CLINICAL STUDY PROTOCOL AMENDMENT 4.1

Protocol Title: A Phase 2, Open-Label, Multi-Center Study of PDS0101 (R-DOTAP [Versamune®] + HPVmix) and Pembrolizumab (KEYTRUDA®) Combination Immunotherapy in Subjects with Recurrent and/or Metastatic Head and Neck Cancer and High-Risk Human Papillomavirus-16 (HPV16) Infection

Protocol Number: VERSATILE-002 (PDS0101-HNC-201)

IND Number:	[redacted]
EudraCT Number:	2021-004046-38
Name of Investigational Product:	PDS0101 (R-DOTAP [Versamune] +HPVmix) and pembrolizumab (KEYTRUDA®)
Phase of Development:	2
Indication:	Recurrent or Metastatic Head and Neck Cancer (HNSCC)
Sponsor:	[redacted] PDS Biotechnology Corporation [redacted] Tel: [redacted]
Protocol Version:	4.1 Amendment 5.0
Protocol Date:	10 October 2022

-CONFIDENTIAL-

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PROTOCOL APPROVAL SIGNATURES

Protocol Title: A Phase 2, Open-Label, Multi-Center Study of PDS0101 (R-DOTAP [Versamune] + HPVmix) and Pembrolizumab (KEYTRUDA®) Combination Immunotherapy in Subjects with Recurrent and/or Metastatic Head and Neck Cancer and High-Risk Human Papillomavirus-16 (HPV16) Infection

Protocol Number: VERSATILE-002 (PDS0101-HNC-201)

This study will be conducted in compliance with the clinical study protocol (and amendments), International Council for Harmonisation (ICH) guidelines for current Good Clinical Practice (GCP) and applicable regulatory requirements.

Sponsor Signatory

[redacted]

[redacted]

Oct 10, 2022

Date (DD-Mmm-YYYY)

INVESTIGATOR SIGNATURE PAGE

Protocol Title: A Phase 2, Open-Label, Multi-Center Study of PDS0101 (R-DOTAP [Versamune] + HPVmix) and Pembrolizumab (KEYTRUDA®) Combination Immunotherapy in Subjects with Recurrent and/or Metastatic Head and Neck Cancer and High-Risk Human Papillomavirus-16 (HPV16) Infection

Protocol Number: VERSATILE-002 **(**PDS0101-HNC-201)

Confidentiality and Current Good Clinical Practice (GCP)/E6(R2) Compliance Statement

- I, the undersigned, have reviewed this protocol (and amendments), including appendices, and I will conduct the study as described in compliance with this protocol (and amendments), GCP, and relevant International Council for Harmonisation (ICH) guidelines.
- I am thoroughly familiar with the appropriate use of the study drug, as described in this protocol and any other information provided by PDS Biotechnology Corporation including, but not limited to, the current investigator's brochure.
- Once the protocol has been approved by the independent ethics committee (IEC)/institutional review board (IRB), I will not modify this protocol without obtaining prior approval of PDS Biotechnology Corporation and of the IEC/IRB. I will submit the protocol amendments and/or any informed consent form modifications to PDS Biotechnology Corporation and the IEC/IRB, and approval will be obtained before any amendments are implemented.
- I ensure that all persons or party assisting me with the study are adequately qualified and informed about the PDS Biotechnology Corporation study drug and of their delegated study-related duties and functions as described in the protocol.
- I ensure that source documents and trial records that include all pertinent observations on each of the site's trial subjects will be attributable, legible, contemporaneous, original, accurate, and complete.
- I understand that all information obtained during the conduct of the study with regard to the subjects' state of health will be regarded as confidential. No subjects' names will be disclosed. All subjects will be identified by assigned numbers on all case report forms, laboratory samples, or source documents forwarded to the Sponsor. Clinical information may be reviewed by the Sponsor or its agents or regulatory agencies. Agreement must be obtained from the subject before disclosure of subject information to a third party.
- Information developed in this clinical study may be disclosed by PDS Biotechnology Corporation to other clinical investigators, regulatory agencies, or other health authority or government agencies as required.

<Name>

<Title>

Investigator Signature

Date (DD-Mmm-YYYY)

Institution

2 SYNOPSIS

Title of Study:	A Phase 2, Open-Label, Multi-Center Study of PDS0101 (R-DOTAP [Versamune] + HPVmix) and Pembrolizumab (KEYTRUDA®) Combination Immunotherapy in Subjects with Recurrent and/or Metastatic Head and Neck Cancer and High-Risk Human Papillomavirus-16 (HPV16) Infection
Protocol Number:	VERSATILE-002 **(**PDS0101-HNC-201)
Investigators/Study Sites:	Approximately 40 study centers
Phase of Development:	Phase 2
Objectives:	**Primary Objective:** • To assess the preliminary activity of the combination of pembrolizumab (KEYTRUDA) and PDS0101 in checkpoint inhibitor (CPI) naïve or refractory subjects with recurrent and/or metastatic head and neck cancer (HNSCC) and high-risk HPV16 infection. **Secondary Objectives:** In both CPI naïve and CPI refractory subjects: • Assess progression-free survival (PFS) per Response Evaluation Criteria in Solid Tumors (RECIST) 1.1. • Assess overall survival (OS). • Assess safety and tolerability of the combination of pembrolizumab and PDS0101. **Exploratory Objectives:** • Duration of response for all subjects seen at time of disease progression or Cycle 35. • Evaluate anti-HPV16 E6 and E7 immune responses elicited by treatment with pembrolizumab and PDS0101 using IsoPlexis Functional Proteomics at Days 85 (Cycle 5) and 253 (Cycle 13) compared to baseline.
Study Endpoints:	**Primary Efficacy Endpoint:** In both CPI naïve and CPI refractory subjects: • The primary efficacy endpoint will be the best overall response (BOR) of confirmed complete response (CR) or confirmed partial response (PR) per RECIST 1.1 of the combination of pembrolizumab and PDS0101. **Key Secondary Endpoints:** In both CPI naïve and CPI refractory subjects: • PFS per RECIST 1.1 in all subjects at 12 and 24 months.

	• Assess OS in all subjects. • Assess safety and tolerability of pembrolizumab and PDS0101.
Study Design:	This is a Phase 2 open-label, non-randomized study of a combination of pembrolizumab and PDS0101 in HPV16 DNA-positive subjects with recurrent and/or metastatic HNSCC. Dosing is based on safety and T-cell induction evaluation for PDS0101 in subjects infected with high-risk HPV16 and on safety and clinical efficacy for pembrolizumab documented in the KEYNOTE-048 study. The study is designed to evaluate the safety and preliminary activity of pembrolizumab and PDS0101 when administered in combination. Subjects will be enrolled into either the checkpoint inhibitor (CPI) naïve group or the CPI refractory group, and up to 95 subjects in total (54 CPI naïve subjects and 41 CPI refractory subjects) will be enrolled in the order in which they are screened and meet eligibility criteria. A regimen of pembrolizumab (200 mg) and PDS0101 (3.0 mg R-DOTAP and 2.7 mg HPV16 mix) will be administered Q3W for the first 4 Cycles: IV infusion of pembrolizumab followed by subcutaneous (SC) injections of PDS0101 on Days 1 (Cycle 1), 22 (Cycle 2), 43 (Cycle 3), and 64 (Cycle 4). The fifth and final PDS0101 injection will be administered again on Day 232 (6 months after the 4th vaccination, Cycle 12 of pembrolizumab). Intravenous infusion of pembrolizumab will occur first followed by SC injection of PDS0101. PDS0101 will be administered no sooner than 30 minutes and before 60 minutes after the completion of the pembrolizumab IV infusion. Pembrolizumab administration will continue Q3W from Day 1, Cycle 1 until unacceptable toxicity or disease progression. Subjects without disease progression will be treated for up to 35 Cycles. A lead-in safety cohort of first 12 subjects (CPI naïve or CPI refractory) will be enrolled to assess safety of the combination of pembrolizumab with PDS0101. There will be a pause in enrollment after the twelfth subject has been dosed until the data monitoring committee (DMC) provides their recommendations of the safety of the study combination treatment. These initial 12 subjects will be monitored through 3 weeks (Cycle 1) after the first administration of pembrolizumab and PDS0101 for any signs of dose-limiting toxicity (DLT). At the end of the assessment period (Cycle 1/21 days; Day 1 to 21), the DMC will assess the DLTs and safety of the combination treatment. The DMC may elect to assess a second cohort of 12 subjects depending on the data from the first 12 subjects. All DLTs will be confirmed by the sponsor medical monitor and DMC.

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	Subjects that experience a DLT related to PDS0101 (possibly/probably/definitely) can continue on the study with a dose reduction of PDS0101 or be discontinued. Immuno-monitoring assessments will be performed prior to the first study combination treatment (baseline), and on Days 85 (Cycle 5, 21 days after Vaccination #4) and 253 (Cycle 13, 21 days after final Vaccination #5).
Selection of Subjects:	**Inclusion Criteria:** Subjects are eligible to be included in the study only if all of the following criteria apply: Type of Subject and Disease Characteristics 1. The subject (or legally acceptable representative if applicable) provides written informed consent for the study. 2. Be ≥18 years of age on the day of signing the informed consent. 3. Checkpoint-naïve subjects: Have a history of histologically-confirmed diagnosis of squamous cell cancer of the head and neck (HNSCC) that is recurrent, metastatic, or persistent with: a. Confirmed HPV16 infection b. Confirmed tumor PDL1 expression defined as a combined positive score (CPS) ≥1 using the FDA-approved Dako PD-L1 immunohistochemistry (IHC) 22C3 PharmDx Assay. c. No prior receipt of any immunological therapy for metastatic disease. 4. Checkpoint experienced subjects have a history of histologically-confirmed diagnosis of HNSCC that is recurrent, metastatic, or persistent with: a. Confirmed HPV16 infection b. Characterization of tumor PDL1 expression using the FDA-approved PD-L1 IHC 22C3 PharmDx Assay. c. Receipt of prior treatment with checkpoint inhibitors as a single agent or in combination, and have received at least 2 doses of the agent or a minimum of 6 weeks on treatment d. Have documented clinical progression or recurrence that has been radiologically confirmed 5. Have recurrent and/or metastatic measurable disease based on RECIST 1.1 as assessed by the local Principal Investigator/radiology. There must be confirmation that the subject's imaging shows at least 1 lesion that is appropriate

	for selection as a target lesion per RECIST 1.1. Lesions situated in a previously irradiated area are considered measurable if progression has been demonstrated in such lesions. 6. Have adequate organ function as defined in **Hematological:** ANC ≥1500/µL, Platelets ≥100 000/µL; Hemoglobin ≥9.0 g/dL or ≥5.6 mmol/L; **Renal:** Creatinine ≤1.5 × ULN or measured or calculated creatinine clearance >30mL/min with creatinine levels **>**1.5 × institutional ULN; **Hepatic:** Total bilirubin ≤1.5 × ULN or direct bilirubin ≤ULN for subjects with total bilirubin levels **>**1.5 × ULN, AST and ALT ≤2.5 ULN (5 × ULN for subjects with liver metastases); **Coagulation:** INR, PT ≤1.5 × ULN. Specimens must be collected within 10 days prior to the start of study combination treatment. 7. If subject received major surgery or radiation therapy of >30 Gy, they must have recovered from the toxicity and/or complications from the intervention. 8. For female subjects defined as women of childbearing potential (WOCBP), a negative urine pregnancy test must be obtained during screening. Women who are surgically sterile or at least 2 years postmenopausal do not require pregnancy testing. **Note:** Female subjects of childbearing potential must be willing to use an effective method of contraception for the course of the study through 120 days after the last dose of study medication. 9. Male subjects of childbearing potential must agree to use a condom as an effective method of contraception starting with the first dose of study therapy through 120 days after the last dose of study therapy. 10. Have an Eastern Cooperative Oncology Group (ECOG) performance status of 0 or 1. **Exclusion Criteria:** Subjects are excluded from study if any of the following criteria apply: Medical Conditions 1. Pregnancy Exclusion: a. A female subject defined as a WOCBP who has a positive urine pregnancy test (within 72 hours) prior to treatment. If the urine test is positive or cannot be confirmed as negative, a serum pregnancy test will be required.

	Prior/Concomitant Therapy 2. Has received prior therapy with an anti-PD-1, anti-PD- L1, or anti-PD-L2 agent or with an agent directed to another stimulatory or co-inhibitory T-cell receptor (eg, CTLA-4, OX40, CD137) and was discontinued from that treatment due to a Grade 3 or higher adverse events (AE). 3. Has received prior systemic anticancer therapy including investigational agents within 30 days prior to treatment. **Note**: Subjects must have recovered from all AEs due to previous therapies to ≤Grade 1 or baseline. Subjects with ≤Grade 2 neuropathy and ≤Grade 2 alopecia are an exception to this criterion and may qualify for therapy. **Note**: If subjects received major surgery, they must have recovered adequately from the toxicity and/or complications from the intervention prior to starting treatment. 4. Coordination and timing of coronavirus disease 2019 (COVID-19) vaccination should be based on local investigator clinical assessment and judgment. **Note:** Whenever possible, it is recommended to avoid COVID vaccination on the day of PDS0101 and/or pembrolizumab dosing because it may be difficult to attribute certain AEs (eg, fever, infusion reaction) to the study drug(s) or the COVID vaccine if they are both administered on the same day. 5. Has received prior radiotherapy within 2 weeks of start of study treatment. Subjects must have recovered from all-radiation-related toxicities, not require corticosteroids and not have had radiation pneumonitis. A 1-week washout is permitted for palliative radiation (<2 weeks of radiotherapy) to non-CNS disease. 6. Has received a live vaccine within 30 days prior to the first dose of treatment. Examples of live vaccines include, but are not limited to, the following: measles, mumps, rubella, varicella/zoster (chicken pox), yellow fever, rabies, Bacillus Calmette-Guérin (BCG), and typhoid vaccine. Seasonal influenza vaccines for injection are generally killed-virus vaccines and are allowed; however, intranasal influenza vaccines (eg, FluMist®) are live attenuated vaccines and are not allowed. 7. Received immunotherapy/immunomodulatory or immunosuppressive agents (eg, IFNs, tumor necrosis factor, interleukins, immunoglobulins or other biological response modifiers [GM-CSF, granulocyte colony-

	stimulating factor, macrophage colony-stimulating factor]) within 6 weeks prior to administration of the first study combination treatment. Prior/Concurrent Clinical Study Experience 8. Is currently participating in or has participated in a study of an investigational agent or has used an investigational device within 30 days prior to the first dose of study treatment. **Note**: Subjects who entered the follow-up phase of an investigational study may participate as long as it has been 30 days after the last dose of the previous investigational agent. 9. Has undergone prior allogeneic hematopoietic stem cell transplantation within the last 5 years. (Subjects who have had a transplant greater than 5 years ago are eligible as long as there are no symptoms of graft-versus-host disease [GVHD]). Diagnostic Assessments 10. Has a diagnosis of immunodeficiency or is receiving chronic systemic steroid therapy (in dosing exceeding 10 mg daily of prednisone equivalent) or any other form of immunosuppressive therapy within 7 days prior to the first dose of study drug. Current or recent use of physiologic doses of intra-articular, topical, or inhaled corticosteroids is acceptable. 11. Has a known additional malignancy that is progressing or has required active treatment within the past 3 years. **Note**: Subjects with basal cell carcinoma of the skin, squamous cell carcinoma of the skin or carcinoma in situ (eg, breast carcinoma, cervical cancer in situ) or other malignant tumors that have undergone potentially curative therapy are not excluded. 12. Has known active central nervous system (CNS) metastases and/or carcinomatous meningitis. Subjects with previously treated brain metastases may participate provided they are radiologically stable, ie, without evidence of progression for at least 4 weeks by repeat imaging (note that repeat imaging should be performed during study screening, clinical stable and without requirement of steroid treatment for at least 14 days prior to first dose of study treatment). 13. Has severe hypersensitivity (≥Grade 3) to pembrolizumab and/or any of its excipients. 14. Has an active autoimmune disease that has required systemic treatment in the past 2 years (ie, with use of

	disease modifying agents, corticosteroids, or immunosuppressive drugs). Replacement therapy (eg, thyroxine, insulin or physiologic corticosteroid replacement therapy for adrenal or pituitary insufficiency) is not consider a form of systemic treatment and is allowed. 15. Has a history of (non-infectious) pneumonitis that required steroids or has current pneumonitis. 16. Has an active infection requiring systemic therapy. 17. Subjects with known human immunodeficiency virus and/or history of hepatitis B or C infections or known to be positive for hepatitis B antigen (HBsAg)/hepatitis B virus (HBV) DNA or hepatitis C antibody or RNA. Active hepatitis C is defined by a known positive hepatitis C Ab result and known quantitative HCV RNA results greater than the lower limits of detection of the assay. 18. Has a history or current evidence of any condition, therapy, or laboratory abnormality that might confound the results of the study, interfere with the subject's participation for the full duration of the study, or is not in the best interest of the subject to participate, in the opinion of the treating investigator. 19. Has a known psychiatric or substance abuse disorder that would interfere with the subject's ability to cooperate with the requirements of the study. Other Exclusions 20. Is pregnant or breastfeeding or expecting to conceive or father children within the projected duration of the study, starting with the screening visit through 120 days after the last dose of any study treatment. 21. Has had an allogenic tissue/solid organ transplant. 22. Has received administration of colony-stimulating factors (including G-CSF, GM-CSF or recombinant erythropoietin) within 30 days prior to Day 1. 23. Has a history of interstitial lung disease. 24. Female subjects defined as WOCBP unwilling or unable to use highly effective contraception method(s) for the duration of the study: a. Combined (estrogen and progestogen containing) hormonal contraception associated with inhibition of ovulation. b. Progestogen-only hormonal contraception c. Intrauterine device d. Intrauterine hormone-releasing system

	e. Bilateral tubal occlusion f. Vasectomized partner is a highly effective birth control method provided that partner is the sole sexual partner of the WOCBP trial participant and that the vasectomised partner has received medical assessment of the surgical success. 25. Any prior Grade ≥3 immune-related adverse event(irAE) while receiving any previous checkpoint inhibitor or immunotherapy agent, or any unresolved irAE >Grade 1 except for endocrine AEs managed with replacement therapy. 26. Developed immune-related toxicity while on prior checkpoint inhibitor therapy that has not yet returned to Grade 1 or better. 27. History of any drug allergies or significant adverse reactions to any of the components of PDS0101
Planned Sample Size:	This study will plan to enroll up to N=95 subjects with central laboratory confirmed HPV16+ HNSCC and PD-L1 expression at the end of the study (up to 54 CPI naïve subjects and 41 CPI refractory subjects).
Investigational Therapy:	Each subject will receive PDS0101 (2.7 mg HPVmix mixed with 3.0 mg R-DOTAP) administered by SC injection, as well as 200 mg of pembrolizumab (KEYTRUDA) administered by IV infusion on the same day.
Reference Therapy:	Not applicable
Treatment Duration:	For each subject, this study will include a pre-screening to allow human papilloma virus (HPV) and PD-L1 characterization, screening period during Days -28 to -1, a treatment period during Days 1 to 715 (up to 35 Cycles), and a safety follow-up period of 30 days (Days 715 to 745). The duration for an individual subject's participation in the study will be up to approximately 24 months (35 Cycles + 30-day follow-up), excluding screening.
Efficacy:	Efficacy of pembrolizumab and PDS0101 administered in combination will be assessed as the BOR, and PFS per investigator-evaluated and central imaging confirmed RECIST 1.1 and OS.
Safety:	Safety and tolerability of pembrolizumab and PDS0101 administered in combination will be measure by reported AEs, changes in clinical laboratory findings, changes in electrocardiogram (ECGs), changes in vital signs, and any signs of DLTs from the combination therapy.
Other Assessments:	Immune monitoring assessments will be performed prior to the first study combination treatment (baseline- Day 1, Cycle 1), at Day 85 (Cycle 5, 21 days after PDS0101 Vaccine #4) and on Day 253 (Cycle 13, 21 days after PDS0101 Vaccine #5).

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	Exploratory immunogenicity will be assessed by anti-HPV16 cytotoxic T-lymphocyte (CTL) (CD8+ CTL) response using IsoPlexis Functional Proteomics.
Statistical Methods and Planned Analyses:	The primary population will be the intent-to-treat (ITT) population, which is defined as all subjects who are enrolled, have central laboratory confirmed HPV16+ HNSCC and PD-L1 expression (for CPI naïve subjects a CPS $\geq$1 by the Dako PD-L1 IHC 22C3 PharmDx Assay is required), and receive at least one dose of pembrolizumab or PDS0101. This population will be used for all summaries of demographic and baseline characteristics. In addition, analysis of PFS and OS will be performed on the ITT population. Analyses will be presented for the CPI naïve group and the CPI refractory group, as well as overall. The primary efficacy analysis population (EFF) will be all ITT subjects who have an assessment of overall tumor response after the initial dose of pembrolizumab or PDS0101. A primary efficacy analysis will also be performed in the ITT population: all subjects irrespective of whether they have undergone a tumor assessment or not will be included in the denominator in this analysis. Subjects with missing efficacy assessments will be treatment failures. Analyses will be presented for the CPI naïve group and the CPI refractory group, as well as overall. The safety analysis population (SAF) includes all subjects who have received at least 1 dose of pembrolizumab or PDS0101 and will be used to summarize all safety and tolerability assessments. Analyses will be presented for the CPI naïve group and the CPI refractory group as well as overall. The primary objective of this study is to assess the preliminary activity of the combination of pembrolizumab (KEYTRUDA) and PDS0101 and in checkpoint inhibitor (CPI) naïve or refractory subjects with recurrent and/or metastatic HNSCC and high-risk HPV16 infection. The primary endpoint in both CPI naïve and CPI refractory subjects is BOR. **Primary Efficacy Endpoint:** • The primary efficacy endpoint will be the BOR of CR or PR per RECIST 1.1 of the combination of pembrolizumab and PDS0101. **Key Secondary Endpoints:** In both CPI naïve and CPI refractory subjects: • PFS per RECIST 1.1 in all subjects at 12 and 24 months. • Assess OS in all subjects. • Assess safety and tolerability of pembrolizumab and PDS0101.

	Secondary endpoints of efficacy will be evaluated. Safety and tolerability endpoints will include reported AEs, changes in clinical laboratory findings, changes in ECGs, and changes in vital signs throughout 24 months of follow-up. Analyses will be performed separately for the CPI naïve group and the CPI refractory group as described below. Sample Size Estimation Subjects will also be required to have central laboratory confirmed HPV16+ HNSCC and PD-L1 expression (for CPI naïve subjects a CPS ≥1 by the Dako PD-L1 IHC 22C3 PharmDx Assay is required). If subjects do not meet these criteria, they will be replaced. *CPI Naïve* This study will utilize a Simon's 2-stage optimum design for the CPI naïve subjects. The null hypothesis (H0) that the true objective response rate (ORR) of the combination of PDS0101 with pembrolizumab is 17% will be tested against a one-sided alternative hypothesis of 33%. Setting the type I error rate to 5% (alpha=0.05), and the power to 80%, we will enroll 17 subjects in the first stage. If 3 or fewer responses (CR or PR) are observed after 17 subjects in Stage 1 have been on the study for at least 6 months (Cycle 10), the study may be stopped for futility or regulatory agency feedback will be incorporated per Sponsor's discretion. If 4 or more objective responses are observed, the study will enroll an additional 37 subjects for a total of 54 subjects. At the completion of the second stage, the combination of PDS0101 with pembrolizumab will be considered efficacious if at least 14 responses have been observed out of the 54 subjects enrolled. If 13 or fewer responses are observed after 54 subjects have been on the study for at least 6 months (Cycle 10), the study may be stopped for futility or regulatory agency feedback will be incorporated per Sponsor's discretion. *CPI Refractory* This study will utilize a Simon's 2-stage optimum design for the CPI refractory subjects. The null hypothesis (H0) that the true ORR of the combination of PDS0101 with pembrolizumab is 5% will be tested against a one-sided alternative hypothesis of 20%. Setting the type I error rate to 5% (alpha=0.05) and the power to 90%, we will enroll 21 subjects in the first stage. If 1 or 0 responses (CR or PR) are observed after 21 subjects have been on the study for at least 6 months (Cycle 10), the study may be stopped for futility or regulatory agency feedback will be incorporated per the sponsor's discretion. If 2 or more responses are observed, the study will enroll an additional 20 subjects for a total of 41 subjects. At the completion of the second stage, the combination of PDS0101 with pembrolizumab will be considered efficacious if at least 5 responses have been observed out of the 41 subjects enrolled. If 4 or fewer responses are observed after 41 subjects have been on the study for at least 6 months (Cycle 10), the study may be stopped for

	futility or regulatory agency feedback will be incorporated per Sponsor's discretion. **Interim Analyses** **Safety Monitoring:** Safety assessment of the pembrolizumab and PDS0101 will be performed in a lead-in safety cohort of the first 12 subjects to assess DLT from the combination therapy. Accrual will resume after the recommendation of the DMC regarding safety, dose regimen, and possible subsequent cohorts. **Futility**: Per the Simon's 2 stage design, futility analyses are incorporated at Stage 1 and Stage 2 for both CPI naïve and CPI refractory groups. Analyses will be presented for the CPI naïve group and the CPI refractory group as well as overall. **Analyses:** Demographic, baseline, and safety results will be summarized descriptively from the ITT population. BOR during the entire study period after initial treatment includes subjects with an assessment of confirmed CR or confirmed PR. The EFF population will be the primary population of interest. The 90% CI will be estimated for BOR using the Clopper-Pearson Exact method. Analyses will also be presented for the ITT population. PFS will include all subjects in the ITT population. Those subjects who are still alive and without disease progression, defined per RECIST 1.1, will be censored at the last known date of contact. Estimates of time-to progression and 95% CI of estimates will be obtained from Kaplan-Meier time-to-event methodology at 75%, 50% and 25% percentiles. OS will include all subjects in the ITT population. Those subjects who are still alive will be censored at their last known date of contact. Estimates of OS time and 95% CI of estimates will be obtained from Kaplan-Meier time-to-event methodology at 75%, 50% and 25% percentiles. Assessment of safety and tolerability will be summarized by treatment group using the SAF population. The incidence of AEs will be summarized by Medical Dictionary for Regulatory Activities (MedDRA) system organ class (SOC) and preferred term by dose group and overall. In addition, AEs will be summarized by severity using NCI-CTCAE, version 5.0 (v.11.27.17) and will be summarized by relationship to study treatment.

