CLINICAL TRIAL PROTOCOL

A Phase 2 Efficacy and Safety Trial of ADU-S100 and Pembrolizumab in Adults with Head and Neck Cancer

Protocol Number:	ADU-CL-20
Amendment 4 Date:	19 January 2021
Investigational Product:	ADU-S100 (MIW815; a synthetic cyclic dinucleotide agonist of human stimulator of interferon genes [STING])
IND Number:	122605
Trial Registration:	NCT03937141
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Protocol Version	**Date**
Original Protocol	08 January 2019
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2 SYNOPSIS

TITLE: A Phase 2 Efficacy and Safety Trial of ADU-S100 and Pembrolizumab in Adults with Head and Neck Cancer

PROTOCOL NUMBER: ADU-CL-20

INVESTIGATIONAL PRODUCT: ADU-S100 (MIW815; a synthetic cyclic dinucleotide agonist of human stimulator of interferon genes [STING])

PHASE: 2

INVESTIGATIONAL SITES: Multicenter clinical trial conducted at approximately 25 sites in North America

INDICATION: Treatment of adults with recurrent or metastatic head and neck squamous cell cancer (HNSCC)

NUMBER OF SUBJECTS: Up to 20 subjects

OBJECTIVES AND ENDPOINTS:

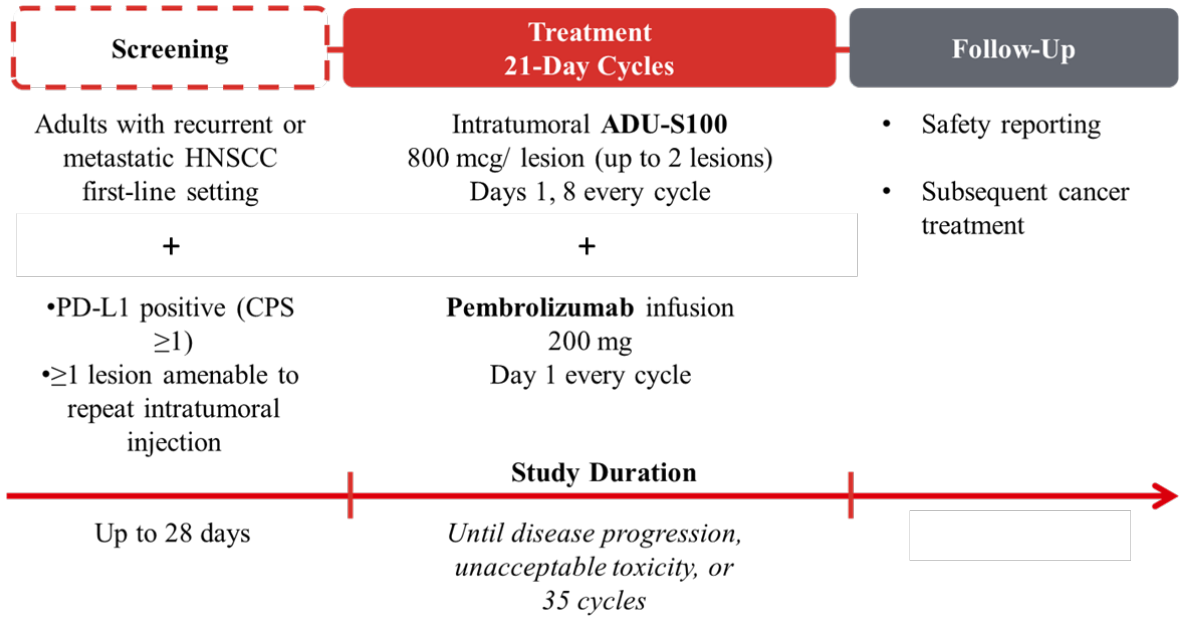
OBJECTIVES	ENDPOINTS
Primary	
• Evaluate the clinical efficacy of ADU-S100 administered in combination with pembrolizumab	• Objective response rate (ORR; complete response [CR] and partial response [PR]) per Response Evaluation Criteria in Solid Tumors (RECIST) v1.1
Secondary	
• Characterize safety and tolerability	• Occurrence and severity of treatment-emergent adverse events • Changes from baseline in safety assessments
• Further evaluate clinical activity	• Overall survival • ORR per modified RECIST v1.1 for immune-based therapeutics (iRECIST) • Progression-free survival, duration of response, disease control, and duration of disease control per RECIST v1.1 and iRECIST
[removed by amendment]	
• *Characterize the pharmacokinetics (PK) of ADU-S100 administered by intratumoral injection following a single dose and multiple doses*	• *Plasma concentration-time profiles and if feasible, derived noncompartmental PK parameters (including C_{max}, AUC)*
Exploratory [removed by amendment]	
• *Assess pharmacodynamic, immunomodulatory, and potential prognostic and/or predictive biomarkers* • *Pharmacogenetic analysis*	• *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 DNA sequence variations (e.g. single nucleotide polymorphisms [SNPs]) and relationship with safety, tolerability, and clinical benefit*

DESIGN:

ADU-CL-20 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 (i.e. pembrolizumab) in the first-line setting. The population will consist of adults with PD-L1 positive recurrent or metastatic HNSCC. Up to twenty (20) evaluable subjects will be enrolled.

The trial design consists of a Screening Period, Treatment Period, and an End of Treatment (EOT) Visit as depicted in the diagram below. All eligible subjects will receive intravenous (IV) infusions of pembrolizumab (200 mg; per approved product labeling) and intratumoral injections of ADU-S100 (800 mcg/lesion; up to 2 lesions). During the Treatment Period ADU-S100 and pembrolizumab will be administered in 21-day dosing cycles; tumor responses will initially be evaluated at 9-week intervals. If the injected lesion(s) shows signs of significant regression (i.e. shrinkage) such that repeat administration of ADU-S100 is no longer possible in any lesion, the subject will be scheduled to complete the EOT visit and may continue treatment with pembrolizumab as monotherapy/standard of care outside the context of the ADU-CL-20 clinical trial. Subjects who do not complete at least one response evaluation, unless they discontinue due to toxicity, will not be considered evaluable. An EOT visit will be conducted to assess subsequent anti-cancer therapy and complete safety reporting requirements. A schedule of visits and procedures is provided in Table 2-1.

ADU-CL-20 Design



DURATION OF SUBJECT PARTICIPATION:

Following a Screening Period (up to 28 days), eligible subjects will be enrolled and receive ADU-S100 and pembrolizumab in continuous, 21-day cycles during the Treatment Period until criteria

for treatment discontinuation are met, or up to 35 cycles. At the end of the Treatment Period, subjects will complete an EOT visit.

POPULATION:

Inclusion Criteria

Individuals eligible to participate must meet the following criteria:

1. Male or female aged ≥18 years
2. Histological or cytological confirmation of recurrent or metastatic HNSCC
3. Measurable disease as defined by RECIST v1.1
4. [Criterion removed in Amendment 3]
5. PD-L1 positive (defined as combined positive score [CPS] ≥1 using the Dako PD-L1 22C3 pharmDx companion diagnostic assay)
6. At least one lesion that is:
   - Superficial (e.g. cutaneous, subcutaneous) and/or nodal
   - Measures ≥10 millimeters (mm; post-biopsy) and <100 mm in longest diameter; nodal lesions must be ≥15 mm (post-biopsy) at short axis
   - Accessible for repeat intratumoral injection: Tumors encasing or abutting major vascular structures (such as the carotid artery) or tumors in locations at high risk for adverse effects (e.g. pneumothorax, brain lesions) are not considered appropriate for intratumoral injection. An irradiated mass cannot be used for intratumoral injection unless radiotherapy was completed at least 28 days prior to first dose of study drug and/or the lesion demonstrates evidence of growth (metabolically active by positive positron emission tomography or an unambiguous increase in size).
7. Eastern Cooperative Oncology Group (ECOG) Performance Status of 0 or 1
8. Adequate organ and marrow function at Screening, as defined by the following laboratory parameters:

Hematologic	**Renal**	**Hepatic**
White blood cell count ≥2000/µL Absolute neutrophil count ≥1000/µL Platelets ≥75,000/µL Hemoglobin ≥9 g/dL [1] Albumin ≥3.0 g/dL aPTT and/or INR ≤1.5 × ULN [2]	Creatinine ≤1.5 × ULN or GFR ≥ 30 mL/min/1.73m^2 by CKD-EPI equation: GFR = 141 x min (SCr /k, 1)$^{\alpha}$ x max (SCr /k, 1)$^{-1.209}$ x 0.993^{Age} x 1.018 [if female] x 1.159 [if black] Note: SCr is standardized serum creatinine in mg/dL, k is 0.7 for females and 0.9 for males, a is -0.329 for females and -0.411 for males, min indicates the minimum of SCr /k or 1, and max indicates the maximum of SCr /k or 1.	AST/ALT ≤2.5 × ULN; or ≤5 × ULN for subjects with liver metastases Bilirubin ≤1.5 × ULN; or ≤3 × ULN if due to Gilbert's disease
ALT = alanine aminotransferase; aPTT= activated partial thromboplastin time; AST = aspartate aminotransferase; INR= International normalized ratio of prothrombin time; ULN = institutional upper limit of normal [1] Transfusions are allowed; hemoglobin must be ≥9 g/dL for at least 7 days after transfusion and prior to dosing [2] If receiving anticoagulant therapy, values should be within therapeutic range of intended use		

9. Women of childbearing potential (WOCBP) and fertile males with WOCBP partners must use highly effective contraception (CTFG 2014) throughout the trial and for the latter of: 4 months following the final dose of pembrolizumab or 30 days after the last dose of ADU-S100
10. Provide written informed consent and is willing and able to comply with all study procedures.

Exclusion Criteria

Individuals who meet any of the following exclusion criteria will not be eligible to participate:

1. Diagnosis of recurrent or metastatic carcinoma of the nasopharynx, squamous cell carcinoma of unknown primary histology; or salivary gland or non-squamous histologies (e.g. mucosal melanoma)
2. Disease amenable to local therapy with curative intent (surgery or radiation therapy with or without chemotherapy)
3. Prior systemic anti-cancer therapy (use of chemotherapeutic agents, targeted small molecules, immunotherapy, or monoclonal antibodies) for the treatment of recurrent or metastatic HNSCC

   [Prior chemotherapy and/or or radiotherapy in the adjuvant or neoadjuvant setting is acceptable provided at least 28 days have elapsed since last dose, and/or the irradiated lesion demonstrates evidence of growth or active tumor).]

   [Prior use of anti-PD-1 (or other drugs targeting immune checkpoint pathways) in the adjuvant or neoadjuvant setting is acceptable provided the total treatment period was ≤3 months in duration; the last dose was ≥6 months before the first dose of study drug; and anti-PD-1 treatment was not discontinued due to treatment-related toxicity.]
4. Symptomatic or untreated leptomeningeal disease
5. Presence of symptomatic central nervous system (CNS) metastases, or CNS metastases that require local CNS-directed therapy (such as radiation or surgery) or increasing doses of corticosteroids within the 2 weeks prior to first dose of study drug. Any symptomatic brain metastases should be neurologically stable (for 4 weeks post treatment and prior to study entry) with no corticosteroids administered for at least 2 weeks before first dose of study drug. Definitively treated CNS disease following gamma knife/stereotactic radiosurgery with no corticosteroids administered for at least 1 week before first dose of study drug should not be excluded.
6. Radiotherapy within 2 weeks of the first dose of study drug, except for palliative radiotherapy to a limited field, such as for the treatment of bone pain or a focally painful tumor mass
7. Participation in an interventional, investigational trial where an intervention was received within 4 weeks of the first dose of study drug
8. Prior severe hypersensitivity (≥ Grade 3) to pembrolizumab or any study drug excipients (e.g. L-histidine, sucrose or polysorbate 80)
9. History of or current drug-induced interstitial lung disease or pneumonitis Grade ≥2

10. Impaired cardiac function or clinically significant cardiac disease, including any of the following:
    - Symptomatic congestive heart failure requiring treatment
    - Clinically significant cardiac arrhythmia
    - Uncontrolled hypertension
    - Corrected QT interval (QTcF) >480 msec at Screening (average of triplicate ECGs) or congenital long QT syndrome
    - Acute myocardial infarction or unstable angina pectoris < 3 months prior to the first dose of study drug
    - New York Heart Association Functional Class III or higher (i.e. marked limitation of physical activity due to symptoms, or unable to carry on any physical activity without discomfort)
11. Diagnosis of immunodeficiency or receiving chronic systemic steroid therapy (>10 mg/day prednisone or equivalent) or any immunosuppressive therapy within 7 days prior to the first dose of study drug. Topical (<class III), inhaled, nasal and ophthalmic steroids are allowed except in the anatomic location of injected and non-injected lesions.
12. Receipt of any live vaccines within 4 weeks prior to first dose of study drug
13. Use of hematopoietic colony-stimulating growth factors [e.g. granulocyte colony-stimulating factor (G-CSF), GM-CSF, macrophage colony-stimulating factor (M-CSF)], thrombopoietin mimetics or erythroid stimulating agents ≤2 weeks prior to first dose of study drug. Erythroid stimulating agents may be maintained if initiated more than 4 weeks prior to the first dose of study drug and the dose is stable.
14. Received a diagnosis of, and/or tests positive at Screening for human immunodeficiency virus (HIV)
15. Active Epstein-Barr virus (EBV), hepatitis B virus (HBV), or hepatitis C virus (HCV) infection
16. Active infection (viral, bacterial, or fungal) requiring systemic therapy
17. Prior history of or active malignant disease other than that being treated in this study. Exceptions: malignancies that were treated curatively and have not recurred within the past 2 years; completely resected basal cell carcinoma and squamous cell carcinoma of the skin; and completely resected carcinoma *in situ* of any type.
18. Active, known, or suspected autoimmune disease or a documented history of autoimmune disease, except vitiligo or resolved childhood asthma/atopy.

    Individuals with vitiligo, type I diabetes, residual hypothyroidism only requiring hormone replacement, psoriasis not requiring systemic treatment, history of Hashimoto's thyroiditis on stable dose of thyroid hormone replacement therapy, adrenal insufficiency only requiring physiologic steroid replacement, or conditions not expected to recur should not be excluded.
19. Major surgery within 2 weeks of the first dose of study drug

20. If WOCBP, pregnant or breastfeeding; negative pregnancy status must be confirmed by serum pregnancy (human chorionic gonadotropin) test at Screening
21. Intercurrent illness that is either life-threatening or of clinical significance such that it might limit compliance with study requirements, or in the Investigator's assessment would place the subject at an unacceptable risk for participation.

DOSAGE AND ROUTE OF ADMINISTRATION:

Investigational Product (ADU-S100): 800 mcg/lesion (up to 1600 mcg maximum total dose in 2 lesions) administered in a volume of 1.0 mL per lesion by intratumoral injection (injection of visceral lesions per Investigator discretion) on Days 1 and 8 of a 21-day cycle

Standard of Care (pembrolizumab): 200 mg administered by IV infusion on Day 1 of a 21-day cycle per approved product label

STATISTICAL ANALYSES:

Descriptive summaries for categorical variables will include counts and percentages. Descriptive summaries for continuous variables will include means, medians, standard deviations and minimum and maximum values. Graphical summaries of the data may be presented. All data will be listed for all subjects. Further details of the analysis, including the handling of missing data, transformations, other data handling procedures, and analytical methodology will be provided in the Statistical Analysis Plan. Exploratory analyses of the data will be conducted as deemed appropriate.

Efficacy Analyses

Tumor response will be determined by the Investigator's assessment. All efficacy endpoints will be defined and analyzed according to RECIST v1.1 (primary evaluation); and iRECIST (secondary evaluation). Occurrence of objective response (complete and partial response), duration of response, occurrence of disease control (complete response, partial response, and stable disease), and duration of disease control will be summarized. Estimates of progression-free survival and overall survival will be assessed using the Kaplan-Meier method. Because of truncated enrollment by amendment, some analyses may not be performed if limited data are available.

Safety Analyses

AEs will be coded according to Medical Dictionary for Regulatory Activities (MedDRA) and assessed for severity using the NCI-CTCAE v. 5.0. AEs will be summarized by system organ class and preferred term and presented in decreasing order of frequency. Changes from baseline for safety laboratory parameters; clinically significant changes from baseline in vital signs and electrocardiogram parameters; and shifts from baseline to most extreme ECOG value will be presented.

Pharmacodynamic and Exploratory Analyses

Pharmacodynamics, pharmacokinetics, biomarkers, and all available data related to research laboratory samples, tumor biopsies, and immune response data may be described in separate analysis documents. By amendment, no further samples will be obtained for analysis.

SAMPLE SIZE DETERMINATION:

The original sample size was based on a Simon's 2-stage minimax design (Simon 1989) to test the null hypothesis that the objective response rate (ORR; complete response [CR] and partial response [PR]) per Response Evaluation Criteria in Solid Tumors (RECIST) v1.1) is less than or equal to 0.19 versus the alternative hypothesis that ORR is greater than or equal to 0.38, with a Type 1 error rate of 0.05 and power of 80%. Because of truncated enrollment, the total sample size will be limited to approximately 20 evaluable subjects as planned for the first stage.

Table 2-1 Schedule of Events

Study Period	Screening	Treatment Period					EOT [2, 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**
Visit Window (days)	**-**	**-**	**-**	**±1**	**±1 (±3 Cycles 3-7; ±5 Cycles 8+)**	**±1 (±3 Cycles 3-7; ±5 Cycles 8+)**	**+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) × 27 wks, then Q12W thereafter [5]		
Vital status (survival), Current cancer therapy							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
Prior and Concomitant medications	X	X	X	X	X	X	X
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					
STUDY DRUG ADMINISTRATION							
Pembrolizumab (IV infusion) [13]		X			X		
ADU-S100 (intratumoral injection)[14]		X [14]		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] 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. Following EOT, subject may be contacted by phone to complete SAE reporting period as applicable.

