Title	A Multi-Center, Open-label Phase Ib-II Trial of the combination of GX-188E Vaccination and Pembrolizumab in Patients with Advanced, Non-Resectable HPV type 16 and/or 18 Positive Cervical Cancer
Protocol Number	GX-188E-005
IND Number	12053
Primary Sponsor	Genexine, Inc. Genexine-Progen Bio Innovation Park Bldg., 172 Magokjungang-ro, Ganseo-gu, Seoul, 07789, Korea
Medical Monitor	Jong Sup Park
Date/Version	29Aug2022 / Amended (V4.0)

Confidentiality Statement

This document contains information that is confidential and proprietary to the Sponsor. This information is being provided to you solely for the purpose of evaluating and/or conducting a clinical study for the Sponsor. You may disclose the contents of this document only to study personnel under your supervision, institutional review boards (IRBs)/independent ethics committees (IECs), or duly authorized representatives of regulatory agencies for this purpose under the condition that they maintain confidentiality. The contents of this document may not be used in any other clinical study, disclosed to any other person or entity, and/or published without the prior written permission of the Sponsor. The foregoing shall not apply to disclosure required by any regulations; however, you will give prompt notice to the Sponsor of any such disclosure. All other nonpublic information provided by the Sponsor and any information that may be added to this document also is confidential and proprietary to the Sponsor and must be kept in confidence in the same manner as the contents of this document.

1.0 Protocol Acknowledgement

I have read this Protocol and agree that it contains all necessary details for carrying out the study described. I understand that it must be reviewed by the Independent Ethics Committee overseeing the conduct of the study and approved or given favorable opinion before implementation.

The signature of the Principal Investigator and Sponsor below constitute their approval of this protocol and proved the necessary assurances that this study will be conducted according to the Declaration of Helsinki, GCP, ICH guidelines, local legal and regulatory regulations as well as to all stipulations of the protocol in both the clinical and administrative sections, including statements regarding confidentiality.

_____ _____

Investigator's name and signature Date

_____ _____

Medical Monitor's name and signature Date

_____ _____

Clinical Development Division Head's name and signature Date

2.0 Table of Contents

3.0 LIST OF TABLES

4.0 LIST OF FIGURE

5.0 Contacts

5.1 Emergency Contacts

Primary Medical Monitor
Jong Sup Park, Genexine, Inc.

Safety Physician and Back-Up Medical Monitor
Charu Gautam, IQVIA

5.2 Additional Contacts

Clinical Project Manager/Lead Clinical Research Associate
Yoon Jeong Choi, Genexine, Inc.

5.3 SAE Reporting Contact

IQVIA Lifecycle Safety
E-mail: QLS_GX188E@IQVIA.com / Fax : 00798-14-800-4270

6.0 List of Abbreviations

Abbreviation or Term[1]	Definition/Explanation
AE	Adverse event
ALT	Alanine aminotransferase
APTT	Activated partial thromboplastin time
aPTT	Activated Partial thromboplastin time
AST	Aspartate aminotransferase
BICR	Blinded Independent Central Review
BID	Twice daily
BORR	Best Overall Response Rate
BP	Blood pressure
BUN	Blood urea nitrogen
Ca^{++}	Calcium
CBC	Complete blood count
CFR	Code of Federal Regulations
CI	Confidence interval
Cl-	Chloride
CL_{cr}	Creatinine clearance
CR	Complete response
CRF	Case Report Form
CT	Computed tomography
CTA	Clinical Trial Agreement
CTCAE	Common Toxicity Criteria for Adverse Events
D/C	Discontinue
DCR	Disease Control Rate
DLT	Dose Limiting Toxicity
DOR	Duration of Response
ECI	Events of Clinical Interest
ECOG	Eastern Cooperative Oncology Group
EDC	Electronic Data Capture
EOS	End of Study
EOT	End of Treatment
EP	Electroporation
FDA	Food and Drug Administration
GCP	Good Clinical Practice
GFR	Glomerular filtration rate
GGT	Gamma glutamyl transpeptidase
GLP	Good Laboratory Practice
GMP	Good Manufacturing Practice
Hb	Hemoglobin
HCO_3^-	Bicarbonate
HIV	Human immunodeficiency virus
HPV	Human papillomavirus
HR	Heart rate
Hr	Hour or hours

Abbreviation or Term[1]	Definition/Explanation
IBC	Institutional Biosafety Committee
IEC	Independent Ethics Committee
IM	Intramuscular
INR	International Normalized Ratio
irAE	Immune-related Adverse Events
IRB	Institutional Review Board
iRECIST	Response Evaluation Criteria In Solid Tumors for Immunotherapeutics
IU	International Unit
IV	Intravenous, intravenously
MedRA	Medical Dictionary for Drug Regulatory Activities
ORR	Overall Response Rate
PD	Progressive disease
PFS	Progression Free Survival
PO	Per os (administered by mouth)
PR	Partial response
PT	Prothrombin time
RBC	Red Blood Cell
RECIST	Response Evaluation Criteria in Solid Tumor
SAE	Serious adverse event
SD	Stable disease
SMC	Safety Monitoring Committee
SOC	Standard of Care
TEAE	Treatment-emergent adverse event
ULN	Upper limit of normal
ULQ	Upper limit of quantitation
WBC	White blood cell
WOCBP	Women of child-bearing potential

[1] All of these abbreviations may or may not be used in protocol.

7.0 Study Synopsis

TITLE

A Multi-Center, Open-label Phase Ib-II Trial of the Combination of GX-188E Vaccination and Pembrolizumab in Patients with Advanced, Non-Resectable HPV-Positive Cervical Cancer

OBJECTIVES

Part A: Evaluation of Safety and Tolerability of GX-188E + Pembrolizumab (P) in Patients with HPV 16+ and/or 18+ Advanced Cervical Cancer

Primary Objective:

- To establish the safety and tolerability of GX-188E +P, and to identify the recommended Phase 2 treatment regimen

Secondary Objectives:

- Objective Response Rate within 24 weeks (ORR_{24}) by RECIST v1.1 and Response Evaluation Criteria In Solid Tumors for Immunotherapeutics (iRECIST)
- Best Overall Response Rate (BORR)
- Time-to-Best Response (TTR)
- Duration of Response (DOR)
- Disease Control Rate (DCR)
- Progression-Free Survival (PFS): median PFS and 6 month PFS rate
- Overall Survival (OS): median OS

Part B: Simon Two-Stage Design to Evaluate the Exploratory Efficacy of Recommended Phase 2 GX-188E + P Regimen in Patients with HPV 16+ and/or 18+ Advanced Cervical Cancer

Primary Objective:

- ORR_{24} by RECIST v1.1

Secondary Objectives:

- Safety and tolerability
- BORR by RECIST v1.1 and iRECIST
- TTR, DOR, DCR, 6-month PFS rate, median PFS and median OS

Part C: To Evaluate the Efficacy of Recommended Phase 2 GX-188E + P Regimen in Larger Number of Patients with HPV 16+ and/or 18+ Advanced Cervical Cancer

Primary Objective:

- ORR_{24} by RECIST v1.1

Secondary Objectives:

- Safety and tolerability
- BORR by RECIST v1.1 and iRECIST
- TTR, DOR, DCR, 6-month PFS rate, median PFS and median OS

All Parts, Exploratory/Biomarker Objectives:

- To evaluate the ability of GX-188E to induce a systemic HPV-16 and HPV-18-specific T-cell response that includes, but is not limited to, expansion of CD4+ and CD8+ T-cells that recognize E6 or E7 peptide epitopes
- To investigate whether GX-188E vaccination promotes a Th1-polarized anti-tumor immune response
- To assess whether GX-188E vaccination increases tumor immunogenicity (e.g. increased expression of antigen presentation and processing machinery, increased TILs)
- Identification of biomarkers that has possibility to implicate clinical response and safety and/or mechanism of action of GX-188E and pembrolizumab.

SAMPLE SIZE

Approximately 46 patients will be enrolled and treated with the investigational combination in Parts A and B. It is expected that Part A will enroll between 6- and 18 patients, based upon the incidence of dose-limiting toxicities.

If at least 8 of the 28 subjects enrolled in Part B, experience an objective response who are considered to be evaluable for efficacy, it will be considered that ORR satisfies the criteria for study expansion and additional 17 subjects (at least) will be enrolled in Part C to evaluate efficacy further in larger population (N=60). Refer to the Section 24.3 Sample Size and Power for detailed assumptions for sample size estimation.

STUDY DESIGN

This is an open-label Phase Ib-II trial to evaluate the safety and efficacy of GX-188E + pembrolizumab (P) in patients with advanced HPV-16+ or HPV-18+ cervical cancer.

Study Design. This study is separated into Parts A, B and C.

Part A. Initial Safety Evaluation

The study will begin with Part A, a safety run-in, employing a "6+3 design", to ensure that the study treatment is not associated with unacceptable acute toxicities.

The starting dose in Part A for GX-188E will be 2mg (1mg/site x 2 vaccination sites). Six (6) vaccination days are planned.(week 1, week 2, week 4, week 7, week 13 and week 19). An optional GX-188E administration may be given at week 46 if it is in the best interests of the patient, as determined by the investigator, once the patient has completed 37 weeks of treatment. Additional GX-188E administration(s) may be given to the subject after discussion with the sponsor."

GX-188E will be administered on Day 1 of the following schedule:

- Weeks 1, 2, 4, 7, 13, 19 and 46 (Optional)

The standard dose of pembrolizumab (200 mg every 3 weeks) will be administered.. No dose escalation of either agent is planned.

The first 6 patients will be enrolled and evaluated for the first 3 weeks (prior to Week 4 Day 1 visit) for dose-limiting toxicities (DLTs). A DLT is defined as any AE that is not clearly due to progression of the patient's malignancy, that occurs within the first 21 days of treatment initiation (prior to Week 4 Day 1 visit), and that meets at least one of the non-hematologic or hematologic criteria below:

Non-Hematologic DLT:

- ≥ Grade 3 non-hematologic toxicity according to the Common Toxicity Criteria for Adverse Events (CTCAE) v4.0 or the most recent version ***except for the following***:
  - nausea, vomiting, or diarrhea lasting ≤ 72 hr
  - Grade 3 fatigue lasting ≤ 7 days
  - hypersensitivity reactions lasting ≤ 72 hrs
  - Grade 3 hyperglycemia lasting ≤ 72 hr with standard anti-diabetic therapy
  - Grade 3 increases in liver transaminases in patients with liver metastases. (Note: Grade 4 increases in LFTs in any patient will be considered a DLT)
  - clinical laboratory abnormalities that are reversible to ≤ Grade 1 or baseline status within 72 hr with outpatient care and/or monitoring, or that are considered *not* clinically significant by the Principal Investigator

Hematologic DLT:

- Grade 4 neutropenia [absolute neutrophil count (ANC) < 0.5 x 10^9/L]
- Grade 3 febrile neutropenia (ANC < 1.0 x 10^9/L with a fever ≥ 38.3ºC)
- Grade 4 thrombocytopenia (< 25.0 x 10^9/L) lasting > 4 days or that requires platelet transfusion
- Grade ≥ 3 thrombocytopenia associated with Grade ≥ 3 bleeding
- Any hematologic toxicity resulting in death (i.e. Grade 5)

In addition, any other AE that is felt to be treatment-limiting in the medical opinions of the Principal Investigator and the Sponsor's Medical Monitor may be considered a DLT. These include, but are not limited to the following:

- Any toxicity leading to more than one missed dose of either GX-188E or pembrolizumab during the DLT-evaluation period
- Any toxicity leading to > 2 weeks delay in initiation of the 2nd cycle of pembrolizumab

No additional patients will be enrolled until all patients in Part A have completed the DLT window and the investigational treatment regimen has been deemed safe. If ≤ 1 patient of 6 enrolled patients experiences DLT, enrollment into Part B will be initiated. If 2 patients experience a DLT, an additional 3 patients will be enrolled and evaluated for DLTs. If 3 or more patients in the first 6 or 9 patients experience a DLT, the combination at the current treatment schedule will be considered too acutely toxic and enrollment will begin at a reduced frequency treatment schedule (see Study Treatment Regimen, Treatment Reduction Plan). Depending on the occurrence rate of DLT, all patients without DLT, who receive the recommended Phase 2 treatment regimen, and who are considered evaluable for efficacy from Part A will be included in the first stage of Part B.

Part B. Exploratory Efficacy Evaluation in Advanced Cervical Cancer Patient (Simon Two-Stage Design)

In Part B, patients will receive the treatment schedule for GX188E + P that was determined from Part A to be well-tolerated. In the first stage of Part B, 15 patients with advanced HPV 16 or 18 positive cervical cancer will be treated. If at least 3 patients experience an objective response (i.e. partial response or better) by RECIST v1.1 in the first 24 weeks of treatment, an additional 13 patients will be enrolled for a total of 28 patients in Part B. If 2 or fewer patients in the first stage experience an objective response, enrollment into Part B will be discontinued for futility. Study has passed the first stage of Simon-Two stage design.

Part C. Efficacy Evaluation in Larger Number of Patients
If at least 8 of the 28 subjects enrolled in Part B, experience an objective response who are considered evaluable for efficacy, it will be considered that ORR satisfies the criteria for study expansion and additional 17 subjects (at least) will be enrolled in Part C to evaluate efficacy further in larger patient population (N=60). If only 7 or fewer subjects in Part B experience an objective response, enrollment to Part C will not open.

STUDY TREATMENT REGIMEN
GX-188E will be administered intramuscularly using electroporation (EP) to alternating injection sites at deltoid and lateralis muscles during the study period, on Week 1 Day 1 and again at Weeks 2, 4, 7, 13, 19, and 46(Optional). Patients will also receive pembrolizumab, administered intravenously per standard prescribing practices. Patients will be radiographically assessed for response (by both RECIST v1.1 and iRECIST) approximately every 9 weeks, or more frequently as clinically indicated. The full Schedule of Events is outlined in Appendix 1.

Starting Schedule

Agent	Treatment Days	Dosage
GX-188E	Week 1 Day 1, Week 2, Week 4, Week 7 and Week 13, Week 19 and Week 46 (Optional)	Two IM injections (1 mg to each deltoid or lateralis muscle; total of 2 mg per vaccination day) with colocalized EP
Pembrolizumab (P)	Day 1 q 3 weeks (e.g. Day 1 of Weeks 1, 4, 7, 10, 13, etc.)	200 mg IV

Treatment Reduction Plan
In the event that the starting treatment schedule is determined to be too toxic according to the DLT rules in Part A, the following treatment-reduction plan will be implemented:

Treatment Schedule	GX-188E	Pembrolizumab (P)
Starting Schedule	Week 1 Day 1, Week 2 Day 1, Week 4, Week 7, Week 13, Week 19, and Week 46(Optional)	Day 1 q 3 weeks
Reduction Level 1	Week 1 Day 1, Week 4, Week 7, Week 13, Week 19, and Week 46 (Optional) (remove Week 2)	Day 1 q 3 weeks (unchanged)

Note: In the event of a protocol-defined DLT, only a reduction in the frequency of GX-188E will be made. There will be no reduction in the dose level of GX-188E and no modifications made to P

If ≥3 in either 6 or 9 patients in Reduction Level 1 experience a DLT, then the combination will be considered too toxic and enrollment into the study will be discontinued.

SAFETY MONITORING PLAN
Safety Monitoring Board. The Safety Monitoring Committee (SMC) will be responsible for evaluating patients' safety data and determining the overall safety and tolerability profile of the investigational treatment regimen. The SMC will be comprised of the Sponsor Medical Monitor, and the Principal Investigator from each participating site.

In Part A, the SMC will convene after the first 6 subjects have completed the DLT observation period, to discuss safety observations and determine (1) whether any AE meets the criteria for a DLT and (2) whether Part B may be initiated.
During Part B and C, the SMC will continue to convene at least once quarterly to discuss the treatment safety profile.

INCLUSION CRITERIA

1. Patients must be female and age ≥ 18 years on day of signing of informed consent; 19 years for patients treated in Korea
2. Patients with histologically or cytologically confirmed advanced or metastatic HPV-positive (HPV-16 or HPV-18) cervical cancer, who have disease progression after treatment with all available therapies for metastatic disease that are known to confer clinical benefit, or are intolerant to treatment, or refuse standard treatment.

   Note: there is no limit to the number of prior treatment regimens.
3. Eastern Cooperative Oncology Group (ECOG) Performance Status of 0-1
4. Life Expectancy of at least 6 months
5. Patients must agree to provide either an archival tumor tissue sample or fresh biopsy sample for baseline biomarker tissue analyses, including staining for PD-L1. If archival tissue is not available and the patient does not have biopsy-accessible tumor lesions, the patient will be excluded.
6. Patients must have adequate organ function as defined in the following table (Table 1). Specimens must be collected within 28 days prior to the start of study treatment.

Table 1: Organ Function Requirements for Eligibility

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 participant with creatinine levels >1.5 × institutional ULN
Hepatic	
Total bilirubin	≤1.5 ×ULN OR direct bilirubin ≤ULN for participants with total bilirubin levels >1.5 × ULN (except in patients with Gilbert's Syndrome who must have a total bilirubin < 3x ULN and ALT < 3x ULN)
AST (SGOT) and ALT (SGPT)	≤2.5 × ULN (≤5 × ULN for participants with liver metastases)

Coagulation	
International normalized ratio (INR) OR prothrombin time (PT) Activated partial thromboplastin time (aPTT)	≤1.5 × ULN unless participant 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; ULN=upper limit of normal.

[1] Criteria must be met without erythropoietin dependency and without packed red blood cell (pRBC) transfusion within last 4 weeks.

[2] Creatinine clearance (CrCl) should be calculated using the Cockroft-Gault equation.

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. Patients must have RECIST 1.1 measurable disease, defined as:
   - Tumor lesion ≥ 1 cm in longest diameter (LD) on an axial CT or MRI image (≤5 mm reconstruction interval)

     -OR-

   - Lymph node ≥1.5 cm in the short axis on CT (≤5 mm reconstruction interval)
8. Women of childbearing potential (WOCBP) must have a negative serum or urine pregnancy test within 72 hours prior to receiving the first dose of study medication. If the urine test is positive or cannot be confirmed as negative, a serum pregnancy test will be required.
9. WOCBP must be willing to use an adequate dual method of contraception during the course of the study through 120 days after the last dose of study medication. Post-menopausal females (> 45 years old and without menses for > 1 year) and surgically sterilized females are exempt from these requirements. *Note: Abstinence is acceptable if this is the usual lifestyle and preferred contraception for the subject.*
10. Be willing and able to provide written informed consent for the trial in accordance with federal, local, and Institutional guidelines.

EXCLUSION CRITERIA

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

1. Patient has disease that is suitable for local therapy administered with curative intent.
2. Has a known additional malignancy that is progressing or has required active treatment within the past 3 years.

   Note: Participants with basal cell carcinoma of the skin, squamous cell carcinoma of the skin, or carcinoma in situ (e.g., breast carcinoma) that have undergone potentially curative therapy are not excluded.
3. Patient is expected to require any other form of antineoplastic therapy while on study; including systemic chemotherapy, radiation therapy (except for palliative purposes) biological therapy, or immunotherapy not specified in this protocol.

4. Patient has a history of active central nervous system (CNS) metastases and/or carcinomatous meningitis.
5. 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 (e.g., CTLA-4, OX 40, CD137) and was discontinued from that treatment due to a Grade 3 or higher immune-related Adverse Event (irAE).
6. Patients with active autoimmune disease requiring systemic immunosuppressive treatment within the past 2 years (i.e. 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, etc.) is not considered a form of systemic treatment and is allowed.
7. Has had an allogeneic solid organ or allogeneic bone marrow transplant
8. Patient has had a prior, non-PD-1/PD-L1/PD-L2, anti-cancer monoclonal antibody (mAb) (e.g., bevacizumab, cetuximab, etc.) within 4 weeks prior to the first dose of study medication or who has not recovered (i.e., $\leq$ Grade 1 or at baseline) from adverse events due to agents administered more than 4 weeks earlier.
9. Has received prior systemic anti-cancer therapy, including investigational agents within 4 weeks, or within 2 weeks for targeted small molecule therapies with a half-life of < 48 hrs prior to the first dose of study medication

   Note: Participants must have recovered from all AEs due to previous therapies to ≤Grade 1 or baseline. Participants with ≤ Grade 2 neuropathy and/or ≤Grade 2 anemia may be eligible.

   Note: If patient received major surgery, they must have recovered adequately from the toxicity and/or complications from the intervention prior to starting therapy.
10. Has received prior radiotherapy within 2 weeks of start of study treatment. Participants must have recovered from all radiation-related toxicities.
11. Patient has received transfusion of blood products (including platelets or red blood cells) or administration of colony stimulating factors (including G-CSF, GM-CSF or recombinant erythropoietin) within 4 weeks prior to the first dose of study medication.
12. Patients with bilateral hydronephrosis that cannot be alleviated with ureteral stents or percutaneous nephrostomy.
13. Has severe hypersensitivity (≥Grade 3) pembrolizumab and/or any of its excipients.
14. Patient has a history of (non-infectious) pneumonitis that required steroids or has current pneumonitis.
15. 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 the first dose of study drug.
16. Patient has risk factors for bowel obstruction or bowel perforation (examples include but not limited to a history of acute diverticulitis, intra-abdominal abscess, and abdominal carcinomatosis).
17. Patient who is currently participating in or has participated in a study of an investigational agent or used an investigational device within 4 weeks of the first dose of study medication.

Note: Participants who have entered the follow-up phase of an investigational study may participate as long as it has been > 4 weeks after the last dose of the previous investigational agent.