3 TABLE OF CONTENTS

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3.1 List of In-text Tables

3.2 List of In-text Figures

4 LIST OF ABBREVIATIONS

Abbreviation	Definition
5-FU	5-Fluorouracil
AAD	alpha-1 and alpha-2 domains of human leukocyte antigen
AE	Adverse event
ADL	activities of daily life
ALT (SGPT)	Alanine aminotransferase (serum glutamic pyruvic transaminase)
ANC	Absolute neutrophil count
aPTT	Activated partial thromboplastin time
AST (SGOT)	Aspartate aminotransferase (serum glutamic oxaloacetic transaminase)
BCG	Bacillus Calmette-Guérin
BOR	best overall response
BUN	Blood urea nitrogen
CD28	Cluster of differentiation 28
CD3ζ	Cluster of differentiation 3 zeta protein complex and T-cell co-receptor
CI	Confidence interval
CIN 1	Cervical intraepithelial neoplasia 1
CIN 2/3	Cervical intraepithelial neoplasia 2/3
CNS	Central nervous system
COVID-19	Coronavirus disease 2019
CPI	checkpoint inhibitor
CPS	Combined positive score
CR	Complete response
CRA	Clinical research associate
CRF	Case report form
CT	Computed tomography
CTLA-4	Cytotoxic T-lymphocyte-associated protein 4
DC	dendritic cells
DILI	Drug-induced liver injury
DLT	dose-limiting toxicity
DMC	Data monitoring committee
DMSO	Dimethylsulfoxide
DBP	Diastolic blood pressure
DOR	Duration of response
EB	Epstein-Barr viral status
ECG	Electrocardiogram
ECI	Event of clinical interest
ECOG PS	Eastern Cooperative Oncology Group Performance Status
eCRF	Electronic case report form
EDC	Electronic data capture
ELISpot	Enzyme-linked immunosorbent spot assays

Abbreviation	Definition
EFF	Efficacy analysis population
FDA	Food and Drug Administration (US)
FT3	Free triiodothyronine
FT4	Free thyroxine
FU	Fluorouracil
GCP	Good clinical practice
GFR	Glomerular filtration rate
GM-CSF	granulocyte-macrophage colony-stimulating factor
GMP	Good manufacturing practice
GVHD	Graft-versus-host disease
HBsAg	Hepatitis B virus surface antigen
HBV	Hepatitis B virus
HIV	Human immunodeficiency virus
HLA	Human leukocyte antigen
HNSCC	Head and Neck Cancer also Head and Neck Squamous Carcinoma Cancer
HPV	Human papillomavirus
HPV16	Human papillomavirus-16
HPVmix	a mixture of 6 non-oncogenic lipidated peptides selected from immunogenic regions of the HPV16 E6 and E7 proteins
HR	Hazard ratio
HSIL	High-grade squamous intraepithelial lesions
IB	Investigator's brochure
ICF	informed consent form
ICH	International Council for Harmonisation
IEC	Independent Ethics Committee
IFN	Interferon
Ig	Immunoglobulin
IgG4	Immunoglobulin G4
IgV type	Ig-variable–type
IHC	Immunohistochemistry
IMP	Investigational medicinal product
irAE	Immune-related adverse event
IRB	institutional review board
IRT	interactive response technology
ITT	Intent-to-Treat
IV	Intravenous
mAb	Monoclonal antibody
MAP	mitogen-activated protein
MDSC	Myeloid derived suppressor cell
MedDRA	Medical Dictionary for Regulatory Activities
MHC	major histocompatibility complex

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Abbreviation	Definition
MSD	Merck Sharp & Dohme LLC, Rahway, NJ, USA
MTD	Maximum tolerated dose
NCI-CTCAE	National Cancer Institute - Common Terminology Criteria for Adverse Events
NSCLC	Non-small cell lung cancer
ORR	objective response rate
OS	Overall survival
OTC	Over-the-counter (medication)
PBPK	Physiologically-based PK
PD-1	Programmed cell death 1
PD-2	Programmed cell death 2
PD-L1	Programmed cell death-ligand 1
PD-L2	Programmed cell death-ligand 2
PFS	Progression-free survival
PI	Principal Investigator
PK	Pharmacokinetics
PKCθ	Protein kinase C-theta
PR	Partial response
pRBC	Packed red blood cells
PT	prothrombin time
Q2W	Every 2 weeks
Q3W	Every 3 weeks
QTc	Corrected QT interval
R-DOTAP	R-enantiomer of 1,2-dioleoyl-3trimethylammonium-propane chloride
RECIST	Response Evaluation Criteria in Solid Tumors
SAE	Serious adverse event
SAF	Safety analysis population
SBP	Systolic blood pressure
SC	Subcutaneous
SHP-1	Src homology region 2 domain-containing phosphatase-1
SHP-2	Src homology region 2 domain-containing phosphatase-2
SIM	Site Imaging Manual
SOC	System organ class
SOP	Standard operating procedure
SUSAR	Suspected unexpected serious adverse reaction
T-regs	Regulatory T-cells
T3	Triiodothyronine
TC-1	tumor cell line 1
TEAE	Treatment-emergent adverse events
TMDD	Target-mediated drug disposition
TPS	Tumor Proportion Score

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Abbreviation	Definition
TSH	Thyroid stimulating hormone
ULN	Upper limit of normal
US	United States
v/v	volume of solute per volume of solvent
WOCBP	Women of childbearing potential
ZAP70	Zeta-chain-associated protein kinase

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5 INTRODUCTION

5.1 Background on Pembrolizumab

Pembrolizumab is a potent humanized immunoglobulin G4 (IgG4) monoclonal antibody (mAb) with high specificity of binding to the programmed cell death 1 (PD-1) receptor, thus inhibiting its interaction with programmed cell death-ligand 1 (PD-L1) and programmed cell death-ligand 2 (PD-L2). Based on preclinical in vitro data, pembrolizumab has high affinity and potent receptor blocking activity for PD-1. Pembrolizumab has an acceptable preclinical safety profile and is in clinical development as an intravenous (IV) immunotherapy for advanced malignancies.

Keytruda® (pembrolizumab) is indicated for the treatment of subjects across a number of indications. For more details on specific indications, refer to the investigator's brochure (IB).

Refer to the IB/approved labeling for detailed background information on MK-3475.

5.2 Pembrolizumab Pharmaceutical and Therapeutic Background

The importance of intact immune surveillance function in controlling outgrowth of neoplastic transformations has been known for decades (Disis, 2010). Accumulating evidence shows a correlation between tumor-infiltrating lymphocytes in cancer tissue and favorable prognosis in various malignancies. In particular, the presence of CD8+ T-cells and the ratio of CD8+ effector T-cells/FoxP3+ regulatory T-cells (T-regs) correlates with improved prognosis and long-term survival in solid malignancies, such as ovarian, colorectal, and pancreatic cancer; hepatocellular carcinoma; malignant melanoma; and renal cell carcinoma. Tumor-infiltrating lymphocytes can be expanded ex vivo and reinfused, inducing durable objective tumor responses in cancers, such as melanoma (Dudley et al., 2002; Hunder et al., 2008).

The PD-1 receptor-ligand interaction is a major pathway hijacked by tumors to suppress immune control. The normal function of PD-1, expressed on the cell surface of activated T-cells under healthy conditions, is to down-modulate unwanted or excessive immune responses, including autoimmune reactions. PD-1 (encoded by the gene Pdcd1) is an immunoglobulin (Ig) superfamily member related to cluster of differentiation 28 (CD28) and cytotoxic T-lymphocyte-associated protein 4 (CTLA-4) that has been shown to negatively regulate antigen receptor signaling upon engagement of its ligands (PD-L1 and/or PD-L2) (Greenwald et al., 2005; Okazaki et al., 2001).

The structure of murine PD-1 has been resolved (Zhang et al., 2004). PD-1 and its family members are type I transmembrane glycoproteins containing an Ig-variable–type (IgV-type) domain responsible for ligand binding and a cytoplasmic tail responsible for the binding of signaling molecules. The cytoplasmic tail of PD-1 contains 2 tyrosine-based signaling motifs, an immunoreceptor tyrosine-based inhibition motif, and an immunoreceptor tyrosine-based switch motif. After T-cell stimulation, PD-1 recruits the tyrosine phosphatases, (SHP-1) Src homology region 2 domain-containing phosphatase-1 and (SHP-2) Src homology region 2 domain-containing phosphatase-2, to the immunoreceptor tyrosine-based switch motif within its

cytoplasmic tail, leading to the dephosphorylation of effector molecules such as CD3 zeta (CD3ζ), protein kinase C-theta (PKCθ), and zeta-chain-associated protein kinase (ZAP70), which are involved in the CD3 T-cell signaling cascade (Okazaki et al., 2001; Chemnitz et al., 2004; Sheppard et al., 2004; and Riley, 2009). The mechanism by which PD-1 down-modulates T-cell responses is similar to, but distinct from, that of CTLA-4 because both molecules regulate an overlapping set of signaling proteins (Parry et al., 2005; Francisco et al., 2010). Consequently, the PD 1/PD-L1 pathway is an attractive target for therapeutic intervention in head and neck cancer (HNSCC).

5.2.1 Preclinical and Clinical Studies

Therapeutic studies in mouse models have shown that administration of antibodies blocking PD-1/PD-L1 interaction enhances infiltration of tumor-specific CD8+ T-cells and ultimately leads to tumor rejection, either as a monotherapy or in combination with other treatment modalities (Hirano, 2005; Blank, 2004;Weber, 2010;Strome, 2003; Spranger, 2014; Curran, 2010; Pilon, 2010). Anti-mouse PD-1 or anti-mouse PD-L1 antibodies have demonstrated anti-tumor responses in models of squamous cell carcinoma, pancreatic carcinoma, melanoma, acute myeloid leukemia, and colorectal carcinoma (Strome, 2003; Curran, 2010; Pilon, 2010; Nomi, 2007; Zhang, 2004). In such studies, tumor infiltration by CD8+ T-cells and increased IFN-γ, granzyme B and perforin expression were observed, indicating that the mechanism underlying the anti-tumor activity of PD-1 checkpoint inhibition involved local infiltration and activation of effector T-cell function in vivo (Curran, 2010). Experiments have confirmed the in vivo efficacy of anti-mouse PD-1 antibody as a monotherapy, as well as in combination with chemotherapy, in syngeneic mouse tumor models (see the IB).

KEYNOTE-048 is a pivotal Phase 3, randomized, open-label study (ClinicalTrials.gov NCT02358031) designed to investigate pembrolizumab for first-line treatment of recurrent or metastatic HNSCC. A total of 882 subjects were randomly allocated to receive pembrolizumab as monotherapy or in combination with a platinum chemotherapy (cisplatin or carboplatin) plus 5-Fluorouracil (5-FU), compared with cetuximab with platinum chemotherapy (cisplatin or carboplatin) plus 5-FU (EXTREME).

On June 10, 2019, the Food and Drug Administration approved pembrolizumab (KEYTRUDA, Merck Sharp & Dohme LLC, Rahway, NJ, USA (hereinafter “MSD”)) for the first line treatment of patients with metastatic or unresectable recurrent HNSCC.

Pembrolizumab was approved for use in combination with platinum and fluorouracil (FU) for all patients and as a single agent for patients whose tumors express PD L1 (Combined Positive Score [CPS] ≥1]) as determined by an FDA-approved test.

The FDA also expanded the intended use for the PD-L1 IHC 22C3 pharmDx kit to include use as a companion diagnostic device for selecting patients with HNSCC for treatment with pembrolizumab as a single agent.

Approval was based on KEYNOTE-048 (NCT02358031), a randomized, multi-center, three-arm, open-label, active-controlled trial conducted in 882 patients with metastatic HNSCC who had not previously received systemic therapy for metastatic disease or with recurrent disease who were considered incurable by local therapies.

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

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

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

There were no significant differences in PFS for either pembrolizumab-containing arm compared to the cetuximab plus chemotherapy arm in any population.

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

The recommended pembrolizumab dose for HNSCC is 200 mg administered as an intravenous infusion over 30 minutes every 3 weeks until disease progression, unacceptable toxicity, or up to 24 months in patients without disease progression.

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5.2.2 Justification for Pembrolizumab Dose

The planned dose of pembrolizumab for this study is 200 mg every 3 weeks (Q3W) as recommended per the FDA approval cited above for the proposed treatment indication. Based on the totality of data generated in the KEYTRUDA development program, 200 mg Q3W is the appropriate dose of pembrolizumab for adults across all indications and regardless of tumor type. As outlined below, this dose is justified by:

- Clinical data from 8 randomized studies demonstrating flat-dose- and exposure-efficacy relationships from 2 mg/kg Q3W to 10 mg/kg every 2 weeks (Q2W),
- Clinical data showing meaningful improvement in benefit-risk including OS at 200 mg Q3W across multiple indications, and,
- Pharmacology data showing full target saturation in both systemic circulation (inferred from pharmacokinetic [PK] data) and tumor (inferred from physiologically-based PK [PBPK] analysis) at 200 mg Q3W.

Among the 8 randomized dose-comparison studies, a total of 2262 subjects were enrolled with melanoma and non-small cell lung cancer (NSCLC), covering different disease settings (treatment naïve, previously treated, PD-L1 enriched, and all-comers) and different treatment settings (monotherapy and in combination with chemotherapy). Five studies compared 2 mg/kg Q3W versus 10 mg/kg Q2W (KN001 Cohort B2, KN001 Cohort D, KN002, KN010, and KN021), and 3 studies compared 10 mg/kg Q3W versus 10 mg/kg Q2W (KN001 Cohort B3, KN001 Cohort F2, and KN006). All these studies demonstrated flat-dose- and exposure-response relationships across the doses studied representing an approximate 5- to 7.5-fold difference in exposure. The 2 mg/kg (or 200 mg fixed-dose) Q3W provided similar responses to the highest doses studied. Subsequently, flat dose-exposure-response relationships were also observed in other tumor types including HNSCC, bladder cancer, gastric cancer, and classical Hodgkin Lymphoma, confirming 200 mg Q3W as the appropriate dose independent of the tumor type.

These findings are consistent with the mechanism of action of pembrolizumab, which acts by interaction with immune cells, not via direct binding to cancer cells.

Additionally, pharmacology data clearly show target saturation at 200 mg Q3W. Firstly, PK data in KN001 evaluating target-mediated drug disposition (TMDD) conclusively demonstrated saturation of PD-1 in systemic circulation at doses much lower than 200 mg Q3W. Secondly, a PBPK analysis was conducted to predict tumor PD-1 saturation over a wide range of tumor penetration and PD-1 expression. This evaluation concluded that pembrolizumab at 200 mg Q3W achieves full PD-1 saturation in both blood and tumor.

Finally, population PK analysis of pembrolizumab, which characterized the influence of body weight and other subject covariates on exposure, has shown that the fixed-dosing provides similar control of PK variability as weight-based dosing, with considerable overlap in the distribution of exposures from the 200 mg Q3W fixed-dose and 2 mg/kg Q3W dose. Supported by these PK characteristics and given that fixed-dose has advantages of reduced dosing

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complexity and reduced potential of dosing errors, the 200 mg Q3W fixed-dose was selected for evaluation across all pembrolizumab protocols.

5.3 PDS Background

5.3.1 Preclinical Studies of PDS0101

PDS0101 (ImmunoMAPK-R-DOTAP/R-enantiomer of 1,2-dioleoyl-3-trimethylammonium-propane chloride [R-DOTAP] +HPV16 E6 and E7 antigens) is a therapeutic vaccine designed to induce anti-E6 and anti-E7 cytolytic T-cell responses against HPV expressed in subjects with high-grade neoplasia, preventing progression to invasive disease, and for use in subjects with HPV-positive cancers. Preclinical studies indicate that R-DOTAP, a cationic lipid, is an effective non-viral vaccine vector that promotes antigen cross-presentation and also a potent vaccine adjuvant capable of bolstering the cytotoxic immune response when coupled with peptide antigens, such as peptide antigens derived from the E7 protein sequence (Yan et al., 2007; Vasievich et al., 2011).

5.3.2 PDS0101 Preclinical Pharmacology

In preclinical studies, PDS0101 has demonstrated robust induction of HPV-specific T-cell responses. Details regarding the mechanism of action of R-DOTAP, as well as the antigen-specific immune-modulating effects of PDS0101 demonstrating effective regression of HPV-positive tumors and IFN-γ induction in both murine and human model systems, are outlined and documented in the IB.

5.3.3 PDS0101 Preclinical Pharmacokinetics

Details of the PK studies performed in rats and mice are provided in the IB. Both R-DOTAP and the HPVmix (a mixture of 6 non-oncogenic lipidated peptides selected from immunogenic regions of the HPV16 E6 and E7 proteins) in the PDS0101 formulation present low systemic bioavailability (<6%) upon subcutaneous (SC) injection. The low systemic bioavailability is supported by a demonstration of effective uptake of the nanoparticles by dendritic cells from the injection site and their subsequent activation and trafficking to the lymph nodes as reported in preclinical studies (Chen et al. 2008). The study is detailed in the IB.

This document is confidential.

5.4 R-DOTAP Pharmacokinetics

The PKs of R-DOTAP have been measured in Sprague-Dawley rats using the PDS0101 prototype (R-DOTAP/palmitoyl-HPV16 E7 [11-20]), as summarized in Table 1.

Table 1 Pharmacokinetics of R-DOTAP in Rats

Subcutaneous Administration									
		t½	**Tmax**	**Cmax**	**AUC0-24hr**	**AUC∞**	**Vz/F**	**CL/F**	**F**
0.35 mg R-DOTAP 50 µg HPV16 E7 peptide		(hr)	(hr)	(ng/mL)	(hr*ng/ mL)	(hr*ng/ mL)	(L)	(L/hr)	(%)
	Sex								
	Male	67	24	5.01	356	414	78.0	0.806	4.73
	Female	86	48	6.72	412	508	81.6	0.657	6.00

Abbreviations: **AUC_{∞} =** area under the drug plasma concentration versus time curve from time zero to infinity; $AUC_{0\text{-}24hr}$ = area under the drug plasma concentration versus time curve from time zero to 24 hours after last administration; CL/F = apparent oral clearance; C_{max} = maximum drug plasma concentration; F = bioavailability; HPV16 = human papillomavirus-16; $t_{1/2}$ = terminal half-life; T_{max} = time to maximum plasma concentration; V_z/F = apparent volume of distribution during terminal phase.

5.4.1 HPVmix Pharmacokinetics

The PK of HPVmix have been measured in female C57BL/6 mice using the PDS0101 clinical formulation (0.009 mg/dose of R-DOTAP – Equivalent low clinical dose by weight of R-DOTAP). High and low doses of peptides were evaluated, as shown in Table 2.

Table 2 Pharmacokinetics of HPVmix in Mice

Lipo-peptide*	**Estimated Bioavailability**							
	Group 1				**Group 2**			
	Dose (µg)	Theoretical Maximum Blood Concentration [1] (ng/mL)	Mean C_{max} (ng/mL)	Estimated Bioavailability [2] (%)	Dose (µg)	Theoretical Maximum Blood Concentration [1] (ng/mL)	Mean C_{max} (ng/mL)	Estimated Bioavailability [2] (%)
pKT23	3.3	2700	82.9	**3.1**	18	15200	301	**2.0**
pKF18	4.5	3800	64.0	**1.2**	21	17700	220	**0.6**
pKT13	3.0	2500	44.7	**2.6**	16	12900	107	**1.7**

Abbreviations: C_{max} = maximum drug plasma concentration; HPV16 = human papillomavirus-16; HPVmix = HPV16 lipidated peptide suspension.

* 3 of the 6 peptides were below the detection limits of the method.

[1] Blood volume for CD-1 female mice at 6 weeks of age assumed to be 1.2 mL.

[2] Bioavailability = Average C_{max}/theoretical maximum blood concentration × 100.

5.4.2 PDS0101 Preclinical Toxicology

Toxicology studies of R-DOTAP and a prototype PDS0101 formulation were evaluated in rats and in non-human primates. The details of the study are provided in the IB. The PDS0101 clinical formulation (HPVmix and ImmunoMAPK-R-DOTAP) was evaluated in humanized alpha-1 and alpha-2 domains of human leukocyte antigen [HLA]-2 (AAD) transgenic mice. No toxicities were observed at both the high and low doses. The high dose utilized in the toxicology study is approximately 30X the highest clinical dose. No inflammatory reactions were observed. No toxicities were observed in the hematology/ clinical chemistry nor in the gross necropsy analysis. Microscopic histopathology demonstrated evidence of minimal fibrosis in 3/8 of the high-dose animals.

5.4.3 R-DOTAP (Versamune) Background

PDS0101 (ImmunoMAPK-RDOTAP/R-enantiomer of 1,2-dioleoyl-3-trimethylammonium-propane chloride [R-DOTAP] +HPV16 E6 and E7 antigens) is a therapeutic vaccine designed to induce anti-E6 and anti-E7 cytolytic T-cell responses against HPV expressed in subjects with high-grade squamous intraepithelial lesions (HSIL) (CIN 2/3), preventing progression to invasive disease, and for use in subjects with cervical cancer or other HPV-associated cancers. Preclinical studies suggested that R-DOTAP, a cationic lipid, is a potent vaccine adjuvant capable of bolstering the cytotoxic immune response when coupled with peptide antigens, such as peptide antigens derived from the E7 protein sequence (Gandhapudi et al., 2019). PDS0101 has subsequently demonstrated good tolerability and strong HPV-specific T-cell induction in a Phase 1/2A dose-escalating human clinical study in subjects with high-risk HPV infection and pre-cervical cancer (CIN 1). The clinical results are summarized in Section 5.4.4.

R-DOTAP nanoparticles (Versamune) works by facilitating several important immunological mechanisms:

1. Accessing the immune system

    - R-DOTAP nanoparticles exploit the documented function of dendritic cells (DCs) to take up particles, and no targeting mechanisms are utilized to facilitate Versamune uptake by DCs.
    - The positive charge of R-DOTAP leads to enhanced association with negatively charged cell surfaces (Stamatatos et al., 1988), thus resulting in high internalization by cells (Wrobel and Collins, 1995).
    - Upon cellular uptake, R-DOTAP destabilizes the endosomal membrane (El Ouahabi et al., 1997, Zhou and Huang 1994), enabling the associated antigens to effectively enter the cytoplasm and access the major histocompatibility complex (MHC) Class-I pathway to prime tumor (HPV) specific CD8+ killer T-cells.
    - Pharmacokinetic and toxicokinetic studies in rats and monkeys confirm the high uptake by the immune system leading to a systemic bioavailability of <6% (Muzzio and Johnson, 2009).

- In preclinical studies, 4 hours after SC injection of R-DOTAP + HPV16 E7, 80% of DCs in the draining lymph node were positive for R-DOTAP (Chen et al., 2008).

2. Activating the immune system
   - It was discovered that certain structurally-specific cationic lipids act as potent immune activators, eg, the enantiomeric specificity of lipids on immune response was recently reported, and PDS0101 contains the proprietary lipid R-DOTAP (Vasievich et al., 2011).
   - Upon uptake of the vaccine by dendritic cells, R-DOTAP activates the cells leading to their maturation. This is an important first step in the anti-tumor immune response *(*Vangasseri et al., 2006).
   - Due to high uptake and accumulation in lymph nodes, R-DOTAP's ability to activate mitogen-activated protein (MAP) kinase signaling facilitates the induction of critical cytokines and chemokines within the lymph nodes (Yan et al., 2007). The local induction of cytokine and chemokines within the lymph nodes strongly promotes T-cell migration into the lymph nodes, as well as activation and proliferation within the lymphatics. The demonstrated lack of significant cytokine increase in the systemic circulation minimizes the opportunity for systemic toxicities.
   - Effective HPV antigen presentation has been shown in preclinical in vivo models to occur via both the MHC Class-I and Class-II pathways leading to effective induction of HPV-specific CD4+ and CD8+ T-cells.
3. Overcoming immune tolerance/suppression
   - R-DOTAP induces a significant reduction in the population of T-reg suppressor cells (Chen et al., 2008). R-DOTAP + HPV peptides has also demonstrated a significant reduction in the population of T-regs within the tumor microenvironment (Gandhapudi et al., 2019*).*
   - Studies performed at the US National Cancer Institute demonstrated a unique synergy between R-DOTAP and granulocyte-macrophage colony-stimulating factor (GM-CSF), leading to a significant reduction of the myeloid derived suppressor cell (MDSC) population within tumors (*PDS-NCI CRADA 2644*), as well as an increase in CD8+ T-cells infiltrating into the tumor microenvironment.

The ability of PDS0101 to lower the T-reg population while increasing the population of HPV-specific CD8+ T-cells has been shown in nonclinical models to result in a significant lowering of the ratio of immune-suppressive cells to CD8+ T-cells within the tumor's microenvironment. These mechanisms are postulated to result in the effective anti-tumor immune responses observed and documented in nonclinical studies.

5.4.4 PDS0101 Clinical Study and Dose Selection

A Phase 1/2A clinical Study of PDS0101 demonstrating strong clinical HPV-specific T-cell responses and safety has recently been completed. The results of the study suggest effective induction of HPV-specific T-cell immunogenicity over a broad dose range and no serious adverse events (SAEs).

Twelve female subjects entered the study: 3 subjects in Cohort 1 (1.0 mg R-DOTAP dose and 2.4 mg HPVmix), 3 subjects in Cohort 2 (3.0 mg R-DOTAP dose and 2.4 mg HPV mix), and 6 subjects in Cohort 3 (10 mg R-DOTAP dose and 2.4 mg HPVmix). All subjects received all 3 doses of PDS0101 administered by SC injection, as scheduled on Days 1, 22, and 43. Per protocol, all subjects were women with confirmed high-risk HPV infection and CIN 1. Ages ranged from 24 to 51 years; the median age was 33.0 years. All subjects had blood draws pre-vaccination and 14 days (±5 days) after each vaccination, and once at 90 days after vaccination 3 for immunogenicity testing.

- T-cell Immunogenicity:
    - Except for 2 subjects (Subject 005-002 in the 1.0-mg R-DOTAP cohort and Subject 002-002 in the 3.0-mg cohort), outliers who had unusually high baseline IFN-γ responses, all remaining 10 subjects had a positive vaccine-induced response (a ≥3-fold increase over baseline at ≥1 of the 4 post-vaccination visits by either the IFN-γ or granzyme B enzyme-linked immunosorbent spot (ELISpot) assays, with background counts subtracted).
        - By IFN-γ assay (HPV-specific T-cells), 9 subjects (9/12, 75%) had a positive vaccine-induced response:
            - In the 1.0-mg cohort, besides the outlier, the remaining 2 subjects (2/3 [67%]) demonstrated a positive vaccine-induced response with average 13.5-fold increase over baseline.
            - In the 3.0-mg cohort, besides the outlier, the remaining 2 subjects (2/3 [67%]) demonstrated a positive vaccine-induced response with average 23.8-fold increase over baseline.
            - In the 10.0-mg cohort, 5 subjects (5/6 [83%]) demonstrated a positive vaccine-induced response with average 25.5-fold increase over baseline.
        - By granzyme B assay (HPV-specific CD8+ T-cells), 6 subjects (6/11 [54.5%]) representing all 3 cohorts, had a positive vaccine-induced response:
            - In the 1.0-mg cohort, besides the outlier and 1 subject without a baseline reading, the remaining subject demonstrated a positive vaccine-induced response with a 3.0-fold increase over baseline.
            - In the 3.0-mg cohort, besides the outlier, the remaining 2 subjects (2/3 [67%]) demonstrated a positive vaccine-induced response with average 21.1-fold increase over baseline.
        - In the 10.0-mg cohort, 3 subjects (3/6 [50%]) demonstrated a positive vaccine-induced response with average 17.9-fold increase over baseline.

