STATISTICAL ANALYSIS PLAN

Aduro Biotech, Inc.

ADU-CL-20

Protocol Title:	A Phase 2 Efficacy and Safety Trial of ADU-S100 and Pembrolizumab in Adults with Head and Neck Cancer
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1 STATISTICAL ANALYSIS PLAN APPROVAL

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3 LIST OF ABBREVIATIONS

Table 1 List of Abbreviations

Abbreviation	Definition
AE	adverse event
ALT	alanine aminotransferase
AST	aspartate aminotransferase
ATC	Anatomical Therapeutic Chemical
AUC	area under curve
BLQ	below the limit of quantification
BMI	body mass index
CI	confidence interval
CR	complete response
CRS	cytokine release syndrome
CSR	clinical study report
CV	coefficient of variation
DCR	disease control rate
DNA	deoxyribonucleic acid
DODC	duration of disease control
DOR	duration of response
EAS	evaluable analysis set
EBV	Epstein-Barr virus
EBNA	Epstein-Barr nuclear antigen
ECG	electrocardiogram
ECOG	Eastern Cooperative Oncology Group
eCRF	electronic Case Report Form
EOT	end of treatment
FT3	free tri-iodothyronine
FT4	free thyroxine
HBV	hepatitis B virus
HCV	hepatitis C virus
HIV	human immunodeficiency virus
HNSCC	head and neck squamous cell cancer
HPV	human papillomavirus
iBOR	immune best overall response
ICH	International Council for Harmonisation
iCR	immune complete response
iCPD	immune confirmed progressive disease

Abbreviation	Definition
IFN	interferon
Ig	immunoglobulin
IL	interleukin
IP	investigational product
iPR	immune partial response
iRECIST	modified RECIST v1.1 for immune-based therapeutics
iSD	immune stable disease
iUPD	immune unconfirmed progressive disease
IV	intravenous
MedDRA	Medical Dictionary for Regulatory Activities
NCI-CTCAE	National Cancer Institute Common Terminology Criteria for Adverse Events
NE	not evaluable
ORR	objective response rate
OS	overall survival
PFS	progression-free survival
PK	pharmacokinetic
PCR	polymerase chain reaction
PR	partial response
Q1	25^{th} percentile
Q3	75^{th} percentile
RECIST	Response Evaluation Criteria in Solid Tumors v1.1
SAE	serious adverse event
SAP	statistical analysis plan
SOD	sum of diameters
SD	stable disease
SI	Système International
SNP	single nucleotide polymorphisms
TEAE	treatment-emergent adverse event
TNF	tumor necrosis factor
TSH	thyroid stimulating hormone
ULN	upper limit of normal
VCA	viral capsid antigen
WHODDE	World Health Organization Drug Dictionary Enhanced

4 INTRODUCTION

The purpose of this statistical analysis plan (SAP) is to provide comprehensive and detailed descriptions of the methods and presentation of data analyses proposed for Aduro Biotech, Inc. Protocol ADU-CL-20 (A Phase 2 Efficacy and Safety Trial of ADU-S100 and Pembrolizumab in Adults with Head and Neck Cancer). Descriptions of planned analyses are provided in order to avoid post hoc decisions that may affect the interpretation of the statistical analysis. The statistical methods applied in the design and planned analyses of this study are consistent with the International Council for Harmonisation (ICH) guideline *Statistical Principles for Clinical Trials* (E9) (1998).

This SAP will be finalized prior to data analysis and before database lock; a separate document with templates for tables, listings, and figures will include the planned displays for the clinical study report (CSR). Any changes between the statistical methods provided in the clinical study protocol and this SAP will be explained herein; any changes or deviations from this SAP relative to the final analysis will be fully documented in the CSR. Minor changes or deviations from the templates for tables, figures, and listings will not be documented in the CSR.

In this SAP, the Investigational Product (IP) ADU-S100 and Standard of Care pembrolizumab are both considered "study drug." Throughout the SAP the term "study drug" is interchangeable between ADU-S100 and pembrolizumab. When referring to only one study drug, the SAP will specify ADU-S100 to indicate the IP or specify pembrolizumab to indicate the Standard of Care.

5 STUDY OBJECTIVES

5.1 Primary Study Objective

The primary objective of this study is to evaluate the clinical efficacy of ADU-S100 administered in combination with pembrolizumab.

5.2 Secondary Study Objectives

The secondary objectives of this study are to:

- Characterize safety and tolerability
- Further evaluate clinical activity
- Characterize the pharmacokinetics (PK) of ADU-S100 administered by intratumoral injection following a single dose and multiple doses

5.3 Exploratory Study Objectives

The exploratory objectives of this study are to:

- Assess pharmacodynamics, immunomodulatory, and potential prognostic and/or predictive biomarkers

- Perform pharmacogenetic analysis

6 INVESTIGATIONAL PLAN

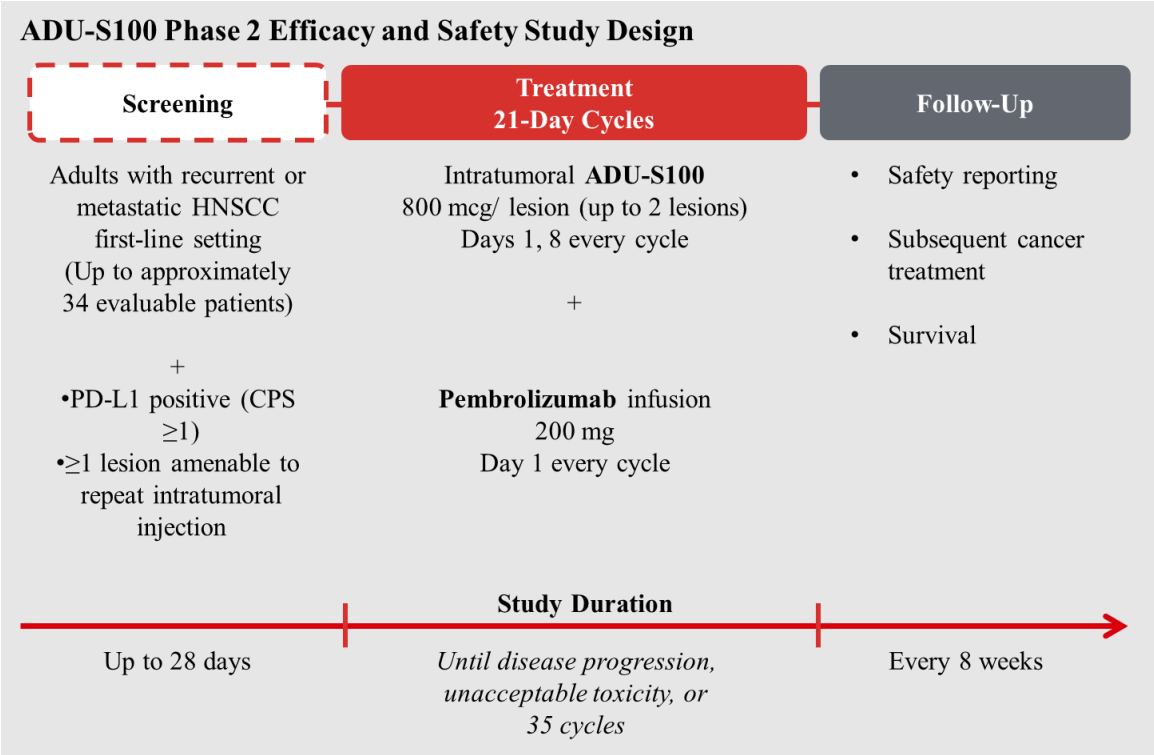
6.1 Overall Study Design

The ADU-CL-20 study is an open-label, multicenter Phase 2 clinical trial to evaluate the efficacy and safety of intratumoral ADU-S100 (also referred to as MIW815) administered with standard of care treatment (ie, pembrolizumab) in the first-line setting. The multicenter clinical trial will be conducted at approximately 25 sites in North America. Twenty evaluable subjects will initially be enrolled. If the total number responding is greater than or equal to 4, then an additional 14 evaluable subjects will be enrolled in the second stage for a total of 34 evaluable subjects.

The population for this study will consist of adults with metastatic head and neck squamous cell cancer (HNSCC) where pembrolizumab is indicated as the standard of care first line treatment. Individuals with intercurrent illnesses, inadequate organ function, various conditions impacting immune function, or other mitigating factors as detailed in the exclusion criteria will not be enrolled as these factors may interfere with the proposed mode of action of ADU-S100 and pembrolizumab, introduce undue safety risks, or confound interpretation of study results.