18. Unstable/inadequate cardiac function:
    - Symptomatic ischemia
    - Uncontrolled or clinically significant conduction abnormalities (e.g., ventricular tachycardia on antiarrhythmics are excluded); 1st degree AV block or asymptomatic LAFB/RBBB are eligible
    - Myocardial infarction in the previous six months
    - Congestive heart failure (New York Heart Association class III to IV)
19. Has an active infection requiring systemic therapy.
20. Participants with known human immunodeficiency virus (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 Hep C Ab result and known quantitative HCV RNA results greater than the lower limits of detection of the assay.
21. Patient has a known history of active TB (Bacillus Tuberculosis)
22. Has received a live or live attenuated vaccine within 30 days prior to the first dose of study intervention. Note: Administration of killed vaccine are allowed.
23. Has a known psychiatric or substance abuse disorder that would interfere with the participant's ability to cooperate with the requirements of the study.
24. Patient who received an implantable electronic medical device (e.g., pace maker)
25. A WOCBP who has a positive urine pregnancy test (e.g. 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.
26. Patients who are pregnant or lactating.
27. Has a history or current evidence of any condition, therapy, or laboratory abnormality that might confound the results of the study, interfere with the participant's participation for the full duration of the study, or is not in the best interest of the participant to participate, in the opinion of the treating investigator.

BIOPSIES AND PERIPHERAL BLOOD SAMPLES

All patients are required to submit either an archival or fresh biopsy sample of their tumor for molecular and histological analysis at Screening/Baseline. In addition, patients with accessible lesions will be requested to submit a tumor biopsy for correlative studies at Week 10. Details for tissue sample requirements can be found in Section 23.1 and the Protocol Laboratory Manual.

All patients will be required to submit peripheral blood samples for exploratory immunological evaluation throughout their participation on the study. Peripheral blood samples will be obtained at Screening, Week 1, Week 4, Week 7, Week 10, Week 16, Week 22, Week 49 and approximately every 27 weeks thereafter until study discontinuation.

DURATION OF PARTICIPATION

Patients may continue treatment for as long as they continue to benefit, for up to 2 years or until confirmed disease progression; intercurrent illness that prevents further administration of the investigational treatment; unacceptable adverse event(s); patient decision to withdraw from the study; significant patient non-compliance with the protocol; or general or specific changes in the patients' condition that, in the opinion of the investigator, render the patient unacceptable for further study participation. Unless a patient withdraws consent or dies during the treatment period of the study, she will be followed for up to 1 year after study treatment discontinuation for survival data.

STATISTICAL METHODS

Maximum 60 patients are planned for enrollment into this clinical trial.

Safety Analysis. All patients who receive at least one dose of the investigational treatment will be included in the safety population. All safety analyses will be performed on the safety population. Adverse Events (AE) will be coded according to the MedDRA adverse event dictionary. The results will be tabulated to examine their frequency, organ systems affected, and relationship to study treatment. The results of laboratory tests will be evaluated similarly.

Efficacy Analysis. Efficacy results, including but not limited to ORR_{24}, BORR, DOR, DCR, TTR, PFS, and OS for patients enrolled into Part A will be provided using descriptive statistics. Objective responses will be evaluated according to both RECIST v1.1 and Response Evaluation Criteria In Solid Tumors for Immunotherapeutics (iRECIST).
Note: Confirmatory scans are required for all determinations of objective response (PR or CR), Stable disease(SD) and disease progression (PD). Confirmatory scans must be performed at least 4 weeks later.

Part B follows a Simon Two-Stage mini-max design. The sample size for the first stage of Part B is 15 patients; the sample size for the second stage is 13 patients, for a total of 28 patients. Patients from Part A without a DLT, who receive the recommended Phase 2 treatment regimen and who are considered evaluable for efficacy will be included in the analysis for Part B Stage 1. For a null hypothesis ORR_{24} of 0.15 and an alternative hypothesis ORR_{24} of 0.35, the sample size of 28 subjects will provide a one-sided significance level of 5% and a power of 80%. For Stage 1, a minimum of three patients must demonstrate a response (PR or better) to proceed to the second stage. Study has passed the first stage of Simon-Two stage design. If Stages 1 and 2 are completed, a minimum of 8 patients must demonstrate a response (PR or better) to reject the null hypothesis. If a patient's responses could not be confirmed, that patient will not be included in the primary efficacy population for ORR_{24}.

Part C is to evaluate efficacy in larger patient population.
In Keynote-158 study (pembrolizumab monotherapy in patients who have progressed with standard of care systemic therapy), ORR in total patients (i.e. regardless of PD-L1 status) and with CPS ≥ 1 were 12.2% and 14.6%, respectively.
Given this, null hypothesis for ORR_{24} was set at $P_0 = 12.2\%$. With an alternative hypothesis for ORR_{24} of $P_a = 37\%$, the sample size of 60 subjects was calculated considering two-sided significance level of 0.05, 97% power, and 25% dropout rate.
The confidence interval (CI) for ORR_{24} will be estimated using exact Clopper-Pearson method, and if the lower bound of the two-sided 95% CI for ORR_{24} exceeds 12.2%, it will be proven to

satisfy the primary efficacy. And it will be analyzed using two-sided exact binomial test for a null hypothesis for ORR_{24} of $P_0 = 12.2\%$ with a significance level of $P < 0.05$.

8.0 Introduction

8.1 Background on HPV-16 and 18 Positive Cervical Cancer

Human Papillomaviruses (HPVs) are DNA viruses, which can infect squamous and mucosal epithelium and drive the pathogenesis of a variety of cancers. It is estimated that HPVs, especially serotypes 16 (HPV 16) and 18 (HPV 18), cause approximately 70% of all cervical cancers. Although the rates of cervical cancer have been declining over the past 40 years, largely due to effective screening and increased use of the Papanicolaou test, and the development of preventive HPV vaccinations (e.g., Gardasil, Gardasil 9, Cervarix), the American Cancer Society estimates that in 2016, approximately 13,000 new cases of invasive cervical cancer will be diagnosed and over 4,000 women will die from this disease in the United States alone. Rates of cervical cancer are significantly higher in less developed countries, making it the second most common cancer in women worldwide[1-3].

HPV-driven tumors have developed a variety of mechanisms to subvert immune surveillance. The tumor and tumor microenvironment is characterized by (1) the downregulation of MHC Class I expression and impaired antigen processing and presentation, (2) resistance to immune-mediated, cytotoxic T-lymphocyte (CTL) cytotoxicity, (3) expression of immunosuppressive cytokines (e.g., TGF-β and IL-10) and immune-checkpoint molecules (e.g. PD-L1) and (4) the presence of immune cells with immunosuppressive properties (e.g., regulatory T cells, myeloid-derived suppressor cells)[4-7]. It follows that therapies aimed at promoting tumor-specific immunity and reversing the immunosuppressive tumor microenvironment may be an effective treatment strategy in these cancers.

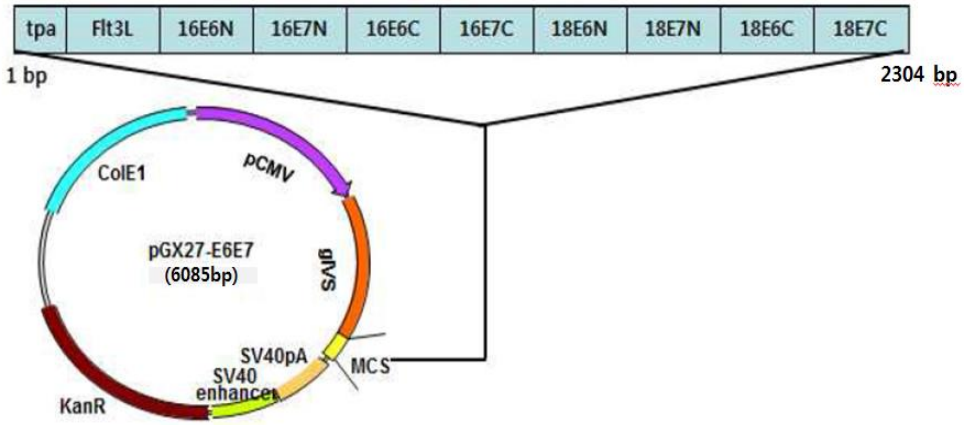
This clinical trial will evaluate the safety and efficacy of a treatment combination that seeks to promote the anti-tumor immune response against HPV-16 and 18 positive cervical cancer by (1) promoting a tumor-specific, CD8+ immune response against the HPV E6 and E7 oncogenic epitopes through vaccination (GX-188E), and (2) preventing CD8+ T-cell exhaustion within the tumor microenvironment through blockade of the PD1 immune checkpoint (pembrolizumab).

8.2 Background on the Compounds

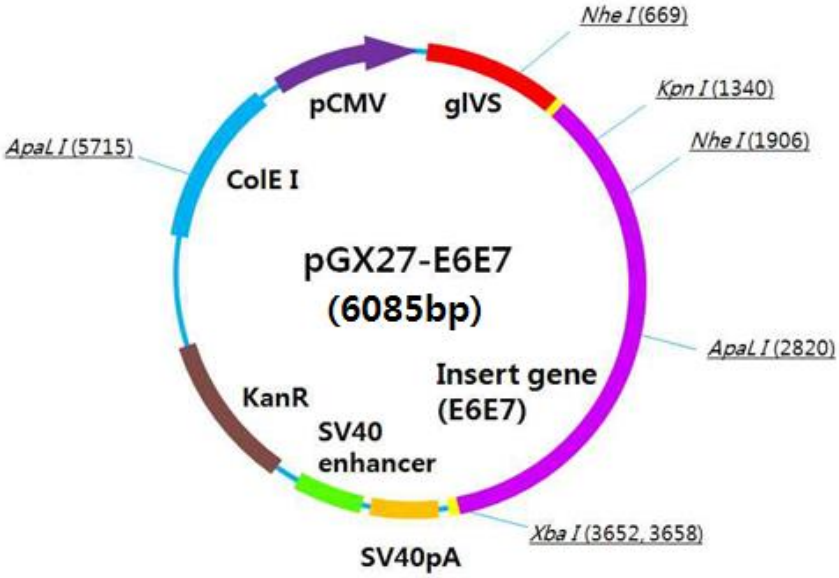
8.2.1 GX-188E: Promoting HPV-16 and 18-Specific Anti-Tumor Immunity

The first step to inducing cell-mediated immunity is the presentation of antigen by "professional" immunostimulatory antigen presenting cells (APCs), such as dendritic cells. GX-188E is a 6085 base pair DNA vaccine containing HPV E6/E7 genes fused to Flt3 ligand. GX-188E was designed to induce a specific immune response against the E6 and E7 oncoproteins associated with the "high-risk" HPV serotypes, HPV-16 and 18. The GX-188E construct is a fusion gene encoding both E6 and E7 antigens as well as the extracellular domain of Flt3L to target and activate dendritic cells. In addition, the GX-188E-encoded sequence contains the secretion signal sequence derived from tissue plasminogen activator (tpa) to promote protein product secretion of the GX-188E-encoded antigenic fusion protein (**Figure** 1). The final expressed protein product is an 85 kDa antigenic (E6/E7) fusion protein with Flt3L-mediated immunostimulatory activity. In clinical trials, GX-188E has demonstrated (1) the ability to induce a tumor-specific CD8+ immune response and (2) functional activity to eliminate target cells against high-grade cervical intra-epithelial neoplasms (CIN3, carcinoma in-situ)[8].

Figure 1. pGX27-E6E7 plasmid DNA map



- tpa : signal sequence of tissue plasminogen activator
- Flt3L : extracellular domain of fms-like tyrosine kinase 3 ligand

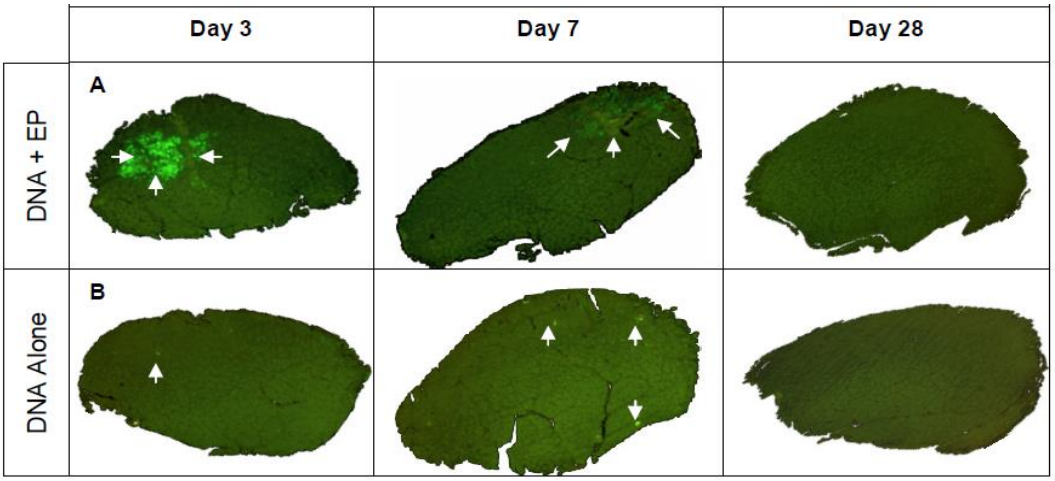


8.2.1.1 Electroporation: Methodology for Cell Transfection

Transfection of cells with naked plasmid DNA, such as GX-188E, requires a mechanism such as electroporation (EP). Although the exact mechanism by which EP facilitates transfection has not been established, the method has been used effectively for more than 3 decades by

molecular biologists to induce the expression of transfected genes. EP, which uses controlled electrical pulses, is thought to temporarily increase permeability of cell membrane and thereby increasing the cellular uptake of DNA plasmid. Recently, EP delivery of DNA has shown to increase antigen expression >10-fold higher and resulted in longer lasting immune response compared to conventional intramuscular injection in preclinical and early stage of clinical trials[9]. Pre-clinical study conducted by Ichor (EP provider) demonstrated that intramuscular EP enhanced transfection efficiency of DNA into muscle cells (myocytes) far more than 10 folds in an analysis using reporter gene expression (Figure 2). This enhanced expression of antigens resulted in increased T cell responses as well as survival rate against tumor challenge[21]. Clinical applications of EP have been tested, especially in cancer treatment and gene therapy[10-12]. Despite what may be lower gene delivery efficiency and shorter duration of gene expression compared to viral vectors, electroporation of DNA is not associated with the production of untoward anti-viral cell-mediated immune responses or the production of neutralizing anti-viral antibodies.

Figure 2. GFP expression in muscle cross sections with or without EP (Ichor)



Currently, a variety of EP devices using similar principles are under development. The intramuscular TriGrid™ Delivery System (TDS-IM) by Ichor was used for GX-188E delivery in a Phase 1 trial in high-grade cervical intraepithelial neoplasia (CIN), and is currently employed in an ongoing Phase 2 multinational trial[8, 13]. At this time, EP-mediated gene transfer remains investigational and is not licensed by the FDA or EMEA except for clinical use.

8.2.1.2 GX-188E Dose and Regimen Rationale

In Phase 1, patients with high-grade CIN were treated with GX-188E at a dose of 1 mg, 2 mg and 4 mg per vaccination. Immunological responses, histological improvement and reduction in viral copy were observed at all doses, and there was no clear evidence for a dose-immune response relationship. Furthermore, all three patients in the 1 mg dose cohort had normal histology, no evidence of intraepithelial lesions, and were negative by PCR for HPV at 36 weeks after GX-188E initial administraion[8]. In addition, since utilizing multiple sites rather than a single site enhanced immune responses[19], the number of inoculation sites will be increased to two sites. Therefore, the decision was made to move forward in cervical cancer at the 1 mg/site x 2 anatomic sites for a total 2 mg per vaccination day dosage.

The vaccination schedule employed in the Phase 1 and Phase 2 trials in high-grade CIN includes only 3 GX-188E vaccinations, administered on the first day of treatment, at Week 4 and Week 12. Although this vaccination schedule has demonstrated efficacy in a pre-malignant condition, a more aggressive schedule may be required for the treatment of advanced cervical cancer. This trial will involve more frequent vaccinations, with the goal of inducing a more robust, rapid and sustained immune response against HPV infected cells. Patients will receive GX-188E vaccinations at Week 1 Day 1, Week 2, Week 4, Week 7, Week 13, Week 19. An optional GX-188E administration may be given at week 46 if it is in the best interests of the patient, as determined by the investigator, once the patient has completed 37 weeks of treatment. Additional GX-188E administration(s) may be given to the subject after discussion with the sponsor. In this case of multiple injections, since repeated inoculation at the same site interferes with efficient transgene expression[20], alternating inoculation between deltoid and lateralis muscles will be applied to overcome the interference.

8.2.2 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 patients across a

number of indications. For more details on specific indications refer to the Investigator Brochure.

Refer to the Investigator's Brochure (IB)/approved labeling for detailed background information on MK-3475

Pembrolizumab contains the S228P stabilizing mutation and has no antibody-dependent cell-mediated cytotoxicity (ADCC) or complement-dependent cytotoxicity (CDC) activity. Pembrolizumab modulates the level of interleukin-2 (IL-2), tumor necrosis factor alpha (TNF-α), interferon gamma (IFN-ɣ), and other cytokines. The antibody potentiates existing immune responses only in the presence of antigen and does not nonspecifically activate T cells. Pembrolizumab strongly enhances T lymphocyte immune responses in cultured blood cells from healthy human donors, cancer patients, and primates. In T cell stimulation assays using human donor blood cells, the EC50 was in the range of 0.1 to 0.3 nM (see pembrolizumab Investigator Brochure).

8.2.2.1 Pembrolizumab Pharmaceutical and Therapeutic Background

The importance of intact immune surveillance function in controlling outgrowth of neoplastic transformations has been known for decades[22] . 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.[23-24]

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)[25-26.]

The structure of murine PD-1 has been resolved.[42] 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 tyrosine-based signaling motifs, an immunoreceptor tyrosine-based inhibition motif, and an immunoreceptor tyrosine-based switch motif. Following T-cell stimulation, PD-1 recruits the tyrosine phosphatases, SHP-1 and SHP-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[26-29] . 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[30-32] . As a consequence, the PD-1/PD-L1 pathway is an attractive target for therapeutic intervention in advanced cervical cancer.

8.2.2.1.1 Pre-Clinical and Clinical Trials

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[32-39] Anti-mouse PD-1 or anti-mouse PD-L1 antibodies have demonstrated antitumor responses in models of squamous cell carcinoma, pancreatic carcinoma, melanoma, acute myeloid leukemia and colorectal carcinoma.[36,39-42] 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 antitumor activity of PD-1 checkpoint inhibition involved local infiltration and activation of effector T cell function *in vivo*[39]. 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 Investigator's Brochure [IB]).

8.2.2.1.2 Justification for Pembrolizumab Dose

The planned dose of pembrolizumab for this study is 200 mg every 3 weeks (Q3W). 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 overall survival 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 participants 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 of 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 head and neck cancer, 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, and not via direct binding to cancer cells.

Additionally, pharmacology data clearly show target saturation at 200 mg Q3W. First, 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. Second, 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 participant 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

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

9.0 Hypothesis and Study Objectives

9.1 Hypothesis

This study is separated into three Parts, Part A, B and C. Part A will establish the recommended Phase 2 regimen for the investigational treatment; thus, Part A is not hypothesis-driven.

Part B of this study will evaluate the exploratory efficacy of the investigational treatment regimen at the schedule established as safe and well-tolerated in Part A (i.e. recommended Phase 2 treament regimen). Part B follows a Simon Two-Stage minimax design. It is hypothesized that the investigational treatment regimen will improve the ORR_{24} from 15% (H_{null}) to 35% (H_{alt}). The null hypothesis assumes an 15% ORR_{24} for this patient population receiving single-agent pembrolizumab[14]. In Part C, the null hypothesis assumes an 12.2% ORR_{24} for patient population receiving single-agent pembrolizumab[44], regardless of PD-L1 status. For additional details, please refer to Section 24.

9.2 Study Objectives

The primary objective of Part A is to establish the safety and tolerability of the investigational treatment regimen, and to determine the recommended treatment schedule for Part B. Secondary objectives of Part A include clinical efficacy and include, but are not limited to, objective response rate (ORR) by both RECIST v1.1 criteria[17] (see Appendix 5) and Response Evaluation Criteria In Solid Tumors for Immunotherapeutics (iRECIST)[18] (see Appendix 6), time-to-best response (TTR), duration of response (DOR), progression-free survival (PFS) and overall survival (OS).

The primary objective of Part B and C is to evaluate the efficacy of the investigational study treatment, as determined by ORR_{24} by RECIST v1.1 criteria. Secondary objectives include, but are not limited to, BORR by RECIST v1.1 and iRECIST, TTR, DOR, OS, PFS, and DCR. In addition, the safety and tolerability of the investigational treatment regimen will also continue to be evaluated.

Exploratory objectives of this study are to generate key biomarker data to understand the biological, and specifically, immunological mechanisms associated with and effects of the investigational treatment regimen. Peripheral blood will be collected to evaluate for the ability of GX-188E to induce a systemic HPV-16 and HPV-18-specific T-cell response that may

include, but is not limited to, expansion of CD4+ and CD8+ T-cells that recognize E6 or E7 peptide epitopes. Tumor tissue will be obtained to determine whether the GX-188E vaccination promotes a Th1-polarized anti-tumor immune response. For further details on planned biomarker evaluations, please refer to Section 23.

10.0 Study Design

10.1 Description and Rationale for Study Design

Compared to previous trials of GX-188E, this clinical trial employs a new GX-188E vaccination schedule, includes concurrent administration of pembrolizumab (P) and will enroll patients with advanced cervical cancer. Therefore, this necessitates a study that is designed to (1) evaluate the safety and tolerability of the GX-188E plus pembrolizumab (P) regimen, (2) establish a recommended Phase 2 treatment schedule, and (3) evaluate the clinical and biological efficacy of the investigational treatment regimen.

Protocol GX-188E-005 is a Phase Ib/II multi-national, multi-center, open-label trial of GX-188E plus pembrolizumab (P), (GX-188E + P). Part A will be principally focused on safety and tolerability, and will establish the recommended Phase 2 treatment schedule for the investigational regimen. In Part B and C, the anti-tumor efficacy of the investigational regimen will be explored.

10.2 Part A: Evaluation of Safety and Tolerability

Part A follows a standard 6 + 3 design and will establish the recommended Phase 2 treatment schedule for the investigational combination.