- Results from both the IFN-γ and the granzyme B assays strongly suggest that there could potentially be an increase in HPV-specific T-cell response with the 3.0 mg R-DOTAP dose over the 1.0 mg dose but show no evidence suggestive of an increased response over the 3.0 mg R-DOTAP dose with the 10.0 mg R-DOTAP dose.
- No clear trend in T-cell response relative to post-vaccination time point (14 days after Vaccinations 1, 2, 3, or 90 days after Vaccination 3) was observed. All doses were active in inducing HPV-specific T-cell responses.
- IFN-γ (all T-cells) and the granzyme B (CD8+ T-cells) responses were elicited in both HPVmix- subjects.
- IFN-γ and the granzyme B responses were elicited in subjects with various HLA types.

Safety

- All subjects reported treatment-emergent adverse events (TEAEs); the majority were administration-site reactions.
- All administration-site reactions were deemed treatment-related.
- Most administration-site reactions were mild or moderate in severity. Some severe administration-site reactions were reported in the 3.0- and 10.0-mg R-DOTAP cohorts (grading of serious as per the FDA Toxicity Grading Scale for Healthy Volunteers in Preventive Vaccine Trials [FDA 2007]). Most administration-site reactions resolved the same day or within a few days, although skin discoloration at the injection site took up to several weeks to resolve in some subjects.
- Per the Subject Symptoms Diary, administration-site reactions were more serious and of longer duration in subjects in the 10.0-mg R-DOTAP cohort.
- No clinically significant differences in the types and pattern of TEAEs were observed between Vaccinations 1, 2, or 3.
- No dose-limiting toxicities (DLTs) were observed; thus, the maximum tolerated dose (MTD) was the 10.0 mg R-DOTAP dose.
- No SAEs, study discontinuations due to adverse events (AEs) or deaths occurred.
- No clinically relevant abnormal hematology, blood chemistry, urinalysis, or physical findings were observed.

This phase I dose escalation study U10-02011-001 was performed in twelve healthy normal volunteers with high-risk HPV infection and biopsy confirmed low-grade cervical intraepithelial neoplasia (CIN1). As detailed above and in summary, the study confirmed that 1.0, 3.0 and 10.0mg of R-DOTAP (Versamune) with a fixed dose of HPVmix (2.4mg) was associated with the absence of dose-limiting toxicities (DLTs) as well as the significant induction of HPV-specific immune responses: mean 26-fold increase in HPV reactivity by IFN-γ ELISpot in 90% of subjects without significant pre-existing responses; mean 18-fold increase in HPV reactivity by Granzyme B ELISpot in 67% of subjects without pre-existing responses.

The 5 dose PDS0101 combination regimen being utilized in PDS0101-HNC-201 was determined empirically following joint development scientific review by PDS Biotechnology and MSD, our formal External Collaborative partner in theVERSATILE-002 study. Additional PDS0101 doses were deemed warranted as the treatment was being delivered to patients with advanced recurrent/metastatic disease characterized by immune suppression and

dysregulation associated with high tumor burdens and prior chemoradiotherapy interventions. A well-established reason for clinical failure of checkpoint inhibitors is the lack of tumor-specific T cell responses able to invade the tumor microenvironment. Hence, PDS0101 combination therapy is given during the first 4 cycles treatment up front to maximize the potential anti-tumor activity of PDS0101's induction of HPV-specific CD8 T cells and concomitant checkpoint inhibition provided by pembrolizumab.

A fifth cycle of PDS0101 combination therapy is delivered at Cycle 12 (6 months following the last combination dose at Cycle 4) to boost HPV-specific immune responses as many patients experience disease progression or intolerance to therapy to pembrolizumab monotherapy after 6 to 8 months of treatment.

The PDS0101 formulation contains 10% volume of solute per volume of solvent (v/v) concentration of dimethylsulfoxide [DMSO] in the vaccine and was demonstrated to be safe and well-tolerated in both the preclinical and human safety studies. Three reported clinical studies of other HPV16 peptide vaccines used 20% (v/v) concentration of DMSO in the formulations (Uppaluri et al., 2008; Chang et al., 2014; Preston et al., 2013). One study also used 100% DMSO for 1 of the dose groups (Dunn et al., 2007).

Refer to the respective IB/approved labeling for detailed background information on pembrolizumab and PDS0101.

5.4.5 Rationale for the Combination of Pembrolizumab and PDS0101

PDS0101 is a T-cell activating immunotherapy designed to induce HPV-specific CD8+ and CD4+ T-cells. As previously noted, extensive preclinical mechanism of action studies provides strong evidence that PDS0101 acts by a 3-pronged mechanism to induce potent anti-tumor immune responses.

The R-DOTAP cationic lipid facilitates effective cross-presentation of the HPV16 E6 and E7 antigens via both the MHC Class-I and Class-II pathways leading to priming of HPV-specific CD8+ and CD4+ T-cells, respectively.

R-DOTAP induces injection site and lymph node-specific induction of a cytokine and chemokine profile that leads to effective activation and proliferation of the primed T-cells, therefore, resulting in a large number of "high-quality" cytolytic HPV-specific T-cells. The localized cytokine induction results in high tolerability with negligible systemic side effects. The induction of active T-cells, including HPV16-specific cytolytic T-cells and the high tolerability has been confirmed in a Phase 1/2A dose-ranging clinical study. An MTD was not established, and no DLTs were observed.

PDS0101 was demonstrated in preclinical studies to induce a significant reduction in the population of immune-suppressive T-regs within the tumor microenvironment (approximately 40% reduction within 1 week of treatment).

In preclinical studies, by activating the above described mechanisms, PDS0101 has demonstrated the ability to significantly lower the ratio of T-regs to HPV-specific CD8+ T-cells within the

tumor microenvironment. PDS0101's ability to significantly alter the tumor's microenvironment leads to the unique ability to effectively regress established tumor cell line 1 (TC-1) tumors with low doses. Strong memory T-cells are also generated leading to protection against tumor re-establishment after TC-1 challenge.

The superior cross-presentation, immune activation and subsequent high HPV-specific T-cell induction has been confirmed in humans in a Phase 1/2A dose-escalating study.

Checkpoint blockade with pembrolizumab shows that endogenous immune responses can induce tumor regression. However, tumors often utilize several immune-suppressive mechanisms that may not always be overcome simply by blocking a single signaling checkpoint. It is, therefore, envisioned that PDS0101 by inhibiting a second immunosuppressive pathway while also inducing high levels of tumor-specific cytolytic T-cells should exhibit a synergy with pembrolizumab leading to an improved and well-tolerated combination immunotherapy.

A critical consideration in combination immuno-oncology is the safety and tolerability of the individual drugs and the potential for compounded toxicity. PDS0101 has exhibited high tolerability in a Phase 1/2A clinical study. No DLTs were observed and the most common AEs observed were transient injection-site reactions which lasted 48 to 72 hours and resolved completely. PDS0101, due to its strong HPV16-specific T-cell induction demonstrated in all subjects, coupled with its strong safety profile, provides excellent potential for safe and effective combination with pembrolizumab.

PDS Biotechnology's R-DOTAP platform (Versamune) and pembrolizumab work by complimentary immunological mechanisms. Both have shown strong and relevant immunological activation in human clinical studies. In addition, strong synergistic anti-tumor activity of R-DOTAP/antigen in combination with a checkpoint inhibitor has been demonstrated in preclinical studies.

5.4.6 Rationale for the Combination of Pembrolizumab and PDS0101 in HPV16 HNSCC

Pembrolizumab has demonstrated efficacy in both HPV-positive and HPV-negative head metastatic head and neck cancer patients.

A significant shift in the epidemiology of head and neck cancer has been reported over the past 30 years. While exposure to chemical mutagens continues to be the most common risk factor, a rapidly expanding subset of HNSCCs are caused by HPV infection. The oropharynx is uniquely susceptible to HPV, and currently in the United States, up to 70% of oropharyngeal cancers are reported to be HPV-mediated oropharyngeal squamous cell carcinomas (Lewis et al 2015). The vast majority of HPV-mediated HNSCC are caused by HPV16 infection. The specific association of HPV16 and oropharyngeal cancer was realized and reported as early as 1995. HPV16 is currently reported to account for 80% to 90% of high-risk HPV cancers and confers a 15- to 230-fold increased risk of oropharyngeal squamous cell carcinomas.

A pembrolizumab-PDS0101 combination, thus, presents a strong rationale to produce an effective therapy for a rapidly growing population of currently underserved subjects in HPV16-positive HNSCC. A successful study will enable the combination to be applied to several other debilitating HPV-mediated cancers such as anal, cervical, vaginal cancers, etc.

This study will explore in a preliminary manner whether the combination of PDS0101 plus pembrolizumab in first-line treatment of HNSCC will improve the objective response rate (ORR), as well as PFS at 12 months, using the responses documented in the KEYNOTE-048 study with pembrolizumab monotherapy. Given the documented T-cell activation and expansion associated with the Versamune platform in PDS0101, it is hypothesized that "cold" tumors with low responsiveness to checkpoint inhibitor therapy will become "hot," resulting in improved sensitivity and response to checkpoint inhibition by pembrolizumab. The impact of PD-L1 expression in tumors on clinical endpoints will also be explored. Because Versamune-associated T-cell activation and expansion is localized, it is hypothesized that an administration of PDS0101 will result in limited systemic exposure and limited systemic toxicity when co-administered with pembrolizumab.

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6 STUDY OBJECTIVES AND ENDPOINTS

6.1 Study Objectives

6.1.1 Primary Objective

- To assess the preliminary activity of the combination of pembrolizumab (KEYTRUDA) and PDS0101 in checkpoint inhibitor (CPI) naïve or refractory subjects with recurrent and/or metastatic HNSCC and high-risk HPV16 infection.

6.1.2 Secondary Objectives

In both CPI naïve and CPI refractory subjects:

- Assess PFS per Response Evaluation Criteria in Solid Tumors (RECIST) 1.1.
- Assess overall survival (OS).
- Assess safety and tolerability of the combination of pembrolizumab and PDS0101.

6.1.3 Exploratory Objectives

- Duration of response for all subjects seen at time of disease progression or Cycle 35.
- Evaluate anti-HPV16 E6 and E7 immune responses elicited by treatment with pembrolizumab and PDS0101 using IsoPlexis functional proteomics at Days 85 (Cycle 5) and 253 (Cycle 13), compared to baseline.

6.2 Study Endpoints

6.2.1 Primary Efficacy Endpoint

In both CPI naïve and CPI refractory subjects:

- The primary efficacy endpoint will be the best overall response (BOR) of confirmed complete response (CR) or confirmed partial response (PR) per RECIST 1.1 of the combination of pembrolizumab and PDS0101.

6.2.2 Key Secondary Endpoints

In both CPI naïve and CPI refractory subjects:

- PFS per RECIST 1.1 in all subjects at 12 and 24 months.
- Assess OS in all subjects.
- Assess safety and tolerability of pembrolizumab and PDS0101.

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7 INVESTIGATIONAL PLAN

7.1 Description of Overall Study Design and Plan

This is a Phase 2 open-label, non-randomized study of a combination of pembrolizumab and PDS0101 in HPV16 DNA-positive subjects with recurrent and/or metastatic HNSCC. Approximately 30 study centers are planned. Dosing is based on safety and T-cell induction evaluation for PDS0101 in subjects infected with high-risk HPV16 and safety and clinical efficacy for pembrolizumab as documented in the KEYNOTE-048 study.

The study is designed to evaluate the safety and efficacy of pembrolizumab and PDS0101 when administered in combination. Subjects will be enrolled into either the CPI naïve group or the CPI refractory group, and up to 95 subjects in total (54 CPI naïve subjects and 41 CPI refractory subjects) will be enrolled in the order in which they are screened and meet eligibility criteria. A regimen of pembrolizumab (200 mg) and PDS0101 (3.0 mg R-DOTAP and 2.7 mg HPV16 mix) will be administered Q3W for the first 4 cycles: IV infusion of pembrolizumab followed by SC injections of PDS0101 on Days 1 (Cycle 1), 22 (Cycle 2), 43 (Cycle 3), and 64 (Cycle 4).

The fifth and final PDS0101 injection will be administered on Day 232 (6 months after the 4th vaccination, Cycle 12 of pembrolizumab). IV infusion of pembrolizumab will occur first followed by SC injection of PDS0101. PDS0101 will be administered no sooner than 30 minutes before and 60 minutes after the completion of the pembrolizumab IV infusion.

Pembrolizumab administration will continue Q3W from Day 1, Cycle 1 until unacceptable toxicity or disease progression. Subjects without disease progression will be treated for up to 35 Cycles.

A lead-in safety cohort of first 12 subjects (CPI naïve or CPI refractory) will be enrolled to assess safety of the combination of pembrolizumab with PDS0101.

There will be a pause in enrollment after the twelfth subject has been dosed until the data monitoring committee (DMC) provides their recommendations of the safety of the study combination treatment.

These initial 12 subjects will be monitored through 3 weeks after the first administration of pembrolizumab and PDS0101 for any signs of DLT. At the end of the assessment period (Cycle 1/21 days; Day 1 to 21), the DMC will assess the DLTs and safety of the combination treatment. The DMC may elect to assess a second cohort of 12 subjects, depending on the data from the first 12 subjects.

All DLTs will be confirmed by the Sponsor medical monitor and DMC.

Subjects that experience a DLT related to PDS0101 (possibly/probably/definitely) may continue on the study with a dose reduction of PDS0101 or be discontinued.

For dose reduction, subjects will be administered only 1 injection of 0.5 mL of PDS0101 (1.5 mg R-DOTAP with 1.35 mg HPV mix) per SC vaccination into the upper anterior arm. PDS0101

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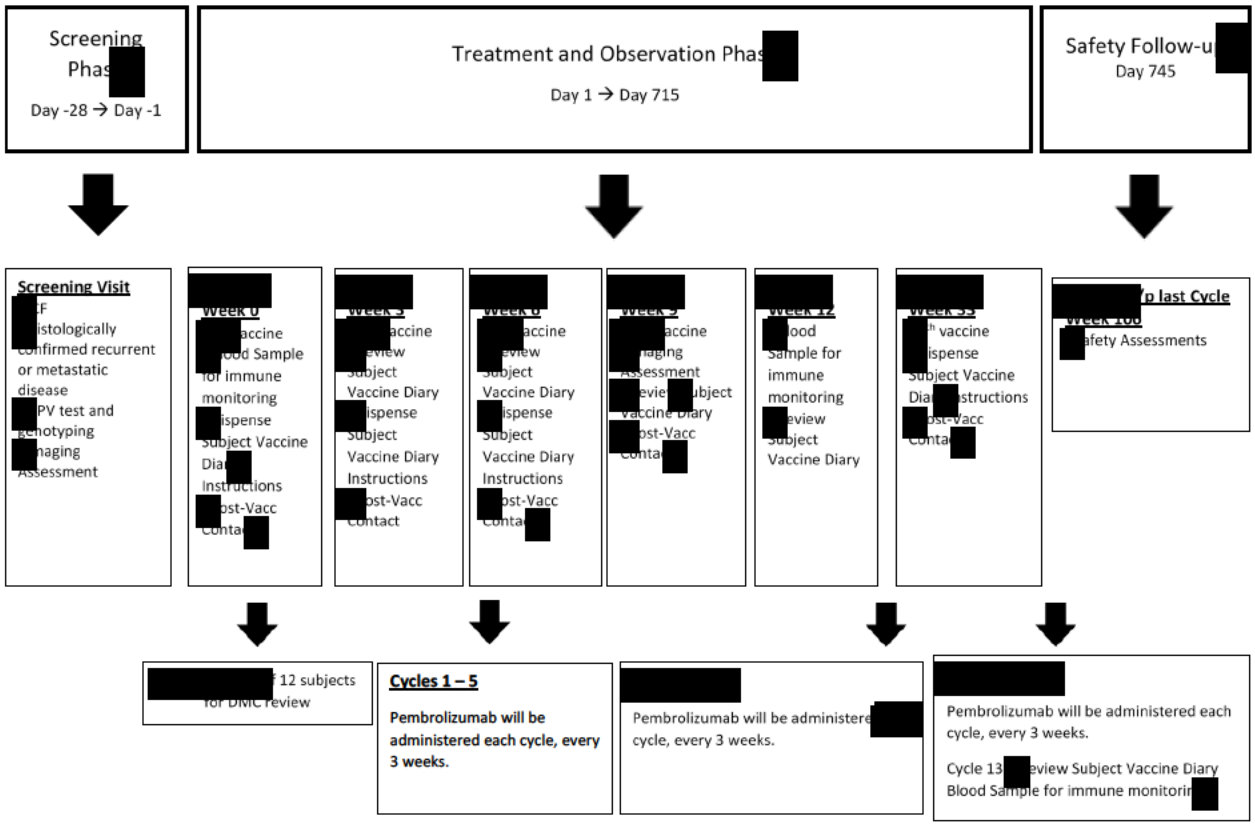
administration will be halted upon any further unacceptable toxicity of the combination that includes a reduced dose of PDS0101.

Immuno-monitoring assessments will be performed prior to the first study combination treatment (baseline), and on Days 85 (Cycle 5, 21 days after vaccination #4) and 253 (Cycle 13, 21 days after final vaccination #5). Figure 1 presents the study design schema.

Figure 1 Study Design Schema



Abbreviations: DMC = data monitoring committee; HPV = human papilloma virus; ICF = informed consent form.

7.2 Discussion and Rationale for Study Design and Endpoints

HPV-positive nasopharyngeal carcinoma is associated with a much poorer clinical prognosis (Stenmark et al 2014). Proportional hazards models were used to compare the risk of death among subjects as stratified by HPV or Epstein-Barr (EB) viral status. Of the evaluable tumors, 43% were EBV-positive/HPV-negative, 30% were EBV-negative/HPV-positive, and 28% were EBV/HPV-negative. EBV/HPV-positive infection was mutually exclusive.

HPV positivity was significantly correlated with World Health Organization Grade 2 tumors, older age, and smoking (all P <.001). At a median follow-up time of 7 years, subjects with HPV-positive tumors exhibited worse outcomes than did those with EBV-positive tumors, including decreased OS (HR 2.98, P = .01; and HR 3.89, P = .002), PFS (HR 2.55, P = .02; and

HR 4.04, P < .001), and locoregional control (HR 4.01, P = 0.03; and HR 6.87, P = .001). Consequently, there is a serious unmet medical need for effective treatment of HPV-positive HNSCC.

HPV16 infection is responsible for over 80% of HPV-positive nasopharyngeal cancers. Notably, HPV16-positive oropharyngeal cancer subjects have a higher response rate and more favorable disease-free survival prognosis after initial treatment (Fakhry et al 2008). These subjects also tend to be younger and are usually in their 40s and 50s. Despite this, initial treatment options including radiation therapy, surgery, and/or chemotherapy are generally as debilitating for this subject group as other head and neck cancers. In addition, therapy for metastatic disease remains purely palliative for all of these subjects. All types of recurrent metastatic HNSCC have a poor prognosis, irrespective of HPV status, with a median OS of 13 months in subjects treated in the first-line setting and 6 months in previously treated subjects.

KEYNOTE-048 is a pivotal Phase 3, randomized, open-label study (ClinicalTrials.gov NCT02358031) designed to investigate pembrolizumab for first-line treatment of recurrent or metastatic HNSCC. A total of 882 subjects were randomly allocated to receive pembrolizumab as monotherapy or in combination with a platinum chemotherapy (cisplatin or carboplatin) plus 5-FU, compared with cetuximab with platinum chemotherapy (cisplatin or carboplatin) plus 5-FU (EXTREME).

On June 10, 2019, the FDA-approved pembrolizumab (KEYTRUDA, MSD) for the first-line treatment of patients with metastatic or unresectable recurrent HNSCC.

Pembrolizumab was approved for use in combination with platinum and FU for all subjects and as a single agent for patients whose tumors express PD-L1 (CPS ≥1), as determined by the FDA-approved PD-L1 IHC 22C3pharmDx kit.

The FDA also expanded the intended use for this test to include use as a companion diagnostic device for selecting patients with HNSCC for treatment with pembrolizumab as a single agent.

Approval was based on KEYNOTE-048 (NCT02358031), a randomized, multi-center, 3-arm, open-label, active-controlled trial conducted in 882 patients with metastatic HNSCC who had not previously received systemic therapy for metastatic disease or with recurrent disease who were considered incurable by local therapies.

Patients were randomized (1:1:1) to receive 1 of the following treatments: pembrolizumab as a single agent; pembrolizumab, carboplatin or cisplatin, and FU; or cetuximab, carboplatin or cisplatin, and FU. Randomization was stratified by tumor PD-L1 expression (TPS ≥50% or <50%), HPV status according to p16 IHC (positive or negative), and ECOG PS (0 vs 1; see Appendix 1). PD-L1 expression (TPS and CPS) was determined using the PD-L1 IHC 22C3 PharmDx kit.

OS, sequentially tested in the subgroup of patients with CPS ≥20 HNSCC, the subgroup of subjects with CPS ≥1 HNSCC and the overall population was the major efficacy measure.

The trial demonstrated a statistically significant improvement in OS in the overall population for patients randomized to pembrolizumab plus chemotherapy, compared with cetuximab plus chemotherapy at a pre-specified interim analysis. The median OS was 13.0 months for the pembrolizumab plus chemotherapy arm and 10.7 months for the cetuximab-plus-chemotherapy arm (HR 0.77; 95% CI: 0.63, 0.93; P = .0067). Results were similar in the CPS ≥20 subgroup (HR 0.69; 95% CI: 0.51, 0.94) and CPS ≥1 subgroup (HR 0.71; 95% CI: 0.57, 0.88).

The trial also demonstrated statistically significant improvements in OS for the subgroups of subjects with PD-L1 CPS ≥1 HNSCC and PD-L1 CPS ≥20 HNSCC randomized to pembrolizumab as a single agent, compared with cetuximab plus chemotherapy. In the CPS ≥1 subgroup, the median OS was 12.3 months for the pembrolizumab arm and 10.3 months for the cetuximab-plus-chemotherapy arm (HR 0.78; 95% CI: 0.64, 0.96; P = .0171). For the CPS ≥20 subgroup, the median OS was 14.9 months for the pembrolizumab arm and 10.7 months for the cetuximab-plus-chemotherapy arm (HR 0.61; 95% CI: 0.45, 0.83; P = .0015). At the time of the interim analysis, there was no significant difference in OS between the pembrolizumab as a single-agent arm and the cetuximab-plus-chemotherapy arm for the overall population.

There were no significant differences in PFS for either pembrolizumab-containing arm compared with the cetuximab-plus-chemotherapy arm in any population.

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

The recommended pembrolizumab dose for HNSCC is 200 mg administered as an IV infusion over 30 minutes every 3 weeks until disease progression, unacceptable toxicity, or up to 24 months in patients without disease progression.

The primary objective of this study is to assess the efficacy of the combination of pembrolizumab (KEYTRUDA) and PDS0101 in first-line treatment of subjects with recurrent and/or metastatic HNSCC and high-risk HPV16 infection.

Key secondary objectives include:

- Assess PFS per RECIST 1.1.
- Assess OS.
- Assess safety and tolerability of the combination of pembrolizumab and PDS0101.

PDS recently completed a Phase 1/2A clinical study evaluating safety and immunogenicity of PDS0101. This study strongly suggested that PDS0101 may result in superior induction of HPV-specific T-cells in addition to high tolerability of the vaccine when compared with published clinical data from other leading therapeutic HPV cancer vaccines.

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A pembrolizumab-PDS0101 combination thus presents a strong rationale to produce an effective therapy for a population of currently underserved subjects in HPV16 DNA-positive HNSCC.

- Pembrolizumab, by blocking PD-L1 in tumors, enables tumor-specific CD8+ T-cells to attack and lyse tumor cells. The completed KEYNOTE-048 Phase 3 study suggested that pembrolizumab has excellent potential to treat a significant percentage of HNSCC.
- PDS0101, which is based on multi-epitope HPV16 E6 and E7 peptides combined with the cationic lipid R-DOTAP nanoparticles, overcomes critical obstacles associated with antigen cross-presentation, and has demonstrated superior ability to elicit active HPV-specific CD4+ helper T-cells and CD8+ effector T-cells in a Phase 1/2A clinical study.
- A combination of pembrolizumab and PDS0101 may result in enhanced clinical benefit when compared with PDS0101 or pembrolizumab alone.
    - A synergistic and significantly enhanced anti-tumor effect was demonstrated in a preliminary preclinical (non-HPV cancer) study involving a Versamune-based vaccine and a similar compound to pembrolizumab.
    - Importantly, induction of HPV-specific CD8+ T-cell cytotoxic responses directed at HPV16-positive HNSCC tumors may minimize the systemic off-target immune-related toxicity associated with checkpoint inhibitors, such as pembrolizumab.

A critical consideration in combination immuno-oncology is the safety and tolerability of the individual drugs and the potential for compounded toxicity. PDS0101 has exhibited high tolerability in a Phase 1/2A clinical study. No DLTs were observed, and the main AEs observed were transient injection-site reactions, the majority of which resolved within 48 to 72 hours.

PDS0101 due to its demonstrated HPV16-specific CD8+ T-cell induction in human studies, coupled with its strong safety profile, provide excellent potential for safe and effective combination with pembrolizumab.

Summary:

Pembrolizumab and PDS0101 work by complimentary immunological mechanisms. Both have shown strong and relevant immunological activation in human clinical studies. In addition, strong synergistic anti-tumor activity of R-DOTAP/antigen in combination with an anti-PD-L1 antibody was demonstrated in preclinical studies. PDS0101 enhances tumor-specific T-cell responses while also reducing a population of immune suppressors that are independent of PD-1. Given that PDS0101 is well-tolerated as a single agent with no SAEs or DLTs in the Phase 1/2A study, and there are no overlapping toxicities with pembrolizumab, the synergistic modes of action should theoretically enhance efficacy without adding any significant toxicity.

This study will explore in a preliminary manner whether the combination of adding PDS0101 to pembrolizumab in first-line treatment of recurrent and/or metastatic HNSCC will improve the ORR, as well as PFS at 12 and 24 months per investigator-evaluated and central imaging confirmed RECIST 1.1, using the responses documented in the KEYNOTE-048 study with pembrolizumab monotherapy for historical comparison.

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RECIST 1.1 will be used to determine the dates of progression as this methodology is accepted by regulatory authorities. The central imaging vendor will receive all images at all time points specified in Table 5 from the sites. Images should be submitted in a timely fashion. Local site study team reading (Principal Investigator (PI) assessment with site radiology reading) based on RECIST 1.1 will be used to making an initial determination of subject progression considered unconfirmed. The final determination of radiologic progression will be confirmed based on the central imaging laboratory assessment of progression rather than site study team assessment because images read by a central imaging vendor minimize bias in response assessments.