The trial design consists of a Screening Period, Treatment Period, and a Follow-up Period as depicted in Figure 1. Screening assessments will be conducted to confirm eligibility and to obtain baseline (pre-treatment) measurements. Screening must be completed within 28 days prior to the first dose of either study drug. An enrollment form will confirm subject eligibility; baseline biopsies will not be performed until enrollment is confirmed. All eligible subjects will receive intravenous (IV) infusions of pembrolizumab (200 mg) and intratumoral injections of ADU-S100 (800 mcg/lesion; up to 2 lesions). During the Treatment Period, study medications will be administered in 21-day dosing cycles until criteria for treatment discontinuation are met, or up to 35 cycles. Tumor responses will be evaluated at 9-week intervals. The Follow-up Period is designed to assess vital status, subsequent anti-cancer therapy, and complete safety reporting requirements.

Figure 1 ADU-CL-20 Study Design



Subjects will be requested to complete multiple clinic visits during all dosing cycles. An end of treatment (EOT) visit will occur 30 (+7) days after the last dose of study drug. All EOT visit assessments will be completed prior to commencing any new anti-cancer therapy.

After completion of the EOT visit, follow-up visits will be conducted at 8-week intervals to satisfy protocol-specified safety reporting periods, and collect data on any subsequent cancer-related therapies as well as vital status. Follow-up visits may be conducted at the site or via telephone call, as appropriate.

Subjects who discontinue study drug early for reasons other than progressive disease will complete the EOT visit and will be asked to continue tumor response assessments. Follow-up visits will also be conducted at 8-week intervals for these subjects.

All study visits (and visit windows), assessments, and procedures will be performed as indicated in Appendix A: Schedule of Events. On days when the study drug is administered, assessments will be performed prior to dosing unless otherwise specified.

6.2 Determination of Sample Size

The study will include up to 34 evaluable subjects to assess the clinical efficacy of ADU-S100 administered in combination with pembrolizumab in adults with head and neck cancer. Power calculations based on a Simon's 2-stage minimax design test the null hypothesis that the objective response rate (ORR) is less than or equal to 0.19 versus the

alternative hypothesis that the ORR is greater than or equal to 0.38 with a Type 1 error rate of 0.05 and power of 80%. A sample size of 20 evaluable subjects will be enrolled in the first stage. If the total number responding is greater than or equal to 4, an additional 14 evaluable subjects will be enrolled in the second stage for a total of 34 evaluable subjects. For the second stage, if the total number responding is less than or equal to 10, the effectiveness of treatment based on ORR will be rejected.

If treatment is actually not effective and ORR ≤ 0.38, then the expected sample size is 25.3 evaluable subjects with a 0.456 probability of early termination and a 0.044 probability of incorrectly concluding the treatment is effective (the target for this Type 1 error rate was 0.05 or less). If the treatment is actually effective, there is a 0.200 probability of incorrectly concluding it is not effective (the target for this Type 2 error rate was 0.200 or less).

Subjects who do not complete a response assessment will not be considered evaluable and will be replaced.

The ORR criteria are based on the pembrolizumab first-in-human study in a similar patient population with similar prior treatment where the response rate was approximately 19% (Burtness et al. 2018; Rischin et al. 2019).

6.3 Schedule of Assessments

For the complete schedule of assessments, refer to Appendix A: Schedule of Events.

6.4 Treatments

6.4.1 Treatments Administered

- ADU-S100 (MIW815; disodium dithio-(RP, RP)-[cyclic [A(2',5')pA(3',5')p]]), is a synthetic CDN composed of two adenosine monophosphate (AMP) analogues cyclized via a 2',5' (noncanonical) and a 3',5' (canonical) phosphodiester bond.

  All lesions designated for ADU-S100 administration will be injected on Days 1 and 8 of each dosing cycle (ie, do not rotate/alternate sites for injection; all designed lesions will be injected on every dosing day).

- Pembrolizumab is an immunoglobulin G4 (IgG4) kappa immunoglobin with an approximate molecular weight of 146 kDa.

  On dosing days where both pembrolizumab and ADU-S100 are indicated, the pembrolizumab infusion will be administered first, followed by an intratumoral injection of ADU-S100.

6.4.2 Method of Assigning Subjects to Treatment Groups

All subjects will be sequentially assigned a unique identification number during Screening. The study is designed as a single-arm study; all subjects will receive ADU-S100 and pembrolizumab as indicated.

6.5 Efficacy and Safety Variables

6.5.1 Efficacy Variables

6.5.1.1 Primary Efficacy Variable

The primary efficacy endpoint is the objective response rate (ORR) defined as the proportion of subjects in whom a complete response (CR) or a partial response (PR) is observed. The Response Evaluation Criteria in Solid Tumors (RECIST) v1.1 will be used to evaluate the primary efficacy endpoint. All responses will be confirmed at the subsequent tumor assessment.

6.5.1.2 Secondary Efficacy Variables

Secondary efficacy endpoints include the following:

- Overall Survival (OS): defined as the time from first dose of either study drug until date of death due to any cause. Subjects without documentation of death at the time of analysis will be censored as of the date the subject was last known to be alive.

- Progression-Free Survival (PFS): defined as the time from first dose of either study drug to first documentation of disease progression or death due to any cause. Subjects who do not experience progressive disease and are alive at the time of analysis will be censored at the time of last evaluable tumor assessment. Subjects who receive anti-cancer therapy prior to documented disease progression will be censored on the date of last evaluable tumor assessment on or prior to the start date of the anti-cancer therapy. Subjects with no on-treatment tumor assessments will be censored on the date of treatment start.

- Duration of Response (DOR): defined as the time from the first tumor assessment that supports the subject's objective disease response to the time of disease progression or death due to any cause. Subjects who have ongoing response at the time of analysis will be censored at the time of last evaluable tumor assessment. Subjects who receive anti-cancer therapy prior to documented disease progression will be censored on the date of last evaluable tumor assessment on or prior to the start date of the anti-cancer therapy. Subjects with no on-treatment tumor assessments will be censored on the date of treatment start.

- Disease Control Rate (DCR): defined as the proportion of subjects with CR, PR, or stable disease (SD).

- Duration of Disease Control (DODC): defined as the time from the first tumor assessment that supports the subject's disease control (CR, PR, SD) to the time of disease progression or death due to any cause; if the subject has a best response of SD, then DODC is calculated from date of baseline tumor assessment to the time of disease progression or death due to any cause. For subjects who have ongoing disease control at the time of analysis, their DODC will be censored at the time of last evaluable tumor assessment. Subjects who receive anti-cancer therapy prior to documented disease progression will be censored on the date of last evaluable tumor assessment on or prior to the start date of the anti-cancer therapy. Subjects with no on-treatment tumor assessments will be censored on the date of treatment start.

- ORR per modified RECIST v1.1 for immune-based therapeutics (iRECIST), where all noted disease progression will be confirmed at the subsequent tumor assessment

- Occurrence and severity of treatment-emergent adverse events

- Changes from baseline in safety assessments

- Plasma concentration-time profiles and derived noncompartmental PK parameters (including C_{max}, area under curve [AUC])

Progression-free survival, DOR, DCR, and DODC will be determined per RECIST v1.1 and iRECIST. Section 7.4.6.2 contains a full table of the censoring rules that will be used in these analyses. Section 7.4.6.3 contains additional information regarding response assessment per iRECIST. Section 7.4.6.8 contains additional information regarding subgroup analysis.

6.5.2 Description of Safety Variables

Safety will be assessed by collection of data on treatment-emergent adverse events (TEAEs), Eastern Cooperative Oncology Group (ECOG) performance status, vital signs, weight, physical examination, electrocardiogram (ECG) parameters, concomitant medications, and routine clinical laboratory assessments. Clinically significant changes from pre-treatment values in safety assessments will be reported as adverse events (AEs). Safety assessments described below will be conducted according to Appendix A: Schedule of Events.

6.5.2.1 Adverse Events

An AE is defined as any untoward medical occurrence associated with the use of a drug in humans, whether or not considered drug-related. An AE can therefore be any unfavorable and/or unintended sign (including an abnormal laboratory finding), symptom, or disease temporally associated with the use of an investigational medicinal product, whether or not related to the investigational medicinal product.

See Section 11.1.2 of the study Protocol for further details regarding the definition of AEs.