A minimum of 6 patients will be enrolled and treated at the Starting Schedule (see Table 3 in Section 12). If none or only 1 of the first 6 patients experiences a dose-limiting toxicity (DLT) (for protocol defined DLTs, please refer to Section 21), the study will move into Part B. If two patients experience a DLT, an additional 3 patients will be enrolled and evaluated for DLTs. If no additional patients experience a DLT (i.e. only 2 out of 9 patients have DLTs), enrollment into Part B will be initiated. If ≥3 patients in 6 or 9 have a DLT, the Starting Schedule will be considered to be too toxic and enrollment into Reduction Level 1 (see Table 3 in Section 12) will be initiated. If one of the first 6 patients, or no more than 2 patients in a total of 9, experiences a DLT at Reduction Level 1, then this regimen will be moved into Part B of the study. If ≥3 patients in 6 or 9 receiving Reduction Level 1 experience a DLT, then the

investigational regimen will be considered to be too toxic and no additional patients will be enrolled into the trial. Only one reduction in the treatment schedule is planned.

Patients without DLT who are treated with the recommended Phase 2 regimen and who are considered to be evaluable for efficacy will be included in the efficacy analysis for the first stage of Part B.

10.3 Part B: Exploratory Efficacy Evaluation of GX-188E + P

Part B of this study employs a Simon Two-Stage design to evaluate the anti-tumor efficacy of the investigational combination at the recommended Phase 2 schedule established as tolerable in Part A. In the first stage (Stage 1) of Part B, 15 patients will be treated. These may include any patients from Part A (1) who do not experience a DLT, (2) receive the recommended Phase 2 treatment regimen, and (3) who are considered evaluable for efficacy. If at least 3 efficacy evaluable patients from Part B Stage 1 (see Section 24.4) have objective responses by RECIST v1.1 criteria (partial response or better) within the first 24 weeks of treatment, an additional 13 patients will be enrolled, for a total of 28 efficacy evaluable patients. If 2 or fewer efficacy evaluable patients in Part B Stage 1 have an objective response, enrollment into the study will be discontinued for futility. Study has passed the first stage of Simon-Two stage design.

10.4 Part C: Efficacy Evaluation in Larger Number of Patients

If at least 8 of the 28 subjects enrolled in Part B, experience an objective response who are considered evaluable for efficacy, it will be considered that ORR satisfies the criteria for study expansion and additional subjects will be enrolled in Part C to evaluate efficacy further in larger population. If only 7 or fewer subjects in Part B experience an objective response, enrollment to Part C will not open.

10.5 Number of Patients

Maximum 60 patients are planned for recruitment to both Parts A, B and C of this study. As previously described in Section 10.2 above, minimum of 6 patients will be enrolled into Part A. The maximum number of safety evaluable patients to be enrolled into Part A is 18.

Part B of this study employs a Simon-Two Stage Design. A minimum of 15 efficacy evaluable patients (see Section 24.4), which may include some patients from Part A, will be included in the analysis for Stage 1. If 3 or more patients in Stage 1 experience objective responses (i.e., Partial Response or better), the study will move into Part B Stage 2 and an additional 13 patients

will be treated, for a total of 28 efficacy evaluable patients. Study has passed the first stage of Simon-Two stage design.

If at least 8 of the 28 subjects enrolled in Part B, experience an objective response who are considered evaluable for efficacy, it will be considered that ORR satisfies the criteria for study expansion and additional 17 subjects (at least) will be enrolled in Part C to evaluate efficacy further in larger population (N=45~60). Refer to the Section 24.3 Sample Size and Power for detailed assumptions for sample size estimation.

10.6 Number of Study Centers

The study will be performed at least 8 investigational sites in the the Republic of Korea. Additional sites may be added as necessary for patient enrollment.

10.7 Selection of Study Population

All patients must participate in the consent process. During the consent process, the person obtaining consent must inform the patient of all elements of informed consent. No protocol-specific procedures, including screening procedures, are to be performed until the patient has signed and dated an institutional review board (IRB)/independent ethics committee (IEC)-approved informed consent form. For each patient, study participation begins with the signing and dating of the informed consent form. Patients must also meet the inclusion and exclusion criteria to be enrolled in the study.

10.7.1 Inclusion Criteria

1. Patients must be female and age ≥ 18 years on day of signing of informed consent; 19 years for patients treated in Korea
2. Patients with histologically confirmed advanced or metastatic HPV-positive (HPV-16 or HPV-18) cervical cancer, who have disease progression after treatment with all available therapies for metastatic disease that are known to confer clinical benefit, or are intolerant to treatment, or refuse standard treatment.

   Note: there is no limit to the number of prior treatment regimens.
3. Eastern Cooperative Oncology Group (ECOG) Performance Status of 0-1
4. Life Expectancy of at least 6 months
5. Patients must agree to provide either an archival tumor tissue sample or fresh biopsy sample for baseline biomarker tissue analyses, including staining for PD-L1. If archival

tissue is not available and the patient does not have biopsy-accessible tumor lesions, the patient will be excluded.

6. Patients must have must have adequate organ function as defined in the following table (Table 1). Specimens must be collected within 28 days prior to the start of study treatment.

Table 1: Organ Function Requirements for Eligibility

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 participant with creatinine levels >1.5 × institutional ULN
Hepatic	
Total bilirubin	≤1.5 ×ULN OR direct bilirubin ≤ULN for participants with total bilirubin levels >1.5 × ULN (except in patients with Gilbert's Syndrome who must have a total bilirubin < 3x ULN and ALT < 3x ULN)
AST (SGOT) and ALT (SGPT)	≤2.5 × ULN (≤5 × ULN for participants with liver metastases)
Coagulation	
International normalized ratio (INR) OR prothrombin time (PT) Activated partial thromboplastin time (aPTT)	≤1.5 × ULN unless participant 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; ULN=upper limit of normal. [1] Criteria must be met without erythropoietin dependency and without packed red blood cell (pRBC) transfusion within last 4 weeks. [2] Creatinine clearance (CrCl) should be calculated using the Cockroft-Gault equation. 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. Patients must have RECIST measurable disease, defined as:

- Tumor lesion ≥ 1 cm in longest diameter (LD) on an axial CT or MRI image (≤5 mm reconstruction interval)

  -OR-

- Lymph node ≥1.5 cm in the short axis on CT (≤5 mm reconstruction interval)

8. Women of childbearing potential (WOCBP) must have a negative serum or urine pregnancy test within 72 hours prior to receiving the first dose of study medication. If the urine test is positive or cannot be confirmed as negative, a serum pregnancy test will be required

9. WOCBP must be willing to use an adequate dual method of contraception during the course of the study through 120 days after the last dose of study medication. Post-menopausal females (> 45 years old and without menses for > 1 year) and surgically sterilized females are exempt from these requirements. *Note: Abstinence is acceptable if this is the usual lifestyle and preferred contraception for the subject*.

10. Be willing and able to written informed consent for the trial in accordance with federal, local, and Institutional guidelines.

10.7.2 **Exclusion Criteria**

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

1. Patient has disease that is suitable for local therapy administered with curative intent

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

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

3. Patient is expected to require any other form of antineoplastic therapy while on study; including systemic chemotherapy, radiation therapy (except for palliative purposes) biological therapy, or immunotherapy not specified in this protocol.

4. Patient has a history of active central nervous system (CNS) metastases and/or carcinomatous meningitis.

5. 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 (e.g., CTLA-4, OX 40, CD137) and was discontinued from that treatment due to a Grade 3 or higher immune-related Adverse Event (irAE).

6. Patients with active autoimmune disease requiring systemic immunosuppressive treatment within the past 2 years (i.e. 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, etc.) is not considered a form of systemic treatment and is allowed.

7. Has had an allogeneic solid organ or allogeneic bone marrow transplant

8. Patient has had a prior, non-PD-1/PD-L1/PD-L2, anti-cancer monoclonal antibody (mAb) (e.g., bevacizumab, cetuximab, etc) within 4 weeks prior to the first dose of study medication or who has not recovered (i.e., ≤ Grade 1 or at baseline) from adverse events due to agents administered more than 4 weeks earlier.

9. Has received prior systemic anti-cancer therapy, including investigational agents within 4 weeks, or within 2 weeks for targeted small molecule therapies with a half-life of <48 hrs prior to the first dose of study medication

   Note: Participants must have recovered from all AEs due to previous therapies to ≤Grade 1 or baseline. Participants with ≤Grade 2 neuropathy and/or ≤Grade 2 anemia may be eligible.

   Note: If patient received major surgery, they must have recovered adequately from the toxicity and/or complications from the intervention prior to starting therapy.

10. Has received prior radiotherapy within 2 weeks of start of study treatment. Participants must have recovered from all radiation-related toxicities

11. Patient has received transfusion of blood products (including platelets or red blood cells) or administration of colony stimulating factors (including G-CSF, GM-CSF or recombinant erythropoietin) within 4 weeks prior to the first dose of study medication.

12. Patients with bilateral hydronephrosis that cannot be alleviated with ureteral stents or percutaneous nephrostomy

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

14. Patient has a history of (non-infectious) pneumonitis that required steroids or has current pneumonitis.

15. 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 the first dose of study drug..

16. Patient has risk factors for bowel obstruction or bowel perforation (examples include but not limited to a history of acute diverticulitis, intra-abdominal abscess, and abdominal carcinomatosis).

17. Patient who is currently participating in or has participated in a study of an investigational agent and received study therapy or used an investigational device within 4 weeks of the first dose of study medication

    Note: Participants who have entered the follow-up phase of an investigational study may participate as long as it has been > 4 weeks after the last dose of the previous investigational agent.

18. Unstable/inadequate cardiac function:

    - Symptomatic ischemia

- Uncontrolled or clinically significant conduction abnormalities (e.g., ventricular tachycardia on antiarrhythmics are excluded); 1st degree AV block or asymptomatic LAFB/RBBB are eligible
- Myocardial infarction in the previous six months
- Congestive heart failure (New York Heart Association class III to IV)

19. Has an active infection requiring systemic therapy.
20. Participants with known human immunodeficiency virus (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 Hep C Ab result and known quantitative HCV RNA results greater than the lower limits of detection of the assay..
21. Patient has a known history of active TB (Bacillus Tuberculosis)
22. Has received a live or live attenuated vaccine within 30 days prior to the first dose of study drug. Note: Administration of killed vaccines are allowed.
23. Has a known psychiatric or substance abuse disorder that would interfere with the participant's ability to cooperate with the requirements of the study.
24. Patient who received an implantable electronic device (e.g., pace maker)
25. A WOCBP who has a positive urine pregnancy test (e.g. 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
26. Patients who are pregnant or lactating.
27. Has a history or current evidence of any condition, therapy, or laboratory abnormality that might confound the results of the study, interfere with the participant's participation for the full duration of the study, or is not in the best interest of the participant to participate, in the opinion of the treating investigator.

10.8 Duration of Patient Participation

All patients will be permitted to remain on study to receive the investigational combination treatment as long as it is well tolerated and both the Investigator and Sponsor agree that the patient may be clinically benefitting from treatment, for up to 2 years. Reasons for treatment discontinuation include, but are not limited to, the following:

- Unacceptable or Dose-Limiting Toxicity
- Disease Relapse or Progression
- Death
- Voluntary withdrawal of consent
- Non-compliance to study procedures and requirements
- Investigator decision

- Sponsor decision to terminate the study

Unless a patient withdraws consent or dies during the treatment period of the study, she will be followed for up to 1 year after study treatment discontinuation for survival data.

10.9 Duration of Study

The duration of the study will depend on the recruitment rate and the duration of treatment for those patients enrolled.

11.0 Investigational Treatments-Product Information

The investigational treatment for this study consists of intramuscular vaccination with GX-188E, delivered with electroporation and intravenous administration of pembrolizumab.

Table 2. Investigational Treatment Product Details

Product	Active Ingredient	Inactive Ingredient(s)
GX-188E	2 mg/mL* pGX27-E6E7	Potassium Chloride (USP)
		Sodium Phosphate Dibasic, Anhydrous (USP)
		Potassium Phosphate Monobasic, Anhydrous, Crystals (NF)
		Sodium Chloride (USP)
		Water for Injection (USP)
Pembrolizumab	pembrolizumab	L-histidine, polysorbate 80, and sucrose. May contain hydrochloric acid/sodium hydroxide, or water for injection

*Target concentration of the DNA plasmid

11.1 GX-188E Product Information

As previously described, GX-188E, is a DNA plasmid that encodes a fusion protein containing the E6 and E7 proteins of HPV16 and 18, and human Fms-like tyrosine kinase 3 ligand (hFLT-3L). GX-188E will be provided by Genexine Inc. or its designee.

The GX-188E vials will be shipped directly from the manufacturer or its designee to regional depot which to be shipped to each individual study site. Each vial will be labeled with a single panel label. Vials will only be handled by designated personnel (e.g. pharmacist) at each site.

11.1.1 Storage and Handling of GX-188E

Genexine, Inc. will be responsible for assuring that the quality of the GX-188E investigational product is adequate for the duration of the trial. Unless otherwise specified, GX-188E will be shipped at -20ºC with a temperature monitoring device. If the temperature monitoring device denotes temperatures outside the pre-specified range, the Sponsor, or its designee should be contacted immediately.

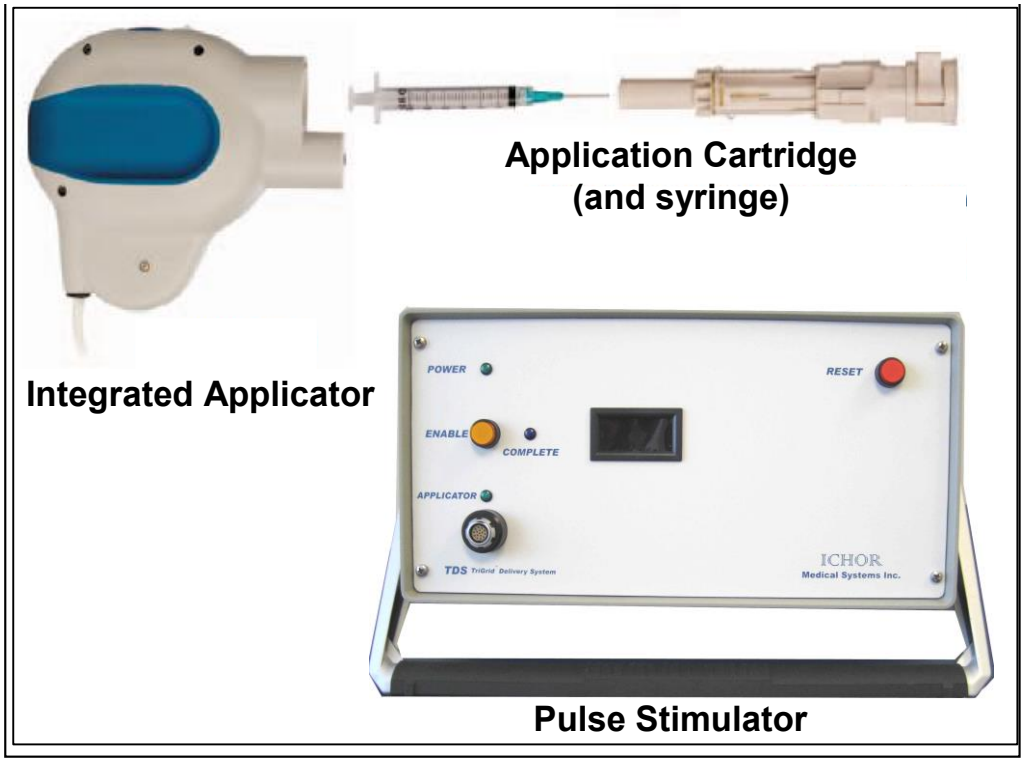
GX-188E should be stored in a secure area according to local regulations, and should be transferred from the shipping container to the appropriate storage conditions (refrigerated at -20ºC) upon arrival. The recommended storage condition for GX-188E is -20°C. The Sponsor should be notified of any deviations from this recommended storage condition. Refrigerator temperature logs must be maintained at the clinical site and temperatures must be recorded and monitored regularly.

11.1.2 Dispensing of GX-188E

It is the responsibility of the Investigator to ensure that GX-188E is only dispensed to study participants. GX-188E must be dispensed only from official study sites by authorized personnel according to local regulations. GX-188E will be provided to the investigational pharmacy in vial form directly from the manufacturing facility or designee.

The designated site staff member will be responsible for dispensing the appropriate volumes (one 0.5 ml volume) of GX-188E according to the instructions provided in the study Pharmacy Manual. In brief, a single injection syringe containing 1 mg of GX-188E will be prepared and loaded into the Cartridge of the Integrated Applicator (Figure 3). A qualified investigator or designee will deliver GX-188E by pressing a single button in the Integrated Applicator, which will deliver all its content at once, into the patient’s deltoid or lateralis muscle.

Figure 3. TDS-IM ® Cartridge and Integrated Applicator



11.1.3 Records of GX-188E Disposition at Investigational Site(s)

It is the responsibility of the Investigator to ensure that a current record of GX-188E disposition is maintained at the study. Records or logs must comply with applicable regulations and guidelines, and should include:

- Amount received and placed in storage area;
- Amount currently in storage area;
- Label ID number or batch number and use date or expiry date;
- Dates and initials of the person responsible for each investigational product inventory entry/movement;
- Amount dispensed to each patient, including unique patient identifiers;
- Amount transferred to another area/site for dispensing or storage;
- Non-study disposition;
- Amount returned to Sponsor;
- Amount destroyed at study site, if applicable.

11.1.4 Return and Destruction of GX-188E

Upon completion or termination of the study, all unused and/or partially used GX-188E product must be returned to Genexine, Inc., or its designee, if not authorized by Genexine, Inc. to be destroyed at the site. GX-188E product that is returned to Genexine Inc., or its designee, must be accompanied by the appropriate documentation. Returned supplies should be in the original containers. Empty containers should not be returned to Genexine Inc. It is the Investigator's responsibility to ensure proper disposal for all empty containers, provided that procedures for proper disposal have been established according to applicable federal, state, local and institutional guidelines and procedures, and provided that appropriate records of disposal are kept. The return of unused investigational product(s) should be arranged by the responsible Site Monitor**.**

If GX-188E products are to be destroyed on site, it is the Investigator's responsibility to ensure that arrangements have been made for the proper disposal, and written authorization has been granted by Genexine, Inc. or its designee. It is the Investigator's responsibility to ensure that procedures for proper disposal have been established according to applicable regulation and guidelines and institutional procedures, and appropriate records of the disposal have been documented. The unused investigational products can only be destroyed after being inspected and reconciled by Genexine Inc. or responsible party designated Site Monitor.

11.2 TDS-IM® Electroporation Device Use and Accountability

Detailed instructions for use of the TDS-IM® device are located in the TDS-IM® Operations Manual. Each clinical site will receive training for the use of the TDS-IM® device.

The GX-188E vaccination and electroporation procedure must be performed by qualified personnel who have been trained to participate in this clinical trial. Any individual designated to perform the procedure should be permitted by the relevant local authorities to administer vaccinations to patients (e.g. MD, DO, PA, NP, RN) in addition to receiving device training from sponsor personnel.

Each clinical site is responsible for maintaining investigational device accountability. This includes recording the TDS-IM® serial number, applicator serial number, and array lot number used for vaccination + EP of each subject.

11.3 Pembrolizumab Product Information

As previously described, 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 patients across a number of indications. For more details on specific indications refer to the Investigator brochure.

Pembrolizumab is provided as a solution for infusion, in 100 mg/vial dose strength. Clinical supplies must be stored in a secure, limited-access location under the storage conditions specified on the label. Receipt and dispensing of trial medication must be recorded by an authorized person at the trial site. *Clinical supplies may not be used for any purpose other than that stated in the protocol.*

12.0 Investigational Treatment Plan-Route and Regimen

The investigational treatment regimen of GX-188E + pembrolizumab (P) will be administered according to the schedules described in this section. The investigational treatment regimen will be offered to each patient as long as both the patient and Investigator agree that it continues to be well tolerated, and there has been no evidence of clinical or radiographic disease progression.

12.1 Part A: Establishing Recommended Phase 2 Treatment Schedule

The full investigational treatment plan is described in Table 3.

12.1.1 Starting Treatment Schedule

The following treatment schedule will be the initial regimen to be explored in this study. If this regimen is considered to be well-tolerated, in accordance with the rules of the "6 + 3" study design and the protocol-defined dose-limiting toxicities (DLTs) (Section 21), the study will move into Part B (Simon Two-Stage) and will employ this treatment schedule. If ≥3 patients in the first 6 or 9 experience DLTs, then the Reduction Level 1 treatment schedule described in Section 12.1.1.3 will be explored.

12.1.1.1 GX-188E Administration

GX-188E will be injected intramuscularly (IM), to either deltoid (D) or lateralis (L) muscles, followed immediately by co-localized electroporation (EP) at each scheduled vaccination day. Each muscle will receive 1 mg of GX-188E, for a total of 2 mg per vaccination day. Vaccination sites should alternate between deltoid and lateralis muscles according to the following schedule: Week 1 Day 1 (both right and left D), Week 2 Day 1 (both right and left L), Week 4 Day 1 (both right and left D), Week 7 Day 1 (both right and left L), Week 13 Day 1 (both right and left D), Week 19 Day 1 (both right and left L).An optional GX-188E administration may be given at week 46 if it is in the best interests of the patient, as determined by the investigator, once the patient has completed 37 weeks of treatment. Additional GX-188E administration(s) may be given to the subject after discussion with the sponsor. For GX-188E administrations at Week 46 Day 1, a 2-week window period is permitted in this protocol because this vaccination is considered to be "booster" and a large window period is not expected to alter the biological effects. Vaccination sites of GX-188E can be alternated to either deltoid or lateralis muscles, if GX-188E is not administered correctly at the vaccincation site. In this cases, altered vaccination sites must be recorded on the CRF.

12.1.1.2 Pembrolizumab (P) Administration

Pembrolizumab will be administered according to standard clinical and institutional practices. In brief, Pembrolizumab will be administered using IV infusion on Day 1 of each 3-week treatment cycle after all procedures and assessments have been completed. For the purposes of this study, pembrolizumab should be administered *after* the GX-188E vaccination on all days in which patients are scheduled to receive both.

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. However, given the variability of infusion pumps from site to site, a window between -5 minutes and +10 minutes is permitted (i.e., infusion time is 30 minutes (-5 min/+10 min).