Given the documented T-cell activation and expansion associated with the Versamune platform in PDS0101, it is hypothesized that "cold" tumors with low responsiveness to checkpoint inhibitor therapy will become "hot," resulting in improved sensitivity and response to checkpoint inhibition by pembrolizumab. The impact of PD-L1 expression in tumors on clinical endpoints will also be explored. Because Versamune-associated T-cell activation and expansion is localized, the Sponsor hypothesizes that administration of PDS0101 will result in limited systemic exposure and limited systemic toxicity when co-administered with pembrolizumab.

7.3 PDS0101 Dose Rationale

Results from this Phase 1/2A study demonstrate a favorable safety profile for PDS0101 and suggest that PDS0101 is effective in inducing HPV16-specific T-cells, including cytotoxic T-lymphocytes (IsoPlexis functional proteomics).

The 3.0 mg R-DOTAP PDS0101 dose (containing 2.7 mg HPVmix) may provide the best combination of safety and potency and will be evaluated in the current clinical study.

7.4 Benefits and Risks to Subjects

This is the first study of pembrolizumab and PDS0101 to be evaluated in combination in humans. PDS0101 is an immune activating platform that results in significant, potent HPV-specific cytolytic CD8 T-cells while the checkpoint inhibitor pembrolizumab "takes the brakes off the immune system." It is hypothesized that the combination of the 2 agents will result in more potent, synergistic anti-tumor responses directed against HPV16-positive HNSCCs, potentially leading to improved ORR, PFS and duration of response (DOR). The purpose of this study is to explore in a preliminary manner, the safety of the combination and its impact on those specified clinical outcomes.

Pembrolizumab has been studied extensively in subjects and no significant side effects beyond the known, well-documented pembrolizumab immune-related AEs are anticipated. However, due to the demonstrated ability of PDS0101 in preclinical studies to lower T-regs coupled with pembrolizumab's ability to block PD-1 pathways, subjects will be closely observed for any autoimmune effects. The main anticipated AEs associated with PDS0101 based on a single clinical study include transient, local injection-site reactions (redness, swelling, pain, bruising, itching) and possible general symptoms, such as headache, fatigue, and nausea. From the injection and blood draws, there is a potential risk of fainting, bruising, pain, scarring, blood

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clots, and infection at the site of the needle sticks. Although not anticipated or observed in previous studies, hypersensitivity reactions ranging from mild reactions, such as rash, hives, or fever, to serious reactions, such as anaphylaxis, could occur.

Pembrolizumab dosing of 200 mg per cycle is administered as an IV infusion over 30 minutes Q3W during this study for up to 35 cycles if disease progression does not occur. A total of 5 doses of PDS0101 will be co-administered as an SC injection on Days 1 (Cycle 1), 22 (Cycle 2), 43 (Cycle 3), 64 (Cycle 4), and 232 (Cycle 12). PDS0101 will be administered no sooner than 30 minutes after the completion of the pembrolizumab infusion and no later than 60 minutes post-pembrolizumab infusion. After the first vaccination of PDS0101, subjects will have vital signs and symptoms monitored for 1 hour (at 0, 15, 30, and 60 minutes). If no significant immediate AEs are identified with the first vaccination, subjects will be monitored for 15 minutes (at 0, and 15 minutes) with subsequent vaccinations 2 through 5.

Risk minimization methods include the following:

- Monitoring the subjects at the study center for the first hour after Vaccine 1, and for 15 minutes after Vaccines 2 through 5, if the first vaccination is well-tolerated. All subjects will be given instructions for a subject vaccine diary to record local injection-site reactions and any other symptoms that occur within the 7 days after the vaccination. In addition, study staff will contact study subjects by phone call or email within 24 hours and no later than 72 hours after administration of each dose of PDS0101 vaccine. Throughout the study, subjects will be instructed to contact the study staff immediately if they experience any side effects of clinical concern whether anticipated or unanticipated.
- Pregnant women, breastfeeding mothers, and those planning to become pregnant are excluded from the study.
- Women of childbearing potential (WOCBP) must use 1 highly effective method of birth control. Acceptable methods of birth control for this study include use of a barrier (diaphragm or condom) with spermicide or use 1 of the following: combined (estrogen and progestogen containing) hormonal contraception associated with inhibition of ovulation, an intrauterine device/system; or an oral, transdermal, or injectable contraceptive. A vasectomised partner is a highly effective birth control method provided that partner is the sole sexual partner of the WOCBP trial participant and that the vasectomised partner has received medical assessment of the surgical success.
  As a precaution, the study will include a lead-in safety assessment of the first 12 subjects who will be carefully monitored for DLTs through 3 weeks after the first administration (Cycle 1) of pembrolizumab and PDS0101 (study combination treatment) to ensure that no unexpected AEs are observed.

7.5 Assessment of the Risk/Benefit Ratio

An extensive safety data package for pembrolizumab has been assembled by MSD, and pembrolizumab has been demonstrated to be well-tolerated in all studies. Reference safety

information for assessment of expectedness of Serious Adverse Events can be found in Section 7.2 of the Pembrolizumab Investigators Brochure.

Extensive PDS0101 toxicology studies, as well as a dose-ranging Phase 1/2A study suggest minimal toxicological impact of clinical significance. In addition, published human safety studies with the HPV16 peptide antigens have demonstrated a lack of toxicity and, as a class, clinical studies of therapeutic vaccines in combination with checkpoint inhibitors have not been associated with any excess safety signals. (R-, S-) DOTAP racemic mixture has also been shown to have a good safety profile in human clinical studies.

PDS Biotechnology Corporation's preclinical and human safety data and human T-cell immunogenicity data combined with MSD's clinical safety and efficacy data with pembrolizumab in the target subject population provide a strong indication of a high likelihood of potential synergy and enhanced efficacy in humans. The studies also suggest the combination should be well-tolerated.

All measures will, however, be taken as described above to ensure the safety of all subjects in the study.

7.6 End of Study

A subject will have fulfilled the requirements for study completion if/when the subject has completed all study periods, including the last scheduled visit, as indicated in the Schedule of Assessments (Table 5).

The end of the study will be the last subject's last visit or the last subject's scheduled visit/assessment as indicated in the Schedule of Assessments (Table 5) or as requested by Sponsor.

8 SELECTION OF STUDY POPULATION

Section 7.1 provides information regarding number of subjects planned to be enrolled.

8.1 Inclusion Criteria

Subjects are eligible to be included in the study only if all of the following criteria apply:

Type of Subject and Disease Characteristics

1. The subject (or legally acceptable representative if applicable) provides written informed consent for the study.
2. Be ≥18 years of age on the day of signing the informed consent.
3. Checkpoint-naïve subjects: Have a history of histologically confirmed diagnosis of squamous cell cancer of the head and neck (HNSCC) that is recurrent, metastatic, or persistent with:
    a. confirmed HPV16 infection
    b. confirmed tumor PDL1 expression defined as a CPS ≥1 using the FDA-approved Dako PD-L1 IHC 22C3 PharmDx Assay.
    c. no prior receipt of any immunological therapy for metastatic disease.
4. Checkpoint experienced subjects: Have a history of histologically confirmed diagnosis of HNSCC that is recurrent, metastatic, or persistent with:
    a. confirmed HPV16 infection
    b. characterization of tumor PDL1 expression using the FDA-approved PD-L1 IHC 22C3 PharmDx Assay
    c. receipt of prior treatment with checkpoint inhibitor as a single agent or in combination and has received at least 2 doses of the checkpoint agent or a minimum of 6 weeks on treatment.
    d. have documented clinical progression or recurrence that has been radiologically confirmed
5. Have recurrent and/or metastatic measurable disease based on RECIST 1.1, as assessed by the local Principal Investigator (PI)/radiology. There must be confirmation that the subject's imaging shows at least 1 lesion that is appropriate for selection as a target lesion per RECIST 1.1. Lesions situated in a previously irradiated area are considered measurable if progression has been demonstrated in such lesions.
6. Have adequate organ function, as defined in Table 3. Specimens must be collected within 10 days prior to the start of study combination treatment.

Table 3 Adequate Organ Function Laboratory Values

System	Laboratory Value
Hematological	
Absolute neutrophil count (ANC)	≥1500/µL
Platelets	≥100 000/µL
Hemoglobin	≥9.0 g/dL or ≥5.6 mmol/L[1]
Renal	
Creatinine **OR** Measured or calculated[2] creatinine clearance (GFR can also be used in place of creatinine or CrCl)	≤1.5 × ULN **OR** ≥30 mL/min for subject with creatinine levels >1.5 × institutional ULN
Hepatic	
Total bilirubin	≤1.5 ×ULN **OR** direct bilirubin ≤ULN for subjects with total bilirubin levels >1.5 × ULN
AST (SGOT) and ALT (SGPT)	≤2.5 × ULN (≤5 × ULN for subjects with liver metastases)
Coagulation	
International normalized ratio (INR) **OR** prothrombin time (PT) Activated partial thromboplastin time (aPTT)	≤1.5 × ULN unless subject is receiving anticoagulant therapy as long as PT or aPTT is within therapeutic range of intended use of anticoagulants

ALT (SGPT) =alanine aminotransferase (serum glutamic pyruvic transaminase); AST (SGOT) =aspartate aminotransferase (serum glutamic oxaloacetic transaminase); GFR=glomerular filtration rate; PT= prothrombin time, ULN=upper limit of normal.

[1] Criteria must be met without packed red blood cell (pRBC) transfusion within the prior 2 weeks. Participants can be on stable dose of erythropoietin (≥ approximately 3 months).

[2] Creatinine clearance (CrCl) should be calculated per institutional standard.

Note: This table includes eligibility-defining laboratory value requirements for treatment; laboratory value requirements should be adapted according to local regulations and guidelines for the administration of specific chemotherapies.

7. If a subject received major surgery or radiation therapy of >30 Gy, he/she must have recovered from the toxicity and/or complications from the intervention.
8. For female subjects defined as WOCBP, a negative urine pregnancy test must be obtained during screening. Women who are surgically sterile or at least 2 years postmenopausal do not require pregnancy testing.

   Note: Female subjects of childbearing potential must be willing to use an effective method of contraception for the course of the study through 120 days after the last dose of study medication.
9. Male subjects of childbearing potential must agree to use a condom as an effective method of contraception starting with the first dose of study therapy through 120 days after the last dose of study therapy.

10. Have an Eastern Cooperative Oncology Group (ECOG) performance status of 0 or 1.

8.2 Exclusion Criteria

Subjects are excluded from study if any of the following criteria apply:

Medical Conditions

1. Pregnancy Exclusion:
   a. A female subject defined as a WOCBP who has a positive urine pregnancy test (within 72 hours) prior to treatment. If the urine test is positive or cannot be confirmed as negative, a serum pregnancy test will be required.

Prior/Concomitant Therapy

2. Has received prior therapy with an anti-PD-1, anti-PD- L1, or anti-PD-L2 agent with an agent directed to another stimulatory or co-inhibitory T-cell receptor (eg, CTLA-4, OX40, CD137) and was discontinued from that treatment due to a Grade 3 or higher AE.
3. Has received prior systemic anticancer therapy including investigational agents within 30 days prior to treatment.

   Note: Subjects must have recovered from all AEs due to previous therapies to ≤ Grade 1 or baseline. Subjects with ≤ Grade 2 neuropathy and ≤ Grade 2 alopecia are an exception to this criterion and may qualify for therapy.

   Note: If the subject received major surgery, the subject must have recovered adequately from the toxicity and/or complications from the intervention prior to starting treatment.
4. Coordination and timing of coronavirus disease 2019 (COVID-19) vaccination should be based on the local investigator's clinical assessment and judgment.

   Note: Whenever possible, it is recommended to avoid COVID vaccination on the day of PDS0101 and/or pembrolizumab dosing because it may be difficult to attribute certain AEs (e.g., fever, infusion reaction) to the study drug(s) or the COVID vaccine if they are both administered on the same day.
5. Has received prior radiotherapy within 2 weeks of start of study treatment. Subjects must have recovered from all-radiation-related toxicities, not require corticosteroids and not have had radiation pneumonitis. A 1-week washout is permitted for palliative radiation (<2 weeks of radiotherapy) to non-CNS disease.
6. Has received a live vaccine within 30 days prior to the first dose of treatment. Examples of live vaccines include, but are not limited to, the following: measles, mumps, rubella, varicella/zoster (chicken pox), yellow fever, rabies, Bacillus Calmette-Guérin (BCG), and typhoid vaccine. Seasonal influenza vaccines for injection are generally killed-virus

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vaccines and are allowed; however, intranasal influenza vaccines (eg, FluMist®) are live attenuated vaccines and are not allowed.

7. Received immunotherapy/immunomodulatory or immunosuppressive agents (eg, IFNs, tumor necrosis factor, interleukins, immunoglobulins or other biological response modifiers [GM-CSF, granulocyte colony-stimulating factor, macrophage colony-stimulating factor]) within 6 weeks prior to administration of the first study combination treatment.

Prior/Concurrent Clinical Study Experience

8. Is currently participating in or has participated in a study of an investigational agent or has used an investigational device within 30 days prior to the first dose of study treatment.

   Note: Subjects who entered the follow-up phase of an investigational study may participate as long as it has been 30 days after the last dose of the previous investigational agent.

9. Has undergone prior allogeneic hematopoietic stem cell transplantation within the last 5 years. Subjects who have had a transplant greater than 5 years ago are eligible as long as there are no symptoms of graft-versus-host disease (GVHD).

Diagnostic Assessments

10. Has a diagnosis of immunodeficiency or is receiving chronic systemic steroid therapy (in dosing exceeding 10 mg daily of prednisone equivalent) or any other form of immunosuppressive therapy within 7 days prior to the first dose of study drug. Current or recent use of physiologic doses of intra-articular, topical, or inhaled corticosteroids is acceptable.

11. Has a known additional malignancy that is progressing or has required active treatment within the past 3 years.

    Note: Subjects with basal cell carcinoma of the skin, squamous cell carcinoma of the skin or carcinoma in situ (e.g., breast carcinoma, cervical cancer in situ) or other malignant tumors that have undergone potentially curative therapy are not excluded.

12. Has known active central nervous system (CNS) metastases and/or carcinomatosis meningitis. Subjects with previously treated brain metastases may participate provided they are radiologically stable, i.e., without evidence of progression for at least 4 weeks by repeat imaging (note that repeat imaging should be performed during study screening clinical stable and without requirement of steroid treatment for at least 14 days prior to first dose of study treatment).

13. Has severe hypersensitivity (≥Grade 3) to pembrolizumab and/or any of its excipients.

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14. Has an active autoimmune disease that has required systemic treatment in the past 2 years (ie, with use of disease modifying agents, corticosteroids, or immunosuppressive drugs). Replacement therapy (eg, thyroxine, insulin, or physiologic corticosteroid replacement therapy for adrenal or pituitary insufficiency) is not considered a form of systemic treatment and is allowed.
15. Has a history of (non-infectious) pneumonitis that required steroids or has current pneumonitis.
16. Has an active infection requiring systemic therapy.
17. Subjects with known HIV and/or history of hepatitis B or C infections or known to be positive for hepatitis B antigen (HBsAg)/hepatitis B virus (HBV) DNA or hepatitis C antibody or RNA. Active hepatitis C is defined by a known positive hepatitis C Ab result and known quantitative HCV RNA results greater than the lower limits of detection of the assay.
18. Has a history or current evidence of any condition, therapy, or laboratory abnormality that might confound the results of the study, interfere with the subject's participation for the full duration of the study, or is not in the best interest of the subject to participate, in the opinion of the treating investigator.
19. Has a known psychiatric or substance abuse disorder that would interfere with the subject's ability to cooperate with the requirements of the study.

Other Exclusions

20. Is pregnant or breastfeeding or expecting to conceive or father children within the projected duration of the study, starting with the screening visit through 120 days after the last dose of any study treatment.
21. Has had an allogenic tissue/solid organ transplant.
22. Has received administration of colony-stimulating factors (including G-CSF, GM-CSF or recombinant erythropoietin) within 30 days prior to Day 1.
23. Has a history of interstitial lung disease.
24. Female subjects defined as WOCBP who are unwilling or unable to use highly effective contraception method(s) for the duration of the study:
    a. Combined (estrogen and progestogen containing) hormonal contraception associated with inhibition of ovulation
    b. Progestogen-only hormonal contraception
    c. Intrauterine device
    d. Intrauterine hormone-releasing system

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e. Bilateral tubal occlusion

f. Vasectomized partner is a highly effective birth control method provided that partner is the sole sexual partner of the WOCBP trial participant and that the vasectomised partner has received medical assessment of the surgical success.

25. Any prior Grade ≥3 immune-related adverse event (irAE) while receiving any previous checkpoint inhibitor or immunotherapy agent, or any unresolved irAE >Grade 1 except for endocrine AEs managed with replacement therapy.
26. Developed immune-related toxicity while on prior checkpoint inhibitor therapy that has not yet returned to Grade 1 or better.
27. History of any drug allergies or significant adverse reactions to any of the components of PDS0101

8.3 Rescreening

Rescreening will be permitted if the initial screening is unable to be completed per protocol (including allowed visit/procedure windows). Prior to rescreening, the study center should notify the sponsor and/or the sponsor's designee to identify which rescreening procedures needs to be completed and obtain approval.

8.4 Study Withdrawal, Removal, and Replacement of Subjects

8.4.1 Criteria for Subject Discontinuation from Treatment

The potential direct benefit to the subject is low if the subject's tumor does not express HPV16 and whether PDS0101-induced HPV16-specific responses will have any cross reactivity to non-HPV16 HNSCC is unknown.

Discontinuation of study combination treatment does not represent withdrawal from the study. Subjects can receive up to 35 treatments (approximately 2 years) with pembrolizumab. During that time, subjects may continue until disease progression, unacceptable toxicity, withdrawal of consent, physician's decision to stop therapy for the subject, or Sponsor's decision to terminate the study.

Subjects who are discontinued from further study combination treatment after receiving at least 1 dose of pembrolizumab + PDS0101 will continue the monotherapy treatment with pembrolizumab. If it is known at the time of treatment discontinuation that the subject cannot tolerate the monotherapy or the HNSCC has progressed, the subject will complete the safety follow-up visit and be withdrawn from the study.

Discontinuation of study combination treatment may be considered for subjects:

- who have attained a confirmed CR that has been treated for at least 8 Cycles (24 weeks) with pembrolizumab and had at least 2 treatments with pembrolizumab beyond the date when the initial CR was declared.

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- Experienced a treatment delay: delay is greater than 6 weeks (+3 days) from the previous treatment, day 1 (D1)

The reason and date for treatment discontinuation is to be collected in the case report form (CRF) for all subjects. If the reason for treatment discontinuation was because of a safety issue, the investigator must notify the Drug Safety Unit within 24 hours of discontinuation of the treatment (Section 12.6.1).

8.4.2 Subject Withdrawal from the Study and Lost to Follow-up

Every effort should be made to obtain information on subjects who withdraw from the study.

A subject will be withdrawn from the study and receive no further treatment for the following reasons:

Medical/Safety

- Subject suffers an AE that, in the judgment of the investigator or medical monitor, presents an unacceptable consequence or risk to the subject, or develops an intercurrent illness or complication that is not consistent with the protocol requirements or for which treatment would be not in compliance with the protocol.

  Note: Subjects that experience a DLT (related to PDS0101) can continue the study with a dose reduction of PDS0101 or be discontinued (see Section 12.8.2).
- Pregnancy (see Section 12.6.10).
- Unable to receive first dose of study combination treatment within the study parameters.

Administrative

- Noncompliance: Any subject determined to be noncompliant by the investigator will not receive further treatments.
- Lost to follow-up (a minimum 3 attempts must be made and documented to find subject, at least 1 attempt should be a certified letter).
- Subject's voluntary withdrawal (consent withdrawal) not related to an AE
- Subject's voluntary withdrawal based on occurrence of AEs that are not of a type or severity that would require discontinuation or risk of recurrence of AEs with future treatment.
- Subject withdraws their authorization to use the data collected on the trial.
- vaccinations is to be considered a discontinuation because of an AE.
- Enrollment in any other clinical studies during the study or participation in any other type of medical research judged not to be scientifically or medically compatible with this study.
- Subject that was discontinued from treatment and cannot continue the subsequent treatment with pembrolizumab until the safety follow-up visit.
- Subject has taken prohibited concomitant medications while on study.

- Investigator decision not related to an AE: The investigator may withdraw a subject, if he/she determines it is in the best interest of the subject, with approval of the medical monitor and Sponsor.
- Study is terminated by the Sponsor.

Subjects who withdraw from the study early may receive appropriate therapy as determined by the investigator.

For subjects who are found to have been entered into the study in violation of any inclusion/exclusion criterion or who meet an exclusion criterion during participation in the study, the investigator must consult with the medical monitor regarding whether the subject should be withdrawn.

If a subject withdraws from the study prior to study completion, all safety follow-up visit procedures should be performed at the time of termination. Any AEs present at the time of study withdrawal should be followed in accordance with the safety requirements outlined in Section 11.1.

The investigator will document the reason(s) for study withdrawal of each subject in the CRF. All data gathered on the subject prior to withdrawal will be made available to the Sponsor.

Events listed above should also be reported to institutional review board (IRB), as applicable.

8.4.3 Subject Replacement Policy

Subjects will be replaced if:

- They failed to complete the screening period and cannot be re-screened (Section 7.1).
- They did not meet the criteria for discontinuation (Section 8.4.2).
- They do not have central laboratory confirmed HPV16+ HNSCC and
    - CPI naïve subjects do not have PD-L1 expression with a CPS ≥1 by the Dako PD-L1 IHC 22C3 PharmDx assay.

In order to collect the appropriate safety data and fulfill the needs of the statistical methodology for the study subjects will be considered withdrawn (per Section 8.4.2).

8.5 Site Replacement and Discontinuation Policy for Sites

The Sponsor has the right to discontinue a site at any time. Reasons may include, but are not limited to, the following:

- Poor protocol adherence.
- Inaccurate or incomplete data recording.
- Noncompliance with the International Council on Harmonisation (ICH) guideline for good clinical practice (GCP) or local regulations.

Replacement policy for sites:

- The Sponsor may decide to replace a site because of absence of or excessively slow recruitment.

Stopping Rules (Criteria for Pausing Study)

- The Sponsor has the right to terminate the study at any time.
- The IRB may terminate at a site.
- The DMC may terminate the study.
- Safety events/DLTs may lead to study termination (Section 12.8.2).

If the study is suspended, further enrollment and immediate treatment will be temporarily halted until a thorough investigation has been conducted by the Sponsor medical monitor and DMC. A suspended study will resume upon written notification from the DMC and/or medical monitor and determine appropriate dosage of subsequent subjects. Investigators will notify their IRBs in writing of the DMC recommendations.

If the study is resumed, subjects whose scheduled visits and study treatments were halted should resume visits and study combination treatments as close as possible to the pre-specified study schedule. Visits outside the protocol-specified windows are allowed under these circumstances and will not be considered protocol deviations.

Any subject who experiences a Grade 2 allergic reaction after PDS0101 Vaccinations 1 through 4 will be treated and allowed to continue the study at the discretion of the PI and study medical monitor.

Guidelines for management of pembrolizumab toxicity are outlined in Table 9 (see also Section 12.10.1).

9 TREATMENTS

9.1 Details of Study Treatments

The combination treatment of pembrolizumab and PDS0101 to be used in this study are outlined below in Table 4.

Table 4 Study Treatments

Study Treatment Name	Dosage Formulation	Unit Dose Strength(s)	Dosage Level(s)	Route of Administration	Regimen/ Treatment Phase/ Vaccination Regimen	Sourcing
Pembrolizumab (MK-3475)	Solution for infusion	100 mg/vial	200 mg Q3W	IV infusion	Day 1 of each Cycle (3-week Cycles) up to 35 Cycles	Provided by PDS Biotechnology
PDS0101 (R-DOTAP)	Solution for subcutaneous injection	3.0 mg	3.0 mg	SC injection	Days 1, 22, 43, 64 and 232 (Cycles 1-4 and 12)	Provided by PDS Biotechnology
PDS0101 (HPVmix)	Solution for subcutaneous injection	2.7 mg	2.7 mg	SC injection	Days 1, 22, 43, 64 and 232 (Cycles 1-4 and 12)	Provided by PDS Biotechnology

Abbreviations: HPV16 = human papillomavirus-16; HPVmix = HPV16 lipidated peptide suspension; IV = intravenous administration; Q3W = dosing every 3 weeks; SC = subcutaneous administration.

Study treatment begins at Day 1 of the first combination treatment administration, after completion of all assessments.

Pembrolizumab will be administered as a dose of 200 mg using a 30-minute IV infusion. Sites should make every effort to target infusion timing to be as close to 30 minutes as possible.

Each subject will receive 200 mg of pembrolizumab administered by IV infusion, as well as PDS0101 (2.7 mg HPV16 E6 and E7 peptides mixed with 3.0 mg R-DOTAP) administered by SC injection on the same day. Pembrolizumab will be administered first; PDS0101 will be administered no sooner than 30 minutes and no later than 60 minutes after the completion of the pembrolizumab IV infusion. Refer to the Pembrolizumab Pharmacy Manual and the PDS0101 Pharmacy Manual for more information.

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

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Pembrolizumab may be interrupted for situations other than treatment-related AEs, such as medical or surgical events and/or unforeseen circumstances not related to study intervention. However, study intervention is to be restarted: within 3 weeks or 21 days (for Q3W dosing)/6 weeks or 42 days (for Q6W dosing) of the originally scheduled dose; and within 42 days (for Q3W dosing)/84 days (for Q6W dosing) of the previously administered dose, unless otherwise discussed with the Sponsor. The reason for interruption is to be documented in the patient's study record.

9.2 Formulation

PDS0101 Active Vials:

Versamune:

- Vial #1 - ImmunoMAPK-R-DOTAP 6.0 mg/mL in 1.0mL in 280 mM sucrose/water sterile suspension.
- Vial #2: HPVmix – 5.4 mg/ml total peptide as micellar particles in 0.6 mL 20% DMSO in 280 mM sucrose/water for injection.

Pembrolizumab will be provided as shown below.

Product Name and Potency	Dosage Form
Pembrolizumab 200 mg IV Q3W	Pembrolizumab 100 mg/ 4 mL solution in single dose vial. Administer 2 vials (200 mg) with each IV infusion Q3W

Abbreviations: IV = intravenous administrations; Q3W = dosing every 3 weeks.

Vials will be labeled and packaged in boxes. Text on the vial labels clearly identify all products.

9.3 PDS0101 Labeling and Packaging

PDS0101 pembrolizumab will be supplied by PDS Biotechnology Corporation and labeled appropriately as investigational material. Labels will include the Sponsor's name, address', the investigational medicinal product (IMP) name, the protocol number, dosage form and strength (where applicable), the quantity of IMP per container, kit number, lot number, expiry date (where applicable), dosing instructions, storage conditions, the quantity of IMP contained and required caution statements and/or regulatory statements as applicable.