[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 27 weeks, the imaging frequency for all subjects will be performed at a Q12W (-14 days) frequency until confirmed disease progression, withdrawal, or study end. 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 (+30 minutes); scheduled time points relative to the start of the ADU-S100 injection (Days 1, 8) = pre-dose, 3 hour (±30 minutes) and 6 hours (±30 minutes) 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] Pembrolizumab: administer 200 mg by IV infusion on Day 1 of each 21-day cycle as specified in Section 9.3.

[14] 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; RECIST = Response Evaluation Criteria in Solid Tumors (v 1.1); WOCBP = women of childbearing potential

Table 2-2 12-lead ECG Collection Timepoints

Triplicate ECGs should be completed at each timepoint, and the mean QTcF values should be calculated.

Cycle	Day	Time
Screening	Anytime during the screening period	
1	1	Pre-dose and within 30 minutes after start of ADU-S100 injection
1	8	Pre-dose and within 30 minutes after start of ADU-S100 injection
2	1	Pre-dose
3	1	Pre-dose
EOT	EOT	
Unscheduled	Anytime if clinically indicated	

ABBREVIATIONS FOR TABLE 2-2
ECG = electrocardiogram; EOT = end of treatment

3 TABLE OF CONTENTS

3.1 LIST OF TABLES

3.2 LIST OF FIGURES

4 LIST OF ABBREVIATIONS AND DEFINITION OF TERMS

Abbreviation	Definition
ADU-S100	synthetic cyclic dinucleotide agonist of human stimulator of interferon genes (also referred to as MIW815)
AE	adverse event
ALT	alanine aminotransferase
aPTT	activated partial thromboplastin time
AST	aspartate aminotransferase
AUC	area under the curve
CDNs	cyclic dinucleotides
CFR	Code of Federal Regulations
C_{max}	maximum concentration
CPS	combined positive score
CR	complete response
CRA	clinical research associate
CRS	cytokine release syndrome
CNS	central nervous system
CSR	clinical study report
CT	computed tomography
CTCAE	Common Terminology Criteria for Adverse Events
DCR	disease control rate
DOR	duration of response
EAS	evaluable analysis set
EBV	Epstein-Barr virus
EC	Ethics Committee
ECG	electrocardiogram
ECOG	Eastern Cooperative Oncology Group
eCRF	electronic case report form
EDC	electronic data capture
EOT	End of Treatment
EU	European Union
FDA	United States Food and Drug Administration
FFPE	formalin-fixed, paraffin embedded
GCP	Good Clinical Practice
G-CSF	granulocyte colony-stimulating factor
GFR	glomerular filtration rate
GLP	Good Laboratory Practice
GMP	Good Manufacturing Practice
HIV	human immunodeficiency virus
HBV	hepatitis B virus
hCG	human chorionic gonadotropin
HCV	hepatitis C virus
hERG	human Ether-à-go-go-related gene

Abbreviation	Definition
HNSCC	head and neck squamous cell cancer
IB	Investigator's Brochure
ICF	informed consent form
ICH	International Council on Harmonisation
IFN	interferon
IL-*x*	interleukin-*type*
IP	investigational product
INR	international normalized ratio of prothrombin time
irAE	immune-related adverse event
IRB	Institutional Review Board
iRECIST	modified RECIST1.1 for immune-based therapeutics
IV	intravenous(ly)
MABEL	minimum anticipated biologic effect level
MedDRA	Medical Dictionary for Regulatory Activities
MRI	magnetic resonance imaging
ORR	objective response rate
OS	overall survival
PD	pharmacodynamic(s)
PD-1/L1	programmed death receptor-1/ligand-1
PET	positron emission tomography
PFS	progression-free survival
PK	pharmacokinetic(s)
PR	partial response
PT	prothrombin time
QTcF	QT interval (Fridericia correction formula)
Q*x*W	once every *x* weeks
RECIST	response evaluation criteria in solid tumors
SAE	serious adverse event
SAP	statistical analysis plan
SoD	Sum of diameters
SCr	Serum creatinine
SRT	safety review team
STING	stimulator of interferon genes
$T_{1/2}$	terminal half-life
TEAE	treatment-emergent adverse event
T_{max}	time of maximum concentration
TME	tumor microenvironment
ULN	upper limit of normal
WOCBP	women of child-bearing potential

Definition of Terms:

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

5 INTRODUCTION

The purpose of this clinical trial is to evaluate the efficacy and safety of ADU-S100 (also referred to as MIW815) when administered in combination with pembrolizumab to adults with head and neck squamous cell cancer (HNSCC) with lesions amenable to intratumoral injection; and in whom programmed death receptor-1/ligand (PD-1/L1) inhibitor therapy is the current standard of care.

A summary of the background and scientific rationale, nonclinical and clinical studies, starting dose selection, and risk/mitigation strategy are presented within this section. For the most comprehensive nonclinical and clinical information refer to the latest version of the Investigator's Brochure (IB) for ADU-S100 and the approved product labeling for pembrolizumab (KEYTRUDA 2020).

5.1 Cancer Immunotherapy Targeting STING

Spontaneous T cell infiltration of tumor lesions in humans is correlated with a type I interferon (IFN) transcriptional profile in the tumor microenvironment (TME) and infiltration of lymphocytes, indicative of ongoing innate immune recognition within the tumor. Stimulator of interferon genes (STING) is an essential receptor of the innate immune response (Ishikawa, and Barber 2008). STING senses cytosolic double-stranded DNA through a signaling intermediate or by directly binding cyclic dinucleotides (CDNs) which serve as danger signals originating from pathogens or the host.

Stimulation of the STING pathway by CDNs has been shown to induce type I IFN, cytokines, and chemokines which together activate innate immune effector cells such as dendritic cells, macrophages and natural killer cells. Dendritic cell production of type I IFN in the TME leads to activation and expansion of a tumor antigen-specific CD8+ T cell response resulting in the inhibition of tumor growth in both treated and untreated lesions.

The proposed therapeutic approach is based on the finding that the responsiveness of tumors to immunotherapy depends, at least in part, on the immunophenotype of the TME (Woo et al. 2015; Gajewski, Woo, et al. 2013; Gajewski et al. 2012; Gajewski, Schreiber, et al. 2013). Substantial evidence indicates the presence of tumor infiltrating lymphocytes is correlated with favorable prognosis in diverse malignancies (Galon et al. 2012). The presence of tumor infiltrating lymphocytes in the TME also predicts a positive clinical outcome in response to several immunotherapy strategies (Postow et al. 2012; Wolchok et al. 2013). One newly explored approach to potentially establish, re-establish, or enhance active immune surveillance conditions within the TME is to inject immune modulators directly into the tumor for the purposes of devascularizing injected lesions and initiating an adaptive tumor-specific immune response.

5.2 ADU-S100

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. ADU-S100 is in clinical development for the potential use as a monotherapy or with other anti-cancer therapies for the treatment of advanced/metastatic solid tumors and lymphomas. ADU-S100 is intended for direct administration to the tumor site via intratumoral injection.

In nonclinical studies, ADU-S100 has demonstrated significantly higher activity than natural STING ligands produced by bacteria or human cells. ADU-S100 acts as an agonist of STING in tumor-resident cells including dendritic cells, endothelial cells and other cell populations in the TME. Direct activation of STING via intratumoral injection of ADU-S100 is hypothesized to overcome active tolerance mechanisms through stimulation of resident leukocyte populations. This results in the local production of type I and type II interferons, TNF and other cytokines and chemokines, and stimulates tumor-specific CD8+ T cell immunity, leading to clearance of treated lesions, and control of distal uninjected lesion growth.

5.2.1 Summary of Nonclinical Studies with ADU-S100

In vitro studies with ADU-S100 demonstrated ADU-S100 broadly activated STING across a diverse human population.

ADU-S100 was evaluated in multiple murine tumor models. Results from preclinical studies demonstrated a potent anti-tumor immune response and significant tumor regression. In murine syngeneic tumor models, intratumoral injection with ADU-S100 inhibited the treated tumor and stimulated an effective systemic CD8+ T cell immune response that controlled the growth of distal, untreated lesions, and conferred protection against tumor challenge. When ADU-S100 was administered intratumorally to mice expressing defective STING, anti-tumor efficacy was completely lost. When ADU-S100 was given as a subcutaneous injection, no tumor regression was observed. These results suggest direct activation of tumor-resident antigen presenting cells through the STING pathway is important for cross-presentation of tumor-specific CD8+ T cells and tumor destruction.

In pharmacology studies, cytokine concentrations increased in the plasma or serum of mice, rabbits, and monkeys. Changes were similar in magnitude following intratumoral or SC injection of ADU-S100 in the mouse but were not present in mice lacking a functional STING gene (*Tmem173*). Thus, changes in cytokine levels were an indication of target engagement.

In a series of pharmacokinetic-pharmacodynamic (PK-PD) studies to define the relationship between the dose of ADU-S100, exposure, and pharmacodynamic (PD) effect on serum cytokines, the minimum anticipated biologic effect level (MABEL) for cytokine changes in the mouse, rabbit, and monkey was determined to be 0.03, 0.01, and 0.03 mg/kg, respectively. There were minimal differences across species in exposure or the sensitivity towards production of a cytokine response.

Evaluation of cardiac safety in an *in vitro* assay for human Ether-à-go-go-related gene (hERG) activity and in conscious telemetry-instrumented rabbits indicated ADU-S100 has a low risk of inducing delayed ventricular repolarization, prolongation of the QTc interval, and unstable

arrhythmias. There were no ADU-S100-related adverse findings in neurobehavioral assessments incorporated in the Good Laboratory Practices (GLP) 4-week repeat-dose toxicity study in mice.

The CD-1 mouse and New Zealand white rabbit were established as relevant toxicity species based on pharmacology data and were used for repeat-dose GLP toxicology studies. Based on results of GLP studies in mouse and rabbit, bone marrow (including hematopoietic parameters), liver, reproductive organs, and skin (injection site) were defined as potential targets of dose-dependent toxicity related to the administration of ADU-S100. Consequently, particular caution should be provided in monitoring for signs of hematopoietic toxicity, liver toxicity, and injection site toxicity. Generally, most adverse findings observed during nonclinical studies were reversible. Overall, nonclinical studies support use of ADU-S100 in humans at the proposed dose levels. A complete summary of nonclinical information on ADU-S100 is provided in the IB.

5.2.2 Summary of Clinical Studies with ADU-S100

ADU-CL-20 is ongoing; as of 17 Dec 2020, treatment related SAEs of Grade 3 laryngeal edema, Grade 3 hypophysitis, Grade 3 cytokine release syndrome (CRS) and Grade 3 neck edema have been reported in 3 of 16 patients treated.

The ADU-S100 clinical development program also includes two additional studies in adults with advanced/metastatic solid tumors or lymphomas. A Phase 1, open label, multicenter study examines the safety and efficacy of ADU-S100 (referred to as MIW815) with or without ipilimumab (CMIW815X2101/ADU-CL-07; NCT02675439); and a Phase 1b, open label, multicenter study examines the safety and efficacy of ADU-S100 (referred to as MIW815) administered with the investigational anti-PD-1 checkpoint inhibitor, PDR001 (CMIW815X2102J; NCT03172936). In these trials, ADU-S100 is administered by intratumoral injection on Days 1, 8 and 15 or on Day 1 only of every 28-day cycle.

Available safety data as of the 09 October 2019 clinical cutoff date and PK data as of the 10 January 2019 data cutoff date are summarized below. Consult the IB for additional current information.

CMIW815X2101/ADU-CL-07

A total of 47 subjects have been treated with ADU-S100 at doses ranging from 50 to 6400 mcg and evaluated for dose-limiting toxicity (DLT) in the first in human study. Following intratumoral dose administration, ADU-S100 exhibits rapid absorption in the plasma, with C_{max} achieved right after injection in most subjects. ADU-S100 showed fast clearance in plasma, with mean apparent clearance (CL/F) ranging from 55.9 to 275 L/h and mean elimination $t_{1/2}$ of approximately 10 to 23 minutes across the dose range of 50 to 6400 mcg. Inter-subject exposure variability was high and exposure of ADU-S100 generally increased with doses increasing from 50 to 6400 mcg.

One DLT has been reported at 6400 µg (injection site ulcer). TEAEs, all grades, suspected to be related to study drug, were reported in 36 subjects (76.6%) overall. To date, the most frequently

reported AEs (>10% of subjects) include pyrexia (8 subjects, 17.0%), chills and injection site pain (7 subjects, 14.9%) and headache (6 subjects, 12.8%). Five subjects experienced Grade 3 events including injection site reaction and lipase increased (2 subjects, 4.3%), injection site ulcer, amylase increased, tumor pain and dyspnea (1 subject, 2.1%). One subject experienced a Grade 4 event, respiratory failure (2.1%). No clinically relevant changes of vital and ECG-parameters were observed.

CMIW815X2102J

A total of 102 subjects have been treated with ADU-S100 plus a PD-1 inhibitor, PDR001, at ADU-S100 doses ranging from 50 to 3200 mcg and on 2 different dosing schedules. Per 28-day cycle, subjects were dosed with PDR001 IV on Day 1, and with ADU-S100 intratumorally on Days 1, 8, and 15 (Group A) or on Day 1 (Group B) per 28-day cycle.

One DLT (injection site reaction) was reported at ADU-S100 3200 mcg dose level in combination with PDR001. TEAEs, all grades, suspected to be related to study drugs, were reported in 65 subjects (63.7%) overall - 41 subjects in Group A (65.1%) and 24 subjects (61.5%) in Group B. To date, the most frequently reported AEs (≥ 10% of subjects) include pyrexia (20 subjects, 19.6%) injection site pain (18 subjects, 17.6%) and diarrhea (11 subjects, 10.8%). Of the 65 subjects who experienced AEs suspected to be related to study drugs, 9 subjects (8.8%) had Grade 3 events including alanine aminotransferase increased, aspartate aminotransferase increased and diarrhea (2 subjects, 2.0%), neutropenia, hyperthyroidism, pyrexia, fatigue, asthenia, lipase increased, lipase, dyspnea, immune-mediated pneumonitis and rash maculo-papular (1 subject, 1.0%). Three subjects (2.9%) reported at least one Grade 4 event including amylase increased, lipase increased, hyponatremia, and partial seizures (1 subject, 1.0%).

Additional details on clinical experience with ADU-S100 are provided in the IB.

5.3 Scientific Rationale for the Use of ADU-S100 with Pembrolizumab

In preclinical models, STING-mediated induction of innate immunity leads to the cross-priming of tumor antigen-specific CD8+ T cells. Treatment of tumor-bearing mice with intratumoral injection of STING agonist ADU-S100 resulted in local and distal tumor shrinkage, improved survival, and induction of immunological memory. When ADU-S100 was administered with an anti-PD-1 antibody, survival and local tumor shrinkage were significantly enhanced suggesting the anti-tumor activity of PD-1 blockade may be complemented by concomitant STING activation. Recent data also suggest that acquired resistance to checkpoint blockade immunotherapy in patients with melanoma was associated with defects in the pathways involved in interferon receptor signaling that may be partially overcome by activation of the STING pathway (Zaretsky et al. 2016).

Immunotherapeutic approaches for a variety of advanced malignancies include use of the PD-1 blocking antibody, pembrolizumab, administered both as monotherapy and with other agents.

Pembrolizumab is approved for the treatment of adults with recurrent or metastatic HNSCC with disease progression on or after platinum-containing chemotherapy (KEYTRUDA 2020).

KEYNOTE-048 was a randomized, active-controlled, open-label study in adults with metastatic or recurrent HNSCC in the first-line setting. Interim analyses demonstrated pembrolizumab (administered as monotherapy or with platinum/5-fluorouracil) significantly improved OS relative to cetuximab/platinum/5-fluorouracil in populations with tumor and/or surrounding cells with high levels of PD-L1 expression (combined positive score [CPS] ≥20; median 14.9 vs 10.7 months; p = 0.0007) and in populations with lower degrees of PD-L1 expression (CPS ≥1; median 12.3 vs 10.3 months; p = 0.0086) (Burtness et al. 2018; Rischin et al. 2019). There were no statistically significant differences in progression-free survival (PFS). In this trial, pembrolizumab showed a lower objective response rate (ORR) than cetuximab/platinum/5-fluorouracil although responses were more durable (CPS ≥1, patients treated with pembrolizumab had an ORR of 19.1% and median duration of response 20.9 months; patients treated with cetuximab/platinum/5-fluorouracil had an ORR of 34.9% and median duration of response 4.5 months). The data support pembrolizumab monotherapy as a new first-line standard of care for patients with recurrent or metastatic HNSCC (Burtness et al. 2018; Rischin et al. 2019).

Immune checkpoint inhibitors such as pembrolizumab have demonstrated significant improvements in duration of response and long-term survival compared to traditional chemotherapy or other standards of care. However, a significant percentage of patients are either nonresponsive to these immunotherapies, most likely due to innate immunosuppressive mechanisms within the TME, or experience disease relapse following an acquired means of immune escape (Chen et al. 2016). This highlights the need for new, additional therapies with novel mechanisms to fill these treatment gaps.

This clinical trial is designed to evaluate the efficacy and safety of ADU-S100 administered with the checkpoint inhibitor, pembrolizumab, in HNSCC with lesions amenable to intratumoral injection, and for which PD-1/L1 inhibitor therapy is standard of care.

