

# **Sensei Biotherapeutics**

## **Statistical Analysis Plan**

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

### **Protocol Number**

**SNS301-2-2 V4.0 (November 6, 2020)**

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## 1.0 ACRONYMS

<u>Term</u>	<u>Definition</u>
ADL	Activities of daily living
AE	Adverse event
AESI	Adverse event of special interest
ALP	Alkaline phosphatase
ALT	Alanine aminotransferase
aPTT	Activated partial thromboplastin time
ASPH	Aspartate beta-hydroxylase
ASR	Administration site reaction
AST	Aspartate aminotransferase
BOR	Best overall response
BUN	Blood urea nitrogen
Cl	Chloride
CO <sub>2</sub>	Bicarbonate or carbon dioxide
CPI	Checkpoint Inhibitor (anti-PD-1/anti-PD-L1 therapy)
CPK	Creatinine phosphokinase
CR	Complete response
CRF	Case report form
CT	Computerized tomography scan
CtDNA	Circulating tumor deoxyribonucleic acid
CTL	Cytotoxic CD8+ T-lymphocytes
DCR	Disease Control Rate DLT Dose-limiting toxicity
DOT	Duration of response
EBV	Epstein Barr virus
ECG	Electrocardiogram
ECOG	Eastern Cooperative Oncology Group
eCRF	Electronic case report form
ELISA	Enzyme-linked immunosorbent assay
HBV	Hepatitis B virus
Hct	Hematocrit
Hgb	Hemoglobin



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HIV	Human immunodeficiency virus
hMTS	3M® hollow microstructured transdermal system
HPV	Human papillomavirus
ICH	International conference on harmonization
ID	Intradermally
IFN	Interferon
IHC	Immunohistochemistry
INR	International normalized ratio
iRECIST	Immune response evaluation criteria in solid tumors
IV	Intravenous
K	Potassium
LDH	Lactate dehydrogenase
mAb	Monoclonal antibody
MDSC	Myeloid derived suppressor cells
mg	Milligrams
Mg	Magnesium
MiRNA	Micro ribosome nucleic acid
MRI	Magnetic resonance imaging
NA	Sodium
NCI-CTCAE	National Cancer Institute Common Terminology Criteria for Adverse Events V 5.0
ORR	Objective response rate
OS	Overall survival
P	Phosphorus
PFS	Progression free survival
PBMC	Peripheral blood mononuclear cells
PD	Progressive disease
PR	Partial response
PS	Performance status
RBC	Red blood count
RECIST	Response evaluation criteria in solid tumors
RNA	Ribosome nucleic acid
SAE	Serious adverse event

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SCCHN	Squamous cell carcinoma of the head and neck
SD	Stable disease
SNS-301	HAAH bacteriophage lambda constructs: HAAH-1 $\lambda$ transaminase
SOC	System organ class
SUSAR	Suspected unexpected serious adverse reaction
TNF	Tumor necrosis factor
TSH	Thyroid stimulating hormone
TT	Thrombin Time
ULN	Upper limit of normal
WBC	White blood count

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## 1. PURPOSE

This Statistical Analysis Plan (SAP) describes the methods to be used in the analysis of trial data from clinical protocol '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' in order to answer the trial objective(s), and is based on the trial protocol SNS301-2-2, dated November 6, 2020 (Version 4.0).

Populations for analysis, data handling rules, statistical methods, and formats for data presentation are described within this document. The statistical analyses and summary tabulations described in this SAP will provide the basis for the results sections of the CSR for this trial. The SAP outlines any differences in data analysis methods relative to those planned in the trial protocol. Any changes to the data analysis methods after the SAP is finalized will be described in the CSR.

## 2. OVERALL STUDY DESIGN AND OBJECTIVE

### 2.1 Trial Objectives

#### *Primary Objective*

- To determine the safety and tolerability of SNS-301 delivered by intradermal injection (ID) using the 3M® hollow microstructured transdermal system (hMTS) device in 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

#### *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.

#### *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.

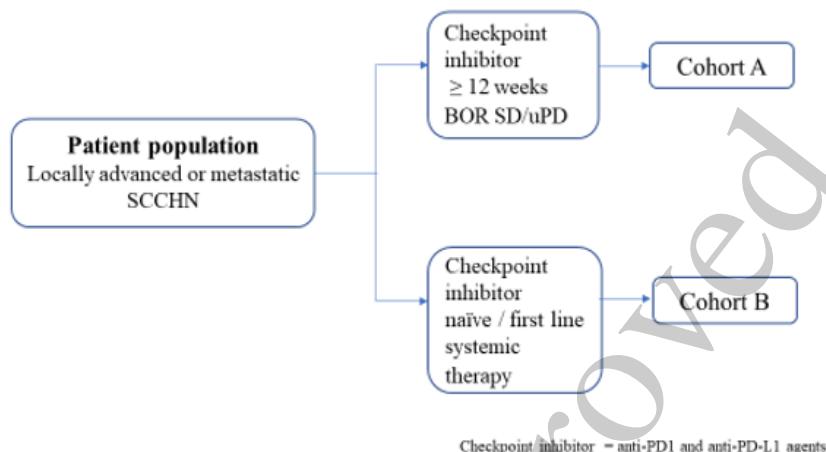
### 2.2 Trial Design and Trial Procedures



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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 checkpoint inhibitor (CPI) therapy (anti-PD1 and anti-PD-L1 agents) (Cohort A) or are naïve to CPI therapy (Cohort B). The cohorts for this study are highlighted below:



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

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 a CPI therapy. 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.

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 2) anti PD(L)-1 treatment-naïve, pending availability. An on-treatment biopsy is required when medically feasible, after the second or 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. The Sponsor may request digitized scans from patients to confirm response.

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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. 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. 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 runin 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.

If at least one responder (ORR per iRECIST) is observed in the first 15 evaluable patients (i.e. meeting the definition for the efficacy evaluable population) by Week 12, then the study will continue to Stage 2 and enroll up to 15 additional patients. If at least 4 responders are observed overall, further research will be deemed warranted.

