An Open-Label, Multi-Center Trial of SNS-301 Added to Pembrolizumab in Patients with Locally Advanced Unresectable or Metastatic/Recurrent Squamous Cell Carcinoma of the Head and Neck

Study product: SNS-301

IND number: 16963

Protocol number: SNS301-2-2

Phase: 1/2

Version: 4.0

Final Protocol Date: November 6, 2020

Study Sponsor:

Sensei Biotherapeutics

620 Professional Drive

Gaithersburg, MD 20879

Regulatory Statement

This study will be performed in compliance with the protocol and in accordance with Good Clinical Practice (International Conference on Harmonization, Guidance E6 (R2), March 2018), principles of human subject protection, and applicable country-specific regulatory requirements.

Confidentiality Statement

SPONSORS PROTOCOL SIGNATURE PAGE

Sponsor:	Sensei Biotherapeutics
Address:	620 Professional Drive Gaithersburg, MD 20879
Protocol Title	An Open-Label, Multi-Center Trial of SNS-301 Added to Pembrolizumab in Patients with Locally Advanced Unresectable or Metastatic/Recurrent Squamous Cell Carcinoma of the Head and Neck
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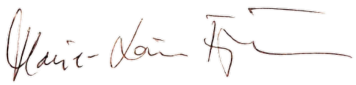
I approved the protocol and confirm that the protocol follows the current ICH/GCP guidelines.



23 November 2020

Marie-Louise Fjaellskog, MD, PhD — Date

Chief Medical Officer

Sensei Biotherapeutics

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1. PROTOCOL SUMMARY

1.1 Clinical Protocol Synopsis

Protocol Title: An Open-Label, Multi-Center Trial of SNS-301 Added to Pembrolizumab in Patients with Locally Advanced Unresectable or Metastatic/Recurrent Squamous Cell Carcinoma of the Head and Neck

Sponsor: Sensei Biotherapeutics
620 Professional Drive
Gaithersburg, MD 20879

Protocol Number: SNS-301-2-2

Trial Phase: 1/2

Estimated Number of Trial Centers and Countries/Regions: Up to 15 sites in the U.S.

Formulation:
1. SNS-301 ($1X10^{11}$ particles in 1ml ID injection)
2. Pembrolizumab (200 mg or 400 mg dose IV infusion over 30 minutes)

Research Hypotheses: SNS-301 delivered by intradermal injection (ID) using the 3M® hollow microstructured transdermal system (hMTS) device in addition to pembrolizumab, will be generally safe, well tolerated, immunogenic and lead to anti-tumor responses in adult patients with locally advanced unresectable or metastatic/recurrent squamous cell carcinoma of the head and neck (SCCHN)

Objectives and Endpoints:

Primary Objectives:	Associated Primary Endpoints:
1. To determine the safety and tolerability of SNS-301 delivered by intradermal injection (ID) using the 3M® hollow microstructured transdermal system (hMTS) device in addition to pembrolizumab among patients with locally advanced unresectable or metastatic/recurrent SCCHN	• All adverse events (AEs) by CTCAE v5 such as clinically significant changes in safety laboratory parameters from baseline: CBC with Differential; Chemistry Panel; Urinalysis; T3, Free T4 and TSH; creatine phosphokinase (CPK) and including adverse events of special interest (AESI) classified by system organ class (SOC), preferred term (PT), severity and relationship to drug
2. To evaluate the anti-tumor activity of SNS-301 delivered by intradermal injection (ID) using the 3M® hollow microstructured transdermal system (hMTS) device in addition to pembrolizumab in patients with locally advanced unresectable or metastatic/recurrent SCCHN	• Objective response rate (ORR) by immune Response Evaluation Criteria in Solid Tumors (iRECIST) • Objective response rate (ORR) by Response Evaluation Criteria (RECIST) version 1.1 by investigator review • Duration of Response (DoR) as assessed by RECIST version 1.1 and iRECIST • Disease control rate (DCR) as assessed by RECIST version 1.1 and iRECIST

	• Progression Free Survival (PFS) as assessed by RECIST version 1.1 and iRECIST • Overall Survival (OS)
Secondary Objective	**Associated Secondary Endpoints**
To evaluate preliminary immune response to SNS-301 delivered by intradermal injection (ID) using the 3M® hollow microstructured transdermal system (hMTS) device in addition to pembrolizumab in patients with locally advanced unresectable or metastatic/recurrent SCCHN	• Antigen-specific cellular immune responses that may be assessed by but not limited to: Interferon-γ secreting T lymphocytes in peripheral blood mononuclear cells (PBMCs) by ELI Spot • Anti-SNS-301 antibody response • Assessment of pro-inflammatory and immunosuppressive elements in neoplastic and adjacent normal tissue, where feasible
Exploratory Objective	**Associated Exploratory Endpoints**
To evaluate tumor and immune biomarkers and their association with treatment outcome (antitumor activity and/or safety) in patients with locally advanced unresectable or metastatic/recurrent SCCHN	• Immune related gene expression in the tumor • Expression of tumor specific oncoproteins including but not limited to ASPH • Correlation of serum ASPH level as determined by ELISA with tissue expression using IHC • miRNA profiling to predict treatment efficacy evaluating pre and post-treatment peripheral blood samples as well as urine samples • Cytokine and chemokine profiles in urine pre- and post-treatment and longitudinally throughout the trial • TCR sequencing of PBMCs for diversity and putative antigen specificity • CtDNA analysis and tracking for progression

Trial Population:
The trial population consists of patients with locally advanced unresectable or metastatic/recurrent SCCHN who are currently receiving a CPI therapy (Cohort A) or are naïve to CPI therapy (Cohort B). Patients who are currently receiving CPI therapy must have a best response of stable disease (SD) or first evidence of progressive disease (PD) after a minimum of 12 weeks of treatment with a CPI. Patients receiving first-line pembrolizumab monotherapy must be PD-L1 positive. Patients receiving a CPI other than pembrolizumab will be switched over to pembrolizumab at the time of entering this study.

Sample Size: Approximately up to 30 patients will be enrolled into each cohort on the trial.

This is a two-stage clinical trial with the primary efficacy endpoint of objective response per iRECIST. Patients enrolled in the first stage will need to be deemed evaluable at 12 weeks, meeting the definition for the efficacy evaluable analysis set; at least one dose of treatment and the Week 12 efficacy assessment or progression prior to Week 12. Approximately15 patients may be enrolled in the first stage and evaluated for objective response (futility assessment) at 12 weeks. All patients will participate in the overall efficacy analysis. If warranted, based on response, up to an additional 15 patients may be enrolled in each cohort in the second stage.

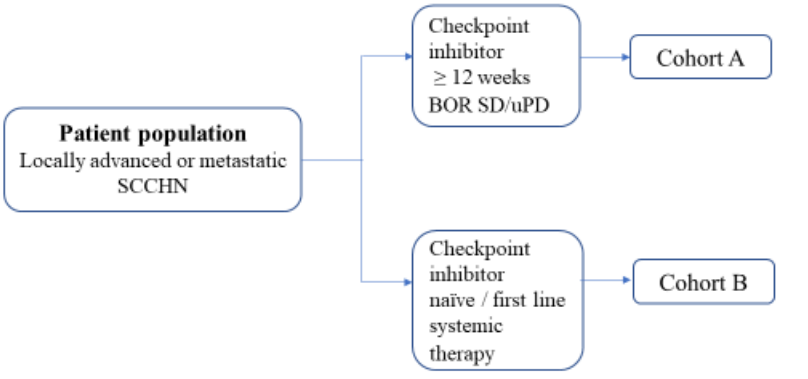
See Section 10 for an explanation of the 2-stage enrollment.

The study enrollment is expected to last approximately 18-24 months.

Study Design:
This is a Phase 1/2, open-label, multi-center trial to evaluate the safety, immunogenicity and preliminary clinical efficacy of SNS-301 delivered intradermally in addition to pembrolizumab in patients with locally advanced unresectable or metastatic/recurrent SCCHN. A safety run-in will be performed using a modified rolling six design which will enroll up to 6 patients and these patients will be included in the first stage of trial assessments pending they meet criteria set forth above.

After consenting to participate in this clinical trial, participants will be screened for enrollment. A tissue sample is required for ASPH expression testing from either a fresh biopsy or archival tissue from a previous biopsy. Ideally, a pre-treatment tissue sample obtained after initiation of ongoing pembrolizumab, nivolumab or other CPI therapy and first dose of SNS-301 and pembrolizumab on this current clinical trial will be collected. Patients are requested to provide archival tissues from a prior biopsy or surgery that is treatment -naïve including prior 1) chemotherapy, radiation and 2) anti PD(L)-1 treatment-naïve, pending availability. The patient may start study treatment prior to receiving the ASPH expression results from the fresh biopsy or archival tissue from a previous biopsy. An on-treatment biopsy is required when medically feasible, after the third dose of the study treatment, treatment week 6. Additionally, up to two optional biopsies may be obtained in select cases at any time during the study, if medically feasible. For patients who progress as determined per RECIST1.1/iRECIST criteria, an optional biopsy will be obtained at the time of disease progression.

Patients will be enrolled into one of two cohorts depending on whether they are currently on a CPI or if they are naïve to CPI therapy as per the flow diagram below.



Checkpoint inhibitor = anti-PD1 and anti-PD-L1 agents

The following procedures will be performed:

1. For eligible patients, the study treatment of SNS-301 in addition to pembrolizumab will be initiated on Day 0 (First dose).
2. SNS-301 will be dosed approximately 1 hour after IV infusion of pembrolizumab for the first dose. Subsequent doses of SNS-301 and pembrolizumab can be dosed in any order. If pembrolizumab is discontinued by the Investigator prior to 24 months, treatment with SNS-301 vaccine therapy may continue for up to 24 months in patients without disease progression.
3. Tumor biopsies will be collected at the time of screening and at Week 6 (± 3 days and at first evidence of radiographic or clinical disease progression if clinically deemed feasible. Patients who are unable to undergo biopsy sample collection during treatment but otherwise meet criteria listed in the protocol may continue to receive study treatment.
4. SNS-301 will be administered intradermally using the 3M micro-needle device. The dosing schedule will be as follows: Day 0, Week 3, Week 6, Week 9 then every 6 weeks (±3 days) for 6 additional doses, thereafter every 12 weeks (±3 days) until confirmed disease progression, unacceptable toxicity, deemed intolerable by the investigator or up to 24 months in patients without disease progression.
5. Pembrolizumab will be administered either every 3 weeks or every 6 weeks until confirmed disease progression, unacceptable toxicity, deemed intolerable by the investigator or up to 24 months in patients without disease progression.
6. Imaging will be performed at 6 weeks (± 7 days) calculated from the first dose and will continue to be performed every 6 weeks (± 7 days), for the first 54 weeks, or earlier if clinically indicated. Thereafter, imaging will be performed approximately every 12 weeks (± 7 days). Imaging timing should follow calendar days and should not be adjusted for delays or changes in treatment administration dates.
7. In patients who discontinue trial therapy for any reason other than radiologically defined confirmed progression, tumor imaging should be performed at the time of treatment discontinuation (± 4 weeks). If previous tumor imaging was obtained within 4 weeks prior to the date of discontinuation, then additional tumor imaging at treatment discontinuation is not required.
8. Patients will be followed for all adverse events (AEs) for 30 days and for adverse events of special interest (AESI) and serious adverse events (SAEs) occurring up until 90 days after the last dose of study treatment or until the start of a new anti-cancer treatment, whichever comes first. If the investigator becomes aware of an AESI or SAE that is considered related to study treatment after discontinuation from the trial, those events should be reported to the Sponsor within 24 hours.
9. All patients who experience disease progression, have unacceptable toxicity or start a new anti-cancer therapy and are discontinued from the trial will be followed for survival and subsequent anti-cancer therapy. Patients should be contacted (i.e. by telephone) every 3 months to assess for survival status for up to 3 years, until death or patient withdraws consent. A pregnancy test is also required for WOCBP every 3 months.
10. Patients who discontinue from study treatment for reasons other than disease progression (e.g., toxicity) will continue scheduled tumor assessment until disease progression, withdrawal of consent, or start of new anti-cancer therapy, death, or trial termination by Sponsor, whichever occurs first.

Safety Run-In: A safety run-in will be performed using a modified rolling six design which will enroll up to six patients (safety lead-in patients). A Safety Committee will review data from the Safety Run-In. (Refer to Section Safety Committee).

Once the first three patients of these six patients have completed Week 6 assessments, in the absence of any dose-limiting toxicity (DLT), enrollment may proceed through stage 1. However, if prior to the first three patients completing Week 6, a single patient from the first six experiences a DLT, then enrollment will be

limited to six patients until all six patients have reached Week 6 and are assessed for DLT. If no additional patients, of these six, experience a DLT within the 6-week safety run in period, then enrollment may proceed to completion.

If a second of these first six patients experiences a DLT within the first six weeks, enrollment will stop, and the Sponsor's medical monitor, in addition to the PI and Investigator(s) at the patients' site(s) will discuss the case, and a decision will be made whether to modify the trial or to cease further enrollment. If enrollment is ceased, it will only be reinitiated after amendment of the protocol and approval of the amended protocol by the IRB.

Safety run-in patients that withdraw from the study for reasons other than a DLT, prior to the end of the safety run-in period, will be replaced. The end of the safety run-in period is defined as the earliest of the following:

- The first three patients in cohort A have all completed Week 6 with no DLTs experienced by any of the safety run-in patients in that cohort (up to six); enrollment may then proceed to completion;
- All six patients of the safety run-in phase, in cohort A, have completed week six with only one patient having experienced a DLT; enrollment may then proceed to completion;
- Two or more of the safety run-in patients, have experienced DLTs prior to completing Week 6; enrollment will be suspended.

Dose-Limiting Toxicities (DLTs) are defined in protocol

Because this trial is treating patients with SNS-301 and pembrolizumab for the first time, there will be a waiting period of one week between enrollment of the first patient and the second patient.

Stopping Rules
The trial will be stopped if any adverse experience of any related death, grade 4 autoimmune toxicity or any grade 4 toxicity that is considered to have a causal relationship to study drug. Any related death, grade 4 autoimmune toxicity and any grade 4 toxicity that is considered to have a causal relationship to study drug will be submitted to regulatory agencies within the expedited safety reporting criteria.

Study treatment:
Study treatment include:
1. SNS-301 ($1x10^{11}$ dose/1ml) ID injection using the 3M® hollow microstructured transdermal system (hMTS) device will be administered on Day 0, Week 3, Week 6 and Week 9 (± 3 days) then every 6 weeks (±3 days) for 6 additional doses, and thereafter every 12 weeks (±3 days) until confirmed disease progression, unacceptable toxicity, deemed intolerable by investigator or up to 24 months in patients without disease progression.
2. Pembrolizumab (200 mg dose) IV infusion over 30 minutes every 3 weeks or Pembrolizumab (400 mg dose) IV infusion over 30 minutes every 6 weeks will be administered until confirmed disease progression, unacceptable toxicity, deemed intolerable by investigator or up to 24 months in patients without disease progression. When possible, pembrolizumab should be given on the same schedule as SNS-301. The investigator should consult the sponsor if there are questions regarding aligning the study treatment schedule.

For the purpose of this protocol, study treatment is defined as SNS-301 added on to pembrolizumab, when given according to the US package insert. Refer to https://www.merck.com/product/usa/pi_circulars/k/keytruda/keytruda_pi.pdf for most recent package insert.

Statistical Methods:

Sample Size Justification:
Each cohort will enroll in two stages. Within each cohort, approximately 15 participants may be enrolled in Stage 1 and an additional approximately 15 participants may be enrolled in Stage 2, if expanded. The sample size for each cohort and stage is based on Simon's two-stage design for tests of one proportion.

Analysis Populations:
Safety Analysis Set:
The safety analysis will be based on the Safety Analysis Set, which comprises all patients who receive at least 1 dose of the study treatment or component of the study treatment.

Efficacy-Evaluable Analysis Set:
The primary efficacy analysis will be based on the Efficacy-Evaluable Analysis Set, which comprises all patients who receive at least 1 dose of the study treatment or component of the study treatment and have a post baseline response assessment per iRECIST at Week 12. Patients who discontinued treatment prior to Week 12 due to disease progression will be included. Patients who do not have a post baseline response assessment conducted will not be included in the analysis of efficacy.

Safety Run-In Set:
All patients who receive at least 1 dose of the study treatment or component of the study treatment apart of the safety run-in.

Immunologic Analysis Set:
All patients who receive at least 1 dose of the study treatment or component of the study treatment and have at least one valid post-baseline immunologic assessment available.

General Methods:
All summarizations will be presented separately for each cohort, and over all subjects combined.

For continuous variables, descriptive statistics (number (n), mean, median, standard deviation, minimum and maximum) will be presented. For categorical variables, frequencies and percentages will be presented. For time-to-event variables, percentages of patients experiencing that event will be presented and median time-to-event will be estimated using the Kaplan-Meier method. As appropriate, a 95% CI will be presented. Graphical displays will be presented, as appropriate. All data collected will be presented in by-patient data listings.

Patients demographic characteristics including age, gender, and race will be analyzed, with categorical variables summarized in frequency tables while continuous variables summarized using mean (standard deviation) and median (range).

Safety evaluations will be based on the incidence, severity, attribution and type of AEs, and changes in the patient's vital signs, and clinical laboratory results. Summarization of toxicity data will focus on incidence of any serious adverse events, adverse events, drug-related adverse events, and adverse events

leading to discontinuation or death, and will be presented in tabular form by system organ class and preferred term. Adverse events will be assessed for severity according to the NCI CTCAE, version 5.0.

Objective response rate (ORR) is defined as the proportion of patients with a confirmed best response of CR or PR by iRECIST.

Inclusion Criteria:

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

1. Provide signed IRB approved informed consent in accordance with institutional guidelines.
2. Be 18 years of age or older on the day of signing the informed consent, and able and willing to comply with all trial procedures.
3. Have histologically or cytologically documented locally advanced unresectable or metastatic/recurrent SCCHN and meet the criteria of either Cohort A or B.
   Cohort A: Patients with Ongoing CPI Therapy
   a. Patients currently receiving a checkpoint inhibitor (CPI; anti-PD-1 and anti-PD-L1 agents).
   b. Patients currently receiving a CPI must be considered by Investigator to have the potential to derive clinical benefit from continued treatment with pembrolizumab.
   c. Based on RECIST 1.1/iRECIST criteria on current CPI treatment (prior to initiation of this study), patients must have a best response of stable disease (SD) or first evidence of progressive disease (PD) after a minimum of 12 weeks of a CPI.
   d. Patients on other CPI therapy than pembrolizumab must be willing to switch over to pembrolizumab therapy.
   Cohort B: Patients without Previous CPI Therapy
   a. Patients must be checkpoint inhibitor naïve (anti-PD-1 and anti-PD-L1 agents)
   b. Patients should receive study treatment as first line (PD-L1 positive) or as second line (PD-L1 negative) systemic therapy in the advanced/metastatic setting.
4. Have measurable disease, as defined by RECIST version 1.1 (investigator assessment).
5. Have a performance status of 0 or 1 on Eastern Cooperative Oncology Group (ECOG) Performance Scale.
6. Have a life expectancy of ≥ 3 months.
7. Be willing to provide a pre-treatment tissue sample obtained after initiation of ongoing CPI therapy (Cohort A, only) and before first dose of SNS-301 and pembrolizumab on this current clinical trial unless clinically contra-indicated per treating physician. Patients unable to provide pre-treatment biopsy while on CPI will be evaluated on a case-by-case basis for enrollment pending Sponsor consultation (Cohort A, only). Patients are requested to also provide archival tissue from a prior biopsy or surgery that is treatment –naïve including prior 1) chemotherapy, radiation and/or 2) anti-PD(L)-1 treatment-naïve, pending availability. Tissue provided pre-treatment (fresh or archival) will be used to determine ASPH expression. Additionally, an on-treatment biopsy is required unless clinically contraindicated, after the third dose of study treatment at week 6. For patients who progress as determined per RECIST1.1/iRECIST criteria, an optional biopsy may be obtained at the time of disease progression.
8. Have an ECG with no clinically significant findings such as stage 2b and 3 heart block, any history of ventricular arrhythmias or NYHA heart failure within the past 6 months, and QTc prolongation > 500 ms or as deemed clinically significant by the investigator and performed within 28 days prior to first dose.

9. Demonstrate adequate organ function: hematological, renal, hepatic, coagulation parameters as defined below and obtained within 28 days prior to the first study treatment. Adequate hematologic and end-organ function:

System	Laboratory Value
Hematological	
Absolute neutrophil count (ANC)	≥1500/ μL
Platelets	≥100,000/ μL
Hemoglobin	≥9 g/dL, or ≥5.6 mmol/L without transfusion or EPO dependency within 7 days
Renal	
Creatinine OR Calculated creatinine clearance	≤ 1.5 x upper limit of normal (ULN) OR ≥ 30 mL/min for patient with creatinine level > 1.5 x institutional ULN Note: Creatinine clearance should be calculated per Cockcroft-Gault formula
Hepatic	
Total bilirubin	≤ 1.5 x ULN **OR** Direct bilirubin ≤ ULN for patients with total bilirubin levels > 1.5 x ULN
AST (SGOT) and ALT (SGPT)	≤ 2.5 x ULN **OR** ≤ 5 x ULN for patients with liver metastases
Coagulation	
International Normalized Ratio (INR) or Prothrombin Time (PT)	≤1.5 x ULN unless patient is receiving anticoagulant therapy as long as PT or PTT is within therapeutic range of intended use of anticoagulants
Activated Partial Thromboplastin Time (aPTT)	≤1.5 x ULN unless patient is receiving anticoagulant therapy as long as PT or PTT is within therapeutic range of intended use of anticoagulants

10. For women of childbearing potential: agreement to remain abstinent (refrain from heterosexual intercourse) or use two highly effective contraceptive methods that result in a combined failure rate of < 1% per year during the treatment period and for at least 180 days after the last dose of study treatment:
    - A woman is considered to be of childbearing potential if she is postmenarchal, has not reached a postmenopausal state (≥ 12 continuous months of amenorrhea with no identified cause other than menopause), and has not undergone surgical sterilization (removal of ovaries and/or uterus)
    - Examples of contraceptive methods with a failure rate of < 1% per year include bilateral tubal ligation, male sterilization, established, proper use of hormonal contraceptives that inhibit ovulation, hormone-releasing intrauterine devices, and copper intrauterine devices
    - The reliability of sexual abstinence should be evaluated in relation to the duration of the clinical trial and the preferred and usual lifestyle of the patient. Periodic abstinence (e.g., calendar, ovulation, sympto-thermal, or post-ovulation methods) and withdrawal are not acceptable methods of contraception

    For male patients: Agree that during the period specified above, men will not father a child. Male patients must remain abstinent (refrain from heterosexual intercourse with women of childbearing

potential), must be surgically sterile (e.g., vasectomy) or use contraceptive methods that result in a failure rate of < 1% per year during the treatment period and for at least 180 days after the last dose of study treatment.

Exclusion Criteria:

Patients who meet any of the following criteria will be excluded from trial entry:

Cancer-specific Exclusion Criteria:

1. Any approved anti-cancer therapy including chemotherapy, targeted small molecule therapy or radiation therapy within 2 weeks prior to trial Day 0; or if patient has not recovered (i.e., Less than or equal to grade 1 or returned to baseline level) from adverse events due to a previously administered agent; the following exceptions are allowed:
    - Palliative radiotherapy for bone metastases or soft tissue lesions should be completed > 7 days prior to baseline imaging
    - Hormone-replacement therapy or oral contraceptives
    - Patients with grade 2 neuropathy or grade 2 alopecia
2. Patients with evidence of rapid progression on prior therapy (if applicable) resulting in rapid clinical deterioration should be excluded from participation in the trial.
3. Currently participating and receiving trial therapy or has participated in a trial of an investigational agent and/or has used an investigational device within 28 days prior to Day 0.
   Note: Patients who have entered the follow-up phase of an investigational trial may participate as long as it has been 28 days since the last dose of the previous investigational agent or device.
4. Uncontrolled tumor-related pain
    - Patients requiring pain medication must be on a stable regimen at trial entry;
    - Symptomatic lesions amenable to palliative radiotherapy per investigator's discretion (e.g., bone metastases or metastases causing nerve impingement) should complete treatment at least 7 days prior to enrollment
5. Uncontrolled pleural effusion, pericardial effusion, or ascites requiring recurrent drainage procedures (once monthly and more frequently)
    - Patients with indwelling catheters (e.g., PluerX) are allowed
6. Malignancies other than indications open for enrollment within 3 years prior to Day 0, with the exception of those with negligible risk of metastasis or death treated with expected curative outcome, undergoing active surveillance or treatment-naïve for indolent tumors.

General Medical Exclusion Criteria

7. Pregnant or lactating or intending to become pregnant or father children within the projected duration of the trial starting with the screening visit through 180 days after the last dose of pembrolizumab and/or SNS-301.
8. History of severe allergic, anaphylactic, or other hypersensitivity reactions to chimeric or humanized antibodies or fusion proteins.
9. Known hypersensitivity allergy or contraindication to biopharmaceuticals produced in Chinese hamster ovary cells or any component of the PD-1/PD-L1 inhibitor formulation.
10. Active autoimmune disease that has required systemic treatment in the past 2 years (i.e. with use of disease modifying agents, corticosteroids or immunosuppressive drugs). Replacement therapy (e.g., thyroxine, insulin, or physiologic corticosteroid replacement therapy for adrenal or pituitary insufficiency, etc.) is not considered a form of systemic treatment.
11. History or any evidence of interstitial lung disease such as idiopathic pulmonary fibrosis, organizing pneumonia (e.g., bronchiolitis obliterans), drug induced or active non-infectious pneumonitis, idiopathic pneumonitis, or evidence of active pneumonitis on screening chest CT scan

- History of radiation pneumonitis in the radiation field (fibrosis) is permitted

12. History of HIV. HIV antibody testing recommended per investigator's clinical suspicion.
13. Active hepatitis B (hepatitis B surface antigen reactive) or active hepatitis C (HCV qualitative RNA detected); testing recommended per investigator's clinical suspicion.
14. Severe infections within 4 weeks prior to enrollment, including, but not limited to, hospitalization for complications of infection, bacteremia, or the presence of any active infection requiring systemic therapy.
15. Received therapeutic oral or IV antibiotics within 2 weeks prior to Day 0
    - Patients receiving prophylactic antibiotics (e.g., for prevention of a urinary tract infection or to prevent chronic obstructive pulmonary disease exacerbation) are eligible
16. History or current evidence of any condition, therapy or laboratory abnormality that in the opinion of the treating investigator might confound the results of the trial or interfere with the patient's participation for the full duration of the trial.
17. Prior allogeneic stem cell or solid organ transplant.
18. Received a live, attenuated vaccine within 28 days prior to randomization or anticipation that such a live attenuated vaccine will be required during the trial.
    Note: Influenza vaccination should be given during influenza season only (approximately October to March). Patients must not receive live, attenuated influenza vaccine (e.g., FluMist®) within 28 days prior to Day 0, during treatment, or within 90 days following the last dose of study treatment.
19. Known previous or ongoing, active psychiatric or substance abuse disorders that would interfere with cooperation with the requirements of the trial.
20. Prisoner or patient who is compulsorily detained (involuntarily incarcerated) for treatment of either a psychiatric or physical (i.e. infectious disease) illness.
21. Treatment with systemic immunomodulating agents (including but not limited to IFNs, IL-2, ipilimumab) within 6 weeks or five half-lives of the drug, whichever is shorter, prior to first dose, excluding current CPI therapy.
22. Treatment with systemic immunosuppressive medication (including, but not limited to, corticosteroids, cyclophosphamide, azathioprine, methotrexate, thalidomide, and anti-TNF-α agents) within 2 weeks prior to initiation of study treatment, or anticipation of need for systemic immunosuppressive medication during the course of the study, with the following exceptions:
    - Patients who received acute, low-dose (≤ 10 mg/day) systemic immunosuppressant medication or a one-time pulse dose of systemic immunosuppressant medication (e.g., 48 hours of corticosteroids for a contrast allergy) are eligible for the study
    - Patients who received inhaled, topical and intranasal steroids are eligible for the study
    - Patients who received mineral corticosteroids (e.g., fludrocortisone), corticosteroids for chronic obstructive pulmonary disease (COPD) for asthma, or low-dose corticosteroids for orthostatic hypotension or adrenal insufficiency are eligible for the study.

Table 1: Trial Schedule of Events

Pembrolizumab Schedule – Every 3 weeks

	Screening[a] Day -28 to Day -1	Cycle 1 Day 0	Cycle 2 Week 3	Cycle 3 Week 6	Cycle 4 Week 9	Every 3 weeks	Every 6 weeks	Discontinuation Visit[b]	Follow-up
Signed Informed Consent Form(s)	X								
Medical, surgical, and cancer histories, including demographic	X								
Inclusion/Exclusion criteria	X	X							
Complete Physical exam[d]	X								
Targeted Physical exam[e]		X[f]	X[f]	X[f]	X[f]	X[f]		X	
ECOG performance status[f]	X	X	X	X	X	X		X	
HIV, Hep B and Hep C serology[g]	X								
Concomitant Medications[h]	X	X	X	X	X	X		X	
Anticoagulant specific drug and/or anticoagulant factor Xa levels[i]	X	X	X	X	X	At week 12 then, Q6w until week 45, thereafter Q12w		X	
	For patients on anticoagulants only								
Vital Signs and Weight[j]	X	X	X	X	X	X		X	
Height	X								
12-lead ECG[k]	X								
Tumor Imaging[l]	X	Q6w from Day 0 until ~12 months, there after Q12w							
RECIST/iRECIST	X	Q6w from Day 0 until~12 months, there after Q12w							
Hematology[m]	X	X[f]	X[f]	X[f]	X[f]	X[f]		X	
Serum Chemistry[n]	X	X[f]	X[f]	X[f]	X[f]	X[f]		X	
Coagulation Panel (aPTT, INR)	X								
Urinalysis[o]	X			X			X	X	
Pregnancy[p]	X	X	X	X	X	X		X	X
TSH, T3 and Free T4[q]	X			X			X		
CPK	X							X	
HPV/EBV, if unknown	X								
PDL-1	X								
Blood samples for immunology assessments[r]		X	X	X	X	At week 12, then Q6 weeks until Week 36 and Q12w thereafter as well as at disease progression			
Tumor specimen	X			X		Up to 2 optional biopsies and at disease progression			
Adverse Events	X	X	X	X	X	X		X	X
Pembrolizumab[u]		X	X	X	X	X			

SNS-301[v]		X	X	X	X	After week 9, Q6w for 6 more doses (week 45), thereafter Q12w until PD or 24 months if no PD			
Survival and new anti-cancer therapy follow-up[w]									X

Note: Assessments scheduled on the days of study treatment should be performed before the study treatment unless otherwise noted.

[a] Written informed consent can be obtained up to 28 days prior to Day 0 and is required for performing any trial-specific tests or procedures. However, tumor tissue collection (archived or fresh) can exceed 28 days to ensure that sufficient time is available for obtaining the requested sample for trial purposes. Additionally, a pre-screening informed consent is available to obtain archived tumor tissue prior to the study's primary consent. Results of standard-of-care tests or examinations performed prior to obtaining informed consent and within 28 days prior to Day 0 may be used for screening assessments rather than repeating such tests. Screening labs (CBC and chemistry) may be used for Day 0 if they are within 10 days of Day 0.