The Pharmacy Manual contains specific instructions for the preparation of the pembrolizumab infusion and administration of infusion solution.

12.1.1.3 Timing of Dose Administration

Trial treatment of pembrolizumab may be administered up to 3 days before or after the scheduled Day 1 of each pembrolizumab cycle due to administrative reasons

12.1.2 Reduction Level 1 Treatment Schedule

If the starting treatment schedule described in Section 12.1.1 is not considered tolerable based on the incidence of dose-limiting toxicities (DLTs) (Section 20), the safety of the following treatment schedule ("Reduction Level 1") will be explored. If Reduction Level 1 is considered to be well-tolerated, in accordance with the rules of the "6 + 3" study design and the protocol-defined DLTs, the study will move into Part B (Simon Two-Stage) and will employ this treatment schedule. If ≥3 patients in 6 or 9 experience a DLT, then the investigational regimen will be considered too toxic and enrollment into the study will be discontinued.

12.1.2.1 Reduction Level 1 GX-188E

The modification to GX-188E administration at Reduction Level 1 involves removal of the GX-188E vaccination at Week 2 Day 1. At Reduction Level 1, GX-188E will be administered Week 1 Day 1, Week 4 Day 1, Week 7 Day 1, Week 13 Day 1, Week 19 Day 1 and Week 46 Day 1(Optional).

12.1.2.2 Reduction Level of Pembrolizumab

The dosage and frequency for pembrolizumab will not be modified. Patients will receive the regimen for pembrolizumab as described in Section 12.1.1.2

Table 3. Investigational Treatment Schedules

Treatment Schedule	GX-188E	Pembrolizumab (P)
Starting Schedule	Week 1 Day 1, Week 2, Week 4, Week 7, Week 13, Week 19 and Week 46 (Optional)	200 mg Day 1 q 3 weeks
Reduction Level 1	Week 1 Day 1, Week 4, Week 7, Week 13, Week 19, and Week 46 (Optional) *(remove Week 2)*	200 mg Day 1 q 3 weeks (unchanged)

12.2 General Dosing Adjustments and Delays and Supportive Care Instructions

Treatment or visit delays for public holidays or weather conditions do not constitute a protocol violation.

12.2.1 Dose Modification and Toxicity Management for Immune-related AEs Associated with Pembrolizumab

AEs associated with pembrolizumab exposure may represent an immune-related response. These 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. Dose modification and toxicity management guidelines for irAEs associated with pembrolizumab are provided in Table 4.

Table 4. Dose Modification and Toxicity Management Guidelines for Immune-related AEs Associated with Pembrolizumab.

General instructions:

1. For Severe and life-threatening irAEs, should be treated with IV corticosteroid should be initiated first corticosteroids followed by oral steroidsteroids. Other immunosuppressive treatment should be initiatedbegin if the irAEs cannot beare 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 v4.0 or the most recent version)	Action with pembrolizumab	Corticosteroid and/or other therapies	Monitor and follow-up
Pneumonitis	Grade 2	Withhold	• Administer corticosteroids (initial dose of 1-2 mg/kg prednisone or equivalent) followed by taper • Add prophylactic antibiotics for opportunistic infections	• Monitor participants for signs and symptoms of pneumonitis • Evaluate participants 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 1-2 mg/kg prednisone or equivalent) followed by taper	• Monitor participants 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- 1 mg/kg	• Monitor with liver function tests (consider weekly or more frequently until liver

			prednisone or equivalent) followed by taper	enzyme value returned to baseline or is stable
	Grade 3 [b] or 4 [c]	Permanently discontinue	• Administer corticosteroids (initial dose of 1-2 mg/kg prednisone or equivalent) followed by taper	
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 participants with T1DM • Administer anti-hyperglycemic in participants with hyperglycemia	• Monitor participants 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 non-selective 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, 4	Continue	• Initiate thyroid replacement hormones (eg, levothyroxine or liothyroinine) 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 1-2 mg/kg or equivalent) followed by taper.	• Monitor changes of renal function
	Grade 3 or 4	Permanently discontinue		
Myocarditis	Grade 1	Withhold	• Based on severity of AE administer corticosteroids	• Ensure adequate evaluation to confirm etiology and/or exclude other causes
	Grade 2, 3 or 4	Permanently discontinue		
All Other immune-related AEs	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 type of event [e]		
	Grade 4 or recurrent Grade 3	Permanently discontinue		

[a.] AST/ALT: >3.0 - 5.0 x ULN if baseline normal; >3.0 5.0 x baseline, if baseline abnormal; bilirubin:>1.5 3.0 x ULN if baseline normal; >1.5 - 3.0 x baseline if baseline abnormal

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

[c.] AST/ALT: >20.0 x ULN, if baseline normal; >20.0 x baseline, if baseline abnormal; bilirubin: >10.0 x ULN if baseline normal; >10.0 x 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: Guillain-Barre Syndrome, encephalitis, Stevens-Johnson Syndrome and toxic epidermal necrolysis.

Requirements for treatment discontinuation are not strict and individual situations will be evaluated on a case-by-case basis. Treatment discontinuation for both non-hematological and hematological toxicities will be based on the Principal Investigator's judgment following discussion with the Sponsor's Medical Monitor.

12.2.2 Dose modification and toxicity management of infusion-reactions related to pembrolizumab

Pembrolizumab may cause severe or life threatening infusion-reactions including severe hypersensitivity or anaphylaxis. Signs and symptoms usually develop during or shortly after drug infusion and generally resolve completely within 24 hours of completion of infusion. Dose modification and toxicity management guidelines on pembrolizumab associated infusion reaction are provided in Table 5.

Table 5. Pembrolizumab Infusion Reaction Dose modification 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 participant is deemed medically stable in the opinion of the investigator.	None
Grade 2 Requires therapy or infusion interruption but responds promptly to symptomatic treatment (e.g., 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 participant 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 (e.g. from 100 mL/hr. to 50 mL/hr.). Otherwise dosing will be held until symptoms resolve and the participant 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 interventionwith: 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 (i.e., not rapidly responsive to symptomatic medication and/or brief interruption of infusion); recurrence of symptoms following initial improvement; hospitalization indicated for other clinical sequelae (e.g., renal impairment, pulmonary infiltrates) **Grade 4:** Life-threatening; pressor or ventilator support indicated	• **Stop Infusion.** • Additional appropriate medical therapy may include but is not limited to: • Epinephrine** • IV fluids • Antihistamines • NSAIDs • Acetaminophen • Narcotics • Oxygen • Pressors • Corticosteroids • Increase monitoring of vital signs as medically indicated until the participant 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.	No subsequent dosing
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 v4.0 or the most recent version (CTCAE) at http://ctep.cancer.gov		

12.2.3 Other Allowed Dose Interruption for Pembrolizumab

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 of the originally scheduled dose and within 42 days 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.

12.2.4 Supportive Care Guidelines for Events of Clinical Interest and Immune-related Adverse Events (irAEs)

Events of clinical interest of a potential immunologic etiology (irECIs) may be defined as an adverse event of unknown etiology, associated with drug exposure and is consistent with an immune phenomenon. irAEs may be predicted based on the nature of the pembrolizumab compound, its mechanism of action, and reported experience with immunotherapies that have a similar mechanism of action. Special attention should be paid to AEs that may be suggestive of potential irAEs. An irAE can occur shortly after the first dose or several months after the last dose of treatment.

If an irAE is suspected, efforts should be made to rule out neoplastic, infectious, metabolic, toxin or other etiologic causes prior to labeling an adverse event as an irAE. Patients who develop a Grade 2 or higher irAE should be discussed immediately with the Sponsor.

13.0 Prior Treatment

Patients should have disease that is relapsed or refractory to standard-of-care treatment regimens. Patients should not be candidates for other approved, standard-of-care therapies. Patients with newly-diagnosed disease that is not amenable to definitive surgery and who refuse treatment with standard regimens are permitted with clear Investigator documentation. In addition, the determination that there are “no available therapies that will confer clinical benefit” for the patient will be based on the medical opinion of the Principal Investigator.

Reasonable efforts will be made to determine all relevant prior treatments received by the patient during the Screening period. All previous cancer treatments, including systemic

therapies, radiation and/or surgical procedures, should be recorded on the patients' case report forms (CRF).

14.0 Meals and Dietary Restrictions

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

15.0 Concomitant Treatments

All treatments that the investigator considers necessary for a patient's welfare may be administered at the discretion of the Investigator in keeping with the community standards of medical care. All concomitant medications must be recorded on the CRF, including all prescription, over-the-counter (OTC), herbal and vitamin supplements, and IV medications and fluids. The reason for treatment, name of the drug, dosage, route, and start and stop dates of administration for each concomitant medication will also be reported on the CRF. All changes (e.g., changes in dose, discontinuation, etc.) in concomitant treatments that occur during the trial period should also be reported.

All concomitant medications received to the subject within 28 days prior to the first dose through the end of the subject's study participation should be recorded. (However, during the follow-up period after the end of the clinical trial, only the data about the antineoplastic therapy (surgical therapy, chemotherapy, radiation therapy, etc.) treated after the end of the subject's study participation is recorded.).Concomitant medications administered 30 days after the last dose of study treatment should be recorded for SAEs and events of clinical interest (ECIs) as defined in Section 20.8

15.1 Acceptable Concomitant Medications

With the exception of medications specifically prohibited in Exclusion Criteria 3 and 6, and during the treatment period of this study (see Section 15.2), patients are permitted to receive any supportive medications and treatments to manage ongoing medical conditions or AEs. .Patients may receive red blood cell and platelet transfusions, or other hematopoietic support (i.e. growth factors) as needed during study participation *after eligibility has been determined* and the patient has been enrolled into the trial.

15.2 Prohibited Concomitant Medications

Medications or vaccinations specifically prohibited in the exclusion criteria are not allowed during the ongoing trial. If there is a clinical indication for any medication or vaccination specifically prohibited during the trial, discontinuation from study intervention or vaccination may be required. The investigator is to discuss prohibited medication/vaccination with the Sponsor's Clinical Director. The final decision on any supportive therapy or vaccination rests with the investigator and/or the participant's primary physician. However, the decision to continue the participant on study treatment requires the mutual agreement of the investigator, the Sponsor and the participant.

Listed below are specific restrictions for concomitant therapy or vaccination during the course of the study: (Note: There are no prohibited therapies during the post-treatment long-term follow-up period).

- Anti-cancer systemic chemotherapy or biological therapy other than those specified in the protocol (GX-188E, pembrolizumab)
- Immunotherapy not specified in this protocol
- Chemotherapy not specified in this protocol
- Investigational agents other than Use of investigational therapeutic agents than those specified in the protocol (i.e., investigational regimen; GX-188E, pembrolizumab).
- Radiation therapy
    - Note: Radiation therapy to a symptomatic solitary lesion, to the brain, or for palliative purposes may be allowed after consultation with Sponsor Medical Monitor.
- Live or live attenuated vaccines within 30 days prior to the first dose of trial treatment and while participating in the trial.

  Note: Administration of killed vaccines are allowed.

  Note: Any licensed COVID-19 vaccine (including for Emergency use) in a particular country is allowed in the study as long as they are mRNA vaccines, adenoviral vaccines, or inactivated vaccines. These vaccines will be treated just as any other concomitant therapy. Investigational vaccines (i.e., those not licensed or approved for Emergency Use) are not allowed.
- 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 Medical Monitor. *Topical and inhaled steroids are permitted*.

- Red blood cell or platelet transfusion, and hematopoietic growth factors are not permitted within 4 weeks prior to the first dose of study medication. However, once a patient has met all eligibility criteria and has enrolled into the trial, hematopoietic support treatments are permitted.

Patients who, in the assessment by the Investigator, require the use of any of the aforementioned treatments for clinical management should be removed from the trial. Patients may receive other medications that the Investigator deems to be medically necessary.

16.0 STUDY PROCEDURES AND OBSERVATIONS

All procedures for Part A,B and C are identical. These procedures are described in table format in the Schedule of Events (Appendix 1)

16.1 Screening Evaluation

The following Screening assessments must be performed **within 28 days** before administration of any component of the investigational treatment regimen. Procedures listed below that are performed as part of the normal standard of care (SOC) and within 28 days prior to Week 1 Day 1 may be used for screening purposes.If there are clinically significant abnormal laboratory test results or suspicious laboratory results, at the discretion of investigator (1) one time re-test for subjects with screening purposes is allowed (2) For screen-fail subjects with same reason above, one time re-screen is allowed.

:

1. Sign and date an IRB/IEC-approved informed consent form before any study-specific (i.e., non-SOC) screening procedures are performed.
2. Demographic information including date of birth, gender, and ethnic origin
3. Medical history, including review of prior cancer treatments and documentation of HPV 16 or 18 positive cervical cancer. HPV-16 or HPV-18 positivity will be determined according to the patients' previous medical records or in situ PCR method using the patients' archival tissue sample or new biopsy tissue sample.
4. Review of concomitant medications
5. ECOG performance evaluation

6. Moore criteria evaluation (APPENDIX 3). Determine whether the patient is classified as low risk, mid risk, or high risk based upon Moore criteria[15, 16]
7. Complete physical examination including weight (kg) and height (cm)
8. Vital signs [sitting blood pressure, pulse rate, respiratory rate, and temperature]
9. Chest X-ray, ECG and Clinical laboratory evaluation (hematology, coagulation, serum chemistry, serology, urinalysis), including blood CEA/TA4 levels and thyroid function tests; see Appendix 4.
10. Serum or urine pregnancy test. This is only required for females of child-bearing potential and must be negative within 3 days prior to Week 1 Day 1.
11. Research blood collection. (including blood sample for Flt-3L level monitoring)
12. Pre-treatment tumor biopsy. All patients must submit either an archival tumor tissue sample or fresh biopsy sample at Screening. Coagulation tests must be performed and evaluated within 24 hr prior to all biopsy procedures.
13. Radiographic evaluation of tumor burden. Scans performed within 28 days of Week 1 Day 1 will be accepted and do not need to be repeated unless a clinically significant difference is suspected. See Appendices 5 and 6.

A patient who meets all of the inclusion criteria may enter the study. Screen failures will be reported into the Screen Failures Log.

16.2 **Week 1 Day 1**

At the Week 1 Day 1 visit, patients will return to the clinic for the first administration of GX-188E and P.

Patients will undergo the following procedures on Week 1 Day 1:

1. AE monitoring
2. Recording of concomitant medications
3. Vital signs and weight
4. Symptom-directed physical exam

5. Clinical laboratory evaluation (hematology, serum chemistry, urinalysis). The laboratory tests may not be performed repately if the screening tests were performed within 7 days of Week 1 Day 1 and the clinically significant changes for the results were not suspected.
6. Research blood collection. This sample must be obtained prior to the first dose of GX-188E and pembrolizumab.
7. Pain Assessment. Within 30 minutes before and 5 minutes (± 2 minutes) after GX-188E administration, pain score in association with the electroporation (EP) procedure should be reported.
8. Administration of GX-188E at *both* right and left deltoid muscles
9. Administration of pembrolizumab. For the purposes of this study, pembrolizumab should be administered *after* the GX-188E vaccination on all days in which patients are scheduled to receive both.

16.3 **Week 2 Day 1 (± 3 days)**

At Week 2 Day 1, patients will return to the clinic for administration of GX-188E (without pembrolizumab) and undergo the following procedures:

1. AE monitoring
2. Recording of concomitant medications
3. Vital signs and weight
4. Symptom-directed physical exam
5. Clinical laboratory evaluation (hematology and serum chemistry).
6. Pain Assessment. Within 30 minutes before and 5 minutes (± 2 minutes) after GX-188E administration, pain score in association with the electroporation (EP) procedure should be reported.
7. Administration of GX-188E at both right and left lateralis muscles

16.4 Week 3 Day 1 (±3 days)

Only safety evaluations will occur at the Week 3 Day 1 visit; no study drugs will be administered. Patients will undergo the following procedures on Week 3 Day 1:

1. AE monitoring
2. Recording of concomitant medications
3. Vital signs and weight
4. Symptom-directed physical exam
5. Clinical laboratory evaluation (hematology and serum chemistry).

16.5 Week 4 Day 1 (± 3 days)

At Week 4 Day 1, patients will return to the clinic for administration of GX-188E + P and undergo the following procedures:

1. AE monitoring
2. Recording of concomitant medications
3. Vital signs and weight
4. Symptom-directed physical exam
5. ECOG Performance Status
6. Clinical laboratory evaluation (hematology and serum chemistry).
7. Research blood collection.
8. Pain Assessment. Within 30 minutes before and 5 minutes (± 2 minutes) after GX-188E administration, pain score in association with the electroporation (EP) procedure should be reported.
9. Administration of GX-188E at both right and left deltoid muscles (or, lateralis muscles for Reduction Level 1)
10. Administration of pembrolizumab. For the purposes of this study, pembrolizumab should be administered *after* the GX-188E vaccination on all days in which patients are scheduled to receive both.

16.6 **Week 7 Day 1 (±3Days)**

At Week 7 Day 1, patients will return to the clinic for administration of GX-188E + P and undergo the following procedures:

1. AE monitoring
2. Recording of concomitant medications
3. Vital signs and weight
4. Symptom-directed physical exam
5. ECOG Performance Status
6. Clinical laboratory evaluation (hematology, serum chemistry, *and both blood CEA/TA4 levels and thyroid function tests*).
7. Research blood collection.
8. Pain Assessment. Within 30 minutes before and 5 minutes (± 2 minutes) after GX-188E administration, pain score in association with the electroporation (EP) procedure should be reported.
9. Administration of GX-188E at both right and left lateralis muscles (or, deltoid muscles for Reduction Level 1)
10. Administration of pembrolizumab. For the purposes of this study, pembrolizumab should be administered *after* the GX-188E vaccination on all days in which patients are scheduled to receive both.

16.7 **Week 10 Day 1 (± 3 days)**

At Week 10 Day 1, patients will return to the clinic to receive pembrolizumab and undergo the following procedures:

1. AE monitoring
2. Recording of concomitant medications
3. Vital signs and weight
4. Symptom-directed physical exam

5. ECOG Performance Status
6. Clinical laboratory evaluation (hematology, serum chemistry, urinalysis, coagulation).
7. Research blood collection. (including blood sample for Flt-3L level monitoring)
8. Optional post-baseline tumor biopsy. Coagulation tests must be performed and evaluated within 24 hr prior to all biopsy procedures.
9. Radiographic evaluation of tumor burden and determination of response by RECIST v1.1 and iRECIST. See Appendices 5 and 6.
10. Administration of pembrolizumab. For the purposes of this study, pembrolizumab should be administered *after* the GX-188E vaccination on all days in which patients are scheduled to receive both.

16.8 **Week 13 Day 1 (± 3 days)**

At Week 13 Day 1, patients will return to the clinic for administration of GX-188E + P and undergo the following procedures:

1. AE monitoring
2. Recording of concomitant medications
3. Vital signs and weight
4. Symptom-directed physical exam
5. ECOG Performance Status
6. Clinical laboratory evaluation (hematology, serum chemistry, *and both blood CEA/TA4 levels and thyroid function tests)*.
7. Pain Assessment. Within 30 minutes before and 5 minutes (± 2 minutes) after GX-188E administration, pain score in association with the electroporation (EP) procedure should be reported.
8. Administration of GX-188E at both right and left deltoid muscles (or, lateralis muscles for Reduction Level 1)

9. Administration of pembrolizumab. For the purposes of this study, pembrolizumab should be administered *after* the GX-188E vaccination on all days in which patients are scheduled to receive both.

16.9 Week 16 Day 1 (± 3 days)

Patients will return to the clinic to receive pembrolizumab. Standard-of-care safety procedures are required only as clinically indicated and per institutional standards of care in association with usual pembrolizumab administration. Only clinically significant abnormalities will be reported into the database and noted as adverse events.

1. AE monitoring
2. Recording of concomitant medications
3. Vital signs and weight
4. Symptom-directed physical exam
5. ECOG Performance Status
6. Clinical laboratory evaluation (hematology and serum chemistry).
7. Research blood collection
8. Pembrolizumab administration. For the purposes of this study, pembrolizumab should be administered *after* the GX-188E vaccination on all days in which patients are scheduled to receive both.

16.10 Week 19 Day 1 (±3 days)

At Week 19 Day 1, patients will return to the clinic for administration of GX-188E + P and undergo the following procedures

1. AE monitoring
2. Recording of concomitant medications
3. Vital signs and weight
4. Symptom-directed physical exam
5. ECOG Performance Status

6. Clinical laboratory evaluation (hematology, serum chemistry, *and both blood CEA/TA4 levels and thyroid function tests*).
7. Radiographic evaluation of tumor burden and determination of response by RECIST v1.1 and irRECIST. See Appendices 5 and 6.
8. Pain Assessment. Within 30 minutes before and 5 minutes (± 2 minutes) after GX-188E administration, pain score in association with the electroporation (EP) procedure should be reported.
9. Administration of GX-188E at both right and left lateralis muscles (or, deltoid muscles for Reduction Level 1)
10. Administration of pembrolizumab. For the purposes of this study, pembrolizumab should be administered *after* the GX-188E vaccination on all days in which patients are scheduled to receive both.

16.11 Other Schedules Subsequent to Week 19 Day 1

After Week 19 Day 1, GX-188E vaccination will occur only one additional time, at Week 46 Day 1. In case that, an optional GX-188E administration may be given at week 46 if it is in the best interests of the patient, as determined by the investigator, once the patient has completed 37 weeks of treatment. Additional GX-188E administration(s) may be given to the subject after discussion with the sponsor.

Pembrolizumab will continue to be administered once every 3 weeks.

Blood CEA/TA4 levels and thyroid function tests will be performed approximately every 6 weeks for the duration of study participation.

Research blood will be collected further at Week 22, Week 49, and every 27 weeks thereafter. (Including blood sample for Flt-3L level monitoring). Research blood collections are not performed on Day 1 of Week 103 visit but at the EOS visit.

16.11.1 Every 3 Weeks (after Week 19 Day 1)(± 3 days)

After Week 19 Day 1, patients will return to the clinic to receive pembrolizumab. Standard-of-care safety procedures are required only as clinically indicated and per institutional standards

of care in association with usual pembrolizumab administration. Only clinically significant abnormalities will be reported into the database and noted as adverse events. The last dose of Pembrolizumab would be administered on Week 103 Day 1 and patients will undergo the following procedures.