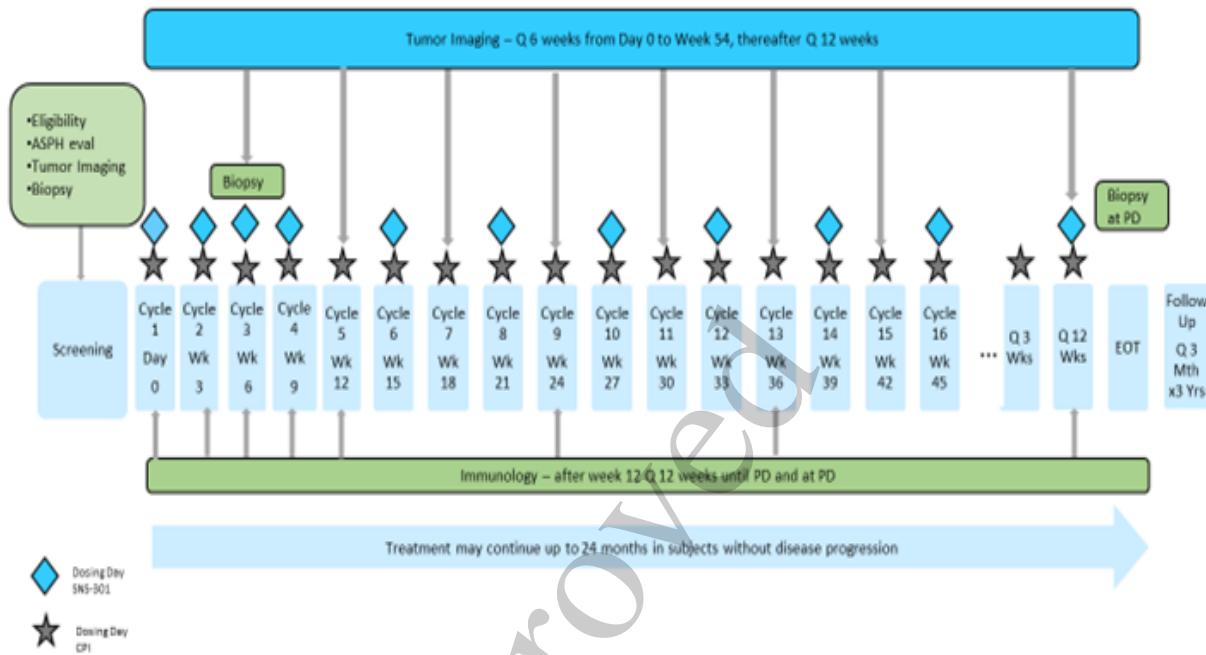
There will be a waiting period of one week between enrollment of the first patient and the second patient because this trial is treating patients with SNS-301 and pembrolizumab for the first time. The interim efficacy assessment, for each cohort, will occur after 15 patients were enrolled and completed the 12-week follow-up period. A safety review will occur in parallel to the efficacy assessment of the first 15 patients

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 should occur. These events will be submitted to regulatory agencies within the expedited safety reporting criteria.

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.

The study schema is presented in Figure 1:

Figure 1: Study Schema



## 2.3 Treatments and Assignment to Treatments

### SNS-301 Dosing

- SNS-301 ( $1 \times 10^{11}$  dose/1ml) ID is administered using the 3M® hollow microstructured transdermal system (hMTS) device.
- 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.

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



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Patients will receive their study treatments until disease progression, unacceptable toxicity, deemed intolerable by investigator or up to 24 months in patients without disease progression.

There will be no SNS-301 dose reductions.

In case of non-DLT AE (grade 2 NCI-CTCAE V5.0 drug related AE), the dosing interval can be extended up to 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 more than 42 days then the patient should be discontinued from study treatment and continue to the study follow up phase.

## 2.4 Determination of Sample Size

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 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.

Subjects 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 the 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 exact binomial distribution is used in the operating characteristics of this design.



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## **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 the total 30 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.

## **3. GENERAL ANALYSIS CONVENTION**

### **3.1 General Methods**

All summaries will be presented separately for each cohort, and overall for 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, 25<sup>th</sup>, 50<sup>th</sup> (median) and 75<sup>th</sup> percentile will be estimated using the Kaplan-Meier method. Number of patients with event and number of patients censored will be presented. As appropriate, a 95% CI will be presented. Graphical displays will also be presented, as appropriate.

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

### **3.2 Trial Periods**

The pre screening period is up to 28 days prior to first drug administration. Patients will undergo tumor assessments every 6 weeks ( $\pm 7$  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 ( $\pm 7$  days). 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. The Trial Schedule of Events is presented in Appendix A.



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### 3.3 Visit Windows

The allowed visit windows are summarized in Table 1 below:

Parameter	Visit	Allowed Window
Tumor Biopsy	Week 6	± 3 days
SNS-301 Administration (When pembrolizumab is given every three weeks)	Day 0, Week 3, 6, 9, 15, 21, 27, 33, 39 and 45	± 3 days
	After week 45, every 12 weeks until confirmed disease progression, unacceptable toxicity, deemed intolerable by the investigator or up to 24 months in patients without disease progression.	± 3 days
SNS-301 Administration (When pembrolizumab is given every six weeks)	Day 0, Week 3, 6, 12, 18, 24, 30, 36, 42 and 48	± 3 days
	After Week 48, every 12 weeks until confirmed disease progression, unacceptable toxicity, deemed intolerable by the investigator or up to 24 months in patients without disease progression.	± 3 days
Pembrolizumab Administration	Every 3 weeks until confirmed disease progression, unacceptable toxicity, deemed intolerable by investigator or up to 24 months in patients without disease progression	± 3 days
Imaging	Week 6	± 7 days
	Every 6 Weeks till Week 54	± 7 days
	Every 12 Weeks after Week 54	± 7 days
Vital Signs (Heart rate, respiratory rate, blood pressure, and temperature)	15 Min after start of first infusion	± 5 Min
	30 Min after start of first infusion	± 5 Min
	45 Min after start of first infusion	± 5 Min



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	60 Min after start of first infusion	± 5 Min
	30 Min after first infusion	± 10 Min
	60 Min before subsequent infusions	<60 Min to infusion
	30 Min after subsequent infusions	± 5 Min

## 4. ANALYSIS POPULATIONS

### *Safety Analysis Set*

The Safety Analysis Set comprises all patients who receive at least 1 dose of the study treatment or component of the study treatment.