[b] Patients who discontinue early from study treatment (i.e., progression, adverse event, etc.), will be asked to return to the clinic within 30 days after the last dose for a treatment discontinuation visit.

[c] Cancer history includes stage, date of diagnosis, and prior anti-tumor treatment. Previous progression data should be collected as well. Demographic information includes sex, age, and self-reported race/ethnicity. HPV, EBV, reproductive status and smoking/alcohol history should also be captured.

[d] A complete physical exam will include head, eyes, ears, nose, throat and cardiovascular, dermatological, musculoskeletal, respiratory, gastrointestinal and neurological systems. Height and weight will also be collected. Any signs and symptoms, other than those associated with a definitive diagnosis, should be collected at baseline and during the study.

[e] A targeted, symptom-directed exam will be performed, as clinically indicated.

[f] ECOG performance status, targeted physical exam, and local laboratory assessments may be obtained ≤ 72 hours before each dosing visit.

[g] Patients should be tested for HIV locally prior to the inclusion into the trial only based on investigator's clinical suspicion for HIV infection and HIV-positive patients will be excluded from the clinical trial. Hepatitis B surface antigen, anti-HBc antibody, anti-HBs antibody, and Hepatitis C antibody immunoassays should be tested only per investigator's clinical suspicion during screening and tested locally. In patients who have positive serology for the anti-HBc antibody, HBV DNA should be tested prior to Day 0.

[h] Concomitant medications include any prescription medications or over-the-counter medications. At screening, any medications the patient has used within the 7 days prior to the screening visit should be documented. At subsequent visits, changes to current medications or medications used since the last documentation of medications will be recorded.

[i] Specific anticoagulant drug and/or anticoagulant factor Xa levels will be obtained only on patients receiving anticoagulant therapy. Drug levels will also be obtained at any time of clinical bleeding. Traditional testing methods can be used for warfarin, heparin (e.g., PT/INR, aPTT, TT). Novel oral anticoagulants may require anticoagulant factor Xa levels or anticoagulant drug specific level testing. See sections Concomitant Medications & Guidance for Investigators for Patients on Anti-coagulants for additional information.

[j] Vital signs include heart rate, respiratory rate, blood pressure, and temperature. For first infusion of pembrolizumab, the patient's vital signs should be determined within 60 minutes before the start of the infusion. If clinically indicated, vital signs should be at 15, 30, 45, and 60 minutes (± 5 minutes for all timepoints) after the start of the infusion, and 30 (± 10) minutes after the infusion. For subsequent infusions, vital signs will be collected within 60 minutes before the start of the infusion and at 30 (± 5) minutes after the infusion. Patients will be informed about the possibility of delayed post-infusion symptoms and instructed to contact their trial physician if they develop such symptoms.

[k] ECG recordings will be obtained during screening and as clinically indicated at other time points. Patients should be resting and in a supine position for at least 10 minutes prior to ECG collection.

[l] Examinations performed as standard of care prior to obtaining informed consent and within 28 days of first dose of study treatment may be used rather than repeating tests. All measurable and evaluable lesions should be assessed and documented at the screening visit. Tumor imaging should be performed by computed tomography (CT), but may be performed by magnetic resonance imaging (MRI) if CT is contraindicated, but the same imaging technique should be used in patient throughout the trial. CT scans (with oral/IV contrast unless contraindicated) must include chest, abdomen and pelvis. The investigator must review before dosing at the next visit. Patients will undergo tumor assessments every 6 weeks (±7 days) for the first 54 weeks (approximately 12 months)

following first dose of study treatment, or earlier if clinically indicated. After 54 weeks, tumor assessments will be required every 12 weeks (±7 days). Patients who discontinue from treatment for reasons other than disease progression (e.g., toxicity) will continue scheduled tumor assessments until disease progression, start of new-anti cancer therapy, withdrawal of consent, or death. Investigators may perform additional scans or more frequent assessments if clinically indicated. Patients who continue treatment beyond radiographic or clinical disease progression will be monitored with a follow-up scan at the next scheduled tumor assessment. Imaging timing should follow calendar days and should not be adjusted for delays or changes in treatment administration dates. The Sponsor may request digitized scans from patients during the study.

[m] Hematology consists of CBC, including RBC count, hemoglobin, hematocrit, WBC count with automated differential (absolute counts of neutrophils, lymphocytes, eosinophils, monocytes, basophils, and other cells (if any)), and platelet count. A manual differential can be done if clinically indicated.

[n] Serum chemistry includes BUN or urea, creatinine, sodium, potassium, magnesium, chloride, bicarbonate or CO_2, calcium, phosphorus, glucose, total bilirubin (direct bilirubin only if total bilirubin is elevated), ALT, AST, alkaline phosphatase, lactate dehydrogenase, total protein, and albumin.

[o] Urinalysis includes specific gravity, pH, glucose, protein, ketones, blood, and a microscopic exam if abnormal results are noted. Urinalysis to be performed every 6 weeks.

[p] Serum pregnancy test (for women of childbearing potential, including women who have had a tubal ligation) must be performed and documented as negative within 72 hours prior to each dose.

[q] Thyroid function tests will be performed before first dose and every 6 weeks thereafter.

[r] Immunology samples are to be drawn at Day 0, Week 3, Week 6, Week 9, Week 12, then Q6 weeks until Week 36 and thereafter every 12 weeks until disease progression, as well as at disease progression. If the patient is unable to have samples obtained at the protocol specified visit (i.e., COVID19 related) then an unscheduled sample may be drawn.

[s] A pre-treatment tumor tissue sample will be analyzed for ASPH expression. After signing of the Informed Consent Form, tumor tissue should be submitted to the Sponsor in a timely manner. A pre-treatment sample is defined as a specimen obtained after initiation of ongoing CPI therapy and before first dose of SNS-301 and pembrolizumab on this current clinical trial. Patients are requested to provide archival tissue from a prior biopsy or surgery that is treatment –naïve including prior 1) chemotherapy, radiation and/or 2) anti-PD(L)-1 treatment-naïve, pending availability. Tumor tissue should be of good quality based on total and viable tumor content. Acceptable samples include core needle biopsies for deep tumor tissue or lymph nodes or excisional, incisional, punch, or forceps biopsies for cutaneous, subcutaneous, or mucosal lesions. Fine-needle aspiration may be acceptable pending Sponsor approval however, brushing, cell pellets from pleural effusion, and lavage samples are not acceptable. For core needle biopsy specimens, at least three cores should be submitted for evaluation. The patient may start study treatment prior to receiving the ASPH expression results from the fresh biopsy or archival tissue from a previous biopsy. All patients will undergo a mandatory tumor biopsy sample collection, if clinically feasible as determined by the trial investigator, at the Week 6 (at the time of third dose +/- 3 days). Additionally, up to two optional biopsies may be obtained at any time during the study, if medically feasible. A biopsy may also be obtained at the first evidence of radiographic or clinical disease progression (i.e., not proceeded by meaningful tumor regression). For patients who respond and subsequently progress, an optional biopsy may be obtained at the time of disease progression. Patients who are unable to undergo biopsy sample collection but otherwise meet criteria outlined in protocol may continue to receive study treatment. If the patient is unable to have the biopsy at the protocol specified visit (i.e., COVID19 related) then an unscheduled biopsy may be performed.

[t] AEs will be collected from the time of informed consent until 30 days after the last dose of study treatment or until initiation of another anti-cancer therapy, whichever occurs first. SAEs and AESIs will be collected from the time of informed consent until 90 days after the last dose of study treatment of until initiation of anti-cancer therapy, whichever occurs first.

[u] Pembrolizumab will be given every 3 weeks until confirmed disease progression, unacceptable toxicity, deemed intolerable by investigator or up to 24 months in patients without disease progression. The window for each visit is ± 3 days unless otherwise noted. A 60 minutes observation period is recommended for the first dose and 30 minutes for subsequent doses.

[v] SNS-301 is administered every 3 weeks until week 9 (ie.,4 doses). Then every 6 weeks for 6 more doses (until week 45). Thereafter it will be administered every 12 weeks until confirmed disease progression, unacceptable toxicity, deemed intolerable by investigator or up to 24 months in patients without disease progression. The window for each visit is ± 3 days unless otherwise noted. A 30-minute observation period is recommended after each study treatment.

[w] Survival follow-up information will be collected via telephone calls, patient medical records, and/or clinical visits approximately every 3 months for up to 3 years, until death, lost to follow-up, withdrawal of consent, or trial termination by Sponsor. All patients will be followed for survival and new anticancer therapy information unless the patient requests to be withdrawn from follow-up; this request must be documented in the source documents and signed by the investigator. If the patient discontinues study treatment without documented clinical disease progression, every effort should be made to follow up regarding survival, progression (, and new anti-cancer therapy.

Pembrolizumab Schedule – Every 6 weeks

	Screening[a] Day -28 to Day -1	Cycle 1 Day 0	Cycle 2 Week 3	Cycle 3 Week 6	Cycle 4 Week 9	Every 6 weeks	Every 12 weeks	Discontinuation Visit[b]	Follow-up
Signed Informed Consent Form(s)	X								
Medical, surgical, and cancer histories, including demographic information[c]	X								
Inclusion/Exclusion criteria	X	X							
Complete Physical exam[d]	X								
Targeted Physical exam[e]		X[f]	X[f]	X[f]	X[f]	X[f]		X	
ECOG performance status[f]	X	X	X	X	X	X		X	
HIV, Hep B and Hep C serology[g]	X								
Concomitant Medications[h]	X	X	X	X	X	X		X	
Anticoagulant specific drug and/or anticoagulant factor Xa levels[i]	X	X	X	X	X	After week 12, Q6w until week 42, thereafter Q12w		X	
	For patients on anticoagulants only								
Vital Signs and Weight[j]	X	X	X	X	X	X		X	
Height	X								
12-lead ECG[k]	X								
Tumor Imaging[l]	X	Q6w from Day 0 until ~12 months, there after Q12w							
RECIST/iRECIST	X	Q6w from Day 0 until ~12 months, there after Q12w							
Hematology[m]	X	X[f]	X[f]	X[f]	X[f]	X[f]		X	
Serum Chemistry[n]	X	X[f]	X[f]	X[f]	X[f]	X[f]		X	
Coagulation Panel (aPTT, INR)	X								
Urinalysis[o]	X			X		X		X	
Pregnancy[p]	X	X	X	X	X	X		X	X
TSH, T3 and Free T4[q]	X			X		X			
CPK	X							X	
HPV/EBV, if unknown	X								
PDL-1	X								
Blood samples for immunology assessments[r]		X	X	X	X	At week 12, then Q6 weeks until Week 36 and Q12w thereafter as well as at disease progression			
Tumor specimen[s]	X			X		Up to 2 optional biopsies and at disease progression			
Adverse Events[t]	X	X	X	X	X	X		X	X
Pembrolizumab[u]		X		X		X			

SNS-301[v]		X	X	X	X	After week 12, Q6w for 6 more doses (week 45), thereafter Q12w until PD or 24 months if no PD			
Survival and new anti-cancer therapy follow-up[w]									X

Note: Assessments scheduled on the days of study treatment should be performed before the study treatment unless otherwise noted.

[a] Written informed consent can be obtained up to 28 days prior to Day 0 and is required for performing any trial-specific tests or procedures. However, tumor tissue collection (archived or fresh) can exceed 28 days to ensure that sufficient time is available for obtaining the requested sample for trial purposes. Additionally, a pre-screening informed consent is available to obtain archived tumor tissue prior to the study's primary consent. Results of standard-of-care tests or examinations performed prior to obtaining informed consent and within 28 days prior to Day 0 may be used for screening assessments rather than repeating such tests. Screening labs (CBC and chemistry) may be used for Day 0 if they are within 10 days of Day 0.

[b] Patients who discontinue early from study treatment (i.e., progression, adverse event, etc.), will be asked to return to the clinic within 30 days after the last dose for a treatment discontinuation visit.

[c] Cancer history includes stage, date of diagnosis, and prior anti-tumor treatment. Previous progression data should be collected as well. Demographic information includes sex, age, and self-reported race/ethnicity. HPV, EBV, reproductive status and smoking/alcohol history should also be captured.

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[e] A targeted, symptom-directed exam will be performed, as clinically indicated.

[f] ECOG performance status, targeted physical exam, and local laboratory assessments may be obtained ≤ 72 hours before each dosing visit.

[g] Patients should be tested for HIV locally prior to the inclusion into the trial only based on investigator's clinical suspicion for HIV infection and HIV-positive patients will be excluded from the clinical trial. Hepatitis B surface antigen, anti-HBc antibody, anti-HBs antibody, and Hepatitis C antibody immunoassays should be tested only per investigator's clinical suspicion during screening and tested locally. In patients who have positive serology for the anti-HBc antibody, HBV DNA should be tested prior to Day 0.

[h] Concomitant medications include any prescription medications or over-the-counter medications. At screening, any medications the patient has used within the 7 days prior to the screening visit should be documented. At subsequent visits, changes to current medications or medications used since the last documentation of medications will be recorded.

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scheduled tumor assessments until disease progression, start of new-anti cancer therapy, withdrawal of consent, or death. Investigators may perform additional scans or more frequent assessments if clinically indicated. Patients who continue treatment beyond radiographic or clinical disease progression will be monitored with a follow-up scan at the next scheduled tumor assessment. Imaging timing should follow calendar days and should not be adjusted for delays or changes in treatment administration dates. The Sponsor may request digitized scans from patients during the study.

[m] Hematology consists of CBC, including RBC count, hemoglobin, hematocrit, WBC count with automated differential (absolute counts of neutrophils, lymphocytes, eosinophils, monocytes, basophils, and other cells (if any)), and platelet count. A manual differential can be done if clinically indicated.

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[o] Urinalysis includes specific gravity, pH, glucose, protein, ketones, blood, and a microscopic exam if abnormal results are noted. Urinalysis to be performed every 6 weeks.

[p] Serum pregnancy test (for women of childbearing potential, including women who have had a tubal ligation) must be performed and documented as negative within 72 hours prior to each dose.

[q] Thyroid function tests will be performed before first dose and every 6 weeks thereafter.

[r] Immunology samples are to be drawn at Day 0, Week 3, Week 6, Week 9, 12, then Q6 weeks until Week 36 and thereafter every 12 weeks until disease progression, as well as at disease progression.

[s] A pre-treatment tumor tissue sample will be analyzed for ASPH expression. After signing of the Informed Consent Form, tumor tissue should be submitted to the Sponsor in a timely manner. A pre-treatment sample is defined as a specimen obtained after initiation of ongoing pembrolizumab, nivolumab or other CPI therapy and before first dose of SNS-301 and pembrolizumab on this current clinical trial. Patients are requested to provide archival tissue from a prior biopsy or surgery that is treatment –naïve including prior 1) chemotherapy, radiation and/or 2) anti-PD(L)-1 treatment-naïve, pending availability. Tumor tissue should be of good quality based on total and viable tumor content. Acceptable samples include core needle biopsies for deep tumor tissue or lymph nodes or excisional, incisional, punch, or forceps biopsies for cutaneous, subcutaneous, or mucosal lesions. Fine-needle aspiration may be acceptable pending Sponsor approval however, brushing, cell pellets from pleural effusion, and lavage samples are not acceptable. For core needle biopsy specimens, at least three cores should be submitted for evaluation. The patient may start study treatment prior to receiving the ASPH expression results from the fresh biopsy or archival tissue from a previous biopsy. All patients will undergo a mandatory tumor biopsy sample collection, if clinically feasible as determined by the trial investigator, at the Week 6 (at the time of third dose of SNS-301 +/- 3 days). Additionally, up to two optional biopsies may be obtained any time during the study, if medically feasible. A biopsy may also be obtained at the first evidence of radiographic or clinical disease progression (i.e., not proceeded by meaningful tumor regression). For patients who respond and subsequently progress, an optional biopsy may be obtained at the time of disease progression. Patients who are unable to undergo biopsy sample collection but otherwise meet criteria outlined in protocol may continue to receive study treatment. If the patient is unable to have the biopsy at the protocol specified visit (i.e., COVID19 related) then an unscheduled biopsy may be performed.

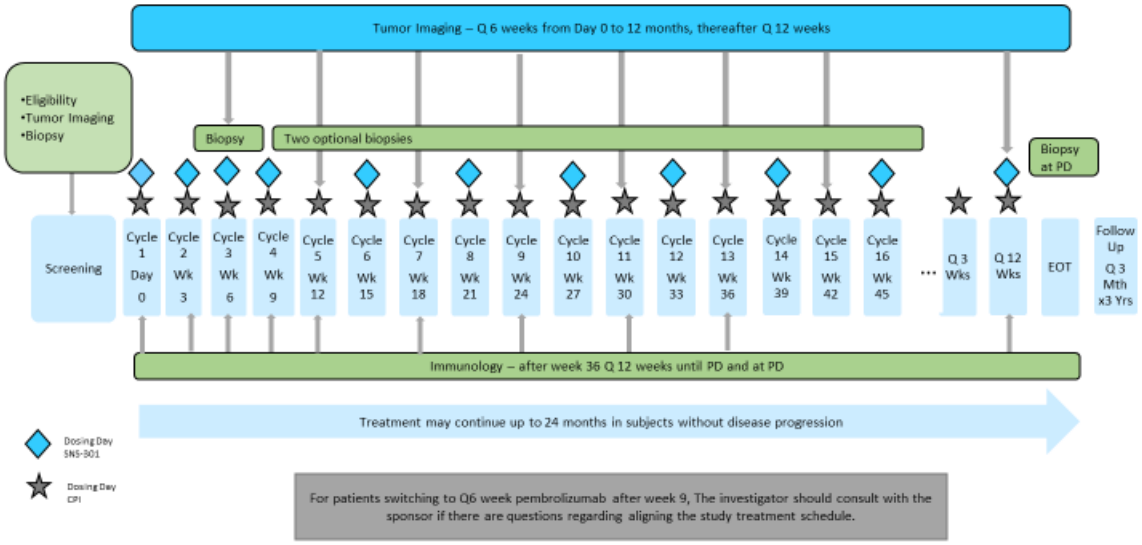
[t] AEs will be collected from the time of informed consent until 30 days after the last dose of study treatment or until initiation of another anti-cancer therapy, whichever occurs first. SAEs and AESIs will be collected from the time of informed consent until 90 days after the last dose of study treatment of until initiation of anti-cancer therapy, whichever occurs first.

[u] Pembrolizumab will be given every 6 weeks until confirmed disease progression, unacceptable toxicity, deemed intolerable by investigator or up to 24 months in patients without disease progression. **After week 9, the pembrolizumab and SNS-301 visits will not coincide. The SNS-301 dosing should not be adjusted. The investigator may choose to give a 3-week dose (i.e., pembrolizumab 200 mg) in order for the visits to align. The investigator should consult the sponsor if there are questions regarding aligning the study treatment schedule**. The window for each visit is ± 3 days unless otherwise noted. A 60 minute observation period is recommended for the first dose and 30 minutes for subsequent doses.

[v] SNS-301 is administered Day 0, Week 3, Week 6 and Week 9, then every 6 weeks for 6 more doses (until week 48). Thereafter it will be administered every 12 weeks until confirmed disease progression, unacceptable toxicity, deemed intolerable by investigator or up to 24 months in patients without disease progression. The window for each visit is ± 3 days unless otherwise noted. A 30-minute observation period is recommended after each study treatment.

[w] Survival follow-up information will be collected via telephone calls, patient medical records, and/or clinical visits approximately every 3 months for up to 3 years, until death, lost to follow-up, withdrawal of consent, or trial termination by Sponsor. All patients will be followed for survival and new anticancer therapy information unless the patient requests to be withdrawn from follow-up; this request must be documented in the source documents and signed by the investigator. If the patient discontinues study treatment without documented clinical disease progression, every effort should be made to follow up regarding survival, progression and new anti-cancer therapy.

1.2 Schema


Tumor Imaging – Q 6 weeks from Day 0 to 12 months, thereafter Q 12 weeks
•Eligibility
•Tumor Imaging
•Biopsy
Biopsy
Two optional biopsies
Biopsy at PD
Screening
Cycle 1 Day 0
Cycle 2 Wk 3
Cycle 3 Wk 6
Cycle 4 Wk 9
Cycle 5 Wk 12
Cycle 6 Wk 15
Cycle 7 Wk 18
Cycle 8 Wk 21
Cycle 9 Wk 24
Cycle 10 Wk 27
Cycle 11 Wk 30
Cycle 12 Wk 33
Cycle 13 Wk 36
Cycle 14 Wk 39
Cycle 15 Wk 42
Cycle 16 Wk 45
Q 3 Wks
Q 12 Wks
EOT
Follow Up Q 3 Mth x3 Yrs
Immunology – after week 36 Q 12 weeks until PD and at PD
Treatment may continue up to 24 months in subjects without disease progression
Dosing Day SNS-301
Dosing Day CPI
For patients switching to Q6 week pembrolizumab after week 9, The investigator should consult with the sponsor if there are questions regarding aligning the study treatment schedule.

2. TERMS, ACRONYMS, ABBREVIATIONS

Term	*Definition*
5-FU	Fluorouracil
ß-HCG	Beta human chorionic gonadotropin
µl	Microliter
ADL	Activities of daily living
AE	Adverse event
AESI	Adverse event of special interest
ALP	Alkaline phosphatase
ALT	Alanine aminotransferase
ANC	Absolute neutrophil count
APC	Antigen-presenting cells
aPTT	Activated partial thromboplastin time
ASPH	Aspartate beta-hydroxylase
ASR	Administration site reaction
AST	Aspartate aminotransferase
BLA	Biologics licensing application
BRPC	Biochemically Recurrent Prostate Cancer
BOR	Best overall response
BUN	Blood urea nitrogen
°C	Celsius
CBC	Complete blood count
CD	Cluster of differentiation
CFR	Code of Federal Regulations
CIOMS	Council for international organizations of medical sciences
Cl	Chloride
CLIA	Clinical laboratory improvement amendments
CNS	Central nervous system
CO_2	Bicarbonate or carbon dioxide
COPD	Chronic obstructive pulmonary disease
CpG	5'-c-phosphate-G-3'(a DNA sequence)
CPI	Checkpoint inhibitor (anti-PD-1/anti-PD-L1 therapy)
CPK	Creatinine phosphokinase
CR	Complete response
CRF	Case report form
CT	Computerized tomography scan

Term	*Definition*
CtDNA	Circulating tumor deoxyribonucleic acid
CTL	Cytotoxic CD8+ T-lymphocytes
DCR	Disease control rate
DLT	Dose-limiting toxicity
DNA	Deoxyribonucleic acid
DOR	Duration of response
EBV	Epstein Barr virus
ECG	Electrocardiogram
ECOG	Eastern Cooperative Oncology Group
eCRF	Electronic case report form
ELI	Enzyme linked immunospot
ELISA	Enzyme-linked immunosorbent assay
EPO	Erythropoietin
FDA	Food and Drug Administration (U.S.)
FFPE	Formalin fixed paraffin embedded
GCP	Good clinical practice
g/dL	Grams per deciliter
gpD	Head DNA stabilization protein of Bacteriophase lambda
HAAH	Human aspartyl-asparaginyl-β-hydroxylase
HBc	Hepatitis B core antigen
HBV	Hepatitis B virus
Hct	Hematocrit
HCV	Hepatitis C virus
Hgb	Hemoglobin
HIPAA	Health Insurance Portability and Accountability Act
HIV	Human immunodeficiency virus
HLA-DR	Human leukocyte antigen – D related
hMTS	3M® hollow microstructured transdermal system
HPV	Human papillomavirus
ICF	Informed consent form
ICH	International conference on harmonization
ID	Intradermally
IDE	Investigational device exemption
IEC	Independent Ethics Committee
IFN	Interferon
IgG	Immunoglobulin G

Term	*Definition*
IHC	Immunohistochemistry
IL	Interleukin
IND	Investigational New Drug
INR	International normalized ratio
IRB	Institutional review board
iRECIST	Immune response evaluation criteria in solid tumors
IV	Intravenous
K	Potassium
kDa	Kilodalton
LDH	Lactate dehydrogenase
mAb	Monoclonal antibody
MDSC	Myeloid derived suppressor cells
mg	Milligrams
Mg	Magnesium
MHC	Major histocompatibility complex
MiRNA	Micro ribosome nucleic acid
mL	Milliliters
mL/min	Milliliters per minute
mm	Millimeter
mmol/L	Millimole per liter
MTD	Maximum tolerable dose
MRI	Magnetic resonance imaging
NA	Sodium
NCI-CTCAE V5.0	National Cancer Institute Common Terminology Criteria for Adverse Events V 5.0
NDA	New drug application
NK	Natural killer
ORR	Objective response rate
OS	Overall survival
P	Phosphorus
PET	Positron emission tomography
PFS	Progression free survival
PBMC	Peripheral blood mononuclear cells
PD	Programmed death
PD	Progressive disease
PD-L	Programmed death ligand

Term	*Definition*
PI	Principal investigator
PR	Partial response
PS	Performance status
PSA	Prostate-specific antigen
PSADT	Prostate-specific antigen doubling time
PT	Prothrombin time
PTT	Partial prothrombin time
R/M	Relapsed/recurrent and metastatic
RBC	Red blood count
RECIST	Response evaluation criteria in solid tumors
RF	Rheumatoid factor
RNA	Ribosome nucleic acid
SAE	Serious adverse event
SCCHN	Squamous cell carcinoma of the head and neck
SD	Stable disease
SEER	Surveillance, epidemiology and end results
SNS-301	HAAH bacteriophage lambda constructs: HAAH-1λ
SGOT	Serum glutamic oxaloacetic transaminase
SGPT	Serum glutamic pyruvic transaminase
SOC	Standard of care
SOC	System organ class
SUSAR	Suspected unexpected serious adverse reaction
T	Thyroxine
TCR	T-cell repertoire
TNF	Tumor necrosis factor
TSH	Thyroid stimulating hormone
TT	Thrombin time
UADE	Unanticipated adverse device effect
ULN	Upper limit of normal
WBC	White blood count
WOCBP	Women of child-bearing potential

3. INTRODUCTION

3.1 Background

Refer to the Investigator's Brochure for more details on SNS-301. For more details on pembrolizumab refer to the package insert https://www.merck.com/product/usa/pi_circulars/k/keytruda/keytruda_pi.pdf.

3.1.1 *Pharmaceutical and Therapeutic Background*

Human aspartyl-asparaginyl-β-hydroxylase (HAAH), also known as aspartate-β-hydroxylase (ASPH), is an ~86 kDa type 2 transmembrane protein that belongs to the α-ketoglutarate-dependent dioxygenase family [1]. It is a highly conserved enzyme, which catalyzes the hydroxylation of aspartyl and asparaginyl residues in epidermal growth factor-like domains of proteins including Notch and homologs [2]. ASPH was initially identified in a novel screen to identify cell surface proteins up-regulated in hepatocellular carcinoma. It has subsequently been detected in a diverse array of solid and blood cancers, including: liver, bile duct, brain, breast, colon, prostate, ovary, pancreas, and lung cancers as well as various leukemias (Table2). ASPH is not found in significant quantities in normal tissue or in proliferative disorders.

Table 2

Tumor Type	ASPH % Positive Expression (Number Tested)		
	IHC of Tissue Samples	Serum ELISA	Flow Cytometry
Normal Bone Marrow	0% (130)	NT	NT
Breast	85% (47)	94% (181)	NT
Cholangiocarcinoma	100% (27)	NT	NT
Colon Cancer	75% (41)	99% (145)	NT
Gastric	80% (51)	NT	NT
Glioblastoma	98% (15)	NT	NT
Head and Neck	91% (22)	75% (12)	NT
Hepatocellular Carcinoma	92% (87)	NT	NT
Lymphoid Leukemia	49% (80)	NT	NT
MDS	NT	50% (10)	91% (11)
Mesothelioma	100% (3)	100% (12)	NT
Myeloid Leukemia	88% (79)	NT	33% (42)
Lung	82% (304)	99% (160)	NT
Osteosarcoma	80% (18)	NT	NT
Pancreatic	97% (109)	NT	NT
Prostate Cancer	96% (46)	95% (233)	NT
Renal cancer	83% (49)	NT	NT
Soft Tissue Sarcoma	84% (30)	NT	NT

Over-expression of ASPH has been demonstrated to be sufficient to induce cellular transformation, increase cellular proliferation and cellular motility while suppression of ASPH expression (small interfering ribonucleic acid) or neutralized activity (monoclonal antibodies) returns cancer cells to a normal phenotype. In cancer cells, it has been shown to be translocated to the cellular surface where it is not normally located. Because ASPH is an embryonic antigen, and as such presents self-antigen tolerance, it is difficult to elicit a robust immune response against it and break immune tolerance. Thus, we hypothesized that effective priming of antigen-presenting cells (APC) by ASPH antigen is an essential step to overcome immune tolerance. Indeed, in vitro activation of dendritic cells with ASPH, prior to re administration to patients with hepatocellular carcinoma has shown promising results [3].

Bacteriophage offers a simple, inexpensive and practical way of achieving favorable presentation of peptides to the immune system. The phage contains deoxyribonucleic acid (DNA) fragments that present the phage CpG motifs, which are known to stimulate the innate immune response and activate the major histocompatibility class (MHC) class II pathway in APC. Previous findings have revealed that recombinant bacteriophage can prime strong CD8+ T-lymphocyte (CTL) responses both in vitro and in vivo against epitopes displayed in multiple copies on their surface [4], activate helper T cells [5] and elicit the production of specific antibodies [6, 7] without requiring any exogeneous adjuvants. Thus, we have selected bacteriophage as a platform for eliciting anti-ASPH immune responses. Bacteriophages are ubiquitous and essentially innocuous to humans, however, as an added safety mechanism, they may be neutralized rendering them non-infective to host bacteria while retaining their immunostimulant properties. Once neutralized, the bacteriophage effectively becomes a nanoparticle, for enhanced delivery of protein fragments to APC.

We have designed a bacteriophage lambda system to display ASPH peptides fused at the C terminus of the head protein gpD of phage lambda. The phages carry 200-300 copies of the gpD protein on their head and thus display many copies of an approximately 25 kDa molecular weight fragment of ASPH on their surface. The drug substance is one of these HAAH bacteriophage lambda constructs: HAAH-1λ (SNS-301).

3.1.2 *Pre-Clinical, Clinical Trials and Other Ongoing Trials*

Pre-Clinical

In non-clinical studies, the SNS-301 vaccine has been evaluated in rodents for immunogenicity and efficacy where dose-dependent humoral responses were demonstrated for ID delivery and solid tumor growth was slowed. Further, rodent repeat-dose toxicology with SNS-301 had no evident toxicity.

For additional information on pre-clinical data refer to the Investigators Brochure.

Current Clinical Data with SNS-301

In clinical studies, the SNS-301 vaccine has been evaluated in a Phase 1 study (Study SNS0216) in patients with biochemically relapsed prostate cancer. The study evaluated 3 dose levels, 2×10^{10}, 1×10^{11} and 3×10^{11} particles in a 1 mL dose for safety, immunogenicity and preliminary efficacy. Results showed that all dose levels were well-tolerated, with the majority of treatment-emergent adverse events (TEAEs) assessed as mild and unrelated to SNS-301; further no dose-limiting toxicities (DLTs) were observed and of the 2 reported serious adverse events (SAEs), both were assessed as unrelated to study treatment. Further, SNS-301 at all dose levels was immunogenic and 58% of patients achieved improvement in prostate specific antigen (PSA) doubling time.