6.5.2.2 Serious Adverse Events

An AE or adverse reaction is considered serious if, in the view of either the Investigator or Sponsor, it results in any of the following outcomes:

- Death
- A life-threatening AE
- Requires hospitalization or prolongation of existing hospitalization
- A persistent or significant incapacity or substantial disruption of the ability to conduct normal life functions
- A congenital anomaly/birth defect
- An important medical event

See Section 11.2 and 11.3 of the study Protocol for further details regarding serious adverse events (SAEs) and reporting.

6.5.2.3 Eastern Cooperative Oncology Group (ECOG) Scale of Performance Status

The ECOG Scale of Performance Status is recognized as a standard tool to measure disease impact on daily living activities (Oken et al. 1982). The ECOG scale will be used by site personnel to determine eligibility and characterize a subject's level of functioning (self-care, daily activity, and basic physical ability) as indicated in Appendix A: Schedule of Events.

The ECOG performance status will be classified according to the following categories:

- 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, eg, 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

6.5.2.4 Vital Signs

Vital signs, including blood pressure, pulse rate, respiratory rate, and temperature will be obtained at each indicated visit (prior to dosing, as applicable). Serial time points following ADU-S100 administration support monitoring for cytokine release syndrome (CRS) during Cycle 1. Vital signs will be collected prior to dosing and as indicated in Appendix A: Schedule of Events. Additional measurements will be obtained if clinically indicated.

6.5.2.5 Comprehensive Physical Examination

Comprehensive physical examinations will be conducted at Screening and EOT. The comprehensive physical examination will include the following organ or body system assessments: skin; head, eyes, ears, nose, and throat; thyroid; lungs; cardiovascular system; abdomen (liver and spleen); extremities; lymph nodes; and a brief neurological examination.

6.5.2.6 Symptom-directed Physical Examination

Symptom-directed physical examinations may be conducted at all other visits as indicated (up to 3 days prior to dosing). The Investigator or medically licensed designee will perform a symptom-directed evaluation as clinically indicated, including assessment(s) of the body systems or organs based on a subject's symptoms, AEs, or other findings.

6.5.2.7 Weight

Weight (kg) will be obtained at each indicated visit (prior to dosing, if applicable).

6.5.2.8 Electrocardiogram (ECG)

At screening and during the study, triplicate ECG assessments will be performed with local 12-lead ECG equipment according to standard procedures to determine the corrected QT interval calculated by Fridericia's formula (QTcF). At screening, the average value of the triplicate will be utilized for enrollment into the study.

The triplicates will be performed no less than 3 minutes apart and within approximately 30 minutes of the initial ECG to determine the mean QTcF interval. All 12-lead ECGs should be performed after the subject has rested in a recumbent or semi-recumbent position for ≥ 5 minutes. Additional ECGs may also be performed throughout the study if clinically indicated. The ECGS will be performed prior to study drug administration for all pre-dose assessments. If blood sampling or vital sign measurement is scheduled for the same visit as an ECG recording, the procedures will be performed in the following order: ECG, vital signs, blood draw.

ECG parameters to be evaluated include heart rate, PR interval, QT interval, QRS duration, and QTcF.

The ECG will be interpreted by the Investigator as normal, not clinically significant abnormal, or clinically significant abnormal. If the mean QTcF is prolonged (ie, > 500 msec, or CTCAE Grade 3) or if the mean change from baseline is ≥ 60 msec, the ECGs will be reevaluated by a qualified person.

6.5.2.9 Prior and Concomitant Medications

Medications used within 28 days prior to the first dose of ADU-S100 will be recorded as prior medications.

Concomitant medications include pre-medications and all prescription, over the counter medications, herbal remedies and dietary supplements administered from Cycle 1 Day 1 until the EOT visit. The generic name, dosage, duration, and reason for the concomitant medication will be documented. If a subject is using biotin supplements (found in multivitamins, biotin supplements, and supplements for hair, skin, and nail growth), these will also be noted for laboratory assessments. Changes in the use of concomitant medications will be captured at each study visit.

Following the EOT visit, concomitant medications will only be collected if associated with the management of an ongoing AE or SAE, or if a new anti-cancer treatment.

6.5.2.10 Screening-Specific Laboratory Assessments

Blood and urine samples will be obtained at screening to confirm eligibility for each subject. These initial laboratory assessments will be conducted at the institution's local laboratory:

- Virology/Serology Screen: human immunodeficiency virus (HIV) antibody, hepatitis B (HBV) surface antigen, hepatitis C (HCV) antibody, HCV viral load (if indicated), Epstein-Barr virus (EBV) (Epstein-Barr nuclear antigen [EBNA], viral capsid antigen [VCA] immunoglobulin G [IgG], VCA immunoglobulin M [IgM], EBV polymerase chain reaction [PCR] as clinically indicated)

- Urinalysis (dipstick or automated analysis): bilirubin, blood, glucose, ketones, leukocytes, nitrite, pH, protein, and specific gravity

    - If dipstick result is abnormal, microscopy will be used to measure sediment (red blood cells, white blood cells, epithelial cells, crystals, casts, bacteria)

    - Additional urinalysis may be performed throughout the study if clinically indicated

6.5.2.11 Safety Laboratory Assessments

Routine hematology, serum chemistry, coagulation panel, and thyroid function testing will be conducted to assess eligibility and as a measure of safety throughout the study per protocol requirements. All clinical laboratory evaluations will be performed by the institution's local laboratory. Laboratory assessments for continued dosing of pembrolizumab must be confirmed prior to dosing; testing may be completed up to 3 days prior to study drug administration for each cycle. Fasting is not required; however fasting blood glucose will be performed if clinically indicated.

The following parameters will be evaluated:

- Hematology: complete blood count (hematocrit, hemoglobin, platelets, red blood cells, white blood cells with differential [absolute counts: basophils, eosinophils, lymphocytes, monocytes, neutrophils])
- Serum chemistry: albumin, alkaline phosphatase, alanine aminotransferase (ALT), aspartate aminotransferase (AST), bicarbonate, calcium, chloride, lactate dehydrogenase, sodium, potassium, creatinine, glucose, magnesium, phosphate (inorganic phosphorus), bilirubin (total, direct), blood urea nitrogen, uric acid, total protein
- Coagulation panel: prothrombin time, international normalized ratio of prothrombin time, activated partial thromboplastin time
- Thyroid function: thyroid stimulating hormone (TSH), free tri-iodothyronine (FT3), free thyroxine (FT4)

6.5.2.12 Drug-induced Liver Injury

The potential for drug-induced liver injury will be monitored using assessments of liver function via serum chemistry at regular intervals. Laboratory values consistent with Hy's Law criteria will be used to indicate the potential for drug-induced liver injury (ie, all 3 of the following must coexist):

1) ALT or AST $\geq 3 \times$ upper limit of normal (ULN)
2) Total bilirubin $\geq 2 \times$ ULN
3) ALP $< 2 \times$ ULN

Should the laboratory parameters suggesting drug-induced liver injury be observed, other potential causative factors may be investigated (eg, viral hepatitis A, HBV, or HCV; preexisting or acute liver disease; or another drug capable of causing the observed injury).

6.5.2.13 Laboratory Assessments for Cytokine Release Syndrome

Blood (plasma) samples will be collected at Screening and as clinically indicated for assessment of interferon gamma (IFN-γ), interleukin 6 (IL-6), IL-1, tumor necrosis factor alpha (TNF-α), C-reactive protein, and ferritin. If CRS is suspected, a blood (plasma) sample will be collected within 5 hours (or as soon as possible) after occurrence of the event, and 1 week after occurrence of the event.

6.5.2.14 Pregnancy Testing and Contraception Requirements

For study eligibility, women of childbearing potential must have a negative serum pregnancy test at Screening and within 24 hours prior to first dose of study drug. A urine pregnancy test may be performed at all other indicated visits. In case of delayed menstrual period (> 1 month), absence of pregnancy will be confirmed prior to next dose of study drug or next study visit, whichever occurs first. If a urine pregnancy test is positive, the results will be confirmed with a serum pregnancy test. Pregnancy of a subject or partner will be reported and followed.