### *Efficacy-Evaluable Analysis Set*

The Efficacy-Evaluable Analysis Set 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. Subjects who discontinued prior to Week 12 due to radiological disease progression will be included. Subjects who do not have a post baseline response assessment conducted will not be included in the analysis of efficacy.

### *Safety Run-In Set*

Safety Run-in Set comprises all patients who receive at least 1 dose of the study treatment or component of the study treatment as part of the safety run-in.

### *Immunologic Analysis Set*

Immunological Analysis Set comprises 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.

## 5. SUBJECT DISPOSITION

Subject disposition will be summarized overall for all subjects who entered the study in a disposition table (i.e., signed the informed consent for the study). In addition, the number of subjects in each population (Safety Analysis Set, Safety Run-in Set, Efficacy Evaluable Analysis Set and Immunologic Analysis Set) and subjects that were removed from a population will be summarized. The number and proportion of subjects who complete the study, as well as those who discontinue the study will be summarized along with the reason for discontinuation.

Primary reason for SNS-301 treatment termination include the following criteria:

- Adverse Event



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- Death
- Progression
- Lost to Follow-up
- Non-Compliance with Study Drug
- Physician Decision
- Pregnancy
- Protocol Deviation
- Site Terminated by Sponsor
- Study Terminated by Sponsor
- Withdrawal by Patient
- Other

Primary reason for Pembrolizumab treatment termination include the following criteria:

- Adverse Event
- Death
- Progression
- Lost to Follow-up
- Non-Compliance with Study Drug
- Physician Decision
- Pregnancy
- Protocol Deviation
- Site Terminated by Sponsor
- Study Terminated by Sponsor
- Withdrawal by Patient
- Other

Primary reason for study discontinuation include the following criteria:

- Death
- Lost to Follow-up
- Withdrawal by patient from Study
- Termination of study by Sponsor
- Completed 24 months of therapy
- Other (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)

Subject disposition data will also be presented in data listings.

If study treatment is definitively discontinued, the patient will remain in the study for long term follow-up post-treatment to be evaluated for survival, including information on subsequent anticancer therapies and progression. In the case where consent for study treatment is withdrawn,



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the patient will be encouraged to continue study participation for long term follow-up post-treatment.

## 6. DEMOGRAPHIC AND BASELINE CHARACTERISTICS

### 6.1 Demographics Characteristics

Demographic and baseline characteristics at study entry will be summarized in tables and listings by study cohort and overall.

Number, mean (SD), median, min and max will be provided for these continuous variables:

- Age (years) at time of consent
- Weight (kg)
- Height (cm)
- Body Mass Index (kg/m<sup>2</sup>)

Number and percentage of patients will be provided for the following categorical variables:

- Sex
- Child-bearing potential (females)
- Race
- Ethnicity

Patients are allowed to select more than one race to define multiple-race.

### 6.2 Smoking History and Alcohol Use

Smoking history and alcohol use data will be collected at study entry and will be summarized in tables and listings by cohort and overall.

Number and percentage of patients will be provided for the following categorical variables:

- Smoking History (Yes/No)
- Status of Tobacco Use (Current/Former)
- Type (Cigarette, Cigar, Pipe, Smokeless tobacco, Electronic cigarette, Other)
- Tobacco use frequency per day (1- 4, 5-10, 10 - 20, >20, Unknown)
- Alcohol use (Never/Current/Former)
- Number of Alcoholic drinks consumed (never, 1 or 2, 3 or 4, 5 or 6, 7 or 8, 10 or more)

Number, mean (SD), median, min and max will be provided for these continuous variables:



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### 6.3 Medical History

Medical History will be collected at the Screening/Baseline visit. 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 and risk stratification. Medical History will be summarized for the Safety Analysis Set.

The frequency count and percentage of subjects experiencing any medical conditions will be tabulated by system organ classifications (SOC) and preferred term (PT). If a preferred term or system organ class was reported more than once for a subject, the subject would only be counted once in the incidence for that preferred term or system organ class.

Medical history data will also be listed for Safety Analysis Set by patient.

### 6.4 Cancer History

Cancer History will be collected at the Screening/Baseline visit. The following data will be summarized by number and percentage of patients in each category for the Safety Analysis Set.

- Histologic Diagnosis
  - Differentiation (Well, Moderate, Poor, Not Specified)
  - Stage at Screening (Stage I, Stage II, Stage III, Stage IV, Stage IVA, Stage IVB, Stage IVC)
- TNM Staging
  - T Stage (T1, T2, T3, T4)
  - N Stage (N0, N1, N2a, N2b, N2c, N3, NX)
  - M Stage (M0, M1, MX)
- Anatomical Location (Lip, Oral cavity, Oropharynx, Hypopharynx, Nasopharynx, Glottic larynx, Supraglottic larynx, Ethmoid sinus, Maxillary sinus, Salivary gland, Other)

### 6.5 Prior Cancer Therapy

Prior cancer therapy data will be collected at the Screening/Baseline visit.

The following data will be summarized by number and percentage of patients in each category for the Safety Analysis Set.

- Did the subject have any prior Cancer therapy? (Yes/No)
- Was the therapy ongoing at the time of consent? (Yes/No)
- Best Overall Response



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- Complete response (CR)
- Partial response (PR)
- Progressive disease (PD)
- Stable disease (SD)
- Unconfirmed Progression (uPD)
- Duration of Response (Weeks) will be summarized as a continuous variable (N, Mean (SD) Median Min Max)

## 6.6 Prior Radiotherapy

Prior radiotherapy data will be collected at the Screening/Baseline visit.