Based on results from the Phase 1 Study SNS0216, the recommended Phase 2 dose (RP2D) of SNS-301 1×10^{11} was chosen for further evaluation in Phase 2 clinical studies of SNS-301 in patients with various solid tumors and hematologic malignancies. See the most recent Investigator's Brochure for additional details.

The Phase 1/2 Study (SNS-301-2-2) of SNS-301, 1×10^{11} administered ID, added to pembrolizumab is currently ongoing. As of the database cutoff (29 October 2020), the study has enrolled 11 patients with locally advanced unresectable or metastatic/recurrent squamous cell carcinoma of the head and neck (SCCHN). Of the 11 patients enrolled 9 (82%) experienced a TEAE, however, majority of the reported TEAEs were mild (Grade 1) and not related to study treatment. There were 3 Grade 3 TEAEs related to study treatment experienced by 2 patients: rash, electrocardiogram QT prolongation and dehydration. There were 4 SAEs reported for 3 patients: Grade 3 dehydration, G3 electrocardiogram QT prolongation, Grade 2 Systemic Inflammatory Response Syndrome, G2 hemoptysis, G2 malnutrition/dehydration. There were no DLTs, Grade 4, or fatal events reported to date.

For additional information clinical data with SNS-301 refer to the Investigators Brochure.

3.2 Rationale

Anti-PD-1 antibodies including nivolumab and pembrolizumab can induce durable remissions <20% of patients with recurrent or metastatic SCCHN in first or subsequent line setting after platinum-containing chemotherapy[8], but the majority of patients fail to respond due to inadequate intra-tumoral immune cell infiltration. Other checkpoint inhibitors (CPI; defined as anti-PD-1/anti-PD-L1 therapy) currently in clinical trials as combination therapy or monotherapy demonstrate limited responses as well, thus underscoring the importance of allowing patients who are unresponsive to CPI therapy the option to participate in a clinical trial, such as the study sponsored by Sensei Biotherapeutics. It is hypothesized that these tumors are generally immunologically "cold," or T-cell excluded for various reasons. Even if there is intra-tumoral T-cell infiltration, these T cells are not able to exert a significant anti-tumor effect, likely owing to the suppressive tumor microenvironment. ASPH is frequently expressed in SCCHN, but de-novo responses to this tumor-specific antigen may be limited due to immune tolerance acquired during development. Our hypothesis is that SNS-301 will help generate functional T cells when added to a CPI can overcome checkpoint refractoriness or lack of checkpoint efficacy. Sensei Biotherapeutics plans to develop SNS-301 in addition to pembrolizumab in a study targeting two different patient cohorts: patients that did not achieve objective responses after at least 12 weeks of CPI and patients that are CPI naïve. The overall goal is to improve clinical outcomes in patients with locally advanced or metastatic SCCHN receiving CPI therapy.

3.2.1 *Rationale for the Trial and Selected Subject Population*

It is hypothesized that SNS-301, given its biologic properties and unique ASPH target, can impact on biologically-relevant (i.e. ASPH-over-expressing) cancer targets in a differentiated and meaningful manner. Accordingly, the Sponsor seeks now to generate initial signals of SNS-301 impact in oncologic investigational spaces of high unmet medical need including ASPH-expressing squamous cell carcinoma of the head and neck (SCCHN). Preliminary expression data prior to the initiation of the current clinical trial demonstrated ASPH expression at any level in about 85% or greater of SCCHN patients. In the current trial, 26 out of the 26 patients considered potentially eligible for enrollment tested positive for ASPH expression. Given the prevalence seen ASPH expression in tumors, the Sponsor proposes foregoing ASPH expression data prior to trial enrollment and proposes to enroll and treat patients regardless of ASPH expression. ASPH expression data will continue to be obtained and recorded however it is anticipated that the numbers of patients without ASPH expression will be low.

3.2.1.1 Unmet Medical Need for Patients with SCCHN

SCCHN are cancers that comprise the oral cavity, pharynx and larynx, and account for >90% of histological subtypes and have an annual incidence of about 45,000 patients in the US alone. According to SEER, less than two-thirds of patients remain alive at 5 years [9]. Tobacco use is the most important risk factor, followed by human papilloma virus (HPV), which is primarily seen in oropharyngeal cancers (tonsils and base of the tongue). Despite an aggressive multidisciplinary approach, up to 30% of patients with locally advanced disease relapse in distant sites, and up to 60% have local recurrence [10].

Until recently, platinum-based combination chemotherapy with or without cetuximab was the standard of care (SOC) for relapsed/recurrent and metastatic (R/M) disease based on the cetuximab in first-line treatment of head and neck cancer (EXTREME) trial, which showed the addition of cetuximab to platinum/5-fluorouracil (5-FU) chemotherapy improved overall survival (OS) from 7.1 to 10.1 months [11]. However, toxicity with this regimen is significant, and responses are relatively short. Unfortunately, patients after disease progression have very low responses to additional chemotherapy and low median OS, thus highlighting the need for novel therapies.

Multiple factors support the use of immunotherapy in SCCHN, which have prompted the development of CPI therapy in SCCHN leading to approval of nivolumab and pembrolizumab in the second line (2L) or subsequent therapies recurrent/metastatic setting. For example, nivolumab was approved on the basis of a randomized Phase

3 trial in platinum-refractory recurrent/metastatic SCCHN [2]. Three hundred sixty-one patients were assigned in a 2:1 ratio to either nivolumab (at a dose of 3 mg/kg of body weight once every 2 weeks) or investigator's choice of single agent standard chemotherapy (methotrexate, docetaxel or cetuximab); 54.6% of patients had at least two prior lines of systemic therapy. Median OS was superior in the nivolumab group (7.5 vs 5.1 months (HR=0.70, p=0.01) and was more than double at 1 year (36% vs 16.6%). The objective response rate (ORR) was also superior with nivolumab (13.3% vs 5.8%), and increased durability of response (DoR) was also demonstrated with nivolumab. The safety profile of nivolumab was better tolerated than chemotherapy, with grade 3 or higher AEs reported in 13.1% vs 35.1%, respectively, with the most common AEs including fatigue (14.0%), nausea (8.5%) and rash (7.6%).

KEYNOTE-048 (NCT02358031) [8], a randomized, multicenter, three-arm, open-label, active-controlled trial conducted in 882 patients with metastatic HNSCC who had not previously received systemic therapy for metastatic disease or with recurrent disease who were considered incurable by local therapies was approved by the FDA in June 2019.

Patients were randomized (1:1:1) to receive one of the following treatments: pembrolizumab as a single agent; pembrolizumab, carboplatin or cisplatin, and FU; or cetuximab, carboplatin or cisplatin, and FU. Randomization was stratified by tumor PD-L1 expression (Tumor Proportion Score [TPS] ≥50% or <50%), HPV status according to p16 IHC (positive or negative), and ECOG PS (0 vs 1). PD-L1 expression (TPS and CPS) was determined using the PD-L1 IHC 22C3 pharmDx kit. Overall survival (OS), sequentially tested in the subgroup of patients with CPS ≥20 HNSCC, the subgroup of patients with CPS ≥1 HNSCC and the overall population, was the major efficacy measure.

The trial demonstrated a statistically significant improvement in OS in the overall population for patients randomized to pembrolizumab plus chemotherapy compared with cetuximab plus chemotherapy at a pre-specified interim analysis. The median OS was 13.0 months for the pembrolizumab plus chemotherapy arm and 10.7 months for the cetuximab plus chemotherapy arm (HR 0.77; 95% CI: 0.63, 0.93; p=0.0067). Results were similar in the CPS ≥20 subgroup (HR 0.69; 95% CI: 0.51, 0.94) and CPS ≥1 subgroup (HR 0.71; 95% CI: 0.57, 0.88).

The trial also demonstrated statistically significant improvements in OS for the subgroups of patients with PD-L1 CPS ≥1 HNSCC and PD-L1 CPS ≥20 HNSCC randomized to pembrolizumab as a single agent compared with cetuximab plus chemotherapy. In the CPS ≥1 subgroup, the median OS was 12.3 months for the pembrolizumab arm and 10.3 months for the cetuximab plus chemotherapy arm (HR 0.78; 95% CI: 0.64, 0.96; p=0.0171). For the CPS ≥20 subgroup, the median OS was 14.9 months for the pembrolizumab arm and 10.7 months for the cetuximab plus chemotherapy arm (HR 0.61; 95% CI: 0.45, 0.83; p=0.0015). At the time of the interim analysis, there was no significant difference in OS between the pembrolizumab as a single agent arm and the cetuximab plus chemotherapy arm for the overall population. There were no significant differences in progression-free survival for either pembrolizumab-containing arm compared to the cetuximab plus chemotherapy arm in any population.

The most common adverse reactions reported in ≥20% of patients who received pembrolizumab as a single agent in KEYNOTE-048 were fatigue, constipation, and rash. The most common adverse reactions reported in ≥20% of patients who received pembrolizumab in combination with chemotherapy in KEYNOTE-048 were nausea, fatigue, constipation, vomiting, mucosal inflammation, diarrhea, decreased appetite, stomatitis, and cough.

Over the last several years advancements regarding the therapeutic role of ICIs led to the approval of pembrolizumab and nivolumab for SCCHN; however, response rates are fairly low in the first and second line metastatic SCCHN population. There are multiple other ICIs that are in clinical trials (e.g., atezolizumab, durvalumab, avelumab, etc.) and these agents as combination therapy or monotherapy demonstrate limited responses as well, thus underscoring the importance of allowing these patients to participate in trials that

potentially can enhance the efficacy of CPI therapy such as the study sponsored by Sensei Biotherapeutics. In order to provide an option to the majority of SCCHN patients who do not respond to CPI therapy, Sensei will allow inclusion of patients who received widely investigated ICIs (anti-PD1, anti-PD-L1 agents) as part of clinical trials as long as patients meet all of the outlined eligibility criteria. All patients enrolled will be switched to pembrolizumab treatment regardless of which ICI therapy the patient was receiving previously. Furthermore, given the modest response rates to CPI therapy even in patients with PD-L1 positive tumors in the first line setting (19%, Keynote-48), Sensei will allow enrollment to a second cohort with patients that are CPI therapy naïve.

3.2.1.2 ASPH Expression Testing in SCCHN

Tissue samples from 22 patient with squamous cell cancer of the head and neck were evaluated for ASPH expression by IHC at a collaborating laboratory. Twenty (91%) of the patients studied showed evidence of ASPH expression with 18 (82%) having moderate to high expression levels (Unpublished data, Dr. Jack Wands, Brown University). As of 29 Oct 2020, 30 additional archived tissue samples have been analyzed from this study. All 30 samples were found to be ASPH positive as assessed by a CLIA validated IHC assay from Fred Hutchinson Cancer Center.

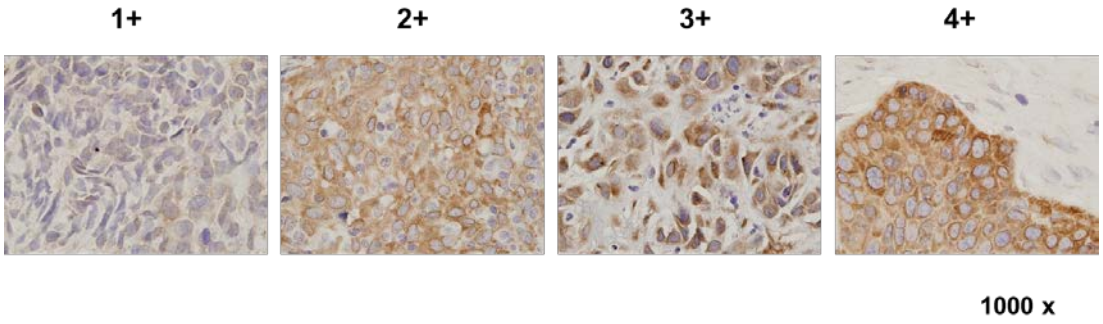


Figure 1. ASPH Expression in patients with SCCHN as expressed by immunohistochemistry

3.2.2 *Rationale for Companion Diagnostic and Translational Biomarkers*

The Sponsor has developed an analytical method to screen for ASPH expression. Immunohistochemistry staining for ASPH will be performed on biopsy samples.

All ASPH (+) samples and a random sample of ASPH negative samples (if available) will be banked in the event that they may be necessary for future analysis.

3.2.3 *Rationale for Dose Selection/Regimen*

The pembrolizumab dose of 200 mg dose IV infusion over 30 minutes every three weeks or pembrolizumab dose of 400 mg IV infusion over 30 minutes every six weeks has been chosen based on the US package insert for this indication. As of April 2020, Merck has extended dosing for all approved indications to allow for three or six week dosing.SNS-301 (1×10^{11} particles in 1ml ID injection) is planned to be administered when pembrolizumab dosing is every 3 weeks SNS-301 will be given at Day 0, Week 3, Week 6, Week 9, then every 6 weeks for 6 more doses (45 weeks). Thereafter, SNS-301 is to be administered every 12 weeks until confirmed disease progression, unacceptable toxicity, or deemed intolerable by the investigator. When pembrolizumab dosing is every 6 weeks SNS-301 dosing will be at Day 0, Week 3, Week 6, Week 12, every 3 weeks for 4 doses (12

weeks), and then every 6 weeks for 6 more doses (45 weeks). Thereafter, SNS-301 is to be administered every 12 weeks until confirmed disease progression, unacceptable toxicity, or deemed intolerable by the investigator.

The SNS-301 dose was chosen based on the safety, immunogenicity and preliminary efficacy data that were available from the Phase 1 dose escalation study (Study SNS0216) conducted in patients with biochemically relapsed prostate cancer. The overall safety profile, SNS-301 was considered to be tolerable with no dose limiting toxicities (DLTs) observed and no discernable safety differences.

The immunogenicity of SNS-301 was evaluated for both antibody and cellular responses. At all dose levels tested, SNS-301 was able to generate specific anti-ASPH responses, however, the mid-dose level (and proposed Phase 2 clinical dose) demonstrated the best ASPH-specific antibody and cellular responses.

The Sponsor evaluated the clinical efficacy of SNS-301 by examining PSA kinetics such as the effect of SNS-301 on PSA doubling time (PSADT), absolute PSA levels and PSA velocity (PSAV). A positive effect in lengthening the time in months to double the PSA value in the treatment phase compared to the pre-treatment phase was observed in 2 of 3 patients in both the low dose (2×10^{10} particles) and the mid dose (1×10^{11} particles) treatment groups. In the high dose (3×10^{11} particles) group, 3 of 6 patients showed a positive treatment effect.

. The efficacy analysis showed a disease stabilizing effect of SNS-301 as evidenced by significant improvements in PSADT post-therapy for the patients. We believe that the excellent safety profile of SNS-301 coupled with the preliminary efficacy observed in patients with prostate cancer warrants further evaluation of SNS-301 at the mid-dose level of 1×10^{11} in the unmet medical need patient population of patients with SCCHN who have failed prior therapy. The dose of pembrolizumab is based on the US package insert. No overlapping toxicities are anticipated.

3.3 Benefit/Risk

Any direct benefit for patients from participating in this clinical trial are unknown. . The median OS of patients even in the first line metastatic setting who do not respond to CPI is less than 12 months. However, this study may likely enroll who have also previously received and progressed on platinum-based chemotherapy, in which population the median OS is less than 6 months. Therefore, the study population represents a high unmet medical need and overall the clinical benefit potential outweighs the risks associated with SNS-301 The known risks of SNS-301 are described in the pre-clinical and clinical background sections, in the SNS-301 Investigators Brochure.

There have been no significant safety findings with no related Grade 3 or Grade 4 adverse events and no related serious adverse events with SNS-301. Of note, no studies assessing the reproductive and developmental toxicity of SNS-301 have been conducted to date. It is not known whether SNS-301 can cross the placenta or cause harm to the fetus when administered to pregnant women or whether it affects reproductive capacity. However, the antigen targeted by SNS-301 is involved in uterine implantation of the embryo. Therefore, SNS-301 should not be administered to pregnant women and pregnancy testing will be performed in women of childbearing potential (WOCBP) at screening and prior to each dose. WOCBP and male partners of such women should take necessary precautions to avoid pregnancy while receiving SNS-301, for the protocol defined period following the last dose of investigational product.

It is not known whether SNS-301 is excreted in human milk. Because of the unknown potential for serious adverse drug reactions in nursing infants, investigational product should not be administered to nursing mothers.

The known risks of pembrolizumab are described in the package insert.

4. OBJECTIVES AND ENDPOINTS

4.1 Study Objectives

4.1.1 Primary Objectives

- To determine the safety and tolerability of SNS-301 delivered by intradermal injection (ID) using the 3M® hollow microstructured transdermal system (hMTS) device in addition to pembrolizumab among patients with locally advanced unresectable or metastatic/recurrent SCCHN.
- To evaluate the anti-tumor activity of SNS-301 delivered by intradermal injection (ID) using the 3M® hollow microstructured transdermal system (hMTS) device in addition to pembrolizumab in patients with locally advanced unresectable or metastatic/recurrent SCCHN

4.1.2 Secondary Objective

- To evaluate preliminary immune response to SNS-301 delivered by intradermal injection (ID) using the 3M® hollow microstructured transdermal system (hMTS) device in addition to pembrolizumab in patients with locally advanced unresectable or metastatic/recurrent SCCHN.

4.1.3 Exploratory Objective

- To evaluate tumor and immune biomarkers and their association with treatment outcome (antitumor activity and/or safety) in patients with locally advanced unresectable or metastatic/recurrent SCCHN.

4.2 Study Endpoints

4.2.1 Primary

1. To determine the safety and tolerability of SNS-301 delivered by intradermal injection (ID) using the 3M® hollow microstructured transdermal system (hMTS) device in addition to pembrolizumab among patients with locally advanced unresectable or metastatic/recurrent SCCHN as measured by the following parameters:

    - All adverse events (AEs) by CTCAE v5 such as clinically significant changes in safety laboratory parameters from baseline: CBC with Differential; Chemistry Panel; Urinalysis; T3, Free T4 and TSH; creatine phosphokinase (CPK) and including adverse events of special interest (AESI) classified by system organ class (SOC), preferred term (PT), severity and relationship to drug

2. To determine anti-tumor activity of SNS-301 delivered by intradermal injection (ID) using the 3M® hollow microstructured transdermal system (hMTS) device in addition to pembrolizumab in patients with locally advanced unresectable or metastatic/recurrent SCCHN as measured by the following parameters:
    - Objective response rate (ORR) by immune Response Evaluation Criteria in Solid Tumors (iRECIST)Duration of Response (DoR) as assessed by RECIST version 1.1 and iRECIST
    - Objective response rate (ORR) by Response Evaluation Criteria (RECIST) version 1.1 by investigator review
    - Disease control rate (DCR) as assessed by RECIST version 1.1 and iRECIST
    - Progression Free Survival (PFS) as assessed by RECIST version 1.1 and iRECIST
    - Overall Survival (OS)

4.2.2 Secondary

To determine preliminary immune response to SNS-301 delivered by intradermal injection (ID) using the 3M® hollow microstructured transdermal system (hMTS) device in addition to with pembrolizumab in patients with locally advanced unresectable or metastatic/recurrent SCCHN by the following parameters:

- Antigen-specific cellular immune responses that may be assessed by but not limited to: Interferon-γ secreting T lymphocytes in peripheral blood mononuclear cells (PBMCs) by ELI Spot
- Anti-SNS-301 antibody response
- Assessment of pro-inflammatory and immunosuppressive elements in neoplastic and adjacent normal tissue, where feasible

4.2.3 Exploratory

To determine tumor and immune biomarkers and their association with treatment outcome (antitumor activity and/or safety) in patients with locally advanced unresectable or metastatic/recurrent solid tumors as measured by the following parameters:

- Immune related gene expression
- Expression of tumor specific oncoproteins including but not limited to ASPH
- Correlation of serum ASPH level as determined by ELISA with tissue expression using IHC
- miRNA profiling to predict treatment efficacy evaluating pre and post-treatment peripheral blood samples as well as urine samples
- Cytokine and chemokine profiles in urine pre- and post-treatment and longitudinally throughout the trial
- TCR sequencing of PBMCs for diversity and putative antigen specificity
- CtDNA analysis and tracking for progression

5. STUDY DESIGN

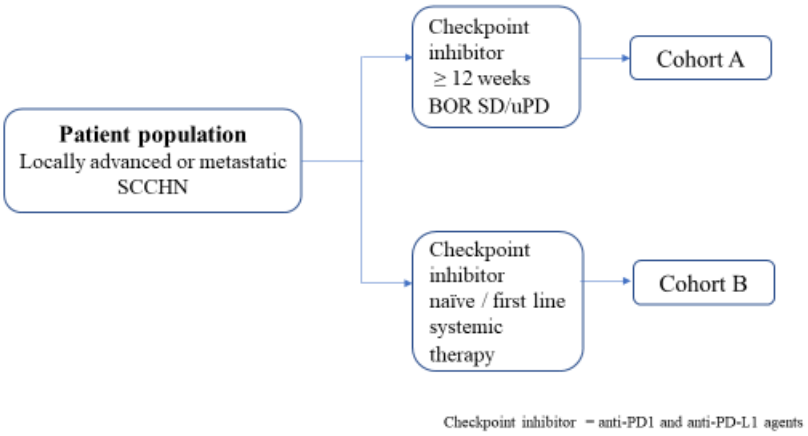
5.1 Research Hypotheses

SNS-301 delivered by intradermal injection (ID) using the 3M® hollow microstructured transdermal system (hMTS) device in addition to pembrolizumab, will be generally safe, well tolerated, immunogenic and lead to anti-tumor responses in adult patients with locally advanced unresectable or metastatic/recurrent SCCHN.

5.2 Overall Design

This is a Phase 1/2, open-label, multi-center trial to evaluate the safety, immunogenicity and preliminary clinical efficacy of SNS-301 delivered by intradermally in addition to pembrolizumab in patients with locally advanced unresectable or metastatic/recurrent SCCHN. The trial population consists of patients with locally advanced unresectable or metastatic/recurrent SCCHN who are currently receiving a CPI therapy (Cohort A) or are naïve to CPI therapy (Cohort B). CPI therapy are considered agents that are anti-PD1 and anti-PD-L1agents. Patients currently receiving CPI therapy must have a best response of stable disease (SD) or first evidence of progressive disease (PD) after a minimum of 12 weeks of a CPI therapy. Patients receiving first-line pembrolizumab monotherapy must be PD-L1 positive. Patients receiving another CPI than pembrolizumab will be switched over to pembrolizumab at the time of entering this study. Each cohort will enroll up to approximately 30 patients. Approximately 60 patients will be enrolled over two cohorts at up to 15 institutions within the United States.

The cohorts for this study are highlighted below.



After consenting to participate in this clinical trial, participants will be screened for enrollment. A tissue sample is required for entry onto the study with either a fresh biopsy or archival tissue from a previous biopsy. Ideally, a pre-treatment tissue sample obtained after initiation of ongoing CPI therapy and before first dose of SNS-301 and pembrolizumab on this current clinical trial will be collected. Patients unable to provide pre-treatment biopsy while on CPI will be evaluated on a case-by-case basis for enrollment pending Sponsor consultation. Patients are requested to provide archival tissue from a prior biopsy or surgery that is treatment -naïve including prior 1) chemotherapy, radiation and/or 2) anti PD(L)-1 treatment-naïve, pending availability. An on-treatment biopsy is required when medically feasible, after the third dose of treatment around treatment week 6. Additionally, up to two optional biopsies may be obtained at any time during the study, if medically feasible. For patients who progress as determined per RECIST1.1/iRECIST criteria, an optional biopsy will be obtained at the time of disease progression.

This study will employ a Simon 2-stage design, with 15 evaluable patients (i.e. meeting the definition for the efficacy evaluable analysis set;at Week 12 for both cohorts . The criteria for advancing to Stage 2 is described in Section 10.2. Non-evaluable patients will be replaced.

The safety run-in will be performed using a modified rolling six design which will enroll up to six patients (safety analysis patients). These patients may contribute to the first 15 in stage 1, assuming they meet the definition for evaluable for efficacy.

Once the first three patients of these six patients have completed Week 6 assessments, in the absence of any dose-limiting toxicity (DLT), enrollment may proceed through stage 1. However, if prior to the first three patients completing Week 6, a single patient from the first six experiences a DLT, then enrollment will be limited to six patients until all six patients have reached Week 6 and are assessed for DLT. If no additional patients, of these six, experience a DLT within the 6-week safety run in period, then enrollment may proceed to completion.

If a second of these first six patients experiences a DLT within the first six weeks, enrollment will stop, and the Sponsor's medical monitor, in addition to the PI and Investigator(s) at the patients' site(s) will discuss the case, and a decision will be made whether to modify the trial or to cease further enrollment. If enrollment is ceased, it will only be reinitiated after amendment of the protocol and approval of the amended protocol by the IRB.

Safety run-in patients that withdraw from the study for reasons other than a DLT, prior to the end of the safety run-in period, will be replaced. The end of the safety run-in period is defined as the earliest of the following:

- The first three patients have all completed Week 6 with no DLTs experienced by any of the safety run-in patients in that cohort (up to six); enrollment may then proceed through stage 1;
- All six patients of the safety run-in phase, have completed week six with only one patient having experienced a DLT; enrollment may then proceed through stage 1;
- Two or more of the safety run-in patients, have experienced DLTs prior to completing Week 6; enrollment will be suspended.

DLTs are defined in the protocol section 9.3.9.

Because this trial is treating patients with SNS-301 and pembrolizumab for the first time, there will be a waiting period of one week between enrollment of the first patient and the second patient.

Stopping rules for adverse events will be employed for this trial. The trial will be stopped if any adverse experience of any related death, grade 4 autoimmune toxicity or any grade 4 toxicity that is considered to have a causal relationship to study drug. Any related death, grade 4 autoimmune toxicity and any grade 4 toxicity that is considered to have a causal relationship to study drug will be submitted to regulatory agencies within the expedited safety reporting criteria.

To ensure patient safety during the study, a Safety Committee will be formed to monitor safety on a periodic basis. Members of the Safety Committee will include a Safety representative, Principal Investigator(s) and the Sponsor Medical Expert. A charter will outline their roles and responsibilities. The Safety Committee will meet at the completion of the safety run-in to review safety data collected from the point of first patient in (FPI) to review safety, or as needed. The safety data will include demographic data, adverse events, serious adverse events, and relevant laboratory data. Following each data review, the Safety Committee will provide recommendations as to whether the study should continue or be amended, or whether the study should be stopped on the basis of safety (i.e., evidence of harm). The final decision will rest with the Sponsor. The interim efficacy assessment, for each cohort, will occur after 15 patients were enrolled and completed the 12-week follow-up period. A safety review will occur in parallel to the efficacy assessment of the first 15 patients. Any outcomes of these safety reviews that affect study conduct will be communicated in a timely manner to the investigators for notification of the Institutional Review boards/Ethics Committees (IRBs/ECs).

5.3 End of Study Definition

The clinical trial will be considered completed when all patients have had their three-year follow-up visit, death, lost to follow-up, withdrawal of consent, or when the Sponsor deems the study completed, whichever comes first.

6. STUDY POPULATION

Inclusion Criteria

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

1. Provide signed IRB approved informed consent in accordance with institutional guidelines.
2. Be 18 years of age or older on the day of signing the informed consent, and able and willing to comply with all trial procedures.
3. Have histologically or cytologically documented locally advanced unresectable or metastatic/recurrent SCCHN and meet the criteria of either Cohort A or B.

   Cohort A: Patients with Ongoing CPI Therapy
   a. Patients currently receiving a checkpoint inhibitor (anti-PD1 and anti-PD-L1 agents).
   b. Patients currently receiving a CPI must be considered by Investigator to have the potential to derive clinical benefit from continued treatment with pembrolizumab.
   c. Based on RECIST 1.1/iRECIST criteria on current CPI treatment (prior to initiation of this study), patients must have a best response of stable disease (SD) or first evidence of progressive disease (PD) after a minimum of 12 weeks of a CPI.
   d. Patients on other CPI therapy than pembrolizumab must be willing to switch over to pembrolizumab therapy.

   Cohort B: Patients without Previous CPI Therapy
   a. Patients must be checkpoint inhibitor naïve (anti-PD1 and anti-PD-L1 agents)
   b. Patients should receive study treatment as first line (PD-L1 positive) or as second line (PD-L1 negative) systemic therapy in the advanced/metastatic setting.
4. Have measurable disease, as defined by RECIST version 1.1 (investigator assessment).
5. Have a performance status of 0 or 1 on Eastern Cooperative Oncology Group (ECOG) Performance Scale.
6. Have a life expectancy of ≥ 3 months.
7. Be willing to provide a pre-treatment tissue sample obtained after initiation of ongoing CPI therapy (Cohort A, only) and before first dose of SNS-301 and pembrolizumab on this current clinical trial unless clinically contra-indicated per treating physician. Patients unable to provide pre-treatment biopsy while on CPI will be evaluated on a case-by-case basis for enrollment pending Sponsor consultation (Cohort A, only). Patients are requested to provide archival tissue from a prior biopsy or surgery that is treatment –naïve including prior 1) chemotherapy, radiation and/or 2) anti-PD(L)-1 treatment-naïve, pending availability. Tissue provided pre-treatment (fresh or archival) will be used to determine ASPH expression . Additionally, an on-treatment biopsy is required unless clinically contraindicated, after the third dose of study treatment at week 6. For patients who progress as determined per RECIST1.1/iRECIST criteria, an optional biopsy may be obtained at the time of disease progression.
8. Have an ECG with no clinically significant findings such as stage 2b and 3 heart block, any history of ventricular arrhythmias or NYHA heart failure within the past 6 months, and QTc prolongation > 500 ms or as deemed clinically significant by the investigator and performed within 28 days prior to first dose.
9. Demonstrate adequate organ function: hematological, renal, hepatic, coagulation parameters as defined below and obtained within 28 days prior to the first study treatment. Adequate hematologic and end-organ function:

System	**Laboratory Value**
Hematological	
Absolute neutrophil count (ANC)	≥1500/ µL
Platelets	≥100,000/ µL
Hemoglobin	≥9 g/dL, or ≥5.6 mmol/L without transfusion or EPO dependency within 7 days

Renal	
Creatinine OR Calculated creatinine clearance	≤ 1.5 x upper limit of normal (ULN) OR ≥ 30 mL/min for patient with creatinine level > 1.5 x institutional ULN Note: Creatinine clearance should be calculated per Cockcroft-Gault formula
Hepatic	
Total bilirubin	≤ 1.5 x ULN **OR** Direct bilirubin ≤ ULN for patients with total bilirubin levels > 1.5 x ULN
AST (SGOT) and ALT (SGPT)	≤ 2.5 x ULN **OR** ≤ 5 x ULN for patients with liver metastases
Coagulation	
International Normalized Ratio (INR) or Prothrombin Time (PT)	≤1.5 x ULN unless patient is receiving anticoagulant therapy as long as PT or PTT is within therapeutic range of intended use of anticoagulants
Activated Partial Thromboplastin Time (aPTT)	≤1.5 x ULN unless patient is receiving anticoagulant therapy as long as PT or PTT is within therapeutic range of intended use of anticoagulants

10. For women of childbearing potential: agreement to remain abstinent (refrain from heterosexual intercourse) or use two highly effective contraceptive methods that result in a combined failure rate of < 1% per year during the treatment period and for at least 180 days after the last dose of study treatment:
    - A woman is considered to be of childbearing potential if she has not reached a postmenopausal state (≥ 12 continuous months of amenorrhea with no identified cause other than menopause), and has not undergone surgical sterilization (removal of ovaries and/or uterus)
    - Examples of contraceptive methods with a failure rate of < 1% per year include bilateral tubal ligation, male sterilization, established, proper use of hormonal contraceptives that inhibit ovulation, hormone-releasing intrauterine devices, and copper intrauterine devices
    - The reliability of sexual abstinence should be evaluated in relation to the duration of the clinical trial and the preferred and usual lifestyle of the patient. Periodic abstinence (e.g., calendar, ovulation, sympto-thermal, or post-ovulation methods) and withdrawal are not acceptable methods of contraception

    For male patients: Agree that during the period specified above, men will not father a child. Male patients must remain abstinent (refrain from heterosexual intercourse with women of childbearing potential), must be surgically sterile (e.g., vasectomy) or use contraceptive methods that result in a failure rate of < 1% per year during the treatment period and for at least 180 days after the last dose of study treatment.