5.3.1 Dose Selection Rationale

Pembrolizumab will be dosed consistent with the product label (KEYTRUDA 2020) and clinical trial experience in the first-line HNSCC setting (KEYNOTE-048) (Burtness et al. 2018; Rischin et al. 2019) at 200 mg every 3 weeks.

The ADU-S100 doses and dosing schedule selected for this study are primarily based on nonclinical data and available clinical data from two clinical trials with ADU-S100. In the Phase 1 trial (CMIW815X2101/ADU-CL-07), ADU-S100 administered at doses up to 3200 mcg has been well-tolerated. Initial results from the Phase 1b trial (CMIW815X2102J) where ADU-S100 is administered with an investigational anti-PD1 (i.e. PDR001) provide preliminary clinical activity and additional safety and tolerability data to support the dose levels of ADU-S100 planned for investigation with pembrolizumab in this trial (Section 5.2.2).

In the Phase 1 study, clinical responses (partial response [PR]) have been observed in subjects with Merkel cell carcinoma (1 subject) and parotid gland (1 subject) at ADU-S100 dose levels of 100 mcg and 800 mcg, respectively (Meric-Bernstam et al. 2018). Changes in biomarkers, including increases in $CD8^+$ TILs, upregulation of genes involved in the anti-tumor immune response and systemic cytokines have also been observed at the 800 mcg ADU-S100 dose level (Meric-Bernstam et al. 2018), providing rationale for further evaluation of ADU-S100 at the 800 mcg dose level.

It is expected that intratumoral administration of ADU-S100 activates cells locally in the tumor environment and draining lymph node to contribute to therapeutic benefit. Administering a consistent dose per lesion provides the same opportunity for response for each injected lesion. The total dose administered will vary by subject depending on the number of accessible target lesions, but will not exceed a maximum total dose of 1600 mcg (i.e. no more than 2 concurrently injected lesions). Lower doses of ADU-S100 would be anticipated to provide limited therapeutic benefit; dose reductions below 200 mcg/lesion will not be allowed.

Thus, adequate safety factors exist to support the proposed dose levels of ADU-S100 administered with pembrolizumab in this study; the maximum dose administered will not exceed a total dose of 1600 mcg (i.e. 800 mcg/lesion in up to 2 lesions; Table 5-1). The maximum dose takes into consideration the proposed mechanism of action of ADU-S100 and prior clinical experience in adults with advanced cancers. The dosing schedule is predicated on available nonclinical and clinical PK-PD data and aligned with the approved pembrolizumab regimen.

Table 5-1 Proposed ADU-S100 Dose Levels

ADU-S100 Dose	ADU-S100 Total Dose Level [1]
800 mcg/lesion	Up to 1600 mcg *(maximum dose)*
[1] A maximum of 2 lesions may be injected. ADU-S100 total dose level assumes maximum number of lesions (2) injected; total dose will vary by subject depending on number of accessible target lesions but will not exceed 1600 mcg.	

5.4 Potential Risks, Benefits and Mitigation Strategy

ADU-S100 is in clinical development for potential use as a monotherapy and in combination with other anti-cancer therapies. Available nonclinical and clinical data indicate ADU-S100 has the potential to exhibit clinical activity in the treatment of HNSCC and other advanced cancers. To date no unexpected safety issues that would preclude use in this study population have been identified.

Although the risk of significant systemic activation of the immune system, including autoimmune disease or CRS, is considered low with intratumoral drug delivery, the risk cannot be excluded. Clinical signs and symptoms of cytokine activation include fever and chills. Approximately 150 subjects have been treated with ADU-S100. As of 28 January 2020), pyrexia was reported in 12 subjects (25.5%) and 26 subjects (25.5%) in the single agent and combination studies, respectively. Chills were reported in 8 subjects (17%) and 9 subjects (8.8%) in the single

agent and combination studies, respectively. No grade 3 or grade 4 fever or chills were reported. In addition, Grade 3 CRS was reported as a SAE in 1 patient receiving ADU-S100 in combination with pembrolizumab enrolled in the ADU-CL-20 study.

Based on clinical trial results (KEYNOTE-048), pembrolizumab is now considered first-line standard of care and will be administered in this trial at a dose level and regimen aligned with KEYNOTE-048 and the approved prescribing information. Treatment with pembrolizumab has been associated with severe and life-threatening immune-mediated adverse reactions in some patients, requiring close monitoring during and after discontinuation of pembrolizumab (KEYTRUDA 2020). The safety mitigation plan (Table 5-2) is based on general risks associated with the route of administration, clinical experience, and the proposed mode of action of ADU-S100/pembrolizumab.

Since this is the first study to investigate administration of ADU-S100 with pembrolizumab, there may be unexpected toxicities. All available data will be reviewed as needed by a Safety Review Team (SRT; Section 5.4.1). The risk to subjects in this trial may be mitigated by compliance with the eligibility criteria and study procedures, close clinical monitoring, and by applying dose modification/dose delay criteria when necessary.

Table 5-2 Key Safety Considerations and Mitigation Strategy

Safety Consideration	Basis for Potential Risk	Mitigation Strategy
Immune-related adverse events	Mechanism of action	• Symptom management and dose modification guidelines based on historical data and current standards of care (e.g. pembrolizumab prescribing information) provided in protocol • Extended safety monitoring and continued dosing eligibility based on warnings and precautions noted in pembrolizumab prescribing information
Infusion-related reaction	Route of administration	Symptom management and dose modification guidelines based on pembrolizumab prescribing information
ADU-S100 related adverse events	Mechanism of action	Dose modification guidelines based on available data and general practices in the development of immunomodulatory drugs provided in protocol
Injection site reactions	Route of administration	Symptom management and dose modification guidelines provided in the protocol and IB
Cytokine release syndrome	Mechanism of action	• Symptom management guidelines provided in protocol and IB • Laboratory assessment of cytokine panel for safety incorporated in Schedule of Events
Embryo-fetal toxicity	Mechanism of action	Trial eligibility includes contraception requirements for WOCBP and male subjects with WOCBP partners; pregnant or breast-feeding WOCBP are excluded

IB=Investigator Brochure; WOCBP=women of child-bearing potential

5.4.1 Safety Review Team

Subject safety will be monitored throughout the trial by an SRT established by the Sponsor. This committee will monitor treatment-emergent safety data (or other available data as warranted) on an ongoing basis for the purpose of ensuring the continued safety of subjects enrolled in this study.

The SRT consists of investigators who enrolled subjects in the study, the Medical Monitor, and Sponsor representatives. The SRT will meet on an *ad hoc* basis to review available data; documentation of meeting outcomes will be maintained by the Sponsor. The SRT may also recommend a pause or discontinuation in enrollment or recommend discontinuation of the study if an unfavorable change in subject risk/benefit assessment is observed.

6 OBJECTIVES AND ENDPOINTS

The study has been designed with an appropriate study population, sufficient size, and duration to meet the study objectives and associated endpoints:

OBJECTIVES	ENDPOINTS
Primary	
• Evaluate the clinical efficacy of ADU-S100 administered in combination with pembrolizumab	• Objective response rate (ORR; complete response [CR] and partial response [PR]) per Response Evaluation Criteria in Solid Tumors (RECIST) v1.1
Secondary	
• Characterize safety and tolerability	• Occurrence and severity of treatment-emergent adverse events • Changes from baseline in safety assessments
• Further evaluate clinical activity	• Overall survival • ORR per modified RECIST v1.1 for immune-based therapeutics (iRECIST) • *Progression-free survival, duration of response, disease control, and duration of disease control per RECIST v1.1 and iRECIST*
[removed by amendment] • *Characterize the pharmacokinetics (PK) of ADU-S100 administered by intratumoral injection following a single dose and multiple doses*	• *Plasma concentration-time profiles and if feasible derived noncompartmental PK parameters (including C_{max}, AUC)*
Exploratory *[removed by amendment]*	
• *Assess pharmacodynamic, immunomodulatory, and potential prognostic and/or predictive biomarkers* • *Pharmacogenetic analysis*	• *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 DNA sequence variations (e.g. single nucleotide polymorphisms [SNPs]) and relationship with safety, tolerability, and clinical benefit*

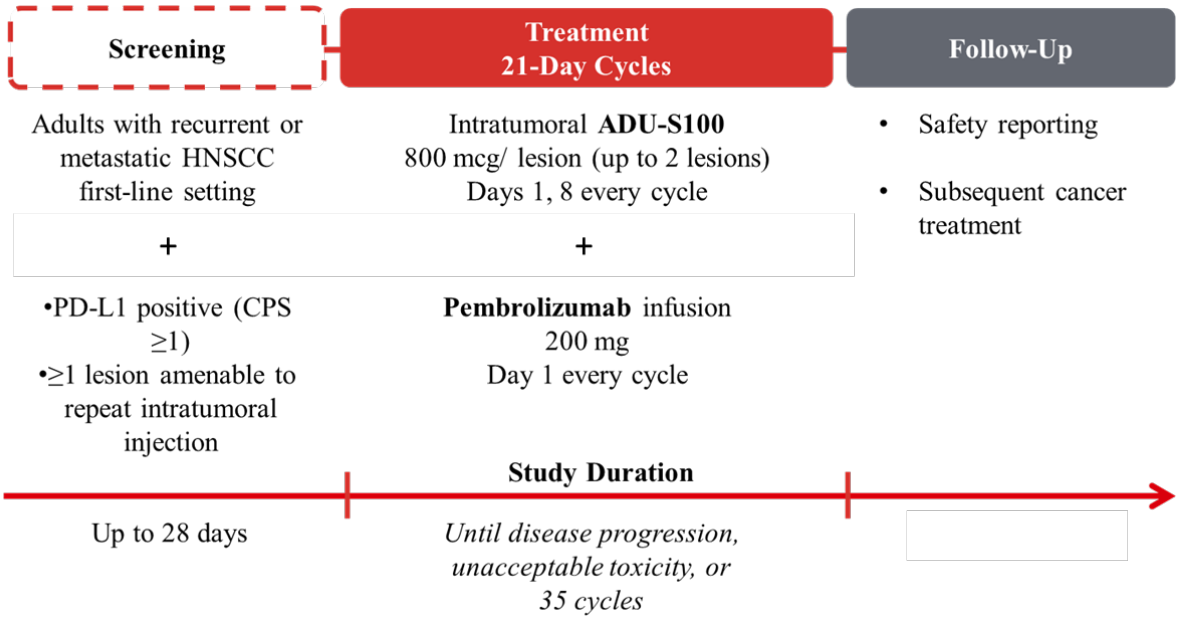
7 INVESTIGATIONAL PLAN

7.1 Study Design

ADU-CL-20 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 (i.e. pembrolizumab) in the first-line setting. The population will consist of adults with PD-L1 positive recurrent or metastatic HNSCC. Up to twenty (20) evaluable subjects will initially be enrolled.

The trial design consists of a Screening Period, Treatment Period, and an End of Treatment (EOT) visit as depicted in Figure 7-1. All eligible subjects will receive intravenous (IV) infusions of pembrolizumab (200 mg; per approved product label) and intratumoral injections of ADU-S100 (800 mcg/lesion). During the Treatment Period, study medications will be administered in 21-day dosing cycles; tumor responses will be evaluated at 9-week intervals. If the injected lesion(s) shows signs of significant regression (i.e. shrinkage) such that repeat administration of ADU-S100 is no longer possible in any lesion, the subject will be scheduled to complete the EOT visit and may continue treatment with pembrolizumab as monotherapy/standard of care outside the context of the ADU-CL-20 clinical trial. Subjects who do not complete at least one response evaluation, unless they discontinued due to toxicity, will not be considered evaluable. An EOT visit will be conducted to assess subsequent anti-cancer therapy, and complete safety reporting requirements. A schedule of visits and procedures is provided in Table 2-1.

Figure 7-1 ADU-CL-20 Study Design



7.2 Duration of Subject Participation

Following a Screening Period (up to 28 days), eligible subjects will be enrolled and receive ADU-S100 and pembrolizumab in continuous, 21-day cycles during the Treatment Period until criteria for treatment discontinuation are met (Section 8.3) or up to 35 cycles. At the end of the Treatment Period, subjects will complete an EOT visit and complete requisite safety reporting periods (Table 10-1).

7.2.1 End of Study

The end of the study is defined as the date when all subjects have completed the final protocol-specified assessment and/or discontinued study participation (withdrawal of consent or lost to follow-up).

The Sponsor may terminate the study at any time for any reason. Should the study be terminated, subjects will be contacted to complete the End of Treatment (EOT) visit and protocol-defined safety follow-up procedures.

7.2.2 Stopping Rules

Subjects will be monitored throughout the study for toxicities; provisions are in place for dose modification and oversight by the SRT. If the SRT considers the safety profile and/or biological activity of ADU-S100/pembrolizumab inadequate (at one or both dose levels), enrollment may be stopped, or the study may be terminated at any time.

The following additional safety rules apply to further mitigate potential risk to subjects:

- Grade 5 toxicity (death) in any subject within 28 days of receipt of study drug(s) unless clearly related to an alternative cause other than study drug
- Unacceptable toxicity leading to treatment discontinuation (per Section 8.3.2) occurring in >33% of subjects

Should these events occur the SRT will evaluate available data within 72 hours of notification of the event(s) and recommend whether to stop the study, suspend dosing and/or enrollment, or determine whether additional dose adjustments are warranted.

7.3 Discussion of Study Design

This trial is a Phase 2 open-label study intended to provide information regarding the efficacy, safety, and biological activity of ADU-S100 when administered with pembrolizumab. The dose of ADU-S100 selected for evaluation is based on available clinical data from other studies of ADU-S100 administered as monotherapy or with another checkpoint inhibitor. As of 28 January 2020, ADU-S100 has been administered to approximately 150 subjects with advanced cancers; no DLTs have been observed at dose levels proposed in this trial.

Given the life-threatening nature of the disease and the availability of pembrolizumab as an approved treatment option in this study population, a placebo-controlled trial is not appropriate in this setting or at this stage of clinical development. Since all subjects will receive the same study drugs (ADU-S100 and pembrolizumab) blinding is unnecessary; study drugs will be provided open-label.

The trial is the first to investigate injection of multiple lesions (where available). The study was also initially designed to characterize the plasma concentrations of ADU-S100 following a single dose and repeat dosing. Abscopal effect (i.e. treatment effect at a site outside the injected lesion) may also be assessed by biomarker analysis using tumor tissue from distal/non-injected lesion or tumor imaging should a distal lesion not be amenable to biopsy.

The data obtained in this study will inform further clinical development decisions and provide necessary data for the design and conduct of future trials.

8 STUDY POPULATION

The population for this study will consist of adults with metastatic HNSCC where pembrolizumab is indicated as 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.

8.1 Inclusion Criteria

Individuals eligible to participate in this study must meet the following criteria:

1. Male or female aged ≥18 years
2. Histological or cytological confirmation of recurrent or metastatic HNSCC
3. Measurable disease as defined by RECIST v1.1
4. [Criterion removed in Amendment 3]
5. PD-L1 positive (defined as combined positive score [CPS] ≥1 using the Dako PD-L1 22C3 pharmDx companion diagnostic assay)
6. At least one lesion that is:
    - Superficial (e.g. cutaneous, subcutaneous) and/or nodal
    - Measures ≥10 millimeters (mm; post-biopsy) and <100 mm in longest diameter; nodal lesions must be ≥15 mm (post-biopsy) at short axis
    - Accessible for repeat intratumoral injection: Tumors encasing or abutting major vascular structures (such as the carotid artery) or tumors in locations at high risk for adverse effects (e.g. pneumothorax, brain lesions) are not considered appropriate for intratumoral injection. An irradiated mass cannot be used for intratumoral injection unless radiotherapy was completed at least 28 days prior to first dose of study drug and/or the lesion demonstrates evidence of growth (metabolically active via positive positron emission tomography or an unambiguous increase in size).
7. Eastern Cooperative Oncology Group (ECOG) Performance Status of 0 or 1

8. Adequate organ and marrow function at Screening, as defined by the following laboratory parameters:

Hematologic	**Renal**	**Hepatic**
White blood cell count ≥2000/µL Absolute neutrophil count ≥1000/µL Platelets ≥75,000/µL Hemoglobin ≥9 g/dL [1] Albumin ≥3.0 g/dL aPTT and/or INR ≤1.5 × ULN [2]	Creatinine ≤1.5 × ULN or GFR ≥ 30 mL/min/1.73m^2 by CKD-EPI equation: GFR = 141 x min(SCr /k, 1)$^{\alpha}$ x max(SCr /k, 1)$^{-1.209}$ x 0.993^{Age} x 1.018 [if female] x 1.159 [if black] Note: SCr is standardized serum creatinine in mg/dL, k is 0.7 for females and 0.9 for males, a is -0.329 for females and -0.411 for males, min indicates the minimum of SCr /k or 1, and max indicates the maximum of SCr /k or 1	AST/ALT ≤2.5 × ULN; or ≤5 × ULN for subjects with liver metastases Bilirubin ≤1.5 × ULN; or ≤3 × ULN if due to Gilbert's disease
ALT = alanine aminotransferase; aPTT= activated partial thromboplastin time; AST = aspartate aminotransferase; INR= International normalized ratio of prothrombin time; ULN = institutional upper limit of normal [1] Transfusions are allowed; hemoglobin must be ≥9 g/dL for at least 7 days after transfusion and prior to dosing [2] If receiving anticoagulant therapy, values should be within therapeutic range of intended use		

9. Women of childbearing potential (WOCBP) and fertile males with WOCBP partners must use highly effective contraception (CTFG 2014) throughout the trial and for the latter of: 4 months following the final dose of pembrolizumab or 30 days after the last dose of ADU-S100
10. Provide written informed consent and is willing and able to comply with all study procedures.