6.5.2.15 Exploratory Safety Variables

Exploratory safety endpoints include the following:

- Changes from baseline in selected protein, cellular, and genomic expression parameters from blood and tissue samples; prognostic and/or predictive value
- Exploration of individual subject deoxyribonucleic acid (DNA) sequence variations (eg, single nucleotide polymorphisms [SNPs]) and relationship with safety, tolerability, and clinical benefit

6.5.3 Description of Pharmacokinetic Variables

Blood samples will be obtained at time points specified in Table 2 to characterize the plasma concentrations of ADU-S100 when administered with pembrolizumab after a single dose (Cycle 1 Day 1) and after repeat dosing (Cycle 1 Day 8 and Cycle 2 Day 1).

Table 2 ADU-S100 PK Sampling Schedule

CYCLE	DAY	SCHEDULED TIME (Sampling Window) [1]
Cycle 1	1	Pre-dose (within 60 min prior to ADU-S100 dosing) Post-dose: 1 h (±15 min), and 2 h (±15 min)
	8	Pre-dose (within 60 min prior to ADU-S100 dosing) Post-dose: 1 h (±15 min), and 2 h (±15 min)
Cycle 2	1	Pre-dose (within 60 min prior to ADU-S100 dosing) Post-dose: 1 h (±15 min), and 2 h (±15 min)

[1] Post-dose is defined as time from completion of first ADU-S100 intratumoral injection.

The time points specified in Table 2 are applicable to subjects who consented under Protocol Amendment 3 or beyond. Subjects who consented under Protocol Amendment 1 will have the following post-dose sampling time points: 2 min (±2 min), 15 min (±2 min), 30 min (±5 min), 1 h (±5 min), and 2 h (±10 min). Subjects who consented under Protocol Amendment 2 will have the following post-dose sampling time points: approximately 2 min, approximately 15 min, 30 min (±5 min), 1 h (±5 min), and 2 h (±10 min).

When feasible, the following PK parameters will be estimated by non-compartmental methods using actual elapsed time from dosing:

- $AUC_{0\text{-last}}$: Area under the concentration-time curve <*insert unit as concentration unit * hours*>(h*ng/mL) from time zero (pre-dose) to the last measureable concentration, calculated by the linear trapezoidal rule;

- C_{max}: Maximum concentration <*insert unit*>(ng/mL), obtained directly from the observed concentration versus time data;

For calculations using the linear trapezoidal rule, the following formula will be used:

$$AUC = \frac{1}{2}(C_1 + C_2)(t_2 - t_1)$$

6.5.4 Biomarker Assessments

Whole blood, plasma, and tumor tissue will be collected from all enrolled subjects (where not prohibited by local regulations or policies). The results may help to inform dose selection, monitor baseline and post-treatment immune responses; and possibly further characterize the mechanism of action and/or determine potential prognostic and/or predictive biomarkers.

6.6 Data Quality Assurance

Report summaries will be generated using validated Base SAS® software, version 9.4 or higher, on a PC or server-based platform. Additional validated software may be used to generate analyses, as needed.

All SAS programs that create outputs or supporting analysis datasets will be validated by a second statistical programmer or biostatistician. At a minimum, validation of programs will consist of a review of the program log, review of output or dataset format and structure, and independent confirmatory programming to verify output results or dataset content. Additionally, all outputs will undergo a review by a senior level team member before finalization.

The content of the source data will be reviewed on an ongoing basis by project statistical programmers and statisticians. Data will be checked for missing values, invalid records, and extreme outliers through defensive programming applications, analysis-based edit

checks, and other programmatic testing procedures. All findings will be forwarded to the project data manager for appropriate action and resolution.

7 STATISTICAL METHODS

7.1 General Methodology

Data will be analyzed by Precision for Medicine biostatistics personnel unless otherwise noted. Statistical analyses will be reported with tables, figures, and listings, presented in rich text format, and using recommended ICH numbering. Output specifications for all tables, figures, and listings will be in conformance with guidelines specified by the ICH in Appendix 7 of the *Electronic Common Technical Document Specification* (Apr 2003).

7.1.1 Reporting Conventions

In general, all data collected and any derived data will be presented in subject data listings, for all enrolled subjects. Listings will be ordered by subject number and assessment or event date.

In general, continuous variables will be summarized to indicate the study population sample size (N), number of subjects with available data (n), mean, standard deviation, median, 25th (Q1) and 75th (Q3) quartiles, minimum, and maximum values. Categorical variables will be summarized by the population size (N), number of subjects with available data (n), number of subjects in each category, and the percentage of subjects in each category. Unless otherwise noted, the denominator to determine the percentage of subjects in each category will be based on the number of subjects with available data. Select ordinal data may be summarized using both descriptive statistics and counts and percentages of subjects in each category, as appropriate.

Non-zero percentages will be rounded to one decimal place. Rounding conventions for presentation of summary statistics will be based on the precision of the variable of summarization, as it is collected in its rawest form (ie, on the electronic Case Report Form [eCRF] or as provided within an external file) and are outlined as follows:

- The mean and median will be rounded to one more decimal place than the precision of the variable of summarization;
- Measures of variability (eg, standard deviation) will be rounded to two more decimal places than the precision of the variable of summarization; and
- Minimum and maximum values will be presented using the same precision as the variable of summarization.

Other statistics (eg, confidence intervals) will be presented using the same general rules outlined above, or assessed for the most appropriate presentation based on the underlying data.

7.1.2 Summarization by Visit

Data summarized by study visit will be based on the nominal, scheduled visit label as reported on the eCRF. Data will also be summarized separately for the last visit completed on study.

Data collected at unscheduled visits will not be included in by-visit summaries, but will be considered when endpoint derivations potentially include multiple visits (eg, determination of baseline value, determination of worst post-baseline value, etc.). All data will be included in subject listings.

7.1.3 Data Handling Rules

Unless otherwise noted, values reported as greater than or less than some quantifiable limit (eg, "< 1.0") will be summarized with the sign suppressed in summary tables and figures, using the numeric value reported. Data will display on subject listings to include the sign.

7.1.4 Standard Calculations

Where appropriate, the calculated study day of each assessment or event will be presented with the assessment or event date on subject data listings, where study day will be determined as:

- The assessment/event date minus the date of study drug dosing, if the assessment/event date is prior to the date of study drug dosing; and
- The assessment/event date minus the date of study drug dosing, plus one, if the assessment/event date is on or after the date of study drug dosing.

Other variables requiring calculations will be derived using the following formulas:

- **Days:** A duration between two dates expressed in days will be calculated using the following conventions:
    - Later date – earlier date + 1, if the earlier date is on or after the date of study drug dosing; or
    - Later date – earlier date, if the earlier date is prior to the date of study drug dosing.
- **Months:** A duration expressed in months will be calculated by dividing the duration in days by (365.25 / 12);
- **Years:** A duration expressed in years will be calculated by dividing the duration in days by 365.25;

- **Change from Baseline:** Baseline is defined as the last available measurement taken prior to the first dose of either study drug. Change from baseline will be calculated as the post-baseline value minus the baseline value;

- **Percentage Change from Baseline:** Percentage change from baseline will be calculated as the change from baseline divided by the baseline value, multiplied by 100.

7.2 Analysis Populations

The analysis populations are defined as follows:

- All Treated Population: Includes all subjects who received any amount of either study drug.

- Evaluable Analysis Set (EAS): Includes all subjects who received any amount of either study drug and additionally who either have at least one evaluable response assessment or who discontinued the study for a reason of toxicity, clinical progression, or death.

- Modified All Treated Population: The protocol inclusion criteria require eligible subjects to be PD-L1 positive (defined as combined positive score [CPS] ≥1). If any subject with baseline CPS<1 were to be enrolled (a protocol deviation), then a Modified All Treated Population is defined as the All Treated Population excluding subjects with baseline CPS<1.

Though subjects with baseline CPS<1 are not expected on study, if this were to occur, the Modified All Treated Population would be used for Efficacy summary analysis, rather than the All Treated Population. Otherwise, the All Treated Population will be used for both Efficacy and Safety analyses. Sensitivity analysis of efficacy on the EAS population will be presented only if there is a considerable difference between the EAS and the All Treated Population.

7.3 Study Subjects

7.3.1 Disposition of Subjects

Subject disposition will be summarized for all enrolled subjects. Summaries will include the number and percentage of subjects in each analysis population, receiving each study drug and both study drugs, study completion, primary reason for early discontinuation of treatment, and primary reason for early discontinuation from study.

7.3.2 Protocol Deviations

Important protocol deviations will be summarized over all subjects combined for the All Treated Population and will be listed for all subjects. Important protocol deviations are

protocol deviations captured on-study that are deemed by the Sponsor to potentially impact the efficacy or safety conclusions of the study.