6.1 Exclusion Criteria

Patients who meet any of the following criteria will be excluded from trial entry:

Cancer-specific Exclusion Criteria:

1. Any approved anti-cancer therapy including chemotherapy, targeted small molecule therapy or radiation therapy within 2 weeks prior to trial Day 0; or if patient has not recovered (i.e., Less than or equal to grade 1 or returned to baseline level) from adverse events due to a previously administered agent; the following exceptions are allowed:
    - Palliative radiotherapy for bone metastases or soft tissue lesions should be completed > 7 days prior to baseline imaging
    - Hormone-replacement therapy or oral contraceptives
    - Patients with grade 2 neuropathy or grade 2 alopecia
2. Patients with evidence of rapid progression or prior therapy (if applicable) resulting in rapid clinical deterioration should be excluded from participation in the trial;
3. Currently participating and receiving trial therapy or has participated in a trial of an investigational agent and/or has used an investigational device within 28 days prior to Day 0;
   Note: Patients who have entered the follow-up phase of an investigational trial may participate as long as it has been 28 days since the last dose of the previous investigational agent or device.
4. Uncontrolled tumor-related pain
    - Patients requiring pain medication must be on a stable regimen at trial entry;
    - Symptomatic lesions amenable to palliative radiotherapy (e.g., bone metastases or metastases causing nerve impingement) should complete treatment at least 7 days prior to enrollment
5. Uncontrolled pleural effusion, pericardial effusion, or ascites requiring recurrent drainage procedures (once monthly and more frequently)
    - Patients with indwelling catheters (e.g., PluerX) are allowed;
6. Malignancies other than indications open for enrollment within 3 years prior to Day 0, with the exception of those with negligible risk of metastasis or death treated with expected curative outcome, undergoing active surveillance or treatment-naïve for indolent tumors.

<u>General Medical Exclusion Criteria</u>

7. Pregnant or lactating or intending to become pregnant or father children within the projected duration of the trial starting with the screening visit through 180 days after the last dose of pembrolizumab and/or SNS-301.
8. History of severe allergic, anaphylactic, or other hypersensitivity reactions to chimeric or humanized antibodies or fusion proteins.
9. Known hypersensitivity allergy or contraindication to biopharmaceuticals produced in Chinese hamster ovary cells or any component of the PD-1/PD-L1 inhibitor formulation.
10. Active autoimmune disease that has required systemic treatment in the past 2 years (i.e. with use of disease modifying agents, corticosteroids or immunosuppressive drugs). Replacement therapy (e.g., thyroxine, insulin, or physiologic corticosteroid replacement therapy for adrenal or pituitary insufficiency, etc.) is not considered a form of systemic treatment.
11. History or any evidence of interstitial lung disease such as idiopathic pulmonary fibrosis, organizing pneumonia (e.g., bronchiolitis obliterans), drug induced or active non-infectious pneumonitis, idiopathic pneumonitis, or evidence of active pneumonitis on screening chest CT scan
    - History of radiation pneumonitis in the radiation field (fibrosis) is permitted
12. History of HIV. HIV antibody testing recommended per investigator's clinical suspicion.
13. Active hepatitis B (hepatitis B surface antigen reactive) or active hepatitis C (HCV qualitative RNA detected); testing recommended per investigator's clinical suspicion.
14. Severe infections within 4 weeks prior to enrollment, including, but not limited to, hospitalization for complications of infection, bacteremia, or the presence of any active infection requiring systemic therapy.
15. Received therapeutic oral or IV antibiotics within 2 weeks prior to Day 0
    - Patients receiving prophylactic antibiotics (e.g., for prevention of a urinary tract infection or to prevent chronic obstructive pulmonary disease exacerbation) are eligible
16. History or current evidence of any condition, therapy or laboratory abnormality that in the opinion of the treating investigator might confound the results of the trial or interfere with the patient's participation for the full duration of the trial.

17. Prior allogeneic stem cell or solid organ transplant.
18. Received a live, attenuated vaccine within 28 days prior to randomization or anticipation that such a live attenuated vaccine will be required during the trial.
    Note: Influenza vaccination should be given during influenza season only (approximately October to March). Patients must not receive live, attenuated influenza vaccine (e.g., FluMist®) within 28 days prior to Day 0, during treatment, or within 90 days following the last dose of study treatment.
19. Known previous or ongoing, active psychiatric or substance abuse disorders that would interfere with cooperation with the requirements of the trial.
20. Prisoner or patient who is compulsorily detained (involuntarily incarcerated) for treatment of either a psychiatric or physical (i.e. infectious disease) illness.
21. Treatment with systemic immunomodulating agents (including but not limited to IFNs, IL-2, ipilimumab) within 6 weeks or five half-lives of the drug, whichever is shorter, prior to first dose, excluding current CPI therapy.
22. Treatment with systemic immunosuppressive medication (including, but not limited to, corticosteroids, cyclophosphamide, azathioprine, methotrexate, thalidomide, and anti-TNF-α agents) within 2 weeks prior to initiation of study treatment, or anticipation of need for systemic immunosuppressive medication during the course of the study, with the following exceptions:
    - Patients who received acute, low-dose (≤ 10 mg/day) systemic immunosuppressant medication or a one-time pulse dose of systemic immunosuppressant medication (e.g., 48 hours of corticosteroids for a contrast allergy) are eligible for the study
    - Patients who received mineral corticosteroids (e.g., fludrocortisone), corticosteroids for chronic obstructive pulmonary disease (COPD) for asthma, or low-dose corticosteroids for orthostatic hypotension or adrenal insufficiency are eligible for the study.

6.2 Screen Failures

If a patient fails to meet an eligibility criterion during the screening period, then the Investigator will complete the screen failure section in the e-CRF.

Patients who have signed informed consent, but do not complete screening and who do not receive treatment on study with SNS-301 may be replaced for efficacy, toxicity and translational analyses.

6.3 Strategies for Recruitment and Retention

It is anticipated that up to 15 sites will be participate in the study in the United States. Patients will be recruited from either standalone outpatient clinics or hospital clinics.

7. STUDY INTERVENTION

7.1 Study Intervention(s) Administration

7.1.1 *Study Treatment Description*

7.1.1.1 SNS-301 Treatment

The HAAH Nanoparticle Vaccine drug substance is a recombinant bacteriophage lambda construct that is engineered to display a fusion protein of phage gpD and a portion of the HAAH protein sequence. The HAAH-1λ (SNS-301) construct contains 199 amino acids from the N-terminal region (amino acids 113 – 311) of the molecule.

The drug substance is characterized by testing that includes appearance, pH, and identity by dot blot using HAAH-specific monoclonal antibody, impurities (bioburden, endotoxin, host cell protein), determination of size distribution by particle analysis, quantitation by particle analysis, protein determination and potency by antigen enzyme-linked immunosorbent assay (ELISA). The drug product is a sterile, preservative-free solution.

7.1.1.2 Pembrolizumab Treatment

Keytruda® (Pembrolizumab) is an FDA-approved programmed death receptor-1 (PD-1)-blocking antibody that is indicated for the treatment of patients with recurrent or metastatic squamous cell carcinoma of the head and neck (HNSCC). humanized monoclonal antibody that blocks the interaction between PD-1 and its ligands, PD-L1 and PD-L2. Pembrolizumab is an IgG4 kappa immunoglobulin with an approximate molecular weight of 149 kDa. Pembrolizumab is produced in recombinant Chinese hamster ovary (CHO) cells.

KEYTRUDA may be supplied in two different formulations:

- KEYTRUDA for injection is a sterile, preservative-free, white to off-white lyophilized powder in single-dose vials. Each vial is reconstituted and diluted for intravenous infusion. Each 2 mL of reconstituted solution contains 50 mg of pembrolizumab and is formulated in L-histidine (3.1 mg), polysorbate 80 (0.4 mg), and sucrose (140 mg). May contain hydrochloric acid/sodium hydroxide to adjust pH to 5.5. Or

- KEYTRUDA injection is a sterile, preservative-free, clear to slightly opalescent, colorless to slightly yellow solution that requires dilution for intravenous infusion. Each vial contains 100 mg of pembrolizumab in 4 mL of solution. Each 1 mL of solution contains 25 mg of pembrolizumab and is formulated in: L-histidine (1.55 mg), polysorbate 80 (0.2 mg), sucrose (70 mg), and Water for Injection, USP.

For the purpose of this protocol, study treatment is defined as SNS-301 and pembrolizumab.

7.1.2 ***Dosing, Administration and Preparation***

The study treatment will be administered only to patients included in this study following the procedures set out in this clinical study protocol. Administration of the study treatment will be supervised by the Investigator or sub-Investigator. Details of the exact time of administration of medication (day/month/year, hour:minute) will also be documented in the eCRF.

7.1.2.1 SNS-301 Dosing

The vaccine will be delivered intra-dermally by a single-use 3M® hollow microstructured transdermal system (hMTS) device. Patients will be administered intradermally the SNS-301 dose of 1.0×10^{11} particles in 1 mL per administration.

Patients will receive SNS-301 on a staged schedule starting every three weeks for four doses, every six weeks for 6 doses and thereafter every twelve weeks.

When pembrolizumab and SNS-301 are dosed on the same day, SNS-301 will be dosed approximately 1 hour after IV infusion of pembrolizumab for the first dose. Subsequent doses of SNS-301 and pembrolizumab can be dosed in any order.

A 60 minutes observation period is recommended for the first dose on this study and 30 minutes for subsequent doses.

Additional information on Dosing, Administration and Preparation can be found in the pharmacy manual for SNS-301.

7.1.2.2 Pembrolizumab Dosing

A fixed dose of 200 mg pembrolizumab as an intravenous infusion over 30 minutes every 3 weeks or a fixed dose of 400 mg pembrolizumab, as an intravenous infusion over 30 minutes every 6 weeks will be administered.

A sterile, non-pyrogenic, low-protein binding 0.2 micron to micron in-line or add-on filter will be utilized. Do not co-administer other drugs through the same infusion line.

A 60 minutes observation period is recommended for the first dose on this study and 30 minutes for subsequent doses.

Additional information of Dosing, Administration and Preparation can be found in the package insert for Keytruda https://www.merck.com/product/usa/pi_circulars/k/keytruda/keytruda_pi.pdf

7.1.2.3 Study Treatment Administration

Patients will receive their study treatment as described in Section 7.1.2.1 & 7.1.2.2 until disease progression, unacceptable toxicity, deemed intolerable by investigator or up to 24 months in patients without disease progression.

A safety run-in will be performed using a modified rolling six design which will enroll up to six patients (safety analysis patients) as per Section 5.2. Once the safety run-in has been cleared and communicated with Investigator's further enrollment may occur.

There will be no dose reductions. See Section 7.5 for Dose Modifications.

7.2 Preparation/Handling/Storage/Accountability

7.2.1 *Acquisition and Accountability*

SNS-301, including the 3M® hMTS transdermal system, will be packaged by the Sponsor, and supplied in an open-label basis. The Investigator or designee is responsible for storing, administering and accounting for the SNS-301 according to the instructions provided by the Sponsor. SNS-301 shall be dispensed in accordance with the Investigator's prescription and it is the Investigator's responsibility to ensure that an accurate record of SNS-301 received, issued, returned and destruction is maintained.

SNS-301, including the 3M® hMTS transdermal system should be placed in a proper disposal container following administration . The person responsible for drug dispensing is required to maintain adequate records of SNS-301. These records (e.g., product accountability log) include the date the SNS-301 is received from the Sponsor and administered to the patient.

After review by the Sponsor or designee, all used and unused SNS-301 should be discarded at the investigational site, in accordance with the site's institutional SOPs and/or polices, and a destruction certificate obtained. The Investigator or designee will submit the copy of Product Accountability Log to the Sponsor. If the investigational site is unable to destroy SNS-301t, the Sponsor will provide alternate instructions for destruction.

Under no circumstances will the Investigator supply SNS-301 to a third party, allow SNS-301 be used other than as directed by this Clinical Trial Protocol, or dispose of SNS-301 in any other manner.

Any quality issue noticed with the receipt or use of a SNS-301, including 3M® hMTS transdermal system (deficiency in condition, appearance, pertaining documentation, labeling, expiry date, etc.) should be promptly notified to the Sponsor, who will initiate a complaint procedure.

A potential defect in the quality of the SNS-301 may be subject to a recall procedure by the Sponsor. In this case, the Investigator will be responsible for promptly addressing any request made by the Sponsor, to recall SNS-301 and eliminate potential hazards.

7.2.2 *Formulation, Appearance, Packaging and Labeling for SNS-301 and Pembrolizumab*

The supplies will be labeled with a minimum of the following:

- Sponsor's name and address
- Content of the cartridge
- Lot/Batch Number
- "Caution: New Drug--Limited by Federal (or United States) law to investigational use."

Drug supply will be labeled in accordance to local regulations if study is run outside of the United States.

The 3M® hollow microstructured transdermal system (hMTS) device will be labeled with the following:

- Lot number
- Hazard classification
- Date of manufacture
- Storage conditions
- "For human clinical evaluation use" and "Caution - Investigational device. Limited by Federal (or United States) law to investigational use."
- Sponsor's name and address

Refer to the SNS-301 Study Pharmacy Manual for a description of the process of preparation for study drug administration

Pembrolizumab will be labeled as per the manufacture's specification.

7.2.3 *Product Storage and Stability*

The SNS-301 is stored at 2 – 8 °C. Temperature excursions to ≤25°C for less than 24 hours are acceptable. Storage at ≤25°C for less than 24 hours is cumulative. Time spent at this temperature should be recorded in the drug accountability records.

The 3M® hollow microstructured transdermal system (hMTS) device can be maintained at room temperature.

Pembrolizumab will be maintained as per the manufacture's specification.

7.3 **Randomization and Blinding**

This is an open-label, single-arm study; there will be no randomization or blinding.

All patients who sign the informed consent form (ICF) will be assigned a patient study number which will be retained for the duration of the study.

7.4 **Concomitant Therapy**

All treatments including any prescription or over the counter medications taken by the patients seven days prior to screening and at any time during the study are regarded as concomitant treatments and must be documented in the appropriate section of the e-CRF. At subsequent visits, changes to current medications or medications used since the last documentation of medications will be recorded. Concomitant medications will be collected until 30 days after the last dose of study medication or until the start of a new anti-cancer treatment, whichever comes first.

7.4.1 *Allowed concomitant treatments*

The following concomitant treatments are permitted during this study:

- Supportive treatment will be given as medically indicated.
- Prophylactic antiemetic premedication including corticosteroids (low dose ≤ 10 mg/day prednisone equivalent) and 5-hydroxytryptamine 3 antagonists.
- Supportive treatment with cannabis will be allowed, if medically indicated.

7.4.2 *Prohibited Medications or Treatments During Study*

Medications such as those listed below are not permitted in the course of the trial:

- Concurrent treatment with other investigational drugs
- Concurrent treatment with any other anticancer therapy including radiotherapy
- Traditional herbal medicines should not be administered because the ingredients of many herbal medicines are not fully studied, and their use may result in unanticipated drug-drug interactions that may cause or confound assessment of toxicity. However, if the investigator feels herbal medication is warranted the Sponsor should be consulted
- Initiation or increased dose of granulocyte colony-stimulating factors (e.g., granulocyte colony-stimulating factor, granulocyte/macrophage colony-stimulating factor, and/or pegfilgrastim) is strongly discouraged
- Patients are not allowed to receive immunostimulatory agents, including but not limited to IFN-α, IFN-γ, or IL-2, during the entire trial. These agents, in combination with study treatment, could potentially increase the risk for autoimmune conditions

7.4.3 *Rescue Medication*

This is the first time the SNS-301 is given in addition to pembrolizumab to any patients. Although most immune-mediated adverse events observed with immunomodulatory agents have been mild and self-limiting, such events should be recognized early and treated promptly to avoid potential major complications. Discontinuation of SNS-301 or pembrolizumab may not have an immediate therapeutic effect due to the long half-life of the drug or longer drug effect, and there is no available antidote for the study treatment. In severe cases, immune-mediated toxicities may be acutely managed with topical corticosteroids, systemic corticosteroids, mycophenolate, or TNF-α inhibitors per investigator's discretion.

For instruction on how to handle pembrolizumab immune response adverse events refer to the pembrolizumab package insert.

Patients should receive appropriate medical intervention necessary to treat medical conditions as they arise.

7.5 **Dose Modification and/or Interruption**

For pembrolizumab, follow the package insert for dose modification instructions.

For SNS-301, there will be no dose reductions allowed for this study.

In case of non-DLT AE (grade 2 NCI-CTCAE V5.0 drug related AE), the dosing interval can be extended to up 42 days to allow the recovery from a related toxicity and the patient will resume at the same dose. If the patient experiences the same grade or higher toxicity and same grade requiring a dose-delay at the subsequent cycle, the patient should be discontinued from study treatment.

Should there be a clinically significant AE or SAE recorded relating to a patient receiving anticoagulants, such as clinically noted bleeding, administration of SNS-301 will be held until the AE/SAE returns to baseline. Should there be two individual events of SNS-301 interruption for the same patient, then SNS-301 will be discontinued after consultation with the Medical Monitor and Study Sponsor.

If a patient is unable to receive study treatment (e.g., due to COVID19) the dosing interval can be extended up to 42 days after consultation with the Sponsor and the rationale to be documented.

Treatment with SNS-301 may continue if pembrolizumab is discontinued by the Investigator, if prior to 24 months. If both study treatments are stopped for >42 days then the patient should be discontinued from study treatment and continue to the study follow up phase.

8. STUDY INTERVENTION DISCONTINUATION AND PARTICIPANT DISCONTINUATION/ WITHDRAWAL

8.1 Discontinuation of Study Intervention

Discontinuation for the study treatment does not mean discontinuation from the study and the remaining study procedures should be completed as per the Time and Event Schedule.

8.2 Participant Discontinuation/Withdrawal from the Study

The patients may withdraw from study treatment if they decide to do so, at any time and irrespective of the reason. In addition, the Investigator or the Sponsor has the right to withdraw the patient from the study and/or stop the study at any time. All efforts should be made to document the reason for discontinuation, and this should be documented in the electronic case report form (eCRF).

Other criteria for possible discontinuation are:

- Disease progression
- Unacceptable toxicity as judged by the Principal Investigator
- Adverse events which are dose-limiting toxicities
- Withdrawal of consent
- Subject is lost to follow-up
- Subject non-compliance
- Use of another non-protocol anti-cancer treatment
- Pregnancy
- Completed 24 months of study treatment

Withdrawn patients will be followed according to the study procedures as specified in this protocol.

The patients may withdraw from the study follow-up period, before study completion if they decide to do so, at any time and irrespective of the reason. The reason for withdrawal from the study treatment or study follow-up will be documented in the eCRF.

A patient who receives at least one study treatment and who discontinues from the trial for any reasons will not be replaced except for patients that withdraw for reasons other than toxicity during the safety run-in phase of the study.

8.3 Lost to Follow-Up

The Investigator should make every effort to re-contact the patient, to identify the reason why he/she failed to attend the visit, and to determine his/her health status, including at least his/her vital status. Attempts to contact

such patients must be documented in the patient's records (e.g. times and dates of attempted telephone contact, receipt for sending a registered letter). It is suggested that the Investigator attempts to contact the patient three times before considering the patient lost to follow up.

9. STUDY ASSESSMENTS AND PROCEDURES

Refer to the Time and Events Schedule Table1 for an outline of the procedures required at each visit along with their associated windows. All patients must sign and date the most current approved ICF before any study specific procedures are performed. Procedures conducted as per standard of care or routine clinical management that are obtained before signing of the ICF may be utilized for screening/baseline purposes. All screening assessments may be performed within 28 days of Day 0 with the exception of screening labs (hematology and chemistry) which may be performed within 10 days of Day 0. Patients who discontinue will be asked to return to the clinic within 30 days of the last dose for a discontinuation visit. Generally, protocol waivers or exemptions will not be granted without discussion with the Sponsor.

9.1 Efficacy Assessments

9.1.1 *Tumor Assessment*

Initial (screening) tumor assessments must be performed within 28 days prior to the first dose of study treatment. The investigator/site radiologist must review pre-trial images to confirm the patient has measurable disease per RECIST 1.1 (Appendix B: Tumor Assessment Criteria). Tumor assessments performed as standard of care prior to obtaining informed consent and within 28 days of the first dose of study treatment may be used rather than repeating tests Beginning with screening, all imaging assessments will be evaluated using RECIST 1.1. On-study imaging assessments will be performed every 6 weeks (Q6W) calculated from the date of therapy initiation and independent of treatment delays. RECIST 1.1 will be used by the site for treatment decisions until the first radiologic evidence of progressive disease (PD). The Sponsor may request digitized scans from patients to confirm response.

Following the first radiologic evidence of PD by RECIST 1.1, treatment decisions may be made by using immune iRECIST (Appendix B: Tumor Assessment Criteria) to accommodate tumor response patterns seen with CPI therapy including pembrolizumab treatment (e.g., tumor flare). This was described by Nishino, et al. 2016 [13] and is used in immunotherapy clinical trials. For a clinically stable subject with first radiologic evidence of PD, it is at the discretion of the site investigator to continue treating the subject with SNS-301 and pembrolizumab until PD is confirmed at least 4 weeks after the date of the first tumor imaging suggesting PD per the site investigator. If radiologic PD is confirmed by the subsequent tumor imaging, the subject should be discontinued from treatment unless, in the opinion of the investigator, the subject is achieving a clinically meaningful benefit. In this case, an exception for continued treatment may be considered following consultation with the Sponsor. Additional treatment response evaluation by RECIST v 1.1 and iRECIST may be performed at the Sponsor's discretion.

Patients will undergo tumor assessments every 6 weeks (±7 days) until approximately 12 months following first dose of study treatment, or earlier if clinically indicated. After 12 months, tumor assessments will be required every 12 weeks (±7 days). Imaging should continue to be performed until disease progression is assessed by the Investigator, the start of new anti-cancer treatment, withdrawal of consent, death or the end of the trial, whichever occurs first for efficacy follow-up. Patients who start a new anti-cancer therapy will be censored for survival and progression analyses at date of last scan prior to the start of new anti-cancer therapy.

Tumor imaging should be performed by computed tomography (CT), but may be performed by magnetic resonance imaging (MRI) if CT is contraindicated, but the same imaging technique should be used in patient throughout the trial. CT scans (with oral/IV contrast unless contraindicated) must include chest, abdomen and pelvis. The investigator must review before dosing at the next visit. Per RECIST 1.1, response should be confirmed by a repeat radiographic assessment. The scan for confirmation of response may be performed no

earlier than 4 weeks after the first indication of response, or at the next scheduled scan, whichever is clinically indicated.

Patients who have unconfirmed disease progression may continue on treatment until progression is confirmed. If radiologic imaging by local/site assessment shows progressive disease (PD), tumor assessment may be repeated 4 weeks later in order to confirm PD with the option of continuing treatment per below while awaiting radiologic confirmation of progression. If repeat imaging shows SD, PR or CR, treatment may be continued as per treatment schedule. If repeat imaging still meets the threshold for PD (≥ 20% increase in tumor burden compared to nadir) but shows a reduction in tumor burden compared to the previous time point, treatment may be continued as per treatment calendar after consultation with Sponsor. If repeat imaging confirms progressive disease without reduction in tumor burden compared to the previous time point, patients will be discontinued from study treatment.

The decision to continue study treatment after the first evidence of disease progression is at the Investigator's discretion based on the clinical status of the patient as described in Table3 below. Confirmatory imaging may be performed as early as 28 days later; alternatively, the scan performed at the next scheduled time point may be used as confirmation. Patients may receive study treatment while waiting for confirmation of PD if they are clinically stable as defined by the following criteria:

- Absence of signs and symptoms (including worsening of laboratory values) indicating disease progression
- No decline in ECOG performance status from baseline
- Absence of rapid progression of disease
- Absence of progressive tumor at critical anatomical sites (e.g., cord compression) requiring urgent alternative medical intervention
- Evidence of clinical benefit (defined as the stabilization or improvement of disease- related symptoms) as assessed by the investigator

Table 3: Imaging and Treatment after First Radiologic Evidence of Progressive Disease

	Clinically Stable		**Clinically Unstable**	
	Imaging	**Treatment**	**Imaging**	**Treatment**
1st radiologic evidence of PD	Repeat imaging at ≥ 4 weeks at site to confirm PD	May continue study treatment at the Investigator's discretion while awaiting confirmatory scan by site	Repeat imaging at ≥4 weeks to confirm PD per physician discretion only	Discontinue Treatment
Repeat scan confirms PD (no reduction in tumor burden from prior scan)	No additional imaging required	Discontinue treatment	No additional imaging required	N/A

Repeat scan confirms PD (reduction in tumor burden from prior scan)	Continue regularly scheduled imaging assessments	Continue study treatment after consultation with Sponsor	Continue regularly scheduled imaging assessments	May restart study treatment if condition has improved and/or clinically stable per Investigator and Sponsor's discretion
Repeat scan shows SD, PR or CR	Continue regularly scheduled imaging assessments	Continue study treatment at the Investigator's discretion	Continue regularly scheduled imaging assessments	May restart study treatment if condition has improved and/or clinically stable per Investigator's discretion

Patients in whom radiographic disease progression is confirmed at a subsequent tumor assessment may be considered for continued study treatment at the discretion of the investigator if they continue to meet the criteria above and have evidence of the clinical benefit (see Figure 2).

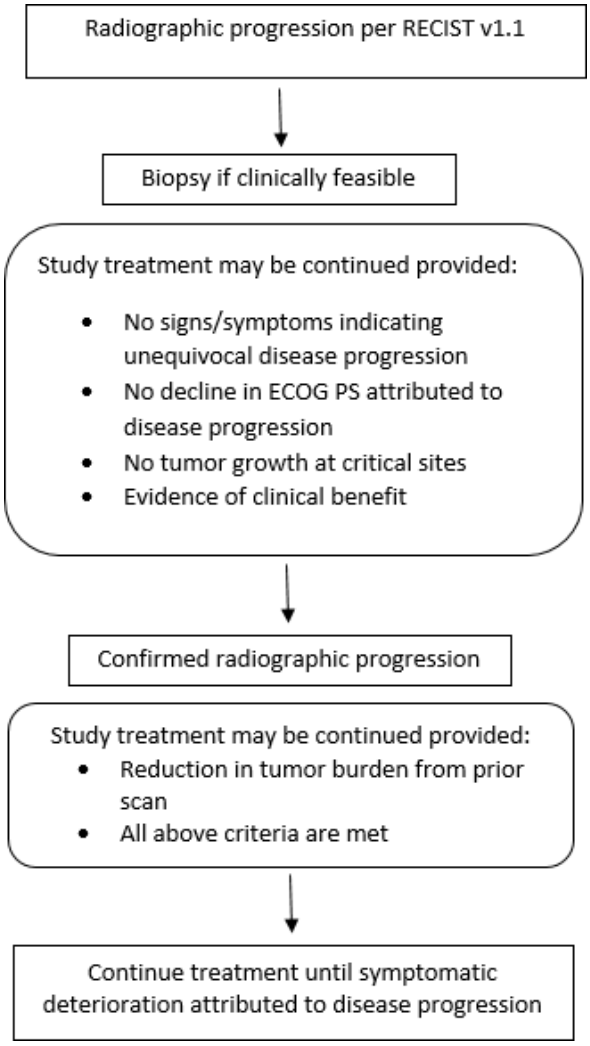


Figure 2: Conditions for Continuing Study Treatment in the Presence of Increased Radiographic Tumor Size

Patients who discontinue from treatment for reasons other than disease progression (e.g., toxicity) will continue scheduled tumor assessments until disease progression, start of new-anti cancer therapy, withdrawal of consent, or death. Investigators may perform additional scans or more frequent assessments if clinically indicated. Patients who continue treatment beyond radiographic or clinical disease progression will be monitored with a follow-up scan at the next scheduled tumor assessment.

Imaging timing should follow calendar days and should not be adjusted for delays or changes in treatment administration dates.

9.2 Safety Assessments

9.2.1 *Demographics and Medical History*

Demographics will include gender, year of birth, race and ethnicity.

Medical history will include details regarding the patients overall medical and surgical history as well as detailed information regarding the patient's previous treatment, including systemic treatments, radiation and surgeries, pathology, risk stratification, etc. since their original diagnosis. HPV status, EBV status and progression data will also be collected. Reproductive status and smoking/alcohol history will also be captured.

9.2.2 *Physical Examinations*

A complete physical exam will include, at a minimum head, eyes, ears, nose, throat and cardiovascular, dermatological, musculoskeletal, respiratory, gastrointestinal and neurological systems. Height (screening only) and weight will also be collected. Additionally, any signs and symptoms, other than those associated with a definitive diagnosis, should be collected at baseline and during the study.

During the study, a targeted, symptom-directed exam, as clinically indicated will be performed within 72 hours of each dosing visit

9.2.3 *Eastern Cooperative Oncology Performance Status*

The health, activity and well-being of the patient will be measured by the ECOG performance status and will be assessed on a scale of 0 to 5 with 0 being fully active and 5 being dead. Full details are described in Appendix B: ECOG Performance Status. ECOG performance status will be collected within 72 hours of each dosing visit.

9.2.4 *Vital Signs*

Vital signs will include temperature, blood pressure, pulse rate and respiratory rate. For first infusion of pembrolizumab, the patient's vital signs should be determined within 60 minutes before the infusion. If clinically indicated, vital signs should be recorded at 15, 30, 45, and 60 minutes (± 5 minutes for all timepoints) after the start of the infusion, and 30 (± 10) minutes after the infusion. For subsequent infusions, vital signs will be collected within 60 minutes before the infusion and at 30 (± 5) minutes after the infusion.

Patients will be informed about the possibility of delayed post-infusion symptoms and instructed to contact their trial physician if they develop such symptoms.

9.2.5 *Electrocardiograms*

A 12-lead ECG will be obtained at screening and when clinically indicated. Patients should be resting in a supine position for at least 10 minutes prior to ECG collection.