8.2 Exclusion Criteria

Individuals who meet any of the following exclusion criteria will not be eligible to participate in the study:

1. Diagnosis of recurrent or metastatic carcinoma of the nasopharynx, squamous cell carcinoma of unknown primary histology; or salivary gland or non-squamous histologies (e.g. mucosal melanoma)
2. Disease amenable to local therapy with curative intent (surgery or radiation therapy with or without chemotherapy)
3. Prior systemic anti-cancer therapy (use of chemotherapeutic agents, targeted small molecules, immunotherapy, or monoclonal antibodies) for the treatment of recurrent or metastatic HNSCC

   [Prior chemotherapy and/or or radiotherapy in the adjuvant or neoadjuvant setting is acceptable provided at least 28 days have elapsed since last dose, and/or the irradiated lesion demonstrates evidence of growth or active tumor).]

[Prior use of anti-PD-1 (or other drugs targeting immune checkpoint pathways) in the adjuvant or neoadjuvant setting is acceptable provided the total treatment period was ≤3 months in duration; the last dose was ≥6 months before the first dose of study drug; and anti-PD-1 treatment was not discontinued due to treatment-related toxicity.]

4. Symptomatic or untreated leptomeningeal disease
5. Presence of symptomatic central nervous system (CNS) metastases, or CNS metastases that require local CNS-directed therapy (such as radiation or surgery) or increasing doses of corticosteroids within the 2 weeks prior to first dose of study drug. Any symptomatic brain metastases should be neurologically stable (for 4 weeks post treatment and prior to study entry) with no corticosteroids administered for at least 2 weeks before first dose of study drug. Definitively treated CNS disease following gamma knife/stereotactic radiosurgery with no corticosteroids administered for at least 1 week before first dose of study drug should not be excluded.
6. Radiotherapy within 2 weeks of the first dose of study drug, except for palliative radiotherapy to a limited field, such as for the treatment of bone pain or a focally painful tumor mass
7. Participation in an interventional, investigational trial where an intervention was received within 4 weeks of the first dose of study drug
8. Prior severe hypersensitivity (≥ Grade 3) to pembrolizumab or any study drug excipients (e.g. L-histidine, sucrose or polysorbate 80)
9. History of or current drug-induced interstitial lung disease or pneumonitis Grade ≥2
10. Impaired cardiac function or clinically significant cardiac disease, including any of the following:
    - Symptomatic congestive heart failure requiring treatment
    - Clinically significant cardiac arrhythmia
    - Uncontrolled hypertension
    - Corrected QT interval (QTcF) >480 msec at Screening (average of triplicate ECGs) or congenital long QT syndrome
    - Acute myocardial infarction or unstable angina pectoris < 3 months prior to the first dose of study drug
    - New York Heart Association Functional Class III or higher (i.e. marked limitation of physical activity due to symptoms, or unable to carry on any physical activity without discomfort)
11. Diagnosis of immunodeficiency or receiving chronic systemic steroid therapy (>10 mg/day prednisone or equivalent) or any immunosuppressive therapy within 7 days prior to the first dose of study drug. Topical (<class III), inhaled, nasal and ophthalmic steroids are allowed except in the anatomic location of injected and non-injected lesions.
12. Receipt of any live vaccines within 4 weeks prior to first dose of study drug
13. Use of hematopoietic colony-stimulating growth factors [e.g. granulocyte colony-stimulating factor (G-CSF), GM-CSF, macrophage colony-stimulating factor (M-CSF)], thrombopoietin

mimetics or erythroid stimulating agents ≤2 weeks prior to first dose of study drug. Erythroid stimulating agents may be maintained if initiated more than 4 weeks prior to the first dose of study drug and the dose is stable

14. Received a diagnosis of, and/or tests positive at Screening for human immunodeficiency virus (HIV)
15. Active Epstein-Barr virus (EBV), hepatitis B virus (HBV), or hepatitis C virus (HCV) infection
16. Active infection (viral, bacterial, or fungal) requiring systemic therapy
17. Prior history of or active malignant disease other than that being treated in this study. Exceptions: malignancies that were treated curatively and have not recurred within the past 2 years; completely resected basal cell carcinoma and squamous cell carcinoma of the skin; and completely resected carcinoma *in situ* of any type.
18. Active, known, or suspected autoimmune disease or a documented history of autoimmune disease, except vitiligo or resolved childhood asthma/atopy.

    Individuals with vitiligo, type I diabetes, residual hypothyroidism only requiring hormone replacement, psoriasis not requiring systemic treatment, history of Hashimoto's thyroiditis on stable dose of thyroid hormone replacement therapy, adrenal insufficiency only requiring physiologic steroid replacement, or conditions not expected to recur should not be excluded.
19. Major surgery within 2 weeks of the first dose of study drug
20. If WOCBP, pregnant or breastfeeding; negative pregnancy status must be confirmed by serum pregnancy (human chorionic gonadotropin) test at Screening
21. Intercurrent illness that is either life-threatening or of clinical significance such that it might limit compliance with study requirements, or in the Investigator's assessment would place the subject at an unacceptable risk for participation.

8.3 Subject Completion, Treatment Discontinuation, or Removal from Study

8.3.1 Subject Completion

Subject completion is defined as completion of scheduled visits and assessments up to and including the last protocol-specified visit; or when the subject has experienced a clinical endpoint (e.g. death, unacceptable toxicity, confirmed disease progression) that precludes further continuation in the study.

8.3.2 Discontinuation from Study Treatment

A subject should be discontinued from treatment for any of the following reasons:

- Withdrawal of consent or subject requests study treatment discontinuation for any reason
- Occurrence of any medical condition or circumstance that exposes the subject to substantial risk and/or does not allow the subject to adhere to the requirements of the protocol
- Confirmed disease progression (Section 10.2.1.1)

- Any unacceptable toxicity, SAE, clinically significant AEs, severe laboratory abnormality, intercurrent illness, or other medical condition which indicates to the Investigator that continued participation is not in the best interest of the subject
- Subject experiences any Grade 4 adverse event, with the exception of those listed in Table 9-2
- Pregnancy
- Subject failure to comply with protocol requirements or study-related procedures. [Dosing compliance issues should be reviewed on a case-by-case basis with Medical Monitor.]
- Termination of the study by the Sponsor or regulatory authority

Subjects who experience unacceptable toxicity directly attributable to pembrolizumab may continue on study and receive ADU-S100 as single agent study treatment with approval by the Medical Monitor.

If a subject's study treatment (ADU-S100 and/or pembrolizumab) is discontinued, this will not result in automatic withdrawal of the subject from the study. The Investigator will provide a reason for treatment discontinuation. Subjects who discontinue treatment will be encouraged to complete EOT and follow-up assessments.

8.3.3 Subject Discontinuation/Withdrawal from the Study

A subject will be withdrawn from the study for any of the following reasons:

- Death
- Lost to follow-up
- Withdrawal of consent
- Termination of the study by the Sponsor or regulatory authority

Subjects who do not complete at least one response evaluation, prior to their withdrawal from the study, unless they discontinued due to toxicity, will not be considered evaluable for the primary efficacy endpoint.

If a subject is lost to follow-up, reasonable efforts must be made by the study site personnel to contact the subject and determine the reason for discontinuation/withdrawal. The measures taken to follow up must be documented.

When a subject withdraws for other reasons before completing the study, the Investigator will provide a reason for withdrawal in the electronic case report form (eCRF).

9 STUDY DRUGS AND ADDITIONAL MEDICATIONS

All subjects will receive the investigational product, ADU-S100, and standard of care, pembrolizumab (per approved label language). Information regarding study drug administration is provided in the sections below.

9.1 Method of Subject Assignment

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.

9.2 Blinding

All study treatments will be administered open-label; no study participants or site personnel will be blinded to study treatment.

9.3 Standard of Care: Pembrolizumab

Pembrolizumab is an IgG4 kappa immunoglobulin with an approximate molecular weight of 146 kDa. Pembrolizumab for injection is supplied in single-dose vials as a sterile, preservative-free, white to off-white lyophilized powder; each vial is reconstituted and diluted for IV infusion.

Pembrolizumab is indicated for the treatment of HNSCC as a single agent for the first-line treatment of patients with metastatic or with unresectable, recurrent HNSCC whose tumors express PD-L1 [Combined Positive Score (CPS) ≥1] as determined by an FDA-approved test. Additional information on the product presentation, formulation, storage, preparation and administration of pembrolizumab may be found in the package insert (KEYTRUDA 2020).

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

9.3.1 Pembrolizumab Pre-Medications

Use of pre-medications (e.g. anti-pyretic or anti-emetic) for infusions should be based on Investigator discretion, institutional guidelines, and the subject's tolerance of prior infusions.

9.3.2 Pembrolizumab Infusion

Prepare, store, and administer pembrolizumab per package insert. The dose of pembrolizumab is 200 mg Q3W by IV infusion over approximately 30 minutes. Record the start and stop times for each infusion.

9.3.3 Supportive Care

Supportive care according to local standards may be used as needed. Record all medications for supportive care as concomitant medications.

9.3.4 Criteria for Continued Pembrolizumab Dosing

Immune-mediated reactions have been associated with pembrolizumab (KEYTRUDA 2020) and can result in severe and life-threatening events. Subjects will be assessed prior to each dose of pembrolizumab per criteria in Table 9-1; symptom-directed examinations according to local standards of care and laboratory tests may be performed up to 3 days before dosing.

Table 9-1 Continued Dosing Requirements [1]

Clinical Assessment	Organ Function
Assess for clinically meaningful signs and symptoms of: • Colitis • Skin adverse reactions • Pneumonitis • Hypophysitis	Monitor for clinically significant, treatment-emergent changes in: • Liver function • Thyroid function • Hyperglycemia • Renal function

[1]Adapted from KEYTRUDA Warnings and Precautions (KEYTRUDA 2020); the most recent label should also be consulted for any updates to Warnings and Precautions.

Subjects who do not meet dosing eligibility requirements will be monitored; guidelines for dose interruption (Section 9.5) and dose modification (Appendix A) should be followed where appropriate.

9.4 Investigational Product: ADU-S100

ADU-S100 is supplied as a sterile solution for injection. ADU-S100 is a clear to slightly opalescent, colorless to pale yellow solution of 1 mg/mL. ADU-S100 is supplied in a single-use, 2 mL, Type 1 clear glass vial with a butyl stopper and a flip-off overseal.

The investigational product was manufactured, packaged, and labeled according to Good Manufacturing Practice (GMP) regulations. Section 14.2.1 provides guidance for disposition and accountability of investigational products. Additional information on physical and chemical properties of ADU-S100 may be found in the IB.

Details for storage, preparation, and administration of ADU-S100 are provided in the Pharmacy Manual. The following sections provide general guidance on ADU-S100 administration, dosing modifications, and management of study-drug associated toxicities.

9.4.1 ADU-S100 Pre-Medications

Use of pre-medications (e.g. local anesthetic and/or acetaminophen) for intratumoral injections will be based on Investigator discretion, institutional guidelines, and the subject's tolerance of prior injections. Local anesthetic should not be injected directly into the target lesion.

9.4.2 ADU-S100 Administration

9.4.2.1 Identification of Lesions for Intratumoral Injection

At the Screening Visit (or prior to first dose of ADU-S100), the Investigator will document all potential lesions available for intratumoral injection, and identify the lesions selected for intratumoral injection.

- Up to 2 cutaneous, subcutaneous, or nodal lesions may be designated for intratumoral injection. Per eligibility criteria, one subcutaneous/cutaneous lesion must measure ≥10 mm (post-biopsy, if applicable), or ≥15 mm if nodal; and <100 mm in longest diameter. The second injectable lesion may be smaller than the specified size if no other injectable lesion of the specified size can be identified. Selection of injectable lesions should be from different regions of the body (if possible) to provide greatest coverage and target multiple draining lymph nodes. Should any initial lesion recede following treatment such that they are no longer visible, or injection is no longer feasible, other lesions may be selected for injection (Section 9.4.2.3). These lesions may also be smaller than the specified size, if no other injectable lesions of the specified size can be identified.
- Tumors encasing or abutting major vascular structures (such as the carotid artery) or tumors in locations at high risk for adverse effects (e.g. pneumothorax, brain lesions) are not considered appropriate for intratumoral injection.
- An irradiated mass cannot be used for intratumoral injection unless radiotherapy has occurred at least 3 months prior to first dose of study drug and/or the lesion demonstrates evidence of growth or active tumor (e.g. positive PET scan or increase in size).
- All injected lesions must be deemed measurable and followed per RECIST 1.1 (see Appendix B)

The priority is to identify and inject ADU-S100 in up to 2 lesions. If a subject has >2 lesions, or if a lesion is not amenable to repeat intratumoral injection, but is accessible and amenable to biopsy, one lesion (or visceral tumor) may be designated a “non-injected” lesion.

9.4.2.2 Intratumoral Injection of Lesions

The intratumoral injection of ADU-S100 should only be performed by trained personnel. On dosing days where pembrolizumab is also administered, ADU-S100 should be administered following completion of the pembrolizumab infusion provided the subject is considered clinically stable.

All lesions designated for ADU-S100 administration should be injected on Days 1 and 8 of each dosing cycle (i.e. do not rotate/alternate sites for injection, all designated lesions will be injected on every dosing day unless repeat administration is no-longer possible, See Section 9.4.2.3). Confirm biopsy area has healed prior to initiating dosing.

ADU-S100 will be diluted as described in the Pharmacy Manual to achieve the assigned dose level prior to administration. An injection volume of 1.0 mL ADU-S100 dosing solution should be administered per lesion.

Local anesthetic may be used per institutional guidelines but should not be injected directly into the lesion. Injection of ADU-S100 should be conducted per institutional guidelines using sterile technique. Ultrasound-guided injection may be utilized per institutional guidelines. The best attempt should be made to distribute the entire volume of ADU-S100 throughout the lesion; multiple passes may be used. Record the start and stop times for each administration.

9.4.2.3 Regression of Injected Lesions

If a lesion shows signs of significant regression (i.e. shrinkage) that precludes the ability to re-inject the lesion, other accessible lesions may be injected after documented discussion between the Investigator and the Medical Monitor.

If the injected lesion(s) shows signs of significant regression such that only scar tissue is remaining, a PET scan should be performed to identify whether any tumor tissue remains. If no tumor tissue remains, administration of ADU-S100 at the lesion may be discontinued.

After all lesions that meet requirements in Section 9.4.2.1 have been successfully treated, additional smaller lesions may be injected with ADU-S100 following consultation with the Medical Monitor.

If the injected lesion(s) shows signs of significant regression (i.e. shrinkage) such that repeat administration of ADU-S100 is no longer possible in any lesion, the subject will be scheduled to complete the EOT visit and may continue treatment with pembrolizumab as monotherapy/standard of care outside the context of the ADU-CL-20 clinical trial. Previously resolved injected lesions that recur can be re-injected as long as the subject has not met criteria for treatment discontinuation (Section 8.3.2).

9.5 Dose Interruptions and Dose Modification for Treatment-related Toxicities

Dose interruptions are recommended for subjects who do not tolerate the protocol-specified dosing schedule. In the case of acute reaction to pembrolizumab infusion, the scheduled dose of ADU-S100 may be delayed (or withheld) following consultation with the Medical Monitor.

Following the first 4 cycles of study treatment, dosing interruptions are also permitted in the case of medical / surgical events, palliative radiation, or logistical reasons not related to study therapy (e.g. elective surgery, unrelated medical events, vacation, and/or holidays), after discussion with the Medical Monitor. Subjects should be placed back on study therapy within 3 weeks of the scheduled interruption, unless otherwise discussed with the Medical Monitor. The reason for interruption should be documented in the subject's study record.

Pembrolizumab: No dose reductions of pembrolizumab are recommended. Subjects who experience unacceptable toxicity directly attributable to pembrolizumab may continue on study and receive ADU-S100 as single agent study treatment with approval by the Medical Monitor.

ADU-S100: For subjects who experience systemic TEAEs with a suspected relationship to ADU-S100, the dose level of ADU-S100 may be reduced following sufficient resolution of the event (Section 9.5.1) and after consultation with the Medical Monitor.

General guidelines for ADU-S100 dose reduction:

- Reduce dose to 400 mcg/lesion
- If tolerability issues persist, the dose level may be further reduced to 200 mcg/lesion
- If tolerability issues persist at 200 mcg/lesion; discontinue ADU-S100 treatment

The following sections provide guidance for management of general and specific toxicities which may be associated with administration of pembrolizumab or ADU-S100.

9.5.1 General Toxicity and Dose Modification Guidelines

Occurrence of any of the TEAEs outlined in Table 9-2 requires dose modification and/or treatment discontinuation. No dose reductions of pembrolizumab are recommended. If discontinuation of pembrolizumab is warranted, a subject may continue on ADU-S100 monotherapy following consultation with the Medical Monitor (Section 9.5.2). If ADU-S100 is discontinued due to a Grade 4 injection site reaction, monotherapy with pembrolizumab should continue and the subject will complete the EOT visit and safety monitoring periods.

ADU-S100 dose reductions may be allowed following consultation with the Medical Monitor (Section 9.5.3).