All important protocol deviations will be determined and appropriately categorized prior to database lock. Important deviations are collected as "major". The number and percentage of subjects with any important protocol deviations as well as the number and percentage of subjects with deviations within each category will presented. Protocol deviations related to the coronavirus (COVID-19) pandemic will be summarized and listed separately.

7.4 Efficacy Evaluation

7.4.1 Datasets Analyzed

All efficacy summaries will be based on the All Treated Population, as described in Section 7.2. A data listing of subjects excluded from the efficacy analysis, to include the reason for exclusion, will be presented.

7.4.2 Demographic and Other Baseline Characteristics

Demographic variables including age, sex, ethnicity and race will be summarized for the All Treated Population. Age will be summarized using descriptive statistics. Sex, ethnicity, and race will be summarized with the number and percentage of subjects in each parameter category.

Baseline characteristics include medical history, cancer history, prior cancer treatment, height, weight, body mass index (BMI), smoking history, and ECOG performance status Disease characteristics include disease stage at study entry, type of staging, site of primary tumor, HPV status, PD-L1 status, time from diagnosis of HNSCC, number of tumors, and sum of target lesion diameters. Height, weight, BMI, time from diagnosis of HNSCC, number of tumors, and sum of target lesion diameters at baseline will be summarized using descriptive statistics; frequency counts and percentages to summarize prior cancer treatment, smoking history, ECOG performance, disease stage, type of staging, site of primary tumor, HPV status, and PD-L1 status at baseline will be presented. Frequency counts and percentages to summarize subjects reporting medical history by body system will also be presented.

7.4.3 Measurements of Treatment Compliance

Treatment compliance will be summarized for the All Treated Population. The numbers of delays of each study drug will be presented. For Pembrolizumab, which is administered as an infusion, the drug administration could be interrupted or discontinued. For ADU-S100, which is administered as an injection, the drug administration could be paused or stopped. The number and percentage of subjects with delays of each study drug will also be presented.

7.4.4 Primary Efficacy Endpoint Analysis Methods

The primary efficacy endpoint is ORR as defined in Section 6.4.1.1 and will be summarized for the All Treated Population.

Summaries of ORR will include the number and percentage of subjects with an objective response and the corresponding two-sided 95% confidence interval (CI) based on the exact binomial method (Clopper-Pearson). Waterfall plots will be provided showing the best overall tumor response. A swimmer plot of disease status for RECIST and iRECIST will be provided. Also, a spider plot of percent change in tumor size relative to baseline will be provided.

Tumor diameters recorded on the Target and New Lesions CRF pages will be utilized for analysis summaries. Diameters recorded on the Dose Administration CRF page or the Injected Lesion Photo CRF page will not be utilized for analysis.

7.4.4.1 Supplemental Analysis for Primary Efficacy Endpoint

Of exploratory interest are potential differences in tumor shrinkage in injected target lesions and non-injected target lesions within the same subject. A waterfall plot showing the maximal percentage change from baseline for sum of diameters (SOD) for injected target lesions and for SOD for non-injected target lesions will be provided dependent on collection of measurement data for both types of target lesions. Tumor measurements recorded on Target Lesion and New Lesion pages will be utilized for analysis. Measurements on the Dose Administration page will not be utilized here.

The protocol specifies that if an injected lesion shows signs of significant regression (i.e. shrinkage) that precludes the ability to re-inject the lesion, other accessible lesions may be injected. As such, a non-injected target lesion may become an injected target lesion at a subsequent timepoint. As stated in Goldmacher et al 2020, "... it is not meaningful to report maximal shrinkage of injected lesions compared with the chronologic baseline. ... measuring the maximal effect on only the lesions initially chosen for injection may miss critical information."

Under these considerations, data for the injected target and non-injected target lesions will be analyzed on an exploratory basis using the following definitions adapted from Goldmacher et al 2020:

A. For injected target lesions, the baseline for each individual lesion will be defined as the measurement obtained prior to first injection of that lesion. Specifically,

    - For target lesions injected at C1D1, the baseline will be defined as the measurement obtained prior to C1D1.

    - As the protocol allows for injection of other accessible lesions if a lesion shows signs of significant regression (i.e. shrinkage) that precludes the ability to re-inject the lesion, the baseline measurement for these newly injected lesions will be the preceding measurement obtained prior to the

lesion's initial injection. The baseline for these lesions will not be the measurement prior to C1D1.

- As this analysis will consider any new lesion target lesions (per iRECIST), if these new target lesions are injected, the baseline measurement for these lesions will be the preceding measurement obtained prior to the lesion's initial injection. The baseline for these lesions will not be the measurement prior to C1D1.

- Baseline SOD is defined as the sum of the individual lesion diameters at baseline. If a lesion becomes injected after C1D1, the baseline injected SOD will incorporate data from different timepoints.

- Best response SOD also can incorporate data from different timepoints, regardless of if a lesion was injected after C1D1. However, only measurements which occur after initial injection can be considered for best response.

B. For non-injected target lesions

- As long as the non-injected target lesions remain non-injected, the non-injected target SOD is compared with measurements obtained prior to C1D1. If any non-injected target lesion must be injected (eg, because disappearance of other injected target lesions or because of inaccessibility of other lesions), the maximal non-injected response has been achieved and any subsequent non-injected response is considered nonevaluable.

A lesion's injection status will be determined based on the ADU-S100 Administration page of the CRF which collects "Was this lesion injected at this visit?". If a lesion is reported as "Yes" at a specific time point, then the lesion is considered injected from that timepoint onwards. Prior to that injection timepoint, it will be considered non-injected. Once a lesion is injected, it will be considered an injected target lesion for all subsequent timepoints, even if it is not injected at a later timepoint.

7.4.5 Secondary Endpoint Analysis Methods

The calculation of ORR and accompanying CI will be repeated for the EAS. The secondary efficacy endpoints described in Section 6.4.1.2 will be summarized for the All Treated Population.

Overall survival and PFS will be analyzed with standard survival methods (Kaplan-Meier estimates) to include the number of subjects who are alive at data cut-off, number of subjects censored, percentiles (including 95% CIs determined by the Brookmeyer and Crowley method) and range. Kaplan-Meier summaries, including graphs of survival curves, will be generated for all subjects receiving study drug.

Progression-free survival at 6, 12, and 24 months (including 95% CIs determined by Greenwood's formula), DOR, and DODC will be analyzed with the same statistical methodologies as applied to OS.

DCR will be calculated along with accompanying CIs, similar to ORR.

Censoring rules for the analysis of each endpoint are described in Section 7.4.6.2. Subgroup analysis is described in Section 7.4.6.8.

7.4.6 Statistical/Analytical Issues

7.4.6.1 Adjustments for Covariates

There are no planned applications of covariate adjustments; all statistical results are descriptive in nature.

7.4.6.2 Handling of Dropouts or Missing Data

Censoring rules for the analysis of each secondary endpoint are summarized in Table 3 shown on the next page.

Table 3 Censoring Rules for OS, PFS, DOR, and DODC

Endpoint	Situation	Date of Censoring
OS	No documentation of death	Date that the subject was last known to be alive
PFS, DODC	No progression and no death	Date of last evaluable tumor assessment
PFS, DODC	Anti-cancer therapy prior to documented disease progression	Date of last evaluable tumor assessment on or prior to the start date of the anti-cancer therapy
PFS, DODC, DOR	No on-treatment tumor assessment	Date of treatment start
DODC	Ongoing disease control at time of analysis	Date of last evaluable tumor assessment
DOR	Ongoing response	Date of last evaluable tumor assessment

No other missing data will be imputed.

7.4.6.3 iRECIST Response Assessment

iRECIST is based on RECIST criteria. There are no changes compared to RECIST to the recommendations regarding the method of measurement. All responses per iRECIST have a prefix of "i" (ie, immune)—eg, "immune" complete response (iCR) or partial response (iPR),

and unconfirmed progressive disease (iUPD) or confirmed progressive disease (iCPD) to differentiate them from responses assigned using RECIST 1.1. Similar nomenclature is used for stable disease (iSD).

The iRECIST response assessment allows for the occurrence of pseudoprogression where a subject may appear to worsen before a delayed response occurs. Thus, instances of iRECIST progressive disease require confirmation. That is, if iUPD is not confirmed as iCPD, then the response effectively resets with the next iRECIST evaluation. In the event that no further response assessment follows the iUPD assessment (eg, subject was not judged to be clinically stable or subject refusal, protocol noncompliance, or death) or if all subsequent timepoint responses are iUPD, then date of iUPD can be used for analysis. Several examples of assignments of best overall response using iRECIST, are presented in Table 4, adapted from the RECIST working group guidelines (Seymour et al. 2017).