9.2.6 *Clinical Safety Laboratory Assessments*

Hematological toxicities will be assessed in term of hemoglobin value, white blood cell, neutrophil, platelet and, lymphocyte count according to NCI-CTCAE V5.0 AE grading.

Laboratory abnormalities (grade 1 and greater that are listed in the NCI-CTCAE V5.0) should be recorded on the AE page regardless of their causality. Laboratory abnormalities associated with a definitive diagnosis will not be recorded as and AE unless it has become worse since baseline. Test analytes are provided in the table below.

See the Time and Events Schedule for timing and frequency. Safety labs will be performed within 72 hours of each dosing visit.

Hematology	**Serum chemistry**
Hematocrit (Hct)	Albumin
Hemoglobin (Hgb)	Alanine aminotransferase (ALT)
Platelet count	Aspartate aminotransferase (AST)
Red blood cell (RBC) count	Alkaline phosphatase (ALP)
White blood cell (WBC) count	Blood Urea Nitrogen (BUN) or Urea
Neutrophils	Bicarbonate or Carbon dioxide (CO_2)
Lymphocytes	Creatinine
Eosinophils	Creatine phosphokinase (CPK)
Monocytes	Electrolytes (Na, K, Mg, Cl, Ca, P)
Basophils	Glucose (either fasting or non-fasting)
Other cells, if any	Lactate dehydrogenase (LDH)
Thyroid	Total bilirubin (direct bilirubin if elevated)
TSH, T3 and FT4	Total protein
Coagulation	**Urinalysis**
International normalized ratio/INR	Specific gravity
Activated partial thromboplastin time (PTT)	pH
Other anticoagulant monitoring (if required)	Glucose
HIV screen (at screening, if indicated)	Protein
Hepatitis screen (at screening, if indicated)	Ketones
HPV/EBV screen (at screening, if unknown)	Blood
Pregnancy test	Microscopic exam, if abnormalities

9.2.7 *Hepatitis and HIV Screening*

Patients should be tested for HIV locally prior to the inclusion into the trial only based on investigator's clinical suspicion for HIV infection and HIV-positive patients will be excluded from the clinical trial. Hepatitis B surface antigen, anti-HBc antibody, anti-HBs antibody, and Hepatitis C antibody immunoassays should be tested only per investigator's clinical suspicion during screening and tested locally. In patients who have positive serology for the anti-HBc antibody, HBV DNA should be tested prior to Day 0.

9.2.8 *Pregnancy Test*

A Serum pregnancy test (for women of childbearing potential, including women who have had a tubal ligation) must be performed and documented as negative within 72 hours prior to each dose.

9.2.9 *Urinalysis*

Urinalysis includes specific gravity, pH, glucose, protein, ketones, blood, and a microscopic exam if abnormal results are noted.

9.2.10 *TSH, T3 and FT4*

Thyroid function tests will be performed at screening and every 6 weeks thereafter.

9.2.11 *Creatine Phosphokinase (CPK)*

CPK will be performed at screening and at the discontinuation visit.

9.2.12 *HPV/EBV Testing*

If the patient's HPV/EBV status is unknown, they should be tested prior to receiving SNS-301. The results do not need to be known before the patient receives study treatment.

9.2.13 *PD-L1 Testing*

If the patient's PD-L1 status is unknown, they should be tested, preferably by 22C3 IHC. Patients who are CPI naïve must be PD-L1 positive prior to entry onto the study. For other patients, the results do not need to be known before the patient receives study treatment. If possible, for patients that started study treatment prior to Amendment 2/Version 3.0, retrospective testing should be done.

9.2.14 *Immunogenicity Assessments*

Detailed instructions on the collection and processing of immunogenicity samples will be located in the Laboratory Manual. See the Time and Events Schedule for a collection timeline for each sample.

9.2.14.1 Blood Assays

Blood assays include those measured in serum, plasma and whole blood/PBMCs.

9.2.14.1.1 Serum and plasma

Serum and plasma are collected for the direct measure of ASPH levels, anti-ASPH antibodies, anti-phage antibodies and other tumor biomarkers.

9.2.14.1.1.1 ASPH

Subject sera and/or plasma will be tested for the presence of ASPH and/or exosomes that contain ASPH on their surface by ELISA using several different monoclonal antibodies that are reactive with the ASPH protein. The presence of ASPH in serum or plasma is an indicator of cancer status. Alterations in ASPH levels may be indicative of response to treatment.

9.2.14.1.1.2 Anti-ASPH antibodies

Production of anti-ASPH antibodies is a direct result of an active immune response to the vaccine. Levels of anti-ASPH antibody are expected to rise during an active immune response and should reach a plateau level at maximal response. Continued and regular boosting of the vaccine during the course of treatment is expected to maintain or restore this level of anti-ASPH antibody in serum.

9.2.14.1.1.3 Anti-phage antibodies

Because the vaccine is delivered using a bacteriophage vector, production of anti-phage antibodies is also expected and is a direct result of an active immune response to the vaccine. High levels of anti-phage antibody may result in neutralization of further doses/boosts of vaccine. During the Phase I clinical study it was found that the use of a lower dose of vaccine during initial vaccination attenuate the production of anti-phage antibodies and this finding contributed to the selection of the dose for the current trial. Levels of anti-phage antibodies will be monitored here to ascertain if any correlation exists between the production of anti-phage antibodies and reduced efficacy of the vaccine.

9.2.14.1.1.4 Other tumor and immune biomarkers

Levels of other cancer biomarkers and cytokines may also be tested in serum and/or plasma and may also be used to monitor cancer status and response to treatment.

9.2.14.1.1.5 Circulating tumor DNA (ctDNA)

Blood samples will be collected in Streck tubes for isolation of ctDNA. ctDNA analysis may be used as a tool to monitor for treatment efficacy and resistance and for predicting the likelihood of relapse.

9.2.14.1.2 Whole blood/peripheral blood mononuclear cells (PBMCs)

PBMCs are collected to monitor overall and specific immune responses.

9.2.14.1.2.1.1 *T-cells Evaluation*

T cell responses will be assessed using antigen-specific IFN-γ ELISpot assay using antigen presenting cells loaded with either full-length recombinant ASPH protein or overlapping peptide libraries covering the SNS-301 antigens. Antigen specific T cell responses may also be assessed via flow cytometry. Flow cytometric assays may include an examination of the influence of immunotherapy on the ability of patient T cells to exhibit phenotypic markers associated with cytolytic potential, activation or exhaustion after stimulation by peptides corresponding to SNS-301 antigens. Markers that may be used for this purpose include CD3, CD4, CD8, CD137, CD69, CD38, PD1, Granzyme A, Granzyme B and Perforin. These markers may change relative to new data becoming available that is informative for this assessment. Additionally, T-cell responses to general immune stimulators may be evaluated in order to track general cellular immune competence during the trial.

Additionally, ASPH-specific T-cells may be isolated, cloned and expanded *ex vivo*. For expansion antigen presenting cells loaded with either full-length recombinant ASPH protein or overlapping peptide libraries covering the SNS-301 antigens would be employed. These T-cells may be characterized by sequencing of their T-cell receptors (TCRs) to assess diversity and putative antigen specificity.

9.2.14.2 Tissue

A tissue sample is required at study entry. Ideally, a pre-treatment tissue sample obtained after initiation of ongoing CPI therapy and first dose of SNS-301 and pembrolizumab on this current clinical trial will be collected. Patients are requested to provide archival tissues from a prior biopsy or surgery that is treatment -naïve including prior 1) chemotherapy, radiation and 2) anti PD(L)-1 treatment-naïve, pending availability. In patients undergoing a pre-treatment biopsy, an archival tumor specimen, if available, should also be submitted. After signing of the Informed Consent Form, tumor tissue should be submitted to the Sponsor in a timely manner. All patients will undergo a mandatory tumor biopsy sample collection, if clinically feasible as determined by the trial investigator in consenting patients, at Week 6/3rd dose (+/- 3 days). Additionally, up to two optional biopsies may be obtained any time during the study, if medically feasible. A biopsy may also be obtained at the time of first evidence of radiographic or clinical disease progression**.** For patients who respond and subsequently progress, an optional biopsy may be obtained at the time of disease progression. Tumor tissue should be of good quality based on total and viable tumor content. Acceptable samples include core needle biopsies for deep tumor tissue or lymph nodes or excisional, incisional, punch, or forceps biopsies for cutaneous, subcutaneous, or mucosal lesions. Fine-needle aspiration may be acceptable pending sponsor approval however, brushing, cell pellets from pleural effusion, and lavage samples are not acceptable. For core needle biopsy specimens, at least three cores should be submitted for evaluation. Patients who are unable to undergo biopsy sample collection but otherwise meet criteria outlined in protocol may continue to receive study treatment.

If a tumor biopsy is to be obtained from an intended target lesion during eligibility assessment, the biopsy should be performed prior to obtaining the baseline scan. Otherwise, a new baseline scan should be obtained.

Archival and fresh tumor tissue samples should be representative tumor specimens in formalin-fixed paraffin embedded (FFPE) blocks (preferred) or at least 15 unstained slides, with an associated pathology report, should be submitted for intra-tumoral immunology assessments. Tissue slices of 4-5 microns are mounted on positively charged glass slides. Slides should be unbaked and stored cold or frozen.

9.2.14.2.1 Tissue Assays

Available tumor tissue collected from pre- and post- treatment may be assessed for the presence of immune cells using immunohistochemistry or immunofluorescence. The presence of immune signatures may also be analyzed through the assessment of various transcripts suggestive of an inflammatory or an immunosuppressive tissue microenvironment.

Tumor tissue will be collected for immunology assessments including but not limited to markers related to inflammation, suppression, T cell infiltration, and associated tumor microenvironment characteristics. Tumor infiltrating lymphocytes may be isolated and subjected to single cell expression profiling and/or TCR sequencing.

In addition, exploratory biomarkers may be evaluated.

9.2.14.2.2 ASPH Immunohistochemistry (IHC) Assay

ASPH testing will be done by immunohistochemistry on either fresh or archival tumor tissue. Samples will be analyzed at Fred Hutchinson Cancer Center via a CLIA validated assay.

9.2.14.3 Future Biomedical Research

The following samples are obtained as part of the study, if any leftover samples remain, they may be used for future biomedical research either during the course of the study or after the study has completed.

- Leftover tumor tissue
- Leftover RNA or DNA isolated from biological samples (blood, urine, tumor)

- Leftover biomarker samples (serum, plasma and PMBCs)

9.2.14.3.1 Withdrawal from Future Biomedical Research

Patients may withdraw their consent for Future Biomedical Research and have their samples destroyed. Patients may withdraw consent at any time by contacting the principal investigator in writing. In turn, the Investigator will contact the Sponsor in writing. Subsequently, the patient's samples will be removed from the biorepository and be destroyed. No future data will be collected, but any data already collected from analysis of samples will remain with the Sponsor. A letter will be sent from the Sponsor to the investigator confirming the destruction. It is the responsibility of the investigator to inform the patient of completion of destruction. Any analyses in progress at the time of request for destruction or already performed prior to the request being received by the Sponsor will continue to be used as part of the overall research trial data and results. No new analyses would be generated after the request is received.

In the event that the medical records for the trial are no longer available (e.g., if the investigator is no longer required by regulatory authorities to retain the main trial records) or the samples have been completely anonymized, there will no longer be a link between the patient's personal information and their samples. In this situation, the request for sample destruction cannot be processed.
request for sample destruction cannot be processed.

9.2.14.4 Concomitant Medications

Concomitant medications include any prescription medications or over-the-counter medications. At screening, any medications the patient has used within the 7 days prior to the screening visit should be documented. At subsequent visits, changes to current medications or medications used since the last documentation of medications will be recorded. See Section Prohibited Medications or Treatments During Study for a list of prohibited medications.

Patients who are receiving anticoagulants will have anticoagulant specific drug level and/or anticoagulant specific factor Xα levels obtained at baseline, at each administration of SNS-301, and at the end of study visit to ensure that these levels remain within therapeutic range throughout the duration of the trial. In the event of clinically noted bleeding, these tests will be obtained at the time of bleeding as well. Investigators should use tests routinely used in clinical practice to monitor patients receiving Warfarin, Heparin and/or Low Molecular Weight Heparins, along with the monitoring schedule provided above. Should there be two individual events of SNS-301 interruption for the same patients, then SNS-301 will be discontinued after consultation with the Medical Monitor and Study Sponsor. Clinical management and further workup of the coagulation pathway disturbance will be at the discretion of the investigator.

9.2.14.5 Adverse Events

AEs will be collected from the time of informed consent until 30 days after the last dose of study treatment or until initiation of another anti-cancer therapy, whichever occurs first. SAEs and AESIs will be collected from the time of informed consent until 90 days after the last dose of study treatment of until initiation of anti-cancer therapy, whichever occurs first. See Section 9.3 for additional details on Adverse Events and Serious Adverse Events.

9.2.14.6 Follow-Up

Survival follow-up information will be collected via telephone calls, patient medical records, and/or clinical visits approximately every 3 months for up to 3 years, until death, lost to follow-up, withdrawal of consent, or trial termination by Sponsor. All patients will be followed for survival and new anticancer therapy information unless the patient requests to be withdrawn from follow-up; this request must be documented in the source documents

and signed by the investigator. If the patient discontinues study treatment without documented clinical disease progression, every effort should be made to follow up regarding survival, progression (if not already progressed), and new anti-cancer therapy.

9.3 Adverse Events and Serious Adverse Events

9.3.1 *Definition of Adverse Event (AE)*

Adverse event is defined as any untoward medical occurrence associated with the use of a drug in humans, whether or not considered drug related. Any AE that occurs prior to the first dose is part of the medical history. AEs will be collected from the time of informed consent until 30 days after the last dose of study treatment or until initiation of another anti-cancer therapy, whichever occurs first.

Abnormal laboratory values should not be listed as separate AEs if they are considered to be part of the clinical syndrome that is being reported as an AE unless worsened on study treatment. It is the responsibility of the Investigator to review all laboratory findings in all patients and determine if they constitute an AE. Medical and scientific judgment should be exercised in deciding whether an isolated laboratory abnormality should be classified as an AE. Any laboratory abnormality (grade 1 and greater that are listed in the NCI-CTCAE V5.0) considered to constitute an AE should be reported on the Adverse Event CRF.

Pre-planned procedures (surgeries or therapies) that were scheduled prior to the start of study drug exposure are not considered AEs. However, if a pre-planned procedure is performed earlier than anticipated (e.g., as an emergency) due to a worsening of the pre-existing condition, the worsening of the condition should be captured as an AE.

Progression of the cancer under trial is not considered an adverse event unless it is considered to be drug related by the investigator. Patients will be encouraged to spontaneously report any AE. Patients will be questioned and/or examined by the Investigator and his/her medically qualified designee for evidence of AEs. The questioning of study patients with regard to the possible occurrence of AEs will be generalized, such as, “How have you been feeling since your last visit?” Information gathering for AEs should generally not begin with direct solicitation from patients regarding the presence or absence of specific AEs. Study personnel will ask open-ended questions to obtain information about AEs at every visit. Date and time of onset and resolution (if applicable) of the AE will be documented in the patient’s clinical notes.

A suspected adverse reaction means any AE for which there is a “reasonable possibility” that the drug caused the AE. For the purpose of reporting under this protocol, “reasonable possibility” means there is evidence to suggest a causal relationship between the drug and the AE .

An AE is considered unexpected if the AE is not listed in the current IB or is not listed in the IB at the specificity or severity observed.

9.3.2 *Definition of Serious Adverse Event (SAE)*

A serious adverse event (SAE) is an AE that:

- Is fatal
- Is life-threatening, meaning the patient was, in the view of the Investigator, at immediate risk of death from the reaction as it occurred, i.e., it does not include a reaction that, had it occurred in a more serious form or progressed, might have caused death
- Is a persistent or significant disability or incapacity or substantial disruption of the ability to conduct normal life functions

- Requires or prolongs inpatient hospitalization
- Is a congenital anomaly or birth defect
- Other important medical events may be considered SAEs when, based upon appropriate medical judgment, they may jeopardize the patient and may require medical or surgical intervention to prevent one of the outcomes as listed above in this definition. Examples of such medical events include allergic bronchospasm requiring intensive treatment in an emergency room or at home, blood dyscrasias or convulsions that do not result in inpatient hospitalization, or the development of drug dependency or drug abuse

The Medical Monitor will advise the Investigator regarding the nature of any further information or documentation that is required. The Investigator should provide the following documentation at the time of notification if available:

- SAE Form
- AE (CRF) page
- Concomitant and support medication pages
- Relevant diagnostic reports
- Relevant laboratory reports
- Admission notes and hospital discharge summary (when available).

Clarification of Serious Adverse Events (SAEs)

- Death in itself is not an AE. Death is an outcome of an AE.
- Progression of the cancer under trial is not considered an adverse event unless it is considered to be drug related by the investigator.
- The patient may not have been receiving an investigational medicinal product at the occurrence of the event.
- Dosing may have been given as treatment cycles or interrupted temporarily before the onset of the SAE but may have contributed to the event.
- Complications that occur during hospitalizations are AEs. If a complication prolongs the hospitalization, it is an SAE.
- Inpatient hospitalization means that the patient has been formally admitted to a hospital for medical reasons, for any length of time. This may or may not be overnight. It does not include presentation and care within an emergency department nor does it include full day or overnight stays in observation status.

  The following hospitalization scenarios are not considered to meet the criteria for a serious adverse events:

  - Hospitalization for respite care
  - Hospitalization to perform an efficacy measurement for the trial

- Hospitalization for an elective surgery for a pre-existing condition.

The Investigator will attempt to establish a diagnosis of the event on the basis of signs, symptoms, and/or other clinical information. In such cases, the diagnosis will be documented as the AE and/or SAE and not the individual signs/symptoms.

9.3.3 *Classification of an Adverse Event*

9.3.3.1 Severity of Event

Adverse events will be graded by the Investigator using the NCI-CTCAE 5.0 graded 1-5. Grade refers to the severity of the AE. For events not described in the NCI CTCAE, the Investigator will assign grades as 1= mild, 2=moderate, 3=severe, 4=life-threatening, and 5=fatal based on this general guideline:

Grade 1: Mild; asymptomatic or mild symptoms; clinical or diagnostic observations only; intervention not indicated.

Grade 2: Moderate; minimal, local or noninvasive intervention indicated; limiting age-appropriate instrumental ADL*

Grade 3: Severe or medically significant but not immediately life-threatening; hospitalization or prolongation of hospitalization indicated; disabling; limiting self-care ADL**.

Grade 4: Life-threatening consequences; urgent intervention indicated.

Grade 5: Death related to AE. (Grade 5 (Death) may not appropriate for some AEs and therefore may not an option.)

The highest level of severity attained for each AE will be recorded in the CRFs.

Activities of Daily Living (ADL)

*Instrumental ADL refer to preparing meals, shopping for groceries or clothes, using the telephone, managing money, etc.

**Self-care ADL refer to bathing, dressing and undressing, feeding self, using the toilet, taking medications, and not bedridden.

9.3.3.2 Relationship to Study Medication

The assessment of relationship of AEs to the administration of study drug is a clinical decision based on all available information at the time of the completion of the CRF. Investigators must systematically assess the causal relationship of AEs to the study drug using the following definitions. Decisive factors for the assessment of causal relationship of an AE to SNS-301 include, but may not be limited to, temporal relationship between the AE and SNS-301, known side effects of SNS-301, medical history, concomitant medication, course of the underlying disease, and study procedures.

Not Related:

Not reasonably suspected to be related to the study drug. The AE could not medically (pharmacologically/clinically) be attributed to the study drug under investigation in this clinical study protocol. A reasonable alternative explanation must be made available.

Related:

Suspected related to the study drug. The AE could medically (pharmacologically/clinically) be attributed to the study drug under investigation in this clinical study protocol.

9.3.4 *Adverse Event Reporting*

9.3.5 *Serious Adverse Event Reporting*

All SAEs occurring during the course of the clinical trial from signing the informed consent through the end of the study will be collected and reported (e-mail) by the Investigator to the Pharmacovigilance Team assigned (see contact information below) by completing a Serious Adverse Event Report Form within 24 hours or next business day, whichever is shorter, from the point in time when the Investigative site becomes aware of the SAE. All SAEs must be reported whether or not considered causally related to the study treatment. The information collected will include patient number, a narrative description of the event and an assessment by the Investigator as to the severity of the event, and relatedness to study drug. Include copies of relevant source documents. (e.g., progress notes, autopsy reports, laboratory and diagnostic test results, discharge summaries) Follow-up information on the SAE may be requested by the Sponsor.

SAEs should be reported to:

Global Safety and Pharmacovigilance, Advanced Clinical

Email: drugsafetypv@advancedclinical.com

The minimum required information for an initial report of an SAE is:

- Reporter name and contact number,
- Protocol number,
- Site and patient ID information, and
- The SAE term with a brief summary of the event including the causality assessment, if possible.

Contact the Sponsor-designated Medical Monitor or designee using the contact information and instructions provided supplemental to this protocol.

The Sponsor must notify FDA and all participating Investigators (i.e., all Investigators to whom the Sponsor is providing drug under its INDs or under any Investigator's IND) in an IND safety report of potential serious risks, from clinical trials or any other source, as soon as possible, but in no case later than 15 calendar days after the Sponsor determines that the information qualifies for reporting under paragraph (c)(1)(i), (c)(1)(ii), (c)(1)(iii), or (c)(1)(iv) of 21CFR 312.32. The Sponsor must identify all IND safety reports previously submitted to FDA concerning a similar suspected adverse reaction and must analyze the significance of the suspected adverse reaction in light of previous, similar reports or any other relevant information.

In addition, The Sponsor must also notify FDA of any unexpected fatal or life-threatening suspected adverse reaction as soon as possible but in no case later than 7 calendar days after the Sponsor's initial receipt of the information.

9.3.6 *Serious and unexpected suspected adverse reaction*

The Sponsor must report any suspected adverse reaction that is both serious and unexpected. The Sponsor must report an adverse event as a suspected adverse reaction only if there is evidence to suggest a causal relationship between the drug and the adverse event, such as:

1. A single occurrence of an event that is uncommon and known to be strongly associated with drug exposure (e.g., angioedema, hepatic injury, Stevens-Johnson Syndrome);
2. One or more occurrences of an event that is not commonly associated with drug exposure, but is otherwise uncommon in the population exposed to the drug (e.g., tendon rupture);

An aggregate analysis of specific events observed in a clinical trial (such as known consequences of the underlying disease or condition under investigation or other events that commonly occur in the study population independent of drug therapy) that indicates those events occur more frequently in the drug treatment group than in a concurrent or historical control group.

Reports will be made as soon as possible, and in no event later than seven (7) calendar days if the event is a death or is life threatening and 15 calendar days for all other reportable events after the Sponsor’s initial receipt of the information. Each written notification may be submitted on a CIOMS-I form, a FDA Form 3500A, or in a tabular or narrative format in accordance with regulatory requirements. In each report, the Sponsor will identify all safety reports previously filed concerning a similar suspected adverse reaction and will analyze the significance of the suspected adverse reaction in light of the previous, similar reports.

Follow-up information to a safety report will be submitted as soon as the relevant information is available. If the results of a Sponsor’s investigation show that an AE not initially determined to be reportable is, in fact, reportable, the Sponsor will report the suspected AE in a written safety report as soon as possible, but in no event later than 15 calendar days after the determination is made. Results of investigations of other safety information will be submitted, as appropriate, in an information amendment or annual report.

If an investigator receives an IND safety report or other specific safety information (e.g., SUSAR, summary or listing of SAEs) from the sponsor, the investigator will review and file along with the Investigator's Brochure and will notify the IRB/IEC, if appropriate according to local regulations. In these instances, the ICF may need to be revised to inform the patient of any new safety concern.

9.3.7 *Unanticipated (Serious) Adverse Device Effect (UADE)*

A UADE is any serious adverse effect on health or safety or any life-threatening problem or death caused by, or associated with, a device, if that effect, problem, or death was not previously identified in nature, severity, or degree of incidence in the investigational plan or application (including a supplementary plan or application), or any other unanticipated serious problem associated with a device that relates to the rights, safety, or welfare of patients.

Per the definition above, a UADE is a type of SAE that requires expedited reporting on the part of the Sponsor. As a reminder, all SAEs regardless of relationship to device, drug or procedure are to be reported to Sponsor by the trial Investigator within 24 hours. Sponsor will assess each device related SAE to determine if anticipated based on prior identification within the investigational plan. The Sponsor may notify a regulatory authority within the time frame specified by local requirements but no later than 10 business days for UADE.

UADE form should be reported to:

Global Safety and Pharmacovigilance, Advanced Clinical

Email: drugsafetypv@advancedclinical.com

9.3.8 *Dose-Limiting Toxicities*

DLTs are events [toxicities] specifically identified in this protocol that must be reported in an expeditious manner. Information regarding DLTs should be recorded on a DLT Confirmation Worksheet and faxed or emailed within 24 hours of site personnel becoming aware of the event. DLTs may or may not be serious adverse events as an Unexpected Adverse Event. DLTs are assessed up to week 6 for patients enrolled in the Safety Run-In period.

Any of the following, if judged to be associated with SNS-301 (i.e., possibly related, probably related, or related to), will be considered a DLT which are based on the NCI-CTCAE V5.0 criteria:

1) Grade 4 non-hematological toxicities (excluding alopecia) of any duration
2) Grade 3 non-hematologic (non-laboratory) toxicity lasting > 3 days despite optimal supportive care
3) Any Grade 3 or Grade 4 non-hematologic laboratory value if: a). Medical intervention is required to treat the patient; b), the abnormality leads to hospitalization; c). The abnormality persists for >1 week.
4) Grade 4 hematologic toxicity, other than those specified in criteria 5 and 6 below, lasting > 7 days
5) Grade 3 or Grade 4 febrile neutropenia of any duration
6) Grade 3 thrombocytopenia in combination with a grade 3 or greater blood and lymphatic system disorder

7) Grade 3 AST or ALT that is associated with a grade 2 rise in bilirubin

Additional information regarding reporting DLTs may be required by the Sponsor.

Completed DLT Confirmation Worksheets should be faxed or e-mailed to:

Global Safety and Pharmacovigilance, Advanced Clinical

Email: drugsafetypv@advancedclinical.com

9.3.9 *Stopping Rules*

Stopping rules for adverse events will be employed for this trial. The trial will be stopped if any adverse experience of any related death, grade 4 autoimmune toxicity or any grade 4 toxicity that is considered to have a causal relationship to study drug. Any related death, grade 4 autoimmune toxicity and any grade 4 toxicity that is considered to have a causal relationship to study drug will be submitted to regulatory agencies within the expedited safety reporting criteria.

9.3.10 *Adverse Events of Special Interest*

Adverse events that occur during or within 24 hours after study treatment administration and are judged to be related to study treatment infusion should be captured as a diagnosis (e.g., "infusion-related reaction") on the Adverse Event eCRF. If possible, avoid ambiguous terms such as "systemic reaction." If a patient experiences both a local and systemic reaction to the same dose of study treatment, each reaction should be recorded separately on the Adverse Event eCRF.

Systemic administration site reactions will be considered an AESI. The area around the administration site will be assessed by a medically qualified individual for adverse reactions at least 30 minutes post study drug administration. The Investigator will grade any ASRs according to the NCI-CTCAE V5.0 (excluding the actual expected micro-injection punctures).

Patients will be required to report any change in the administration site and return to the clinic for evaluation by the Investigator.

Adverse events of special interest (AESI) are required to be reported by the investigator to the Sponsor immediately (i.e., no more than 24 hours after learning of the event; see Section Adverse Event Reporting for reporting instructions).

AESI s should be reported to:

Global Safety and Pharmacovigilance, Advanced Clinical

Email: drugsafetypv@advancedclinical.com

9.3.11 *Guidance for Investigators for Patients on Anti-coagulants*

Based on the preclinical data and the role of ASPH in post-translational modification of proteins involved in the clotting and anticoagulant pathways (Factors VII, IX, X , Protein C), there may a potential for abnormal coagulation with SNS-301. Should there be a clinically significant AE or SAE recorded, such as clinically noted bleeding, administration of SNS-301 will be held until the AE/SAE returns to baseline. Should there be two individual events of SNS-301 interruption for the

same patient, then SNS-301 will be discontinued after consultation with the Medical Monitor and Sponsor. Clinical management and further workup of the coagulation pathway disturbance will be at the discretion of the treating physician.

9.3.12 *Reporting of Pregnancy*

If pregnancy occurs in a female patient, or female partner of a male patient while the patient is on treatment or until six months after the last dose, the sponsor will be notified within 24 hours of learning of the pregnancy. The pregnancy will be followed until birth or termination. Abnormal pregnancy outcomes (e.g., spontaneous abortion, fetal death, stillborn, congenital anomalies, ectopic pregnancy) are considered SAEs.

Pregnancy should be reported to:

Global Safety and Pharmacovigilance, Advanced Clinical

Email: drugsafetypv@advancedclinical.com

9.3.13 *Time Period and Frequency for Event Assessment and Follow-Up*

All AESIs and SAEs, including death due to any cause, that occur during this study and until 90 days after the last dose of study treatment or until the start of a new anti-cancer treatment, whichever comes first, whether or not expected and regardless of causality, must be reported to the Medical Monitor immediately upon discovery of the event, using an SAE Form.

All AEs will be collected from the time of signing the informed consent form until 30 days after the last dose after the last dose of study treatment or until the start of a new anti-cancer treatment, whichever comes first.

Any medical condition that begins after obtaining informed consent will be recorded the AE section of the CRF. If the patient's condition worsens during the study, the event will be recorded as an AE.

All AEs/SAEs will be captured on the appropriate case report form. Information to be collected includes event description, date of onset, severity, relationship to study intervention and date of resolution.

10. Statistical Considerations

10.1 Statistical Hypotheses

Cohort A

Thirty (30) patients will be enrolled in a two-stage design, with 15 patients in the first stage and 15 patients in the second stage to assess the null hypothesis that the objective response rate per iRECIST is 5%, versus the alternative hypothesis that the ORR is 18%, as described in Section 10.2.

Cohort B

Thirty (30) patients will be enrolled in a two-stage design, with 15 patients in the first stage and 15 patients in the second stage to assess the null hypothesis that the objective response rate per

iRECIST is 13.3%, versus the alternative hypothesis that the ORR is 29%, as described in Section 10.2.

10.2 Sample Size Determination

Adverse events will be continuously monitored. Among the first phase of 15 patients, for adverse events that occur at an incidence of 18% the probability of observing at least one event is approximately 95%. Among all 60 patients, for adverse events that occur at an incidence of 5% the probability of observing at least one event is approximately 95%.

The sample size for each cohort and stage is based on Simon's two-stage design for tests of one proportion.

Cohort A

To evaluate the primary endpoint of objective response rate per iRECIST at 12 weeks with a null hypothesis of an objective response rate (ORR) of 5% and an alternative hypothesis of an ORR of 18%, 30 patients in a two-stage design with 15 patients in the first stage and 15 patients in the second stage will be enrolled. At the first stage analysis if at least 1 response is observed out of 15 patients, the study will continue through the second stage. At the second stage analysis, if at least 4 responses are observed out of 30 total patients, the null hypothesis will be rejected and further research considered warranted. The overall power for objective response rate at 12 weeks is 80%. The overall type I error, the chance of incorrectly rejecting the null hypothesis is 6% (targeted alpha of 0.10). The probability of stopping at the first stage under the null hypothesis is 46%. The operating characteristics of this design are calculated using the exact binomial distribution.