1. AE monitoring
2. Recording of concomitant medications
3. Vital signs and weight
4. Symptom-directed physical
5. Clinical laboratory evaluation (as indicated; only clinically significant findings will be reported).
6. Pembrolizumab administration

16.11.2 Every 9 Weeks (after Week 19 Day 1) (± 1 week)

Approximately every 9 weeks after Week 19 Day 1, patients will return to the clinic to undergo the following procedures:

1. AE monitoring
2. Recording of concomitant medications
3. Vital signs and weight
4. Symptom-directed physical exam
5. ECOG Performance Status
6. Clinical laboratory evaluation (hematology, serum chemistry).
7. Radiographic evaluation of tumor burden and determination of response by RECIST v1.1 and iRECIST. See Appendices 5 and 6.

In accordance with the standard administration schedule (i.e. every 3 weeks), pembrolizumab will also be administered at these visits as appropriate.

16.11.3 Week 46 Day 1 (± 1 week, GX-188E optional administration)

At Week 46 Day 1, patients will return to the clinic to receive undergo the following procedures:

1. AE monitoring

2. Recording of concomitant medications
3. Vital signs and weight
4. Symptom-directed physical exam
5. ECOG Performance Status
6. Clinical laboratory evaluation (hematology, serum chemistry).
7. An optional GX-188E administration may be given at week 46 if it is in the best interests of the patient, as determined by the investigator, once the patient has completed 37 weeks of treatment. Additional GX-188E administration(s) may be given to the subject after discussion with the sponsor. (Optional) Pain Assessment. Within 30 minutes before and 5 minutes (± 2 minutes) after GX-188E administration, pain score in association with the electroporation (EP) procedure should be reported.
8. (Optional) Administration of GX-188E at both right and left deltoid muscles (or, lateralis muscles for Reduction Level 1)

In accordance with the standard administration schedule (i.e. every 3 weeks), pembrolizumab will also be administered as appropriate. For the purposes of this study, pembrolizumab should be administered *after* the GX-188E vaccination on all days in which patients are scheduled to receive both.

16.12 **End of Study (EOS)**

The End of Study (EOS) visit must occur within 28 days of treatment discontinuation / completion (Week 103 Day 1) and prior to initiation of any new anti-cancer therapy/regimen. All patients discontinuing study treatment for any reason should undergo the following EOS procedures:

1. AE monitoring
2. Recording of concomitant medications
3. Vital signs and weight
4. Complete physical examination
5. ECOG performance status evaluation

6. Clinical laboratory values (hematology, coagulation, chemistry, urinalysis, *and both blood CEA/TA4 levels and thyroid function tests*)
7. Serum or urine pregnancy test for women of child-bearing potential
8. Research blood collection
9. Optional post-baseline tumor biopsy (only requested for patients with biopsy-accessible lesions and who discontinue from study prior to Week 10). Coagulation tests must be performed and evaluated within 24 hr prior to all biopsy procedures.
11. Radiographic evaluation of tumor burden and determination of response by RECIST v1.1 and iRECIST. See Appendices 5 and 6. Note: This is not required if confirmed PD is the reason for study discontinuation.

16.13 Long-Term Follow-Up

Patients will enter into the long-term follow-up phase of the study after the EOS visit to obtain survival data. Survival data may be obtained either by clinic visit or by remote communication (e.g., telephone call or email) or hospital medical records. Sites must follow up with patients approximately every 4 months for up to 1 year to obtain the following data:

- Survival status: Is the patient still living? (Yes or No)
    - If "No", what was the approximate date of death?
- Has the patient received any subsequent active anti-cancer treatment (this does not include palliative measures)? (Yes or No)
    - If "Yes", what treatments has the patient received?

Family members, primary care giver, public records, or primary treating oncologist/oncologist's office may confirm a patient's death.

17.0 Patient Identification and Tracking

Each patient will be assigned a unique number and will keep this number for the duration of the study. Patient numbers will not be reassigned or reused for any reason. Patients should be identified to the Sponsor only by their assigned number, initials, date of birth, and sex. The Investigator must maintain a patient master log.

18.0 Screen Failures

Patients who sign an informed consent form but who do not meet all inclusion and exclusion criteria and who do not receive any part of the investigational treatment regimen, are defined as Screen Failures. For all screen failures, the Investigator (or designee) will record the screening number, patient initials, and reason(s) for screen failure into the Screen Fail Log. These data will be retained in the Investigator's study files, reviewed for completeness and collected at the end of the study.

19.0 Discontinuation/Withdrawal criteria

19.1 Discontinuation of Study Treatment

Discontinuation of study treatment does not represent withdrawal from the study.

A participant must be discontinued from study treatment but continue to be monitored in the study for any of the following reasons:

- Recurrent Grade 2 pneumonitis
- Discontinuation of treatment may be considered for participants who have attained a confirmed complete response (CR) and have been treated for at least 8 pembrolizumab cycles (at least 24 weeks), including 2 doses of pembrolizumab beyond the date when the initial CR was declared.
- Completion of 35 treatments (approximately 2 years) with pembrolizumab. Note: The number of treatments is calculated starting with the first dose of pembrolizumab.

The reasons a patient may discontinue or be withdrawn from the study include, but are not limited to, adverse events, disease progression, patient request, Investigator decision, protocol violation, patient noncompliance, and study termination by the Sponsor.

When a patient discontinues or is withdrawn, the Investigator will notify the Sponsor (or designee) and should perform the procedures indicated in the EOS column in the Schedule of Events (Appendix 1) within 28 days after discontinuation of study drug and prior to initiation of any therapy.

20.0 SAFETY REPORTING AND DOCUMENTATION OF CLINICAL RESULTS

20.1 Safety Evaluations

For safety information on GX-188E, refer to the most recent version of the Investigator's Brochure. For safety information on pembrolizumab, please refer to the package inserts.

Routine safety and tolerability will be evaluated from the results of reported signs and symptoms, scheduled physical examinations, vital sign measurements, and clinical laboratory test results.

More frequent safety evaluations than required by this protocol may be performed if clinically indicated and at the discretion of the Investigator. All adverse events (AEs) will be recorded from the time the patient receives the first dose of the investigational treatment regimen to 28 days after the last dose.

20.1.1 Physical Examination

Complete physical examinations will be performed by a licensed physician (or physician's assistant or nurse practitioner) at Screening and End of Treatment. Symptom-directed physical exam are required at each clinical visit and as clinically indicated. Please refer to the Schedule of Events (Appendix 1).

20.1.2 Vital Signs

Vital signs (blood pressure, respiratory rate, pulse rate, and temperature) will be obtained in the sitting position. All patients should be sitting for 3-5 min prior to obtaining vital signs. Please refer to the Schedule of Events (Appendix 1).

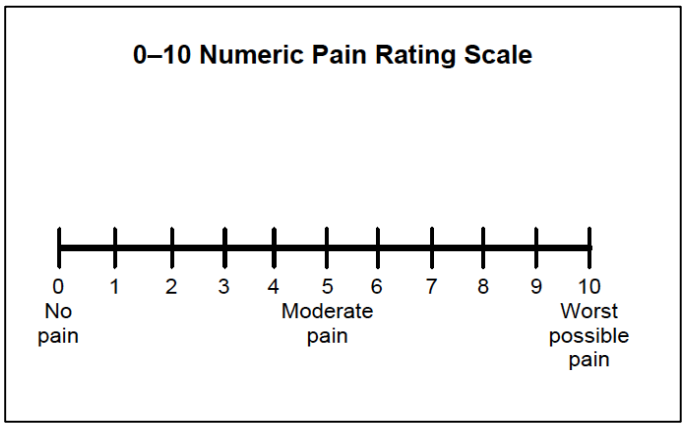
20.1.3 Safety Laboratory Determinations

Laboratory evaluations, including complete blood count with differential, comprehensive chemistry panel, coagulation tests, thyroid function tests, and urinalysis, will be performed as noted in the Schedule of Events (Appendix 1).

20.1.4 Pain Assessment

On each GX-188E vaccination day, Pain Assessment Monitoring will be performed within 30 minutes before and 5 minutes (± 2 minutes) after the vaccination procedure using a 0-10 numeric pain rating scale (Figure 4).

Figure 4. Numeric Pain Rating Scale



20.2 Adverse Events (AE)

The Investigator will evaluate all adverse events (AEs) according to the NCI Common Terminology Criteria for Adverse Events Version 4.0 or the most recent version. An **adverse event** (AE) is any untoward, undesired, or unplanned event in the form of signs, symptoms, disease, or laboratory or physiologic observations occurring in a person given a test article in a clinical study. The event does not need to be causally related to the investigational treatment. An AE includes, but is not limited to, the following:

- Any clinically significant worsening of a preexisting condition
- An AE occurring from overdose (i.e., a dose higher than that indicated in the protocol) of a test article, whether accidental or intentional
- An AE occurring from abuse (e.g., use for nonclinical reasons) of a test article
- An AE that has been associated with the discontinuation of the use of a test article

Any treatment-emergent abnormal laboratory result which is clinically significant, i.e., meeting one or more of the following conditions, should be recorded as a single diagnosis on the adverse event page in the CRF:

- Accompanied by clinical symptoms
- Leading to a change in study medication (e.g., dose modification, interruption, or permanent discontinuation)

- Requiring a change in concomitant therapy (e.g., addition of, interruption of, discontinuation of, or any other change in a concomitant medication, therapy or treatment)

Clear progression of the patient's primary malignancy should not be reported as an AE, unless it results in hospitalization or death. Findings that are clearly consistent with the expected progression of the underlying cancer should not be reported as an adverse event, and hospitalizations due to the progression of cancer do not necessarily qualify for an AE. If there is any uncertainty about a finding being due solely to progression of primary malignancy, the finding should be reported as an AE as appropriate.

AEs should be considered treatment-related, unless they fulfill the following criteria:

- Evidence exists that the AE has an etiology other than the investigational product (e.g., preexisting medical condition, underlying disease, intercurrent illness, or concomitant medication), and/or
- The AE has no plausible temporal relationship to administration of the investigational product (e.g., a new cancer diagnosed 2 days after first dose of study drug).

Relatedness to study medication will be graded as either,"probably", "possibly", "unlikely", or "unrelated" as follows:

Probably Related – The adverse event

- Follows a reasonable temporal sequence from drug administration
- Abates upon discontinuation of the drug
- Cannot be reasonably explained by the known characteristics of the patient's clinical state

Possibly Related – The adverse event

- Follows a reasonable temporal sequence from drug administration
- Could have been produced by the patient's clinical state or by other modes of therapy administered to the patient

Unlikely Related - The adverse event

- Does not follow a reasonable sequence from drug administration
- Is readily explained by the patient's clinical state or by other modes of therapy administered to the patient

Unrelated – The adverse event

- Does not follow a reasonable sequence from drug administration
- Is readily explained by and considered by the Principal Investigator to be an expected complication of the patient's primary malignancy, clinical state, concurrent medical conditions, or by other modes of therapy administered to the patient

A **protocol-related adverse event** is an AE occurring during a clinical study that is not related to the investigational treatment, but is considered by the Investigator and/or the Sponsor's Medical Monitor (or designee) to be related to the research conditions, i.e., related to the fact that a patient is participating in the study. For example, a protocol-related AE may be an untoward event related to a medical procedure required by the protocol (e.g. bleeding from a protocol-required biopsy).

20.3 Serious Adverse Event (SAE)

All AEs will be evaluated for seriousness. A **serious adverse event** (SAE) is an AE that meets at least one of the following criteria:

- Results in death (NOTE: death is an outcome, not an event)
- Is life-threatening
- Requires inpatient hospitalization or prolongation of an existing hospitalization
- Results in a persistent or significant disability or incapacity
- Results in a congenital anomaly or birth defect
- Additionally, important medical events that may not result in death, be life-threatening, or require hospitalization may be considered SAEs when, based on appropriate medical judgment, they may jeopardize the patient and may require medical or surgical intervention to prevent one of the outcomes listed in this definition. Examples of such events include allergic bronchospasm requiring intensive treatment in an emergency room or at home, blood dyscrasias or convulsions that do not result in hospitalization, or development of drug dependency or drug abuse.

Life-threatening, in the context of an SAE, refers to *immediate risk of death* as the event occurred per the reporter. A life-threatening experience does not include an experience, had it occurred in a more severe form, which might have caused death, but as it actually occurred,

did not create an immediate risk of death. For example, hepatitis that resolved without evidence of hepatic failure would not be considered life-threatening, even though hepatitis of a more severe nature can be fatal. Similarly, an allergic reaction resulting in angioedema of the face would not be life-threatening, even though angioedema of the larynx, allergic bronchospasm, or anaphylaxis can be fatal.

Hospitalization is official admission to a hospital. Hospitalization or prolongation of a hospitalization constitutes criteria for an AE to be serious; however, it is not in itself considered a serious adverse event (SAE). In the absence of an AE, a hospitalization or prolongation of a hospitalization should not be reported as an SAE. This is the case in the following situations:

- The hospitalization or prolongation of hospitalization is needed for a procedure required by the protocol. Day or night survey visits for biopsy or surgery required by the protocol are not considered serious.
- The hospitalization or prolongation of hospitalization is part of a routine procedure followed by the center (e.g., stent removal after surgery). This should be recorded in the study file.
- Emergency room visit less than 24hrs or other department visits that do not result in hospitalization (if the case is not considered as important medical or life-threatening event) is not included as SAE.
- Hospitalization for survey visits or annual physicals falls into the same category.

In addition, hospitalizations planned before the start of the study, for a preexisting condition that has not worsened, do not constitute an SAE.

Disability is defined as a substantial disruption in a person's ability to conduct normal life functions.

If there is any doubt about whether the information constitutes an SAE, the information is treated as an SAE.

20.4 Other Reportable Information

Certain information, although not considered an SAE, must be recorded, reported, and followed up as indicated for an SAE. This includes:

- A case involving a pregnancy exposure to the investigational therapy. Please refer to Section 20.4.1 for further details and requirements. Pregnancies occurring up to 6 months after completion of the study treatment must also be reported to the Investigator.
- Overdose (e.g., a dose higher than that indicated in the protocol) with or without an AE. If an adverse event(s) is associated with or results from an overdose of one or more of the investigational agents, the event must be reported as an SAE, even if no other criteria for SAE are met. Any overdoses of pembrolizumab must be reported to the Sponsor and to Merck Global Safety (Attn: Worldwide Product Safety; FAX 215 993-1220) within 24 hours.
- Abuse (e.g., use for nonclinical reasons) with or without an AE
- Inadvertent or accidental exposure with or without an AE

20.4.1 Contraception and Pregnancy

GX-188E and pembrolizumab 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.

Participants 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, participants 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 study medication. If there is any question that a participant of childbearing potential will not reliably comply with the requirements for contraception, that participant should not be entered into the study.

20.4.1.1 **Acceptable Methods of Contraception**

Highly effective methods are defined as those that result in a low failure rate (ie, less than 1% per year) when used consistently and correctly. Below is a list of highly effective methods of contraception:

- Intrauterine device (IUD)
- Hormonal (birth control pill, injections, implants, patch)
- Tubal ligation
- Partner's vasectomy

Additional effective methods (barriers) are noted below:

- Male condom with spermicidal agent
- Diaphragm or cervical cap with spermicidal agent

Abstinence is acceptable if this is the usual lifestyle and preferred contraception for the subject. The reliability of sexual abstinence should be evaluated in relation to the duration of the clinical trial and the preferred and usual lifestyle of the subject. Periodic abstinence (eg., calendar, or post-ovulation symptothermal methods) and withdrawal are NOT acceptable methods alone and must be supplemented with one of the methods considered highly effective, listed above

20.4.2 **Pregnancy**

.If a participant inadvertently becomes pregnant while on study, the participant will be immediately discontinued from study treatment. The site will contact the participant at least monthly and document the participant’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 (e.g., 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.

20.4.3 Use in Nursing Women

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, participants who are breastfeeding are not eligible for enrollment.

20.5 Unexpected AE and SAE

An AE is considered *unexpected* if it is not listed in the investigator brochure or package insert for GX-188E or pembrolizumab, is not listed at the specificity or severity that has been observed, or, is not consistent with the risk information described.

"Unexpected," as used in this definition, also refers to adverse events that are mentioned in the investigator brochure or package inserts as occurring with a class of drugs or as anticipated from the pharmacological properties of the drug, but are not specifically mentioned as occurring with the particular drug under investigation.

Adverse events that would be anticipated to occur as part of the disease process are not considered *unexpected* if the event is clearly due to disease progression.

20.6 Reporting and Follow-Up Requirements for Adverse Events, Serious Adverse Events and Other Reportable Safety Events

20.6.1 Time Period and Frequency for Collecting AE, SAE and Other Reportable Safety Event Information

- All AE's or ECI's = from the time of treatment through **30 days** following cessation of study treatment
- All SAE's =**90 days** following cessation of study treatment, or **30 days** following cessation of study treatment if the participant initiates new anticancer therapy, whichever is earlier
- All pregnancies and exposure during breastfeeding, from the time of treatment through **120 days** following cessation of study treatment, or **30 days** following cessation of study treatment if the participant initiates new anticancer therapy
- Additionally, any SAE brought to the attention of an investigator at any time outside of the time period specified above must be reported immediately to the Sponsor if the event is considered to be drug-related.

The Investigator must follow-up on all treatment-related AEs, SAEs, and other reportable events until the events have subsided, returned to baseline, the patient has initiated any other anti-cancer treatment, or in case of permanent impairment, until the condition stabilizes.

All AEs and SAEs must be recorded on source documents and collected in EDC.

Although AEs should be based on the signs or symptoms detected during the physical examination and on clinical evaluation of the patient, a specific diagnosis should be reported as the AE whenever feasible. In addition to the information obtained from those sources, the patient should be asked the following nonspecific question: "How have you been feeling since your last visit?" Signs and symptoms should be recorded using standard medical terminology.

Any unanticipated risks to the patients must be reported promptly to the IRB/IEC.

20.7 Serious Adverse Event (SAE)-Specific and Expedited Reporting

All SAEs, other reportable information, and SAE follow-up information must be reported within 24 hr of learning of the event by completing the Adverse Event eCRF in the Medidata database. Genexine, Inc (or designee) will process and evaluate all SAEs as soon as the reports are received. For each SAE received, Genexine, Inc. (or designee) will make a determination as to whether the criteria for expedited reporting have been met.

Genexine, Inc. (or designee) is responsible for reporting relevant SAEs to the relevant regulatory authorities and participating Investigators, in accordance with FDA regulations *21 CFR 312.32, ICH Guidelines, European Clinical Trials Directive (Directive 2001/20/EC)*, and/or local regulatory requirements. To meet this requirement, Genexine, Inc. (or designee) may request additional information from the sites, including but not limited to, hospitalization records. Any requests for such information should be addressed in a timely manner.

Reporting of SAEs by the Investigator to the Institutional Review Board (IRB) or Ethics Committee (EC) will be done in accordance with the standard operation procedures and policies of the IRB/EC. Adequate documentation must be maintained showing that the IRB/EC was properly notified.

Adverse Events that are considered related to the investigational treatment, unexpected and serious will be reported as an IND Safety Report to the FDA in accordance with the standards set in the Code of Federal Regulations [21 CFR 312.32 (c)(1), 21 CFR 312.32(c)(2), 21 CFR 312.32(d)(2)].

20.8 Events of Clinical Interest (ECI)

Selected non-serious and serious AEs are also known as Events of Clinical Interest (ECI) and must be recorded as such on the Adverse Event electronic case report forms and reported within 24 hours to the Sponsor.

ECIs for this trial include:

- An overdose of investigational product that is not associated with clinical symptoms or abnormal laboratory results.
- an elevated AST or ALT lab value that is greater than or equal to 3X the upper limit of normal and an elevated total bilirubin lab value that is greater than or equal to 2X the upper limit of normal and, at the same time, an alkaline phosphatase lab value that is less than 2X 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 trial site guidance for assessment and follow up of these criteria can be made available. It may also be appropriate to conduct additional evaluation for an underlying etiology in the setting of abnormalities of liver blood tests including AST, ALT, bilirubin, and alkaline phosphatase that do not meet the criteria noted above. In these cases, the decision to proceed with additional evaluation will be made through consultation between the study investigators and the Sponsor Clinical Director. However, abnormalities of liver blood tests that do not meet the criteria noted above are not ECIs for this trial.

ECIs that occur in any patient from the date of first dose through 30 days following cessation of treatment, or the initiation of a new anticancer therapy, whichever is earlier, whether or not related to the investigational product, must be reported within 24 hours to the Sponsor.

20.9 Treatment of Pembrolizumab Overdose

For this study, an overdose of pembrolizumab will be defined as any dose of 1000 mg or $\geq$5 times the indicated dose.

No specific information is available on the treatment of overdose of pembrolizumab. In the event of overdose, the participant should be observed closely for signs of toxicity. Appropriate supportive treatment should be provided if clinically indicated.

21.0 Dose-Limiting Toxicities (DLTs)

All toxicities will be graded using NCI-CTCAE Version 4.0 or the most recent version based on the investigator assessment.

