection and Correlative Studies Blood Sampling

Tumor biopsy collection methodology will be determined by the investigator and should occur from the safest anatomic site. If there is no site deemed safe for biopsy by the treating investigator the biopsy procedure will be omitted.

Exploratory blood biomarker specimens are collected at enrollment, and every 4 cycles. 2 blood collection tubes (EDTA and Streck Cell Free RNA BCT) will be sent at room temperature to:

USC/Norris Cancer Center, Gill Laboratory
1441 Eastlake Avenue, NOR6332
Los Angeles, CA 90033
Tel 323-865-3909

Blood specimens for anti-drug antibodies and serum banking (serum separator tube) will be collected at baseline, cycle 1,2, 8 and every 8th cycle thereafter. These will also be sent to the Gill Laboratory for long term storage.

An additional blood collection tube (Streck Cell Free DNA BCT) will be sent at baseline and every 4 cycles as a CTC specimen to the Kuhn Laboratory.

Handling of CTC specimens
Packages must be shipped the same day of sample collection to ensure processing within24 hours of collection time. Please select:
1. Priority Overnight
2. No signature required

3. Email Notifications going to kuhnlab@usc.edu as recipient. Select all notifications types: ship, tendered, exception, and delivery.

Samples collected on Monday to Thursday must be shipped to:

Kuhn-Hicks Laboratory @ USC 1002 Childs Way, MCB 340 Los Angeles, CA 90089-3502 Phone: (213) 740-9945
Samples collected on Friday must be shipped for Saturday delivery and held for pick up at a local FedEx location. Please request the name of the Saturday on-call person to kuhnlab@usc.edu in order to address the package appropriately.

Kuhn-Hicks Laboratory @ USC 1002 Childs Way, MCB 340 Los Angeles, CA 90089-3502 Phone: (213) 740-9945
Email Notification (VERY IMPORTANT)
E-mail the Kuhn Lab (kuhnlab@usc.edu) the same day samples are collected and shipped. The e-mail must contain the following information:
1. Sample ID and type of sample (blood, bone marrow aspirate, tissue touch preparation)
2. # of tubes
3. # of tissue touch prep slides if applicable
4. Date and time of sample collection
5. FedEx tracking number

All tissue shipments must be coordinated with the PI via email jorge.nieva@med.usc.edu 2 business days prior to shipment. All shipments must be addressed to:

Jorge J. Nieva
USC/Norris Cancer Hospital
1441 Eastlake Ave, NTT-3447
Los Angeles, CA 90033
Tracking number for shipment must be provided to jorge.nieva@med.usc.edu

7.1.3 Laboratory Procedures/Assessments

Details regarding specific laboratory procedures/assessments to be performed in this trial are provided below. Laboratory Safety Evaluations (Hematology, Chemistry and Urinalysis)

Laboratory tests for hematology, chemistry, urinalysis, and others are specified in Table 5.

Table 5 Laboratory Tests

Hematology	Chemistry	Urinalysis	Other
Hematocrit	Albumin	Blood	Serum β-human chorionic gonadotropin†
Hemoglobin	Alkaline phosphatase	Glucose	(β-hCG)†
Platelet count	Alanine aminotransferase (ALT)	Protein	PT (INR)
WBC (total and differential)	Aspartate aminotransferase (AST)	Specific gravity	aPTT
Red Blood Cell Count	Lactate dehydrogenase (LDH)	Microscopic exam *(If abnormal)*	Total triiodothyronine (T3)
Absolute Neutrophil Count	Carbon Dioxide ‡	results are noted	Free thyroxine (T4)
Absolute Lymphocyte Count	*(CO_2 or bicarbonate)*	Urine pregnancy test †	Thyroid stimulating hormone (TSH)
	Uric Acid		PK
	Calcium		
	Chloride		Blood for correlative biomarker studies
	Glucose		Stored serum for anti-drug antibodies
	Phosphorus		
	Potassium		
	Sodium		
	Magnesium		
	Total Bilirubin		
	Direct Bilirubin *(If total bilirubin is elevated above the upper limit of normal)*		
	Total protein		
	Blood Urea Nitrogen		

† Perform on women of childbearing potential only. If urine pregnancy results cannot be confirmed as negative, a serum pregnancy test will be required.

‡ If considered standard of care in your region.

Laboratory tests for screening or entry into the Second Course Phase should be performed within 10 days prior to the first dose of treatment. After Cycle 1, pre-dose laboratory procedures can be conducted up to 72 hours prior to dosing. Results must be reviewed by the investigator or qualified designee and found to be acceptable prior to each dose of trial treatment.

7.1.4 Other Procedures

7.1.4.1 Withdrawal/Discontinuation

When a subject discontinues/withdraws prior to trial completion, all applicable activities scheduled for the final trial visit should be performed at the time of discontinuation. Any adverse events which are present at the time of discontinuation/withdrawal should be followed in accordance with the safety requirements outlined in Section 7.2 - Assessing and Recording Adverse Events. Subjects who a) attain a CR or b) complete 24 months of treatment with pembrolizumab may discontinue treatment with the option of restarting treatment if they meet the criteria specified in Section 7.1.5.5. After discontinuing treatment following assessment of CR, these subjects should return to the site for a Safety Follow-up Visit (described in Section 7.1.5.3.1) and then proceed to the Follow-Up Period of the study (described in Section 7.1.5.4).

7.1.4.2 Blinding/Unblinding

Not applicable

7.1.5 Visit Requirements

Visit requirements are outlined in Section 6.0 - Trial Flow Chart. Specific procedure-related details are provided above in Section 7.1 - Trial Procedures.

7.1.5.1 Safety Follow-Up Visit

The mandatory Safety Follow-Up Visit should be conducted approximately 30 days after the last dose of trial treatment or before the initiation of a new anti-cancer treatment, whichever comes first. All AEs that occur prior to the Safety Follow-Up Visit should be recorded. Subjects with an AE of Grade > 1 will be followed until the resolution of the AE to Grade 0-1 or until the beginning of a new anti-neoplastic therapy, whichever occurs first. SAEs that occur within 90 days of the end of treatment or before initiation of a new anti-cancer treatment should also be followed and recorded. Subjects who are eligible for retreatment with pembrolizumab (as described in Section 7.1.5.5) may have up to two safety follow-up visits, one after the Treatment Period and one after the Second Course Phase.