Cohort B

To evaluate the primary endpoint of objective response rate per iRECIST at 12 weeks with a null hypothesis of an objective response rate (ORR) of 13.3% and an alternative hypothesis of an ORR of 29%, 30 patients in a two-stage design will be enrolled, with 15 patients in the first stage and 15 patients in the second stage. At the first stage analysis if at least 2 responses are observed out of 15 patients, the study may continue through the second stage. At the second stage analysis, if at least 7 responses are observed out of 30 total patients, the null hypothesis will be rejected and further research considered warranted. The overall power for objective response rate at 12 weeks is 80.1%. The overall type I error, the chance of incorrectly rejecting the null hypothesis is 9.2% (targeted alpha of 0.10). The probability of stopping at the first stage under the null hypothesis is 38.8%. The operating characteristics of this design are calculated using the exact binomial distribution.

10.3 Populations for Analyses

The following analysis populations will be used for presentation of the data:

Safety Analysis Set: The safety analysis will be based on the Safety Analysis Set, which comprises all patients who receive at least 1 dose of the study treatment or component of the study treatment.

Efficacy-Evaluable Analysis Set: All patients who receive at least 1 dose of the study treatment or component of the study treatment and have a post baseline response assessment per iRECIST at Week 12. Patients who discontinued prior to Week 12 due to disease clinical progression will be included. Patients who do not have a post baseline response assessment conducted will not be included.

Safety Run-In Set: All patients who receive at least 1 dose of the study treatment or component of the study treatment apart of the safety run-in.

Immunologic Analysis Set: All patients who receive at least 1 dose of the study treatment or component of the study treatment and have at least one valid post-baseline immunologic assessment available.

10.4 Statistical Analyses

The statistical analysis plan will be developed and finalized before database lock and will describe the patient populations to be included in the analyses, and procedures for accounting for missing, unused and spurious data.

The statistical analysis plan will specify how lost to follow-up patients will be addressed in the primary analysis.

10.4.1 *General Methods*

All summarizations will be presented separately for each cohort, and over all subjects combined.

For continuous variables, descriptive statistics (number (n), mean, median, standard deviation, minimum and maximum) will be presented. For categorical variables, frequencies and percentages will be presented. For time-to-event variables, percentages of patients experiencing that event will be presented and median time-to-event will be estimated using the Kaplan-Meier method. As appropriate, a 95% CI will be presented. Graphical displays will be presented, as appropriate.

Patients demographic characteristics including age, gender, and race will be analyzed, with categorical variables summarized in frequency tables while continuous variables summarized using mean (standard deviation) and median (range).

All data collected will be presented in by-patient data listings.

10.4.2 *Efficacy Analyses*

ORR is defined as the proportion of patients with a confirmed best response of iCR or iPR by iRECIST. Objective response rate will be estimated, and 90% CI based on the exact binomial distribution will be presented by cohort and overall, including number and percent of patients in each overall response category.

The primary analysis will be based on objective response at Week 12. An additional analysis of ORR based on best objective response during the study will be performed.

DOR, DCR, PFS, and OS will also be calculated, defined as follows:

- DOR: time from date of first response to date of progression, where patients without progression are censored at date of last valid disease assessment
- DCR: proportion of patients with SD or better (PR and CR). SD for at least six months
- PFS: time from date of start of treatment to date of progression, where patients without progression are censored at date of last valid disease assessment
- OS: time from date of start of treatment to date of death or censored at date of last contact

Efficacy analyses will be performed using the efficacy-evaluable analysis set.

10.4.3 *Safety Analyses*

Safety evaluations will be based on the incidence, severity, attribution and type of AEs, and changes in the patient's vital signs, and clinical laboratory results, analyzed using the safety analysis set.

Summarization of toxicity data will focus on incidence of treatment-emergent adverse events. Treatment-emergent adverse events are defined as any AE that occurs during or after administration of the first dose of treatment through 30 days after the last dose, any event that is considered study drug-related regardless of the start date of the event, or any event that is present at baseline but worsens in intensity. The incidence of serious adverse events, adverse events, drug-related adverse events, and adverse events leading to discontinuation or death will be presented in tabular form by system organ class and preferred term. Adverse events will be assessed for severity according to the NCI CTCAE, version 5.0.

A presentation of dose-limiting toxicities among patients in the safety run-in set will be presented.

Other safety evaluations including vital sign, laboratory and physical exam results will be presented over time.

10.4.4 *Other Analyses*

Antigen-specific cellular immune response assessed by but not limited to Interferon-γ secreting T lymphocytes will be summarized by visit. Immune related gene expression will be evaluated with pre- and post-treatment tissue biopsies. Cytokine and chemokine profiles will be summarized by visit.

Additional exploratory analyses may be performed, including evaluation of relationship between efficacy endpoints and immunology parameters.

10.4.4.1 Pharmacodynamics

Exploratory pharmacodynamic (PD) analysis will be performed using dose, vaccine-specific antibody response (geometric mean titer), antigen-specific T and B cell indices, and the relative expression of ASPH in each patient's tumor. The PD will be balanced and optimized to the degree of antigen-specific immune response and minimized for the production of regulatory immune processes.

10.5 **Interim Analyses**

For each cohort, the objective response rate will be assessed at the completion of stage 1 of the 2-stage design, after 15 patients complete the 12-week follow-up period or discontinue prior due to disease progression. See Section 10.2 for additional details.

10.5.1 *Safety Committee*

To ensure patient safety during the study, a Safety Committee will be formed to monitor safety on a periodic basis. Members of the Safety Committee will include a Safety representative, Principal Investigator(s) and the Sponsor Medical Expert. A charter will outline their roles and responsibilities The Safety Committee will meet at the completion of the safety run-in to review safety data collected from the point of first patient in (FPI) to review safety, or as needed. The safety data will include demographic data, adverse events, serious adverse events, and relevant laboratory data. Following each data review, the Safety Committee will provide recommendations as to whether the study should continue or be amended, or whether the study should be stopped on the basis of safety (i.e., evidence of harm). The final decision will rest with the Sponsor. For each cohort, the interim efficacy assessment will occur after 15 patients were enrolled and completed the 12-week follow-up period. A safety review will occur in parallel to the efficacy assessment of the first 15 patients in each cohort. Any outcomes of these safety reviews that affect study conduct will be communicated in a timely manner to the investigators for notification of the Institutional Review boards/Ethics Committees (IRBs/ECs).

11. SUPPORTING DOCUMENTATION & OPERATIONAL CONSIDERATIONS

11.1 Regulatory, Ethical and Study Oversight Considerations

11.1.1 *Regulatory and Ethical Issues*

The study will be conducted in accordance with the ethical principles of the current version of the Declaration of Helsinki. The Sponsor and Investigator will comply with their responsibilities as defined in 21 CFR 312.50-312.70, International Conference on Harmonization Guidance for Industry: E6 (R2) Good Clinical Practice (March 2018) and the local regulatory/legal regulations.

The protocol, protocol amendments, ICF, Investigator Brochure and other relevant documents (e.g., advertisements) must be submitted to an IRB/IEC by the investigator and reviewed and approved by the IRB/IEC before the study is initiated. Any amendments to the protocol will require IRB/IEC approval prior to implementation, except when necessary to eliminate immediate hazard to patients.

The investigator will be responsible for the following:

- Providing written summaries of the status of the study to the IRB/IEC annually or more frequently in accordance with the requirements, policies, and procedures established by the IRB/IEC
- Notifying the IRB/IEC of SAEs or other significant safety findings as required by IRB/IEC procedures
- Providing oversight of the conduct of the study at the site and adherence to requirements of 21 CFR, ICH guidelines, the IRB/IEC, European regulation 536/2014 for clinical studies (if applicable), and all other applicable local regulations
- While every effort should be made to avoid protocol deviations, should an important deviation be discovered, Sponsor must be informed immediately. Any protocol deviation impacting patient safety must be reported to the Medical Monitor immediately and to the IRB/IEC, as required per institution

11.1.2 *Financial Disclosure*

Investigators and sub-investigators will provide the sponsor with sufficient, accurate financial information as requested to allow the sponsor to submit complete and accurate financial certification or disclosure statements to the appropriate regulatory authorities. Investigators are responsible for providing information on financial interests during the course of the study and for 1 year after completion of the study.

11.1.3 *Informed Consent Process*

The Investigator will obtain informed consent from each patient enrolled in the study, in accordance with requirements of 21 CFR 50, local regulations, ICH guidelines, Health Insurance Portability and Accountability Act (HIPAA), Data Protection regulations, where applicable, IRB/IEC and any local laws and regulations in which the investigation is being conducted.

The IRB must approve the ICF to be used by the Investigator. It is the responsibility of the Investigator to ensure that informed consent is obtained from the patient or his/her guardian or legal representative before any activity or treatment is undertaken which is not part of routine care. This includes, but is not limited to, the performance of diagnostic, screening, or therapeutic procedures and the administration of the first dose of study treatment. The draft version of the ICF will be modified by each site and reviewed and approved in writing by Sensei prior to submission to the IRB.

The investigator or his/her representative will explain the nature of the study to the patient or his/her legally authorized representative and answer all questions regarding the study. The medical record must include a statement that written informed consent was obtained before the patient was enrolled in the study and the date the written consent was obtained. The authorized person obtaining the informed consent must also sign the ICF. A copy of the ICF(s) must be provided to the patient or the patient's legally authorized representative.

Should a protocol amendment be made, the patient ICF may be revised to reflect the changes of the protocol. If the ICF is revised, it is the responsibility of the Investigator to ensure that an amended ICF is reviewed and approved by the IRB and signed by all patients subsequently, as applicable to their treatment and/or follow up status in the study.

11.1.4 *Data Protection*

All local legal requirements regarding data protection will be enforced. All study findings and documents will be regarded as confidential. The Investigator and members of his/her research team must not disclose such information without prior written approval from Sensei. The anonymity of participating patients must be maintained. Throughout documentation and evaluation, the patients will be identified on CRFs and other documents submitted to Sensei by an unique identifier. Documents that are not to be submitted to Sensei, and that identify the patient (e.g., the signed ICF), must be maintained in confidence by the Investigator. The patients will be told that all study findings will be stored and handled in strictest confidence, according to local requirements. Patients will be informed that authorized research Investigators, IRB/IEC, agents of the FDA or other recognized regulatory authorities, and authorized representatives of the Sponsor, Sensei, have the right to inspect their medical records.

11.1.5 *Committee Structure*

This is a Phase 2 trial involving 20 study centers located in the United States. The Investigator(s) responsible for the conduct of the study at their site, in compliance with this Protocol, are identified on the *Signature of Agreement Page* (Appendix D: Principal Investigator Signature of Agreement Page).

All questions regarding the enrollment of patients, regulatory requirements for the conduct of the study, safety reporting, or study conduct should be addressed to the Medical Monitor.

11.1.6 *Data Quality Assurance*

The following requirements are necessary to ensure quality data from the study:

- All patient data relating to the study will be recorded on electronic CRF unless transmitted to the sponsor or designee electronically (e.g., laboratory data). The investigator is responsible for verifying that data entries are accurate and correct by physically or electronically signing the CRF.
- The investigator must maintain accurate documentation (source data) that supports the information entered in the CRF.
- The investigator must permit study-related monitoring, audits, IRB/IEC review, and regulatory agency inspections and provide direct access to source data documents.
- The sponsor or designee is responsible for the data management of this study including quality checking of the data. Programmed computer edit checks will be run against the database to check for discrepancies and plausibility of the data. All issues resulting from the computer-generated checks will be resolved according to the Sponsor's standard data management practices in conjunction with the medical monitor, clinical study personnel, and the study Investigators.
- The sponsor assumes accountability for actions delegated to other individuals (eg, Contract Research Organizations).
- Study monitors will perform ongoing source data verification to confirm that data entered into the CRF by authorized site personnel are accurate, complete, and verifiable from source documents; that the safety and rights of participants are being protected; and that the study is being conducted in accordance with the currently approved protocol and any other study agreements, ICH GCP, and all applicable regulatory requirements.
- Records and documents, including signed ICFs, pertaining to the conduct of this study must be retained by the investigator for the following timeframes:
    - for a minimum of two years following the date the marketing application (NDA/BLA) is approved for the indication for which the drug was investigated; or,
    - for a minimum of two years following the release date of the final report, if no marketing application is to be filed by Sensei, or if the marketing application is not approved for the indication for which the drug was investigated or is discontinued, and the FDA has been notified; or,
    - for a minimum of 15 years after the completion or discontinuation of the study to be filed in support of the registration in the European Union.
    - No records may be destroyed without the written approval of the sponsor. No records may be transferred to another location or party without written notification to the sponsor.

11.1.7 *Source Documents*

Source documents provide evidence for the existence of the patient and substantiate the integrity of the data collected. Source documents are filed at the investigator's site.

Data reported on the CRF or entered in the eCRF that are transcribed from source documents must be consistent with the source documents or the discrepancies must be explained. The investigator may need to request previous medical records or transfer records, depending on the study. Also, current medical records must be available.

11.1.8 *Study and Site Closure*

The sponsor designee reserves the right to close the study site or terminate the study at any time for any reason at the sole discretion of the sponsor. Study sites will be closed upon study completion. A study site is considered closed when all required documents and study supplies have been collected and a study-site closure visit has been performed.

The investigator may initiate study-site closure at any time, provided there is reasonable cause and sufficient notice is given in advance of the intended termination.

Reasons for the early closure of a study site by the sponsor or investigator may include but are not limited to:

- Failure of the investigator to comply with the protocol, the requirements of the IRB/IEC or local health authorities, the sponsor's procedures, or GCP guidelines
- Inadequate recruitment of patients by the investigator
- Discontinuation of further study intervention development

Upon terminating the study, the Investigator will submit a final report to the IRB in keeping with local IRB regulations. This report should include any deviations from the protocol, the number and types of patients evaluated, the number of patients who discontinued, including reasons, results of the study, AEs, and a conclusion summarizing the results.

If requested by the Investigator, at the completion of the study and following analysis of the data, Sensei will supply a tabulated listing of data and a final clinical statistical report. A copy of the final study report and final CRFs, will be provided to each Investigator.

11.1.9 *Publication Policy*

By signing the study protocol, the Investigator agrees with the use of results of the study for the purposes of national and international registration, publication, and information for medical and pharmaceutical professionals. If necessary, the authorities will be notified of the Investigator's name, address, qualifications, and extent of involvement. The results of the study may appear on public websites, such as www.clinicaltrials.gov, in compliance with clinical trial reporting requirements. Sensei will prepare an *Integrated Clinical/Statistical Report*. Any publication/presentation of data must include the entire study population. Submission of data for publication/presentation will be reviewed, coordinated and approved by Sensei in collaboration with the Investigator. Sensei will determine authorship of any publication by enrollment or by contributing to the protocol, in consultation with the principal investigator.

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APPENDIX **A: TUMOR ASSESSMENT CRITERIA**

RECIST 1.1

Definitions as per Eisenhauer EA, Therasse P, Bogaerts J, et al. New response evaluation criteria in solid tumors: Revised RECIST guideline (Version 1.1). Eur J Cancer 2009; 45:228–47.

At baseline, tumor lesions/lymph nodes will be categorized measurable or non-measurable as follows:

Measurable Tumor Lesions
Tumor lesions must be accurately measured in at least one dimension (longest diameter in the plane of measurement is to be recorded) with a minimum size of:

- 10 mm by computed tomography (CT) or magnetic resonance imaging (MRI) scan (CT/MRI scan slice thickness/interval no greater than 5 mm)
- 10-mm caliper measurement by clinical examination (lesions that cannot be accurately measured with calipers should be recorded as non-measurable)
- 20 mm by chest X-ray

Malignant Lymph Nodes. To be considered pathologically enlarged and measurable, a lymph node must be ≥15 mm in the short axis when assessed by CT scan (CT scan slice thickness recommended to be no greater than 5 mm). At baseline and in follow-up, only the short axis will be measured and followed. See also notes below on "Baseline Documentation of Target and Nontarget Lesions" for information on lymph node measurement.

Non-Measurable Tumor Lesions
Non-measurable tumor lesions encompass small lesions (longest diameter <□10 mm or pathological lymph nodes with ≥10 to <□15 mm short axis), as well as truly non-measurable lesions. Lesions considered truly non-measurable include leptomeningeal disease, ascites, pleural or pericardial effusion, inflammatory breast disease, lymphangitic involvement of skin or lung, peritoneal spread, and abdominal masses/abdominal organomegaly identified by physical examination that is not measurable by reproducible imaging techniques.

Special Considerations Regarding Lesion Measurability
Bone lesions, cystic lesions, and lesions previously treated with local therapy require particular comment, as outlined below.
Bone lesions:

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

Cystic lesions:

- Lesions that meet the criteria for radiographically defined simple cysts should not be

considered malignant lesions (neither measurable nor non-measurable) since they are, by definition, simple cysts.

- Cystic lesions thought to represent cystic metastases can be considered measurable lesions if they meet the definition of measurability described above. However, if noncystic lesions are present in the same patient, these are preferred for selection as target lesions.

Lesions with prior local treatment:

- Tumor lesions situated in a previously irradiated area, or in an area subjected to other loco-regional therapy, are usually not considered measurable unless there has been demonstrated progression in the lesion. Study protocols should detail the conditions under which such lesions would be considered measurable.

SPECIFICATIONS BY METHODS OF MEASUREMENTS

Measurement of Lesions

All measurements should be recorded in metric notation, using calipers if clinically assessed. All baseline evaluations should be performed as close as possible to the treatment start and never more than 4 weeks before the beginning of the treatment.

Method of Assessment

The same method of assessment and the same technique should be used to characterize each identified and reported lesion at baseline and during study. Imaging-based evaluation should always be done rather than clinical examination unless the lesion(s) being followed cannot be imaged but are assessable by clinical exam.

Clinical Lesions. Clinical lesions will only be considered measurable when they are superficial and ≥10 mm in diameter as assessed using calipers (e.g., skin nodules). For the case of skin lesions, documentation by color photography, including a ruler to estimate the size of the lesion, is suggested.

Chest X-Ray. Chest CT is preferred over chest X-ray, particularly when progression is an important endpoint, since CT is more sensitive than X-ray, particularly in identifying new lesions. However, lesions on chest X-ray may be considered measurable if they are clearly defined and surrounded by aerated lung.

CT, MRI. CT is the best currently available and reproducible method to measure lesions selected for response assessment. This guideline has defined measurability of lesions on CT scan based on the assumption that CT slice thickness is 5 mm or less. When CT scans have slice thickness greater than 5 mm, the minimum size for a measurable lesion should be twice the slice thickness. MRI is also acceptable.

Ultrasound. Ultrasound is not useful in the assessment of lesion size and should not be used as a method of measurement.

Endoscopy, Laparoscopy, Tumor Markers, Cytology, Histology. The utilization of these techniques for objective tumor evaluation is not advised.

TUMOR RESPONSE EVALUATION

ASSESSMENT OF OVERALL TUMOR BURDEN AND MEASURABLE DISEASE

To assess objective response or future progression, it is necessary to estimate the overall tumor burden at baseline and to use this as a comparator for subsequent measurements. Measurable disease is defined by the presence of at least one measurable lesion.

BASELINE DOCUMENTATION OF TARGET AND NONTARGET LESIONS

When more than one measurable lesion is present at baseline, all lesions up to a maximum of five lesions total (and a maximum of two lesions per organ) representative of all involved organs should be identified as target lesions and will be recorded and measured at baseline (this means in instances where patients have only one or two organ sites involved, a maximum of two and four lesions, respectively, will be recorded).

Target lesions should be selected on the basis of their size (lesions with the longest diameter) and be representative of all involved organs, but in addition should be those that lend themselves to reproducible repeated measurements. It may be the case that, on occasion, the largest lesion does not lend itself to reproducible measurement, in which circumstance the next largest lesion that can be measured reproducibly should be selected.

Lymph nodes merit special mention since they are normal anatomical structures that may be visible by imaging even if not involved by tumor. As noted above, pathological nodes that are defined as measurable and may be identified as target lesions must meet the criterion of a short axis of ≥15 mm by CT scan. Only the short axis of these nodes will contribute to the baseline sum. The short axis of the node is the diameter normally used by radiologists to judge if a node is involved by solid tumor. Nodal size is normally reported as two dimensions in the plane in which the image is obtained (for CT scan, this is almost always the axial plane; for MRI the plane of acquisition may be axial, sagittal, or coronal). The smaller of these measures is the short axis. For example, an abdominal node that is reported as being 20 mm x 30 mm has a short axis of 20 mm and qualifies as a malignant, measurable node. In this example, 20 mm should be recorded as the node measurement. All other pathological nodes (those with short axis ≥10 mm but <15 mm) should be considered nontarget lesions. Nodes that have a short axis <10 mm are considered nonpathological and should not be recorded or followed.

A sum of the diameters (longest for non-nodal lesions, short axis for nodal lesions) for all target lesions will be calculated and reported as the baseline sum of diameters. If lymph nodes are to be included in the sum, then, as noted above, only the short axis is added into the sum. The baseline sum of diameters will be used as a reference to further characterize any objective tumor regression in the measurable dimension of the disease.

All other lesions (or sites of disease), including pathological lymph nodes, should be identified as nontarget lesions and should also be recorded at baseline. Measurements are not required and these lesions should be followed as “present,” “absent,” or in rare cases “unequivocal progression.”
In addition, it is possible to record multiple nontarget lesions involving the same organ as a single item on the Case Report Form (CRF) (e.g., “multiple enlarged pelvic lymph

nodes" or "multiple liver metastases").

RESPONSE CRITERIA

Evaluation of Target Lesions

This section provides the definitions of the criteria used to determine objective tumor response for target lesions.

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

Special Notes on the Assessment of Target Lesions

Lymph Nodes. Lymph nodes identified as target lesions should always have the actual short axis measurement recorded (measured in the same anatomical plane as the baseline examination), even if the nodes regress to below10 mm on study. This means that when lymph nodes are included as target lesions, the sum of lesions may not be zero even if CR criteria are met since a normal lymph node is defined as having a short axis <10 mm.

Target Lesions That Become Too Small to Measure.

While on study, all lesions (nodal and non-nodal) recorded at baseline should have their actual measurements recorded at each subsequent evaluation, even when very small (e.g., 2 mm). However, sometimes lesions or lymph nodes that are recorded as target lesions at baseline become so faint on the CT scan that the radiologist may not feel comfortable assigning an exact measure and may report them as being too small to measure. When this occurs, it is important that a value be recorded on the CRF as follows:

- If it is the opinion of the radiologist that the lesion has likely disappeared, the measurement should be recorded as 0 mm.
- If the lesion is believed to be present and is faintly seen but too small to measure, a default value of 5 mm should be assigned and below measurable limit (BML) should be ticked. (Note: It is less likely that this rule will be used for lymph nodes since they usually have a definable size when normal and are frequently surrounded by fat such as in the retroperitoneum; however, if a lymph node is believed to be present and is faintly seen but too small to measure, a default value of 5 mm should be assigned in this circumstance as well). To reiterate, however, if the radiologist is able to provide an actual measure, that should be recorded, even if it is below 5 mm.

Lesions That Split or Coalesce on Treatment

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

vector of the longest diameter in this instance should be the maximal longest diameter for the coalesced lesion.

Evaluation of Nontarget Lesions
This section provides the definitions of the criteria used to determine the tumor response for the group of nontarget lesions. While some nontarget lesions may actually be measurable, they need not be measured and, instead, should be assessed only qualitatively at the timepoints specified in the protocol.

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

Special Notes on Assessment of Progression of Nontarget Disease
When the Patient Also Has Measurable Disease
In this setting, to achieve "unequivocal progression" on the basis of the nontarget disease, there must be an overall level of substantial worsening in nontarget disease in a magnitude that, even in the presence of SD or PR in target disease, the overall tumor burden has increased sufficiently to merit discontinuation of therapy. A modest increase in the size of one or more nontarget lesions is usually not sufficient to qualify for unequivocal progression status. The designation of overall progression solely on the basis of change in nontarget disease in the face of SD or PR of target disease will therefore be extremely rare.

When the Patient Has Only Non-Measurable Disease
This circumstance arises in some Phase III studies when it is not a criterion of study entry to have measurable disease. The same general concepts apply here as noted above; however, in this instance, there is no measurable disease assessment to factor into the interpretation of an increase in non-measurable disease burden. Because worsening in nontarget disease cannot be easily quantified (by definition: if all lesions are truly non-measurable), a useful test that can be applied when assessing patients for unequivocal progression is to consider if the increase in overall disease burden based on the change in non-measurable disease is comparable in magnitude to the increase that would be required to declare PD for measurable disease, that is, an increase in tumor burden representing an additional 73% increase in volume (which is equivalent to a 20% increase in diameter in a measurable lesion). Examples include an increase in a pleural effusion from "trace" to "large," an increase in lymphangitic disease from localized to widespread or may be described in protocols as "sufficient to require a change in therapy." If unequivocal progression is seen, the patient should be considered to have had overall PD at that point. While it would be ideal to have objective criteria to apply to non-measurable disease, the very nature of that disease makes it impossible to do so; therefore, the increase must be substantial.

New Lesions
The appearance of new malignant lesions denotes disease progression; therefore, some comments on detection of new lesions are important. There are no specific criteria for the identification of new radiographic lesions; however, the finding of a new lesion should be unequivocal, i.e., not attributable to differences in scanning technique,

change in imaging modality, or findings thought to represent something other than tumor (for example, some “new” bone lesions may be simply healing or flare of preexisting lesions). This is particularly important when the patient’s baseline lesions show partial or complete response. For example, necrosis of a liver lesion may be reported on a CT scan report as a “new” cystic lesion, which it is not.

A lesion identified on a follow up study in an anatomical location that was not scanned at baseline is considered a new lesion and will indicate disease progression.

If a new lesion is equivocal, for example because of its small size, continued therapy and follow-up evaluation will clarify if it represents truly new disease. If repeat scans confirm there is definitely a new lesion, then progression should be declared using the date of the initial scan.

EVALUATION OF RESPONSE

Table 1 provides a summary of the overall response status calculation at each timepoint for patients who have measurable disease at baseline.
Table 2 provides a summary of non-measurable (therefore nontarget) disease only
Table 3 provides the best overall response when confirmation of CR and PR required

Table 1: Time point response: patients with target (+/- non-target disease)

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

CR = complete response, PR = partial response, SD=stable disease, PD = progressive disease, and NE = inevaluable

Table 2 Time point response: patients with non-target disease only

Non-target lesions	New lesions	Overall response
CR	No	CR
Non-CR/non-PD	No	Non-CR/non-PD[a]
Not all evaluated	No	NE
Uniequivocal PD	Yes or No	PD
Any	Yes	PD
CR = complete response, PD = progressive disease, and NE = inevaluable [a] Non-CR/non-PD is preferred over stable disease for non-target disease since SD is increasingly used as endpoint for assessment of efficacy in some trials so to assign this category when no lesions can be measured is not advised.		

Table 3 Best overall response when confirmation of CR and PR required

Overall response First time point	Overall response Subsequent time point	Best overall response
CR	CR	CR
CR	PR	SD, PD or PR[a]
CR	SD	SD provided minimum criteria for SD duration met, otherwise PD

CR	PD	SD provided minimum criteria for SD duration met, otherwise PD
CR	NE	SD provided minimum criteria for SD duration met, otherwise NE
PR	CR	PR
PR	PR	PR
PR	SD	SD
PR	PD	SD provided minimum criteria for SD duration met, otherwise PD
PR	NE	SD provided minimum criteria for SD duration met, otherwise NE
NE	NE	NE

CR = complete response, PR = partial response, SD=stable disease, PD = progressive disease, and NE = inevaluable

[a] If a CR is truly met at first time point, then any disease seen at a subsequent time point, even disease meeting PR criteria relative to baseline, makes the disease PD at that point (since disease must have reappeared after CR). Best response would depend on whether minimum duration for SD was met. However, sometimes CR may be claimed when subsequent scans suggest small lesions were likely still present and in fact the patient had PR, not CR at the first time point. Under these circumstances, the original CR should be changed to PR and the best response is PR.

iRECIST

Definitions as per Seymour, L, et al. iRECIST: guidelines for response criteria for use in trials testing immunotherapeutics. Lancet 2017; PE143-E152.

iRECIST Response Assessment

Overall response will also be assessed using iRECIST. Immunotherapeutics may result in infiltration of immune cells leading to transient increase in the size in malignant lesions, or undetectable lesions becoming detectable. The criteria are identical to those of RECIST 1.1 in many respects but have been adapted to account for instances where an increase in tumour burden, or the appearance of new lesions, does not reflect true tumour progression.

Key differences are described below. All responses defined using iRECIST criteria are designated with a prefix. iRECIST time-point and best overall responses will be recorded separately.

Confirming Disease Progression

Unlike RECIST 1.1, iRECIST requires the confirmation of progression and uses the terms iUPD (unconfirmed progression) and iCPD (confirmed progression). Confirmatory scans should be performed at least 4 weeks, but no longer than 8 weeks after iUPD.

iCPD is confirmed if further increase in tumour burden, compared to the last assessment, is seen as evidenced by one or more of the following:

- Continued increase in tumour burden (from iUPD) where RECIST 1.1 definitions of progression had been met (from nadir) in target, non-target disease or new lesions
    - Progression in target disease worsens with an increase of at least 5 mm in the absolute value of the sum
    - Continued unequivocal progression in non-target disease with an increase in tumor burden
    - Increase in size of previously identified new lesion (s) (an increase of at least 5 mm in the absolute value of the sum of those considered to be target new lesions) or additional new lesions.
- RECIST 1.1 criteria are met in lesions types (target or non-target or new lesions) where progression was not previously identified, including the appearance of additional new lesions.

If iUPD is not confirmed at the next assessment, then the appropriate response will be assigned (iUPD if the criteria are still met, but no worsening, or iSD, iPR or iCR if those criteria are met compared to baseline). As can be seen in table 2, the prior documentation of iUPD does not preclude assigning iCR, iPR, or iSD in subsequent time-point assessments or as best overall response (BOR) providing that iCPD is not documented at the next assessment after iUPD.

New lesions

New lesions should be assessed and measured as they appear using RECIST 1.1 criteria (maximum of 5 lesions, no more than 2 per site, at least 10 mm in long axis (or 15 mm in short

axis for nodal lesions) and recorded as New Lesions-Target (NLT) and New Lesion-Non-Target (NLNT) to allow clear differentiation from baseline target and non-target lesions.

New lesions may either meet the criteria of NLT or NLNT to drive iUPD (or iCPD). However, the measurements of target lesions should NOT be included in the sum of measures of original target lesions identified at baseline. Rather, these measurements will be collected on a separate table in the case record form.

PD is confirmed in the New Lesion category if the next imaging assessment, conducted at least 4 weeks (but not more than 8 weeks) after iUPD confirms further progression from iUPD with either an increase of at least 5 mm in the absolute value of the sum of NLT OR an increase (but not necessarily unequivocal increase) in the size of NLNT lesions OR the appearance of additional new lesions

Response and Stable Disease Duration (RECIST 1.1 and iRECIST)

Response duration will be measured from the time measurement criteria for CR/PR or iCR/iPR (whichever is first recorded) are first met until the first date that recurrent or progressive disease is objectively documented, taking as reference the smallest measurements recorded on study (including baseline).