The R-DOTAP (Versamune) will be supplied by PDS Biotechnology Corporation in a single-use vial in single count cartons. R-DOTAP is a slightly turbid suspension and will be supplied in 5-mL vials.

The HPVmix will be supplied by PDS Biotechnology Corporation in a single-use vial in a single count carton. HPVmix is a slightly turbid suspension and will be supplied in 3-mL vials.

The pembrolizumab (MK-3475) will be supplied by PDS Biotechnology Corporation in a carton containing 2 x Type I glass vial containing 100 mg/4 mL of pembrolizumab (MK-3475)

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All supplies will be packaged, labeled, and released in accordance with both Good Manufacturing Practice (GMP) and GCP.

9.4 Shipping and Storage

The ImmunoMAPK-R-DOTAP and HPV16 peptides active 2-vial kits will be shipped directly from the distribution depot to each individual study site. The kits will be shipped frozen under dry ice conditions at a temperature ≤ -70°C with a temperature recorder. The R-DOTAP and HPV16mix must be stored at ≤ -70°C in a temperature-controlled freezer in a secure area from receipt of shipment to completion of the study. Pembrolizumab is to be shipped and stored refrigerated at 4°C to 8°C.

For additional information on the storage of PDS0101 or Pembrolizumab, refer to the Study Pharmacy Manual [containing both manuals].

Freezer and refrigerator temperature logs must be maintained at the study center and temperatures must be recorded and monitored regularly and all temperature excursions reported to the Sponsor.

9.5 Preparation and Dispensing

It is the responsibility of the Investigator to ensure that the pembrolizumab and PDS0101 is only dispensed to study subjects. It must be dispensed only from the official study site by authorized personnel according to local regulations.

The site must identify trained staff to dispense the IMP. Duties will include the receipt, storage, preparation, and maintenance of records for the IMP. These individuals should have experience in handling of IMP. This role should preferably be given to a pharmacist; however, an MD, DO, physician's assistant, nurse practitioner, RN or other individuals licensed by the relevant local authorities to dispense drug may be assigned these duties. Any deviation from this procedure must be approved by the Sponsor or its designee.

For additional information on preparation and dispensing of PDS0101 or pembrolizumab, refer to the Study Pharmacy Manual.

9.6 Administration of Pembrolizumab

Pembrolizumab will may be administered using IV infusion on Day 1 of each 3-week treatment Cycle (no more than 29 days from obtaining the informed consent) and after all assessments have been completed as detailed in Table 5.

The IV infusion will be about 30 minutes with a window between -5 minutes and +10 minutes permitted. Dose modification of pembrolizumab is not allowed.

On days when pembrolizumab and PDS0101 (study combination treatment) are dosed on the same day, the pembrolizumab infusion should be administered first followed by injection of PDS0101 30 to 60 minutes after the completion of the pembrolizumab infusion.

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Refer to Study Pharmacy Manual - Appendix 5: Pembrolizumab Pharmacy Manual for details on dosing and method of administration.

9.7 Administration of PDS0101

The first day of study combination treatment is considered Day 1 Cycle 1.

Administration must be performed by a medically-qualified site study staff.

Subjects will be administered a divided dose of 1.0 mL as 2 injections (Injection A and Injection B) of 0.5 mL SC into the upper anterior arm at each dosing time point.

Note: The first vaccine should be administered in the non-dominant arm. Each subsequent vaccination should be alternated.

PDS0101 (3.0 mg R-DOTAP and 2.7 mg HPV16 mix) will be injected on Week 0 Day 1 (Cycle 1), Week 3 Day 22 ± 3 days (Cycle 2), Week 6 Day 43 ± 3 days (Cycle 3), Week 9 Day 64 ± 3 days (Cycle 4), and Week 33 Day 232 ± 3 days (Cycle 12).

For detailed information on PDS0101 dose preparation and administration, refer to Pharmacy Manual.

9.8 Accountability

PDS Biotechnology Corporation will review the process, roles, and responsibilities for drug accountability including IMP return, disposal, and/or destruction with the investigator and relevant study personnel. Refer to the Pharmacy Manual for more information.

9.9 Investigational Product Compliance

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

9.10 Dosage Modification

Dose modification of PDS0101 administration is allowed in subjects that experience a DLT designated as possibly/probably/definitely related to PDS0101 (see Section 12.10.2).

9.11 Prior and Concomitant Therapy

Medications or vaccinations specifically prohibited in the exclusion criteria (Section 8.2 and 9.11) are not allowed during the ongoing study. If there is a clinical indication for any medication or vaccination specifically prohibited during the study, discontinuation from study therapy or vaccination may be required. The PI should discuss any questions regarding this with the Sponsor medical monitor. The final decision on any supportive therapy or vaccination rests with the PI and/or the subject's primary physician. However, the decision to continue the subject on study therapy or vaccination schedule requires the mutual agreement of the PI, the Sponsor, and the subject.

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9.11.1 Acceptable Concomitant Medications

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

All concomitant medications received within 30 days before the first dose of study combination treatment and 30 days after the last dose of study treatment should be recorded. Concomitant medications administered after 30 days after the last dose of study treatment should be recorded for SAEs and events of clinical interest (ECIs) as defined in Section 12.6.3 and Section 12.6.4.

9.11.2 Prohibited Concomitant Medications

Subjects are prohibited from receiving the following therapies or vaccinations during the course of the study:

- Antineoplastic systemic chemotherapy or biological therapy.
- Immunotherapy not specified in this protocol.
- Chemotherapy not specified in this protocol.
- Investigational agents other than PDS0101.
- Radiation therapy.
    - **Note:** Radiation therapy to a symptomatic solitary lesion or to the brain may be considered on an exceptional case-by-case basis after consultation with the Sponsor. The subject must have clear measurable disease outside the radiated field. Administration of palliative radiation therapy will be considered clinical progression for purposes of determining PFS.

Live vaccines within 30 days prior to the first dose of study combination treatment and while participating in the study. Examples of live vaccines include, but are not limited to, the following: measles, mumps, rubella, chicken pox, yellow fever, rabies, BCG, and typhoid (oral). Seasonal influenza vaccines for injection are generally killed-virus vaccines and are allowed. However, intranasal influenza vaccines (eg, FluMist® Quadrivalent) are live attenuated vaccines and are not allowed. See Section 8.2 (Exclusion Criteria) for the COVID-19 vaccine.

- Systemic glucocorticoids for any purpose other than to modulate symptoms from an event of clinical interest of suspected immunologic etiology. The use of physiologic doses of corticosteroids may be approved after consultation with the Sponsor.
  Note: Inhaled steroids are allowed for management of asthma as are topical steroids.

Systemic steroids and immunosuppressive drugs are prohibited within 30 days prior to the first dose of study combination treatment and throughout the duration of the treatment and follow-up- phases. See Section 8.2 (Exclusion Criteria) for the definition of systemic steroids.

Immunotherapy/immunomodulatory agents (eg, IFNs, tumor necrosis factor, interleukins, immunoglobulins or other biological response modifiers [GM-CSF]) are prohibited within 6 weeks before first dose of study combination treatment and for the duration of the study up until the safety follow-up visit. See Section 8.2 (Exclusion Criteria).

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

All concomitant medications received with 30 days prior to the first dose of study combination treatment (baseline) and up to 30 days after the last dose of study treatment should be recorded as concomitant medications (including any herbal and nutrition supplements). Concomitant medications administered 30 days after the last dose of study treatment should be recorded as part of the safety follow-up and ECIs, as defined in Section 12.6.4.

The exclusion criteria (Section 8.2) describe other medications that are prohibited in this study.

10 STUDY PROCEDURES

Table 5 outlines the timing of procedures and assessments to be performed throughout the study. Time points are further summarized in Table 6. See Sections 11 and 11.1 for additional details regarding efficacy assessments and safety assessments, respectively. Section 12.5 specifies laboratory assessment samples to be obtained.

For each subject, this study will include a pre-screening to allow human papilloma virus (HPV) and PD-L1 characterization.

10.1 Screening Phase (Day-28 to Day-1)

The purpose of the screening phase is to obtain informed consent and establish protocol eligibility. The screening phase will end upon confirmation of study eligibility. All screening procedures must be completed within the 28 days (-1 day) prior to Day 1/first dose.

The following will be assessed/collected and entered into the CRF:

- Informed consent will be obtained from the subject or the subject's legal representative (if applicable) prior to any study-specific procedure being performed. Once the informed consent form (ICF) is signed, enter the specific subject number into the EDC system.
- Demographic information, including birth date/year, sex, and ethnicity.
- Documented medical history of all significant events, including all prior surgeries and procedures with at a minimum month and year noted. Should have a completed history for the last 5 years and all HNSCC procedures/treatments.
- Prior/concomitant medications: Medications taken within 30 days prior to the first dose of study combination treatment must be recorded in the CRF (including herbal and nutrition supplements). There must be documentation that no prohibited medications have been taken within the 6 weeks prior to the study for immunotherapy and immunomodulatory drugs.
- Complete physical examination (including height, weight, cardiorespiratory, abdominal, basic neurological, and skin examination [eg rashes, discoloration]).
- Brain MRI
- Vital signs (blood pressure, pulse, respiration rate, and temperature) will be taken with the subjected seated.
- Blood samples for chemistry, hematology, and coagulation profile will be sent to the local laboratory.
- Blood samples for HIV testing will be sent to the local laboratory.
- Pregnancy test (urine or serum) will be sent to the local laboratory.
- Thyroid function test will be done at the local laboratory.
- HPV positivity can be determined using a local high-risk HPV test for screening purposes. HPV samples must be sent to a central laboratory (see Laboratory Manual) to confirm the HPV16 positivity. The investigator should contact the Sponsor medical monitor or designee if the local laboratory and the central laboratory are discrepant.

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Subjects may start Cycle 1 Day 1 if the local laboratory result is positive, and the central laboratory result is pending.

- Imaging assessment will be assessed locally and by the central imaging vendor for eligibility (see Site Imaging Manual). This must be done within 28 days of first study combination treatment.
- Biomarker PD-L1: Characterization of tumor PD-L1 expression using the FDA-approved PD-L1 IHC 22C3 PharmDx assay. Local laboratory results may be used for screening, but central laboratory results are available if local testing is not possible. The investigator should contact the Sponsor medical monitor or designee if there is a different result from the local laboratory versus the central laboratory. Subject can start Cycle 1 Day 1 without the central laboratory result.
- ECOG PS (0 or 1).

10.1.1 Treatment Phase Visits (Cycles 1-35, Weeks 0-102, Days 1-715) and Cycle 1 (Week 0, Day 1)

Prior to enrollment in the study, the following will be assessed/collected:

- Review of all laboratory results obtained during the screening phase. Week 0, Day 1 laboratory tests should be done only if they were conducted more than 10 days before first dose to determine if entry criteria are still met.
- Assess AEs and concomitant medications (including herbal and nutrition supplements).
- A urine pregnancy test within 72 hours of first study combination treatment with negative results.
- Targeted physical examination (including a general assessment, cardiac, pulmonary, and previous injection-site assessments.)
- Review local hematology and chemistry laboratory values to confirm eligibility prior to dosing the subject.
- A baseline 12-lead electrocardiogram (ECG) will be collected for each eligible subject for safety monitoring.
- A baseline 25-hydroxy vitamin D test.
- Blood samples will be obtained to send to the Central Laboratory (see Lab Manual for instructions):
    - HLA typing
    - Immune monitoring

Confirm study eligibility (inclusion/exclusion criteria) and obtain eligibility approval from the Sponsor:

Once the Sponsor has approved eligibility perform the following:

- Vital signs will be measured with the subject in the seated position 15 minutes (±5 minutes) prior to study combination treatment.

- Administer pembrolizumab as an IV infusion over 30 minutes.
- Administer Vaccine #1 (A and B) per instructions in the Pharmacy Manual. Vaccine must be administered by a medically-qualified site study staff within the defined timeframe. (See Section 9.7 and Section 9.8).
- Vital signs (blood pressure, pulse, respiration rate, temperature) will be measured with the subject seated at the following time points: 0, 15, 30, and 60 minutes post-study combination treatment. A ± 5-minute window is allowed.
- 12-lead ECG post-study combination treatment prior to the subject leaving the institution/clinic.
- Thyroid function test done locally.
- Review subject vaccine diary instructions with subject and provide the injection-site reaction gauge (see Section 12.13).
- Schedule and conduct post-vaccination contact (phone call or email) 24 to 72 hours after the study combination treatment to evaluate AEs and injection-site reactions (see Section 12.12).

Cycle 2 (Week 3, Day 22)

The following will be assessed/performed during this visit:

- Review subject diary for potential AEs/injection-site reactions, new medications, or changes in current medications.
- Targeted physical examination (including a general assessment, cardiac, pulmonary, and previous injection-site assessments.)
- Assess AEs and concomitant medications (including herbal and nutrition supplements).
- Urine pregnancy test (local lab). Results must be available prior to study combination treatment. Pregnancy test (urine or serum) will be sent to the local laboratory.
- Clinical laboratory tests (hematology, chemistry, urinalysis) done locally.
- Vital signs will be measured with the subject in the seated position within 20 minutes prior to study combination treatment.
- Administer pembrolizumab as an IV infusion over 30 minutes.
- Administer Vaccine #2 (A and B) per instructions in the Pharmacy Manual. Vaccine must be administered by a medically-qualified site study staff within defined timeframe (see Section 9.7 and Section 9.8).
- Vital signs (blood pressure, pulse, respiration rate, and temperature) will be measured with the subject seated at the following time points: 0 and 15 minutes post-study combination treatment. A ± 5-minute window is allowed.
- 12-lead ECG post-study combination treatment prior to the subject leaving the institution/clinic.
- Review subject vaccine diary instructions with subject (see Section 12.13).
- Schedule and conduct post-vaccination contact (phone call or email) 24 to 72 hours after the vaccination to evaluate AEs and injection-site reactions (see Section 12.12).

Cycle 3 (Week 6, Day 43)

The following will be assessed/performed during this visit:

- Review subject vaccine diary for potential AEs/injection-site reactions, new medications, or changes in current medications.
- Assess AEs and concomitant medications (including herbal and nutrition supplements).
- Targeted physical examination (including a general assessment, cardiac, pulmonary, and previous injection-site assessments.)
- Urine pregnancy test (local lab). Results must be available prior to study combination treatment.
- Local clinical laboratory tests (hematology, chemistry, urinalysis).
- Vital signs will be measured with the subject in the seated position within 20minutes prior to study combination treatment.
- Administer pembrolizumab as an IV infusion over 30 minutes.
- Administer Vaccine #3 (A and B) per instructions in the Pharmacy Manual. Vaccine must be administered by a medically-qualified site study staff within defined timeframe (see Section 9.7 and Section 9.8).
- Vital signs (blood pressure, pulse, respiration rate, temperature) will be measured with the subject seated at the following time points: 0, and 15 minutes post-study combination treatment. A ± 5-minute window is allowed.
- 12-lead ECG post-study combination treatment prior to the subject leaving the institution/clinic.
- Thyroid function test done locally.
- Review subject vaccine diary instructions with subject (see Section 12.13)
- Schedule and conduct post-vaccination contact (phone call or email) 24 to 72 hours after the study combination treatment to evaluate AEs and injection-site reactions (see Section 12.12).

Cycle 4 (Week 9, Day 64)

The following will be assessed/performed during this visit:

- Review subject diary for potential AEs/injection-site reactions, new medications, or changes in current medications.
- Targeted physical examination (including a general assessment, cardiac, pulmonary, and previous injection-site assessments.)
- Assess AEs and concomitant medications (including herbal and nutrition supplements).
- Urine pregnancy test (local lab). Results must be available prior to study combination treatment.
- Local clinical laboratory tests (hematology, chemistry, urinalysis).
- Imaging assessment.
- Vital signs will be measured with the subject in the seated position within 20 minutes prior to study combination treatment.

- Administer pembrolizumab as an IV infusion over 30 minutes.
- Administer Vaccine #4 (A and B) per instructions in the Pharmacy Manual. Vaccine must be administered by a medically-qualified site study staff within defined timeframe (see Section 9.7 and Section 9.8).
- Vital signs (blood pressure, pulse, respiration rate, and temperature) will be measured with the subject seated at the following time points: 0, and 15 minutes post-study combination treatment. A ± 5-minute window is allowed.
- 12-lead ECG post-study combination treatment prior to the subject leaving the institution/clinic.
- Review subject vaccine diary instructions with subject (see Section 12.13)
- Schedule and conduct post-vaccination contact (phone call or email) 24 to 72 hours after the study combination treatment to evaluate AEs and injection-site reactions (see Section 12.12).

Cycles 5 – 11 (Week 12, Day 85 – Week 30, Day 211)

The following will be assessed/performed during this visit:

- Targeted physical examination (including a general assessment, cardiac, pulmonary, and previous injection-site assessments).
- Assess AEs and concomitant medications (including herbal and nutrition supplements).
- Urine pregnancy test (local laboratory).
- Local clinical laboratory tests (hematology, chemistry, urinalysis).
- Local thyroid function test at Cycles 5, 7, 9, and 11.
- Imaging assessment at Cycles 7 and 10.
- Vital signs will be measured with the subject in the seated position within 20 minutes prior to treatment.
- Administer pembrolizumab as an IV infusion over 30 minutes.
- Pembrolizumab will continue to be administered via IV infusion for each Cycle (Q3W).
- Cycle 5 (Week 12): Blood sampling for immune monitoring, review subject vaccine diary for potential AEs/injection-site reactions, new medications, or changes in current medications.

Cycle 12 (Week 33, Day 232)

The following will be assessed/performed during this visit:

- Targeted physical examination (including a general assessment, cardiac, pulmonary, and previous injection-site assessments.)
- Urine pregnancy test (local laboratory). Results must be available prior to study combination treatment.
- Local clinical laboratory tests (hematology, chemistry, urinalysis.)
- Assess AEs and concomitant medications (including herbal and nutrition supplements).

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- Vital signs will be measured with the subject in the seated position within 20 minutes prior to study combination treatment.
- Administer pembrolizumab as an IV infusion over 30 minutes.
- Administer Vaccine #5 (A and B) per instructions in the Pharmacy Manual. Vaccine must be administered by a medically-qualified site study staff within defined timeframe (see Section 9.7 and Section 9.8).
- Vital signs (blood pressure, pulse, respiration rate, temperature) will be measured with the subject seated at the following time points: 0 and 15 minutes post-study combination treatment A ± 5-minute window is allowed.
- 12-lead ECG post-study combination treatment prior to the subject leaving the institution/clinic.
- Review subject vaccine diary instructions with subject (see Section 12.13).
- Schedule and conduct post-vaccination contact (phone call or email) 24-72 hours after the study combination treatment to evaluate AEs and injection-site reactions (see Section 12.12).

Cycle 13 (Week 36 Day 253)

The following will be assessed/performed during this visit:

- Review subject vaccine diary for potential AEs/injection-site reactions, new medications, or changes in current medications.
- Targeted physical examination (including a general assessment, cardiac, pulmonary, and previous injection-site assessments).
- Assess AEs and concomitant medications (including herbal and nutrition supplements).
- Urine pregnancy test (local laboratory).
- Local clinical laboratory tests (hematology, chemistry, urinalysis).
- Local thyroid function test
- Imaging assessment.
- Blood sample for immune monitoring.
- Vital signs will be measured with the subject in the seated position within 20 minutes prior to treatment.
- Administer pembrolizumab IV infusion over 30 minutes.

Cycles 14 – 35 (Week 39 – Week 102, Day 274 - 715)

- Targeted physical examination.
- Assess AEs and concomitant medications (including herbal and nutrition supplements).
- Urine pregnancy test (local lab).
- Local clinical laboratory tests (hematology, chemistry, urinalysis).
- Local thyroid function test at Cycles 15, 17, 19, 21, 23, 25, 27, 29, 31, 33, 35.
- Imaging assessment at Cycles 16, 19, 23, 27, 31, and 35.
- Vital signs will be measured with the subject in the seated position within 20 minutes prior to treatment

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- Administer pembrolizumab as an IV infusion over 30 minutes.
- Pembrolizumab will continue to be administered via IV infusion for each Cycle (Q3W).

10.2 Post Treatment Phase

Subjects may discontinue treatment at any time for any reason or be dropped from treatment at the discretion of the investigator should any untoward effect occur. In addition, a subject may be discontinued from treatment by the investigator or the Sponsor if treatment is inappropriate, the trial plan is violated, or for administrative and/or other safety reasons. See Section 8.4 for description of reasons of treatment discontinuation.

After the end of treatment, each subject will be followed for 30 days for AE monitoring and serious adverse events will be collected for 90 days after the end of treatment as described in Section 12.6.11 and Section 12.6.12.

10.2.1 Safety Follow-up Visit (30 Days After Final Cycle)

The following will be assessed/performed during this visit:

- Assess AEs.
- Targeted physical examination (including weight).
- Vital signs.

The following are to be performed, as needed, for follow-up on treatment-emergent conditions identified at the final on-treatment visit:

- Local clinical laboratory tests (hematology, chemistry, urinalysis).
- Local thyroid function test (if clinically indicated).
- If imaging assessments are due or near due (within 2 weeks) at the time of discontinuation or withdrawal.

10.2.2 Survival Follow-up

Once a subject discontinues study drug treatment, the subject enters the Survival Follow-Up Phase and should be contacted by telephone approximately **every 12 weeks** to assess for survival status until death, withdrawal of consent, or the end of the study, whichever occurs first. In addition to survival status confirmation, the following may also apply:

- If a subject discontinued the study drug treatment prior to disease progression, the status of disease progression will also be followed during the survival follow-up phase. If disease progressed the date of disease progression confirmation will be collected
- If a subject discontinued the study drug treatment and started new anti-cancer treatment, the name and the date of this new anti-cancer treatment will be collected

The Sponsor may request survival status to be assessed at additional time points during the course of the study. For example, these additional assessments may be requested prior to an external DMC safety review, efficacy interim analysis, and/or final analysis.
All subjects who do not have a death reported will be contacted at the time of the Sponsor's request.

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10.2.3.1 Survival Status

To ensure current and complete survival data is available at the time of database locks, updated survival status may be requested during the course of the study by the Sponsor. For example, updated survival status may be requested prior to but not limited to an external Data Monitoring Committee review, interim and/or final analysis. Upon Sponsor notification, all subjects who do not/will not have a scheduled study visit or study contact during the sponsor defined time period will be contacted for their survival status (excluding subjects that have previously recorded a death event in the collection tool).

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Table 5. Schedule of Assessments

Phase	Pre-screening	Screening	Treatment									Safety Follow-up[a]	LT Follow-Up
Cycle			**1[b]**	**2**	**3**	**4**	**5**	**6-11**	**12**	**13**	**14-35**		
Week, Day, and Visit Window	**Week –6 to Week -4**	**Days -28 to -1**	**Week 0 Day 1**	**Week 3 Day 22 ±3 days**	**Week 6 Day 43 ±3 days**	**Week 9 Day 64 ±3 days**	**Week 12 Day 85 ±3 days**	**Week 15-30 Days 106-211 ±3 days**	**Week 33 Day 232 ±3 days**	**Week 36 Day 253 ±3 days**	**Week 39-102 Days 274-715**	**Week 106 Day 745**	
Initial Eligibility Procedures													
Informed consent	X	X											
Demographic information		X											
History of histologically-confirmed recurrent or metastatic disease and baseline imaging[c]	**X**	X											
Biomarker PD-L1 (Dako PD-L1 IHC 22C3 PharmDx Assay)[d]	**X**												
Blood sample for HIV testing		X											
HPV positivity and genotyping[e]	**X**												
ECOG PS (0 or 1)		X											
Inclusion/exclusion criteria			X										
Brain MRI or Scan[f]		X											
Medical history[g]		X											
Procedure or Observation													
Complete physical examination[h]		X	X	X	X	X	X	X	X	X	X	X	

Phase	**Pre-screening**	**Screening**	**Treatment**									**Safety Follow-up[a]**	**LT Follow-Up**
Cycle			**1[b]**	**2**	**3**	**4**	**5**	**6-11**	**12**	**13**	**14-35**		
Vital signs		X	X	X	X	X	X	X	X	X	X	X	
ECG			X	X	X	X			X				
Prior and concomitant medications[i]		X	X	X	X	X	X	X	X	X	X		
Clinical laboratory tests (hematology, chemistry, urinalysis)[j]		X	X[j]	X	X	X	X	X	X	X	X		
25-Hydroxy vitamin D test			X										
Urine pregnancy test[k]		X	X	X	X	X	X	X	X	X	X		
Blood sample for immuno- monitoring[l]			X				X			X			
Blood sample for HLA typing			X										
Pembrolizumab administration[m]			**X**	**X**	**X**	**X**	**X**	**X**	**X**	**X**	**X**		
Study vaccine injection[n]			**X**	**X**	**X**	**X**			**X**				
AE monitoring[o]			X	X	X	X	X	X	X	X	X	X	
Post-vaccination Contact[p]			X	X	X	X			X				
Dispense subject vaccine diary instructions[q,r]			X	X	X	X			X				
Review subject vaccine				X	X	X	X			X			
Thyroid function test[t]		X	X		X		X	X		X	X		
Imaging assessment[u]						X		X		X	X		
Survival Follow-up													X[v]

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Abbreviations: AE = adverse event; ALT = alanine aminotransferase; AST = aspartate aminotransferase; BUN = blood urea nitrogen; C1D1 = Cycle 1, Day 1; CRF = case report form; CTL = cytotoxic T-lymphocyte; CRF = case report form; ECG = electrocardiogram; ECI = events of clinical interest; ECOG PS = Eastern Cooperative Oncology Group performance status; FFPE = formalin-fixed paraffin-embedded; FT3 = free triiodothyronine; FT4 = free thyroxine; HIV = human immunodeficiency virus; HLA = human leukocyte antigen; HNSCC = head and neck squamous cell carcinomas; HPV = human papillomavirus; MRI = magnetic resonance imaging; PD-L1 = programmed death-ligand 1; Q3W = dosing every 3 weeks; RECIST = Response Evaluation Criteria in Solid Tumors; SAE = serious adverse event; SC = subcutaneous; T3 = triiodothyronine; TSH = thyroid stimulating hormone; WOCBP = women of childbearing potential.