The following data will be summarized by number and percentage of patients in each category for the Safety Analysis Set.

- Did the subject have any prior radiotherapy? (Yes/No)
- Was radiotherapy ongoing at the time of consent? (Yes/No)
- Type of radiotherapy
  - Intensity-Modulated Radiation
  - Therapy (IMRT)
  - AP-PA Therapy
  - Proton Therapy
  - Other

The following parameters will be summarized as continuous variables (N, Mean (SD) Median Min Max)

- Dose per fraction
- Number of fractions

## 6.7 Target, Non-target and New 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. Target lesions must meet the criterion of a short axis of  $\geq 15$  mm by CT scan. All other pathological nodes (those with short axis  $\geq 10$  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.



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The following categorical variables for target, non-target and new lesions will be summarized using descriptive statistics (number (percent))

- Site of lesion (Bone, Brain, Chest Wall, Liver, Lung, Lymph Node, Neck, Oral Cavity, Skin; Soft Tissue, Other)
- Modality (CT with Contrast, CT without Contrast, MRI)

The following continuous variables for target, non-target and new lesions will be summarized using descriptive statistics (n mean (SD), median, min, max))

- Longest Diameter
- Sum of the longest diameter (Derived)

Summaries for target, non-target and new lesions' data as assessed using iRECIST will also be presented. Data listings will also be presented for target, non-target and new lesions' data.

## 6.8 Prior and Concomitant Medications

Prior medications any prescription medications or over-the-counter medications taken or performed within 7 days prior to screening and before the first dose of study drug. At subsequent visits, changes to current medications or medications used since the last documentation of medications will be recorded.

Concomitant medications are all medications, other than the study drug, taken on or after the first day of study drug dose through 30 days after end of study medication or until the start of a new anti-cancer treatment, whichever comes first. Concomitant medications will be categorized into the following categories (listed in section 8.4 of the protocol):

- Allowed concomitant treatments
- Prohibited medications or treatments during study
- Rescue medications

Prior and concomitant medications and procedures will be coded using the World Health Organization Drug Dictionary.

- Prior and concomitant medications will be summarized by the number and proportion of the subjects who took each medication, or had qualifying concomitant procedures and will be tabulated by the ATC-2 level and preferred name. A subject will only be counted once within each ATC-2 code and within each preferred name.

Prior and concomitant medications will also be listed for Safety Analysis Set .



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## 6.9 Serology Testing Results (HIV, Hepatitis and PD-L1 Status)

If the patient's tumor's HPV/EBV status is unknown, they will be tested prior to receiving SNS-301. If the patient's tumor'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. For patients that started study treatment prior to Amendment 2/Version 3.0, retrospective PD-L1 testing should be done, whenever possible.

The results of the following tests will be summarized using descriptive statistics (Number (percent))

- HIV Testing (Positive, Negative, Unknown)
- Hepatitis B surface Testing Antigen (Positive, Negative, Unknown)
- Anti-HBc Antibody Testing (Positive, Negative, Unknown)
- Anti-HBs Antibody Testing (Positive, Negative, Unknown)
- Hepatitis C Antibody Testing (Positive, Negative, Unknown)
- PD-L1 Status (Positive, Negative, Unknown)

## 6.10 Virology Testing Results (HPV and EPV)

The results of the following tests will be summarized using descriptive statistics (Number (percent))

- HPV Status (Positive, Negative, Unknown)
- EBV Status (Positive, Negative, Unknown)

# 7. EFFICACY ANALYSIS

## 7.1 Primary Efficacy Analysis

The primary efficacy analysis will be based on the Efficacy-Evaluable Analysis Set at week 12. All efficacy variables will be presented by cohort. The following primary efficacy variables will be summarized to determine the anti-tumor activity of SNS-301:

Objective Response Rate (ORR)

- ORR is defined as the proportion of patients with a confirmed best response of iCR or iPR by iRECIST.
- ORR, and 90% CI at week 12 based on the exact binomial distribution will be presented, including number and percent of patients in each overall response category.



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- Best Overall Response ( BOR) will also be presented.

#### Disease Control Rate (DCR)

DCR is defined as the proportion of patients with SD or better (PR and CR) as assessed by RECIST version 1.1 and iRECIST. SD must be for at least six months.

- A 95% Confidence Interval based on binomial distribution will be constructed for the estimated DCR at 12 weeks.
- Subjects who drop out prior to meeting the responder criteria for DCR will be considered as non-responders.

#### Clinical Benefit Rate (CBR)

- CBR is defined as the proportion of patients with CR, PR or had stable disease for at least 6 Months as assessed by RECIST version 1.1 and iRECIST.
- A 95% Confidence Interval based on binomial distribution will be constructed for the estimated CBR.

#### Progression Free Survival (PFS)

- PFS is defined as the time from date of start of treatment to date of progression or death (whichever comes first) as assessed by RECIST version 1.1 and iRECIST.
- Subjects who are alive and without documentation of progression at the time of the analysis will be censored at the date of last tumor assessment.
- Subjects with no tumor response assessment will be censored at the start date of the treatment.
- Subjects who discontinued treatment or withdrew from the study for reasons other than documented PD or death will be censored at the date of last tumor assessment prior to discontinuation or withdrawal.
- PFS rate at 12 weeks and the corresponding 95% CIs will be calculated based on Kaplan-Meier product limit estimates and will be displayed along with the corresponding number of subjects at risk.
- The 25<sup>th</sup> percentile, Median, and 75<sup>th</sup> percentile of PFS as well as the corresponding 95% confidence limits will be estimated using Kaplan-Meier method. Number of patients with PD, number of deaths and number censored will be presented.
- Kaplan-Meier curves of PFS by cohort will be displayed graphically.

#### Duration of Response (DOR)

- DOR is defined as time from date of first loss of response as assessed by RECIST version 1.1 and iRECIST.
- DOR in weeks = (Date of PD or death – date of first response + 1) / 7. Patients without progression or death are censored at the date of last tumor assessment.