7.1.5.2 Survival Follow-up

Once a subject experiences confirmed disease progression or starts a new anti-cancer therapy, the subject moves into the survival follow-up phase and should be contacted by telephone

every 12 weeks to assess for survival status until death, withdrawal of consent, or the end of the study, whichever occurs first.

7.2 Assessing and Recording Adverse Events

An adverse event is defined as any untoward medical occurrence in a patient or clinical investigation subject administered a pharmaceutical product and which does not necessarily have to have a causal relationship with this treatment. An adverse event can therefore be any unfavorable and unintended sign (including an abnormal laboratory finding, for example), symptom, or disease temporally associated with the use of a medicinal product or protocol-specified procedure, whether or not considered related to the medicinal product or protocol-specified procedure. Any worsening (i.e., any clinically significant adverse change in frequency and/or intensity) of a preexisting condition that is temporally associated with the use of the Vasgene's and/or Merck's product, is also an adverse event.

Changes resulting from normal growth and development that do not vary significantly in frequency or severity from expected levels are not to be considered adverse events. Examples of this may include, but are not limited to, teething, typical crying in infants and children and onset of menses or menopause occurring at a physiologically appropriate time.

Merck product includes any pharmaceutical product, biological product, device, diagnostic agent or protocol-specified procedure, whether investigational (including placebo or active comparator medication) or marketed, manufactured by, licensed by, provided by or distributed by Merck for human use.

Adverse events may occur during the course of the use of Merck product in clinical trials, or as prescribed in clinical practice, from overdose (whether accidental or intentional), from abuse and from withdrawal.

Progression of the cancer under study is not considered an adverse event.

All adverse events that occur after the consent form is signed but before treatment allocation/randomization must be reported by the investigator if they cause the subject to be excluded from the trial, or are the result of a protocol-specified intervention, including but not limited to washout or discontinuation of usual therapy, diet, placebo treatment or a procedure.

From the time of treatment allocation/randomization through 30 days following cessation of treatment, all adverse events must be reported by the investigator. Such events will be recorded at each examination on the Adverse Event case report forms/worksheets. The reporting timeframe for adverse events meeting any serious criteria is described in section 7.2.3.1. The investigator will make every attempt to follow all subjects with non-serious adverse events for outcome.

Adverse events will not be collected for subjects during the pre-screening period

7.2.1 Definition of an Overdose for This Protocol and Reporting of Overdose to the Sponsor, Vasgene Therapeutics and to Merck

For purposes of this trial, an overdose of pembrolizumab will be defined as any dose of 1,000 mg or greater (≥5 times the indicated dose). No specific information is available on the treatment of overdose of pembrolizumab. Appropriate supportive treatment should be provided if clinically indicated. In the event of overdose, the subject should be observed closely for signs of toxicity. Appropriate supportive treatment should be provided if clinically indicated.

If an adverse event(s) is associated with ("results from") the overdose of a Merck product, the adverse event(s) is reported as a serious adverse event, even if no other seriousness criteria are met.

If a dose of Merck's product meeting the protocol definition of overdose is taken without any associated clinical symptoms or abnormal laboratory results, the overdose is reported as a non-serious Event of Clinical Interest (ECI), using the terminology "accidental or intentional overdose without adverse effect."

All reports of overdose with and without an adverse event must be reported within 24 hours to the Sponsor, Vasgene Therapeutics and within 2 working days hours to Merck Global Safety. (Attn: Worldwide Product Safety; FAX 215 993-1220)

7.2.2 Reporting of Pregnancy and Lactation to the Sponsor, Vasgene Therapeutics and to Merck

Although pregnancy and lactation are not considered adverse events, it is the responsibility of investigators or their designees to report any pregnancy or lactation in a subject (spontaneously reported to them) that occurs during the trial.

Pregnancies and lactations that occur after the consent form is signed but before treatment allocation/randomization must be reported by the investigator if they cause the subject to be excluded from the trial, or are the result of a protocol-specified intervention, including but not limited to washout or discontinuation of usual therapy, diet, placebo treatment or a procedure.

Pregnancies and lactations that occur from the time of treatment allocation/randomization through 120 days following cessation of Sponsor's product, or 30 days following cessation of treatment if the subject initiates new anticancer therapy, whichever is earlier, must be reported by the investigator. All reported pregnancies must be followed to the completion/termination of the pregnancy. Pregnancy outcomes of spontaneous abortion, missed abortion, benign hydatidiform mole, blighted ovum, fetal death, intrauterine death, miscarriage and stillbirth must be reported as serious events (Important Medical Events). If the pregnancy continues to term, the outcome (health of infant) must also be reported.

Such events must be reported within 24 hours to the Sponsor, Vasgene Therapeutics and within 2 working days to Merck Global Safety. (Attn: Worldwide Product Safety; FAX 215 993-1220)

7.2.3 Immediate Reporting of Adverse Events to the Sponsor, Vasgene Therapeutics and to Merck

7.2.3.1 Serious Adverse Events

A serious adverse event is any adverse event occurring at any dose or during any use of Vasgene's and/or Merck's product that:

- Results in death;
- Is life threatening;
- Results in persistent or significant disability/incapacity;
- Results in or prolongs an existing inpatient hospitalization;
- Is a congenital anomaly/birth defect;
- Is an other important medical event

- **Note:** In addition to the above criteria, adverse events meeting either of the below criteria, although not serious per ICH definition, are reportable to the Merck in the same timeframe as SAEs to meet certain local requirements. Therefore, these events are considered serious by Merck for collection purposes.
    - Is a new cancer (that is not a condition of the study);
    - Is associated with an overdose.

Refer to Table 6 for additional details regarding each of the above criteria.

For the time period beginning when the consent form is signed until treatment allocation/randomization, any serious adverse event, or follow up to a serious adverse event, including death due to any cause other than progression of the cancer under study, that occurs to any subject must be reported within 24 hours to the Sponsor, Vasgene Therapeutics and within 2 working days to Merck Global Safety if it causes the subject to be excluded from the trial, or is the result of a protocol-specified intervention, including but not limited to washout or discontinuation of usual therapy, diet, placebo treatment or a procedure.

For the time period beginning at treatment allocation/randomization through 90 days following cessation of treatment, or 30 days following cessation of treatment if the subject initiates new anticancer therapy, whichever is earlier, any serious adverse event, or follow up to a serious adverse event, including death due to any cause other than progression of the cancer under, whether or not related to the Vasgene Therapeutics product and/or Merck product, must be reported within 24 hours to the Sponsor, Vasgene Therapeutics and within 2 working days to Merck Global Safety.