The DLT window of observation will be during Cycle 1 of pembrolizumab (ie., the first 3 weeks of treatment prior to Week 4 Day 1 visit). A DLT is defined as any AE that is not clearly due to progression of the patient's primary malignancy, occurs within the DLT window of observation period, and that meets at least one of the criteria below:

Non-Hematologic Dose Limiting Toxicities:

- Any CTCAE (v4.0 or the most recent version) Adverse Event of ≥ Grade 3 treatment-related non-hematological toxicity ***except the following***:
  - nausea, vomiting, or diarrhea lasting ≤ 72 hr
  - Grade 3 fatigue lasting ≤ 7 days
  - hypersensitivity reactions lasting ≤ 72 hrs
  - Grade 3 hyperglycemia lasting ≤ 72 hr with standard anti-diabetic therapy
  - Grade 3 increases in liver transaminases in patients with liver metastases. (Note: Grade 4 increases in LFTs in any patient will be considered a DLT)
  - clinical laboratory abnormalities that are reversible to ≤ Grade 1 or baseline status within 72 hr with outpatient care and/or monitoring, or that are considered *not* clinically significant by the Principal Investigator

Hematologic Dose Limiting Toxicities:

- Grade 4 neutropenia (ANC < 0.5 $x10^9$/L)
- Grade 3 febrile neutropenia (ANC < 1.0 x 10^9/L with temperature ≥ 38.3°C)
- Grade 4 thrombocytopenia (platelet count < 25.0 x 10^9/L) lasting > 4 days or that requires platelet transfusion
- Grade ≥ 3 thrombocytopenia (platelet count < 50.0 x 10^9/L) associated with Grade ≥ 3 bleeding

- Any hematologic toxicity resulting in death (i.e. Grade 5)

In addition, any other AE that is felt to be treatment-limiting in the medical opinions of the Principal Investigator and the Sponsor's Medical Monitor may be considered a DLT. These include, but are not limited to the following:

- Any toxicity leading to more than one missed dose of either GX-188E or pembrolizumab during the DLT-evaluation period
- Any toxicity leading to > 2 weeks delay in initiation of the 2nd cycle of pembrolizumab

22.0 Evaluation and Reporting of Efficacy Data

22.1 Tumor Imaging and Assessment of Disease

For the abdomen and pelvis, contrast-enhanced magnetic resonance imaging (MRI) may be used when CT with iodinated contrast is contraindicated, or when mandated by local practice. MRI is the strongly preferred modality for imaging the brain. The same imaging technique regarding modality, ideally the same scanner, and the use of contrast should be used in a participant throughout the study to optimize the reproducibility of the assessment of existing and new tumor burden and improve the accuracy of the assessment of response or progression based on imaging.

22.1.1 Initial Tumor Imaging

Initial tumor imaging at Screening must be performed within 28 days prior to the date of treatment initiation. The site study team must review screening images to confirm the participant 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 initiation.

22.1.2 Tumor Imaging During the Study

The first on-study imaging assessment should be performed approximately 9 weeks (±3 days]) from the date of treatment initation. Subsequent tumor imaging should be performed every 9 weeks (±3 days at Week 19, ±7 days for subsequent timepoints) or more frequently if clinically indicated. Imaging timing should follow calendar days and should not be adjusted for delays

in cycle starts. Imaging should continue to be performed until disease progression is identified by the investigator (unless the investigator elects to continue treatment and follow iRECIST), the start of new anticancer treatment, withdrawal of consent, or death, whichever occurs first. All supplemental imaging must be submitted to the central imaging vendor.

Objective response and stable disease should be confirmed by a repeat imaging assessment. Tumor imaging to confirm SD, PR or CR should be performed at least 4 weeks after the first indication of a response is observed. Participants will then return to regular scheduled imaging, starting with the next scheduled imaging time point. Participants who receive additional imaging for confirmation do not need to undergo the next scheduled tumor imaging if it is less than 4 weeks later; tumor imaging may resume at the subsequent scheduled imaging time point. Note: Response does not typically need to be verified in real time by the central imaging vendor.

Per iRECIST (Appendix 6 and Section 22.3), disease progression should be confirmed by the site 4 to 8 weeks after site-assessed first radiologic evidence of PD in clinically stable participants. Participants, who have unconfirmed disease progression may continue on treatment at the discretion of the investigator until progression is confirmed by the site, provided they have met the conditions detailed in Section 22.3. Participants who receive confirmatory imaging do not need to undergo the next scheduled tumor imaging if it is less than 4 weeks later; tumor imaging may resume at the subsequent scheduled imaging time point, if clinically stable. Participants, who have confirmed disease progression by iRECIST, as assessed by the site, will discontinue study treatment. Exceptions are detailed in Section 22.3.

22.1.3 End of Treatment and Follow-Up Tumor Imaging

For participants who discontinue study treatment, tumor imaging should be performed at the time of treatment discontinuation (±4 week window). If previous imaging was obtained within 4 weeks prior to the date of discontinuation, then imaging at treatment discontinuation is not mandatory. For participants who discontinue study treatment due to documented disease progression, this is the final required tumor imaging if the investigator elects not to implement iRECIST.

For participants who discontinue study treatment without documented disease progression, every effort should be made to continue monitoring disease status by tumor imaging using the same imaging schedule used while on treatment (every 9 weeks) until the start of a new anticancer treatment, disease progression, pregnancy, death, withdrawal of consent, or the end of the study, whichever occurs first.

22.2 RECIST 1.1 Assessment of Disease

RECIST 1.1 will be used by the blinded, independent central reviewers (BICR) as the primary measure for assessment of tumor response, date of disease progression, and as a basis for all protocol guidelines related to disease status (e.g., discontinuation of study treatment).

All efficacy endpoints, including the primary response endpoint of Part 2, overall response rate within the first 24 weeks of treatment (ORR_{24}), will be evaluated and categorized using the new international criteria proposed by the Response Evaluation Criteria in Solid Tumors (RECIST) Committee, version 1.1.[17]

RECIST v1.1 response definitions are briefly described below; for detailed instructions on RECIST v1.1, please refer to Appendix 5.

RECIST v1.1 Response Definitions for the Evaluation of Target Lesions

Complete Response (CR)	Disappearance of all target lesions. Any pathological lymph nodes (whether target or non-target) must have reduction in short axis to < 10 mm.
Partial Response (PR)	*At least a 30% decrease* in the sum of diameters of target lesions, taking as reference the baseline sum diameters.
Progressive Disease (PD)	*At least a 20% increase* in the sum of diameters of target lesions, taking as reference the smallest sum on study (this includes the baseline sum if that is the smallest on study). In addition to the relative increase of 20%, the sum must also demonstrate an absolute *increase of at least 5 mm*. (Note: the appearance of one or more new lesions is also considered progression).

Stable Disease (SD)	Neither sufficient shrinkage to qualify for PR nor sufficient increase to qualify for PD, taking as reference the smallest sum diameters while on study.

RECIST v1.1 Response Definitions for the Evaluation of Non-Target Lesions

Complete Response (CR)	Disappearance of all non-target lesions and normalization of tumor marker level
Incomplete Response/Stable Disease (SD)	Persistence of one or more non-target lesion(s) or/and maintenance of tumor marker level above the normal limits
Progressive Disease (PD)	Appearance of one or more new lesions and/or unequivocal progression of existing non-target lesions*

*Although a clear progression of "non target" lesions only is exceptional, in such circumstances, the opinion of the treating physician should prevail and the progression status should be confirmed later on by the review panel (or study chair)

RECIST v1.1 Definitions for the Evaluation of Overall Response

Target lesions	Non-Target lesions	New Lesions	**Overall response**
CR	CR	No	**CR**
CR	Incomplete response/SD	No	**PR**
PR	Non-PD	No	**PR**
SD	Non-PD	No	**SD**
PD	Any	Yes or No	**PD**
Any	PD	Yes or No	**PD**
Any	Any	Yes	**PD**

ORR is defined as the proportion of efficacy evaluable patients (see Section 24.3) with a tumor size reduction that meets the RECIST v1.1 Overall Response definition of a Partial Response (PR) or Complete Response (CR). If a CR has been confirmed for a patient, the sponsor will

discuss with the patient's investigator whether the study treatments need to be continued or not.

If a patient's responses could not be confirmed, that patient will not be included in the primary efficacy population for ORR_{24}.

In addition, efficacy endpoints will also be determined using the immune-related RECIST (iRECIST)[18] (please refer to Appendix 6).

22.3 iRECIST Assessment of Disease

iRECIST is based on RECIST 1.1, but adapted to account for the unique tumor response seen with immunotherapeutic drugs. iRECIST will be used by the Investigator to assess tumor response and progression, and make treatment decisions. When clinically stable, participants should not be discontinued until progression is confirmed by the Investigator, working with local radiology, according to the rules outlined in Appendix 6. This allowance to continue treatment despite initial radiologic PD takes into account the observation that some participants can have a transient tumor flare in the first few months after the start of immunotherapy, and then experience subsequent disease response. This data will be captured in the clinical database.

Clinical stability is defined as the following:

- Absence of symptoms and signs indicating clinically significant progression of disease
- No decline in ECOG performance status
- No requirements for intensified management, including increased analgesia, radiation, or other palliative care

Any participant deemed **clinically unstable** should be discontinued from study treatment at site-assessed first radiologic evidence of PD, and is not required to have repeat tumor imaging for confirmation of PD by iRECIST.

If the Investigator decides to continue treatment, the participant may continue to receive study treatment and the tumor assessment should be repeated 4 to 8 weeks later to confirm PD by iRECIST, per Investigator assessment. Images should continue to be sent in to the central imaging vendor for potential retrospective BICR.

If repeat imaging does not confirm PD per iRECIST, as assessed by the Investigator, and the participant continues to be clinically stable, study treatment may continue and follow the regular imaging schedule. If PD is confirmed, participants will be discontinued from study treatment.

If a participant has confirmed radiographic progression (iCPD) as defined in Appendix 6, study treatment should be discontinued; however, if the participant is achieving a clinically meaningful benefit, an exception to continue study treatment may be considered following consultation with the Sponsor. In this case, if study treatment is continued, tumor imaging should continue to be performed following the intervals as outlined in the Schedule of Events (Appendix 1) and submitted to the central imaging vendor.

A description of the adaptations and iRECIST process is provided in Appendix 6, with additional details in the iRECIST publication[43]. A summary of imaging and treatment requirements after first radiologic evidence of progression is provided in Table 6 and illustrated as a flowchart in Figure 5.

Table 6. Imaging and Treatment after First Radiologic Evidence of Progressive Disease

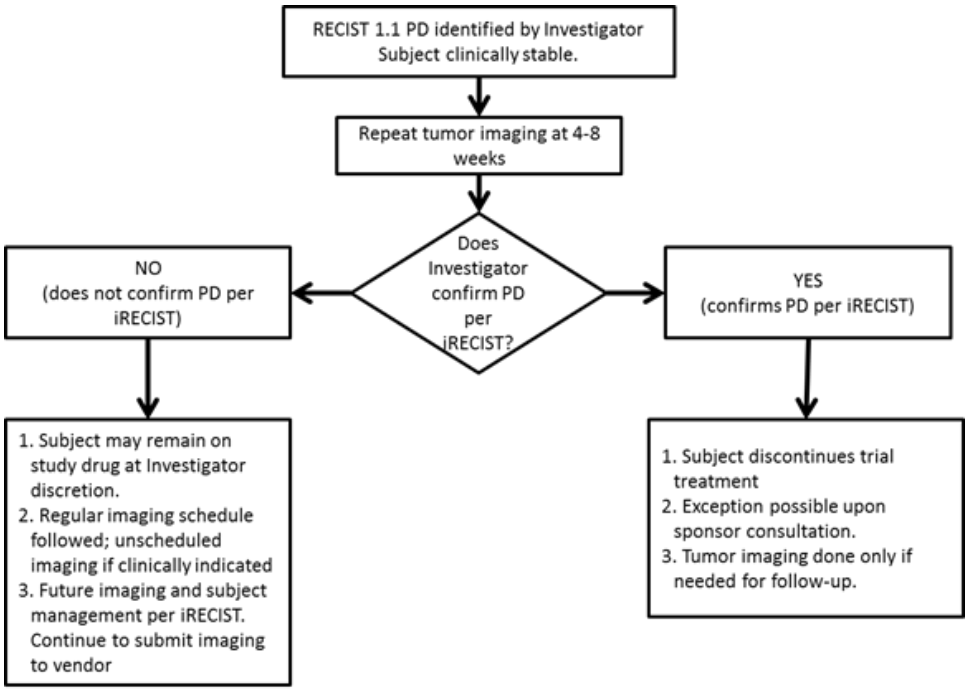
	Clinically Stable		Clinically Unstable	
	Imaging	**Treatment**	**Imaging**	**Treatment**
First radiologic evidence of PD by RECIST 1.1 [For those studies in which PFS is the primary endpoint, add the following: that has been verified by BICR]	Repeat imaging at 4 to 8 weeks to confirm PD.	May continue study treatment at the Investigator's discretion while awaiting confirmatory tumor imaging by site by iRECIST.	Repeat imaging at 4 to 8 weeks to confirm PD per Investigator's discretion only.	Discontinue treatment
Repeat tumor imaging confirms PD (iCPD) by iRECIST per Investigator assessment	No additional imaging required.	Discontinue treatment (exception is possible upon consultation with Sponsor).	No additional imaging required.	Not applicable
Repeat tumor imaging shows iUPD by iRECIST per Investigator assessment	Repeat imaging at 4 to 8 weeks to confirm PD. May occur at next regularly scheduled imaging visit.	Continue study treatment at the Investigator's discretion.	Repeat imaging at 4 to 8 weeks to confirm PD per Investigator's discretion only.	Discontinue treatment
Repeat tumor imaging shows iSD, iPR, or iCR by iRECIST per Investigator assessment.	Continue regularly scheduled imaging assessments.	Continue study treatment at the Investigator's discretion.	Continue regularly scheduled imaging assessments.	May restart study treatment if condition has improved and/or clinically stable per Investigator's discretion. Next tumor imaging should occur according to the regular imaging schedule.

	Clinically Stable		Clinically Unstable	
	Imaging	**Treatment**	**Imaging**	**Treatment**

BICR = Blinded Independent Central Review; iCPD = iRECIST confirmed progressive disease; iCR = iRECIST complete response; iRECIST = modified Response Evaluation Criteria in Solid Tumors 1.1 for immune-based therapeutics; iSD = iRECIST stable disease; iUPD = iRECIST unconfirmed progressive disease; PD = progressive disease; RECIST 1.1 = Response Evaluation Criteria in Solid Tumors 1.1.; VOP=verification of progression

[*For studies, in which PFS is the primary endpoint, add the following:* Note: If progression has been centrally verified, further management is by the site, based on iRECIST. Any further imaging should still be submitted to the central imaging vendor, but no rapid review will occur. If RECIST 1.1 disease progression has not been centrally verified, ideally the site should continue treatment. Whether or not treatment continues, imaging should be collected and submitted to the central imaging vendor with VOP request until RECIST 1.1 progression is verified by BICR.]

Figure 5: Imaging and Treatment for Clinically Stable Participants Treated with pembrolizumab after First Radiologic Evidence of PD Assessed by the Investigator



23.0 Correlative studies and biomarker evaluations

Establishing proof-of-biological concept is a key objective of this study. As previously described, the goal of GX-188E + P treatment is to induce a tumor-specific anti-tumor immunological response that does not become halted at the PD1 immune checkpoint. To explore the biological mechanisms and pharmacodynamic effects of the investigational treatment regimen, paired tumor biopsies and peripheral blood samples will be obtained from all study participants.

23.1 Tumor Tissue for Biomarker Analyses

A key exploratory objective of the study is to evaluate the additional immunological treatment effects of GX-188E + P on the tumor microenvironment depending on the PD-L1 expression at baseline. Tumor biopsy samples will be evaluated for molecular and histological changes, particularly as these changes pertain to the inflammatory mechanisms. This will be assessed by comparing paired biopsies whenever feasible, one obtained at baseline (archival or fresh sample) prior to study treatment initiation, and one obtained at approximately 10 weeks on study. The changes in the intratumoral inflammatory infiltrate and PD-L1 expression at baseline will be analyzed by immunohistochemical(IHC) staining and the tumor evaluation will be conducted by a central laboratory.

All patients must submit either an archival tumor tissue sample, or a fresh biopsy sample for biomarker testing, including staining for PD-L1. For this study, it is expected that archival tumor tissues will be the principal source for baseline tumor biomarker analysis. Patients who do not have either archival tumor tissues available or biopsy-accessible lesions for a fresh biopsy will be excluded from the study.

Ideally, archival samples should have been obtained within 30 days of study enrollment and without administration of other anti-cancer treatment(s) in the interim period. In cases where archival samples were obtained >30 days from study enrollment or other cancer treatments were administered in the interim, the biopsy date and interim cancer treatments should be documented.

For patients without archival tissue samples but who have biopsy-accessible lesions and agree to undergo a biopsy procedure, the baseline sample must be obtained prior to administration of the first dose of either GX-188E or pembrolizumab.

For patients with biopsy-accessible lesions, a second biopsy will be requested optionallyat approximately 10 weeks following study treatment initiation in order to evaluate the effects of the investigational treatment regimen on the tumor microenvironment. For patients who discontinue from study prior to Week 10 and with accessible lesions, every effort should be made to obtain an optional post-baseline biopsy. For detailed instructions on biopsy sample processing, please refer to the study Laboratory Manual.

Submission of formalin-fixed paraffin embedded tumor tissue sample blocks is preferred; if submitting unstained slides, the slides should be freshly cut and submitted to the testing laboratory otherwise a new specimen may be requested. For additional details on tissue sample submission, please refer to the study Laboratory Manual.

23.2 Planned Peripheral Blood Biomarker Analyses

All study participants are required to provide peripheral blood samples for exploratory immunological evaluation throughout their study participation according to the schedule described in the Schedule of Events (Appendix 1). In brief, peripheral blood samples will be obtained at Screening, Week 1, Week 4, Week 7, Week 10, Week 16, Week 22, Week 49, and approximately every 27 weeks thereafter. For detailed instructions on peripheral blood research sample processing, please refer to the study Laboratory Manual.

Peripheral blood samples will be evaluated for molecular markers of an antigen-specific cellular and humoral immune response. For example, paired pre- and post-baseline PMBC-derived T cells may be assessed for (1) increased HPV-specific T-cell responses by ELISPOT analysis; (2) modulation of T-cell receptor diversity; (3) epitope-spreading to non-HPV epitopes, including mutation-derived neoantigens; (4) multiparametric flow cytometry to assess additional leukocyte populations of immunologic interest.

24.0 Statistical Analysis

24.1 Statistical Plan Summary

Study Design Overview	This is a Phase Ib/II multicenter, open-label study in patients with advanced, non-resectable HPV 16 or 18-positive cervical cancer. The study consists of two different parts. Part A employs a standard 6 + 3 design to evaluate the safety of the investigational study regimen. Part B uses a Simon Two-Stage design to explore the efficacy of the investigational study regimen at the treatment schedule established as safe in Part A. Additional subjects will be enrolled in Part C to evaluate efficacy in larger population.

Analysis Populations	**Safety Population:** All patients who receive at least 1 dose of 1 agent in the investigational treatment regimen (i.e. either GX-188E or P) will be included in the analysis of safety, regardless of the duration of treatment. **DLT-evaluable Population**. Part A patients who receive all of the planned administrations of both agents (GX-188E and P) within the DLT-evaluation period (the first three weeks of treatment prior to Week 4 Day 1 visit), unless doses are missed within the first two weeks of treatment (i.e., Week 1 Day -1 to Week 2 Day 7) due to DLT(s). **Efficacy Evaluable Population.** • All patients who discontinue the study treatment regimen early due to treatment-related toxicity • Patients who discontinue study due to disease-related death, unequivocal tumor progression or with at least 1 post-baseline tumor assessment AND who received at least 45 days of treatment • Patients from Part A, who receive the recommended Phase 2 regimen and who meet the aforementioned criteria
Primary Endpoint(s)	Part A: Safety: Incidence of Dose-limiting toxicities (DLTs) Part B&C: Objective Response Rate within 24 weeks (ORR_{24}) by RECIST 1.1. Response determinations from the BICR will be used for the primary endpoint
Secondary Endpoints	• Incidence, nature and severity of adverse events and serious adverse events • Best Overall Response Rate (BORR), Time-to-Best Response (TTR), Duration of Response (DOR), Disease Control Rate (DCR), median Progression-Free Survival (mPFS) and 6 month PFS rate and Median Overall Survival(mOS) • Response endpoints by iRECIST
Statistical Methods for Efficacy & Immunogenicity/ Analyses	**Efficacy Analyses.** Descriptive statistics will be employed to analyze the efficacy data. It also provides subject plots for individual patients. Summary statistics for continuous variables will include the mean, standard deviation, median, interquartile range, and range (minimum/maximum). Categorical variables will be presented as frequency counts and percentages, and time-to-event variables will be summarized with number of non-missing observations, median survival time, and survival probability using Kaplan-Meier method if applicable. Kaplan Meier plot will also be provided. **Immunogenicity Analyses.** Immunogenicity will be described to explore humoral and cellular immune responses to GX-188E and P (e.g., antibodies to E6 and E7 and the number of antigen-specific IFN-γ secreting T lymphocytes in samples of PBMC) in blood samples obtained from study subjects
Treatment Assignment	All participants will be allocated GX-188E + pembrolizumab
Statistical Methods for Safety Analyses	Summary statistics will be provided for the safety endpoints as appropriate.
Interim Analyses	An interim analysis will be performed with safety and efficacy data in case of at least 22 patients in efficacy evaluable population, after obtaining week 10 tumor assessment results (either by investigator/BICR).
Final Analysis	The final analysis will be performed to report a primary CSR based on a data cut off after all 60 patients in the planned efficacy evaluable population have completed tumor assessment within 24 weeks by the investigator per RECIST v1.1 Since patient will be treated until they met one of the discontinuation criteria, some patients may still be ongoing at the time of final analysis. Therefore, a long-term follow-up study can be performed after final analysis with all available data (no cut-off date applied).
Multiplicity	No multiplicity adjustment is planned in this trial.
Sample Size and Power	**Part A Safety Evaluation:** For Part A, the goal is to determine a treatment schedule for which the rate of DLTs is less than 33% in 6 or 9 patients. A minimum of 6 patients

	are planned with a maximum of 18 DLT-evaluable patients for the Starting Treatment Schedule and Reduction Level 1 **Part B:** Part B follows a 1-sided Simon 2-Stage design; 15 patients, will be included in the first stage analysis. If ≥ 3 objective responses (PR or better) are observed in the first stage, another 13 patients will be enrolled into the second stage, for a total of 28 patients. For a null hypothesis ORR_{24} of 0.15 and an alternative hypothesis ORR_{24} of 0.35, the sample size of 28 patients will provide a one-sided significance level of approximately 5% and a power of 80%. **Part C:** Part C is to evaluate efficacy in larger patient population. In Keynote-158 study (pembrolizumab monotherapy in patients who have progressed with standard of care systemic therapy), ORR in total patients (i.e. regardless of PD-L1 status) and with CPS ≥ 1 were 12.2% and 14.6%, respectively. Given this, null hypothesis for ORR_{24} was set at $P_0 = 12.2\%$. With an alternative hypothesis for ORR_{24} of $P_a = 37\%$, the sample size of 60 subjects was calculated considering two-sided significance level of 0.05, 97% power, and 25% dropout rate. The confidence interval (CI) for ORR_{24} will be estimated using exact Clopper-Pearson method, and if the lower bound of the two-sided 95% CI for ORR_{24} exceeds 12.2%, it will be proven to satisfy the primary efficacy. And it will be analyzed using two-sided exact binomial test for a null hypothesis for ORR_{24} of $P_0 = 12.2\%$ with a significance level of $P < 0.05$.