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- The median DOR with 2-sided 95% confidence intervals will be presented for subjects who have a confirmed CR or PR at 12 weeks.
- The 25th percentile, Median, and 75th percentile of DOR as well as the corresponding 95% confidence limits will be estimated using Kaplan-Meier method. Number of patients who lost response and number censored will be presented.
- Kaplan-Meier curves of DOR by cohort will be displayed graphically.

#### Overall Survival (OS)

- OS is defined as time from date of start of treatment to date of death.
- OS rate at 12 weeks and the corresponding 95% CIs will be calculated and summarized based on Kaplan-Meier product limit estimates and will be displayed along with the corresponding number of subjects at risk.
- Subjects who are still alive will be censored on the date of last contact.
- The 25th percentile, Median, and 75th percentile of OS as well as the corresponding 95% confidence limits will be estimated using Kaplan-Meier method. Number of patients who died and number censored will be presented.
- Kaplan-Meier curves of OS by cohort will be displayed graphically.

### 7.2 Secondary Efficacy Analysis

To determine preliminary immune response to SNS-301, the following parameters will be assessed:

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

Categorical results will be summarized using the number (percent) format and continuous results will be presented in the n, mean(SD), median, min and max format.

### 7.3 Exploratory Efficacy Analysis



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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 SCCHN, the following parameters will be assessed:

- 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
- 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

Categorical results be summarized using the number (percent) format and continuous results will be presented in the n, mean(SD), median, min and max format.

## 8. SAFETY ANALYSIS

Safety evaluations will be based on exposure and compliance to study drugs, the incidence, severity, attribution and type of AEs, and changes in the patient's vital signs, and clinical laboratory results.

### 8.1 Trial drug Exposure and Compliance

Extent of treatment exposure to SNS-301, will be assessed for each of the two study stages.

- Duration of SNS-301 treatment (week), will be calculated as: (Last dose date – first dose date + 1) / 7
- Was full dose of SNS-301 administered? (Yes/No)
- Were any injection or device malfunctions noted? (Yes/No)
- Type of Malfunction (Device failed, User Error)
- Did the malfunction affect the dose received by the subject? (Yes/No)

Pembrolizumab exposure will be summarized by the following parameters:

- Duration of Pembrolizumab treatment (week), calculated as: (Last dose date – first dose date + 1) / 7
- Was full dose of Pembrolizumab administered? (Yes/No)
- Was infusion interrupted? (Yes/No)



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- Reason for interruption (AE, IV Issue Other)

## 8.2 Dose-Limiting Toxicities

Dose-Limiting Toxicities (DLTs) are events identified below that must be reported in an expeditious manner. DLTs may or may not be serious adverse events as an Unexpected Adverse Event (SUSAR). DLTs are assessed up to week 6 for patients enrolled in the Safety Run-In period.

- 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

Safety analysis will be based on the safety analysis set.

## 8.3 Adverse Events

### Adverse event (AE)

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.

Adverse events (AEs) will be coded using MedDRA v20 or later and will be classified by System Organ Class (SOC) and preferred term (PT).

Treatment-emergent adverse events (TEAEs) 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.

Severity of AEs will be assessed according to CTCAE (v5.0):



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- 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.)

Prior AEs are those occurring after subject sign off the informed consent and before the administration of the first dose of study treatment.

Relationship to study medication is categorized as follows based on clinical decision using all available information at the time of completing the CRF:

- Related (The AE could medically (pharmacologically/clinically) be attributed to the study drug under investigation in this clinical study protocol)
- Not related (The AE could not medically (pharmacologically/clinically) be attributed to the study drug under investigation in this clinical study protocol.)

Systemic administration site reactions will be considered as Adverse Events of Special Interest (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).

An unanticipated (serious) Adverse Device Effect (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.

An overall AE summary for number of subjects will be presented for the following categories:

- Any Adverse Event
- Any Treatment-Emergent Adverse Event (TEAE)
- Any deaths within the AE reporting period



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- Any study drug-related adverse event (TRAЕ) (i.e. related to SNS-301 or Pembrolizumab)
- Any SNS-301-related adverse event (TRAЕ)
- Any Pembrolizumab-related adverse event (TRAЕ)
- Any AE related to device for injection
- Any AE related to a Dose-Limiting Toxicity (DLT)
- Any TEAE  $\geq$  CTCAE Grade 3
- Any TRAE  $\geq$  CTCAE Grade 3
- Any treatment-emergent Serious AEs (SAEs)
- Any Serious TRAEs
- Any TEAE leading to treatment (SNS-301 or Pembrolizumab) discontinuation
- Any TEAE leading to SNS-301 treatment discontinuation
- Any TEAE leading to Pembrolizumab treatment discontinuation
- AESIs
- UADEs

The following events will be tabulated by SOC and PT. Summaries will be sorted by decreasing frequency of PT within SOC which is sorted alphabetically.

- TEAEs by SOC and PT
- TEAEs by PT frequency only
- Treatment-emergent SAEs
- SNS-301 Treatment-related AEs
- Pembrolizumab Treatment-related AEs
- SNS-301 Treatment-related SAEs
- Pembrolizumab Treatment-related SAEs
- TEAEs leading to SNS-301 treatment discontinuation or death
- TEAEs leading to Pembrolizumab treatment discontinuation or death
- DLTs
- AESIs



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A summary of TEAEs by SOC, PT and maximum severity, sorted by decreasing frequency of PT within SOC which is sorted alphabetically, will also be provided for:

- All TEAEs
- TEAEs  $\geq$  CTCAE Grade 3
- SNS-301 Treatment-related AEs
- Pembrolizumab Treatment-related AEs
- TRAEs  $\geq$  CTCAE Grade 3

In tabulation by severity grade, only the most severe SOC for each subject will be included for a given SOC. For a given PT, only the most severe PT for each subject will be included.