Additionally, any serious adverse event, considered by an investigator who is a qualified physician to be related to Merck and/or Vasgene product that is brought to the attention of the investigator at any time following consent through the end of the specified safety follow-up period specified in the paragraph above, or at any time outside of the time period specified in the previous paragraph also must be reported immediately to the Sponsor, Vasgene Therapeutics and to Merck Global Safety.

All subjects with serious adverse events must be followed up for outcome.

SAE Notification to Merck and Vasgene Therapeutics Inc:

All investigate sites are required to complete MedWatch 3500A (Mandatory Reporting Form) for SAEs. All sites must submit the form as two separate communications:1) Vasgene Therapeutics, Inc. within 24hr of site becoming aware of the event 2) Merck Global Safety within 2 working days of becoming aware of the event. Please see the Appendix for SAE cover forms.

Please include the principal investigator in all communications with Merck and Vasgene Therapeutics, Inc.

- SAE reports and any other relevant safety information are to be forwarded to the Merck Global Safety facsimile number: +1-215-993-1220

- SAE reports and any other relevant safety information are to be forwarded to Vasgene Therapeutics Inc. contacts: Linda@vasgene.com, Maricela Oviedo-Collins (OVIEDOCO@med.usc.edu) and Valery Krasnoperov (valeryhome@gmail.com)

SAE notification to the FDA:

- USC: Study team to work with CISO QA to submit to the FDA using MedWatch 3500A form in accordance within the FDA required timelines

SAE reports and any other relevant safety information are to be forwarded to the Merck

A copy of all 15 Day Reports and Annual Progress Reports is submitted as required by FDA, European Union (EU), Pharmaceutical and Medical Devices agency (PMDA) or other local regulators. Investigators will cross reference this submission according to local regulations to the Merck Investigational Compound Number (IND, CSA, etc.) at the time of submission. Additionally investigators will submit a copy of these reports to Merck & Co., Inc. (Attn: Worldwide Product Safety; FAX 215 993-1220) at the time of submission to FDA.

7.2.3.2 Events of Clinical Interest

Selected non-serious and serious adverse events are also known as Events of Clinical Interest (ECI) and must be reported within 24 hours to the Sponsor, Vasgene Therapeutics and within 2 working days to Merck Global Safety. (Attn: Worldwide Product Safety; FAX 215 993-1220).

For the time period beginning when the consent form is signed until treatment allocation/randomization, any ECI, or follow up to an ECI, that occurs to any subject must be reported within 24 hours to the Sponsor, Vasgene Therapeutics and within 2 working days to Merck Global Safety if it causes the subject to be excluded from the trial, or is the result of a protocol-specified intervention, including but not limited to washout or discontinuation of usual therapy, diet, placebo treatment or a procedure.

For the time period beginning at treatment allocation/randomization through 90 days following cessation of treatment, or 30 days following cessation of treatment if the subject initiates new anticancer therapy, whichever is earlier, any ECI, or follow up to an ECI, whether or not related to Merck and Vasgene product, must be reported within 24 hours to the Sponsor, Vasgene Therapeutics and within 24 hours to Merck Global Safety.

Events of clinical interest for this trial include:

1. an overdose of Merck product, as defined in Section 7.2.1 - Definition of an Overdose for This Protocol and Reporting of Overdose to the Sponsor, that is not associated with clinical symptoms or abnormal laboratory results.

2. an elevated AST or ALT lab value that is greater than or equal to 3X the upper limit of normal and an elevated total bilirubin lab value that is greater than or equal to 2X the upper limit of normal and, at the same time, an alkaline phosphatase lab value that is less than 2X the upper limit of normal, as determined by way of protocol-specified laboratory testing or unscheduled laboratory testing.*

*Note: These criteria are based upon available regulatory guidance documents. The purpose of the criteria is to specify a threshold of abnormal hepatic tests that may require an additional evaluation for an underlying etiology.

7.2.3.3 Protocol-Specific Exceptions to Serious Adverse Event Reporting

Efficacy endpoints as outlined in this section will not be reported to Merck as described in Section 7.2.3.- Immediate Reporting of Adverse Events to the Sponsor and to Merck, unless there is evidence suggesting a causal relationship between the drug and the event. Any such event will be submitted to the Sponsor within 24 hours and to Merck Global Safety within 2 working days either by electronic or paper media.

Specifically, the suspected/actual events covered in this exception include any event that is disease progression of the cancer under study.

The Sponsor will monitor unblinded aggregated efficacy endpoint events and safety data to ensure the safety of the subjects in the trial. Any suspected endpoint which upon review is not progression of the cancer under study will be forwarded to Vasgene Therapeutics and Merck Global Safety as a SAE within 2 working days of determination that the event is not progression of the cancer under study

Hospitalization related to convenience (e.g.transportation issues etc.) will not be considered a SAE.

7.2.4 Evaluating Adverse Events

An investigator who is a qualified physician will evaluate all adverse events according to the NCI Common Terminology for Adverse Events (CTCAE), version 4.0. Any adverse event which changes CTCAE grade over the course of a given episode will have each change of grade recorded on the adverse event case report forms/worksheets.

All adverse events regardless of CTCAE grade must also be evaluated for seriousness.

Table 6 Evaluating Adverse Events

An investigator who is a qualified physician, will evaluate all adverse events as to:

V4.0 CTCAE Grading	**Grade 1**	**Mild; asymptomatic or mid symptoms; clinical or diagnostic observations only; intervention not indicated.**
	Grade 2	**Moderate; minimal, local or noninvasive intervention indicated; limiting age-appropriate instrumental ADL.**
	Grade 3	**Severe or medically significant but not immediately life-threatening; hospitalization or prolongation or hospitalization indicated; disabling; limiting self-care ADL.**
	Grade 4	**Life threatening consequences; urgent intervention indicated.**
	Grade 5	**Death related to AE**
Seriousness	A serious adverse event is any adverse event occurring at any dose or during any use of Merck product that:	
	†**Results in death**; or	
	†**Is life threatening; or** places the subject, in the view of the investigator, at immediate risk of death from the event as it occurred (Note: This does not include an adverse event that, had it occurred in a more severe form, might have caused death.); or	
	†**Results in a persistent or significant disability/incapacity** (substantial disruption of one's ability to conduct normal life functions); or	
	†**Results in or prolongs an existing inpatient hospitalization** (hospitalization is defined as an inpatient admission, regardless of length of stay, even if the hospitalization is a precautionary measure for continued observation. (Note: Hospitalization for an elective procedure to treat a pre-existing condition that has not worsened is not a serious adverse event. A pre-existing condition is a clinical condition that is diagnosed prior to the use of a Merck product and is documented in the patient's medical history.); or	
	†**Is a congenital anomaly/birth defect** (in offspring of subject taking the product regardless of time to diagnosis);or	
	Is a new **cancer** (that is not a condition of the study) **(**although not serious per ICH definition, is reportable to the Sponsor within 24 hours and to Merck within 2 working days to meet certain local requirements); **or**	
	Is an overdose (whether accidental or intentional). Any adverse event associated with an overdose is considered a serious adverse event for collection purposes. An overdose that is not associated with an adverse event is considered a non-serious event of clinical interest and must be reported within 24 hours to the Sponsor and to Merck within 2 working days..	