Stable disease duration will be measured from the time of start of treatment until the criteria for progression are met, taking as reference the smallest sum on study (including baseline).

Methods of Measurement

The same method of assessment and the same technique should be used to characterize each identified and reported lesion at baseline and during follow-up. Assessments should be identified on a calendar schedule and should not be affected by delays in therapy. While on study, all lesions recorded at baseline should have their actual measurements recorded at each subsequent evaluation, even when very small (e.g. 2 mm). If it is the opinion of the radiologist that the lesion has likely disappeared, the measurement should be recorded as 0 mm. If the lesion is believed to be present and is faintly seen but too small to measure, a default value of 5 mm should be assigned. For lesions which fragment/split add together the longest diameters of the fragmented portions; for lesions which coalesce, measure the maximal longest diameter for the “merged lesion”.

Clinical Lesions. Clinical lesions will only be considered measurable when they are superficial and ≥10 mm as assessed using calipers (e.g. skin nodules). For the case of skin lesions, documentation by colour photography including a ruler to estimate the size of the lesion is recommended. If feasible, imaging is preferred.

Chest X-ray. Chest CT is preferred over chest X-ray, particularly when progression is an important endpoint, since CT is more sensitive than X-ray, particularly in identifying new lesions. However, lesions ≥20 mm on chest X-ray may be considered measurable if they are clearly defined and surrounded by aerated lung.

CT, MRI. CT is the best currently available and reproducible method to measure lesions selected for response assessment. This guideline has defined measurability of lesions on CT scan based on the assumption that CT slice thickness is 5 mm or less. When CT scans have slice thickness greater than 5 mm, the minimum size for a measurable lesion should be twice

the slice thickness. MRI is also acceptable in certain situations (e.g. for body scans). Other specialized imaging or other techniques may also be appropriate for individual case.4 For example, while PET scans are not considered adequate to measure lesions, PET-CT scans may be used providing that the measures are obtained from the CT scan and the CT scan is of identical diagnostic quality to a diagnostic CT (with IV and oral contrast).

Ultrasound. Ultrasound is not useful in assessment of lesion size and should not be used as a method of measurement. If new lesions are identified by ultrasound in the course of the study, confirmation by CT is advised.

Endoscopy, Laparoscopy. The utilization of these techniques for objective tumour evaluation is not advised. However, they can be useful to confirm complete pathological response when biopsies are obtained or to determine relapse in trials where recurrence following complete response or surgical resection is an endpoint.

Tumour Markers. Tumour markers alone cannot be used to assess objective tumour response. If markers are initially above the upper normal limit, however, they must normalize for a patient to be considered in complete response.

Cytology, Histology. These techniques can be used to differentiate between PR and CR in rare cases if required by protocol (for example, residual lesions in tumour types such as germ cell tumours, where known residual benign tumours can remain). When effusions are known to be a potential adverse effect of treatment (e.g. with certain taxane compounds or angiogenesis inhibitors), the cytological confirmation of the neoplastic origin of any effusion that appears or worsens during treatment when the measurable tumour has met criteria for response or stable disease is advised to differentiate between response or stable disease and progressive disease

Table 1: Assigning time point response for iRECIST

Target Lesions*	Non-Target Lesions*	New Lesions*	Time Point Response	
			No prior iUPD**	Prior iUPD**; ***
iCR	iCR	No	iCR	iCR
iCR	Non-iCR/Non-iUPD	No	iPR	iPR
iPR	Non-iCR/Non-iUPD	No	iPR	iPR
iSD	Non-iCR/Non-iUPD	No	iSD	iSD

iUPD with no change OR decrease from last TP	iUPD with no change OR decrease from last TP	Yes	NA	NLs confirms iCPD if NLs were previously identified and increase in size (≥5 mm in SOM for NLT or any increase for NLNT) or number. If no change in NLs (size or number) from last TP, remains iUPD
iSD	iUPD	No	iUPD	Remains iUPD unless iCPD confirmed based in further increase in size of NT disease (need not meet RECIST 1.1 criteria for unequivocal PD)
iUPD	Non-iCR/Non-iUPD	No	iUPD	Remains iUPD unless iCPD confirmed based on: o further increase in SOM of at least 5 mm, otherwise remains iUPD
iUPD	iUPD	No	iUPD	Remains iUPD unless iCPD confirmed based on further increase in: o previously identified T lesion iUPD SOM ≥5 mm and / or o NT lesion iUPD (prior assessment - need not be unequivocal PD)
iUPD	iUPD	Yes	iUPD	Remains iUPD unless iCPD confirmed based on further increase in: o previously identified T lesion iUPD ≥5 mm and / or o previously identified NT lesion iUPD (need not be unequivocal) and /or o size or number of new lesions previously identified
Non-iUPD/PD	Non-iUPD/PD	Yes	iUPD	Remains iUPD unless iCPD confirmed based on o increase in size or number of new lesions previously identified
* Using RECIST 1.1 principles. If no PSPD occurs, RECIST 1.1 and iRECIST categories for CR, PR and SD would be the same. ** in any lesion category. *** previously identified in assessment immediately prior to this TP.				
iCR- immune complete response; iPR – immune partial response; iSD – immune stable disease; iUPD – immune unconfirmed progression; iCPD – immune confirmed progression; NL – new lesions; NLNT – new lesion non target; T – target; TP – time point; NA – not applicable; NE – not evaluable/evaluated				

Table 2: Assigning best overall response for iRECIST

All patients will have their iBOR from the start of study treatment until the end of treatment classified as outlined below.

TPR1	TPR2	TPR3	TPR4	TPR5	iBOR
iCR	iCR, iPR, iUPD, NE	iCR, iPR, iUPD, NE	iUPD	iCPD	iCR
iUPD	iPR, iSD, NE	iCR	iCR, iPR, iSD, iUPD, NE	iCR, iPR, iSD, iUPD, iCPD, NE	iCR
iUPD	iPR	iPR, iSD, iUPD, NE	iPR, iSD, iUPD, NE, iCPD	iPR, iSD, iUPD, NE, iCPD	iPR
iUPD	iSD, NE	PR	iPR, iSD, iUPD, NE	iPR, iSD, iUPD, iCPD, NE	iPR
iUPD	iSD	iSD, iUPD, NE	iSD, iUPD, iCPD, NE	iSD, iUPD, ICPD, NE	iSD
iUPD	iCPD	Anything	Anything	Anything	iCPD
iUPD	iUPD	iCPD	Anything	Anything	iCPD
iUPD	NE	NE	NE	NE	iUPD

- Table assumes a randomised study where confirmation of CR or PR is not required.
- NE = not evaluable that cycle.
- Designation "I" for BOR can be used to indicate prior iUPD to aid in data interpretation.
- For patients with non-target disease only at baseline, only CR or non-CR/non-PD can be assigned at each TPR but is not shown in the table for ease of presentation.

iCR- immune complete response; iPR – immune partial response; iSD – immune stable disease; iUPD – immune unconfirmed progression; iCPD – immune confirmed progression; iBOR – immune best response; TPR – time point response

APPENDIX B: ECOG PERFORMANCE STATUS

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

*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.

APPENDIX C: SUMMARY OF CHANGES

	Version Number	Version Date
Current Approved Protocol:	1.0	February 6, 2019
Amended Protocol:	2.0	June 27, 2019
Administrative Letter	NA	October 9, 2019
Administrative Letter	NA	April 3, 2020
Amended Protocol	3.0	July 24, 2020
Amended Protocol	4.0	November 6, 2020

Changes to Amended Protocol Version 4.0 Dated November 6, 2020				
Section #	**Section Title**	**Old Text**	**New Text**	**Rationale for Change**
Synopsis, 4.2.2	Secondary Endpoints	• T-cell activation and cytolytic cell phenotype in PBMCs by Flow Cytometry or secretion of immune molecules • B cell activation/ secretion • Assessment of Myeloid Derived Suppressor Cells (MDSC) • Immune gene transcript profiling of PBMCs	Deleted	Deleted to align with Sensei's updated immunogenicity testing.
Synopsis, 4.2.3	Exploratory Endpoints	NA	• TCR sequencing of PBMCs for diversity and putative antigen specificity	Moved from Secondary Endpoints to Exploratory Endpoints since the assay is not CLIA certified.
Synopsis, 5.2	Trial Population, Overall Design	NA	Expanded patient population to include patient who are naïve to CPI therapy.	Given the modest response rates to CPI therapy even in patients with PD-L1 positive tumors in the first line setting, Sensei will allow enrollment to a second cohort with patients that

				are CPI therapy naïve.
Synopsis, 5.2	Sample Size, Overall Design	Approximately 30 patients will be enrolled in the trial.	Approximately up to 30 patients will be enrolled into each cohort on the trial.	Adjusted to include Cohort B.
Synopsis		A minimum accrual rate is expected to be 2-3 patients per month. With a minimal accrual rate of 2-3 patients per month we expect the study enrollment is expected to last approximately 12-15 months.	The study enrollment is expected to last approximately 18-24 months.	Updated to account for new cohort.
Synopsis, 5.2	Overall Design	NA	Additionally, up to two optional biopsies may be obtained at any time during the study, if medically feasible.	Optional biopsies added in select cases to increase scientific knowledge of the study treatment.
Synopsis, 5.2	Statistical Methods: Sample Size Justification, Overall Design	Approximately 15 participants will be enrolled in Stage 1 and an additional approximately 15 participants will be enrolled in Stage 2, if the cohort is expanded. To evaluate the primary endpoint of objective response per	Each cohort will enroll in two stages. Within each cohort, approximately 15 participants will be enrolled in Stage 1 and an additional approximately 15 participants may be enrolled in Stage 2, if expanded. The sample size for each cohort and stage is based on Simon's two-stage design for tests of one proportion.	Updated for Cohort B. Deleted detailed information on sample size justification in the synopsis. The reader should refer to

		iRECIST at 12 weeks with a null hypothesis of an objective response rate (ORR) of 5% and an alternative hypothesis of an ORR of 18%, 30 patients in a two-stage design with 15 patients in the first stage and 15 patients in the second stage will be enrolled. Patients with evidence of disease progression or deemed unevaluable at 12 weeks will not be counted towards assessment of futility. At the first stage analysis if at least 1 response is observed out of 15 patients, the study will continue through the second stage. At the second stage analysis, if at least 4 responses are observed out of 30 total patients, the null hypothesis will be rejected, and further research considered warranted. The overall power for objective response rate at 12 weeks is 80%. The overall type I error, the chance of incorrectly rejecting the null hypothesis is 6% (targeted alpha of 0.10). The probability of stopping at the first stage under the null hypothesis is 46%. The operating characteristics of this design are calculated using the exact binomial distribution.		the Statistics section of the protocol.

Synopsis	General Methods	NA	All summarizations will be presented separately for each cohort, and over all subjects combined.	Added information regarding Cohort B.
Synopsis	General Methods	Objective response rate (ORR) is defined as the proportion of patients with a confirmed best response of CR or PR by RECIST 1.1. Objective response rate will be estimated, and 95% CI based on the exact binomial distribution will be presented.	Objective response rate (ORR) is defined as the proportion of patients with a confirmed best response of CR or PR by iRECIST.	Sentence simplified. Statistics section includes additional details.
Synopsis, 6	Inclusion Criteria	Have histologically or cytologically documented locally advanced unresectable or metastatic/recurrent SCCHN and currently receiving a checkpoint inhibitor (anti-PD1 and anti-PD-L1 agents). a. Eligible patients currently receiving a checkpoint inhibitor must be considered by Investigator to have the potential to derive clinical benefit from continued treatment with pembrolizumab.	Have histologically or cytologically documented locally advanced unresectable or metastatic/recurrent SCCHN and meet the criteria of either Cohort A or B. **Cohort A**: Patients with Ongoing CPI Therapy a. Patients currently receiving a checkpoint inhibitor (anti-PD1 and anti-PD-L1 agents). b. Patients currently receiving a CPI must be considered by Investigator to have the potential to derive clinical benefit from	Updated to account for new cohort.

		b. Based on RECIST 1.1/iRECIST criteria on current checkpoint inhibitor treatment (prior to initiation of this study), patients must have a best response of stable disease (SD) or first evidence of progressive disease (PD) after a minimum of 12 weeks of a checkpoint inhibitor. c. Patients receiving first-line pembrolizumab monotherapy prior to this study must be PD-L1 positive. d. Patients on other checkpoint inhibitor therapy than pembrolizumab must be willing to switch over to pembrolizumab therapy.	continued treatment with pembrolizumab. c. Based on RECIST 1.1/iRECIST criteria on current CPI treatment (prior to initiation of this study), patients must have a best response of stable disease (SD) or first evidence of progressive disease (PD) after a minimum of 12 weeks of a CPI. d. Patients on other CPI therapy than pembrolizumab must be willing to switch over to pembrolizumab therapy. **Cohort B**: Patients without Previous CPI Therapy a. Patients must be checkpoint inhibitor naïve (anti-PD1 and anti-PD-L1 agents) b. Patients should receive study treatment as first line (PD-L1 positive) or as second line (PD-L1 negative) systemic therapy in the advanced/metastatic setting.	

Synopsis, 6	Exclusion Criteria	10. Active or history of autoimmune disease or immune deficiency, including but not limited to myasthenia gravis, myositis, autoimmune hepatitis, systemic lupus erythematosus, rheumatoid arthritis, inflammatory bowel disease, vascular thrombosis associated with anti-phospholipid syndrome, Wegener granulomatosis with polyangiitis, Sjögren's syndrome, Guillain-Barrè syndrome, multiple sclerosis, vasculitis, or glomerulonephritis (See protocol Appendix A: PREEXISTING AUTOIMMUNE DISEASE for a more comprehensive list of autoimmune diseases and immune deficiencies) • Patients with history of autoimmune-related hypothyroidism on a stable dose of thyroid replacement hormone as well as patients with adrenal insufficiency may be eligible for this trial • Patients with controlled Type I diabetes mellitus on a	Active autoimmune disease that has required systemic treatment in the past 2 years (i.e. with use of disease modifying agents, corticosteroids or immunosuppressive drugs). Replacement therapy (e.g., thyroxine, insulin, or physiologic corticosteroid replacement therapy for adrenal or pituitary insufficiency, etc.) is not considered a form of systemic treatment.	Simplified exclusion criteria for previous autoimmune diseases.

		stable dose of insulin regimen may be eligible for this trial		
Synopsis	Trial Schedule of Events Pembrolizumab Schedule – Every 3 & 6 Weeks	SNS Dosing Schedule for Pembro Q6 weeks Day 0, Week 3, Week 6, Week 12, etc.	SNS Dosing Schedule for Pembro Q6 weeks Day 0, Week 3, Week 6, Week 9, etc. <u>Q6W Pembro</u> After week 9, the pembrolizumab and SNS-301 visits will not coincide. The SNS-301 dosing should not be adjusted. The investigator may choose to give a 3-week dose (i.e., pembrolizumab 200 mg) in order for the visits to align. The investigator should consult the sponsor if there are questions regarding aligning the study treatment schedule	SNS-301 dosing schedule updated to administer same SNS-301 regimen regardless of pembrolizumab dosing regimen.
Synopsis	Trial Schedule of Events	Anticoagulants - After week 9, Q6 w until week 45, thereafter Q 12 w	<u>Q3W Pembro</u> Anticoagulants - At week 12 then, Q6w until week 45, thereafter Q12w <u>Q6W Pembro</u> Anticoagulants - At week 12 then, Q6w until week 42, thereafter Q12w	Changed schedule to line up with SNS-301 dosing.
Synopsis, 9.1.1, 9.2.14.2	Trial Schedule of Events - Pembrolizumab Schedule – Every 3 & 6 Weeks, Tumor	Tumor Imaging RECIST/iRECIST - Q6w from Day 0 for first 54 weeks (~12 months), there after Q12w PD-L1 – Day 0	Tumor Imaging RECIST/iRECIST - Q6w from Day 0 until~12 months, there after Q12w PD-L1 – Screening	Tumor imaging should be at approximately 12 months from Day 0.

	Assessment, Tissue	Blood Samples for immunology assessments - At week 12 and Q12w thereafter until disease progression as well as at disease progression Tumor specimen - At first evidence of disease progression	Blood Samples for immunology assessments - At week 12, then Q6 weeks until Week 36 and Q12w thereafter until disease progression as well as at disease progression Tumor specimen - Up to 2 optional biopsies and at disease progression	PD-L1 should be done at screening since CPI naïve patients are allowed onto the study. Increase the number of blood draws to allow further evaluations of the immunogenicity of the phage and tumor associated antigen (ASPH), and the dynamics thereof. Increased optional biopsies in select cases of special interest to further understand how study treatment affects the patient's tumor.
Synopsis	Trial Schedule of Events	If the first dose of SNS-301 is given one week before or one week after pembrolizumab vital signs will be collected within 60	Deleted	This statement was included in error.

	Pembrolizumab Schedule – Every 3 & 6 Weeks	minutes before the injection and at 30 (± 5) minutes after the injection.		
Synopsis	Trial Schedule of Events Pembrolizumab Schedule – Every 6 Weeks		Anticoagulants - after week 12, Q6w until week 42, thereafter Q12w	Updated to reflect the 6W pembrolizumab dosing schedule.
3.1.2	Pre-Clinical, Clinical Trials and Other Ongoing Trials	The Phase 2 Study (SNS-301-2-2) of SNS-301, 1 x 1011 administered ID, added to pembrolizumab is currently ongoing. As of the database cutoff (23 July 2020), the study has enrolled 9 patients with ASPH positive locally advanced unresectable or metastatic/recurrent squamous cell carcinoma of the head and neck (SCCHN). Of the 9 patients enrolled 7 (77.8%) experienced a TEAE, however, majority of the reported TEAEs were mild (Grade 1) and not related to study treatment. There were 2 Grade 3 TEAEs (Dehydration and Hypertension) and only Grade 3 Dehydration was assessed as related to study treatment. There were 2 SAEs (Grade 3 Dehydration and Grade 1	The Phase 1/2 Study (SNS-301-2-2) of SNS-301, 1 x 10^{11} administered ID, added to pembrolizumab is currently ongoing. As of the database cutoff (29 October 2020), the study has enrolled 11 patients with locally advanced unresectable or metastatic/recurrent squamous cell carcinoma of the head and neck (SCCHN). Of the 11 patients enrolled 9 (81.8.8%) experienced a TEAE, however, majority of the reported TEAEs were mild (Grade 1) and not related to study treatment. There were 3 Grade 3 TEAEs related to study treatment experienced by 2 patients: rash, electrocardiogram QT prolongation and dehydration. There were 4 SAEs reported for 3 patients: Grade 3 dehydration, G3 electrocardiogram QT prolongation, Grade 2 Systemic Inflammatory Response Syndrome, G2 hemoptysis, G2 malnutrition/dehydration. There	Updated data for this clinical trial.

		Systemic Inflammatory Response Syndrome). There were no DLTs, Grade 4, or fatal events reported to date.	were no DLTs, Grade 4, or fatal events reported to date.	
3.2	Rationale	Anti-PD-1 antibodies including nivolumab and pembrolizumab can induce durable remissions in 13-18% of patients with SCCHN, but the majority of patients fail to respond due to inadequate intra-tumoral immune cell infiltration. Other checkpoint inhibitors currently in clinical trials as combination therapy or monotherapy demonstrate limited responses as well, thus underscoring the importance of allowing patients who are unresponsive to checkpoint inhibitor therapy the option to participate in a clinical trial, such as the study sponsored by Sensei Biotherapeutics. Sensei Biotherapeutics plans to develop SNS-301 in addition to pembrolizumab in a study targeting patients with SCCHN that is resistant to CPI which is a population with high unmet medical need. The overall goal is to improve clinical outcomes in patients who have failed to respond to CPI therapy.	Anti-PD-1 antibodies including nivolumab and pembrolizumab can induce durable remissions <20% of patients with recurrent or metastatic SCCHN in first or subsequent line setting and after platinum-containing chemotherapy[8], but the majority of patients fail to respond due to inadequate intra-tumoral immune cell infiltration. Other checkpoint inhibitors (CPI; defined as anti-PD-1/anti-PD-L1 therapy) currently in clinical trials as combination therapy or monotherapy demonstrate limited responses as well, thus underscoring the importance of allowing patients who are unresponsive to CPI therapy the option to participate in a clinical trial, such as the study sponsored by Sensei Biotherapeutics. Sensei Biotherapeutics plans to develop SNS-301 in addition to pembrolizumab in a study targeting two different patient cohorts: patients that did not achieve objective responses after at least 12 weeks of CPI and patients that are CPI naïve. The overall goal is to improve clinical outcomes in patients with locally advanced or	Updated to provide rationale to include CPI naïve patients.

			metastatic SCCHN receiving CPI therapy.	
3.2.1.1	Unmet Medical Need for Patients with SCCHN	There are multiple other ICIs that are in clinical trials (e.g., atezolizumab, durvalumab, avelumab, etc.) and these agents as combination therapy or monotherapy demonstrate limited responses as well, thus underscoring the importance of allowing these unresponsive checkpoint inhibitor therapy patients to participate in trials such as the study sponsored by Sensei Biotherapeutics. In order to provide an option to the majority of SCCHN patients who do not respond to checkpoint inhibitors, Sensei will allow inclusion of patients who received widely investigated ICIs (anti-PD1, anti-PD-L1 agents) as part of clinical trials as long as patients meet all of the outlined eligibility criteria. All patients enrolled will be switched to pembrolizumab treatment regardless of which ICI therapy the patient was receiving previously. However, patients that do not respond to immune checkpoint inhibitors continue to represent a significant number of the	There are multiple other ICIs that are in clinical trials (e.g., atezolizumab, durvalumab, avelumab, etc.) and these agents as combination therapy or monotherapy demonstrate limited responses as well, thus underscoring the importance of allowing these patients to participate in trials that potentially can enhance the efficacy of CPI therapy such as the study sponsored by Sensei Biotherapeutics. In order to provide an option to the majority of SCCHN patients who do not respond to CPI therapy, Sensei will allow inclusion of patients who received widely investigated ICIs (anti-PD1, anti-PD-L1 agents) as part of clinical trials as long as patients meet all of the outlined eligibility criteria. All patients enrolled will be switched to pembrolizumab treatment regardless of which ICI therapy the patient was receiving previously. Furthermore, given the modest response rates to CPI therapy even in patients with PD-L1 positive tumors in the first line setting (19%, Keynote-48), Sensei will allow enrollment to a second cohort with patients that are CPI therapy naïve.	Updated to provide rationale to include CPI naïve patients.

		SCCHN patients and thus remain a high unmet medical need population with a median OS of 12 months or less. Furthermore, for patients who have also previously received and progressed on platinum-based chemotherapy, the median OS is less than 6 months. The need to develop novel clinically meaningful therapies for these patients. Sensei Bio plans to evaluate SNS-301 in patients with SCCHN who have failed to respond to CPI therapy, but investigators feel that continued treatment with a CPI and another targeted agent may provide clinical benefit for these patients.		
3.2.1.2	ASPH Expression Testing in SCCHN	As of 16 July 2020, 26 additional archived tissue samples have been analyzed from this study. All 26 samples were found to be ASPH positive as assessed by a CLIA validated IHC assay from Fred Hutchinson Cancer Center.	As of 29 Oct 2020, 30 additional archived tissue samples have been analyzed from this study. All 30 samples were found to be ASPH positive as assessed by a CLIA validated IHC assay from Fred Hutchinson Cancer Center.	Updated with current data.
3.2.3	Rationale for Dose Selection/Regimen	In summary, SNS-301 was considered to be well tolerated at all dose levels evaluated with no DLTs or grade 4/5 AEs noted. Three patients experienced a total	Deleted	Deleted text from the Rationale for Dose Selection/Regim

		of five adverse events considered by investigators to be at least possibly related to study drug and all AEs were considered to ≤ grade 3. One patient experienced an AE in the form of migratory arthralgia that was attributed as possibly related to the study drug given that the patient was diagnosed with RF+ rheumatoid arthritis and the immunization contributed to the pain flare. One patient 001-004 in the high dose cohort experienced mild erythema at the injection site which resolved within 3 days. There was one serious treatment related TEAE reported. The patient (004-003), a 72-year-old, white male experienced positional vertigo that was deemed definitely not related by the reporting Investigator. No other noteworthy AEs have been observed..		en section. Safety is addressed in Section 3.1.2.
7.1.2.1	SNS Dosing	SNS-301 Dosing Schedule when pembrolizumab dosing at 3 week intervals: Patients will receive SNS-301 on a staged schedule starting every three weeks for	Patients will receive SNS-301 on a staged schedule starting every three weeks for four doses, every six	SNS-301 dosing schedule updated to administer same SNS-301

		four doses, every six weeks for 6 doses and thereafter every twelve weeks. SNS-301 Dosing Schedule when pembrolizumab dosing at 6 week intervals: Patients will receive SNS-301 on Day 0, Week 3, Week 6, Week 12 then every six weeks for 6 doses and thereafter every twelve weeks.	weeks for 6 doses and thereafter every twelve weeks. When pembrolizumab and SNS-301 are dosed on the same day, SNS-301 will be dosed approximately 1 hour after IV infusion of pembrolizumab for the first dose. Subsequent doses of SNS-301 and pembrolizumab can be dosed in any order.	regimen regardless of pembrolizumab dosing regimen.
9.2.1, 9.2.13	Demographics and Medical History, PD-L1 Testing	PD-L1 status will also be collected, if available. New	Deleted Patients who are CPI naïve must be PD-L1 positive prior to entry onto the study.	PD-L1 status will be collected for all patients
9.2.14.1.1.4, 9.2.14.1.2..1, 9.2.14.1.2.2, 9.2.14.1.2.2.1	Other tumor and immune biomarkers, Immunophenotyping, T-cells, T-cell profiling	miRNA profiling of pre and post-treatment serum and/or plasma samples may also be performed to predict treatment efficacy. Immunophenotyping will be performed by flow cytometry to monitor the levels of all immune cells including B-cells, CD4+ T-cells, CD8+ T-cells, NK cells, monocytes, neutrophils, eosinophils and myeloid derived suppressor cells (MDSCs). In patients mounting an active immune response it is expected for	Deleted	Analyses will not be done on blood samples.

		the percentages of certain cell types to increase. T-cells form the cellular arm of the immune response. Vaccination with SNS-301 is expected to result in maturation and activation of ASPH specific T-cells. The cellular immune response can generally be characterized as having to primary arms, CD4+ helper T-cell responses and CD8+ cytotoxic T-cell responses. In preclinical studies as well as the phase I clinical trial of SNS-301, activation of both T-cell subsets was noted. Furthermore, immune responses are often hampered by the presence of regulatory T-cells which may downregulate T-cell responses. Multi-parameter flow cytometry will be used to characterize the various subsets of T-cells in peripheral blood during the entire course of the study. Flow cytometric assays will also be utilized to assess the presence of cells that are known to play a role in immune suppression and may include an examination of the influence of these cells on the induction or expansion of an immune response after immunotherapy. Markers that may be used for this purpose include CD3, CD16, CD19,		

		CD20, CD56, CD11b, CD14, CD15, CD33 and HLA-DR. These markers may change relative to new data becoming available that is informative for this assessment.		
9.3.10	Adverse Events of Special Interest	Administration site reaction will be considered an AESI.	Systemic administration site reactions will be considered an AESI.	Clarified to address systemic reactions versus mild local reactions.
10.1	Statistical Hypotheses	New	Cohort B Thirty (30) patients will be enrolled in a two-stage design, with 15 patients in the first stage and 15 patients in the second stage to assess the null hypothesis that the objective response rate per iRECIST is 13.3%, versus the alternative hypothesis that the ORR is 29%, as described in Section 10.2.	Updated to include statistics for the CPI naïve patient population.
10.2	Sample Size Determination	Among all 30 patients, for adverse events that occur at an incidence of 9.5% the probability of observing at least one event is approximately 95%.	Among all 60 patients, for adverse events that occur at an incidence of 5% the probability of observing at least one event is approximately 95%. The sample size for each cohort and stage is based on Simon's two-stage design for tests of one proportion.	Updated to include statistics for the CPI naïve patient population.

			Cohort A At the second stage analysis, if at least 4 responses are observed out of 30 total patients, the null hypothesis will be rejected and further research considered warranted. The overall power for objective response rate at 12 weeks is 80%. The overall type I error, the chance of incorrectly rejecting the null hypothesis is 6% (targeted alpha of 0.10). The probability of stopping at the first stage under the null hypothesis is 46%. The operating characteristics of this design are calculated using the exact binomial distribution. Cohort B To evaluate the primary endpoint of objective response rate per iRECIST at 12 weeks with a null hypothesis of an objective response rate (ORR) of 13.3% and an alternative hypothesis of an ORR of 29%, 30 patients in a two-stage design will be enrolled, with 15 patients in the first stage and 15 patients in the second stage. At the first stage analysis if at least 2 responses are observed out of 15 patients, the study may continue through the second stage. At the	

			second stage analysis, if at least 7 responses are observed out of 30 total patients, the null hypothesis will be rejected and further research considered warranted. The overall power for objective response rate at 12 weeks is 80.1%. The overall type I error, the chance of incorrectly rejecting the null hypothesis is 9.2% (targeted alpha of 0.10). The probability of stopping at the first stage under the null hypothesis is 38.8%. The operating characteristics of this design are calculated using the exact binomial distribution.	
10.4.1	General Methods	New	All summarizations will be presented separately for each cohort, and over all subjects combined.	Updated to include statistics for the CPI naïve patient population.
10.4.2	Efficacy Analyses	ORR is defined as the proportion of patients with a confirmed best response of iCR or iPR by iRECIST. Objective response rate will be estimated, and 95% CI based on the exact binomial distribution will be presented, including number and percent of patients in each overall response category.	ORR is defined as the proportion of patients with a confirmed best response of iCR or iPR by iRECIST. Objective response rate will be estimated, and 90% CI based on the exact binomial distribution will be presented by cohort and overall, including number and percent of patients in each overall response category.	Clarified the confidence interval.