24.2 General Statistical Considerations

This is a Phase Ib/II multicenter, open-label study in patients with advanced, non-resectable HPV 16 or 18-positive cervical cancer. The study consists of two different parts. Part A employs a standard 6 + 3 design to evaluate the safety of the investigational study regimen. Part B uses a Simon Two-Stage design to explore the efficacy of the investigational study regimen at the treatment schedule established as safe in Part A.

Since this is an open-label clinical trial, in general, descriptive statistics will be employed to analyze the data. Summary statistics for continuous variables will include the mean, standard deviation, median, interquartile range and range (minimum/maximum). Categorical variables will be presented as frequency counts and percentages, and time-to-event variables will be summarized with number of non-missing observations, median survival time, and survival probability using Kaplan-Meier method if applicable. Kaplan Meier plot will also be provided.

The data will be tabulated and analyzed with respect to patient enrollment and disposition, demographic and baseline characteristics, prior and concomitant medications, efficacy, and safety measures. The efficacy analysis will be conducted on the Efficacy Evaluable Population, and the safety analysis will be performed on the Safety Population.

All confidence intervals will be constructed at the 95% confidence level. Data listings will be created to support each table and to present all data collected.

In Part C, the significance level of 5% will be used for two-sided exact binomial test for a null hypothesis for ORR_{24} of $P_0 = 12.2\%$.

24.3 Sample Size and Power

Part A Safety Evaluation: For the traditional 6+3 design of Part A, the goal is to determine a treatment schedule for which the rate of DLTs is less than 33% in 6 or 9 patients. A minimum of 6 patients are planned for Part A, with a maximum of 18 DLT-evaluable patients for the Starting Treatment Schedule and Reduction Level 1. If ≥3 in 6 or 9 patients at Reduction Level 1 have DLTs, then the investigational treatment regimen will be considered too toxic and enrollment into the study will be discontinued.

Part B: Part B follows a 1-sided Simon 2-Stage design; 15 patients, including all patients from Part A without a DLT, who receive the recommended Phase 2 regimen and who meet the criteria for the Efficacy Evaluable Population (see Section 24.4), with HPV 16 or 18 positive advanced cervical cancer will be included in the first stage analysis. If 3 or more objective responses (PR or better) are observed in the first stage, another 13 patients will be enrolled into the second stage, for a total of 28 patients in Part B. Study has passed the first stage of Simon-Two stage design. For a null hypothesis ORR_{24} of 0.15 and an alternative hypothesis ORR_{24} of 0.35, the sample size of 28 patients will provide a one-sided significance level of approximately 5% and a power of 80%. If Stages 1 and 2 are completed, a minimum of 8 patients must demonstrate a response (PR or better) to reject the null hypothesis.

Part C: Part C is to evaluate efficacy in larger patient population.In Keynote-158 study (pembrolizumab monotherapy in patients who have progressed with standard of care systemic therapy), ORR in total patients (i.e. regardless of PD-L1 status) and with CPS ≥ 1 were 12.2% and 14.6%, respectively.

Given this, null hypothesis for ORR_{24} was set at $P_0 = 12.2\%$. With an alternative hypothesis for ORR_{24} of $P_a = 37\%$, the sample size of 60 subjects was calculated considering two-sided significance level of 0.05, 97% power, and 25% dropout rate.

The confidence interval (CI) for ORR_{24} will be estimated using exact Clopper-Pearson method, and if the lower bound of the two-sided 95% CI for ORR_{24} exceeds 12.2%, it will be proven to satisfy the primary efficacy.

24.4 **Analysis Populations**

Safety Population. All patients who receive at least 1 dose of 1 agent in the investigational treatment regimen (i.e. either GX-188E or P) will be included in the analysis of safety, regardless of the duration of treatment.

DLT-evaluable. Unless doses are missed within the first two weeks of treatment (i.e., Week 1 Day -1 to Week 2 Day 7) due to DLT(s), a patient must receive all of the planned administrations of both agents (GX-188E and P) within the DLT-evaluation period to be considered evaluable for DLT. If a patient misses any treatment within the first two weeks of the study for reasons other than a DLT, the patient will be considered non-evaluable for DLT and replaced.

Efficacy Evaluable Population. All patients who discontinue the study treatment regimen early due to treatment-related toxicity will be considered evaluable for efficacy. Patients who discontinue study due to disease-related death, unequivocal tumor progression or with at least 1 post-baseline tumor assessment must have received at least 45 days of treatment to be considered evaluable for efficacy. Patients in Part B and C who do not meet the aforementioned requirements will be considered non-evaluable for response and may be replaced. Patients from Part A, who receive the recommended Phase 2 regimen and who meet the aforementioned criteria for the Efficacy Evaluable Population will be included in the analysis for Part B and C. The following table provides further, more specific details.

Table 7. Determination of Patients to be Included in Efficacy Evaluable.

Patient Cohort	Reason for Discontinuation	Number of Days on Protocol Treatment	Include in Efficacy Evaluable Population (Yes/No)?
Part A receiving RP2 regimen*	Protocol-Defined Dose Limiting Toxicity (DLT), or other toxicity	Not applicable	Yes, included in Efficacy Evaluable Population
Part A receiving RP2 regimen*	Disease-related death, unequivocal tumor progression or at least 1 post-baseline tumor assessment	< 45 days	No
Part A receiving RP2 regimen*	Disease-related death, unequivocal tumor progression or at least 1 post-baseline tumor assessment	≥ 45 days	Yes, included in Efficacy Evaluable Population
Part A, receiving dose > RP2 regimen*	Any	Not applicable	No
Part B and C	Disease-related death, unequivocal tumor progression, or at least 1 post-baseline tumor assessment	< 45 days	No, patient may be replaced
Part B and C	Disease-related death, unequivocal tumor progression, or at least 1 post-baseline tumor assessment	≥ 45 days	Yes, included in Efficacy Evaluable Population
Part B and C	Toxicity	Not applicable	Yes, included in Efficacy Evaluable Population

*RP2 regimen = Recommended Phase 2 regimen of GX-188E

24.5 **Efficacy Analysis**

Response to treatment will be evaluated using both RECIST v1.1 (Appendix 5) and iRECIST (Appendix 6). For each patient with objectively measurable disease and who meet the criteria for inclusion in the Efficacy Evaluable population (Section 24.44), response to therapy (overall

response within 24 weeks and best overall response), time-to-best-response, duration of response (DOR), progression-free survival (PFS), and overall survival (OS) will be calculated. Responses for patients who do not meet the criteria for inclusion into the Efficacy Evaluable population may also be described.

Definitions for response and survival outcomes are provided below:

Efficacy Endpoints for Individual Patients

Endpoint	Definition
Overall Response within 24 weeks (OR_{24})	The best objective response achieved within the first 24 weeks of treatment initiation
Best Overall Response (BOR)	The best objective response achieved prior to study discontinuation
Time-to-Best Response (TTR)	Time from treatment initiation to the best objective response achieved. This endpoint is only determined for patients who have a PR or CR.
Duration of Response (DOR)	Time from documentation of objective tumor response (PR or CR) to disease progression. This endpoint is only determined for patients who have a PR or CR.
Progression-Free Survival (PFS)	Time from treatment initiation until documented disease progression or death
Overall Survival (OS)	Time from treatment initiation until death from any cause

The Kaplan-Meier method will be used to estimate the median Duration of Response (DOR), median Progression-Free Survival (PFS), and median Overall Survival (OS).

Endpoints for the Efficacy Evaluable Study Population

Population efficacy endpoints will only include those patients who meet the criteria for inclusion in the Efficacy Evaluable population (Section 24.4). The definition of statistics calculated by the endpoints is as follows.

Statistics	Definition
Overall Response Rate within 24 weeks (ORR_{24})	The proportion of efficacy evaluable patients who achieve an objective response (PR or CR) within the first 24 weeks of treatment initiation
Best Overall Response Rate (BORR)	The proportion of efficacy evaluable patients who achieve an objective response (PR or CR) prior to study discontinuation
Median Progression-Free Survival time (mPFS)	Timepoint at which the probability of progression-free survival equlas to 50% in the efficacy evaluable population

6-month PFS rate	Probability that the progression has not occurred by 6 months
Median Overall Survival time (mOS)	Timepoint at which the probatility of survival equlas 50% in the efficacy evaluable population
Disease Control Rate (DCR)	The proportion of efficacy evaluable patients who had a CR, PR or Stable Disease
Median Duration of Response (mDOR)	Timepoint at which the probability of disease progression equals 50% after documented objective tumor response (PR or CR). This endpoint only includes patients who have achieved an objective response. Kaplan-Meier method will be used to estimate mDOR.
Median Time to Best Response (mTTR)	Timepoint from treatment initiation to the best objective response achieved (i.e., PR or CR whichever occurs earlier) in 50% of patients. Median TTR will be calculated using descriptive statistics in the population restricted to subjects with the best objective response

In addition, relationships between antitumor activity and exploratory biomarkers of immune system changes may be explored.

24.6 **Safety Analysis**

Safety variables to be analyzed are AEs, laboratory test results (e.g., hematology, coagulation, serum chemistry, thyroid function tests, and urinalysis), and vital signs. Clinically significant changes from baseline will be summarized using descriptive statistics.

Adverse event severity will be graded according to the CTCAE v4.0 or the most recent version and terms recorded on the CRFs will be mapped to preferred terms using the most recent version of the Medical Dictionary for Drug Regulatory Activities (MedDRA®). All AEs will be summarized according to the system organ class and preferred term within the organ class. Adverse events will be tallied for overall frequency (number and percentage of patients), worst reported severity, and relationship to the investigational study drugs for each preferred term per patient. Serious adverse events will be similarly summarized. Listings of deaths, SAEs, and AEs leading to early termination of study treatment or premature withdrawal from study will also be provided.

24.7 **Interim Analysis**

An interim analysis will be performed with safety and efficacy data in case of at least 22 patients in efficacy evaluable population, after obtaining week 10 tumor assessment results (either by investigator/BICR).

24.8 Final Analysis

The final analysis will be performed to report a primary CSR based on a data cut off after all 60 patients in the planned efficacy evaluation population have completed tumor assessment within 24 weeks by the investigator per RECIST v1.1

Since patient will be treated until they met one of the discontinuation criteria, some patients may still be ongoing at the time of final analysis. Therefore, a long-term follow-up study can be performed after final analysis with all available data (no cut-off date applied).

25.0 GENERAL STUDY MANAGEMENT INFORMATION

25.1 Informed Consent

The Investigator will provide for the protection of the patients by following all applicable regulations. These regulations are available upon request from the Sponsor. The Informed Consent Form used during the informed consent process must be reviewed by the Sponsor and approved by the IRB/IEC.

Before any procedures specified in the protocol are performed, a patient must:

- Be informed of all pertinent aspects of the study and all elements of informed consent
- Be given time to ask questions and time to consider the decision to participate
- Voluntarily agree to participate in the study
- Sign and date an IRB/IEC approved Informed Consent Form

25.2 Institutional Review Board and Institutional Biosafety Committee Approvals

An Institutional Review Board (IRB), which is operating in accordance with Title 21 of the Code of Federal Regulations Part 56, must approve the clinical protocol and corresponding informed consent form and agree to monitor the conduct of the trial and review its progress at regular intervals. Before the Sponsor or its designate will make investigational product available, and before the trial begins, the investigator will provide to the Sponsor documented evidence of IRB approval, demonstrating review and approval of this clinical protocol, and informed consent form.

An Institutional Biosafety Committee (IBC), which is duly registered with the NIH Office of Biotechnology Activity (NIH/OBA) in accordance with NIH Guidelines, must approve the

clinical protocol. The investigator will provide to the Sponsor documented evidence of IBC approval prior to initiation of the clinical trial.

25.3 Pre-Study Documentation

The Investigator must provide the Sponsor with the following documents BEFORE enrolling any patients:

- Completed and signed form 1572
- All applicable country-specific regulatory forms
- Current, dated curricula vitae for the Investigator, Subinvestigators, and other individuals having significant investigator responsibility who are listed on the Form 1572 or equivalent, or the clinical study information form.
- Copy of the IBC approval letter
- Copy of the IRB/IEC approval letter for the protocol and informed consent. All advertising, recruitment, and other written information provided to the patient must be approved by the IRB/IEC. Written assurance of continuing approval (at least annually) as well as a copy of the annual progress report submitted to the IRB/IEC must also be provided to the Sponsor.
- Copy of the IRB/IEC-approved Informed Consent Form to be used
- Where applicable, a list of the IRB/IEC members or a FWA/DHHS number
- Copy of the protocol sign-off page signed by the Investigator
- Copy of the current medical license (online verification is also acceptable) of the Principal Investigator, any Subinvestigators and any other individuals having significant responsibility as listed in the 1572
- Fully executed Clinical Trial Agreement (CTA)
- Where applicable, a financial disclosure form for the Principal Investigator and any other persons listed in the 1572
- A written document containing the name, location, certification number, and date of certification of the laboratory to be used for laboratory assays and those of other facilities conducting tests. This document should be returned along with the 1572. The

Sponsor must be notified if the laboratory is changed or if any additional laboratory is to be used.

- List of normal laboratory values and units of measure for all laboratory tests required by the protocol. This is required for each laboratory to be used during the study. The Sponsor must be notified if normal values or units of measurement change.

25.4 Protocol Amendments

Any significant change in the study requires a protocol amendment. An Investigator must not make any changes to the study without IRB/IEC and Sponsor approval. All protocol amendments must be reviewed and approved following the same process as the original protocol.

25.5 Direct Access, Data Handling, and Record Keeping

25.5.1 Confidentiality

All study-related laboratory and clinical data gathered in this protocol will be stored in a password-protected database. All patient information will be handled using anonymous identifiers. Linkage to patients' study data is only possible after accessing a password-protected database. Access to the database is only available to individuals directly involved in the study.

Patient personal health information that is accessed for this study will not be reused or disclosed to any other person or entity, or for other research.

25.5.2 Case Report Forms (CRFs)

The Investigator will permit study-related monitoring, audits, IRB/IEC review, and regulatory inspections by providing direct access to source data and documents.

All study-related information will be recorded on source documents. All required data will be recorded in the CRFs. All CRF data must be submitted to the Sponsor throughout and at the end of the study.

The Clinical Research Coordinator (CRC), or other properly trained site personnel, will complete the CRFs as soon as possible upon completion of the study visit; the Investigator will review and approve the completed CRFs.

The information collected on CRFs shall be identical to that appearing in original source documents. Source documents will be found in the patient's medical records maintained by site

personnel. All source documentation should be kept in separate research folders for each patient.

In accordance with federal regulations, the Investigator is responsible for the accuracy and authenticity of all clinical and laboratory data entered onto CRFs. The PI will approve all completed CRFs to attest that the information contained on the CRFs is true and accurate.

All source documentation will be available for review/monitoring by the Sponsor (or designee) and regulatory agencies.

The Principal Investigator will be responsible for ensuring the accurate capture of study data. At study completion, when the CRFs have been declared to be complete and accurate, the database will be locked. Any changes to the data entered into the CRFs after that time can only be made by joint written agreement among the Study Chair, the Trial Statistician, and the Protocol Project Manager.

25.5.2.1 **Records Retention**

The Investigator shall retain and preserve one copy of all data generated in the course of the study, specifically including but not limited to those defined by GCP as essential, for the longer of: (i) 3 years after the last marketing authorization for the study drug has been approved or 3 years after study completion or (ii) such longer period as required by applicable global regulatory requirements. At the end of such period, the Investigator shall notify the Sponsor in writing of its intent to destroy all such material. The Sponsor shall have 30 days to respond to the Investigator's notice, and the Sponsor shall have a further opportunity to retain such materials at the Sponsor's expense.

25.5.3 **Oversight and Monitoring**

The Sponsor (or designee) will be the monitoring entity for this study. The data will be checked for completeness and correctness in real-time online and during scheduled site monitoring visits.

Discrepancy reports will be generated and transferred to the study center for resolution by the Investigator or his/her designee.

The Sponsor (or designee), in collaboration with all participating Investigators, will routinely review all adverse events and suspected adverse reactions considered "serious". The Sponsor

(or designee) will audit study-related activities to ensure that the study is conducted in accordance with the protocol, local standard operating procedures, FDA regulations, and Good Clinical Practice (GCP). Significant findings will be communicated to the site Investigator and, as applicable, the local IRB. For additional information, please refer to the Clinical Monitoring Plan and Safety Monitoring Plan.

25.6 Study Suspension, Termination, and Completion

The Sponsor may suspend or terminate the study or any part of the study at any time for any reason. If the Investigator suspends or terminates the study, the Investigator must promptly inform the Sponsor and the IRB/IEC and provide a detailed written explanation. The Investigator will also return all study-specific investigational treatment agents (i.e. GX-188E, pembrolizumab), study-specific equipment (e.g., TDS-IM ® Electroporation Device), containers, and other study materials to the Sponsor or designee, unless specific permissions and instructions have been provided for on-site destruction of the materials. Upon study completion, the Investigator will provide the Sponsor, IRB/IEC, and regulatory agency with final reports and summaries as required by regulations.

26.0 Protection of Human Patients

26.1 Protection from Unnecessary Harm

Each clinical site is responsible for protecting all patients involved in human experimentation. This is accomplished through the IRB mechanism and the process of informed consent. The IRB reviews all proposed studies involving human experimentation and ensures that the subject's rights and welfare are protected and that the potential benefits and/or the importance of the knowledge to be gained outweigh the risks to the individual. The IRB also reviews the informed consent document associated with each study in order to ensure that the consent document accurately and clearly communicates the nature of the research to be done and its associated risks and benefits.

26.2 Protection of Privacy

Patients will be informed of the extent to which their confidential health information generated from this study may be used for research purposes. Following this discussion, they will be asked to sign the HIPAA form and informed consent documents. The original signed document will become part of the patient's medical records, and each patient will receive a copy of the

signed document. The use and disclosure of protected health information will be limited to the individuals described in the informed consent document.

27.0 References

1. Trottier H, Franco EL. The epidemiology of genital human papillomavirus infection. *Vaccine* 2006; 24 Suppl 1: S1-15.
2. Ferlay J, Soerjomataram I, Ervik M et al. Cancer incidence and mortality worldwide: sources, methods and major patterns in GLOBOCAN 2012. *Int J Cancer* 2015 Mar 1;136(5): E359-86
3. 2015 Cancer Facts and Figures. American Cancer Society.
4. Grabowska AK, Riemer AB. The invisible enemy – how human papillomaviruses avoid recognition and clearance by the host immune system. *Open Virol J* 2012; 6: 249-256.
5. Kanodia S, Fahey LM, Kast WM. Mechanisms used by human papillomaviruses to escape the host immune response. *Curr Cancer Drug Targets* 2007; 7: 79-89
6. Kobayashi A, Weinberg V, Darragh T et al. Evolving immunosuppressive microenvironment during human cervical carcinogenesis. *Mucosal Immunol* 2008; 1: 412-420.
7. Piersma SJ. Immunosuppressive tumor microenvironment in cervical cancer patients. *Cancer Microenviron* 2011; 4: 361-75
8. Kim TJ, Jin H-T, Hur S-Y, et al. Clearance of persistent HPV infection and cervical lesion by therapeutic DNA vaccine in CIN3 patients. *Nature Communications*. 2014;5:5317
9. van Drunen L, van den Hurk S and Hannaman D. Electroporation for DNA immunization: clinical application. *Expert Rev Vaccines* 2010; 9(5): 503-517
10. Gothelf A., Mir LM and Gehl J. Electrochemotherapy: results of cancer treatment using enhanced delivery of bleomycin by electroporation. *Cancer Treat Rev* 2003; 29(5): 371-387
11. Cemazar M, Golzio M, Sersa G et al. Electrically-assisted nucleic acids delivery to tissues in vivo: where do we stand? *Curr Pharm Des* 2006; 12(29): 3817-3825
12. Favard C, Dean DS and Rols MP. Electrotransfer as a non viral method of gene delivery. *Curr Gene Ther* 2007; **7**(1): 67-77.
13. Phase 2 Clinical Trial to Evaluate the Safety and Efficacy of Plasmid DNA Therapeutic Vaccine (GX-188E). ClinicalNCT02596243
14. Frenel JS, Le Tourneau C, O'Neil BH, et al. Pembrolizumab in patients with advanced cervical squamous cell cancer: Preliminary results from the phase Ib KEYNOTE-028 study. J Clin Oncol 34, 2016 (suppl; abstr 5515)
15. Moore DH, Tian C, Monk BJ et al. Prognostic factors for response to cisplatin-based chemotherapy in advanced cervical carcinoma: A Gynecologic Oncology Group Study. *Gynecol Oncol* 116:44-49, 2010
16. Tewari KS, Still MW, Monk BJ et al., Prospective validation of pooled prognostic factors in advanced cervical cancer: A Study of the Gynecologic Oncology Group. *Society of Gynecologic Oncology 45th Annual Meeting on Women's Cancer.* Tampa, FL. March 22-25 2014 (abstr 143-144)
17. Eisenhauer EA, Therasse P, Verweij J, et al., New response evaluation criteria in solid tumors: Revised RECIST guideline (version 1.1). Eur J Cancer. 2009;45:228-247.
18. Nishino M, Giobbie-Hurder A, Gargano M, et al., Developing a Common Language for Tumor Response to Immunotherapy: Immune-Related Response Criteria Using Unidimensional Measurements. Clin Cancer Res. 2013;19(14):3936-43.
19. Gardiner DF, Huang Y, Basu S, et al., Multiple-site DNA vaccination enhances immune responses in mice. Vaccine. 2006;24:287-92
20. Ren Y, Wang N, Hu W, et al., Successive site translocating inoculation potentiates DNA/recombinant vaccinia vaccination. Sci Rep. 2015;5:18099