	Other important medical events that may not result in death, not be life threatening, or not require hospitalization may be considered a serious adverse event when, based upon appropriate medical judgment, the event may jeopardize the subject and may require medical or surgical intervention to prevent one of the outcomes listed previously (designated above by a †).	
Duration	Record the start and stop dates of the adverse event. If less than 1 day, indicate the appropriate length of time and units	
Action taken	Did the adverse event cause Merck product to be discontinued?	
Relationship to Merck Product	Did Merck product cause the adverse event? The determination of the likelihood that Merck product caused the adverse event will be provided by an investigator who is a qualified physician. The investigator's signed/dated initials on the source document or worksheet that supports the causality noted on the AE form, ensures that a medically qualified assessment of causality was done. This initialed document must be retained for the required regulatory time frame. The criteria below are intended as reference guidelines to assist the investigator in assessing the likelihood of a relationship between the test drug and the adverse event based upon the available information. **The following components are to be used to assess the relationship between Merck product and the AE**; the greater the correlation with the components and their respective elements (in number and/or intensity), the more likely Merck product caused the adverse event (AE):	
	Exposure	Is there evidence that the subject was actually exposed to Merck product such as: reliable history, acceptable compliance assessment (pill count, diary, etc.), expected pharmacologic effect, or measurement of drug/metabolite in bodily specimen?
	Time Course	Did the AE follow in a reasonable temporal sequence from administration of Merck product? Is the time of onset of the AE compatible with a drug-induced effect (applies to trials with investigational medicinal product)?
	Likely Cause	Is the AE not reasonably explained by another etiology such as underlying disease, other drug(s)/vaccine(s), or other host or environmental factors

Relationship to Merck Product (continued)	**The following components are to be used to assess the relationship between the test drug and the AE: (continued)**	
	Dechallenge	Was Merck product discontinued or dose/exposure/frequency reduced? If yes, did the AE resolve or improve? If yes, this is a positive dechallenge. If no, this is a negative dechallenge. (Note: This criterion is not applicable if: (1) the AE resulted in death or permanent disability; (2) the AE resolved/improved despite continuation of the Sponsor's product; or (3) the trial is a single-dose drug trial); or (4) Sponsor's product(s) is/are only used one time.)
	Rechallenge	Was the subject re-exposed to Merck product in this study? If yes, did the AE recur or worsen? If yes, this is a positive rechallenge. If no, this is a negative rechallenge. (Note: This criterion is not applicable if: (1) the initial AE resulted in death or permanent disability, or (2) the trial is a single-dose drug trial); or (3) Sponsor's product(s) is/are used only one time). NOTE: IF A RECHALLENGE IS PLANNED FOR AN ADVERSE EVENT WHICH WAS SERIOUS AND WHICH MAY HAVE BEEN CAUSED BY MERCK PRODUCT, OR IF REEXPOSURE TO MERCK PRODUCT POSES ADDITIONAL POTENTIAL SIGNIFICANT RISK TO THE SUBJECT, THEN THE RECHALLENGE MUST BE APPROVED IN ADVANCE BY THE SPONSOR AS PER DOSE MODIFICATION GUIDELINES IN THE PROTOCOL.
	Consistency with Trial Treatment Profile	Is the clinical/pathological presentation of the AE consistent with previous knowledge regarding Merck product or drug class pharmacology or toxicology?
The assessment of relationship will be reported on the case report forms /worksheets by an investigator who is a qualified physician according to his/her best clinical judgment, including consideration of the above elements.		
Record one of the following		**Use the following scale of criteria as guidance (not all criteria must be present to be indicative of Merck product relationship).**
Yes, there is a reasonable possibility of Merck product relationship.		There is evidence of exposure to Merck product. The temporal sequence of the AE onset relative to the administration of Merck product is reasonable. The AE is more likely explained by Merck product than by another cause.
No, there is not a reasonable possibility of Merck product relationship		Subject did not receive the Merck product OR temporal sequence of the AE onset relative to administration of Merck product is not reasonable OR the AE is more likely explained by another cause than the Merck product. (Also entered for a subject with overdose without an associated AE.)

7.2.5 Sponsor Responsibility for Reporting Adverse Events

All Adverse Events will be reported to regulatory authorities, IRB/IECs and investigators in accordance with all applicable global laws and regulations.

8.0 STATISTICAL ANALYSIS PLAN

8.1 Statistical Analysis Plan Summary

This is a single arm phase IIa clinical trial, conducted in 2 independent patient groups, consisting of (a) non-small cell lung and (b) head and neck squamous cell carcinoma patients, intended to determine the safety of the combination as well overall response rate, together with the impact of the two drug combination on T cell and NK cell trafficking into the tumor.

8.2 Statistical Analysis Plan and Sample Size Determination

Determination of overall response rate will be calculated based on the evaluable population of patients who received at least 1 dose of therapy. Best overall response at any time will be compared in the study population to benchmark values in the literature. Overall and progression free survival will be determined according to the method of Kaplan and Meier and analyzed for each cohort. For the endpoints of ORR, OS and PFS, each of these will be analyzed in groupings of patients according to biomarkers of interest including (a) PD-L1 expression on archival tissue and current peripheral blood CTCs, (b) peripheral blood T cell subset analysis, (c) quantitative T-cell tumor infiltration, and (d) genomic complexity and (e) integrin expression pattern in tumor blood vessels. The impact of treatment on the levels of PD-L1 expression, T-cell subsets and Tumor infiltrating lymphocytes will be compared in archival and post treatment biopsy specimens. Adverse events will be tabulated for the duration of the trial and reported in tabular format.