Table 4 Scenarios of Assignments of Best Overall Response using iRECIST

	Timepoint Response 1	**Timepoint Response 2**	**Timepoint Response 3**	**Timepoint Response 4**	**Timepoint Response 5**	**iBOR**
Ex. 1	iCR	iCR, iUPD, or NE	iCR, iUPD, or NE	iUPD	iCPD	iCR
Ex. 2	iUPD	iPR, iSD, or NE	iCR	iCR, iUPD, or NE	iCR, iPR, iSD, iUPD, iCPD, or NE	iCR
Ex. 3	iUPD	iPR	iPR, iSD, iUPD, or NE	iPR, iSD, iUPD, NE, or iCPD	iPR, iSD, iUPD, NE, or iCPD	iPR
Ex. 4	iUPD	iSD or NE	iPR	iPR, iSD, iUPD, or NE	iPR, iSD, iUPD, iCPD, NE	iPR
Ex. 5	iUPD	iSD	iSD, iUPD, or NE	iSD, iUPD, iCPD, or NE	iSD, iUPD, iCPD, NE	iSD
Ex. 6	iUPD	iCPD	Any	Any	Any	iCPD
Ex. 7	iUPD	iUPD (no iCPD)	iCPD	Any	Any	iCPD
Ex. 8	iUPD	NE	NE	NE	NE	iUPD

Abbreviations for Table 4: iBOR = immune best overall response; iCPD = immune confirmed progressive disease; iCR = immune complete response; iPR = immune partial response; iSD = immune stable disease; iUPD = immune unconfirmed progressive disease; NE = not evaluable

7.4.6.4 Interim Analyses and Data Monitoring

There are no interim analyses planned, nor is there a plan to establish a data monitoring committee for this study.

7.4.6.5 Multicenter Studies

This is a multicenter study, with approximately 25 sites expected to participate. Efficacy data collected from all study sites will be pooled for data analysis. The effect of study site on the efficacy analysis results may be explored post-hoc, as needed.

7.4.6.6 Multiple Comparisons/Multiplicity

There will be no adjustments for multiple comparisons in the efficacy analysis for this study. Results are descriptive in nature and there will be no formal comparisons made.

7.4.6.7 Active-Control Studies Intended to Show Equivalence

This study does not include an active-control product and is not intended to demonstrate equivalence between any two drug products.

7.4.6.8 Examination of Subgroups

Subgroup analysis provides further exploratory information. Subgroups may have small samples sizes insufficient for statistical inference, and statistical information such as CIs would be informational only. The ORR, OS, and PFS will be summarized by various subgroups of interest including combined positive score (1% ≤ PD-L1 expression < 20% and ≥ 20% PD-L1 expression) and human papillomavirus (HPV) status.

Waterfall plots will be provided showing the best overall tumor response by primary tumor location and by disease status. A swimmer plot will be provided by primary tumor location and by disease status.

A forest plot showing the ORR of subgroups will be created for subgroups of interest provided that sufficient data are collected within the subgroups. Subgroups of interest could include the following characteristics: combined positive score (1 ≤ PD-L1 expression < 20 and ≥ 20% PD-L1 expression), HPV status, age (< 65 years old and ≥ 65 years old), gender, race, ECOG performance status at baseline, disease stage at baseline, tobacco use, prior surgery, prior radiotherapy, site of primary tumor (larynx, oral cavity, oropharynx, hypopharynx, and all other [nasal cavity, paranasal sinuses, other]), and subsequent therapy.

7.4.7 Plasma Concentrations

Plasma concentration values will be summarized for the All Treated Population by sampling time point using descriptive statistics, to include the geometric mean and geometric CV (%). The geometric CV is calculated as 100*sqrt[exp(σ^2)-1], where σ^2 is the variance of the log-transformed data. Each subject's plasma concentrations will be plotted over time. For the purposes of plotting the data, plasma concentrations below the limit of quantification (BLQ) that are imbedded between two measurable concentrations will be set to missing; however, BLQ values occurring prior to the first measurable concentration or after the last measurable concentration will be set to zero. For summaries of plasma concentrations, BLQ values will be set to missing. The number and percentage of subjects with BLQ values will be summarized by time point and treatment group.

7.4.8 Pharmacokinetic Analysis

Pharmacokinetic parameters will be analyzed based on the All Treated Population. For each subject, the PK parameters described in Section 6.5.3 will be determined by a non-compartmental approach when feasible. For the purpose of the non-compartmental PK analysis, all plasma concentration BLQ values occurring prior to the first measurable concentration will be set to zero. BLQ values occurring after the first measurable plasma concentration will be set to missing.

PK parameters will be summarized for the All Treated Population using descriptive statistics that includes the CV. Summaries of C_{max} and AUC will also include point estimates for the geometric mean and geometric CV. The geometric mean is calculated by computing the mean of the log-transformed concentration values and then presented in the original scale by calculating the anti-log of the mean result. The geometric CV is calculated as 100*sqrt[exp(σ^2)-1], where σ^2 is the variance of the log-transformed data. Listings of calculated PK parameters will be provided.

7.4.9 Biomarker Analysis

Biomarker analysis is outside the scope of this SAP.

7.5 Safety Evaluation

Safety analysis will be carried out for the All Treated Population, to include all subjects who receive at least one dose of either study drug. Subjects who do not complete the study, for whatever reason, will have all available data up until the time of termination included in the analysis. For safety analysis presented by study visit, the baseline value will be defined as the last value reported prior to first administration of either study drug.

7.5.1 Extent of Exposure

Extent of exposure to study treatment will be summarized for the All Treated Population. The duration of exposure will be presented in days and calculated as the date of last dose of study drug minus the date of first dose of study drug, plus one. The dose intensity will

be calculated as the total dose administered divided by the duration of exposure. Duration of exposure, total dose received (mg for Pembrolizumab; mcg for ADU-S100), and dose intensity will be summarized using descriptive statistics. The number of injected lesions per subject will be summarized.

7.5.2 Adverse Events

Treatment-emergent adverse events are defined as those AEs with onset after the first dose of either study drug or existing events that worsened after the first dose during the study. Treatment-emergent AEs will be summarized for all subjects combined. Events reported with a partial onset date (eg, month and year are reported but the day is missing) will be considered to be treatment-emergent if it cannot be confirmed that the event onset was prior to the first dose of either study drug based on the available date entries.

Verbatim terms on case report forms will be mapped to preferred terms and system organ classes using the Medical Dictionary for Regulatory Activities (MedDRA, version 23.0). Adverse events will be graded according to the National Cancer Institute Common Terminology Criteria for Adverse Events (NCI-CTCAE).

Summaries that are displayed by system organ class and preferred terms will be ordered by descending incidence of system organ class and preferred term within each system organ class. Summaries displayed by preferred term only will be ordered by descending incidence of preferred term. Summaries of the following types will be presented:

- Overall summary of number of unique TEAEs and treatment-emergent SAEs and subject incidence of TEAEs meeting various criteria;
- Subject incidence of TEAEs by MedDRA system organ class and preferred term;
- Subject incidence of the most frequently-occurring TEAEs (ie, TEAEs occurring in ≥ 10% of the All Treated Population) by MedDRA preferred term;
- Subject incidence of TEAEs by NCI-CTCAE grade, MedDRA system organ class, and preferred term;
- Subject incidence of TEAEs related to each study drug and both study drugs by NCI-CTCAE grade, MedDRA system organ class, and preferred term;
- Subject incidence of TEAEs by relationship to each study drug, MedDRA system organ class, and preferred term;
- Subject incidence of the most frequently-occurring TEAEs related to each study drug and both study drugs (ie, related TEAEs occurring in ≥ 10% of the All Treated Population) by MedDRA preferred term;
- Subject incidence of TEAEs with NCI-CTCAE grade ≥ 3 and related to each study drug and both study drugs by MedDRA system organ class and preferred term;

- Subject incidence of treatment-emergent SAEs by MedDRA system organ class and preferred term;

- Subject incidence of treatment-emergent SAEs by NCI-CTCAE grade, MedDRA system organ class, and preferred term;

- Subject incidence of treatment-emergent SAEs related to each study drug and both study drugs by NCI-CTCAE grade, MedDRA system organ class, and preferred term; and

- Subject incidence of TEAEs leading to withdrawal, delay, reduction, or interruption of each study drug and both study drugs by MedDRA system organ class and preferred term.