The following listings will be provided:

- All AEs
- DLTs
- SAEs
- AESIs
- TEAEs leading to study treatment discontinuation
- Deaths in the AE reporting period

#### 8.4 Clinical Safety Laboratory Assessments

Hematology, serum chemistry, coagulation and urinalysis data will be collected as specified in the study schedule of Assessments (Appendix A). Hematological toxicities will be assessed according to NCI-CTCAE V5.0 AE grading.

All laboratory results will be presented in the listings. Abnormal laboratory values with their clinical significance status will be presented in a listing. The laboratory tests cut off values are presented in Appendix B.

**Table 2: Clinical Laboratory Tests**

Hematology	Serum Chemistry
Hematocrit (Hct)	Albumin
Hemoglobin (Hgb)	Alanine aminotransferase (ALT)
Platelet count	Aspartate aminotransferase (AST)
	Alkaline phosphatase (ALP)



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Red blood cell (RBC) count	Blood Urea Nitrogen (BUN) or Urea
White blood cell (WBC) count	Bicarbonate or Carbon dioxide (CO <sub>2</sub> )
Neutrophils	Creatinine
Lymphocytes	Creatine phosphokinase (CPK)
Eosinophils	Electrolytes (Na, K, Mg, Cl, Ca, P)
Monocytes	Glucose (either fasting or non-fasting)
Basophils	Lactate dehydrogenase (LDH)
Other cells, if any	Total bilirubin (direct bilirubin if elevated)
Platelets	Total protein
<b>Thyroid</b>	<b>Urinalysis</b>
TSH, T3 and FT4	Specific gravity
<b>Coagulation</b>	pH
International normalized ratio/INR	Glucose
Activated partial thromboplastin time (PTT)	Protein
Other anticoagulant monitoring (if required)	Ketones
<b>HIV screen</b> (at screening, if indicated)	Blood
<b>Hepatitis screen</b> (at screening, if indicated)	Microscopic exam, if abnormalities
<b>HPV/EBV screen</b> (at screening, if unknown)	
<b>Pregnancy test</b>	

The following summaries will be presented for Clinical Laboratory tests:

- Overall values by time point utilizing continuous descriptive statistics for each study stage.
- For categorical parameters, the n and percentage will be displayed for each study stage.
- The change from baseline to each time point for continuous parameters.
- Frequencies and percentages for the shifts in these categories (i.e., low to normal, low to high, high to low, etc.) from baseline to each post-treatment assessment time point. For each continuous laboratory (hematology and chemistry) parameter, results will be categorized as low, normal, or high based on the laboratory normal ranges. Percentages for the shift tables will be calculated based on the number of subjects who had results for both baseline and the corresponding post-treatment assessment time point.



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## 8.5 Urinalysis

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

Summaries will be presented by cohort.

- Categorical urinalysis variables (Glucose, Blood, Protein, Ketones, RBC, WBC, Casts) will be summarized by number and percentage (n(%)) of subjects.
- The urine pH and specific gravity will be summarized using descriptive statistics (n, mean (SD), median, Min and Max).

## 8.6 Thyroid Function

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

- TSH, T3 and FT4 data will be summarized using descriptive statistics (n, mean (SD), median, Min and Max).

## 8.7 Coagulation and Anticoagulation Levels

Anticoagulant specific drug and/or anticoagulant factor Xa levels will be obtained from patients receiving anticoagulation therapy at Screening, Day 0, Week 3, Week 6, Week 9, Q6W until Week 45 , thereafter Q12W .

- aPTT, INR, PT, TT and Xa data will be summarized using descriptive statistics (n, mean (SD), median, Min and Max).

## 8.8 Electrocardiograms

12-Lead ECG will be completed at screening/baseline visit.

- The overall assessment categories (Normal, Abnormal; not clinically significant, Abnormal; clinically significant) will be summarized.
- ECG data will be presented in a data listing.

## 8.9 Eastern Cooperative Oncology Performance Status

ECOG performance will be completed at screening/baseline, Cycles 1,2,3,4 and every 3 weeks thereafter, and at the discontinuation visit on a 6-point scale from grade 0-5 as presented in Appendix C.



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- ECOG PS assessments will be summarized overall as categorical variables by time point utilizing descriptive statistics.

## 8.10 Vital Signs and Weight

Vital signs and Weight will be taken at various timepoints: Baseline/Screening visit, Cycle 1 Day 0, Cycle 2 Week 3, Cycle 3 Week 6, Cycle 4 Week 9, Every 3 weeks, and at the discontinuation visit. Height will only be taken at baseline/screening visit.

- Descriptive statistics will be presented for each timepoint.
- Descriptive statistics will also be presented for the changes in vital signs from baseline to each post-treatment assessment time point.

## 8.11 Physical Examinations

A full physical examination will be performed at screening/baseline. There will also be targeted physical examinations at these timepoints: Cycle 1 Day 0, Cycle 2 Week 3, Cycle 3 Week 6, Cycle 4 Week 9, Every 3 weeks afterwards and at discontinuation visit.

- Physical exams will be presented in data listings

## 8.12 Pregnancy Testing

Pregnancy testing (when applicable) will be carried out at every visit except the every 6 weekly visits.

- Pregnancy testing results will be presented in data listings

## 8.13 Immunogenicity Assessments

Processing of immunogenicity samples will be performed at Sensei Biotherapeutics or designee. The analyses of these assessments is beyond the scope of this SAP.

## 8.14 ASPH Immunohistochemistry (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. Staining intensity and distribution of ASPH levels will be evaluated according to the following scale:

- Negative =0;
- Moderate =1+
- Strong=2+



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- Very strong immunoreactivity = 3+

Preparation of the slides will be performed at Sensei Biotherapeutics or designee. The analyses of these assessments is beyond the scope of this SAP.

## 9. STATISTICAL/ANALYTICAL ISSUES

### 9.1 Handling of Dropouts or Missing Data

All available data will be presented on the data listings as collected.

Algorithms for imputing partial or missing dates related to AEs and prior/concomitant medications are shown below.