Table 9-2 Toxicities Requiring Dose Modification or Treatment Discontinuation

Any Grade 4 AEs will lead to permanent treatment discontinuation with the exception of: • Neutropenia lasting ≤ 5 days that is not associated with fever or other clinical symptoms • Lymphopenia or leukopenia • Electrolyte abnormalities not associated with clinical sequelae or deemed not clinically significant and are corrected with appropriate management or supplementation within 72 hours of onset
Drug Induced Liver Injury (DILI) will lead to permanent study treatment discontinuation as indicated by serum chemistry values consistent with Hy's Law criteria (all 3 of the following must co-exist): • ALT or AST ≥3× institutional upper limit of normal (ULN) • Total bilirubin ≥2× ULN • Alkaline phosphatase <2× ULN
Grade 4 injection site reaction will lead to discontinuation of ADU-S100
Grade 3 or higher infusion-related reaction will lead to discontinuation of pembrolizumab
Any Grade 3 AEs may lead to dose modification or delay of either ADU-S100 or pembrolizumab after consultation with the medical monitor with the exception of: • Serum lipase and/or serum amylase (asymptomatic) CTCAE Grade 3 < 7 consecutive days • Nausea and vomiting that resolves within 2 days after starting optimal anti-emetic therapy • Thrombocytopenia without significant bleeding • Anemia that resolves within 7 days in the absence of transfusion • Diarrhea that resolves within 2 days after starting optimal anti-diarrhea treatment • Hypertension that resolves within 7 days after starting treatment • Infection or fever in the absence of neutropenia that resolves within < 5 days • Rash or photosensitivity that resolves within 7 days after starting treatment • Fatigue that resolves within 7 days
Grade 2 or 3 clinically significant injection site reactions will lead to delay and/or dose modification of ADU-S100 (See Section 9.5.4)
Grade 2 clinically significant immune-related toxicities, including a single event or multiple occurrences of the same event per investigator discretion may lead to discontinuation of pembrolizumab
Eye pain or reduction of visual acuity that does not respond to topical therapy and does not improve to Grade 1 severity within 2 weeks of the initiation of topical therapy OR requires systemic treatment may lead to discontinuation of pembrolizumab
Any immune related AE that meets criteria for discontinuation (Appendix A)

The following general dose modification guidelines should be followed for AEs outlined in Table 9-2 or other suspected study drug-related events:

- If a subject experiences an AE outlined in Table 9-2 or other unacceptable toxicity, consult the Medical Monitor prior to resuming treatment
- Generally if a dose is interrupted or withheld for AE, treatment may be resumed following resolution of the AE to Grade 1 or baseline
    - If the Investigator considers it in the subject's best interest to resume treatment before the AE has resolved to Grade 1, the Medical Monitor should first be consulted.

- If dose interruptions persist > 6 weeks (from the expected day of dosing), the subject will be discontinued from the study treatment unless there is evidence of clinical benefit and the Investigator deems it is in the subject's best interest to remain on study. In such cases, the Medical Monitor must be consulted.
- ADU-S100 only: If a subject requires more than 2 dose interruptions for the same toxicity, ADU-S100 should be discontinued.

9.5.2 Management of Immune-related Adverse Events

AEs with suspected immunologic etiology, which may be severe or fatal, can occur in any organ system or tissue in subjects receiving immunotherapy. These immune-related AEs (irAEs) may occur after the first dose or several months after the treatment discontinuation. Suspected irAEs should be adequately evaluated to confirm etiology or exclude other causes; additional procedures or tests may be included as part of the evaluation.

Guidelines for dose modification and toxicity management for irAEs are provided in Appendix A; additional recommendations are provided in the American Society of Clinical Oncology clinical practice guideline for the management of irAE (Brahmer et al. 2018).

Consult the current prescribing information for any updates to dose modification language for irAE or infusion reactions.

9.5.3 Guidelines for Pembrolizumab Infusion-related Reactions

Per approved product label (KEYTRUDA 2020) the following guidelines are recommended for infusion-related reactions associated with pembrolizumab:

- Grades 1 or 2: Interrupt or slow the rate of infusion
- Grades 3 or 4: Discontinue pembrolizumab permanently

9.5.4 Guidelines for ADU-S100 Injection Site Reactions

The following guidelines are recommended for injection site reactions related to ADU-S100:

- Grade 1: Continue study treatment
- Grade 2: Delay study treatment until resolved to ≤ Grade 1
- Grade 3: Delay study treatment until resolved to ≤ Grade 1; resume treatment after consultation with the Medical Monitor
- Grade 4: Permanently discontinue ADU-S100 treatment.

9.5.5 Cytokine Release Syndrome

CRS is caused by a release of inflammatory cytokines such as IL-6, IL-1b, IFN-γ, and TNF-α. This type of reaction is sometimes observed in cancer immunotherapy and typically presents with symptoms including fever, nausea, chills, rash, flushing, rigors, hypotension, tachycardia, headache, throat tightness, and dyspnea. Capillary leak with fluid retention can be worsened by

hydration commonly given to treat hypotension. CRS may also be associated with pulmonary infiltrates, pulmonary edema, arrhythmias, and cardiac arrest. Note that symptoms of CRS vary greatly and may be difficult to distinguish from other conditions.
If CRS is suspected, all subjects should be managed per local institutional practice based upon clinical signs and symptoms, and response to interventions. Patient management in an intensive care unit may be required and the timing is dependent upon local institutional practice.

Tocilizumab may be administered in cases of moderate to severe CRS if any of the following are present:

- Hemodynamic instability despite IV fluid challenges and moderate stable vasopressor support
- Worsening respiratory distress, including pulmonary infiltrates, increasing oxygen requirement including high-flow O_2, and/or need for mechanical ventilation
- Any other signs or symptoms of rapid deterioration despite medical management

Supportive care measures should be undertaken immediately as per institutional guidelines to include frequent vital signs, IV fluids, oxygen, steroids, and vasopressors as clinically indicated.

If CRS is suspected, cytokines IL-6, IL-1, IFN-γ, and TNF-α and serum C-reactive protein (CRP) and ferritin will be analyzed at central laboratories to determine if cytokine elevation and biochemical abnormalities associated with CRS are observed. Refer to laboratory manual for further information.

9.6 Concomitant Medications

Subjects may receive concomitant medications and procedures as required or deemed necessary for supportive care, unless specifically restricted or prohibited in this study (Section 9.6.1).

During the course of the study, subjects should continue the use of prescribed medications identified during the screening procedures, consistent with study inclusion and exclusion criteria.

- Anticoagulation therapy is permitted. Ongoing anticoagulant therapy should be temporarily discontinued to allow tumor biopsies according to institutional guidelines.
- Coronavirus (COVID-19) vaccines are encouraged provided the vaccine is not a live vaccine (i.e. RNA vaccines are allowed); the vaccine should not be administered on the same day as study drug administration

9.6.1 Prohibited Medications

A subject may be discontinued from study drug for use of prohibited medications or procedures. Approval must be obtained from the Medical Monitor for a subject to continue dosing if a prohibited medication is administered during study treatment. The following therapies are not permitted or are restricted during the study:

- Non-study chemotherapy, small molecule, immunotherapy, or other therapeutic monoclonal antibodies or biologics (approved or investigational) intended to treat the disease under study.
- Additionally, no other immunosuppressive medication may be administered while on study treatment unless given for the management of immune toxicity.
- Radiation therapy (non-palliative)
  NOTE: limited field palliative radiotherapy to non-target lesion(s) may be allowed as concomitant therapy after documented discussion with Medical Monitor
- Any other investigational product or device
- Systemic corticosteroids > 10 mg/day of prednisone or equivalent (unless used for treatment of study drug-related toxicity) except if given as a pre-medication or for contrast dye allergy
- Live vaccines (including, but not limited to measles, mumps, rubella, chicken pox, yellow fever, rabies, BCG, and typhoid [oral] vaccine). Seasonal influenza vaccines for injection are generally killed virus vaccines and are allowed. Intranasal influenza vaccines (e.g. Flu-Mist®) are live attenuated vaccines and are not allowed.

There are no prohibited therapies or procedures once the subject has completed the EOT visit.

9.7 Treatment Compliance

Study drug will be administered by a qualified health care professional at an approved study site. The date, time, volume, location, and route of each dose of study drug administered to each subject must be recorded in the appropriate source document.

10 STUDY ASSESSMENTS AND PROCEDURES

Screening assessments will be conducted to confirm eligibility and to obtain baseline (pre-treatment) measurements. Screening must be completed within 28 days prior to Cycle 1 Day 1. An enrollment form will confirm subject eligibility; baseline biopsies should not be performed until enrollment is confirmed.

Subjects will be requested to complete multiple clinic visits during all dosing cycles. An EOT Visit should occur 30 (+7) days after the last dose of ADU-S100 and/or pembrolizumab. All EOT Visit assessments should be completed prior to commencing any new anti-cancer therapy.

Subjects who discontinue ADU-S100 and pembrolizumab early for reasons other than progressive disease will complete the EOT.

The EOT visit will be conducted to satisfy protocol-specified safety reporting periods (Table 10-1) and collect data on any subsequent cancer-related therapies.

All study visits (and visit windows), assessments, and procedures will be performed as indicated in the Schedule of Events (Table 2-1). On days when ADU-S100 or pembrolizumab is administered, assessments should be performed prior to dosing unless otherwise specified. Further details of study procedures and assessments can be found in the Study Reference and Laboratory Manuals.

10.1 General Assessments

10.1.1 Informed Consent

Before any screening assessments are conducted, an individual must be given a complete explanation of the purpose and requirements of the study; an informed consent form (ICF) and an authorization for use and disclosure of protected health information must be signed. An original signed consent form will be retained in the subject's source documentation at the site; a copy will be provided to the subject.

Assessments conducted as standard of care prior to signing informed consent may be considered toward eligibility requirements if performed within the 28-day Screening Period.

10.1.2 Demographics, Medical History, and Height

Demographic data and a complete medical history will be collected at Screening by the Investigator or qualified designee. Demographic information (as allowed by local regulations) will include date of birth, age, gender, ethnicity, and race. Medical history should include all active conditions and any past condition considered to be clinically significant by the Investigator.

Details regarding the disease for which the subject has enrolled in this study (e.g. date of diagnosis, primary tumor histology, prior surgery(ies), radiation therapy, other prior treatment regimens, and current stage of cancer) will be recorded.

Height (without shoes) will be obtained at Screening with a stadiometer.

10.1.3 Eligibility

Potential subjects will be evaluated for entry into the study according to the stated inclusion and exclusion criteria (Sections 8.1 and 8.2). Individuals deemed ineligible for study enrollment do not need to complete all screening procedures. The reason for ineligible status will be documented. Tests with results that fail eligibility requirements may be repeated once during the Screening Period if the Investigator believes the results to be in error. Additionally, a subject who fails screening may repeat the screening process one time if the Investigator believes there has been a change in eligibility status (e.g. after recovery from an infection).

For subjects who meet all inclusion/exclusion criteria, an enrollment form will be completed and sent to Sponsor or designee for review and approval. No protocol eligibility waivers will be granted. The first dose of pembrolizumab and ADU-S100 will not be administered until the Investigator receives approval of the enrollment form.

10.2 Efficacy Measures

The assessments to derive efficacy variables are described below and will be conducted according to the Schedule of Events in Table 2-1. Efficacy variables and associated analyses are described in Sections 6 and 12.5.

10.2.1 Tumor Imaging and Response Assessments

Radiographic tumor evaluation should include baseline computed tomography (CT) scans with contrast of the chest, abdomen, head and neck. Magnetic resonance imaging (MRI) is the preferred imaging method for brain metastasis should be conducted if there are known or suspected CNS metastases. MRI is also the preferred imaging method for bone metastasis. In either case, if CT is performed instead of MRI, ambiguous results may be confirmed by MRI. An MRI scan may also be conducted for known or suspected bone metastases. Collect scans electronically. All injected lesions identified at baseline will be considered measurable lesions and measurements will be recorded per RECIST v1.1 (see Appendix B). Additional lesions that are injected following successful treatment of initial injected lesions do not have to be measurable lesions.

If CT scan is contraindicated (e.g. allergy to contrast dye), MRI should be performed. However, if lesion being followed cannot be imaged but can be assessed by clinical examination, measurements taken by usage of calipers will be acceptable. Tumor imaging will be performed using the same assessment technique throughout the study as indicated.

For each scan, tumor measurements and assessment should be obtained using RECIST v1.1 (Eisenhauer et al. 2009), see Appendix B; response assessment will be determined by the local Investigator. The Investigator/local radiology review will also use iRECIST (Seymour et al. 2017) to assess tumor response and progression and make treatment decisions (see Appendix C).

10.2.1.1 Confirmation of Disease Progression

If disease progression is observed, another scan should be performed at 4-9 weeks later to confirm disease progression per iRECIST prior to treatment discontinuation (see Appendix C). While awaiting confirmation of disease progression subjects may continue to receive pembrolizumab and/or ADU-S100 provided the treatment discontinuation criteria in Section 8.3.2 do not apply.

Subjects who have confirmed disease progression but have evidence of clinical benefit per the Investigator's assessment may be considered for continued treatment after documented discussion with the Medical Monitor. Following that discussion, the subject should be informed by the Investigator of the option to continue study treatment or consider other therapeutic options with proven benefit, if those exist.

In cases of clinical deterioration or suspicion of disease progression, follow-up imaging assessment should be performed promptly rather than waiting for the next scheduled assessment. Subjects with evidence of further disease progression and who are no longer deriving clinical benefit will be discontinued from treatment; the subject should complete the EOT Visit and enter the Follow-Up Period.

Subjects who do not complete at least one response evaluation prior to their withdrawal from the study, unless they discontinued due to toxicity, will not be considered evaluable for the primary efficacy endpoint.

10.2.2 Photography of Injected Lesions

[Removed by Amendment 4]

10.2.3 Subsequent Anti-Cancer Therapy Follow-Up

At the EOT visit, any subsequent cancer-related therapy will be assessed until completion of the required safety reporting periods, death of the subject, withdrawal of consent, loss to follow-up, or close of study by the Sponsor.

All deaths must be reported on the eCRF.

10.3 Safety Assessments

Safety will be assessed by collection of data on ECOG performance status, vital signs, weight, physical examination, electrocardiogram (ECG) parameters, TEAEs, concomitant medications, and routine clinical laboratory assessments. Clinically significant changes from pre-treatment values in safety assessments should be reported as AEs. Safety assessments described below will be conducted according to the Schedule of Events (Table 2-1).

10.3.1 Eastern Cooperative Oncology Group 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 Table 2-1.

10.3.2 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 CRS during Cycle 1. Collect vital signs prior to dosing and as indicated in Table 2-1. Additional measurements should be obtained if clinically indicated.

10.3.3 Physical Examination and Weight

Comprehensive Physical Examination

Comprehensive physical examinations will be conducted at Screening and EOT. Comprehensive physical examinations must be performed by a medically qualified individual such as a licensed Physician, Physician's Assistant, or an advanced Registered Nurse Practitioner, as local law permits.

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.

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.

Weight

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

10.3.4 Electrocardiogram

At screening and during the study (Table 2-2), 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 formula (QTcF). At screening, the average value of the triplicate will be utilized for enrollment into the study.

The triplicates should 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. Perform the ECGs prior to study drug administration for all pre-dose assessments, as outlined in Table 2-2. If

blood sampling or vital sign measurement is scheduled for the same visit as an ECG recording, the procedures should 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 (Fridericia's correction):

$$QTcF = QT/ (RR)^{0.33}$$

The ECG will be interpreted by the Investigator as normal, not clinically significant abnormal, or clinically significant abnormal. If the mean QTcF is prolonged (i.e. >500 msec, or CTCAE Grade 3) or if the mean change from baseline (value obtained at screening) is ≥60 msec, the ECGs should be reevaluated by a qualified person. Abnormalities in the ECG that lead to a change in subject management (e.g. dose reduction, interruption, treatment discontinuation, requirement for additional medication or monitoring) or results in clinical signs and symptoms that are considered clinically significant will be deemed AEs or SAEs if serious criteria are met (see Section 10.3.5).

10.3.5 Adverse Events

After signing informed consent, and prior to the first study drug administration, any medical occurrence considered related to screening procedures (e.g. tumor biopsy, venipuncture) will be captured as an AE; all other medical events will be captured in the subject's medical history (Section 10.1.2).

Safety reporting periods for this study are defined in Table 10-1. The determination, evaluation, reporting, and follow-up of AEs will be performed as outlined in Section 11 (irrespective of timing of withdrawal of consent of a subject).

Table 10-1 Safety Reporting Periods

Event Type	Reporting Period	Additional Requirements
Adverse Events/Serious Adverse Events (Screening)	Date of informed consent and prior to first dose of pembrolizumab	Report as AE/SAE only if related to study procedures during Screening
Adverse Events (treatment-emergent)	First dose of pembrolizumab through 30 days following last dose of ADU-S100 or pembrolizumab	Report new AEs outside of window if assessed as related to study drug(s)
Serious Adverse Events (treatment-emergent)	First dose of pembrolizumab through 30 days following last dose of ADU-S100 or 90 days following last dose of pembrolizumab (if the subject initiates new anticancer therapy following cessation of pembrolizumab treatment, SAEs will be collected up to 30 days following cessation of pembrolizumab treatment.)	Report new SAEs outside of window if assessed as related to study drug(s) Contact the subject by phone to complete the SAE reporting periods as applicable.
Drug-induced liver injury (treatment-emergent)	First dose of pembrolizumab through 30 days following last dose of ADU-S100 or pembrolizumab	Report outside of window if assessed as related to study drug(s)
Pregnancy of subject or partner	Date of informed consent through 120 days following last dose of pembrolizumab (if the subject initiates new anticancer therapy following cessation of pembrolizumab treatment, pregnancy information will be collected up to 30 days following cessation of pembrolizumab treatment.), or 30 days following last dose of ADU-S100	Follow pregnancy reporting and follow-up procedures per Section 11.5

10.3.6 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 should be documented. If a subject is using biotin supplements (found in multivitamins, biotin supplements, and supplements for hair, skin, and nail growth), also note for laboratory assessments (Section 10.4.2). 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.