Sample size is determined independently for each of the 2 patient groups, and is based on overall response rate using a Simon Optimal 2-stage design.

H_0: $\pi<20\%$

H_a: $\pi> 45\%$

where π = the true response rate (same rate used for NSCLC and H&N Cancer)

For the type 1 and type 2 error probability, $\alpha=\beta=0.10$, up to 25 patients are required in each arm to have sufficient power to test the hypothesis. Interim response rate will be determined after 14 patients have been enrolled on each arm. If there are fewer than 3 responses in the first 14 patients, the alternate hypothesis will be rejected and that arm of the study will be closed. If 4 or more responses occur, then accrual will continue on that arm until 25 patients have been treated and evaluated. If 8 or more of the 25 patients experience an objective response, then we will conclude that the true response rate is clearly greater than 20% and not incompatible with a response rate of 45% - and this will serve as a signal indicating that the

two drugs together are better than either alone. However, if 7 or fewer patients experience a response, then we will conclude that the true response rate is less than 45% and not incompatible with a response rate of 20%.

Once 14 patients in each cohort have been enrolled, accrual to the study can continue for up to 4 additional patients while waiting for the first 14 patients to be evaluated. Patients will be considered evaluable for response if they are eligible for treatment, and receive 1 dose of therapy. Those patients who are deemed not evaluable will be replaced.

Toxicity Stopping Rules

Unacceptable toxicity is defined as drug related CTCAE v4.0 toxicity of grade 3 or more that does not resolve within 12 weeks. Patients who are removed from the trial for unacceptable toxicity and have not yet been evaluable for response will be classified as non-responders. We anticipate a drug related discontinuation rate of 10%.

For the purpose of assessing tolerability on an on-going manner and to have criteria to lead to review of all safety and toxicity in order to consider modifying the starting dose of either sEphB4-HSA or Pembrolizumab or both, unacceptable toxicity (TOX) will be defined as the inability to continue treatment to a 3rd course. Each cohort, a) lung and b) head/neck will be evaluated separately for:

- any toxicity (at least possibly related to treatment) that lead to treatment discontinuation prior to the start of the 3rd course
- inability for immune related toxicities to resolve within 42 days, during the 1st two courses.

Criteria for flagging an excessive number of patients with TOX are based on the sequential probability ratio test with α=0.10, β=0.10, p_o=0.10 and p_a=0.30. Every time a patient is classified as having had a TOX, the cumulative number of patients (X) who have experienced a TOX will be compared to the number of patients (N) who were enrolled at the time that the patient who experienced TOX, was enrolled. If the number of patients, N, is greater than N_X, the number given in the bottom row of the Table below, then the boundary has not been crossed. If N is less than or equal to N_X, then the boundary has been crossed and a careful review of all the toxicities and tolerability will be initiated.

Table: Boundary for Monitoring Safety/Tolerability

X: # pts who experienced a TOX	3	4	5	6
N_x: Boundary crossed if # pts. at risk (N) is ≤ N_x	≤7	≤12	≤18	≤23

9.0 LABELING, PACKAGING, STORAGE AND RETURN OF CLINICAL SUPPLIES

9.1 Investigational Product

The investigator shall take responsibility for and shall take all steps to maintain appropriate records and ensure appropriate supply, storage, handling, distribution and usage of investigational product in accordance with the protocol and any applicable laws and regulations.

Clinical Supplies will be provided by Merck and Vasgene as summarized in Table 7.

Table 7 Product Descriptions

Product Name & Potency	Dosage Form
pembrolizumab 50 mg	Lyophilized Powder for Injection
pembrolizumab 100 mg/ 4mL	Solution for Injection
sEphB4-HSA 25 mg/mL	Solution in 10 mM L-Histidine, 150 mM Sodium Chloride, and 10% Sucrose, pH 7.0

9.2 Packaging and Labeling Information of sEphB4-HSA

The study drug will be packaged and labeled according to current Good Manufacturing Practices (GMP). Details of the packaging and labeling of clinical supplies may be found in the Pharmacy Manual. sEphB4-HSA is supplied in a single-use vial containing 10 mL (250mg) of sEphB4-HSA. Each vial contains a concentrated solution with the equivalent of 250 mg of sEphB4HSA (25 mg/mL).

Dose calculations for sEphB4-HSA will be on the basis of actual body weight at the start of each cycle.

- Allow the appropriate number of vials of sEphB4-HSA to stand at room temperature for approximately 15 minutes before preparation.
- Ensure that the sEphB4-HSA solution is a colorless, clear to slightly opalescent solution, essentially free of particles on visual inspection.
- Aseptically withdraw the required volume of sEphB4-HSA solution into a syringe, and dispense into an i.v. bag. (If multiple vials are needed for a subject, it is important to use a separate sterile syringe and needle for each vial to prevent problems such as dulling of needle tip, stopper coring, repeated friction of plunger against syringe barrel wall and so on).
- The total dose to be administered will be diluted to a total volume of 200 mL with sterile normal saline and placed in EVA mixing container (B.Braun Cat #2112389).

- Prepare the sEphB4-HSA solution for infusion per the example provided below: Total dose should be calculated as follows: Subject body weight in kg x 10 mg (for the 10 mg/kg dose) = total dose in mg; a subject with a body weight of 70 kg would be administered 700 mg of sEphB4-HSA (70 kg x 1o.0 mg/kg = 700 mg). thirty two mL of sEphB4-HSA and 168 mL of normal saline would be mixed in the i.v. bag and the solution would be infused over 60 minutes.
- Mix by GENTLY inverting several times. DO NOT shake.
- Visually inspect the final solution. If the infusion is not clear or the contents appear to contain precipitate, the solution should be discarded and documented on the Drug Accountability Log.
- Record the time sEphB4-HSA was prepared on the i.v. bag label.
- Attach the i.v. bag containing the sEphB4-HSA solution to the Non- PVC tubing with infusion set, 0.2 μm in-line filter, and infusion pump.
- The infusion rate of the infusion pump should be adjusted to allow for a total infusion time of 60 minutes.
- At the end of the infusion period, flush the line with a sufficient quantity of normal saline. Do not enter into each vial more than once. Do not prepare sEphB4-HSA for infusion in glass syringes. Do not administer study drug as an i.v. push or bolus injection.

9.3 Packaging and Labeling Information of Pembrolizumab

Clinical supplies will be affixed with a clinical label in accordance with regulatory requirements.