Table 3      Imputation Rules for Partially Missing Dates

Variable	Missing Day	Missing Day, Month	Missing Day, Month, Year
Date of Last Therapy/Date of Initial Diagnosis	Assign 1	Assign January 1 if prior to date of informed consent, otherwise use date of informed consent	Missing (do not impute)
Adverse Event/Medication Start Date	Assign first day of month unless it is the month of first dose of study medication. Otherwise, assign date of first dose of study medication.	Assign January 1 unless the year is year of first dose of study medication Otherwise, assign date of first dose of study medication.	Assign date first dose of study medication.
Adverse Event/Medication End Date	Assign the last day of the month or end of study date, whichever is earlier.	Assign December 31 or end of study date, whichever is earlier.	If ongoing, end date is missing. Otherwise, assign end of study date.

Every effort to re-contact the patient lost to follow-up patients will be made, 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. Data from lost to follow-up subjects to the date of last recorded contact will be included in the analyses.

Non-evaluable patients will be replaced.



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## 9.2 Pooling of Centers in Multi-Center Trials

There will be no pooling of centers.

## 9.3 Multiple Comparisons/Multiplicity

No adjustments for multiple comparisons or multiplicity will be made.

## 9.4 Examination of Subgroups

No subgroup analysis will be performed in this study.

## 9.5 Interim Analysis and Data Monitoring

A Safety Committee will be formed to monitor safety on a periodic basis. 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.

The interim efficacy assessment, for each cohort, will occur after 15 patients were enrolled and completed the 12-week follow-up period. The objective response rate, for each cohort, 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. A safety review will occur in parallel to the efficacy assessment of the first 15 patients in each cohort.

## 10. QUALITY CONTROL

All data displays and analyses will adhere to the International Conference on Harmonization (ICH) *Harmonized Tripartite Guideline: Structure and Content of Clinical Study Reports*.

All analyses will be performed using SAS® Version 9.4 (or later). Advanced Clinical will follow its standard operating procedures in the creation and quality control of all tables, listings, figures, and analyses.

Sensei Biotherapeutics will review all tables, listings, and figures prior to final database lock. Final SAS datasets, programs and outputs will be transferred to Sensei biotherapeutics at project completion.

## 11. RECORD RETENTION

Records related to the activities listed in this plan will be retained according to AC SOP AD-005.



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## 12. TABLES AND LISTING CONVENTIONS

Mock-ups for statistical tables and listings will be provided. Final formats for the statistical tables and listings may deviate from these mock-ups upon agreement with Sensei. Footnotes will be used as needed to clarify the information that is presented in the tables and listings. Unless otherwise requested by Sensei, the term 'patient' will be used in all tables and listings, in accordance with CDISC standards.

The general layout of tables and listings will be as follows.

<Sponsor name>  
 Protocol: <protocol identifier>  
 Clinical/Statistical Report  
 Listing 16.2\_x (or Table 14.x\_x)  
 <Title>  
 <Population>  
 Col 1    Col 2    Col 3    etc  
  
 <Any footnotes>  
 File Name: <pathname for SAS program>

All tables and listings will use landscape orientation. Margins will be at least 2.0 cm at the top and bottom and at least 0.8 cm on the left and right, excluding headers and footers, in accordance with electronic Common Technical Document (eCTD) guidelines. Font will be Courier New, unless otherwise specified, with an 8-point font size in most cases. Page numbering will be sequential within each table, listing, and figure. Column headers should be in initial capital letters. Units for numeric data will be included when appropriate.

Tables and data listings will be created from different SAS programs. A single program may produce multiple tables or multiple data listings from the same dataset (e.g., all clinical chemistry data listings may be generated by a single program).



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## 12.1 Statistical Table Conventions

Mock-ups for statistical tables will include headers, title numbers, titles, column headers and footers, and a proposed layout for the display of data. The final decision on the precision (i.e., number of decimal places) for presentation of descriptive statistics will be made by Sensei Biotherapeutics after review of draft statistical tables and before database freeze.

## 12.2 Data Listing Conventions

Mock-ups for data listings will include headers, title numbers, titles, column headers, and footers. Data listings will provide all data collected on the corresponding eCRF page or provided by external vendors, unless otherwise indicated. If there are too many fields to be fit into a single page, data should be grouped logically and the listings will be generated as Part I, Part II, etc.

In general, data listings should include all patients with data. However, if only patients who meet a certain condition are listed (e.g., patients with SAEs) and no patients meet the condition, the data listing will so indicate.

The data presented in data listings will be sorted by patient ID. Within a patient, data will be listed in chronological order. Whenever possible, formatted values will be displayed (i.e., decoded). Where applicable, calendar date and study day of evaluations/events will be provided in the data listings.

## 13. REFERENCES

1. Common Terminology Criteria for Adverse Events (CTCAE) Version 5.0. Published: November 27, 2017. National Cancer Institute, National Institutes of Health. U.S. Department of Health and Human Services.
2. International Conference on Harmonization (ICH, 1996) E6 Guideline for Good Clinical Practice
3. International Conference on Harmonization (ICH, 1997) E8 Guideline: General Considerations for Clinical Trials
4. Medical Dictionary for Regulatory Activities (MedDRA), Version 20.
5. World Health Organization (WHO) Drug Dictionary (WhoDrugDDEB2\_201703).



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## 14. CHANGE HISTORY

Version	Date	Description of Changes
0.1	16JAN2020	Original Document
0.2	27FEB2020	Internal review, Not reviewed by Sensei
0.3	01MAY2020	Internally Revised and resubmitted to reduce overall review cycles. Protocol amendments pending
0.4	29JUN2020	Reviewed by Sensei. Protocol amendments still pending
0.5	24SEP2020	First version incorporating protocol amendment (protocol V3.0)
1.0	20NOV2020	Revisions following protocol amendment (protocol V4.0)
2.0	25JAN2021	Revisions to Section 1 and Section 2 and section 6 following protocol amendment V4.0
3.0	15MAR2021	Final version approved by Sensei Biotherapeutics
1.0	05MAY2021	Version Number Change only. Change history updated. eTMF Lead directed that this should revert to V1.0 as it is the first version signed by Sensei Biotherapeutics. Previous versions had been reviewed but not signed off by sponsor.