* Pre-screening Informed Consent is optional to perform baseline imaging, PD-L1 and HPV positivity. The period between prescreening and C1 Day 1 must not exceed 42 days.

a Subjects who withdraw early from the study will be requested to complete all safety follow-up procedures at the time of early termination.

b Treatment Day 1 begins at the time of administration of the first study combination treatments, after completion of all baseline assessments.

c Historical metastatic head and neck cancer diagnosis with confirmation of 1 target lesion per RECIST 1.1. Initial tumor imaging at screening must be performed within 28 days prior to the date of the first dose of study combination treatment.

d Biomarker analysis for PD-L1 will be done at baseline (pre-treatment). Obtain local laboratory results but confirmation by central laboratory. Call Sponsor medical monitor if different result local versus central. Subject may start Cycle 1, Day 1 without central result.

e A central laboratory will confirm HPV positivity for all subjects. A local high-risk HPV test result may be used for screening purposes, but a central laboratory result must be obtained for confirmation. The site will provide either an FFPE block or slides (see Laboratory Manual) from the primary tumor or cervical nodal metastases for the central laboratory within 28 days of initiating dosing.

f Subjects with known active brain metastases and/or carcinomatous meningitis must have a brain MRI or scan to prove they are radiologically stable without evidence of progression for at least 4 weeks prior to the first dose.

g Medical history of all significant events, including all prior surgeries and procedures with at a minimum month and year noted. Should have a completed history for the last 5 years and all HNSCC procedures/treatments.

h Complete physical examination at screening, including cardiorespiratory, abdominal, basic neurological, and skin examination (eg, rashes, discoloration); targeted physical examination at all other time points; blood pressure, pulse, respiration rate, temperature, weight (at screening and study discharge only) with subject seated, and height (at screening only) to be recorded.

i All concomitant medications, including herbal and nutritional supplements, must be recorded in the CRF. Evidence of absence of prohibited medication should be evident. See concomitant medications in Section 9.11.

j Hematology (hemoglobin, white blood cell count with differential, platelet count, red blood cell count, and hematocrit; screening [only] coagulation profile [active partial thromboplastin time, prothrombin time, and fibrinogen]), chemistry (alkaline phosphatase, ALT, AST, bilirubin [total], BUN, creatinine phosphokinase, creatinine, electrolytes [sodium, potassium, calcium, phosphorus, and magnesium], glucose [non-fasting], albumin, and total protein), and urinalysis (urine dipstick for protein, hematuria, glucose). If abnormal (presence of protein, hematuria, or glucose ≥1+), a microscopic examination will be performed. Week 0, Day 1 laboratory tests should be done only if they were conducted more than 10 days before first dose to determine if entry criteria are still met.

k A urine pregnancy test will be performed at screening for all female subjects defined as WOCBP and repeated within 72 hours prior to the first study combination treatment; negative test results are required before the first study combination treatment. Urine pregnancy tests will be performed prior to administration of all study combination treatments for all WOCBP; negative results must be documented prior to all treatments and continuation in the study.

l For measurement of CTL response (IsoPlexis Functional Proteomics) and CD4/CD8 lymphocyte subsets.

m Pembrolizumab will continue to be administered Q3W for up to 35 Cycles (approximately 102 weeks).

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n Administered as a divided dose by 2 SC injections of 0.5 mL each to the upper anterior arm of same arm. NOTE: The first vaccine should be administered in the non-dominant arm. Injection sites will be separated by a minimum of 6 centimeters. Each subject will receive a total of 5 vaccine doses in alternating anterior arms. Timing of Vaccinations 2 and 3 is based on date of Vaccination #1. **No vaccination should be administered fewer than 14 days after the previous vaccination.** Treatment must be 21 days (**±3** days) after actual prior vaccination date. PDS0101 administrations on Day 232 (Cycle 12), will be adjusted to coincide with the date of the closest pembrolizumab administration.

o AEs, including injection-site reactions: AEs are required to be captured through 30 days after cessation of study combination treatment. SAEs and ECIs are required to be captured through 90 days after cessation of study combination treatment (or to a minimum of 30 days post-treatment if the subject starts alternate anticancer therapy). Any and all pregnancies that occur within 120 days post-treatment are to be captured. Directed physical examination, as needed, as determined by Principal Investigator, based on occurrence of AEs.

p 24-72 hours post-vaccination contact: no sooner than 24 hours post-study combination treatment and no later than 72 hours post-study combination treatment.

q Subjects will also receive an injection-site reaction gauge (see Appendix 2) after the first vaccination to measure injection-site reactions throughout the study.

r Subjects are to record daily, for 7 days post-study combination treatment, the occurrence of any AEs, including injection-site reactions.

s The subject vaccine diary will be reviewed at the following study visit post-study combination treatment: Cycles 2, 3, 4, and 5 for Vaccines #1, #2, #3, and #4 respectively, and Cycle 13 for Vaccine 5.

t The thyroid panel should include Triiodothyronine (T3) or Free Triiodothyronine (FT3), Free thyroxine (FT4), and Thyroid stimulating hormone (TSH). Blood samples for TSH, T3 or FT3, and FT4 are to be collected at screening, every 6 weeks from C1D1 until Cycle 35 (at Cycles 3, 5, 7, 9, 11, 13, 15, 17, 19, 21, 23,25, 27, 29, 31, 33,and 35). Blood samples for TSH, T3 or FT3, and FT4 to be collected at 30-day post-treatment safety follow-up only if assessment is clinically indicated.

u Imaging will be performed at screening and again every 9 weeks ±7 days for the first year of treatment, and every 12 weeks ±7 days, thereafter, if the subject remains in the study (at Cycles 4, 7, 10, 13, 16, 19, 23, 27, 31, and 35). If a subject discontinues or withdraws from the study and is due for an imaging assessment, imaging will be performed at the 30-day safety follow-up visit (see also footnote c above for screening requirement).

v Once a subject experiences disease progression by site assessment or starts a new anticancer therapy, whichever occurs first, the subject enters the Survival Follow-Up Phase and should be contacted by telephone approximately every 12 weeks to assess for survival status until death, withdrawal of consent, or the end of the study, whichever occurs first.

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Table 6. PDS0101/Pembrolizumab (KEYTRUDA) HNSCC Protocol Study Time Point Summary

Study Cycle (Open-Label Pembrolizumab)	Study Day	Study Week	Study Month	Comments
Pre-screening	**-42 to -28**	**-6 to -4**		**Optional: Prescreening Days –42 to Day-28**
Study Screening			**-1 Month**	**Screening Phase: Days -28 to Day - 1**
				Treatment Phase: Days 1 to 715
1	**1#**	**0**	Month 0	**PDS0101 Vaccine #1**
2	**22^**	**3**		**PDS0101 Vaccine #2**
3	**43^**	**6**		**PDS0101 Vaccine #3**
4	**64^**	**9**		**PDS0101 Vaccine #4 / Imaging every 9 weeks**
5	85^	12		Blood sample for immune monitoring
6	106*	15		
7	127*	18		Imaging
8	148*	21		
9	169*	24		
10	190*	27		Imaging
11	211*	30		
12	**232^**	**33**		**PDS0101 Vaccine #5 (6 mos s/p #4)**
13	253^	36		Continued pembrolizumab q 3wks until disease progression Imaging Blood sample for immune monitoring
14	274*	39		
15	295*	42		
16	316*	45		Imaging
17	337*	48		
18	358*	51	Month 12	Imaging every 12 weeks
19	379*	54		
20	400*	57		Imaging
21	421*	60		
22	442*	63		
23	463*	66		
24	484*	69		Imaging
25	505*	72		
26	526*	75		

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Study Cycle (Open-Label Pembrolizumab)	Study Day	Study Week	Study Month	Comments
27	547*	78		
28	568*	81		Imaging
29	589*	84		
30	610*	87		
31	631*	90		
32	652*	93		Imaging
33	673*	96		
34	694*	99		
35	715*	102	~Month 23	Imaging
Study Safety Follow-Up	745*	106	~Month 24	**Safety F/U: Days 715 to 745**
				(30 days s/p Cycle 35)$^{\pm}$
Long Term Follow-Up				Long term F/U: (q12 weeks)

Abbreviations: F/U = follow-up; q3 = every 3 weeks; s/p = after Cycle 35.
Notes: Study Time Point Windows: #: + 0d; ^: + 3d *: + 7d ±: or 30 days s/p last Cycle at which disease progression is documented, whichever occurs first.

10.3 Informed Consent

The investigator will obtain a written informed consent from each subject participating in this study or his/her legal representative, after adequate explanation of the aims, methods, objectives, and potential hazards of the study. The investigator will explain to each subject that he/she is free to refuse to enter the study or to withdraw from it at any time for any reason. A consent form for documenting written informed consent will be used for the study. The subject must understand the requirements of the study and be given the appropriate time to consider the voluntary participation. A prescreening ICF can be utilized at the discretion of the investigational site to perform prescreening testing such as HPV16 testing, PD-L1 IHC 22C3 assay and imaging assessment to provide for an additional window of 14 days for screening procedures.

In the event that rescreening occurs, the individual is required to sign a new ICF and must be assigned a new identification number (see Section 8.3).

11 EFFICACY ASSESSMENTS

The Schedule of Assessments (Table 5) outlines the efficacy assessments to be performed throughout the study and their timing.

11.1 Primary Efficacy Endpoint

In both CPI naïve and CPI refractory subjects:

- The primary efficacy endpoint will be the BOR of confirmed CR or confirmed PR per RECIST 1.1 of the combination of pembrolizumab and PDS0101.

11.2 Key Secondary Endpoints

In both CPI naïve and CPI refractory subjects:

- PFS per RECIST 1.1 in all subjects at 12 and 24 months.
- Assess OS in all subjects.
- Assess safety and tolerability of pembrolizumab and PDS0101.

11.3 Tumor Imaging and RECIST 1.1 Assessment

The process for image collection and transmission to the central imaging vendor can be found in the Site Imaging Manual (SIM) (if applicable). Tumor imaging is strongly preferred to be performed by computed tomography (CT) magnetic resonance imaging (MRI) should only be used when a CT is contraindicated, but the same imaging technique should be used in a subject throughout the study. A CT scan is the more commonly used modality and is preferred for most subjects. An MRI can be utilized if clinically appropriate.

Imaging should include the chest, abdomen, and pelvis, as well as head and neck is required. Imaging via CT is required and PET alone is not an adequate substitute.

Local site study team reading (investigator assessment with site radiology reading) and confirmation from the central imaging vendor based on RECIST 1.1 will be used to determine subject eligibility. The central imaging vendor will receive all images at the time points specified in Table 5 from the sites. All scans should be submitted to the imaging labs for evaluation and should be submitted in a timely fashion.

Confirmation that the subject's imaging shows at least 1 lesion that is appropriate for selection as a target lesion per RECIST 1.1 is required prior to subject treatment.

All scheduled images for all study subjects from the sites will be submitted to the central imaging vendor. In addition, images (including via other modalities) that are obtained at an unscheduled time point to determine disease progression, as well as imaging obtained for other reasons, but captures radiologic progression based on investigator assessment, should also be submitted to the central imaging vendor.

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11.4 Initial Tumor Imaging

Initial tumor imaging at screening must be performed within 28 days prior to the date of the first dose of study combination treatment. The site study team must review screening images to confirm the subject has measurable disease per RECIST 1.1.

The screening images must be submitted to the central imaging vendor for confirmation of measurable disease per RECIST 1.1 for eligibility prior to treatment.

Scans performed as part of routine clinical management are acceptable for use as initial tumor imaging if they are of diagnostic quality and performed within 28 days prior to the date of first dose.

11.5 On-Study Tumor Imaging

The first on-study imaging assessment should be performed at 9 weeks (63 days ±7 days) from the first dose of study combination treatment. Subsequent tumor imaging should be performed every 9 weeks (63 day ±7 days) or more frequently if clinically indicated. After 1 year, subjects who remain on treatment will have imaging performed every 12 weeks (±7 days). Imaging should not be delayed in cycle starts or extension of pembrolizumab cycle intervals. Imaging should continue to be performed until disease progression is identified by the investigator or notified by the Sponsor, whichever occurs first. All supplemental imaging must be submitted to the central imaging vendor.

Per RECIST 1.1, PR or CR will be confirmed by a repeat tumor imaging assessment not less than 4 weeks from the date that the response was first documented. The tumor imaging for confirmation of response may be performed at the earliest 4 weeks after the first indication of response, or at the next scheduled scan (ie, 9 weeks later), whichever is clinically indicated.

Continue to perform imaging until whichever of the following occurs first:

- initial site-assessed disease progression is verified by the central imaging vendor
- start of new anticancer treatment
- withdrawal of consent
- death

11.6 Blood Samples for Immune Monitoring

Blood samples will be obtained for immune monitoring before the first study combination treatment (Cycle 1, Day 1; Cycle 5, Day 85; and Cycle 13, Day 253).

Detailed instructions will be provided in the Laboratory Manual.

11.7 Blood Samples for HLA Typing

A blood sample for HLA typing will be obtained at Cycle 1 (Day 1) before the first dose of pembrolizumab and PDS0101 study combination treatment.

Detailed instructions will be provided in the Laboratory Manual.

12 SAFETY ASSESSMENTS

All subjects receiving study treatment will be followed for safety through completion of Cycle 35 of pembrolizumab (Week 102, Day 715) and for 30 days following out to Week 106, Day 745. Safety assessments will be performed at each visit beginning at first dose of study combination treatment and continue through the safety follow-up visit, as specified in the Schedule of Assessments (Table 5).

The safety of pembrolizumab and PDS0101 will be measured and graded in accordance with the following the National Cancer Institute Common Terminology Criteria for Adverse Events (NCI-CTCAE), Version 5.0 issued by the US Department of Health and Human Services on 27 November 2017 as outlined in Table 8.

Assessment of DLTs resulting in dose modification for PDS0101 are outlined in Section 12.8 will utilize NCI-CTCAE v5.0, 27 November 2017.

12.1 Medical History

Medical history will be recorded at screening. Investigators should document the occurrence, signs, and symptoms of the subject's preexisting conditions, including all significant events (complete for last 5 years) and include all prior surgeries and procedures within the last 5 years with, at a minimum, month and year should be recorded. All procedures done for the HNSCC should be documented.

Illnesses first occurring or detected during the study and/or worsening of a concomitant illness during the study are to be documented as AEs on the eCRF in accordance with Section 12.6. All changes not present at baseline or described in the past medical history and identified as clinically noteworthy must be recorded as AEs.

Additionally, demographic data will be collected for all subjects and include birth date/year, sex, and ethnicity.

12.2 Vital Signs

The following vital signs will be assessed at the visits indicated in the Schedule of Assessments (Table 5): systolic blood pressure (SBP), diastolic blood pressure (DBP), pulse, respiratory rate, and temperature. Assessments should be taken with the subject in the seated position. Any clinically significant finding pre-treatment allocation should be recorded as medical history. A clinically significant finding post-treatment should be recorded as an AE.

12.3 Physical Examination

A medically-qualified investigator listed on FDA Form 1572 will conduct physical examinations at the visits indicated in the Schedule of Assessments (Table 5). Any clinically significant event post-treatment allocation should be recorded as an AE. Screening visit will consist of a full comprehensive physical examination, including cardiorespiratory, abdominal, basic neurological, and skin examination (eg, rashes, discoloration). Subsequent physical examinations will be

targeted and include a general assessment, cardiac, pulmonary, and previous injection-site assessments.

12.4 Electrocardiograms

A 12-lead, resting ECG will be obtained at the visits indicated in the Schedule of Assessments (Table 5).

The 12-lead ECG will be collected for every subject at baseline once eligibility is confirmed and after each study combination treatment (Cycles 1, 2, 3, 4, and 12) as part of the safety monitoring and to document the effect of the study combination treatment on corrected QT (QTc) intervals. Print-out should be retained until the end of the study. If the investigator is made aware of any significant abnormal effects, they should contact the Medical Monitor to discuss.

12.5 Laboratory Assessments

The following laboratory tests will be assessed at designated visits as detailed in the Schedule of Assessments (Table 5).

- Chemistry: Alkaline phosphatase, alanine aminotransferase (ALT), aspartate aminotransferase (AST), bilirubin (total), blood urea nitrogen (BUN), creatinine phosphokinase, creatinine, sodium, potassium, calcium, phosphorus, magnesium, glucose, albumin, and total protein
- Urinalysis (urine dipstick for protein, hematuria, and glucose)
- 25-hydroxy vitamin D
- Hematology: hemoglobin, hematocrit, red blood cell count, platelet count, and white blood cell count with differential (for Screening only: coagulation profile, active partial thromboplastin time, prothrombin time, and fibrinogen)
- Pregnancy tests (urine) will be conducted for WOCBP
- HLA
- Immune Monitoring
- Thyroid Function
- HIV

Any clinically significant finding during screening should be recorded as medical history. Any clinically significant finding after first dose of treatment should be recorded as an AE.

12.6 Adverse Events

12.6.1 Adverse Events Definition

An AE is any unfavorable and unintended sign, symptom, or disease temporally associated with the use of a drug, whether or not considered drug-related. AEs should be described using appropriate medical terminology.

AEs also include:

- exacerbation of a preexisting disease

- increase in frequency or intensity of a preexisting episodic disease or medical condition
- disease or medical condition detected or diagnosed after study combination treatment, even though it may have been present prior to the start of the study
- continuous persistent disease or symptoms present at baseline that worsen after the start of the study
- abnormal assessments (eg, ECG findings) if determined by the investigator to be a clinically significant finding that was not present at baseline or worsened during the course of the study
- an overdose (ie, a dosage higher than that prescribed by a healthcare professional for clinical reasons, or a dosage higher than that described on the marketed product label) of an investigational or marketed product, whether accidental or intentional
- cases of pregnancy that occur during the clinical study.
- laboratory test abnormalities are considered AEs if they:
    - result in discontinuation from the study
    - require treatment or any other therapeutic intervention
    - are associated with death or any other SAE or are considered by the investigator to be clinically significant

If a laboratory abnormality or other assessment is a component of a diagnosis or syndrome, then only the diagnosis or syndrome should be recorded as an AE on the AE page. If the abnormality was not a part of a diagnosis or syndrome then the abnormality should be recorded as an AE.

If a subject's treatment is discontinued because of an AE (related or not), this must be reported to PDS Biotechnology Corporation/designee and documented in the CRF with the AE as the reason leading to discontinuation.

12.6.2 Evaluation of Adverse Events and Events of Clinical Interest

Progression of the cancer under study is not considered an AE unless it is considered by the investigator to be drug-related.

The terms "severe" and "serious" are not synonymous.

Seriousness of an AE follows the regulatory definition provided in Section 12.6.3.

Severity refers to the intensity of an AE (rated as mild, moderate, or severe, or according to the NCI-CTCAE criteria; see Section 12.6.7); the event itself may be of relatively minor medical significance (such as severe headache without any further findings).

Severity and seriousness must be independently assessed for each AE recorded on the CRF.

12.6.3 Serious Adverse Events (Immediately Reportable to PDS Biotechnology Corporation)

An SAE is defined as any AE that:

- is fatal
- is life-threatening (ie, the subject is, in the opinion of the investigator, at immediate risk of death from the AE)
- requires subject's hospitalization or prolongation of existing hospitalization
- results in persistent or significant disability or incapacity
- is a congenital anomaly or birth defect
- is medically significant or requires intervention to prevent at least 1 of the outcomes listed above

Important medical events that may not immediately result in death, be life-threatening, or require hospitalization may be considered SAEs when, based upon appropriate medical judgment, they may jeopardize the subject and may require medical or surgical intervention to prevent one of the outcomes listed in the definitions 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 subject hospitalization; or the development of drug dependency, or drug abuse.

For fatal SAEs, the reportable event is what directly led to the subject's death and not the event of death itself.

SAEs are required to be reported by the investigator to the Sponsor within 24 hours after learning of the event (see Section 12.6.12 for reporting instructions).

The following are not considered SAEs:

- Treatment on an emergency or outpatient basis for an event not fulfilling the definition of seriousness given above and not resulting in hospitalization.
- Hospitalizations planned prior to entry into the study. Hospitalizations or prolongation of hospitalization without a precipitating clinical AE (administrative or observation) should not be considered an AE.
- Standard monitoring of a preexisting disease or medical condition that did not worsen, (eg, hospitalization for coronary angiography in a subject with stable angina pectoris).

Planned surgeries should not be reported as SAEs, unless the underlying medical condition has worsened during the study.

The investigator does not need to actively monitor subjects for AEs after the study has ended (safety follow-up visit). However, if an investigator becomes aware of an SAE after the safety follow-up visit for a subject and it is believed that this event is related to the IMP, it should be reported to PDS Biotechnology Corporation to be entered into our safety database.

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12.6.4 Events of Clinical Interest

Selected non-serious and SAEs are also known as Events of Clinical Interest (ECI) and must be reported to the Sponsor within 24 hours or the next business day of awareness.

Events of clinical interest for this study-related to pembrolizumab include:

1. An overdose of pembrolizumab, as defined in Section 12.5 that is not associated with clinical symptoms or abnormal laboratory results.
2. An elevated AST or ALT lab value that is greater than or equal to 3 × the upper limit of normal and an elevated total bilirubin lab value that is greater than or equal to 2 × the upper limit of normal and, at the same time, an alkaline phosphatase lab value that is less than 2 × the upper limit of normal, as determined by way of protocol-specified laboratory testing or unscheduled laboratory testing.

Note: These criteria are based upon available regulatory guidance documents. The purpose of the criteria is to specify a threshold of abnormal hepatic tests that may require an additional evaluation for an underlying etiology. The study site guidance for assessment and follow-up of these criteria can be found in the Investigator Study File Binder (or equivalent).

Events of clinical interest related to PDS0101 include:

1. Possible temporary discoloration (other than redness) of skin at local injection sites. Description (hyper- or hypopigmentation) and duration will be captured.

For the period beginning at treatment through 30 days after cessation of treatment, any ECI, or follow-up to an ECI, whether or not related to the PDS0101 investigational vaccine or pembrolizumab therapy, must be reported within 24 hours or the next business day of awareness to the sponsor, either by electronic media or paper. Electronic reporting procedures can be found in the electronic data capture (EDC) data entry guidelines. Paper reporting procedures can be found in the Investigator Study File Binder (or equivalent).

12.6.5 Causality Assessment

All AEs and SAEs will be assessed by the PI for causal relationship to combination treatment:

- **Definitely:** This causal relationship is assigned when the AE starts a reasonable time after study treatment administration, stops/improves when study treatment has been stopped, and can reasonably be explained by known characteristics of the study vaccine.
- **Probably:** This causal relationship is assigned when the AE starts a reasonable time after study treatment administration, stops/improves when study treatment has been stopped, and cannot be reasonably explained by known characteristics of the subject's clinical state.
- **Possibly:** This causal relationship is assigned when the AE starts a reasonable time after study treatment administration but could have been produced by the subject's clinical state or other modes of therapy administered to the subject.

Categories of "definitely," "probably," and "possibly" will be considered related or associated with the use of study treatment.

- **Unrelated:** This causal relationship is assigned when the AE is definitely not associated with the study treatment administered and another etiology has been identified and documented.

12.6.6 Severity Assessment for Injection-Site Reactions

Table 7 Severity Assessment for Injection-Site Reactions

Grade 1	Grade 2	Grade 3	Grade 4	Grade 5
Tenderness with or without associated symptoms (eg, warmth, erythema, itching)	Pain, lipodystrophy; edema; phlebitis	Ulceration or necrosis; severe tissue damage; operative intervention	Life- threatening consequences; urgent intervention indicated	Death
Source: NCI-CTCAE v5.0 – 27 November 2017				

12.6.7 Severity Assessment for Adverse Events

The investigator must assess the severity of both AEs and SAEs. Severity will be graded based on the subject's symptoms according to the National Cancer Institute – Common Terminology Criteria for Adverse Events (NCI-CTCAE), Version 5.0. Adverse events that are not defined in the NCI-CTCAE should be evaluated for toxicity grading according to the following scale:

- Grade 1 – Mild; asymptomatic or mild symptoms; clinical or diagnostic observations only; intervention not indicated.
- Grade 2 – Moderate; minimal, local, or non-invasive intervention indicated; limiting age-appropriate instrumental activities of daily life (ADLs). Instrumental ADL refers to preparing meals, shopping for groceries or clothes, using the telephone, managing money, etc.
- Grade 3 - Severe or medically significant but not immediately life-threatening; hospitalization or prolongation of hospitalization indicated; disabling; limiting self- care ADL. Self-care ADLs refer to bathing, dressing and undressing, feeding one's self, using the toilet, taking medications, and not being bedridden.
- Grade 4 - Life-threatening consequences; urgent intervention indicated.
- Grade 5 - Death related to AE.

If the severity fluctuates, the maximum severity will be recorded for each event.

12.6.8 Action Taken and Treatment Required

The investigator will report:

- the action taken with each component of the combination treatment as none, dose reduced, or discontinued treatment.

- the administration of concomitant medications or procedures/therapies performed to resolve the AE.

12.6.9 Outcome

The investigator will report the outcome of the event (ongoing, resolved, or resolved with sequelae) for all AEs.

12.6.10 Contraception and Pregnancy

The pembrolizumab and PDS0101 may have adverse effects on a fetus *in utero*. Furthermore, it is not known if pembrolizumab has transient adverse effects on the composition of sperm.

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

Investigator must stress the importance of using a reliable method of contraception for at least 120 days after the last dose of plus pembrolizumab plus the PDS0101 vaccine or for pembrolizumab alone for female subjects of childbearing potential as described below:

Female subjects who are not of childbearing potential are exempted from the requirements to use contraception in this study. Females who are not of childbearing potential are defined as:

- postmenopausal (minimum age 50 years with complete absence of menstruation for at least 2 continuous years).
- surgically or naturally sterile (eg, having undergone bilateral tubectomy, hysterectomy, bilateral ovariectomy)

Male subjects must agree to use a condom as an effective method of contraception for at least 120 days after the last dose of pembrolizumab plus PDS0101 vaccine and or pembrolizumab alone.

Subjects who become pregnant at any time during the study will discontinued treatment and be followed per the instructions listed below.

If a subject inadvertently becomes pregnant while on treatment with pembrolizumab and/or PDS0101 (during combination therapy or subsequent pembrolizumab monotherapy), the subject will be immediately discontinued from all study treatments. Any pregnancy occurring during the study must be reported to the investigator within 24 hours of learning of its occurrence. The investigator should then report the pregnancy to the Medical Monitor within 24 hours of notification who will in turn forward the appropriate forms to the investigator for completion. The site will contact the subject at least monthly and document the subject's status until the pregnancy

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has been completed or terminated. The outcome of the pregnancy will be reported to the Sponsor without delay and within 24 hours if the outcome is a serious adverse experience (eg, death, abortion, congenital anomaly, or other disabling or life-threatening complication to the mother or newborn). The Investigator will make every effort to obtain permission to follow the outcome of the pregnancy and report the condition of the fetus or newborn to the Sponsor.

Report timing of all pregnancies and exposure during breastfeeding from the time of treatment through 120 days following cessation of all study treatments, or 30 days following cessation of study treatments if the subject initiates new anticancer therapy. It is unknown whether pembrolizumab is excreted in human milk. Since many drugs are excreted in human milk, and because of the potential for serious adverse reactions in the nursing infant, subjects who are breastfeeding are not eligible for enrollment.

12.6.11 Reporting of Adverse Events and Reporting Period

Reporting of Adverse Events

All AEs, regardless of causal relationship, are to be collected and recorded in the CRF from enrollment through the safety follow-up visit 30 days after the final study Cycle.

For all AEs and SAEs, the Investigator will provide a record of the start and stop dates of the event.

Once an AE is detected, it should be followed until resolution.