9.4 Clinical Supplies Disclosure

This trial is open-label; therefore, the subject, the trial site personnel, the Sponsor and/or designee are not blinded to treatment. Drug identity (name, strength) is included in the label text; random code/disclosure envelopes or lists are not provided.

9.5 Storage and Handling Requirements

Clinical supplies must be stored in a secure, limited-access location under the storage conditions specified on the label.

Receipt and dispensing of trial medication must be recorded by an authorized person at the trial site.

Clinical supplies may not be used for any purpose other than that stated in the protocol.

9.6 Returns and Reconciliation

The investigator is responsible for keeping accurate records of the clinical supplies received from Merck, Vasgene or designee, the amount dispensed to and returned by the subjects and the amount remaining at the conclusion of the trial.

Upon completion or termination of the study, all unused and/or partially used investigational product will be destroyed at the site per institutional policy. It is the Investigator's responsibility to arrange for disposal of all empty containers, provided that procedures for proper disposal have been established according to applicable federal, state, local and institutional guidelines and procedures, and provided that appropriate records of disposal are kept.

10.0 ADMINISTRATIVE AND REGULATORY DETAILS

10.1 Compliance with Trial Registration and Results Posting Requirements

Under the terms of the Food and Drug Administration Modernization Act (FDAMA) and the Food and Drug Administration Amendments Act (FDAAA), the Sponsor of the trial is solely responsible for determining whether the trial and its results are subject to the requirements for submission to the Clinical Trials Data Bank, http://www.clinicaltrials.gov. Information posted will allow subjects to identify potentially appropriate trials for their disease conditions and pursue participation by calling a central contact number for further information on appropriate trial locations and trial site contact information.

10.2 Study Management

10.2.1 Conflict of Interest

All investigators will follow the University conflict of interest policy. Any USC investigator who has a conflict of interest with this study (patent ownership, royalties, or financial gain greater than the minimum allowable by their institution, etc.) must complete a "Statement of Outside Interests Related to Research" Form. The application is reviewed and approved by the Conflict of Interest Review Committee (CIRC) USC conflict of interest policy is available at

http://ooc.usc.edu/conflict-interest-research

10.2.2 Institutional Review Board (IRB) Approval and Consent Process

It is expected that the IRB will have the proper representation and function in accordance with federally mandated regulations. The IRB should approve the consent form and protocol and all study related documents used in the study (e.g. QOL questionnaire, pill diary, brochure, advertisement etc).

In obtaining and documenting informed consent, the investigator should comply with the applicable regulatory requirement(s), and should adhere to Good Clinical Practice (GCP) and to ethical principles that have their origin in the Declaration of Helsinki.

Before recruitment and enrollment onto this study, the patient will be given a full explanation of the study and will be given the opportunity to review the consent form. Each consent form must include all the relevant elements currently required by the FDA Regulations and local or state regulations. Once this essential information has been provided to the patient and the investigator is assured that the patient understands the implications of participating in the study, the patient will be asked to give consent to participate in the study by signing a dated IRB-approved consent form.

Prior to a patient's participation in the trial, the written informed consent form should be signed and personally dated by the patient and by the person authorized to obtain the informed consent

10.2.3 Registration Procedures

10.2.3.1 USC Registration

For patients enrolled at USC, the Research Coordinator must complete the protocol eligibility form to ensure that the patient is eligible. The PI will review the patient eligibility (with assistance from the Research Coordinator- who will assemble the required source documents, and do an initial review) prior to registering the patient on study.

The Research Coordinator or data manager will then register the patient into the Cancer Center database, Café, by accessing the Registration forms. Likewise, after the patient has completed the study, the Off Study forms in cafe will need to be completed, for Off Treatment and Off Study.

10.2.4 Records and Data Submission

10.2.4.1 Confidentiality of Records

The original data collection forms will be kept in secure file cabinets, for USC patients forms will be kept in the Clinical Investigations Support Office (CISO).

10.2.4.2 Patient Consent Form

At the time of registration, signed and dated copies of the patient Informed Consent with the Human Rights and the HIPAA authorization must be given to the patient. Institutional policy regarding distribution and location of original consent documents should be followed. When a study is opened at two or more institutions, a copy of the signed consent and HIPAA should be sent to USC CISO QA team as soon as possible, and not later than within 5 business days of obtaining consent. For patients consented at USC/LAC, institutional policy should be followed: a copy of ICF and HIPAA should be uploaded through True to USC CRO and to CISO QA Team. The original will be kept in the patient research chart maintained by the study assigned Data Manager.

10.2.4.3 Registration Eligibility Worksheet

At the time of registration, the completed Eligibility Worksheet will be submitted to the QA Monitor at CISO for review of eligibility compliance.

10.2.4.4 Data Collection Forms and Submission Schedule

If a treatment trial, protocol data will be entered into eCRFs in MediData.

Within two weeks of registration, the data manager will complete the initial set of On Study forms and baseline Toxicities

Within two weeks of completion of each course of treatment, the data manager must complete the Course Assessment, Toxicities, and if appropriate Response data.

After Off Treatment, within two weeks of each follow up, complete the Follow Up forms.

10.2.5 Data Management and Monitoring/Auditing

10.2.5.1 Active Monitoring Program Details

a) **Adherence to Protocol/Per Patient**: It is the responsibility of the USC Principal Investigator (PI) to ensure that patient recruitment and enrollment, treatment, follow-up for toxicities and response, and documentation and reporting at USC are all performed as specified in the protocol. When a study is opened at two or more institutions, the PI at each institution will assume the responsibilities for the day-to-day monitoring of the trial, as described below.

b) **Day-to-Day Monitoring – Eligibility:** At USC, the Study Coordinator will assist the Investigator in reviewing eligibility and will assemble the required source documents, and do a final review by completing an Eligibility Registration Worksheet. When a study is opened at two or more institutions, the PI at each institution will review the patient eligibility in accordance with that institution's policy. For all institutions, the Eligibility Registration Worksheet with a copy of Informed Consent and supporting source documents will be submitted to CISO QA via email or Fax for verification prior to registering the patient on study.

c) **Day-to-Day Monitoring – Informed Consent:** Prior to registering the patient on study, the Study Coordinator will review the informed consent, to ensure that the patient has signed and dated the most current IRB-approved form, and that the form has been signed and dated by the person obtaining the consent as well as appropriate witnesses. A copy of the ICF will also be provided to CISO QA for review. CISO SOP 3.3 will be followed.