10.3.7 Clinical Laboratory Evaluation for Safety

Routine hematology, serum chemistry, coagulations, urinalysis, and thyroid function testing will be performed throughout the study as a safety measure (Section 10.4.2). The Medical Monitor may, depending on study criteria, be consulted before enrollment about a potential subject with abnormal laboratory values that are not considered clinically significant by the Investigator.

The clinical significance of laboratory parameter findings will be determined by the Investigator throughout the study. More frequent clinical laboratory tests may be performed if indicated by the overall clinical condition of the subject or by abnormalities that warrant more frequent monitoring.

Additional safety laboratory assessments include baseline cytokine levels and additional cytokine monitoring associated with CRS when clinically indicated.

10.4 Laboratory Assessments

Laboratory assessments on blood, urine, and tumor tissue samples may be used to characterize the study population, assess safety, and characterize PD throughout the study per the Schedule of Events (Table 2-1). If indicated, collect Screening blood samples after requisite tests for eligibility have been completed. Samples indicated on dosing days must be pre-dose and may be obtained up to 3 days before Day 1 of each dosing cycle, unless otherwise indicated.

10.4.1 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: HIV antibody, HBV surface antigen, HCV antibody, HCV viral load (if indicated), EBV (EBNA, VCA IgG, VCA IgM, EBV 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

10.4.2 Safety Laboratory Assessments

Routine hematology, serum chemistry, 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. Communicate to the laboratory if the subject is taking biotin (Section 10.3.6). Laboratory assessments for continued dosing of pembrolizumab must be confirmed prior to dosing (Section 9.3.4); testing may be completed up to 3 days prior to study drug administration for each cycle. Fasting is not

required; however fasting blood glucose should be performed if clinically indicated (Section 9.3.4).

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, ALT, 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)

10.4.2.1 Pregnancy Testing and Contraception Requirements

The effects of ADU-S100 on a fetus *in utero* or on the composition of sperm are unknown. Based on its mechanism of action and data from animal studies, pembrolizumab can cause fetal harm when administered to a pregnant woman. Therefore WOCBP and fertile males must consent to use highly effective contraception per (CTFG 2014) while receiving study drug and for 4 months after the last dose of pembrolizumab (and/or 30 days after the last dose of ADU-S100, whichever occurs later).

A WOCBP is defined as any female who has experienced menarche and who has not undergone surgical sterilization (hysterectomy or bilateral oophorectomy) and is not postmenopausal. Menopause is defined clinically as 12 months of amenorrhea in a woman over age 45 years in the absence of other biological or physiological causes.

For study eligibility, WOCBP must have a negative serum pregnancy test (hCG) at Screening and within 24 hours prior to first dose of study drug (unless Screening assessment completed within 72 hours of Cycle 1 Day 1 visit). A urine pregnancy test may be performed at all other indicated visits. In case of delayed menstrual period (>1 month), confirm absence of pregnancy prior to next dose of study drug or next study visit, whichever occurs first. If a urine pregnancy test is positive, the results should be confirmed with a serum pregnancy test. Pregnancy of a subject or partner must be reported and followed (Section 11.4).

10.4.2.2 Laboratory Assessments for Cytokine Release Syndrome

Blood (plasma) samples will be collected at Screening and as clinically indicated (Section 9.5.5) for assessment of IFN-γ, IL-6, IL-1, TNF-α, C-reactive protein, and ferritin. If CRS is suspected, a 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. Samples will be shipped to the central laboratories for analysis.

10.4.3 Drug Concentration Measurements

[Sample acquisition removed by Amendment 4]

10.4.4 Biomarker Assessments

[Sample acquisition removed by Amendment 4]

Evaluations that may be performed in this study include but are not limited to:

- Measurement of systemic cytokines to assess PD
- Determine relationship of STING genotype to response
- Assess gene expression changes in the TME and the periphery
- Determine phenotype and function of immune cells
- Assessment of TME markers associated with immune infiltrate in injected and distal lesions

10.4.4.1 Pharmacogenetic Sample

[Sample acquisition removed by Amendment 4]

10.4.4.2 Tumor Tissue (Biopsy)

[Sample acquisition removed by Amendment 4]

10.4.4.3 Pharmacodynamics, Biomarkers, and Indicators of Biological Activity

[Sample acquisition removed by Amendment 4]

Additional analytical assessments and methodologies may be used to understand the mechanism of action ADU-S100 and pembrolizumab, or to understand factors associated with response or cancer progression. These tests may be performed at the Sponsor's discretion and may include: additional phenotyping and cellular function analysis in the periphery; and gene expression changes in the tumor or periphery.

10.5 Appropriateness of Measures

Clinical indicators of efficacy will be evaluated using RECIST v1.1 criteria for tumor response assessments, which are widely accepted as uniform response criteria for HNSCC. Since immunotherapeutic agents may produce antitumor effects by potentiating endogenous cancer-specific immune responses, tumor response will also be evaluated using iRECIST. These response patterns may extend beyond the typical time course of responses seen with cytotoxic

agents and can manifest a clinical response after an initial increase in tumor burden or even the appearance of new lesions.

Assessments of progression-free and overall survival are also planned; PFS and OS are objective, direct measures of benefit, although interpretation may not only be limited by the size of the data set but also confounded by subsequent anti-cancer therapies and non-cancer deaths.

The safety parameters to be evaluated in this study include standard assessments such as recording of medical history, AEs and SAEs, physical examination, vital signs, ECGs, serum chemistry and hematology, urinalysis, concomitant medications, and other routine clinical and laboratory procedures.

The criteria for dose modification or treatment discontinuation are based on available clinical and nonclinical data for ADU-S100 combined with clinical experience and label language for pembrolizumab, and general practices in the development of immunotherapeutic agents. Since the safety profile of ADU-S100 has not been fully characterized and pembrolizumab is associated with serious risks, additional safety precautions (i.e. dosing eligibility and extended safety-reporting period) have been included to monitor subject safety.

As may occur with any immunotherapeutic agent, ADU-S100 may elicit an immune response resulting in CRS. Subjects will therefore be monitored at baseline and as clinically indicated for cytokine levels as added safety measure (Section 9.5.5).

Pre-treatment and on-treatment blood samples and tumor biopsies will provide an initial investigation into the mechanism of action of ADU-S100 when administered with pembrolizumab. Characterization of a broad panel of biomarkers may be predictive of response to therapy and may also give insight into appropriate endpoints in additional clinical studies.

11 ADVERSE EVENT REPORTING

AEs, SAEs, and pregnancy occurring during the protocol-specified timeframes defined in Section 10.3.5 will be assessed and reported following guidelines provided in the following sections.

11.1 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.

Subjects should be instructed to report any AE that they experience to the Investigator. At each indicated visit, Investigators will assess for AEs. AEs will be monitored and documented on the AE eCRF.

Wherever possible, a specific disease or syndrome rather than individual associated signs and symptoms should be identified by the Investigator and recorded on the eCRF. However, if an observed or reported sign or symptom is not considered a component of a specific disease or syndrome by the Investigator, it should be recorded as a separate AE on the eCRF. Additionally, the condition that led to a medical or surgical procedure (e.g. surgery, endoscopy, tooth extraction, or transfusion) should be recorded as the AE term, not the procedure.

For existing medical conditions reported as part of the medical history, clinically significant changes in signs or symptoms, or change in severity or seriousness should be reported as an AE.

Clinically significant abnormal laboratory or other examination (e.g. ECG) findings that are detected during the study or are present at Screening and significantly worsen during the study should be reported as AEs. The Investigator will exercise his or her medical and scientific judgment in deciding whether an abnormal laboratory finding or other abnormal assessment is clinically significant. Any abnormal test that is determined to be an error does not require reporting as an AE.

Examples of AEs include the following:

- Exacerbation of a chronic or intermittent preexisting condition, including an increase in frequency or intensity of the condition
- Signs, symptoms, or the clinical sequelae of a suspected interaction with another medical product
- Signs, symptoms, or the clinical sequelae of a suspected overdose of either investigational agent or a concurrent medication.

Examples of AEs do not include the following:

- Medical or surgical procedures (e.g. endoscopy, appendectomy); instead, the medical condition that led to the procedure is the AE term
- Situations that are unwanted but in which an untoward medical occurrence did not occur (e.g. admissions for respite care)
- Anticipated day-to-day fluctuations of a pre-existing disease or condition (present or detected before enrollment) that does not worsen overall

11.1.1 Disease-Related Events

The term "disease progression" should be recorded as an AE only if there are no other identifiable AEs associated with the disease progression at the time of reporting. For events associated with disease progression, the relevant signs and symptoms should be reported using a diagnosis whenever possible rather than individual underlying signs and symptoms. When a clear diagnosis cannot be identified, each sign or symptom should be reported as a separate AE. If the events resulting from disease progression meet the criteria for an SAE (e.g. resulted in hospitalization, a life-threatening event, or death), the specific event(s) should be reported as an SAE(s).

11.1.2 Assessment of Adverse Events by the Investigator

The Investigator will assess the severity (intensity) of each AE and the potential relationship between the AE and the study drug(s).

11.1.2.1 Assessment of Severity

The severity of all AEs should be graded according to the National Cancer Institute Common Terminology Criteria for Adverse Events (NCI-CTCAE v. 5.0; http://ctep.cancer.gov/reporting/ctc.html). For AEs not listed in the CTCAE, the following grading system should be used:

- Mild (CTCAE Grade 1): Mild; asymptomatic or mild symptoms; clinical or diagnostic observations only; intervention not indicated
- Moderate (CTCAE Grade 2): Moderate; minimal, local or noninvasive intervention indicated; limiting instrumental activities of daily living
- Severe (CTCAE Grade 3): Severe or medically significant but not immediately life-threatening; hospitalization or prolongation of hospitalization indicated; disabling; limiting self-care activities of daily living
- Life-threatening (CTCAE Grade 4): Life-threatening consequences; urgent intervention indicated
- Death (CTCAE Grade 5): Death related to AE

11.1.2.2 Assessment of Attribution

The Investigator is obligated to estimate the relationship between the study drug(s) and the occurrence of each AE or SAE. The relationship (synonym: causality) is based on the Investigator's clinical judgment regarding the likelihood that study drug caused the AE and may include consideration of some or all of the following factors:

- Alternative possible causes of the AE, including the subject's underlying disease or co-morbid conditions, other drugs, or other host and environmental factors
- The temporal sequence between the exposure to study drug and the AE
- Whether the clinical or laboratory manifestations of the AE are consistent with known actions or toxicity of the study drug
- Whether the AE resolved or improved with decreasing the dose or stopping the study drug (i.e. dechallenge); or recurred or worsened with re-exposure to the drug (i.e. rechallenge).

The Investigator should consult the IB in the determination of the assessment. The Investigator should consider all possible etiologies for the AE and render a causality assessment based on the most likely contributing factor to the AE.

There may be situations when an SAE has occurred and the Investigator has minimal information to include in the initial report. However, the Investigator must assess causality for every event before the transmission of the SAE. The Investigator may change his or her opinion of the causality in light of follow-up information, amending the SAE report.

The assessment of the relationship between the AE and the study drug will be determined using one of the following attribution categories:

RELATIONSHIP	**DESCRIPTION**
Unrelated to investigational agent/intervention	The AE *is clearly NOT related* to the intervention
	The AE *is doubtfully related* to the intervention
Related to investigational agent/intervention	The AE *may be related* to the intervention
	The AE *is likely related* to the intervention
	The AE *is clearly related* to the intervention

AEs listed as related are considered to have a suspected "reasonable causal relationship" to the investigational agent/intervention (ICH E2A). Per the ICH E2A and FDA guidelines, the expression "reasonable causal relationship" is meant to convey in general that there are facts (evidence) or arguments to suggest a causal relationship.

Additional guidelines in describing relationship:

- Related AEs follow a reasonable temporal sequence from the study drug administration and cannot be excluded as possibly or probably being caused by the study drug (e.g.

existence of similar reports attributed to the suspected drug and/or its analogues; reactions attributable to the pharmacologic effect of the drug) and can be excluded as possibly being caused by other factors such as underlying disease, complications, concomitant drugs, or concurrent treatment. The AE can be fully explained by the administration of study drug.

- Not Related: AE does not follow a reasonable temporal sequence from the study drug administration and can be reasonably explained by other factors, including underlying disease, complications, concomitant drugs, or concurrent treatment. Another factor is clearly the cause of the AE.
- For AEs occurring prior to initiation of study drug administration, the Investigator will assess relationship between the event and the protocol-required study procedures.

11.1.3 Adverse Event Follow-up

Follow-up is required for all subjects with AEs until the event has been resolved or the condition has stabilized. Clinically significant abnormal laboratory values occurring during the clinical trial or at the EOT Visits should be followed until repeat tests return to normal, stabilize, or are no longer clinically significant.

11.2 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
  - NOTE: An AE or adverse reaction is considered “life-threatening” if, in view of either the Investigator or Sponsor, its occurrence places the subject at immediate risk of death. It does not include an event that, had it occurred in a more severe form, might have caused death.
- Requires hospitalization or prolongation of existing hospitalization
  - NOTE: Any hospital admission with at least one overnight stay will be considered an inpatient hospitalization. An emergency room visit without hospital admission will not be recorded as an SAE under this criterion, nor will hospitalization for a procedure scheduled or planned before signing of informed consent. However, unexpected complications and/or prolongation of hospitalization that occur during elective surgery should be recorded as AEs and assessed for seriousness. Admission to the hospital for social or situational reasons (i.e. no place to stay, live too far away to come for hospital visits) or for observation post-study drug administration will not be considered a SAE.
- 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.
    - NOTE: Important medical events that may not result in death, be life-threatening, or require hospitalization may be considered an SAE when, based upon appropriate medical judgment, they may jeopardize the subject and/or may require medical or surgical intervention to prevent one of the outcomes listed above. Examples of such medical events include allergic bronchospasm requiring intensive treatment in an emergency room or at home, blood dyscrasias or convulsions that do not result in inpatient hospitalizations, or the development of drug dependency.

11.3 Serious Adverse Event Reporting

11.3.1 Initial Reports

An SAE report will be completed for each observed or reported SAE as thoroughly as possible including all available details about the event and the signature of the Investigator. If the Investigator does not have all information about an SAE, the Investigator will not wait to receive additional information before notifying the Sponsor of the event. The report will be updated when additional information is received.

SAE information will be reported to the Sponsor or designee within 24 hours of awareness of the initial or any follow-up information.

11.3.2 Safety Reporting Contact Information

SAE and pregnancy reporting contact information may be found in the Study Reference Manual. Sites should contact the Medical Monitor for any safety concerns or questions.

11.3.3 Expedited Reporting Requirements

The Sponsor (or designee) will report all SAEs that are unexpected and considered related to the administration of the study drug to the appropriate health and regulatory authorities and Investigators in the form of an expedited safety report within 15 calendar days after receiving information on the SAE. The Investigators will notify their reviewing IRB/EC and other committee(s) as required by institutional policies.

The Sponsor will also report to the appropriate health and regulatory authorities by facsimile, email, or phone within 7 days of receiving the information, any unexpected life-threatening or fatal SAEs that are considered related to the study drug.

11.3.4 Follow-Up Reports

The Investigator must continue to follow the subject until the SAE has subsided or until the condition becomes chronic in nature, stabilizes (in the case of persistent impairment), or the subject dies.

Within 24 hours of receipt of follow-up information, the Investigator must update the SAE report and submit any supporting documentation (e.g. subject discharge summary or autopsy reports) via facsimile or email to the Sponsor or designee.

11.4 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 (i.e. all 3 of the following must coexist):

1) ALT or AST $\geq 3 \times$ 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 (e.g. viral hepatitis A, HBV, or HCV; preexisting or acute liver disease; or another drug capable of causing the observed injury).

11.5 Pregnancy Reporting

If the subject or partner of a subject participating in the study becomes pregnant the Investigator should report the pregnancy and any follow-up information to the Sponsor or its designee within 24 hours of awareness of the information.

A subject becoming pregnant while on study drug will immediately be withdrawn from the study treatment and EOT and follow-up visit study procedures will be performed as appropriate. The Investigator should counsel the subject, discussing any risks of continuing the pregnancy and any possible effects on the fetus. If the subject gives permission for her treating physician to be informed, the Investigator is to notify the physician that she was participating in a clinical trial at the time she became pregnant and provide details of the treatment that the subject received.

Monitoring of the subject or partner and pregnancy should occur until the conclusion of the pregnancy or final outcome. Therapeutic, accidental, or spontaneous abortion should be reported as an SAE. Similarly, maternal and/or newborn complications, any congenital anomaly or birth defect in a child born to a subject exposed to the study drug should be reported as an SAE.

Report the outcome, including any premature termination. Follow live births for a minimum of 12 months. Any relevant information received by the Investigator after these time periods will be forwarded to the sponsor.

The pregnancy reporting form along with completion instructions are provided in the Study Reference Manual.

12 STATISTICAL ANALYSIS

The completeness of the data affects the integrity and accuracy of the final study analysis. Therefore, efforts will be made to ensure complete, accurate and timely data collection, and to avoid missing data. The procedures for handling missing, unused, or spurious data, along with the detailed method for analysis of each variable, transformations, and exploratory analyses will be presented in the Statistical Analysis Plan (SAP).

Collection and Sponsor analysis of PK, PD, and other exploratory assessments was discontinued (Protocol Amendment 4); analysis of available PK/PD data and other exploratory laboratory assessments (obtained prior to Amendment 4) will be described separately. The information below is intended as a guide to planned analyses.