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## APPENDICES

## 14.1 Appendix A: Schedule of Trial Assessments

	Screening <sup>a</sup>	Cycle 1 Day 0	Cycle 2 Week 3	Cycle 3 Week 6	Cycle 4 Week 9	Every 3 weeks	Every 6 weeks	Discontinuation Visit <sup>b</sup>	Follow-up
	Day -28 to Day -1								
Signed Informed Consent Form(s)	X								
Medical, surgical, and cancer histories, including demographic	X								
Inclusion/Exclusion criteria	X	X							
Complete Physical exam <sup>d</sup>	X								
Targeted Physical exam <sup>e</sup>		X <sup>f</sup>	X <sup>f</sup>	X <sup>f</sup>	X <sup>f</sup>	X <sup>f</sup>		X	
ECOG performance status <sup>f</sup>	X	X	X	X	X	X		X	
HIV, Hep B and Hep C serology <sup>g</sup>	X								
Concomitant Medications <sup>h</sup>	X	X	X	X	X	X		X	
Anticoagulant specific drug and/or anticoagulant factor Xa levels <sup>i</sup>	X	X	X	X	X	At Week12, then Q6w until week 45, thereafter Q12w		X	
For patients on anticoagulants only									
Vital Signs and Weight <sup>j</sup>	X	X	X	X	X	X		X	
Height	X								
12-lead ECG <sup>k</sup>	X								
Tumor Imaging <sup>l</sup>	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 <sup>m</sup>	X	X <sup>f</sup>	X <sup>f</sup>	X <sup>f</sup>	X <sup>f</sup>	X <sup>f</sup>		X	
Serum Chemistry <sup>n</sup>	X	X <sup>f</sup>	X <sup>f</sup>	X <sup>f</sup>	X <sup>f</sup>	X <sup>f</sup>		X	
Coagulation Panel (aPTT, INR)	X								
Urinalysis <sup>o</sup>	X			X			X	X	
Pregnancy <sup>p</sup>	X	X	X	X	X	X		X	X
TSH, T3 and Free T4 <sup>q</sup>	X			X			X		
CPK	X							X	



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HPV/EBV, if unknown	X							
Blood samples for immunology assessments <sup>r</sup>		X	X	X	X	At week 12, then Q6 weeks until week 36 and Q12w thereafter as well as at disease progression		
Tumor specimens <sup>s</sup>	X			X		Up to 2 optional biopsies and at disease progression		
Adverse Events <sup>t</sup>	X	X	X	X	X	X	X	X
Pembrolizumab <sup>u</sup>		X	X	X	X	X		
SNS-301 <sup>v</sup>		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 <sup>w</sup>								X

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

<sup>a</sup> 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. Tumor tissue may be submitted up to 28 days prior to Day 0. 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.

<sup>b</sup> 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.

<sup>c</sup> 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. PD-L1 status will also be collected, if available.

<sup>d</sup> 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.

<sup>e</sup> A targeted, symptom-directed exam will be performed, as clinically indicated.

<sup>f</sup> ECOG performance status, targeted physical exam, and local laboratory assessments may be obtained  $\leq$  72 hours before each dosing visit.

<sup>g</sup> 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.



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<sup>h</sup> 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.

<sup>i</sup> 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.

<sup>j</sup> 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 infusion. If clinically indicated, vital signs should be at 15, 30, 45, and 60 minutes ( $\pm$  5 minutes for all timepoints) after the start of the infusion, and 30 ( $\pm$  10) minutes after the infusion. For subsequent infusions, vital signs will be collected within 60 minutes before the infusion and at 30 ( $\pm$  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.

<sup>k</sup> 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.

<sup>l</sup> 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 ( $\pm$  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 ( $\pm$  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.

<sup>m</sup> 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.

<sup>n</sup> Serum chemistry includes BUN or urea, creatinine, sodium, potassium, magnesium, chloride, bicarbonate or CO<sub>2</sub>, calcium, phosphorus, glucose, total bilirubin (direct bilirubin only if total bilirubin is elevated), ALT, AST, alkaline phosphatase, lactate dehydrogenase, total protein, and albumin.

<sup>o</sup> 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.

<sup>p</sup> 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.

<sup>q</sup> Thyroid function tests will be performed on first dose and every 6 weeks thereafter.



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<sup>r</sup> 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.

<sup>s</sup> A pre-treatment tumor tissue sample will be analyzed for ASPH expression as part of the screening process. After signing of the Informed Consent Form, tumor tissue should be submitted to the Sponsor in a timely manner. Samples will be collected and analyzed preferably before other non-SOC procedures. Eligibility based on ASPH expression will be provided back to the sites within 5-8 business days. 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. 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.

<sup>t</sup> 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 or until initiation of anti-cancer therapy, whichever occurs first.

<sup>u</sup> 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  $\pm$  3 days unless otherwise noted. A 60 minutes observation period is recommended for the first dose and 30 minutes for subsequent doses.

<sup>v</sup> 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  $\pm$  3 days unless otherwise noted. A 30-minute observation period is recommended after each study treatment.

<sup>w</sup> 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.



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## 14.2 Appendix B: Laboratory Cut off Values

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



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## 14.3 Appendix C: 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.



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## 14.4 Appendix D: Overall Status Calculation (Measurable Disease)

Time point response: patients with target (+/- non-target disease) at baseline			
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



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## 14.5 Appendix E: Overall Status Calculation (Non\_target Disease)

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 <sup>a</sup>
Not all evaluated	No	NE
Unequivocal PD	Yes or No	PD
Any	Yes	PD

CR = complete response, PD = progressive disease, and NE = inevaluable

<sup>a</sup>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.



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## 14.6 Appendix F: Calculation of Best Overall Response

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 <sup>a</sup>
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

<sup>a</sup> 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.