d) **Day-to-Day Monitoring – Treatment:** The PI and co-investigators are responsible for ensuring that treatment is given per protocol. The Study Coordinator will review the treatment orders with the treating investigator. Regardless of who the treating physician is, there will be only one responsible Study Coordinator for each study at each of the hospitals affiliated with the USC Norris Cancer Center. The treating investigator will review the status of each patient on-study, with the Study Coordinator and treating physicians, on an on-going basis. When a study is opened at two or more institutions, CISO QA will periodically audit medical records for the subjects on study at other institutions to ensure compliance and adherence to the protocol.

e) **Data Management – Patient Charts:** When a study is opened at two or more institutions, the policy in place at each institution will be followed for maintaining medical and research related records. Such policies will be provided to the CISO QA prior to enrolling 1st patient. At USC, All written source documents not associated with the study research are maintained in the patient chart, which is stored in the Department of Medical Records at the appropriate hospital. At the Norris Hospital, the official medical record is the Electronic Patient File (EPF). Radiographical images are stored in the Department of Radiology and in an electronic system called Synapse. At Los Angeles County General Hospital the official medical record is called Affinity. These are the permanent, official documents for each patient on-study. A copy of the signed informed consent, physician's notes, orders, test results and pathology notes are maintained in the patients' hospital charts. It is the responsibility of the research staff to ensure that the patient chart contains the required documents and work closely with treating investigators to ensure all protocol-related assessments are carefully documented.

f) **Data Management – Research Charts:** When a study is opened at two or more institutions, the policy in place at each institution will be followed for maintaining medical and research related records. Such policies will be provided to the CISO QA prior to enrolling 1st patient. At USC, to facilitate adherence to the protocol schedule and data management, research charts are created to collect copies of the relevant notes, orders and results, that are in the Patient Chart. In Addition, all source documents related to the research, such as original informed consent forms, HIPAA Forms, AE assessment worksheets, disease response worksheets and NTFs are maintained in the Research Charts. Protocol calendars, worksheets, and checklists, are also kept in the research chart. These are maintained in the Clinical Investigation Support Office until the study is completed and the results are published and no further need is anticipated. These are then stored off-site. It is the responsibility of the Data Manager to ensure that the research chart contains all the required documents.

g) **Data Management – Case Report Forms:** It is the responsibility of the Data Manager to complete the required case report forms. For in-house trials, case report forms are developed for each trial; these are used to finalize the data entry screens in the Cancer Center clinical trials database. It is the responsibility of the PI to review the Off-Study Summary form which summarizes pertinent toxicity, response and adherence information, once the patient has completed treatment.

10.2.5.2 Quality Assurance Monitoring Committee (QAMC) Oversight

The Quality Assurance and Monitoring Committee (QAMC) of the NCCC has the responsibility for study auditing and monitoring for protocol compliance, data accuracy, performance of audits and monitoring of accrual. QAMC procedures are detailed in the NCCC Data Safety and Monitoring Plan available on CISO Website.

10.2.5.2.1 QAMC Annual Patient Audits

The QAMC is responsible for conducting audits and providing the initial review of the audits, for all open institutional (i.e. USC initiated), CCCP-sponsored trials, and any trials identified by the CIC. These trials are audited by the QAMC once a year. Faculty and staff at the Cancer Center involved in clinical research – but not directly involved in the research under evaluation – are asked to serve as auditors. Twenty percent of patients accrued during the past 12 months – and a minimum of 2 patients – are selected at random; however, additional patients may be selected for audit if there is some indication that there might have been a problem or unusual circumstance (possibly related to compliance, toxicity, response or some indication of an irregularity). The audit involves a review of the research chart, hospital medical record (i.e., source documentation) and evaluates the following: documentation of eligibility (including failure to obtain appropriate informed consent) and baseline status of the patient; documentation of adherence to protocol-specified treatment and follow-up; evaluation of toxicity; and evaluation of response or other outcome. In addition, for investigative agents, a drug audit is also performed for these patients by the Research Pharmacist. In addition, for Institutional, Investigator Initiated Trials, Data in the CAFÉ database are compared to the information in the medical record.

10.2.5.2.2 QAMC Annual Protocol Review

All open trials are reviewed at least once a year by the QAMC (or more often if stipulated by the CIC). This annual review includes the following: evaluation of the current accrual relative to the planned total accrual; examination of gender and minority accrual; examination of all reported violations; review of past audits and correspondence with the PI; review of results of current audit (by an outside agency or by the NCCC QAMC); review of previous correspondence between the PI and the QAMC/DSMC. The QAMC review process is detailed in USC NCCC DSM Plan available on the CISO website.

10.2.5.2.3 Data and Safety Monitoring Committee (DSMC) Oversight

The Data and Safety Monitoring Committee (DSMC) is an independent body responsible for the safety of study subjects through the review of new protocols to ensure an adequate adverse event assessment/reporting plan, study stopping rules and through the real-time and periodic monitoring of severe adverse events (SAEs) or those AEs that require expedited reporting. The DSMC performs quarterly and annual safety reviews as well as interim efficacy/futility analyses on institutional trials. DSMC procedures are detailed in USC NCCC DSM Plan available on the CISO website.

10.2.6 Adherence to the Protocol

Except for an emergency situation in which proper care for the protection, safety, and well being of the study patient requires alternative treatment, the study shall be conducted exactly as described in the approved protocol.

10.2.6.1 Emergency Modifications

Investigators may implement a deviation from, or a change of, the protocol to eliminate an immediate hazard(s) to trial subjects without prior IRB approval.

For any such emergency modification implemented, an IRB modification form must be completed within five (5) business days of making the change.

10.2.6.2 Non-Emergency departures from protocol

A protocol deviation is any variance from an IRB approved protocol.

If the deviation meets all of the following criteria, it is considered a minor protocol deviation that:

- Is generally noted or recognized only after it occurs
- Has no substantive effect on the risks to research participants
- Has no substantive effect on the scientific integrity of the research plan or the value of the data collected
- Did not result from willful or knowing misconduct on the part of the investigator(s).

If the deviation meets any of the following criteria, it is considered a protocol violation:

- Has harmed or increased the risk of harm to one or more research participants.
- Has damaged the scientific integrity of the data collected for the study.
- Results from willful or knowing misconduct on the part of the investigator(s).
- Demonstrates serious noncompliance with federal regulations, State laws, or University policies.

Protocol Deviations: personnel will report to any sponsor or data and safety monitoring committee in accordance with their policies.