12.1 Sample Size Determination

The original sample size was based on a Simon's 2-stage minimax design (Simon 1989) test the null hypothesis that the objective response rate (ORR; complete response [CR] and partial response [PR]) per Response Evaluation Criteria in Solid Tumors (RECIST) v1.1) is less than or equal to 0.19 versus the alternative hypothesis that ORR is greater than or equal to 0.38, with a Type 1 error rate of 0.05 and power of 80%.

Because of truncated enrollment, the total sample size will be limited to approximately 20 evaluable subjects as planned for the first stage.

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

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).

12.2 General Considerations

Descriptive statistics will be provided for selected demographic, safety, and clinical activity data. Descriptive summaries on continuous data will include number of subjects, means, medians, standard deviations, minimum and maximum values. Categorical data will be summarized using frequency counts and percentages. Descriptive summaries of time to event data from Kaplan Meier estimates will include the number of events, number censored, medians, quartiles and 95% CIs. Graphical summaries of the data may be presented. All data will be listed for all subjects. Because of truncated enrollment by amendment, some analyses may not be performed if limited data are available.

12.3 Analysis Sets

The following analysis sets will be used for this study:

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.

Safety population, defined as all subjects who receive any amount of study drug. All safety analyses will be based on this population.

12.4 Subject Information

Subject disposition summaries will include the number of enrolled subjects, the number of subjects receiving any study drug, the number of subjects completing the study, the number of subjects withdrawing prematurely, and the reasons for treatment and study discontinuation.

Demographics, baseline disease characteristics, prior disease related therapies, and concomitant medications will be summarized using descriptive statistics.

12.5 Efficacy Variables and Analyses

Clinical response to ADU-S100/pembrolizumab will be determined by Investigator assessment. All efficacy endpoints will be defined and analyzed according to RECIST v1.1 (Eisenhauer et al. 2009) (primary evaluation) and iRECIST (Seymour et al. 2017) (secondary evaluation).

The following efficacy endpoints will be derived and summarized descriptively.

12.5.1 Primary Efficacy Endpoint

Objective Response Rate defined as occurrence of complete response (CR) and partial response (PR).

Response Evaluation Criteria in Solid Tumors (RECIST) v1.1 will be used for the primary efficacy endpoint.

12.5.2 Secondary Efficacy Endpoints

Secondary efficacy endpoints are defined as:

Overall Survival (OS) is defined as the time from first dose of 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) is defined as the time from first dose of study drug to first documentation of disease progression or death due to any cause. Subjects who do not experience progressive disease and are alive will be censored at the time of last evaluable tumor assessment.

Duration of response (DOR) is 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.

Disease control rate (DCR) is defined as subjects with CR, PR, or stable disease (SD).

Duration of disease control (DODC) is 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.

ORR per iRECIST

RECIST v1.1 and iRECIST will be used for all secondary efficacy endpoints, as applicable. Estimates of PFS and OS will be assessed using Kaplan-Meier methodology.

12.6 Safety Analyses

AEs will be coded according to the Medical Dictionary for Regulatory Activities (MedDRA) and assessed for severity by the Investigator using the National Cancer Institute Common Terminology Criteria for Adverse Events (NCI-CTCAE) v. 5.0. TEAEs will be summarized by system organ class and preferred term and presented in decreasing order of frequency. Incidences of TEAEs and serious TEAEs will be summarized overall and with respect to CTCAE grade and relationship to study drug. TEAEs leading to study drug discontinuation, dose reduction/interruption, and with an outcome of death will also be summarized. Incidences of SAEs will be summarized overall and with respect to relationship to study drug.

Changes from baseline for safety laboratory parameters; clinically significant changes from baseline in vital signs and electrocardiogram parameters; and shifts from baseline to most extreme ECOG value will be presented.

12.7 Pharmacodynamic, Pharmacokinetic and Research Analyses

Available PK analyses and PD, biomarkers, and immune response data related to research laboratory samples may be described in a separate analysis document outside the context of this protocol and the associated SAP. Per amendment, no further samples will be obtained for analysis.

12.8 Timing of Analyses

Analyses will be conducted after all subjects have discontinued study drug, and/or have documented disease progression, withdrawn from the study; or when the study is terminated by the Sponsor.

Available data will be reviewed periodically by the SRT.

12.9 Interim Analysis

No formal interim analyses are planned during this study.

12.10 Data Monitoring Committee

There will be no independent Data Monitoring Committee for this study. Safety data and other relevant data will be reviewed by the SRT comprised of participating Investigators in the study, the Medical Monitor, and Sponsor representatives.

13 DATA MANAGEMENT AND RECORD KEEPING

13.1 Data Handling

Data will be recorded at the site on eCRFs and reviewed by the clinical research associate (CRA) during monitoring visits. The CRA will verify data recorded in the electronic data capture (EDC) system with source documents. All corrections or changes made to any study data must be appropriately tracked in an audit trail in the EDC system. An eCRF will be considered complete when all missing, incorrect, and/or inconsistent data has been accounted for and electronically signed by the Investigator or assignee.

Data will be processed using a validated computer system conforming to regulatory requirements.

13.2 Data Entry

Data must be recorded using the EDC system as the study is in progress. All site personnel must log into the system using their secure username and password in order to enter, review, or correct study data. These procedures must comply with Title 21 of the Code of Federal Regulations (21 CFR Part 11) and other appropriate international regulations. All passwords will be strictly confidential.

13.3 Data Validation

Validation checks programmed within the EDC system, as well as supplemental validation performed via review of the data, will be applied to the data in order to ensure accurate, consistent, and reliable data. Data identified as erroneous, or data that are missing, will be referred to the site for resolution through data queries.

The eCRFs must be reviewed and electronically signed by the Investigator in order to be considered complete.

13.4 Record Keeping

Records of subjects, source documents, monitoring visit logs, eCRFs, inventory of study drugs, regulatory documents, and other Sponsor correspondence pertaining to the study must be kept in the appropriate study files at the site. Source data is defined as all information in original records and certified copies of original records of clinical findings, observations, or other activities in a clinical study necessary for the evaluation and reconstruction of the clinical study. Source data are contained in source documents (original records or certified copies). These records will be retained in a secure file for the period as set forth in the Clinical Study Agreement. Prior to transfer or destruction of these records, the Sponsor must be notified in writing and be given the opportunity to further store such records.

14 INVESTIGATOR REQUIREMENTS AND QUALITY CONTROL

14.1 Ethical Conduct of the Study

Good Clinical Practice (GCP) is an international ethical and scientific quality standard for designing, conducting, recording, and reporting studies that involve human subjects. Compliance with this standard provides public assurance that the rights, safety, and well-being of study subjects are protected, consistent with the principles that have their origin in the Declaration of Helsinki, and that the clinical study data are credible.

14.2 Investigator Requirements

Each Investigator must provide the Sponsor and/or its designee completed and signed documentation as required by national competent authorities or regulatory agencies. Investigators may only initiate the study upon authorization by appropriate regulatory authorities and the Sponsor.

14.2.1 Disposition and Accountability of Investigational Products

The Investigator is responsible for the control of investigational products under study. An investigational product dispensing log must be kept current and should contain the following information:

- The identification number for each subject who is administered the investigational product
- The date(s) and quantity of the investigational product administered to the subject
- Documentation of proper disposal of used investigational product vials or unused vials subjected to temperature excursion
- Documentation of proper disposal (or return, at Sponsor's request) of unused investigational product vials.

The Investigator is responsible for investigational product accountability during on-site monitoring visits. All records and used/unused supplies of the investigational product must be available for inspection at every monitoring visit.

The study sites, per institutional guidelines, will destroy used investigational product vials after formulation for administration. The formulation of investigational product for administration and the destruction of each used vial will be documented in the investigational product accountability log. Unused investigational product will be destroyed at the study site, if possible, after final investigational product accountability and notification by Sponsor, unless otherwise directed by Sponsor.

14.3 Institutional Review Board/Ethics Committee

The IRB/EC will review all appropriate study documentation in order to safeguard the rights, safety, and well-being of subjects. The study will only be conducted at sites where IRB/EC approval has been obtained. The protocol, IB, ICF, advertisements (if applicable), written information given to the subjects, safety updates, annual progress reports, and any revisions to these documents will be provided to the IRB/EC by the Investigator.

Federal regulations and International Council on Harmonisation (ICH) require that approval be obtained from an IRB/EC prior to participation of subjects in research studies. Prior to study onset, the protocol, any protocol amendments, ICFs, advertisements to be used for subject recruitment, and any other written information regarding this study to be provided to a subject or subject's legal guardian must be approved by the IRB/EC.

No study drug will be released to the site for dosing until written IRB/EC authorization has been received by the Sponsor.

14.4 Informed Consent

The ICF and any changes to the ICF made during the course of the study must be agreed to by the Sponsor or designee and the IRB/EC prior to its use and must be in compliance with all ICH GCP, local regulatory requirements, and legal requirements.

The Investigator must ensure each study subject is fully informed about the nature and objectives of the study and possible risks associated with participation and must ensure the subject has been informed of his/her rights to privacy. The Investigator will obtain written informed consent from each subject before any study-specific activity is performed and will document consent was obtained prior to enrollment in the study in the source documentation. The original signed copy of the ICF must be maintained by the Investigator and is subject to inspection by a representative of the Sponsor, auditors, the IRB/EC, and/or regulatory agencies. A copy of the signed ICF will be given to the subject.

14.5 Study Monitoring Requirements

To ensure the study is conducted in accordance with the protocol, ICH, GCP and applicable government regulations, the study monitor will aid the Investigator and, at the same time, the Sponsor in the maintenance of complete, legible, well organized and easily retrievable data. Before the enrollment of any subject in this study, the Sponsor or their designee will review with the Investigator and site personnel the following documents: protocol, IB, eCRFs and procedures for their completion, informed consent process, study drug management, and the procedure for reporting SAEs.

The Investigator will permit the Sponsor or their designee to monitor the study as frequently as deemed necessary to determine that data recording and protocol adherence are satisfactory. During monitoring visits, information recorded on the eCRFs will be verified against source documents and requests for clarification or correction may be made. After the eCRF data are

entered by the site, the monitor will review the data for safety information, completeness, accuracy, and logical consistency. Computer programs that identify data inconsistencies may be used to help monitor the clinical study. If necessary, requests for clarification or correction will be sent to Investigators. The Investigator and his/her staff will be expected to cooperate with the monitor and provide any missing information, whenever possible.

All monitoring activities will be reported and archived. In addition, monitoring visits will be documented at the site by signature and date on the study-specific monitoring log.

14.6 Disclosure of Data

Data generated by this study must be available for inspection by health and regulatory authorities (such as FDA, Health Canada, European Medicines Authority, and others), the Sponsor or designee, and the IRB/EC as appropriate. Subjects or their legal representatives may request their medical information be given to their personal physician or other appropriate medical personnel responsible for their welfare.

Subject medical information obtained during the study is confidential and disclosure to third parties other than those noted above is prohibited.

14.7 Retention of Records

To enable evaluations and/or audits from regulatory authorities or the Sponsor, the Investigator will keep records, including the identity of all participating subjects (sufficient information to link records, e.g. eCRFs and hospital records), all original signed ICFs, copies of all eCRFs, SAE forms, source documents, and detailed records of treatment disposition. The records should be retained by the Investigator according to specifications in the ICH guidelines, local regulations, or as specified in the Clinical Study Agreement, whichever is longer. The Investigator must obtain written permission from the Sponsor before disposing of any records, even if retention requirements have been met.

If the Investigator relocates, retires, or for any reason withdraws from the study, the Sponsor should be prospectively notified. The study records must be transferred to an acceptable designee, such as another Investigator, another institution, or to the Sponsor.

14.8 Publication Policy

Following completion of the study, the data may be considered for publication in a scientific journal or for reporting at a scientific meeting. Each Investigator is obligated to keep data pertaining to the study confidential. The Investigator must consult with the Sponsor before any study data are submitted for publication. The Sponsor reserves the right to deny publication rights until mutual agreement on the content, format, interpretation of data in the manuscript, and journal selected for publication are achieved.

14.9 Financial Disclosure

Investigators are required to provide financial disclosure information to the Sponsor to permit the Sponsor to fulfill its obligations under 21 CFR §54. In addition, Investigators must commit to promptly updating this information if any relevant changes occur during the study and for a period of 1 year after the completion of the study.

14.10 Insurance and Indemnity

In accordance with the relevant national regulations, the Sponsor has taken out subject liability insurance for all subjects who have given their consent to the clinical study. This cover is designed for the event that a fatality, physical injury, or damage to health occurs during the clinical study's execution.

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Appendix A: Management and Dose Modifications of Immune-Mediated Adverse Reactions

These general guidelines for management of toxicities (Postow 2015) constitute guidance to the Investigator and are not intended to substitute for institutional standard of care practice. Additional recommendations are provided in the American Society of Clinical Oncology clinical practice guideline for the management of irAE (Brahmer et al. 2018). A general principle is that differential diagnoses should be diligently evaluated according to standard medical practice. Non-inflammatory etiologies should be considered and appropriately treated.

irAE	SEVERITY per CTCAE v 5.0	DOSE MODIFICAT-ION OR TREATMENT DELAY	MANAGEMENT	FOLLOW UP
Pneumonitis	Grade 1	Consider delay of IO therapy	• Monitor for symptoms every 2-3 days • Consider Pulmonary and ID consults	• Re-image at least every 3 weeks • If worsen, treat as Grade 2 or 3-4
	Grade 2	Withhold [a]	• Pulmonary and ID consults. • Monitor symptoms daily, consider hospitalization • 1.0mg/kg/day methyl prednisolone IV or oral equivalent • Consider bronchoscopy, lung biopsy	• Re-image every 1-3 days • If improves, taper steroids over at least 1 month and then resume IO therapy and consider prophylactic antibiotics • If does not improve after 2 weeks or worsen: Treat as Grade 3 or 4
	Grades 3 or 4 or recurrent Grade 2	Permanently discontinue	• Hospitalize • Pulmonary and ID consults • 2-4 mg/kg/day methyl prednisolone IV or oral equivalent • Add prophylactic antibiotics for opportunistic infections • Consider bronchoscopy, lung biopsy	• If improves to baseline, taper steroids over at least 6 weeks • If does not improve after 48 hrs or worsen: Add additional immunosuppression (e.g. infliximab, cyclophosphamide, IVIG or mycophenolate mofetil)
Diarrhea/ Colitis	Grade 1	Consider delay of IO therapy	Symptomatic treatment	• Close monitoring for worsening symptoms • Educate subject to report worsening symptoms immediately • If worsen, treat as Grade 2 or Grade 3/4

irAE	SEVERITY per CTCAE v 5.0	DOSE MODIFICAT-ION OR TREATMENT DELAY	MANAGEMENT	FOLLOW UP
	Grade 2	Withhold [a]	Symptomatic treatment	• If improves to Grade 1, resume IO therapy • If persists >5-7 days or recur: 0.5-1.0 mg/kg/day methylprednisolone or oral equivalent • When symptoms improve to Grade 1, taper steroids over at least 1 month, consider prophylactic antibiotics for opportunistic infections and resume IO therapy per protocol • If worsens or persists >3-5 days with oral steroids: treat as Grade 3
	Grade 4	Permanently discontinue	• -2.0 mg/kd/day methylprednisolone IV or IV equivalent • Add prophylactic antibiotics for opportunistic infections • Consider lower endoscopy	• If improves, continue steroids until Grade 1, then taper over at least 1 month • If persists >3-5 days or recurs after improvement, add infliximab 5 mg/kg (if no contraindication). Note: infliximab should not be used in cases of perforation or sepsis
Liver Test Elevation	Grade 1	Continue IO therapy		• Continue LFT monitoring per protocol • If worsen, treat as Grade 2 or Grade 3/4
	Grade 2	Withhold [a]	Increase frequency of monitoring to every 3 days	• If returns to baseline, resume monitoring, resume IO therapy per protocol • If elevations persist >5-7 days or worsen, 0.5-1.0 mg/kg/day methylprednisolone or oral equivalent and when LFT returns to grade 1 or baseline, taper steroids over at least 1 month, consider prophylactic antibiotics for opportunistic infections and resume IO therapy

irAE	SEVERITY per CTCAE v 5.0	DOSE MODIFICAT-ION OR TREATMENT DELAY	MANAGEMENT	FOLLOW UP
	Grade 3-4	Permanently discontinue	• Increase frequency of monitoring to every 1-2 days • 1.0-2.0 mg/kg/day methylprednisolone or IV equivalent • Add prophylactic antibiotics for opportunistic infections • Consult gastroenterologist	• If returns to grade 2, taper steroids over 1 month • If does not improve in >3-5 days, worsens or rebounds, add mycophenolate mofetil 1g BID. If no response within an additional 3-5 days, consider other immunosuppressants per local guidelines
Endocrino-pathies	Asymptomatic TSH elevation	Continue IO therapy	If TSH <0.5 X LLN or TSH >2 X ULN, or consistently out of range in 2 subsequent measurements: include fT4 at subsequent cycles as indicated; consider endocrinology consult	
	Symptomatic endocrinopathy	Withhold [a]	Evaluate endocrine function Consider pituitary scan • If symptomatic with abnormal lab/pituitary scan, 1-2 mg mg/kg/day methylprednisolone or PO equivalent and initiate appropriate hormone therapy • If no abnormal lab/ pituitary MRI scan but symptoms persist, repeat labs in 1-3 weeks/ MRI in 1 month	If improves (with or without hormone replacement), taper steroids over 1 month and consider prophylactic antibiotics for opportunistic infections. IO therapy should resume. Subjects with adrenal insufficiency may need to continue steroids with mineralocorticoid component.
	Suspicion of adrenal crisis (e.g. severe dehydration, hypotension, shock out of proportion to current illness	Withhold until clinically stable or discontinue	• Rule out sepsis • Stress dose of IV steroids with mineralocorticoid activity • IV fluids • Consult endocrinologist • If adrenal crisis ruled out, then treat as for symptomatic endocrinopathy	
Creatinine Elevation	Grade 1	Continue IO therapy	Monitor creatinine weekly	• If returns to baseline, resume routine creatinine monitoring per protocol • If worsen, treat as Grade 2 or 3/4