Resolution of an AE is defined as the return to baseline status or stabilization of the condition with the expectation that it will remain chronic.

To determine reporting requirements for single AE cases, the Sponsor will assess the expectedness of these events using the IB.

Sites will be responsible for knowing their institutional guidelines for AE and SAE submission to their local institutional review and/or ethics committee.

Deaths that occur during the protocol-specified AE reporting period below that are attributed by the Investigator solely to progression disease should be recorded only on the Study Completion/Early Discontinuation CRF. Events directly leading to death will be recorded as a reportable SAE (per Section 12.6.3). All other on-study deaths, regardless of relationship to study drug/treatment, will be submitted as SAEs and immediately reported to the Sponsor (see Section 12.6.3).

The Sponsor will keep detailed records of all adverse events which are reported by the investigators. These records will be reported to the competent authorities in all the Member States concerned, and to the Ethics Committee in whose countries the clinical trial is being conducted, if required.

Adverse Events Reporting Period

All AEs that occur after the consent form is signed, but before treatment administration, must be reported by the investigator if they cause the subject to be excluded from the study or are the

result of a protocol-specified intervention, including but not limited to washout or discontinuation of usual therapy, diet, placebo treatment, or a procedure.

All AEs or ECIs from the time of treatment through 30 days following cessation of any study treatment must be reported by the Investigator.

All pregnancies and exposure during breastfeeding, from the time of treatment through 120 days following cessation of any study treatment, or 30 days following cessation of any study treatment if the subject initiates new anticancer therapy, must be reported by the investigator.

Additionally, any SAE brought to the attention of an investigator at any time outside of the period specified above must be reported immediately to the Sponsor if the event is considered to be drug-related.

From the time of treatment allocation through 30 days after cessation of treatment, all AEs must be reported by the investigator. Such events will be recorded at each examination on the Adverse Event CRF/worksheets. The reporting timeframe for AEs meeting any serious criteria is described in Section 12.6.12. The investigator will make every attempt to follow all subjects with non-serious AEs for outcome.

If a subject's dosage is reduced due to a DLT/AE, the signs, symptoms, or diagnosis must be indicated as the AE, and the dose reduction listed as the action taken with the drug, but not as the AE itself.

For withdrawn subjects, every attempt should be made to collect AE data to resolution unless the reason for withdrawal is death, in which case, the date of death will be the stop date for the AE.

12.6.12 Immediate Reporting of Serious Adverse Events and Events Leading to Discontinuation of Treatment

All SAEs are reported 90 days following cessation of any study treatment, or 30 days following cessation of any study treatment if subject initiates new anticancer therapy, whichever is earlier.

The investigator must email or fax the following events to [redacted] within 24 hours of discovery:

- all SAEs;
- events leading to discontinuation of the combination or pembrolizumab as described in Section 8.4.1 (Criteria for Subject Discontinuation from Study Treatment)

Drug Safety Contact information: Contract Research Organization (CRO)

[redacted]

Events listed above should also be reported to the IRB, as applicable.

The initial report should include **at least** the following information:

- subject number
- description and date of the event
- criteria for seriousness
- preliminary assignment of causality to study drug

[redacted] will contact the investigator either by email or telephone for follow-up information regarding the SAE, as appropriate.

Regarding sudden unexpected serious adverse reactions (SUSARs), blinded reports will be disseminated and provided to the investigators at each study site.

When required and according to local law and regulations, unblinded SUSARs or other SAEs will be reported by an unblinded designee to the IRB and regulatory authorities.

12.7 Definition of Pembrolizumab Overdose

For this study, an overdose will be defined as 1000 mg (5 times the dose) of pembrolizumab. No specific information is available on the treatment of overdose of pembrolizumab. In the event of overdose, the subject should be observed closely for signs of toxicity. Appropriate supportive treatment should be provided, if clinically indicated. All pembrolizumab overdoses, whether associated with or without clinical symptoms or abnormal laboratory results, are reportable as SAEs (refer to Section 12.6.4).

An overdose without any associated clinical symptoms or abnormal laboratory results is reported using the terminology (accidental or intentional overdose without adverse effect).

12.8 Safety and Toxicity Management

12.8.1 Safety Monitoring

For all studies conducted by PDS Biotechnology Corporation using PDS0101 information safety, information will be collected and assessed by the Sponsor.

The PDS Biotechnology Corporation Medical Monitor/designee will be responsible for the overall safety monitoring of the study.

Safety data will be monitored on a case-by-case basis in real time and in aggregate periodically during the conduct of the study.

The Medical Monitor/designee will consult with the Site investigator and the DMC chair.

All SAEs will be provided monthly to the Medical Monitor and DMC for review for the duration of the study.

All unexpected and new information will be communicated to sites and subjects per GCP guidelines and will be used to update the IB.

12.8.2 Dose-Limiting Toxicities: Definition of Dose-Limiting Toxicities

All toxicities will be graded using NCI-CTCAE Version 5.0.

The DLT window of observation will be during Cycle 1. Refer to Section 12.10 for Toxicity Management.

The occurrence of any of the following toxicities during Cycle 1 will be considered a DLT, if assessed to be possibly, probably, or definitely related to the study combination treatment administration:

- Grade 4 non-hematologic toxicity (not laboratory).
- Grade 4 hematologic toxicity lasting ≥7 days, except thrombocytopenia.
- Grade 4 thrombocytopenia of any duration.
- Grade 3 thrombocytopenia associated with clinically significant bleeding.
- Any non-hematologic AE Grade >3 in severity should be considered a DLT, with the following exceptions: Grade 3 fatigue lasting <3 days; Grade 3 diarrhea, nausea, or vomiting without use of anti-emetics or anti-diarrheal per standard of care; Grade 3 rash without use of corticosteroids or anti-inflammatory agents per standard of care.
- Any Grade 3 or Grade 4 non-hematologic laboratory value if:
    - Clinically significant medical intervention is required to treat the subject, or
    - The abnormality leads to hospitalization, or
    - The abnormality persists for >1 week.
    - The abnormality results in a drug-induced liver injury (DILI)
    - Exceptions: Clinically nonsignificant, treatable, or reversible laboratory abnormalities including liver function tests, uric acid, etc.
- Febrile neutropenia Grade 3 or Grade 4:
    - Grade 3 is defined as an absolute neutrophil count (ANC) <1000/mm^3 with a single temperature of >38.3°C (101°F) or a sustained temperature of ≥38°C (100.4°F) for more than 1 hour.
    - Grade 4 is defined as ANC <1000/mm^3 with a single temperature of >38.3°C (101°F) or a sustained temperature of ≥38°C (100.4°F) for more than 1 hour, with life-threatening consequences and urgent intervention indicated.
- Prolonged delay (>2 weeks) in initiating Cycle 2 because of treatment-related toxicity.
- Any treatment-related toxicity that causes the subject to discontinue treatment during Cycle 1.
- Missing >25% of pembrolizumab and PDS0101 doses as a result of drug-related AE(s) during Cycle 1.

Other AEs not specifically listed in Section 12.6.1 will be graded according to the severities defined in NCI-CTCAE, version 5.0 issued by the US Department of Health and Human Services on 27 November 2017.

At each treatment visit and post-treatment follow-up visit, subjects will be followed for safety and tolerability.

12.9 Injection-Site Reactions

Upon administration of PDS0101, injection-site pain and other transient local symptoms may develop during and shortly after treatment. These reactions have been transient and have not required medication other than occasional analgesics (eg, acetaminophen, ibuprofen) as required to manage any pain.

With pembrolizumab, signs and symptoms usually develop during or shortly after drug infusion and generally resolve completely within 24 hours of completion of infusion.

Table 8 shows treatment guidelines for subjects who experience an infusion reaction associated with administration of pembrolizumab.

Table 8 Pembrolizumab Infusion Reaction Dose Modifications and Treatment Guidelines

NCI-CTCAE Grade	Treatment	Premedication at Subsequent Dosing
Grade 1 Mild reaction; infusion interruption not indicated; intervention not indicated	• Increase monitoring of vital signs as medically indicated until the subject is deemed medically stable in the opinion of the Investigator.	None

Grade 2
 	
Requires therapy or infusion interruption but responds promptly to symptomatic treatment (eg, antihistamines, NSAIDs, narcotics, IV fluids); prophylactic medications indicated for ≤24 hrs
	• **Stop Infusion.**
	• Additional appropriate medical therapy may include but is not limited to:
	  ○ IV fluids
	  ○ Antihistamines
	  ○ NSAIDs
	  ○ Acetaminophen
	  ○ Narcotics
	• Increase monitoring of vital signs as medically indicated until the subject is deemed medically stable in the opinion of the Investigator.
	• If symptoms resolve within 1 hour of stopping drug infusion, the infusion may be restarted at 50% of the original infusion rate (eg, from 100 mL/hr. to 50 mL/hr.). Otherwise dosing will be held until symptoms resolve and the subject should be premedicated for the next scheduled dose.
	
	Participants who develop Grade 2 toxicity despite adequate premedication should be permanently discontinued from further study drug treatment
		Participant may be premedicated 1.5h (± 30 minutes) prior to infusion of study intervention with:
		• Diphenhydramine 50 mg po (or equivalent dose of antihistamine).
		• Acetaminophen 500-1000 mg po (or equivalent dose of analgesic).

Grades 3 or 4
 	
Grade 3:
 	
Prolonged (ie, not rapidly responsive to symptomatic medication and/or brief interruption of infusion); recurrence of symptoms
	• **Stop Infusion.**
	• Additional appropriate medical therapy may include but is not limited to:
	  ○ Epinephrine**
	  ○ IV fluids
	  ○ Antihistamines
	  ○ NSAIDs
	  ○ Acetaminophen
	  ○ Narcotics
	  ○ Oxygen
	  ○ Pressors
		No subsequent dosing

NCI-CTCAE Grade	Treatment	Premedication at Subsequent Dosing
following initial improvement; hospitalization indicated for other clinical sequelae (eg, renal impairment, pulmonary infiltrates) **Grade 4:** Life-threatening; pressor or ventilator support indicated	○ Corticosteroids • Increase monitoring of vital signs as medically indicated until the subject is deemed medically stable in the opinion of the Investigator. • Hospitalization may be indicated. ****In cases of anaphylaxis, epinephrine should be used immediately. Participant is permanently discontinued from further study drug treatment.**	
Appropriate resuscitation equipment should be available at the bedside and a physician readily available during the period of drug administration. For further information, please refer to the Common Terminology Criteria for Adverse Events v5.0 (CTCAE) at http://ctep.cancer.gov.		

Abbreviations: IV = intravenous administration; NCI-CTCAE = National Cancer Institute's Common Terminology Criteria for Adverse Events; NSAIDs = nonsteroidal anti-inflammatory drugs; po = *per os* (oral administration).

12.10 Toxicity Management

12.10.1 Toxicity Management for Pembrolizumab

If a subject experiences an AE, administration of pembrolizumab may be held in cases of treatment-related AEs as indicated in Table 9. There will be no dose reductions for pembrolizumab. AEs associated with pembrolizumab exposure may represent an immunologic etiology. These immune-related AEs (irAEs) may occur shortly after the first dose or several months after the last dose of pembrolizumab treatment and may affect more than 1 body system simultaneously. Therefore, early recognition and initiation of treatment is critical to reduce complications. Based on existing clinical study data, most irAEs were reversible and could be managed with interruptions of pembrolizumab, administration of corticosteroids and/or other supportive care. For suspected irAEs, ensure adequate evaluation to confirm etiology or exclude other causes. Additional procedures or tests such as bronchoscopy, endoscopy, and skin biopsy may be included as part of the evaluation. Based on the severity of irAEs, withhold or permanently discontinue administration of pembrolizumab and administer corticosteroids.

Toxicity management guidelines for irAEs associated with pembrolizumab are provided in Table 9.

12.10.2 Toxicity Management for PDS0101

For PDS0101, subjects will be administered a divided dose of 3.0 mg R-DOTAP with 2.7 mg HPVmix. The 1.0-mL divided dose is administered as 2 injections of 1 mL SC into the upper anterior arm. For subjects that experience a DLT designated as possibly/probably/definitely related to PDS0101 will undergo a 50% dose reduction with all subsequent vaccinations. For dose reduction, subjects will be administered only 1 injection of mL of PDS0101 (1.5 mg R-DOTAP with 1.35 mg HPVmix) per vaccination SC into the upper anterior arm. PDS0101 administration will similarly be halted upon unacceptable toxicity of the combination after a reduced dose of PDS0101.

The study will be temporarily paused or suspended for the following events while the Medical Monitor investigates the case and confers with the DMC and appropriate regulatory agencies are consulted as appropriate:

- If 2 or more subjects experience a SUSAR (event is not listed in the IB and the event is possibly, probably, or definitely related to study vaccine), further enrollment and all treatments will temporarily be halted immediately until a thorough investigation.
- If 3 or more subjects experience the same Grade 3 or higher AE and assessed as possibly, probably, or definitely related to study vaccine.

12.10.3 Dose Modifications

AEs associated with pembrolizumab combination exposure, including coadministration with additional compounds may represent an immune-related response. These immune-related AEs (irAEs) may occur shortly after the first dose or several months after the last dose of

pembrolizumab treatment and may affect more than one body system simultaneously. Therefore, early recognition and initiation of treatment is critical to reduce complications. Based on existing clinical study data, most irAEs were reversible and could be managed with interruptions of pembrolizumab, administration of corticosteroids, and/or other supportive care. For suspected irAEs, ensure adequate evaluation to confirm etiology or exclude other causes. Additional procedures or tests such as bronchoscopy, endoscopy, skin biopsy may be included as part of the evaluation. Based on the severity of irAEs, withhold or permanently discontinue pembrolizumab and administer corticosteroids. Dose modification and toxicity management guidelines for irAEs associated with pembrolizumab are provided in Table 9.

Attribution of Toxicity:

When study interventions are administered in combination, attribution of an AE to a single component is likely to be difficult. Therefore, while the investigator may attribute a toxicity event to the combination, to PDS0101 alone, or to pembrolizumab alone, for AEs listed in Table 9, both interventions must be held according to the criteria in Table 9.

Holding Study Interventions:

When study interventions are administered in combination, if the AE is considered immune-related, both interventions should be held according to recommended dose modifications.

Restarting Study Interventions:

Participants may not have any dose modifications (no change in dose or schedule) of pembrolizumab in this study, as described in Table 9.

If the toxicity does not resolve or the criteria for resuming treatment are not met, the subject must be discontinued from all study interventions.

If the toxicities do resolve and conditions are aligned with what is defined in Table 9, the combination of PDS0101 and pembrolizumab may be restarted at the discretion of the investigator. In these cases where the toxicity is attributed to the combination or to PDS0101 alone, re-initiation of pembrolizumab as a monotherapy may be considered after communication with and agreement by the Sponsor.

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Table 9 Dose Modification and Toxicity Management Guidelines for Immune-related AEs Associated with Pembrolizumab

General instructions:

1. Severe and life-threatening irAEs should be treated with IV corticosteroids followed by oral steroids. Other immunosuppressive treatment should begin if the irAEs are not controlled by corticosteroids.
2. Pembrolizumab must be permanently discontinued if the irAE does not resolve or the corticosteroid dose is not ≤10 mg/day within 12 weeks of the last pembrolizumab-treatment.
3. The corticosteroid taper should begin when the irAE is ≤Grade 1 and continue at least 4 weeks.
4. If pembrolizumab has been withheld, pembrolizumab may resume after the irAE decreased to ≤Grade 1 after corticosteroid taper.

irAEs	Toxicity grade (CTCAE V5.0)	Action with pembrolizumab	Corticosteroid and/or other therapies	Monitoring and follow-up
Pneumonitis	Grade 2	Withhold	Administer corticosteroids (initial dose of 1 to 2 mg/kg prednisone or equivalent) followed by taper Add prophylactic antibiotics for opportunistic infections	Monitor subjects for signs and symptoms of pneumonitis Evaluate subjects with suspected pneumonitis with radiographic imaging and initiate corticosteroid treatment
	Recurrent Grade 2, Grade 3 or 4	Permanently discontinue		
Diarrhea / Colitis	Grade 2 or 3	Withhold	Administer corticosteroids (initial dose of 1 to 2 mg/kg prednisone or equivalent) followed by taper	Monitor subjects for signs and symptoms of enterocolitis (ie, diarrhea, abdominal pain, blood or mucus in stool with or without fever) and of bowel perforation (ie. peritoneal signs and ileus) Participants with ≥Grade 2 diarrhea suspecting colitis should consider GI consultation and performing endoscopy to rule out colitis Participants with diarrhea/colitis should be advised to drink liberal quantities of clear fluids. If sufficient oral fluid intake is not feasible, fluid and electrolytes should be substituted via IV infusion
	Recurrent Grade 3 or Grade 4	Permanently discontinue		
AST or ALT elevation or Increased Bilirubin	Grade 2 [a]	Withhold	Administer corticosteroids (initial dose of 0.5 to 1 mg/kg prednisone or equivalent) followed by taper	Monitor with liver function tests (consider weekly or more frequently until liver enzyme value returned to baseline or is stable)
	Grade 3 [b] or 4 [c]	Permanently discontinue	Administer corticosteroids (initial dose of 1 to 2 mg/kg	

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			prednisone or equivalent) followed by taper	
irAEs	**Toxicity grade (CTCAE V5.0)**	**Action with pembrolizumab**	**Corticosteroid and/or other therapies**	**Monitoring and follow-up**
Type 1 diabetes mellitus (T1DM) or Hyperglycemia	New onset T1DM or Grade 3 or 4 hyperglycemia associated with evidence of β-cell failure	Withhold [d]	Initiate insulin replacement therapy for subjects with T1DM Administer antihyperglycemc in subjects with hyperglycemia	Monitor subjects for hyperglycemia or other signs and symptoms of diabetes
Hypophysitis	Grade 2	Withhold	Administer corticosteroids and initiate hormonal replacements as clinically indicated	Monitor for signs and symptoms of hypophysitis (including hypopituitarism and adrenal insufficiency)
	Grade 3 or 4	Withhold or permanently discontinue [d]		
Hyperthyroidism	Grade 2	Continue	Treat with nonselective beta-blockers (eg, propranolol) or thionamides as appropriate	Monitor for signs and symptoms of thyroid disorders
	Grade 3 or 4	Withhold or permanently discontinue [d]		
Hypothyroidism	Grade 2, 3 or 4	Continue	Initiate thyroid replacement hormones (eg, levothyroxine or liothyronine) per standard of care	Monitor for signs and symptoms of thyroid disorders
Nephritis: grading according to increased creatinine or acute kidney injury	Grade 2	Withhold	Administer corticosteroids (prednisone 1 to 2 mg/kg or equivalent) followed by taper	Monitor changes of renal function
	Grade 3 or 4	Permanently discontinue		
Neurological Toxicities	Grade 2	Withhold	Based on severity of AE administer corticosteroids	Ensure adequate evaluation to confirm etiology and/or exclude other causes
	Grade 3 or 4	Permanently discontinue		
Myocarditis	Grade 2, 3 or 4	Permanently discontinue	Based on severity of AE administer corticosteroids	Ensure adequate evaluation to confirm etiology and/or exclude other causes
Exfoliative Dermatologic Conditions	Suspected SJS, TEN, or DRESS	Withhold	Based on severity of AE administer corticosteroids	Ensure adequate evaluation to confirm etiology or exclude other causes
	Confirmed SJS, TEN, or DRESS	Permanently discontinue		

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irAEs	Toxicity grade (CTCAE V5.0)	Action with pembrolizumab	Corticosteroid and/or other therapies	Monitoring and follow-up
All Other irAEs	Persistent Grade 2	Withhold	Based on severity of AE administer corticosteroids	Ensure adequate evaluation to confirm etiology or exclude other causes
	Grade 3	Withhold or discontinue based on the event [e]		
	Recurrent Grade 3 or Grade 4	Permanently discontinue		

AE(s)=adverse event(s); ALT= alanine aminotransferase; AST=aspartate aminotransferase; CTCAE=Common Terminology Criteria for Adverse Events; DRESS=Drug Rash with Eosinophilia and Systemic Symptom; GI=gastrointestinal; IO=immuno-oncology; ir=immune-related; IV=intravenous; SJS=Stevens-Johnson Syndrome; T1DM=type 1 diabetes mellitus; TEN=Toxic Epidermal Necrolysis; ULN=upper limit of normal.

Note: Non-irAE will be managed as appropriate, following clinical practice recommendations.

[a] AST/ALT: >3.0 to 5.0 × ULN if baseline normal; >3.0 to 5.0 × baseline, if baseline abnormal; bilirubin:>1.5 to 3.0 × ULN if baseline normal; >1.5 to 3.0 × baseline if baseline abnormal

[b] AST/ALT: >5.0 to 20.0 × ULN, if baseline normal; >5.0 to 20.0 × baseline, if baseline abnormal; bilirubin:>3.0 to 10.0 × ULN if baseline normal; >3.0 to 10.0 × baseline if baseline abnormal

[c] AST/ALT: >20.0 × ULN, if baseline normal; >20.0 × baseline, if baseline abnormal; bilirubin: >10.0 × ULN if baseline normal; >10.0 × baseline if baseline abnormal

[d] The decision to withhold or permanently discontinue pembrolizumab is at the discretion of the Investigator or treating physician. If control achieved or ≤Grade 2, pembrolizumab may be resumed.

[e] Events that require discontinuation include but are not limited to: encephalitis and other clinically important irAEs (eg. vasculitis and sclerosing cholangitis).

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Dosing interruptions are permitted in the case of medical/surgical events or logistical reasons not related to study therapy (eg, elective surgery, unrelated medical events, subject vacation, and/or holidays). Subjects should be placed back on study therapy within 3 weeks of the scheduled interruption, unless otherwise discussed with the Sponsor. The reason for the interruption should be documented in the subject's study record.

12.11 Diet/Activity/Other Considerations

12.11.1 Diet

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

12.11.2 Contraception

As noted in Section 12.6.10, pembrolizumab and PDS0101 may have adverse effects on a fetus in utero. Furthermore, it is not known if pembrolizumab has transient adverse effects on the composition of sperm.

Subjects should be informed that taking the study medication may involve unknown risks to the fetus (unborn baby) if pregnancy were to occur during the study. In order to participate in the study, subjects of childbearing potential must adhere to the contraception requirement of effective methods of contraception from the day of study medication initiation (or 14 days prior to the initiation of study medication for oral contraception) throughout the study period up to 120 days after the last dose of study medication: PDS0101 in combination with pembrolizumab or pembrolizumab monotherapy. If there is any question that a subject of childbearing potential will not reliably comply with the requirements for contraception, that subject should not be entered into the study. Monthly pregnancy testing should be conducted as per local regulations where applicable.

12.11.3 Use in Pregnancy

As noted in Section 12.6.10, if a subject inadvertently becomes pregnant while on treatment with pembrolizumab, the subject will immediately be removed from the study. Any pregnancy occurring after the subject receives the first PDS0101 vaccine and until 30 days after the fifth and final PDS0101vaccine must be reported to the investigator within 24 hours of learning of its occurrence. The investigator should then report the pregnancy to the Medical Monitor within 24 hours of notification who will in turn forward the appropriate forms to the investigator for completion. The site will contact the subject at least monthly and document the subject’s status until the pregnancy has been completed or terminated. The outcome of the pregnancy will be reported to the Sponsor without delay and within 24 hours if the outcome is a serious adverse experience (eg, death, abortion, congenital anomaly, or other disabling or life-threatening complication to the mother or newborn). The study Investigator will make every effort to obtain permission to follow the outcome of the pregnancy and report the condition of the fetus or newborn to the Sponsor.

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12.11.4 Use in Nursing Women

As noted in Section 12.6.10, it is unknown whether pembrolizumab is excreted in human milk. Since many drugs are excreted in human milk, and because of the potential for serious adverse reactions in the nursing infant, subjects who are breastfeeding are not eligible for enrollment.

12.12 Post-Vaccination Contact

Study staff will contact each subject via phone call or email at least 24 hours after, but within 72 hours of, study combination treatment at Day 1 (Week 0), Day 22 (Week 3),Day 43 (Week 6), Day 64 (Week 9) and Day 232 (Week 33) (Cycles 1, 2, 3, 4, and 12). Refer to Appendix 4.

12.13 Subject Vaccine Diary

Electronic subject vaccine diary completion instructions will be provided to study subjects at Day 1 (Week 0), Day 22 (Week 3), Day 43 (Week 6), Day 64 (Week 9) and Day 232 (Week 33). Refer to Appendix 3. If the subject is unable to access the electronic subject diary, study staff will provide a print-out of the electronic diary for the subject to complete.

Subject will also receive an Injection Site Reaction Gauge (Appendix 2) after the first vaccination to measure injection-site reactions throughout the study.

Diaries must be reviewed by study staff to identify any AEs experienced since the subject's last visit and to identify any new concomitant medications taken. This must be done prior to study combination treatment at Day 22 (Week 3), Day 43 (Week 6), Day 64 (Week 9) and Day 232 (Week 33) (Cycles 2, 3, 4, and 12).

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13 STATISTICAL METHODS AND SAMPLE SIZE CALCULATION

The primary objective of this study is to evaluate the efficacy in subjects with high-risk HPV16 infection who have recurrent and/or metastatic HNSCC after initial treatment with curative intent. Efficacy will be assessed as the BOR, and PFS per investigator-evaluated and central imaging confirmed RECIST 1.1. The study will also evaluate OS and the safety and tolerability of pembrolizumab and PDS0101 administered in combination.

13.1 Size and Power Calculation

The KEYNOTE-48 study enrolled 301 subjects with CPS ≥1 in the monotherapy arm and observed an ORR of 19.1% (90% CI: 15.1%, 23.6%). The study will enroll CPI naïve and CPI refractory subjects and so a separate sample size is calculated for each group. For CPI naïve subjects, it is expected that the combination therapy will yield 1.7 times increase in ORR over monotherapy (70% increase in ORR), thus the expected ORR for combination therapy is approximately 32.5% in CPI naïve subjects. For CPI refractory subjects, we anticipate a lower ORR since these subjects have already experienced progression or recurrence after treatment with CPIs. Given this consideration, the CPI naïve and CPI refractory groups will be examined separately as described below. Subjects will also be required to have a central laboratory confirmed HPV16+ HSNCC and PD-L1 expression, the CPI naive group are required to have a CPS ≥1 by the Dako PD-L1 IHC 22C3 PharmDx Assay. If subjects do not meet these criteria, they will be replaced.

CPI Naïve

A Simon's 2-stage optimum design (Simon, 1989) will be used to determine the enrollment for the CPI naïve subjects. Setting the type I error rate to 5% (alpha=0.05), and the power to 80%, we will test the true ORR of 17% (null hypothesis) versus the alternative ORR of 33% (alternative hypothesis) for CPI naïve subjects.