At each level of summarization (eg, any AE, system organ class, and preferred term), subjects experiencing more than one TEAE will be counted only once. In the summary of TEAEs by severity grade, subjects will be counted once at the highest severity reported at each level of summarization; in the summary of TEAEs by relationship, subjects will be counted once at the closest relationship to study drug.

Adverse event data will be presented in data listings by subject and event.

7.5.3 Deaths, Other Serious Adverse Events, and Other Significant Adverse Events

All deaths during the study, including the post-treatment follow-up period, will be listed by subject, to include the primary cause of death. Serious AEs and other significant AEs, including those that led to withdrawal, delay, interruption, or reduction of each study drug, will be provided in separate subject data listings.

7.5.4 Clinical Laboratory Evaluation

All descriptive summaries of laboratory results will be based on data collected on the eCRF and presented in Système International (SI) units, as suggested by the Center for Biologics Evaluation and Research and the Center for Drug Evaluation and Research *Position on Use of SI Units for Lab Tests* (Oct 2013). All data will be included in by-subject data listings. Laboratory measurements identified as abnormal (ie, outside the normal range) will also be listed separately by subject, laboratory test, and unit. In addition, normal ranges provided by each site will be presented in a separate listing.

Clinical laboratory measurements, including serum chemistry and hematology, will be summarized for all subjects combined. Descriptive statistics will be presented for observed values and changes from baseline at each visit where parameters were scheduled to be collected per the clinical study protocol.

Where applicable, laboratory results will be classified as “low,” “normal,” or “high” with respect to the parameter-specific reference ranges (ie, below the lower limit of the normal range, within the normal range, or above the upper limit of the normal range). Three-by-

three contingency tables will be presented for each laboratory parameter to summarize the shift from the baseline category to the worst post-baseline measurement, defined as the value numerically farthest outside of the normal range across all post-baseline visits through the end of the study.

Summary results will include the count and percentage of subjects within each shift category.

Where applicable, hematology, chemistry, and coagulation results for select parameters will be assigned a toxicity grade based on the NCI-CTCAE. If the quantitative criteria for grading are equivalent for two grades and the differentiation is described by clinical interventions, the clinical intervention component will not be considered and the highest NCI-CTCAE grade will be assigned. Similarly, death related to AE (ie, Grade 5) cannot be determined with available laboratory-based data collection and, thus, will not be summarized as a category. Laboratory parameters that include multiple sets of criteria for each direction (eg, separate criteria for potassium measures to assess hyperkalemia and hypokalemia) will be summarized separately to reflect each set of criteria.

A five-by-five contingency table will be presented for lab tests where toxicity grading can be applied, to summarize the shift from the baseline grade to the worst post-baseline grade. Grades will be presented as none (Grade 0; ie, measurements did not meet any NCI-CTCAE criteria for Grades 1 through 4), mild (Grade 1), moderate (Grade 2), severe (Grade 3), or life-threatening (Grade 4). Summary results will include the count and percentage of subjects within each shift category.

A separate table will be provided to assess the potential for drug-induced liver injury. Laboratory values consistent with Hy's Law criteria will be presented. Summary results will include the count and percentage of subjects within each shift category.

7.5.5 Vital Signs, Physical Findings, and Other Observations Related to Safety

7.5.5.1 Vital Signs

Vital sign parameter measurements will be summarized for all subjects combined. Descriptive statistics will be presented for observed values and changes from baseline at each visit where parameters were scheduled to be collected.

7.5.5.2 12-Lead Electrocardiogram

Twelve-lead ECG interval parameters will be summarized for all subjects combined. Descriptive statistics will be presented for observed values and changes from baseline at each visit where parameters were scheduled to be collected. Measurements will be taken in triplicate, and the average measurement will be summarized.

Twelve-lead ECG will be classified by the investigator as "normal," "abnormal, not clinically significant," or "abnormal, clinically significant." Three-by-three contingency tables will be presented to summarize the shift from the baseline category to the worst

post-baseline value. Summary results will include the count and percentage of subjects within each shift category.

Prolonged QTcF intervals will be summarized as QTcF measurements (msec) that are > 450, > 480, and > 500 at each visit where ECG is routinely collected per the clinical study protocol. Change from baseline categories will also be summarized for measurements that represent an average change > 30 or > 60 relative to the average baseline value. Summary results will include the percentage of subjects within each category.

7.5.5.3 Physical Examination

Results of the physical examination will be presented in subject data listings by subject and study visit.

7.5.5.4 Eastern Cooperative Oncology Group (ECOG) Scale of Performance Status

The ECOG performance status will be summarized for all subjects combined. Descriptive statistics will be presented for observed values and changes from baseline at each visit where status was scheduled to be collected. Five-by-five contingency tables will be presented to summarize the shift from the baseline category to the worst post-baseline value. Summary results will include the count and percentage of subjects within each shift category.

7.5.5.5 Prior and Concomitant Medications

Medications will be coded using the World Health Organization Drug Dictionary Enhanced (WHODDE) Global B3, March 1, 2019. Medications entered on the eCRF will be mapped to Anatomic Therapeutic Chemical (ATC) drug class (level 4) and drug name.

Prior and concomitant medications will be summarized separately and the study phase of each medication will be determined programmatically based on medication start and end dates. A prior medication is defined as any medication used within 28 days prior to the first dose of ADU-S100. A concomitant medication is defined as any medication administered from Cycle 1 Day 1 until the EOT visit. A medication may be defined as both prior and concomitant. If it cannot be determined whether a medication was received prior to the start of study drug dosing due to partial or missing medication start and/or end dates, it will be considered a prior medication. Likewise, if it cannot be determined whether a medication was received after the start of study drug dosing, it will be considered concomitant.

For both prior and concomitant medications summaries, the number and percentage of subjects receiving any medication by ATC drug class and generic drug name will be summarized. Prior and concomitant medications will also be summarized over all subjects combined. Subjects reporting use of more than one medication at each level of summarization (any medication received, ATC class, and generic drug name) will be counted only once. ATC class terms will be displayed by descending order of incidence,

as will generic drug names within each ATC class. The study phase during which each medication was received (eg, prior, concomitant, or both) will be presented on the listing of prior and concomitant medications.

7.5.6 Exploratory Safety Endpoint Analysis Methods

All exploratory endpoint laboratory data will be presented in by-subject data listings.

7.6 Changes in the Conduct of the Study or Planned Analyses

Section 12.3 ("Analysis Sets") of the protocol states the following:

Evaluable Analysis Set (EAS): All subjects who received any amount of study drug and have at least one evaluable response assessment or were discontinued due to toxicity. The EAS will be used for analysis of the primary efficacy endpoint and clinical activity.

- The EAS will also include subjects who died or discontinued due to clinical progression or toxicity.

- The All Treated Population will be used for analysis of the primary efficacy endpoint and clinical activity. The All Treated Population is identical to the Safety Population that is described in the protocol.

- For RECIST response SD in the calculation of DODC, duration of SD is calculated from date of baseline tumor assessment to the time of disease progression or death due to any cause. The protocol specifies to calculate this duration "from the first tumor assessment that supports the subject's disease control" for all associated RECIST responses. This SAP further clarifies that the baseline tumor assessment can be taken as the date "supporting" the period of stable disease.