irAE	SEVERITY per CTCAE v 5.0	DOSE MODIFICAT-ION OR TREATMENT DELAY	MANAGEMENT	FOLLOW UP
	Grade 2-3	Withhold [a]	• Monitor creatinine every 2-3 days • 0.5-1.0 mg/kg/day methylprednisolone or oral equivalent • Consider renal biopsy	• If returns to Grade 1, taper steroids over at least 1 month, consider prophylactic antibiotics for opportunistic infections, and resume IO therapy and routine creatinine monitoring per protocol • If elevation persist > 7 days or worsen, treat as Grade 4
	Grade 4	Permanently discontinue	• Monitor creatinine daily • 1.0-2.0 mg/kg/day methylprednisolone or IV equivalent • Consult nephrologist • Consider renal biopsy	• If returns to Grade 1, taper steroids over at least 1 month, and add prophylactic antibiotics for opportunistic infections
Skin	Grade 1-2 (covering ≥ 30% BSA)	Continue IO therapy	Symptomatic therapy (e.g. antihistamines, topical steroids)	• If persists >1-2 weeks or recurs, consider skin biopsy, delay IO therapy, consider 0.5-1.0 mg/kg/day methylprednisolone or oral equivalent. Once improving, taper steroids over at least 1 month, consider prophylactic antibiotics for opportunistic infections, and resume IO therapy • If worsens, treat as Grade 3-4
	Grade 3 (covering > 30% BSA) or suspected Stevens-Johnson syndrome (SJS) or toxic epidermal necrolysis (TEN)	Withhold [a]	• Consider skin biopsy • Dermatology consult • 1.0-2.0 mg/kg/day methylprednisolone or IV equivalent	If improves to Grade 1, taper steroids over at least 1 month and add prophylactic antibiotics for opportunistic infections. Resume IO therapy.
	Grade 4 (covering > 30% BSA) or confirmed SJS or TEN	Permanently discontinue	• Consider skin biopsy • Dermatology consult • 1.0-2.0 mg/kg/day methylprednisolone or IV equivalent	If improves to Grade 1, taper steroids over at least 1 month and add prophylactic antibiotics for opportunistic infections

irAE	SEVERITY per CTCAE v 5.0	DOSE MODIFICAT-ION OR TREATMENT DELAY	MANAGEMENT	FOLLOW UP
Other	Grades 2 or 3 based on severity and type of adverse reaction	Withhold [a]		
	Grade 3 based on the severity and type of reaction or Grade 4	Permanently discontinue		
Recurrent immune-mediated reactions	Recurrent Grade 2 pneumonitis Recurrent Grades 3 or 4	Permanently discontinue		
Inability to taper corticosteroid	Requirement for ≥10 mg/day prednisone or equivalent for more than 12 weeks after last dose of pembrolizumab	Permanently discontinue		
Persistent immune-mediated reaction (excluding endocrino-pathy)	Grades 2 or 3 adverse reactions lasting 12 weeks or longer after last dose of pembrolizumab	Permanently discontinue		
Infusion-related reactions	See Section 9.5.3			

***** Toxicity was graded per National Cancer Institute Common Terminology Criteria for Adverse Events. Version 5.0 (NCI-CTCAE v5.0).

[a] Resume treatment when adverse reaction improves to Grade 0 or 1 after corticosteroid taper

Appendix B: RECIST V1.1 CRITERIA

Adapted from (Eisenhauer et al. 2009).

Imaging Methods: The same method of assessment and same technique should be used at baseline and all follow up assessments. CT is the preferred method of tumor evaluation for this study. If lesion being followed cannot be imaged but can be assessed by clinical examination, measurements taken by usage of calipers will be acceptable. MRI is the preferred method for brain and bone lesions. If CT is performed instead of MRI, ambiguous results may be confirmed by MRI. MRI is also indicated if CT scan is contraindicated (e.g. allergy to contrast dye). Chest x-rays, positron emission tomography (PET), ultrasound and bone scans will not be used for response assessments in this study.

Lesion Definitions:

1) **Measurable lesions**: Those lesions (except lymph node lesions) that can be accurately measured and longest diameter to be recorded as ≥10 mm with CT scan (if CT scans have slice thickness greater than 5 mm, the minimum size for a measurable lesion is twice the slice thickness).

   Pathological lymph nodes will be considered measurable if they are ≥15mm in the short axis as measured by CT scan (CT scan thickness is recommended to be no greater than 5mm).

   At least 1 injectable lesion will be considered a measurable lesion and measurements will be recorded per RECIST v1.1.

   Cystic lesions thought to represent cystic metastasis can be measurable lesions, if they meet measurable lesion criteria. Simple cysts should not be considered measurable lesions.

   If CT scan is contraindicated, MRI should be performed. The minimal size for measurability is the same as for CT, i.e. 10 mm for non-nodal lesions (if scans have slice thickness greater than 5mm, the minimum size for a measurable lesion is twice the slice thickness), or ≥15mm for nodal lesions.

2) **Non-measurable lesions**: All other lesions, including small lesions that are <10mm (or for pathological lymph node lesions, short axis that is <15mm and ≥10mm) are considered non-measurable lesions. Lymph nodes that have a short axis that is <10mm are considered non-pathological are not recorded or followed.

   Bone disease is considered non-measurable, with the exception of soft tissue components that can be evaluated with CT or MRI and meet the definition of measurable (see above). Bone scans, PET scans or plain films are not considered appropriate for the evaluation of bone lesions.

   A previously irradiated lesion, or a lesion that is in an area that has been subjected to loco-regional therapy, is considered non-measurable unless it has progressed since last treatment.

   Simple cysts should not be considered non-measurable lesions.

Tumor Assessments: Baseline assessments should be conducted at screening, within 28 days prior to C1D1. Tumor assessments should be fixed according to calendar, regardless of treatment

delays. At each evaluation, progression status is based upon the timepoint status of target, non-target and new lesions.

1) **Target lesions:** Measurable lesions, up to a maximum of 5 total lesions (up to 2 lesions per organ) representing all involved organs should be identified as target lesions at baseline. They should be selected based on size and accuracy for repeated measurements.

   At each assessment, the sum of diameters (SoD; longest diameter for non-nodal lesions, and short axis for nodal lesions) will be calculated and recorded in source documents. If 2 lesions coalesce, the measurement of the coalesced mass is used. If a target lesion splits, the sum of the parts is used. If a target lesion is considered to have disappeared, 0 mm should be recorded. If a target lesion becomes too small to measure, a default value of 5 mm should be recorded.

   The baseline SoD should be used as a comparison for any objective tumor regression. The lowest SoD (nadir) should be used as reference for evaluating progression.

   Response Criteria for target lesions

Response Criteria	Evaluation of Target Lesions
Complete Response (CR):	Disappearance of all non-nodal target lesions. In addition, any pathological lymph nodes assigned as target lesions must have a reduction in short axis to < 10 mm[1]
Partial Response (PR):	At least a 30% decrease in the sum of diameter of all target lesions, taking as reference the baseline sum of diameters.
Progressive Disease (PD):	At least a 20% increase in the sum of diameter of all measured target lesions, taking as reference the smallest sum of diameter of all target lesions recorded at or after baseline. In addition to the relative increase of 20%, the sum must also demonstrate an absolute increase of at least 5 mm[2].
Stable Disease (SD):	Neither sufficient shrinkage to qualify for PR or CR nor an increase in lesions which would qualify for PD
Unknown (UNK)	Progression has not been documented and one or more target lesions have not been assessed or have been assessed using a different method than baseline.

[1] SOD for CR may not be zero when nodal lesions are part of target lesions
[2] Following an initial CR, a PD cannot be assigned if all non-nodal target lesions are still not present and all nodal lesions are <10 mm in size. In this case, the target lesion response is CR

2) **Non-target lesions:** All non-measurable lesions are non-target lesions. Measurement of these lesions are not required; instead, the presence, absence or unequivocal progression of each are to be recorded. Following CR, non-target and new lymph node lesions are to be measured to determine if they have become pathological in size.

3) **New lesions:** these are to be recorded separately in the eCRF. Finding of new lesions should not be attributed to differences in scanning technique, change in imaging modality or findings thought to represent something other than tumor. A lesion identified in an anatomic location that was not scanned at baseline is considered a new lesion.

   If a new lesion is equivocal, continue assessment until etiology can be clarified. If at the next assessment the new lesion is confirmed, the date of progression should be recorded as the date the new lesion was first noted.

Evaluation of Overall Response:

Target Lesion	Non-target lesion	New Lesion	Objective Status
CR	CR	No	CR
CR	Non-CR/ Non-PD	No	PR
CR	Indeterminate or missing	No	PR
PR	Non-CR/ Non-PD, Indeterminate or missing	No	PR
SD	Non-CR/ Non-PD, Indeterminate or missing	No	SD
Indeterminate or missing	Non-PD	No	Indeterminate
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= progression; non-CR/non-PD=criteria for neither CR nor PD have been met.

All noted regressions should be confirmed at next tumor assessment.

Appendix C: IRECIST CRITERIA

Increasing experience indicates that traditional response criteria may not be sufficient to fully characterize activity in this new era of immunotherapeutic agents. For example, agents such as anti-CTLA-4 and anti-PD1 and anti-PD-L1 exert anti-tumor activity by augmenting activation and proliferation of T-cells, thus leading to tumor infiltration by T cells and tumor regression rather than direct cytotoxic effects. In early trials of immune-based therapeutics in melanoma, investigators described unique response patterns, termed pseudo-progression, whereby subjects met the criteria based on traditional response criteria such as RECIST were noted to have late but deep and durable responses.

On the basis of these observations, a number of immune related criteria were developed and substantial variability in their usage across clinical studies were noted. This led to the development of iRECIST (immune RECIST) criteria by the RECIST working group in 2017 (Seymour et al. 2017).

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" (i.e. immune)—e.g. "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 major concept is resetting the bar once progression is identified per RECIST v1.1. This initial progression is identified as iUPD per iRECIST. Note that treatment past RECIST 1.1 PD should only be considered if:

1) Subject clinically stable
2) There is no worsening of ECOG status
3) No clinically relevant increase in disease related symptoms
4) No requirement for intensified management of disease related symptoms (analgesics, radiation, palliative care)

Any new lesions identified at iUPD will be assessed and subcategorized into those that qualify as target lesions (new lesion, target; maximum of 5 target lesions and maximum of 2 per organ should be identified) or non-target lesions (new lesion, non-target) and will be recorded separately from the original target and non-target lesions.

Progression must be confirmed on the next scan that is completed 4 to 9 weeks following initial iUPD; if confirmed, this will be categorized as iCPD (for immune confirmed progression). As such, should an iCR, iPR or iSD follow the initial iUPD, the next progression that follows will also be categorized as iUPD. However, if the next assessment following iUPD is not done or not evaluable, then if the following assessment is progression, then it should be labeled as iCPD.

Progression is only confirmed (i.e. iCPD) if the next scan following iUPD indicates a ≥5mm increase in target lesions, any size increase in non-target lesions, a ≥5mm increase in new lesion target lesions, any size increase in new lesions non-target lesions, or the appearance of another

new lesion. If progression is not confirmed, and there is no subsequent iSD, iPR or iCR, the reasons for a lack of confirmation must be recorded. The reasons should include:

1. Not stable
2. Worsening of ECOG status
3. Clinical increase in disease related symptoms
4. Treatments stopped and subject not reassessed/ imaging not performed
5. Subject has died
6. iCPD never occurred

In this case, for statistical purposes, the progression event date should be the iUPD date.

Assignment of Timepoint Response Using iRECIST

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

	Timepoint response with no previous iUPD in any category	**Timepoint response with previous iUPD in any category***
		iUPD (does not need to be unequivocal), or an increase in the size or number of new lesions previously identified
Target lesions: non-iUPD or progression; non-target lesions: non-iUPD or progression; new lesions: yes	iUPD	Remains iUPD unless iCPD is confirmed on the basis of an increase in the size or number of new lesions previously identified

*Previously identified in assessment immediately before this timepoint. "i" indicates immune responses assigned using iRECIST. iCR=complete response; iPR=partial response; iSD=stable disease; iUPD=unconfirmed progression; non-iCR/non-iUPD=criteria for neither CR nor PD have been met; iCPD=confirmed progression; RECIST=Response Evaluation Criteria in Solid Tumors.

Appendix D: COVID-19 GUIDANCE

All provisions outlined should be viewed as temporary and will be applicable only for the duration of the pandemic. If any provisions are modified due to the coronavirus (COVID-19) pandemic, please clearly document the planned deviation was due to COVID-19 and document the effective date of the interim measure in the subject's medical records.

In general, the subject and Investigator should together make the best and safest decision for the subject. Due to the requirement for certain individuals to self-isolate, and the issuance of shelter in place policies in a number of metropolitan areas, we recommend all sites contact each subject by telephone or email prior to the scheduled visit to determine if an in-person visit is feasible.

COVID-19 Screening

Incorporation of the following screening questions to identify potential COVID-19 exposure during the telephone or email contact prior to the scheduled visits are recommended:

- Have you traveled anywhere in the past 14 days?
- Have you had any of the following symptoms in the past 14 days without confirmation as something other than COVID-19 (such as a positive flu test, chronic medical condition, etc.)?
    - Fever greater than 100.4°F (38ºC)
    - Cough
    - Difficulty breathing
    - Sore throat
- In the last 14 days, have you lived with, visited, cared for, or been in a room for a prolonged period of time with someone who is under investigation or has been confirmed for COVID-19?

Should a subject respond yes to any of the above questions, it is recommended site personnel identify a resource to direct the subject to. Scheduled visits should be rescheduled if possible; if this is not possible, the visit should be marked as "not done" and reasons should be noted in study files.

For Subjects who are Unable to Travel to Site

If the subject is unable to travel to the trial site due to COVID-19 infection, self-quarantines, or travel restrictions, we recommend the following procedures be completed by phone, email or telehealth:

- Concomitant medications
- Adverse events
- If available, physical exams may be conducted using telehealth methods

Sites should also determine if home visits can be conducted with visiting nurses or home health aides. If available, safety evaluations (labs, vital signs and ECG [if available]) should be completed. If available, treatment with pembrolizumab may continue; however, treatment with ADU-S100 outside of a clinical setting is not recommended.

Limited Site Staff

The Sponsor also recognizes that site staff may also be limited during this pandemic. Though we ask that the sites be as compliant with the protocol as possible, we recognize that this might not be feasible at this

time. In this case, priority should be given to the following protocol specific procedures (from the highest to the lowest priority):

1. Administration of pembrolizumab and ADU-S100
2. Concomitant medications, adverse events
3. Safety labs
4. Vital signs, physical examination
5. ECG
6. Tumor imaging

If tumor imaging is not feasible, for example due to shortage of staff, and if the Principal Investigator or designee considers the subjects clinically stable and it's in the subject's best interest, treatment should continue. Images should be taken at the next available opportunity. Reasons for imaging delay should be documented in source documents and the sponsor (or its representatives) should be notified.

If shipping capabilities are no-longer available, sites should hold samples till shipping capabilities are restored. Please refer to the Central Laboratory Manual for appropriate storage conditions **Reduced Visits for Subject Safety**

If it is determined that frequent visits to the site is not safe for the subject, visits whereby treatment (pembrolizumab and/ or ADU-S100) is administered should be prioritized.

SIGNATURE PAGE

TITLE: A Phase 2 Efficacy and Safety Trial of ADU-S100 and Pembrolizumab in Adults with Head and Neck Cancer

I, the undersigned, have read study protocol ADU-CL-20 Amendment 4 and agree it contains all necessary information required to conduct the study.

Signature	Date
DocuSigned by: Jackie Walling Signer Name: Jackie Walling Signing Reason: I approve this document Signing Time: 19-Jan-2021 | 3:13 PM PST 7CC9C55A51F84524BB2B746742FBF103	19-Jan-2021 | 3:13 PM PST

Jackie Walling, MBChB PhD
Sponsor Responsible Medical Officer
Chinook Therapeutics, Inc. (f/k/a Aduro Biotech, Inc.)

INVESTIGATOR AGREEMENT

TITLE: A Phase 2 Efficacy and Safety Trial of ADU-S100 and Pembrolizumab in Adults with Head and Neck Cancer

By signing below I agree that:

I have read the protocol and agree it contains all necessary details for carrying out the study as described. I will conduct this study in accordance with the design and specific provisions of this protocol and will make a reasonable effort to complete the study within the time designated. I will provide copies of this protocol and access to all information furnished by the Sponsor to study personnel under my supervision. I will discuss this material with them to ensure they are fully informed about the study product and study procedures. I will let them know this information is confidential and proprietary to the Sponsor and may not be further disclosed to third parties. I understand that the study may be terminated or enrollment suspended at any time by the Sponsor, with or without cause. I have the right to suspend enrollment of subjects at my study site if necessary to protect the best interests of the study subjects.

I agree to conduct this study in full accordance with United States Food and Drug Administration Regulations, Institutional Review Board/Ethics Committee Regulations, and International Council on Harmonisation (ICH) Guidelines for Good Clinical Practices.

_____ _____

Investigator's Signature Date

_____

Investigator's Printed Name