12	Reference List	New	8. Burtness, B., Harrington, K., Greil, R., Soulières, D., et al. "Pembrolizumab alone or with chemotherapy versus cetuximab with chemotherapy for recurrent or metastatic squamous cell carcinoma of the head and neck (KEYNOTE-048): a randomised, open-label, phase 3 study." Lancet. 2019 October 31; 394: 1915–28.	Added reference for Keynote-048.
Appendix A	Pre-existing Autoimmune Disease		Deleted	Simplified exclusion criteria for previous autoimmune diseases.
Multiple	Multiple	NA	NA	Updated typos, provided additional clarification, abbreviations

Changes to Amended Protocol Version 3.0 Dated July 24, 2020 includes Administrative Letters (October 9, 2019 & April 3, 2020 {University of California San Francisco only})				
Section #	**Section Title**	**Old Text**	**New Text**	**Rationale for Change**
Multiple	Title, Inclusion Criteria, Rationale for the Trial and Selected Subject Population, Study Population, Screen Failures	An Open-Label, Multi-Center Trial of SNS-301 Added to Pembrolizumab in Patients with ASPH+ Locally Advanced Unresectable or Metastatic/Recurrent Squamous Cell Carcinoma of the Head and Neck	An Open-Label, Multi-Center Trial of SNS-301 Added to Pembrolizumab in Patients with Locally Advanced Unresectable or Metastatic/Recurrent Squamous Cell Carcinoma of the Head and Neck	Given that 26 of 26 obtained tumor samples for pre-screening were positive for ASPH per IHC, the requirement for ASPH + has been dropped. ASPH will still be analyzed, but patients can be enrolled prior results received.
	Sponsors Protocol Signature Page	Ildiko Csiki	Marie-Louise Fjaellskog	Personnel change
Multiple	Synopsis, Pembrolizumab Dosing	Pembrolizumab 200 mg every 3 weeks	Pembrolizumab 200 mg every 3 weeks or 400 mg every 6 weeks	To allow patients more flexibility in dosing as per Merck's expanded pembrolizumab usage (refer to USPI).
Multiple	Trial Population, Inclusion Criteria, Rationale, Overall Design	The trial population consists of patients with ASPH+ locally advanced unresectable or metastatic/recurrent SCCHN who are currently receiving pembrolizumab or nivolumab	The trial population consists of patients with locally advanced unresectable or metastatic/recurrent SCCHN who are currently receiving a checkpoint inhibitor therapy	To expand to all previous PD-1/PDL-1inhibitors

Multiple	Synopsis, Rationale for Dose Selection/ Regimen, SNS-301 Dosing	SNS-301 will be administered intradermally using the 3M micro-needle device every 3 weeks (± 3 days) for 4 doses then every 6 weeks (±3 days) for 6 additional doses, thereafter every 12 weeks (±3 days) until confirmed disease progression, unacceptable toxicity, deemed intolerable by the investigator or up to 24 months in patients without disease progression.	SNS-301 will be administered intradermally using the 3M micro-needle device. The dosing schedule will be as follows: a. When pembrolizumab is given every three weeks: Day 0, Week 3, Week 6, Week 9 then every 6 weeks (±3 days) for 6 additional doses, thereafter every 12 weeks (±3 days) until confirmed disease progression, unacceptable toxicity, deemed intolerable by the investigator or up to 24 months in patients without disease progression. b. When pembrolizumab is given every six weeks: Day 0, Week 3, Week 6 and Week 12, then every 6 weeks (±3 days) for 6 additional doses, thereafter every 12 weeks (±3 days) until confirmed disease progression, unacceptable toxicity, deemed intolerable by the	SNS-301 dosing updated to account for either the every 3 or 6 week pembrolizumab dosing schedule

			investigator or up to 24 months in patients without disease progression.	
Synopsis , 5.2, 9.3.9	Stopping Rules, Overall Design, Stopping Rules	The trial will be stopped if any adverse experience of any related death, grade 4 autoimmune toxicity or any grade 4 toxicity that is furthermore considered possibly, probably or definitely related to study drug should occur. Any related death, grade 4 autoimmune toxicity and any grade 4 toxicity that is furthermore considered to be possibly, probably or definitely related to study drug will be submitted will be submitted to regulatory agencies within the expedited safety reporting criteria.	The trial will be stopped if any adverse experience of any related death, grade 4 autoimmune toxicity or any grade 4 toxicity that is considered to have a causal relationship to study drug. Any related death, grade 4 autoimmune toxicity and any grade 4 toxicity that is considered to have a causal relationship to study drug will be submitted to regulatory agencies within the expedited safety reporting criteria.	Clarification
Synopsis	Trial Schedule of Events		1. Deleted: Urine immunology sample 2. Added: PDL-1 testing 3. Added: The Sponsor may request digitized	1. Sample determined to be unnecessary 2.PDL-1 added to understand patient characteristics and interpret objective

			scans from patients during the study. 4. If the patient is unable to have samples obtained at the protocol specified visit (i.e., COVID19 related) then an unscheduled sample may be drawn 5. Added: Pembrolizumab Schedule – Every 6 weeks	responses to study treatment 3. In order to assess tumor responses imaging scans may be requested 4.To allow flexibility for missed visit due to COVID19 or other reasons
3.1.2	Pre-Clinical, Clinical Trials and Other Ongoing Trials		1.Deleted: Pre-Clinical section 2.Added: Data for this study	1.Refer to Investigators Brochure for updated information 2. Emerging clinical data added.
3.2.1.1	Unmet Medical Need for Patients with SCCHN		Over the last several years advancements regarding the therapeutic role of ICIs led to the approval of pembrolizumab and nivolumab for SCCHN; however, response rates are fairly low in the first and second line metastatic SCCHN population. There are multiple other ICIs that are in clinical	Rationale for including all PD-1/PD-L1 inhibitors

			trials (e.g., atezolizumab, durvalumab, avelumab, etc.) and these agents as combination therapy or monotherapy demonstrate limited responses as well, thus underscoring the importance of allowing these unresponsive checkpoint inhibitor therapy patients to participate in trials such as the study sponsored by Sensei Biotherapeutics. In order to provide an option to the majority of SCCHN patients who do not respond to checkpoint inhibitors, Sensei will allow inclusion of patients who received widely investigated ICIs (anti-PD1, anti-PD-L1 agents) as part of clinical trials as long as patients meet all of the outlined eligibility criteria. All patients enrolled will be switched to pembrolizumab treatment regardless of which ICI therapy the patient was receiving previously.	

3.2.1.2	ASPH Expression Testing in SCCHN		Added: As of 16 July 2020, 26 additional archived tissue samples have been analyzed from this study. All 26 samples were found to be ASPH positive as assessed by a CLIA validated IHC assay from Fred Hutchinson Cancer Center.	Provide update on the ASPH testing for this study
7.5	Dose Modification and/or Interruption		Added: If a patient is unable to receive study treatment (e.g., due to COVID19) the dosing interval can be extended up to 42 days after consultation with the Sponsor and the rationale to be documented.	To allow flexibility for missed visit due to COVID19 or other reasons
9.1.1	Tumor Assessment		Added: The Sponsor may request digitized scans from patients to confirm response.	In order to assess tumor responses imaging scans may be requested
9.2.13	PD-L1 Testing		Added: If the patient's PD-L1 status is unknown, they should be tested, preferably by 22C3 IHC. The results do not need to	PDL-1 added to understand patient characteristics and interpret objective responses

			be known before the patient receives study treatment. If possible, for patients that started study treatment prior to Amendment 2/Version 3.0, retrospective testing should be done.	
10.2.13.1	Urine		Deleted	Sample determined to be unnecessary
10.2.13.2 .2.2, 10.2.13.2 .2.2.1, 10.2.13.2 .2.2.2	B-cells, B-cell profiling, ASPH specific B cells		Deleted	Assays determined to be unnecessary
9.2.14.22	ASPH Immuno-histochemistry (IHC) assay	ASPH testing will be done by immunohistochemistry on either fresh or archival tumor tissue. Additional preparation of the slides will be performed at Sensei Biotherapeutics or designee. Tissue will be deparaffinized and rehydrated, quenched with hydrogen peroxide and blocked with horse serum. Slides are stained	ASPH testing will be done by immunohistochemistry on either fresh or archival tumor tissue. Samples will be analyzed at Fred Hutchinson Cancer Center via a CLIA validated assay	Deleted detailed instruction on analysis in the protocol.

		overnight at 4 °C with an ASPH-specific murine monoclonal or a non-relevant mouse IgG as a negative control. Detection employs a secondary anti-mouse antibody and a chromogenic substrate. Slides are counterstained with hematoxylin and cover slipped. Semiquantitative analysis of staining intensity and distribution of ASPH levels is evaluated according to the following scale (0, negative; 1+, moderate; 2+, strong; and 3+, very strong immunoreactivity).		
9.3.1	Definition of Adverse Event (AE)	Adverse event is defined as any untoward medical occurrence associated with the use of a drug in humans, whether or not considered drug related and occurs after the patient is given the first dose of study drug. Any AE that occurs prior to the first dose is part of the medical history.	Adverse event is defined as any untoward medical occurrence associated with the use of a drug in humans, whether or not considered drug related. Any AE that occurs prior to the first dose is part of the medical history. AEs will be collected from the time of informed consent until 30 days after the last dose	Clarification on when to initiate collection of adverse events

			of study treatment or until initiation of another anti-cancer therapy, whichever occurs first.	
9.3.2.2	Relationship to Study Medication	Listed categories: of Not Related Unlikely Related, Possibly Related, Probably Related and Related	Listed categories: Not Related and Related	Streamlined the choices for relationship to study medication
10.4.2	Efficacy Analysis	DCR: proportion of patients with SD or better (PR and CR	DCR: proportion of patients with SD or better (PR and CR). SD for at least six months	Include timeframe for stable disease
Multiple	Multiple	NA	NA	Updated typos, provided additional clarification

Changes to Amended Protocol Version 2.0 Dated June 27, 2019				
Section #	**Section Title**	**Old Text**	**New Text**	**Rationale for Change**
1	Summary of Changes	New	Summary of changes from final protocol to amendment 1	To assist sites in identifying changes to the protocol.
2.1, 5.1.1, 6.1	-Protocol Title -Signature Page -Clinical Protocol Synopsis -Primary Objectives -Research Hypotheses	An Open-Label, Multi-Center Trial of SNS-301 Added to Pembrolizumab in Previously Treated Patients with ASPH+ Locally Advanced Unresectable or Metastatic/Recurrent Squamous Cell Carcinoma of the Head and Neck	An Open-Label, Multi-Center Trial of SNS-301 Added to Pembrolizumab in Patients with ASPH+ Locally Advanced Unresectable or Metastatic/Recurrent Squamous Cell Carcinoma of the Head and Neck	Removed previously treated patient population to allow for patients receiving pembrolizumab as first line treatment to be consistent with the new standard of care.

2.1, 6.2	-Clinical Protocol Synopsis -Overall Design	The trial population consists of previously treated patients with ASPH+ locally advanced unresectable or metastatic/recurrent SCCHN who are currently receiving pembrolizumab and have not had evidence of disease progression within the first 12 weeks of pembrolizumab therapy. Patients must have received platinum-based therapy with evidence of disease progression or had intolerable toxicity to platinum-based chemotherapy prior to initiation of pembrolizumab.	The trial population consists of patients with ASPH+ locally advanced unresectable or metastatic/recurrent SCCHN who are currently receiving pembrolizumab or nivolumab therapy. Patients must have a best response of stable disease (SD) or first evidence of progressive disease (PD) after a minimum of 12 weeks of pembrolizumab or nivolumab therapy. Patients may or may not have received platinum-based therapy with evidence of disease progression prior to initiation of pembrolizumab or nivolumab. Patients receiving first-line pembrolizumab monotherapy prior to this study must be PD-L1 positive. Patients receiving nivolumab will be switched over to pembrolizumab at the time of entering this study.	Added previous treatment to also include nivolumab to be consistent with treatment paradigms within participating institutions. Dropped the requirement for previous platinum-based therapy to allow for first line pembrolizumab treatment.
2.1, Table 1	-Clinical Protocol Synopsis -Time Schedule of Events	Ideally, a pre-treatment tissue sample obtained after initiation of ongoing pembrolizumab therapy and first dose of SNS-301 and pembrolizumab on this current clinical trial will be collected.	Ideally, a pre-treatment tissue sample obtained after initiation of ongoing pembrolizumab or nivolumab therapy and first dose of SNS-301 and pembrolizumab on this current clinical trial will be collected.	Expanded previous PD-1 therapy to include both pembrolizumab and nivolumab to allow for standard of care paradigms at clinical sites.
2.1, Table 1	-Clinical Protocol Synopsis -Time Schedule of Events	An on-treatment biopsy is required when medically feasible, after the second or third	An on-treatment biopsy is required when medically feasible, after the third dose of	Clarified the biopsy timeframe.

		dose of the study treatment, treatment around week 6.	the study treatment, treatment week 6.	
2.1	Clinical Protocol Synopsis	New follow up procedure	A pregnancy test is also required for patients of WOCBP every 3 months.	To track pregnancy during the survival follow up period.
2.1, 6.2	-Clinical Protocol Synopsis -Overall Design	If a second of these first six patients experiences a DLT within the first six weeks, enrollment will stop, and the Sponsor's medical monitor, in addition to the PI and Investigator(s) at the patients' site(s) will discuss the case, and a decision will be made whether to modify the trial such as continue dosing respective patient at lower dose of SNS-301, or to cease further enrollment.	If a second of these first six patients experiences a DLT within the first six weeks, enrollment will stop, and the Sponsor's medical monitor, in addition to the PI and Investigator(s) at the patients' site(s) will discuss the case, and a decision will be made whether to modify the trial or to cease further enrollment.	Delete allowance of lowering SNS-301 dose since dose modifications are not allowed.
2.1, 6.2, 10.3.9	-Clinical Protocol Synopsis -Overall Design -Stopping Rules	New	Stopping Rules The trial will be stopped if any adverse experience of any related death, grade 4 autoimmune toxicity or any grade 4 toxicity that is furthermore considered possibly, probably or definitely related to study drug should occur. Any related death, grade 4 autoimmune toxicity and any grade 4 toxicity that is furthermore considered to be possibly, probably or definitely	To implement stopping rules to protect patients.

			related to study drug will be submitted will be submitted to regulatory agencies within the expedited safety reporting criteria.	
2.1, 7.0	-Clinical Protocol Synopsis -Inclusion Criteria	3. Have histologically or cytologically documented locally advanced unresectable or metastatic/recurrent ASPH+ SCCHN and currently receiving pembrolizumab. Patients must have received platinum-based therapy with evidence of disease progression or had intolerable toxicity to platinum-based chemotherapy prior to initiation of pembrolizumab. a. Eligible patients currently receiving pembrolizumab must be considered by Investigator to have the potential to derive clinical benefit from continuing treatment with pembrolizumab. b. Based on RECIST version 1.1 criteria on current pembrolizumab treatment (prior to initiation of this study),	3. Have histologically or cytologically documented locally advanced unresectable or metastatic/recurrent ASPH+ SCCHN and currently receiving pembrolizumab or nivolumab. a. Eligible patients currently receiving pembrolizumab or nivolumab must be considered by Investigator to have the potential to derive clinical benefit from continued treatment with pembrolizumab. b. Based on RECIST 1.1/iRECIST criteria on current pembrolizumab or nivolumab treatment (prior to initiation of this study), patients must have a best response of stable disease (SD) or first evidence of progressive disease (PD) after a minimum of 12 weeks of pembrolizumab or nivolumab therapy. c. Patients receiving first-line pembrolizumab monotherapy prior to this study must be PD-L1 positive.	Added previous treatment to also include nivolumab to be consistent with treatment paradigms within participating institutions. Dropped the requirement for previous platinum-based therapy to allow for first line pembrolizumab treatment.

		patients must have a best response of confirmed stable disease (SD) or progressive disease (PD) after a minimum of 12 weeks of pembrolizumab therapy.	d. Patients on nivolumab therapy must be willing to switch over to pembrolizumab therapy.	
2.1, 6.2, 7.0	-Clinical Protocol Synopsis -Inclusion Criteria -Overall Design	8. Be willing to provide a pre-treatment tissue sample obtained after initiation of ongoing pembrolizumab therapy and first dose of SNS-301 and pembrolizumab on this current clinical trial. Subjects are requested to provide archival tissue from a prior biopsy or surgery that is treatment –naïve including prior 1) chemotherapy, radiation and 2) anti-PD(L)-1 treatment-naïve, pending availability. An on-treatment biopsy is required when medically feasible, after the second dose of the study treatment. For patients who progress as determined per RECIST1.1/iRECIST criteria, an optional biopsy will be obtained at the time of disease progression.	8. Be willing to provide a pre-treatment tissue sample obtained after initiation of ongoing pembrolizumab or nivolumab therapy and first dose of SNS-301 and pembrolizumab on this current clinical trial unless clinically contra-indicated per treating physician. Patients unable to provide pre-treatment biopsy while on CPI will be evaluated on a case-by-case basis for enrollment pending Sponsor consultation. Patients are requested to also provide archival tissue from a prior biopsy or surgery that is treatment –naïve including prior 1) chemotherapy, radiation and/or 2) anti-PD(L)-1 treatment-naïve, pending availability. Tissue provided pre-treatment (fresh or archival) will be used to determine ASPH expression and eligibility for the trial. Additionally, an on-	Added previous nivolumab treatment. Clarified collection of fresh versus archived biopsy for enrollment purposes and timing of on treatment biopsy.

			treatment biopsy is required unless clinically contraindicated, after the third dose of study treatment at week 6.	
2.1	Clinical Protocol Synopsis	Albumin ≥ 3.0 g/dL	Deleted	Deleted for consistency. Albumin is not required for eligibility.
2.1, 7.0	-Clinical Protocol Synopsis -Exclusion Criteria	21. Treatment with systemic immunomodulating agents (including but not limited to IFNs, IL-2, ipilimumab) within 6 weeks or five half-lives of the drug, whichever is shorter, prior to first dose, excluding current pembrolizumab therapy.	21. Treatment with systemic immunomodulating agents (including but not limited to IFNs, IL-2, ipilimumab) within 6 weeks or five half-lives of the drug, whichever is shorter, prior to first dose, excluding current pembrolizumab or nivolumab therapy.	Added previous nivolumab treatment.
Table 1	Trial Schedule of Events	New	Anticoagulant specific drug and/or anticoagulant factor Xa levels obtained at Screening, Day 0, Week 3, Week 6, Week 9, Q6W until Week 45 , thereafter Q12W. For patients on anticoagulants only	To monitor patients on anticoagulation therapy.
Table 1	Trial Schedule of Events	New	Pregnancy test at Discontinuation Visit and Follow Up	To track pregnancy at discontinuation and during the survival follow up period.
Table 1	Trial Schedule of Events	TSH, T3 and T4	TSH, T3 and Free T4	For consistency for on treatment thyroid testing.

Table 1	Trial Schedule of Events	Patients who discontinue early from study treatment for progression will be asked to return to the clinic within 30 days after the last dose for a treatment discontinuation visit.	Patients who discontinue early from study treatment (i.e., progression, adverse event, etc.), will be asked to return to the clinic within 30 days after the last dose for a treatment discontinuation visit.	Clarified the treatment discontinuation visit for all patients.
Table 1, 10.2.1	-Trial Schedule of Events -Demographics & Medical History	Demographic information includes sex, age, and self-reported race/ethnicity. HPV, EBV, reproductive status and smoking history should also be captured.	Demographic information includes sex, age, and self-reported race/ethnicity. HPV, EBV, reproductive status and smoking/alcohol history should also be captured. PD-L1 status will also be collected, if available.	Added alcohol history and PD-L1 status.
Table 1	Trial Schedule of Events	New footnote "i"	Specific anticoagulant drug and/or anticoagulant factor Xa levels will be obtained only on patients receiving anticoagulant therapy. Drug levels will also be obtained at any time of clinical bleeding. Traditional testing methods can be used for warfarin, heparin (e.g., PT/INR, aPTT, TT). Novel oral anticoagulants may require anticoagulant factor Xa levels or anticoagulant drug specific level testing. See sections Concomitant Medications & Guidance for Investigators for Patients on Anti-coagulants for additional information.	To monitor patients on anticoagulation therapy.

Table 1, 10.2.4	-Trial Schedule of Events -Vital Signs	If clinically indicated, vital signs should be recorded during the infusion at 15, 30, 45, and 60 minutes (± 5 minutes for all timepoints) during the infusion, and 30 (± 10) minutes after the infusion. For subsequent infusions, vital signs will be collected within 60 minutes before the infusion and at 30 (± 5) minutes after the infusion.	If clinically indicated, vital signs should be recorded at 15, 30, 45, and 60 minutes (± 5 minutes for all timepoints) after the start of the infusion, and 30 (± 10) minutes after the infusion. For subsequent infusions, vital signs will be collected within 60 minutes before the infusion and at 30 (± 5) minutes after the infusion.	Clarified 45 & 60 minute vitals are after the start of the infusion.
Table 1	Trial Schedule of Events	Eligibility based on ASPH expression will be provided back to the sites within 5 calendar days.	Eligibility based on ASPH expression will be provided back to the sites within 5-8 business days.	Timeline extended to account for ASPH testing process.
2.2	Schema	-Stage 1 review 3-6 patients -Biopsy at PD	Biopsy at PD (arrow)	-Removed Stage 1 review box -Removed arrow for Biopsy at PD box for clarity.
3	Terms, Acronyms, Abbreviations	New	TT- Thrombin Time	New definition.
4.2	Rationale	Sensei Biotherapeutics plans to develop SNS-301 in addition to pembrolizumab in a study targeting patients with refractory SCCHN, a population with high unmet medical need.	Sensei Biotherapeutics plans to develop SNS-301 in addition to pembrolizumab in a study targeting patients with SCCHN that is resistant to CPI which is a population with high unmet medical need.	Changed wording based on patient eligibility.
4.2.1.1	Unmet Medical Need for Patients with SCCHN	New	KEYNOTE-048 (NCT02358031), a randomized, multicenter, three-arm, open label, active controlled trial conducted in 882 patients with metastatic HNSCC who had not previously received systemic	To provide additional background.

			therapy for metastatic disease or with recurrent disease who were considered incurable by local therapies was approved by the FDA in June 2019. Patients were randomized (1:1:1) to receive one of the following treatments: pembrolizumab as a single agent; pembrolizumab, carboplatin or cisplatin, and FU; or cetuximab, carboplatin or cisplatin, and FU. Randomization was stratified by tumor PD-L1 expression (Tumor Proportion Score [TPS] ≥50% or <50%), HPV status according to p16 IHC (positive or negative), and ECOG PS (0 vs 1). PD-L1 expression (TPS and CPS) was determined using the PD-L1 IHC 22C3 pharmDx kit. Overall survival (OS), sequentially tested in the subgroup of patients with CPS ≥20 HNSCC, the subgroup of patients with CPS ≥1 HNSCC and the overall population, was the major efficacy measure. The trial demonstrated a statistically significant improvement in OS in the overall population for patients randomized to pembrolizumab plus chemotherapy compared with cetuximab plus	

			chemotherapy at a pre-specified interim analysis. The median OS was 13.0 months for the pembrolizumab plus chemotherapy arm and 10.7 months for the cetuximab plus chemotherapy arm (HR 0.77; 95% CI: 0.63, 0.93; p=0.0067). Results were similar in the CPS ≥20 subgroup (HR 0.69; 95% CI: 0.51, 0.94) and CPS ≥1 subgroup (HR 0.71; 95% CI: 0.57, 0.88). The trial also demonstrated statistically significant improvements in OS for the subgroups of patients with PD L1 CPS ≥1 HNSCC and PD-L1 CPS ≥20 HNSCC randomized to pembrolizumab as a single agent compared with cetuximab plus chemotherapy. In the CPS ≥1 subgroup, the median OS was 12.3 months for the pembrolizumab arm and 10.3 months for the cetuximab plus chemotherapy arm (HR 0.78; 95% CI: 0.64, 0.96; p=0.0171). For the CPS ≥20 subgroup, the median OS was 14.9 months for the pembrolizumab arm and 10.7 months for the cetuximab plus chemotherapy arm (HR 0.61; 95% CI: 0.45, 0.83; p=0.0015).	

			At the time of the interim analysis, there was no significant difference in OS between the pembrolizumab as a single agent arm and the cetuximab plus chemotherapy arm for the overall population. There were no significant differences in progression-free survival for either pembrolizumab-containing arm compared to the cetuximab plus chemotherapy arm in any population. The most common adverse reactions reported in ≥20% of patients who received pembrolizumab as a single agent in KEYNOTE-048 were fatigue, constipation, and rash. The most common adverse reactions reported in ≥20% of patients who received pembrolizumab in combination with chemotherapy in KEYNOTE-048 were nausea, fatigue, constipation, vomiting, mucosal inflammation, diarrhea, decreased appetite, stomatitis, and cough.	
4.2.1.1	Unmet Medical Need for Patients with SCCHN	However, patients that do not respond to immune checkpoint inhibitors represent a high unmet medical need with a median OS of 6 months or less and there is a high unmet medical need to	However, patients that do not respond to immune checkpoint inhibitors continue to represent a significant number of the SCCHN patients and thus remain a high unmet medical need	Updated based on change in patient population.

		develop novel clinically meaningful therapies for these patients. Sensei Bio plans to evaluate SNS-301 in patients with recurrent/metastatic SCCHN who have failed to respond to CPI therapy in the post-platinum setting.	population with a median OS of 12 months or less. Furthermore, for patients who have also previously received and progressed on platinum-based chemotherapy, the median OS is less than 6 months. The need to develop novel clinically meaningful therapies for these patients remains. Sensei Bio plans to evaluate SNS-301 in patients with SCCHN who have failed to respond to CPI therapy, but investigators feel that continued treatment with a CPI and another targeted agent may provide clinical benefit for these patients.	
4.3	Benefit/Risk	However, the median OS of SCCHN post-platinum progression and refractory to CPI is about 6 months.	The median OS of patients even in the first line metastatic setting who do not respond to CPI is less than 12 months. However, this study may likely enroll who have also previously received and progressed on platinum-based chemotherapy, in which population the median OS is less than 6 months.	Included OS for first line metastatic setting.
8.2.2	Formulation, Appearance, Packaging & Labeling of SNS-301 & Pembrolizumab	New	-… "Caution - Investigational device. Limited by Federal (or United States) law to investigational use." -Sponsor's name and address	Added additional labeling for hMTS device.

8.5	Dose Modification and/or Interruption	If the subject experiences the same toxicity requiring a dose-delay at the subsequent cycle, the subject should be discontinued from study treatment.	If the subject experiences the same grade or higher toxicity requiring a dose-delay at the subsequent cycle, the subject should be discontinued from study treatment. Should there be a clinically significant AE or SAE recorded relating to a patient receiving anticoagulants, such as clinically noted bleeding, administration of SNS-301 will be held until the AE/SAE returns to baseline. Should there be two individual events of SNS-301 interruption for the same patient, then SNS-301 will be discontinued after consultation with the Medical Monitor and Study Sponsor.	Provide guidance on dose interruptions.
10.1.1	Tumor Assessment	New	Beginning with screening, all imaging assessments will be evaluated using RECIST 1.1. On-study imaging assessments will be performed every 6 weeks (Q6W) calculated from the date of therapy initiation and independent of treatment delays. RECIST 1.1 will be used by the site for treatment decisions until the first radiologic evidence of progressive disease (PD). Following the first radiologic evidence of PD by RECIST 1.1, treatment decisions may be made	Clarified on study assessments utilizing iRECIST.

			by using immune iRECIST (Appendix B: Tumor Assessment Criteria) to accommodate tumor response patterns seen with checkpoint inhibitor therapy including pembrolizumab treatment (e.g., tumor flare). This was described by Nishino, et al. 2016 [12] and is used in immunotherapy clinical trials. For a clinically stable subject with first radiologic evidence of PD, it is at the discretion of the site investigator to continue treating the subject with SNS-301 and pembrolizumab until PD is confirmed at least 4 weeks after the date of the first tumor imaging suggesting PD per the site investigator. If radiologic PD is confirmed by the subsequent tumor imaging, the subject should be discontinued from treatment unless, in the opinion of the investigator, the subject is achieving a clinically meaningful benefit. In this case, an exception for continued treatment may be considered following consultation with the Sponsor. Additional treatment response evaluation by RECIST v 1.1 and iRECIST may be	

			performed at the Sponsor's discretion.	
10.2.6	Clinical Safety Laboratory Assessments	New	Other anticoagulant monitoring (if required)	To monitor patients on anticoagulation therapy.
10.2.13.3	Tissue	Moved and modified from section 10.2.13.3.2	Archival and fresh tumor tissue samples should be representative tumor specimens in formalin-fixed paraffin embedded (FFPE) blocks (preferred) or at least 15 unstained slides, with an associated pathology report, should be submitted for intra-tumoral immunology assessments. Tissue slices of 4-5 microns are mounted on positively charged glass slides. Slides should be unbaked and stored cold or frozen.	Provide clearer instruction on biopsy under broader title of Tissue.
10.2.13.3.2	ASPH Immunohisto-chemistry (IHC) Assay	New	ASPH testing will be done by immunohistochemistry on either fresh or archival tumor tissue. Additional preparation of the slides will be performed at Sensei Biotherapeutics or designee.	Provide clarification of ASPH testing.
10.2.13.5	Concomitant Medications	New	Patients who are receiving anticoagulants will have anticoagulant specific drug level and/or anticoagulant specific factor Xα levels obtained at baseline, at each administration of SNS-301, and at the end of study visit to ensure that these	Provide guidance on treating patients receiving anticoagulation therapy.

			levels remain within therapeutic range throughout the duration of the trial. In the event of clinically noted bleeding, these tests will be obtained at the time of bleeding as well. Investigators should use tests routinely used in clinical practice to monitor patients receiving Warfarin, Heparin and/or Low Molecular Weight Heparins, along with the monitoring schedule provided above. Should there be two individual events of SNS-301 interruption for the same patients, then SNS-301 will be discontinued after consultation with the Medical Monitor and Study Sponsor. Clinical management and further workup of the coagulation pathway disturbance will be at the discretion of the investigator.	
10.3.11	Guidance for Investigators for Patients on Anti-coagulants	New	Based on the preclinical data and the role of ASPH in post-translational modification of proteins involved in the clotting and anticoagulant pathways (Factors VII, IX, X , Protein C), there may a potential for abnormal coagulation with SNS-301. Should there be a clinically significant AE or SAE recorded, such as clinically noted bleeding,	Provide guidance on treating patients receiving anticoagulation therapy.

			administration of SNS-301 will be held until the AE/SAE returns to baseline. Should there be two individual events of SNS-301 interruption for the same patient, then SNS-301 will be discontinued after consultation with the Medical Monitor and Sponsor. Clinical management and further workup of the coagulation pathway disturbance will be at the discretion of the treating physician.	
13	References	Guidance for Industry: Estimating the maximum safe starting dose in initial clinical trials for therapeutics in adult healthy volunteers. U.S. Department of Health and Human Services; Food and Drug Administration Center for Drug Evaluation and Research (CDER); July 2005, Pharmacology and Toxicology.	Deleted	Obsolete reference.
13	References	Added	12. Nishino M. "Immune-related response evaluations during immune-checkpoint inhibitor therapy: establishing a "common language" for the new arena of cancer treatment." Journal for ImmunoTherapy of Cancer. 2016 4:30 doi:10.1186/s40425-016-0134-0.	New reference.

Multiple	Multiple	Subjects	Patients	Updated for consistency.
Multiple	Multiple	NA	NA	Updated typos, provided additional clarification for Background section (4.2.1.1) which do not have an impact on study procedures, moved paragraph in Background section (4.2.1.1).

APPENDIX E: PRINCIPAL INVESTIGATOR SIGNATURE OF AGREEMENT PAGE

INVESTIGATORS AGREEMENT

This document is a confidential communication of Sensei Biotherapeutics, Inc. (Sensei). The recipient agrees that no unpublished information contained herein will be published or disclosed without prior written permission of Sensei. However, this document may be disclosed to appropriate Institutional Review Boards, ethics review committees, or authorized representatives of the Investigator or regulatory agencies under the condition that they are requested to respect the confidentiality of the document.

The signature of the Principal Investigator below constitutes his/her agreement to comply with the contents of this Protocol.

Principal Investigator's Name	
Principal Investigator's Institution	
Principal Investigator's Signature	Date