Protocol Violations: All protocol violations will be entered in the clinical trial database by the Research Coordinator. In addition, Research Coordinator and Investigator should report all protocol violations within one (1) week of the knowledge of the event using iStar.

10.2.6.3 Amendments to the Protocol

Should amendments to the protocol be required, the amendments will be originated and documented by the Principal Investigator. It should also be noted that when an amendment to the protocol substantially alters the study design or the potential risk to the patient, a revised consent form might be required.

The written amendment, and if required the amended consent form, must be sent to the IRB as well as to all the sponsoring agencies (FDA, NCI, etc.) for review and for approval prior to implementation. It is the responsibility of the study PI to ensure that the appropriate agencies have been informed of the proposed amendments and that these have been reviewed and approved.

10.2.7 Record Retention

Study documentation includes all Case Report Forms, data correction forms or queries, source documents, Sponsor-Investigator correspondence, monitoring logs/letters, and regulatory documents (e.g., protocol and amendments, IRB correspondence and approval, signed patient consent forms).

Source documents include all recordings of observations or notations of clinical activities and all reports and records necessary for the evaluation and reconstruction of the clinical research study.

Government agency regulations and directives require that the study investigator must retain all study documentation pertaining to the conduct of a clinical trial. In the case of a study with a drug seeking regulatory approval and marketing, these documents shall be retained for at least two years after the last approval of marketing application in an International Conference on Harmonization (ICH) region. In all other cases, study documents should be kept on file until three years after the completion and final study report of this investigational study.

10.2.8 Obligations of Investigators

The Principal Investigator is responsible for the conduct of the clinical trial at the site in accordance with Title 21 of the Code of Federal Regulations and/or the Declaration of Helsinki. The Principal Investigator is responsible for personally overseeing the treatment of all study patients. The Principal Investigator must assure that all study site personnel, including sub-investigators and other study staff members, adhere to the study protocol and all FDA/GCP/NCI regulations and guidelines regarding clinical trials both during and after study completion.

The Principal Investigator at each institution or site will be responsible for assuring that all the required data will be collected and entered onto the Case Report Forms. Periodically, monitoring visits will be conducted and the Principal Investigator will provide access to his/her original records to permit verification of proper entry of data. At the completion of the study, all case report forms will be reviewed by the Principal Investigator and will require his/her final signature to verify the accuracy of the data.

11.0 APPENDICES

11.1 ECOG Performance Status

Grade	Description
0	Normal activity. Fully active, able to carry on all pre-disease performance without restriction.
1	Symptoms, but ambulatory. Restricted in physically strenuous activity, but ambulatory and able to carry out work of a light or sedentary nature (e.g., light housework, office work).
2	In bed <50% of the time. 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	In bed >50% of the time. Capable of only limited self-care, confined to bed or chair more than 50% of waking hours.
4	100% bedridden. Completely disabled. Cannot carry on any self-care. Totally confined to bed or chair.
5	Dead.
* As published in Am. J. Clin. Oncol.: *Oken, M.M., Creech, R.H., Tormey, D.C., Horton, J., Davis, T.E., McFadden, E.T., Carbone, P.P.: Toxicity And Response Criteria Of The Eastern Cooperative Oncology Group. Am J Clin Oncol 5:649-655, 1982.* The Eastern Cooperative Oncology Group, Robert Comis M.D., Group Chair.	

11.2 Common Terminology Criteria for Adverse Events V4.0 (CTCAE)

The descriptions and grading scales found in the revised NCI Common Terminology Criteria for Adverse Events (CTCAE) version 4.0 will be utilized for adverse event reporting. (http://ctep.cancer.gov/reporting/ctc.html)

11.3 Response Evaluation Criteria in Solid Tumors (RECIST) 1.1 Criteria for Evaluating Response in Solid Tumors

RECIST version 1.1* will be used in this study for assessment of tumor response. While either CT or MRI may be utilized, as per RECIST 1.1, CT is the preferred imaging technique in this study.

* As published in the European Journal of Cancer:

E.A. Eisenhauer, P. Therasse, J. Bogaerts, L.H. Schwartz, D. Sargent, R. Ford, J. Dancey, S. Arbuck, S. Gwyther, M. Mooney, L. Rubinstein, L. Shankar, L. Dodd, R. Kaplan, D. Lacombe, J. Verweij. New response evaluation criteria in solid tumors: Revised RECIST guideline (version 1.1). Eur J Cancer. 2009 Jan;45(2):228-47.

11.4

SERIOUS ADVERSE EVENT FAX COVER SHEET

Complete and fax Medwatch 3500A within 2 working days of learning of a new SAE

To: Merck Global Safety
FAX: +1-215-993-1220

EMAIL TO NOTIFY SPONSOR (Site Responsibility):
USC Principal Investigator: **Jorge Nieva, MD**
Phone: 323-865-0421
Fax: 323-865-0061
Email: jorge.nieva@med.usc.edu

PROTOCOL: 0S-16-8 A Phase IIa trial of sEphB4-HSA in combination with Anti PD-1 Antibody (Pembrolizumab, MK-7435) in patients with non-small cell lung and head/neck cancer (IND#**131141)**

Site Name: Name of Submitter:

Phone #: Date of submission:

Please Complete:

Subject #: Subject Initials:

____ NEW SAE

____ FOLLOW- UP TO PREVIOUSLY REPORTED SAE

11.5

SERIOUS ADVERSE EVENT E-MAIL COVER SHEET

Complete and email Medwatch 3500A within 24 hours of learning of a new SAE

To: Vasgene Therapeutics Inc.
Email: Maricela Oviedo-Collins (OVIEDOCO@med.usc.edu);
Valery Krasnoperov (valeryhome@gmail.com)
Linda@vasgene.com

EMAIL TO NOTIFY SPONSOR (Site Responsibility):
USC Principal Investigator: **Jorge Nieva MD**
Phone: 323-865-0421
Fax: 323-865-0061
Email: jorge.nieva@med.usc.edu

PROTOCOL: 0S-16-8 A Phase IIa trial of sEphB4-HSA in combination with Anti PD-1 Antibody (Pembrolizumab, MK-7435) in patients with non-small cell lung and head/neck cancer (IND#**131141)**

Site Name: Name of Submitter:

Phone #: Date of submission:

Please Complete:

Subject #: Subject Initials:

____ NEW SAE

____ FOLLOW- UP TO PREVIOUSLY REPORTED SAE