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APPENDIX A: SCHEDULE OF EVENTS

Table 2-1 Schedule of Events

Study Period	Screening	Treatment Period					EOT[2]	Follow Up [3]
		Cycle 1			Cycle 2 and Beyond			
Cycle Day (21-day cycles)[1]	-28 to -1	1	2	8	1	8	30 d post last dose	Q8W after EOT visit
Visit Window (days)	-	-	-	±1	±1 (±3 Cycles 3-7; ±5 Cycles 8+)	±1 (±3 Cycles 3-7; ±5 Cycles 8+)	+7	+7
Informed consent	X							
Demographics, Medical history, Height [4]	X							
Inclusion/Exclusion criteria	X							
SAFETY & EFFICACY EVALUATIONS								
Tumor imaging & response assessment [5]	X				Cycle 4 Day 1 (-7 days), Q9W (-14 days) thereafter [5]			
Photography of injected lesions		(pre-dose)			(pre-dose)		X	
Vital status (survival), Current cancer therapy							X	X
ECOG performance status	X	X			X		X	
Vital signs [6]	X	X		X	X	X	X	
Physical examination, Weight [7]	X	X			X		X	
Electrocardiogram [8]	X	X		X	Cycles 2-3		X	
Adverse events [9]	X	X	X	X	X	X	X	X
Prior and Concomitant medications	X	X	X	X	X	X	X	X [3]
LABORATORY ASSESSSMENTS (obtain prior to dosing unless otherwise indicated)								
Virology, Serology [10]	X							
Urinalysis, Coagulation panel [10]	X	As clinically indicated						
Hematology, Chemistry [10]	X	X [10]		X	X [10]		X	
Thyroid function [10, 11]	X	X [11]			odd cycles [11]		X	
Pregnancy (WOCBP) [10]	Serum	Serum			X		X	
Plasma cytokines (safety) [12]	X	As clinically indicated for CRS initial diagnosis & follow up monitoring						
ADU-S100 PK (plasma) [13, 14]		X		X	Cycle 2			
Plasma cytokines (research) [13, 15]	X	X	X	X	X [15]		X [15]	if at site [15]
Whole blood (PGx) [13]		X						
Whole blood (transcriptomics) [13, 15]	X	X	X	X	X [15]		X [15]	if at site [15]
Whole blood (PBMC; select sites only) [13, 16]	X	X	X	X	Cycles 2-3		X [16]	if at site [16]
Tumor tissue (lesion for injection) [13, 17]	X		X			C2D15 (±3)	Optional[17]	
Tumor tissue (non-injected lesion) [13, 17]	X					C2D15 (±3)	Optional[17]	
STUDY DRUG ADMINISTRATION								
Pembrolizumab (IV infusion) [18]		X			X			
ADU-S100 (intratumoral injection)[19]		X [19]		X	X	X		

FOOTNOTES FOR TABLE 2-1 (See Sections 9 and 10 for additional information)

[1] Cycle length is 21 days. If a dose of either study drug is delayed, shift scheduled assessments accordingly.

[2] EOT Visit occurs 30 days (+7 days) after the last dose of study drug (ADU-S100 or standard of care (pembrolizumab) or prior to commencing new anti-cancer therapy.

[3] Follow-up: Visit may be conducted at site or via phone for vital status assessment, any subsequent cancer-related therapies, and safety follow-up to complete required Safety Reporting Periods (Table 10-1), as indicated. Concomitant medications will only be collected if associated with the management of an ongoing AE or SAE, or if a new anti-cancer treatment. Continue imaging if a subject discontinues study treatment for reasons other than progressive disease per Section 10.2.1.

[4] Demographics, Medical History, Height: includes date of birth, age, gender, ethnicity, and race. Medical history includes all active conditions and any condition considered to be clinically significant by the Investigator. Disease-specific details include date of diagnosis, primary tumor histology, prior surgery(ies), radiation therapy, chemo- and biological therapies, and stage of cancer. Obtain standing height.

[5] Tumor imaging: See Section 10.2.1. Collect scans electronically; perform response assessments per RECIST 1.1 and iRECIST. Tumor assessments should be fixed according to calendar, regardless of treatment delays. After 45 weeks, the imaging frequency for all subjects will be performed at a Q12W (-14 days) frequency until confirmed disease progression, withdrawal, or study end. If a subject discontinues study treatment for reasons other than progressive disease and has not received other anti-cancer therapy, continue imaging at designated frequency. Perform at EOT if more than 6 weeks have passed since last evaluation.

[6] Vital Signs: Blood pressure, pulse, respiratory rate, and temperature. Cycles 1 and 2: scheduled time points relative to the start of the pembrolizumab infusion (Day 1) = pre-dose, end of infusion; scheduled time points relative to the start of the ADU-S100 injection (Days 1, 8) = pre-dose, 3 hours and 6 hours post-dose. On all other dosing days, perform vital sign assessment prior to the start of each study drug or more frequently as clinically indicated.

[7] Physical Examination: Complete physical examinations at Screening and EOT; all other indicated visits are symptom-directed physical examinations. Weight at each indicated visit. Assessment may be done up to 3 days prior to visit.

[8] Electrocardiogram: Collect 12-lead ECGs as specified in Table 2-2. Perform routine 12-lead ECG with subject in recumbent or semi-recumbent position after 5 minutes rest. Additional ECGs may also be performed throughout the study if clinically indicated. Perform ECGs prior to study drug administration unless otherwise indicated. Procedures should be performed in the following order: ECG, vital signs, blood draw.

[9] Adverse events: Collect from date of informed consent according to safety-reporting periods specified in Table 10-1 and reporting procedures in Section 11.

[10] Virology, Serology, Urinalysis, Coagulation panel, Hematology, Chemistry, Thyroid function, Pregnancy Tests (WOCBP only): See Sections 10.4.1 and 10.4.2 for specific analytes. Collect samples as outlined in the Laboratory Manual; testing performed at local laboratory unless otherwise indicated. Collect Screening blood samples after other requisite tests for eligibility have been completed. Samples indicated on dosing days must be pre-dose and Cycle 1-3 samples may be obtained up to 3 days before dosing. For WOCBP, perform serum pregnancy test (hCG) at Screening and within 24 hours prior to first dose of study drug (unless Screening assessment performed within 72 hours of Cycle 1 Day 1); perform urine pregnancy test at all other indicated visits.

[11] Thyroid function: Repeat on Cycle 1 Day 1 only if Screening result was abnormal (Section 10.4.2). Required during odd-numbered cycles only; additional tests may be performed if clinically indicated.

[12] Plasma cytokines (safety): See Section 10.4.2.2 for specific analytes. Collect at Screening and as clinically indicated. If CRS is suspected, blood (plasma) sample should be collected within 5 hours (or as soon as possible) after occurrence of the event, and 1 week after occurrence of the event. Ship all samples to central laboratory(ies) as outlined in the Laboratory Manual.

[13] ADU-S100 PK (plasma), Plasma cytokines (research), Whole blood (PGx, transcriptomics, PBMC), Tumor tissue: Process and ship all samples to central laboratory(ies) as outlined in the Laboratory Manual.

[14] ADU-S100 PK (plasma): Collect blood samples as specified in Table 2-3

[15] Plasma cytokines (research), Whole Blood (Transcriptomics): Baseline samples should be collected near the end of screening assessments to avoid unnecessary procedures on individuals who may not meet eligibility. Scheduled time points (Table 2-5) are relative to the start of the ADU-S100 injection. After Cycle 3 Day 1 collect sample on days where tumor imaging indicated. Collect at EOT (or at determination of progressive disease). Collect plasma and whole blood during safety follow-up (only if visit conducted at trial site and not by phone; and subject has not started another anti-cancer treatment).

[16] Whole Blood (PBMC; select sites only): Baseline samples should be collected near the end of screening assessments to avoid unnecessary procedures on individuals who may not meet eligibility. Collect whole blood for PBMC isolation prior to any study drug administration. Process PBMCs and ship to central laboratory as outlined in the Laboratory Manual. Collect at EOT (or at determination of progressive disease). Collect and process PBMCs during safety follow-up (only if visit conducted at trial site and not by phone; and subject has not started another anti-cancer treatment).

[17] Tumor Tissue: If no archival tumor sample collected within 90 days prior to start of study treatment is available, then collect fresh biopsy(ies) during Screening and at time points indicated in Table 2-4 (unless subject opts out, site is not amenable to biopsy, or Investigator deems biopsy would pose unnecessary risk). If additional biopsies or relevant samples (e.g. pleural fluid) are collected for routine care during the course of trial or at disease progression, a sample should be retained if possible and submitted for Sponsor research evaluation.

[18] Pembrolizumab: administer 200 mg by IV infusion on Day 1 of each 21-day cycle as specified in Section 9.3.

[19] ADU-S100: administer by intratumoral injection on Days 1 and 8 of each 21-day cycle as specified in Section 9.4. Confirm biopsy area has healed prior to initiating dosing.

ABBREVIATIONS FOR TABLE 2-1
CRS = cytokine release syndrome; ECG = electrocardiogram; ECOG = Eastern Cooperative Oncology Group; EOT = End of treatment; hCG = human chorionic gonadotropin; iRECIST = modified RECIST1.1 for immune-based therapeutics; IV = intravenous; PBMC = peripheral blood mononuclear cells; PD = pharmacodynamic(s); PGx = pharmacogenetic(s); RECIST = Response Evaluation Criteria in Solid Tumors (v 1.1); PK = pharmacokinetics; WOCBP = women of childbearing potential