We will enroll 17 subjects in the first stage. If 3 or fewer responses (CR or PR) are observed after 17 subjects in Stage 1 have been on the study for at least 6 months (Cycle 10), the study may be stopped for futility, or regulatory agency feedback will be incorporated per sponsor's discretion. If 4 or more responses are observed, the study will enroll an additional 37 subjects for a total of 54 subjects. At the completion of the second stage, the combination of PDS0101 with pembrolizumab will be considered efficacious if at least 14 responses have been observed out of the 54 subjects enrolled. If 13 or fewer responses are observed after 54 subjects have been on the study for at least 6 months (Cycle 10), the study may be stopped for futility, or regulatory agency feedback will be incorporated per sponsor's discretion.

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	Response Probability of Poor Drug (P0)	Response Probability of Good Drug (P1)	Method	Alpha	Power	Total Sample Size (N=N1+N2)	Sample Size at Stage 1 (N1)	Sample Size at Stage 2 (N2)	Stop if Stage 1 Response ≤	Reject Treatment if Total Responses ≤
CPI Naïve	17%	33%	Simon's 2-stage Optimum Design	0.05	80%	54	17	37	3	13

CPI Refractory

A Simon's 2-stage optimum design will be used to determine the enrollment for the CPI refractory subjects. Setting the type I error rate to 5% (alpha=0.05), and the power to 90%, we will test the true ORR of 5% (null hypothesis) versus the alternative ORR of 20% (alternative hypothesis) for CPI refractory subjects.

We will enroll 21 subjects in the first stage. If 1 or 0 responses (CR or PR) are observed after 21 subjects have been on the study for at least 6 months (Cycle 10), the study may be stopped for futility, or regulatory agency feedback will be incorporated per sponsor's discretion. If 2 or more responses are observed, the study will enroll an additional 20 subjects for a total of 41 subjects. At the completion of the second stage, the combination of PDS0101 with pembrolizumab will be considered efficacious if at least 5 responses have been observed out of the 41 subjects enrolled. If 4 or fewer responses are observed after 41 subjects have been on the study for at least 6 months (Cycle 10), the study may be stopped for futility or regulatory agency feedback will be incorporated per sponsor's discretion.

	Response Probability of Poor Drug (P0)	Response Probability of Good Drug (P1)	Method	Alpha	Power	Total Sample Size (N=N1+N2)	Sample Size at Stage 1 (N1)	Sample Size at Stage 2 (N2)	Stop if Stage 1 Response ≤	Reject Treatment if Total Responses ≤
CPI Refractory	5%	20%	Simon's 2-stage Optimum Design	0.05	90%	41	21	20	1	4

Thus, if significant efficacy were observed in both groups at completion of Stage 1 of enrollment, expansion to a total of 95 subjects would be allowed. These sample size and power estimations were performed using Power Analysis & Sample Size (PASS) 2020, v20.0.1.

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13.2 Analysis Populations

13.2.1 Intent-to-Treat

The primary study population will be the intent-to-treat (ITT) population, which is defined as all subjects who are enrolled, have central laboratory confirmed HPV16+ HNSCC and characterized PD-L1 expression, (for the CPI naïve group a CPS $\geq$1 by the Dako PD-L1 IHC 22C3 PharmDx Assay), and receive at least 1 dose of pembrolizumab or PDS0101. This population will be used for all summaries of demographic and baseline characteristics. In addition, analysis of PFS and OS will be performed on the ITT population. A primary efficacy analysis will also be performed in the ITT population: all subjects irrespective of whether they have undergone a tumor assessment or not will be included in the denominator in this analysis. Subjects with missing efficacy assessments will be treatment failures. Analyses will be presented for the CPI naïve group and the CPI refractory group as well as overall.

13.2.2 Primary Efficacy Analysis Population

The primary efficacy analysis population (EFF) will be all ITT subjects who have an assessment of overall tumor response after the initial dose of pembrolizumab or PDS0101. Analyses will be presented for the CPI naïve group and the CPI refractory group as well as overall.

13.2.3 Safety Population

The safety population (SAF) includes all subjects who have received at least 1 dose of either PDS0101 or pembrolizumab and will be used to summarize all safety and tolerability assessments. Analyses will be presented for the CPI naïve group and the CPI refractory group as well as overall.

13.3 Subject Disposition

The number of subjects enrolled, treated with pembrolizumab or PDS0101 and completing all treatments will be summarized using counts and frequencies with the denominator as the total number of subjects in the ITT population. In addition, discontinuations and reasons for withdrawal will be summarized.

13.4 Extent of Exposure and Treatment Compliance

The number of doses of both pembrolizumab and PDS0101 will be summarized for the duration of the study period until subjects are discontinued or complete treatment for all subjects in the ITT population.

13.5 Demographics and Baseline Characteristics

Demographic and baseline characteristics of the ITT population will be summarized.

13.6 Efficacy Analyses

13.6.1 Primary Efficacy Endpoint

BOR during the entire study period after initial treatment includes subjects with an assessment of confirmed CR or confirmed PR. The EFF population will be the primary population of interest. Exact 90% CI will be estimated for BOR of CR or PR using the Clopper-Pearson method. Analyses will also be presented for the ITT population.

13.6.2 Key Secondary Efficacy Endpoints

PFS will include all subjects in the ITT population. Those subject who are still alive and without disease progression, defined per RECIST1.1, will be censored at the last known date of contact. Estimates of time to PFS and 95% CI of estimates will be obtained from Kaplan-Meier time-to-event methodology at 75%, 50%, and 25% percentiles.

OS will include all subjects in the ITT population. Those subjects who are still alive will be censored at their last known date of contact. Estimates of time to OS and 95% CI of estimates will be obtained from Kaplan-Meier time-to-event methodology at 75%, 50%, and 25% percentiles.

13.6.3 Other Efficacy Endpoints

Exploratory Analyses:

- Evaluation of DOR for all subjects who demonstrated BOR.
- Evaluation of anti-HPV16 E6 and E7 immune responses elicited by treatment with pembrolizumab and PDS0101 using IsoPlexis Functional Proteomics at Days 85 (Cycle 5) and 253 (Cycle 13) compared with baseline.
- Examination of PD-L1 expression levels and clinical outcomes: BOR, DOR, PFS, and OS.

13.6.4 Handling of Missing Data

No missing data will be imputed. BOR will be determined by the number of subjects who demonstrate confirmed CR or confirmed PR, per the RECIST1.1 criterion. The denominator will be all subjects in the EFF population. For time-to-event endpoints (PFS and OS), subjects alive and without events will be censored at the last known date of contact.

13.7 Safety Analyses

13.7.1 Adverse Events

AEs will be coded using the Medical Dictionary for Regulatory Activities (MedDRA). The incidence of AEs will be summarized by system organ class (SOC) and preferred term . In addition, AEs will be summarized by severity (see Section 12.6.7 for severity grading scales) and will be summarized by relationship to study drug. For these 2 latter displays, subjects will be

included within the most severe (or most related) category for each preferred term or SOC summarized.

13.7.2 Clinical Laboratory Findings

Laboratory findings and their changes from baseline (last value obtained prior to Day 1) will be summarized at each scheduled visit.

13.7.3 Vital Signs

Vital signs will be summarized as actual results and as change from baseline for all assessment visits.

13.8 Other Safety Parameters

Data will be monitored and summarized to determine:

- The number of subjects that experienced a DLT during Cycle 1 of combination treatment with pembrolizumab and PDS0101.
- The number of subjects requiring any dose reduction of PDS0101 for DLTs as previously outlined, the combination treatment Cycle during which dose reduced PDS0101 was started, and the total number of PDS0101 reduced-dose treatment Cycles received per subject.

13.9 Interim Analysis

13.9.1 Safety Monitoring

Safety assessment of the pembrolizumab and PDS0101 will be performed in a lead-in safety cohort of the first 12 subjects to assess safety and any signs of DLT from the combination therapy. Accrual will resume after the recommendation of the DMC regarding safety, dose regimen and possible subsequent cohorts.

13.9.2 Futility

Per the Simon's 2-stage design, futility analyses are incorporated at Stage 1 and Stage 2 for both CPI naïve and CPI refractory groups.

Futility analysis will be performed to guard against an unacceptably low ORR.

13.10 Data Monitoring Committee

The study will have an independent DMC that will review safety and efficacy study data according to a pre-specified schedule. Prior to study start, a DMC charter will be ratified. The charter will include, but is not limited to:

- Membership, roles, and responsibilities.
- Meeting organization, format, and materials to be provided and reviewed.
- Ongoing safety data review.
- Meeting reports and recommendations.

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The DMC will review study data according to a pre-specified schedule. A DMC charter will guide the DMC and will be approved prior to subject enrollment. SAE listings will also be provided monthly for review.

In addition, DLTs, and SUSARs, will be reviewed by the medical monitor and reported to the DMC within 24 hours of receipt of the report of the event. The sponsor medical monitor will suspend the study immediately if any of the stopping criteria are met. The DMC will review the data within 24 hours of notification to determine whether to discontinue the study or take other action.

The DMC will confirm the DLTs and can recommend further actions for newly enrolled and existing subjects.

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14 DATA QUALITY ASSURANCE

14.1 Study Monitoring

All aspects of the study will be monitored by PDS Biotechnology Corporation or its representative, for compliance with applicable government regulations, current ICH/GCP guidelines and standard operating procedures (SOPs).

PDS Biotechnology Corporation/designee will ensure that appropriate monitoring procedures are performed before, during, and after the study. Before any subject enters the study, a representative of PDS Biotechnology Corporation/designee will meet with the PI and the study center staff to review the procedures to be followed during the study.

14.1.1 Clinical Research Associates

Clinical research associates (CRAs) will provide site training, evaluate study progress at the site, perform source document verification, assure compliance with the study protocol, ensure proper handling and storage of IMP, and review drug accountability. The CRAs will also be responsible for destroying drug and pharmacy logs and ensuring compliance with ICH/GCP.

At the site initiation visit and/or the investigator meeting, the CRA will review all aspects of the study including the protocol, CRFs, procedures for obtaining informed consent, record keeping, reporting of AEs/SAEs, and drug supply with the investigator/staff.

Routine site monitoring visits will be conducted per the CROs SOPs. Monitoring will include on-site visits with the investigator and his/her staff, as well as any appropriate communications by mail, email, fax, or telephone. The PI must agree to regular monitoring visits and will make available to the CRA source documents (written notes and electronic medical records, if used), signed consent forms, drug accountability records, and all other study-related documents to confirm consistency with the CRF entries. Key study personnel must be available to assist the CRA during these visits.

At each monitoring visit, the CRA will perform source data verification by comparing the data in the subjects' files with data in the CRF. The PI and the study center staff will be responsible for data entry of subject data into the CRFs via the EDC system, resolving data queries generated via the EDC system and providing missing or corrected data. Electronic CRFs will not constitute source documentation, and all data entered in the CRF must be traceable to an original source record (electronic or paper), either as part of the electronic database or in the subject's file. Upon source document review and clarification, any resulting discrepancies will be reviewed with the investigator and his/her staff. Any necessary corrections will be made directly to the CRFs or via queries by the investigator/staff. The PI is responsible for ensuring completion of the CRFs. Data should be entered within 5 days of subject visits.

The presence of a signed, written informed consent form, as well as compliance with inclusion and exclusion criteria will be checked, as will the proper recording and documentation of AEs, TEAEs, and SAEs. Routine monitoring visit frequency will be closely adjusted according to the

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timing of subject enrollment. A monitoring report will be provided for each blinded monitoring visit.

14.2 Audits and Inspections

In addition to the routine monitoring procedures, authorized members of the sponsor or designee, national regulatory authorities, and/or IRBs are permitted to inspect the study documents (study protocol, CRFs, drug accountability records, original medical records/files) at any time to assure the validity of the study data. Such audits/inspections will evaluate compliance with ICH/GCP guidelines and regulations and will be conducted in accordance with applicable SOPs.

If an audit/inspection is requested, PDS Biotechnology Corporation should be notified immediately. The PI should make every effort to be available. Direct access to the facilities where the study took place, source documents, CRFs, and applicable supporting records of study subject participation must be permitted. All subject data will be treated confidentially. Should direct access to medical records require a waiver or authorization separate from subjects' signed ICFs, it is the responsibility of the investigator to obtain such permission in writing from the appropriate individual.

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15 DATA HANDLING AND RECORD RETENTION

The PI must ensure that the records and source documents are complete, accurate, filed, and retained.

15.1 Data Management

Data collection will be performed, primarily with an eCRF. The investigator must ensure the accuracy, completeness, legibility, and timeliness of the data.

Qualified site personnel will enter the data into the EDC. Data validation will be performed by the system at data entry (data type, format, and electronic data validation checks). The blinded CRA will regularly review the CRFs and identify incomplete or inconsistent data. Discrepancies and their subsequent resolutions will be generated within the EDC, and an audit trail will track all changes. Data recorded in the EDC will be pseudo-anonymized, and data security and protection rules are strictly followed according to PDS Biotechnology Corporation/designee SOPs. The site will be provided with a CRF of the study subjects after investigator sign off at the end of the study.

15.2 Record Retention

Archiving of study documents and study data will be performed according to applicable SOPs. Essential documents, including but not limited to: signed ICFs; worksheets; subject identification lists; IRB composition and communications; site correspondence with PDS Biotechnology Corporation or its designee; lists of site personnel delegated significant study-related duties; drug accountability records; and all other source documents that must be retained by the PI. Records should be retained: for at least 2 years after the last approval of a marketing application in an ICH region; until there are no pending or contemplated marketing applications in an ICH region; or for at least 2 years after the formal discontinuation of clinical development of the IMP. These documents should be retained for a longer period, however, if required by the applicable regulatory requirement(s) or if needed by PDS Biotechnology Corporation.

The PI must notify PDS Biotechnology Corporation if they: wish to assign the essential documents to someone else; remove them to another location; or are unable to retain them for a specified period. The PI must obtain approval in writing from PDS Biotechnology Corporation prior to destruction of any records. All study documents should be made available, if required by the relevant health authorities.

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16 REPORTS AND PUBLICATIONS

16.1 Reports

Study results will be documented in a final clinical study report.

16.2 Publications

Results of the study will be published in accordance with standard editorial and ethical practice and along with generally accepted academic and scientific standards set forth at www.icmje.org.

PDS Biotechnology Corporation will be responsible for analysis and interpretation of the data. It is mandatory that the first publication is based on all data obtained from all sites and not on data from individual centers. Results from multi-center studies must be published or presented at congresses only in their entirety and not as individual center data, except for ancillary studies. Any study-related article or abstract written independently by investigators should be submitted to PDS Biotechnology Corporation for review at least 60 days prior to submission for publication or presentation along with the PI curriculum vitae.

The list of authors of any formal publication or presentation of study results may include, as appropriate, representatives of PDS Biotechnology Corporation and will be determined by mutual agreement.

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17 ETHICS AND GOOD CLINICAL PRACTICE COMPLIANCE

17.1 Institutional Review Board or Independent Ethics Committee

The study protocol must be approved by the local IRB, as appropriate, before any study-related procedures are performed. The investigators will submit this protocol and any related document provided to the subject (eg, subject information used to obtain informed consent) to their IRB. Approval from the IRB will be obtained before starting the study and documented in a dated letter to the investigator, clearly identifying the study, the documents reviewed, and the date of approval. A list of members of the IRB involved in the approval or equivalent must be provided, including the functions of these members. Modifications to the protocol after receipt of the IRB approval must be submitted by the investigator to the IRB in accordance with local procedures and regulatory requirements. Renewal of local IRB approval, as appropriate, is the responsibility of each investigator site and must be secured in due time so that the conduct and the integrity of the study is not affected or interrupted by lack of IRB re-approval.

17.2 Ethical Basis of the Study

This is the first study of pembrolizumab and PDS0101 to be evaluated in combination in humans. PDS0101 is an immune activating platform that results in significant, potent HPV-specific cytolytic CD8 T-cells while the checkpoint inhibitor pembrolizumab “takes the brakes off the immune system.” It is hypothesized that the combination of the 2 agents will result in more potent, synergistic anti-tumor responses directed against HPV16-positive HNSCCs, potentially leading to improved ORR, PFS, and DOR. The purpose of this study is to explore in a preliminary manner, the safety of the combination and its impact on those specified clinical outcomes.

17.3 Changes to the Conduct of the Study

Any amendment to this protocol will be provided to the PI in writing by PDS Biotechnology Corporation. No protocol amendment may be implemented (with the exceptions noted below) before it has been approved by the IRB and the signature page, signed by the PI, has been received by the CRO or PDS Biotechnology Corporation. If the protocol is amended to eliminate or reduce the risk to subjects, the amendment may be implemented before IRB review and approval. However, the IRB must be informed in writing of such an amendment, and approval must be obtained within reasonable time limits.

17.4 Legislation and Guidelines Directing the Study

This study will be conducted according to the principles of the “Declaration of Helsinki” (Somerset-West) and with the laws and regulations of each participating country. A copy of the Declaration of Helsinki will be provided in the investigator folder, if necessary. The investigator will follow ICH/GCP guidelines.

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17.5 Notification of the Authorities, Approval, and Registration

Before start, the study will be registered at clinicaltrials.gov or at a different WHO-approved study registry. The study will be reported to respective local health authorities where the study is being conducted.

17.6 Data Protection

By signing the protocol, the investigator agrees to keep all information provided by PDS Biotechnology Corporation in strict confidence and to request similar confidentiality from his/her staff and the IRB. Study documents provided by PDS Biotechnology Corporation (protocols and other material) will be stored appropriately to ensure their confidentiality. The information provided by PDS Biotechnology Corporation to the investigator may not be disclosed to others without direct written authorization from PDS Biotechnology Corporation, except to the extent necessary to obtain informed consent from subjects who wish to participate in the study. Data collected for the study will be stored and managed with adequate precautions to ensure confidentiality of those data, and in accordance with the applicable national and/or local laws and regulations on personal data protection.

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18 STUDY SPONSORSHIP

18.1 Sponsor and Contract Research Organization Contact Information

Sponsor: PDS Biotechnology Corporation, Inc.

[redacted]

18.2 Study Termination

PDS Biotechnology Corporation reserves the right to terminate the study in its entirety or at a specific study center before study completion.

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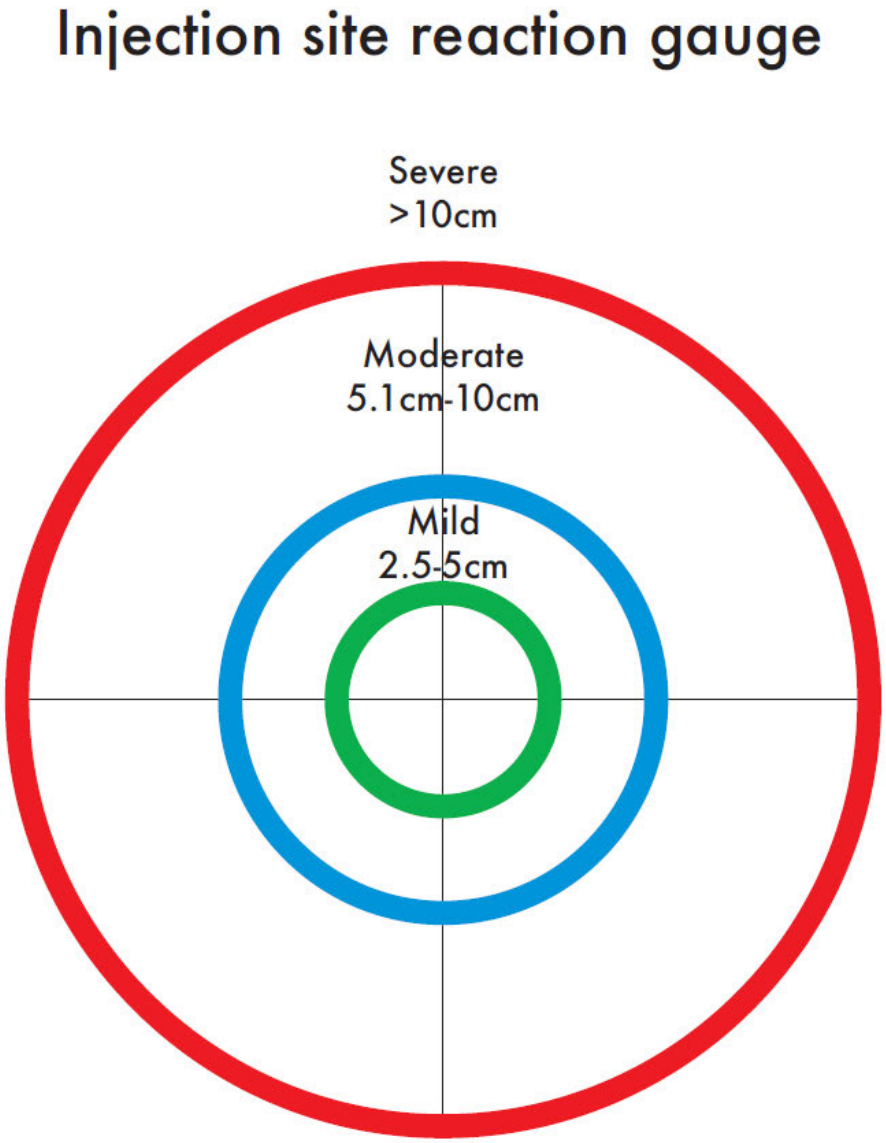
20 APPENDICES

APPENDIX 1 ECOG PERFORMANCE STATUS

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

ECOG, Eastern Cooperative Oncology Group.

APPENDIX 2 INJECTION SITE REACTION GAUGE



APPENDIX 3 SUBJECT VACCINE DIARY

The following is an example of the subject vaccine diary that is to be completed by the subject every day for 7 days after the administration of the investigational medicinal product.

1. Is the area of the local injection site better, worse, or about the same or completely resolved compared to when the vaccine was initially given? (Choice options: better, worse, about the same)
2. Are you experiencing tenderness, warmth, itching, or skin discoloration? (Y/N)
3. Are you experiencing swelling, pain, soreness, or inflammation? (Y/N)
4. Is there any evidence of rash or sores? (Y/N)
5. Are your local injection site reaction(s) impacting your daily activities? (Y/N)
6. Is there any evidence of blistering or skin breakdown at injection site? (Y/N)
    a. If YES, prompt subject to upload a photo
7. Are you experiencing any systemic symptoms such as body aches, headache, fatigue, or malaise or other symptoms? (Y/N)
    a. If YES, provide symptom(s) in text box.
8. Have you had to take or use any medications for pain relief (such as Aleve, Tylenol or Motrin), itching (Benadryl or other antihistamine, topical hydrocortisone) or for relief of other symptoms? (Y/N)

This document is confidential.

APPENDIX 4 POST-VACCINATION CONTACT

1. Before we get started, do you have any questions or concerns?
2. Have you experienced any systemic symptoms such as muscle or body aches, headache, fatigue, or malaise?
    a. If YES, please provide details.
    b. If YES, have you had to take any medications for relief of these symptoms?
3. We would like to learn more about the vaccine injection sites and any reactions you may be having.
4. Is the area of the local injection site better, worse, or about the same, compared to when the vaccine was initially given?
5. Are you experiencing redness, swelling, pain, soreness, itching, or skin discoloration?
    a. If YES, please provide details.
6. Is there any evidence of rash, sores, or skin breakdown?
    a. If YES, please take a picture of the area and forward it immediately to your research team.

    Note: A member of the research team will review the picture(s) and get back to you with suggestions for management within 24 to 48 hours.
7. Have you had to take or use any medications for pain relief (such as Aleve, Tylenol or Motrin), itching (Benadryl or other antihistamine, topical hydrocortisone), or for relief of other symptoms?
    a. If YES, please provide details of medications or other agents used.
8. Are your local injection-site reactions impacting your daily activities?
    a. If YES, please provide details. For example, “injection sites are sore so I’m not able to do my usual exercise activities.”

These questions do not apply to the first dose of vaccine.

9. Is the injection-site reaction to your most recent dose of vaccine better, worse, or about the same, compared with your previous dose of vaccine?
10. Do you have any local injection-site reactions (for example, discoloration that is still present from a vaccine given previously)?
    a. If YES, please specify the vaccine dose (Vaccines #1, #2, #3, #4 or #5) and provide details.

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11. Since your last visit, have you received any other routine vaccines or immunizations for general health maintenance? Some examples are flu vaccines, tetanus/diphtheria booster vaccine.
    a. If YES, please confirm what vaccine you received.
12. How would you describe your overall response to your vaccine treatment?
    a. I am tolerating the treatment(s) well.
    b. I am tolerating the treatment(s) OK.
    c. I find the treatment very hard to tolerate and would not receive any further vaccines if I were given the option.

This document is confidential.

APPENDIX 5 PROTOCOL AMENDMENT 4.1 SUMMARY

Protocol version 3.1 dated 1 September 2021 is being amended to create Protocol Amendment version 4.1 dated 1 September 2022; this amended version of the protocol supersedes version 3.1. The purpose of this amendment is:

1. To update the protocol as a result of the UK MHRA review and request for an amended protocol as detailed below:
   - Add rationale for the number of doses, schedule of dosing of PDS0101 and duration of pembrolizumab treatment (Section 5.4.4)
   - Clarify the approach to the use of highly effective method of birth control for WOCBP (Section 2 and Section 7.4)
   - Clarify the use of condoms for male participants as a highly effective method of birth control (Section 8.1 and Section 12.6.10).
   - Exclusion criteria #24 - Amend the list of highly effective methods of contraception (Synopsis and Section 8.2)
   - Add Exclusion Criteria #27 (Synopsis and Section 8.2).
   - Clarify where the pembrolizumab RSI is located (Section 7.5).
2. To update the protocol in Section 12.6.11.1 as per the Health Products Regulatory Authority (HPRA), Ireland to include information on the reporting of Adverse Events as per the Clinical Trials Directive 2001/20/EC.
3. Synopsis – To clarify the renal organ function in inclusion criteria #6 to align with Section 8.1 (Table 3) of the protocol.
4. Section 9.1 – To clarify PDS0101 dose to be received by each subject.
5. Section 9.2 – To update the formulation language for HPVmix.
6. Section 9.6 – To clarify the dose modification of pembrolizumab in Section 9.6
7. Section 10.1.1- To clarify the acceptable timing for collection of vital signs prior to dosing.
8. Table 5 and Table 6 – To update the timing and process of collecting Survival Data for those subjects who have discontinued treatment (for any reason) and to include Prescreening Informed Consent before C1 Day 1.
9. Section 10.2 – To update the protocol with additional language in Section 10.2 and Table 5 to describe the timing and process of collecting Survival Data for those subjects who have discontinued treatment (for any reason).
10. Section 10.3 – To include additional language on the use of a Prescreening ICF for performing prescreening activities such as HPV16 testing, PD-L1 IHC 22C3 assay and imaging assessment.
11. Section 11.3 – To clarify the required imaging assessment tests for chest, abdomen, pelvis, head and neck.
12. Section 13.6.4 – Section on handling of missing data moved from Section 13.2 to a new subsection.
13. To clarify the acronym for Prothrombin time from PTT to PT to align with the EDC.
14. To align the Versamune nomenclature with the Investigator's Brochure for consistency.

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