21. Seo SH, Jin HT, Park SH, et al., Optimal induction of HPV DNA vaccine-induced CD8+ T cell responses and therapeutic antitumor effect by antigen engineering and electroporation. Vaccine. 2009 27:5906-12
22. Disis, Mary L. Immune Regulation of Cancer. Journal of Clinical Oncology.2010; 28 (29):4531-4538
23. Dudley, Mark E., Wunderlich, John E.,Yang, James C., Sherry, Richard M., Topalian, Suzzane L., Restifo, Nicholas P., Royal, Richard E., Kammula, Udai, White, Don E., Mavroukakis, Sharon A., et al. Adoptive Cell Transfer Therapy Following Non-Myeloablative but Lymphodepleting Chemotherapy for the Treatment of Patients With Refractory Metastatic Melanoma. Journal of Clinical Oncology.2005; 0732-183
24. Hunder NN, Wallen H, Cao J, Hendricks DW, Reilly JZ, Rodmyre R, et al. Treatment of metastatic melanoma with autologous CD4+ T cells against NY-ESO-1. N Engl J Med 2008;358(25):2698-703
25. Greenwald, Rebecca J., Freeman, Gordon J., and Sharpe, Arlene H. The B7 Family Revisited. Annual Reviews.2005; 23:515–48
26. Okazaki T, Maeda A, Nishimura H, Kurosaki T, Honjo T. PD-1 immunoreceptor inhibits B cell receptor-mediated signaling by recruiting src homology 2-domain-containing tyrosine phosphatase 2 to phosphotyrosine. Proc Natl Acad Sci U S A 2001;98(24):13866-71.
27. Chemnitz, Jens M., Parry, Richard V., Nichols, Kim E., June, Carl H., Riley, James L., SHP-1 and SHP-2 Associate with Immunoreceptor Tyrosine-Based Switch Motif of Programmed Death 1 upon Primary Human T Cell Stimulation, but Only Receptor Ligation Prevents T Cell Activation. The Journal of Immunology.2004, 173: 945–954
28. Riley, James L., PD-1 signaling in primary T cells. Immunological Reviews. 2009; 0105-2896
29. Shepard, Kelly-Ann., Fitz, Lori J., Lee, Julie M., Benander, Christina, George, Judith A., Wooter, Joe, Qiu, Yongchang, Jussif, Jason M., Carter, Laura L., Wood, Clive R., Chaudhary, Divya. PD-1 inhibits T-cell receptor induced phosphorylation of the ZAP70/CD3 signalosome and downstream signaling to PKC. FEBS Letters. 2004; 0014-5793
30. Francisco, Loise M., Sage, Peter T., and Sharpe, Arlene H. The PD-1 pathway in tolerance and autoimmunity. Immunological Reviews.2010; 0105-2896
31. Parry, Richard V., Chemnitz, Jens M., Frauwirth, Kenneth A., Lanfranco, Anthony R., Braunstein, Inbal., Kobayashi, Sumire V., Linsley, Peter S., Thompson, 4 Craig B.and Riley, James L. CTLA-4 and PD-1 Receptors Inhibit T-Cell Activation by Distinct Mechanisms. MOLECULAR AND CELLULAR BIOLOGY, 2005; 0270-7306
32. Pilon-Thomas, S., et al., Blockade of programmed death ligand 1 enhances the therapeutic efficacy of combination immunotherapy against melanoma. J Immunol, 2010. 184(7): p. 3442-9.
33. Hirano, F., et al., Blockade of B7-H1 and PD-1 by monoclonal antibodies potentiates cancer therapeutic immunity. Cancer Res, 2005. 65(3): p. 1089-96.
34. Blank, C., et al., PD-L1/B7H-1 inhibits the effector phase of tumor rejection by T cell receptor (TCR) transgenic CD8+ T cells. Cancer Res, 2004. 64(3): p. 1140-5.
35. Spranger, S., et al., Mechanism of tumor rejection with doublets of CTLA-4, PD-1/PD-L1, or IDO blockade involves restored IL-2 production and proliferation of CD8(+) T cells directly within the tumor microenvironment. J Immunother Cancer, 2014. 2: p. 3.
36. Strome, S.E., et al., B7-H1 blockade augments adoptive T-cell immunotherapy for squamous cell carcinoma. Cancer Res, 2003. 63(19): p. 6501-5.

37. Weber, J., Immune checkpoint proteins: a new therapeutic paradigm for cancer--preclinical background: CTLA-4 and PD-1 blockade. Semin Oncol, 2010. **37**(5): p. 430-9.
38. tor Programmed Death-1. Immunity.2004; 337-347
39. Curran, M.A., et al., PD-1 and CTLA-4 combination blockade expands infiltrating T cells and reduces regulatory T and myeloid cells within B16 melanoma tumors. Proc Natl Acad Sci U S A, 2010. 107(9): p. 4275-80.
40. Pilon-Thomas, S., et al., Blockade of programmed death ligand 1 enhances the therapeutic efficacy of combination immunotherapy against melanoma. J Immunol, 2010. 184(7): p. 3442-9.
41. Nomi, T., et al., Clinical significance and therapeutic potential of the programmed death-1 ligand/programmed death-1 pathway in human pancreatic cancer. Clin Cancer Res, 2007. 13(7): p. 2151-7.
42. Zhang, PDXuewu, Schwartz, Jean-Claude D., Guo, Xiaoling, Bhatia, Sumeena, Cao, Erhu,Chen, Lieping, Zhang, Zhong-Yin, Edidin, Michael A., Nathenson, Stanley G. Almo, Steven C. Structural and Functional Analysis of the Costimulatory Receptor Programmed Death-1. Immunity.2004; 337-347
43. Seymour L, Bogaerts J, Perrone A, Ford R, Schwartz LH, Mandrekar S, et al. iRECIST: guidelines for response criteria for use in trials testing immunotherapeutics. Lancet Oncol. 2017 Mar;18(3):e143-e152
44. Chung HC et al., Efficacy and safety of pembrolizumab in previously treated advanced cervical cancer: Results from the phase II KEYNOTE-158 study. J Clin Oncol, 2019. 37(17): p. 1470-8

APPENDIX 1: SCHEDULE OF EVENTS (SCREENING -WEEK 10)

	Screening (-28 to 0)	**Treatment Week**					
		Week 1 Day 1	**Week 2 Day 1** (± 3 days)	**Week 3Day 1** (± 3 days)	**Week 4 Day 1** (± 3 days)	**Week 7 Day 1** (± 3 days)	**Week 10 Day 1** (± 3 days)
Informed Consent	**X**						
Demographics	**X**						
Medical History[1]	**X**						
Physical Exam[2] and Vital Signs[3]	**X**	**X**	**X**	**X**	**X**	**X**	**X**
Performance Status (ECOG)	**X**				**X**	**X**	**X**
Moore Criteria Risk Categorization[4]	**X**						
Adverse Events[5]		**X**	**X**	**X**	**X**	**X**	**X**
Concomitant Medications[6]	**X**	**X**	**X**	**X**	**X**	**X**	**X**
CBC (w/diff, platelet count)[7]	**X**	**X**	**X**	**X**	**X**	**X**	**X**
Serum Chemistry[8]	**X**	**X**	**X**	**X**	**X**	**X**	**X**
Serology[9], Chest X-ray, ECG	**X**						
Thyroid Function Tests and CEA/TA4[10]	**X**					**X**	
Urinalysis[11]	**X**	**X**					**X**
Coagulation Assessment[12]	**X**						**X**
Pregnancy Test[13]	**X**						
Research Blood Collection [14]	**X**	**X**			**X**	**X**	**X**
GX-188E Vaccinationn (i.m.)		**X**	**X**[13]		**X**[13]	**X**	
Pain Assessment[15]		**X**	**X**		**X**	**X**	
Pembrolizumab (i.v.)		**X**			**X**	**X**	**X**
Tumor Biopsy Sample[16]	**X**						**X**
Radiographic Evaluation of Tumor Burden[17]	**X**						**X**

1. Medical history includes any significant comorbid conditions requiring active treatment as well as surgeries and therapies related to the treatment of malignancies, including cervical cancer. Cervical cancer history includes review of prior treatments and documentation of HPV-16 or -18 positivity. Medical records and/or local laboratory results will be considered adequate documentation HPV-16 or -18 positivity
2. Screening and End of Study require a complete physical exam. For all other study, physical exams should be symptom-directed and clinically significant findings reported as adverse events.
3. Vitals to include heart rate, respiratory rate, temperature, blood pressure (systolic and diastolic) weight, and height. Height only required at screening
4. Determine whether the patient has low risk, mid risk or high risk disease based upon Moore criteria (See Appendix 3).
5. Adverse event monitoring begins once a patient receives the first dose of study treatment and continues until 28 days after the last administration of study treatment, or until the initiation of a new anti-cancer therapy, whichever occurs first. For Serious Adverse Events (SAEs), follow up will continue for 90 days.
6. Concomitant medication is defined as any prescription or over-the-counter preparation, including vitamins and supplements. All concomitant medications from 28 days before Day 1 through the end of the subject's study participation must be recorded. (During the follow-up period after the end of the clinical trial, only the data about the antineoplastic therapy (surgical therapy, chemotherapy, radiation therapy, etc.) treated after the end of the subject's study participation is recorded.)
7. CBC w/differential to include: Hemoglobin, Platelets, Red Blood Cells, White Blood Cells, Basophils (%)), Eosinophils (%)), Lymphocytes (%)), Monocytes (%), Neutrophils (Abs) and Hematocrit.
8. Serum Chemistry at Screening to include: Sodium, Potassium, CO_2 or bicarbonate, Chloride, Albumin, Alkaline Phosphatase, ALT, AST, Total Bilirubin, Blood Urea Nitrogen, Calcium, Creatinine, Glucose, Magnesium, Phosporus, Total Protein, LDH, and Cockcroft-Gault calculated Creatinine Clearance. At all other time points, only a basic metabolic panel (Na, K, CO_2 or bicarbonate, Cl, Ca, BUN, creatinine & glucose) plus AST and ALT are required. Other tests may be ordered as clinically indicated. However, if subjects had the result of serum chemistry tests at the screening which met the all in/exclusion criteria and the investigators judged that the result of same tests at W1D1 were no clinical significance, they can be enrolled.
9. Serology at Screening to include: HIV Ag/Ab, HAV Ab (IgM), HBV Ab, HBV sAg, HCV Ab, HCV RNA (HCV real time PCR)
10. Includes thyroid-stimulating hormone (TSH), free thyroxine (FT4), and T3. Thyroid function tests and CEA/TA4 levels will be performed approximately every 6 weeks.
11. Urinalysis is only required at Screening, Week 1 Day 1, Week 10 Day 1, and End of Study. Urinalysis should be ordered as clinically indicated at any other timpoint.
12. Coagulation assessment includes: prothrombin time, partial thromboplastin time, and international normalized ratio (PT/PTT/INR). Coagulation assessments are only required at Screening and End of Study. On-treatment coagulation assessments (e.g., Week 10) are only required if a biopsy is planned and must be evaluated within 24 hours prior to biopsy collection on the same day.
13. All females of child-bearing potential must have a negative serum or urine pregnancy test within 3 days prior to the first dose of study treatment.
14. Blood collection. Samples will include serum for immune response Flt-3L(Screening, Week10, Week22, Week49 then after every 27 weeks) and whole blood for PBMC T cell responses(Screening, Week1, Week4, Week7, Week10, Week16, Week22, Week49 then after every 27 weeks). Samples obtained at all time points associated with study treatment administration, except for Screening, should be obtained prior to administration of either/both agents. Blood sample for Flt-3L will be collected at screening visit, week 10, week 22, week 49 and every 27 weeks thereafter.
15. Pain assessment using a 0-10 numeric pain rating scale will be administered prior to and 5 minutes ($\pm$ 2 minutes) following each GX-188E electroporation procedure
16. All patients must submit either an archival tumor tissue sample OR fresh biopsy sample at Screening. Biopsies will be evaluated for bio-markers using immunohistochemistry but not limited to it.Patients with biopsy-accessible lesions will be asked to provide an optional biopsy sample at approximately Week 10 (or End of Study if the patient discontinues prior to Week 10) for paired biopsy analysis.

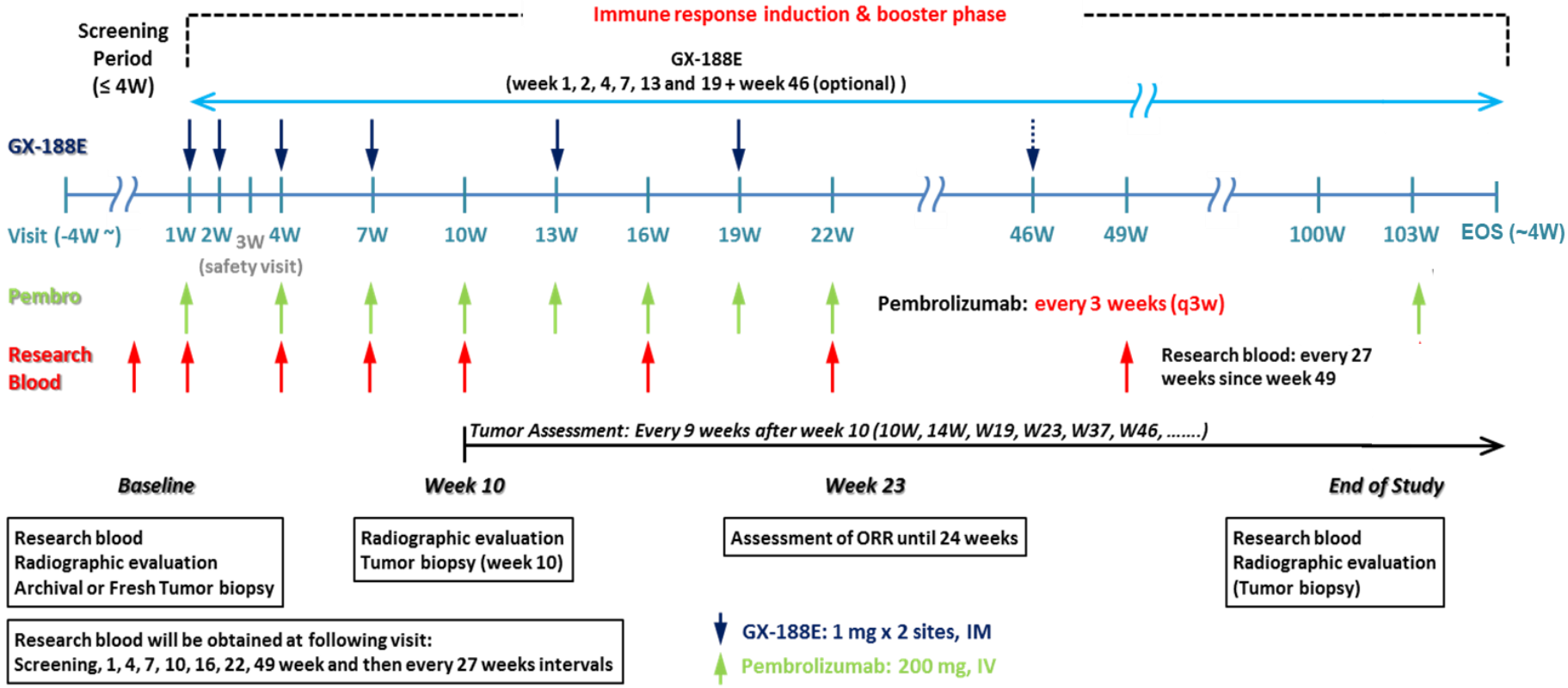
17. Radiographic evaluations of tumor burden by RECIST v1.1 will be performed by a blinded independent central reviewer at Screening, approximately every 9 weeks during the treatment period, or more frequently as clinically indicated, and at End of Study if the reason for discontinuation is other than for confirmed radiologic disease progression. Scans obtained within 28 days prior to Week 1 Day 1 will be accepted for Screening and do not need to be repeated unless a clinically significant difference is suspected. Confirmatory scans are required approximately 4 weeks after any scan that indicates either an objective response, stable disease or disease progression,

SCHEDULE OF EVENTS (SUBSEQUENT TO WEEK 10)

	Treatment Week						
	Week 13 Day 1 (± 3 days)	**Week 16 Day 1** (± 3 days)	**Week 19 Day 1** (± 3 days)	**Every 3 Weeks after Week 19 Day 1** (± 3 days)	**Approx. every 9 Weeks after Week 19 Day 1** (± 1 week)	**Week 46 Day 1** (± 1 week)	**End of Study[17] Follow-Up**
Physical Exam[1] and Vital Signs[2]	**X**	**X**	**X**	**X**	**X**	**X**	**X**
Performance Status (ECOG)	**X**	**X**	**X**		**X**	**X**	**X**
Adverse Events[3]	**X**	**X**	**X**	**X**	**X**	**X**	**X**
Concomitant Medications[4]	**X**	**X**	**X**	**X**	**X**	**X**	**X**
CBC (w/diff, platelet count) [5]	**X**	**X**	**X**		**X**	**X**	**X**
Serum Chemistry[6]	**X**	**X**	**X**		**X**	**X**	**X**
Thyroid Function Tests and CEA/TA4[7]	**X**		**X**	**X**			**X**
Urinalysis[8]							**X**
Coagulation Assessment[9]							**X**
Pregnancy Test[10]							**X**
Research Blood Collection [11]		**X**	**(X + 3 wk)[11]**			**(X + 3 wk)[11]**	**X**
GX-188E Vaccination (i.m.)	**X**		**X**			**(X)[16]**	
Pain Assessment[12]	**X**		**X**			**X**	
Pembrolizumab (i.v.)[13]	**X**	**X**	**X**	**X**		**X**	
Tumor Biopsy[14] (optional)							**X**
Radiographic Evaluation of Tumor Burden[15]			**X**		**X**		**X**

1. Screening and End of Study require a complete physical exam. For all other study, physical exams should be symptom-directed and clinically significant findings reported as adverse events.
2. Vitals to include heart rate, respiratory rate, temperature, blood pressure (systolic and diastolic) weight, and height. Height only needs to be obtained at screening.
3. Adverse event monitoring begins once a patient receives the first dose of either agent of the investigational study regimen and continues until 28 days after the last administration of study treatment, or until the initiation of a new anti-cancer therapy, whichever occurs first. For Serious Adverse Events (SAEs), follow up will continue for 90 days.
4. Concomitant medication is defined as any prescription or over-the-counter preparation, including vitamins and supplements. All concomitant medications from 28 days before Day 1 through the end of the subject's study participation must be recorded. (During the follow-up period after the end of the clinical trial, only the data about the antineoplastic therapy (surgical therapy, chemotherapy, radiation therapy, etc.) treated after the end of the subject's study participation is recorded.)
5. CBC w/differential to include: Hemoglobin, Platelets, Red Blood Cells, White Blood Cells, Basophils (%), Eosinophils (%), Lymphocytes (%), Monocytes (%), Neutrophils (Abs) and Hematocrit.
6. At all timepoints, (except for Screening), only a basic metabolic panel (Na, K, CO_2 or bicarbonate, Cl, Ca, BUN, creatinine & glucose) plus AST and ALT are required. Other tests may be ordered as clinically indicated.
7. Includes thyroid-stimulating hormone (TSH), free thyroxine (FT4), and T3. Thyroid function tests and CEA/TA4 levels will be evaluated approximately every 6 weeks for the duration of study participation (i.e., Screening/Baseline, Week 7, Week 13, Week 19, Week 25, etc).
8. Urinalysis is only required at Screening, Week 1 Day 1, Week 10 Day 1, and End of Study. Urinalysis should be ordered as clinically indicated at any other timpoint.
9. Coagulation assessment includes: prothrombin time, partial thromboplastin time, and international normalized ratio (PT/PTT/INR). Coagulation assessments are only required at Screening and End of Study. On-treatment coagulation assessments (e.g., Week 10) are only required if a biopsy is planned and must be evaluated within 24 hours prior to biopsy collection on the same day.
10. All females of child-bearing potential must have serum or urine pregnancy test at End of Study.
11. Blood collection.Samples will include serum for immune response Flt-3L(Screening, Week10, Week22, Week49 then after every 27 weeks) and whole blood for PBMC T cell responses(Screening, Week1, Week4, Week7, Week10, Week16, Week22, Week49 then after every 27 weeks). Samples obtained at all time points associated with study treatment administration, except for Screening, should be obtained prior to administration of either/both agents.
12. Pain assessment using a 0-10 numeric pain rating scale will be administered prior to and 5 minutes ($\pm$ 2 minutes) following each GX-188E electroporation procedure
13. Pembrolizumab will be administered every 3 weeks for the duration of study participation
14. Patients with biopsy-accessible lesions will be asked to provide an optional biopsy sample at approximately Week 10 (or End of Study if the patient discontinues prior to Week 10) for paired biopsy analysis. Biopsies will be evaluated for bio-markers using immunohistochemistry but not limited to it.
15. Radiographic evaluations of tumor burden by RECIST v1.1 will be performed by a blinded independent central reviewer approximately every 9 weeks, or more frequently as clinically indicated, and at End of Study if the reason for discontinuation is other than for confirmed radiologic disease progression. Confirmatory scans are required approximately 4 weeks after any scan that indicates either an objective response, stable disease or disease progression.
16. An optional GX-188E administration may be given at week 46 if it is in the best interests of the patient, as determined by the investigator, once the patient has completed 37 weeks of treatment. Additional GX-188E administration(s) may be given to the subject after discussion with the sponsor.
17. The End of Study (EOS) visit must occur within 28 days of treatment discontinuation/completion (Week 103 Day 1) and prior to initiation of any new anti-cancer thepapy/regimen.

Schematic Flow Chart



APPENDIX 2: LIST OF LIVE VACCINES.

Source: https://www.cdc.gov/vaccines/pubs/pinkbook/downloads/appendices/B/us-vaccines.pdf

Patients who received any of the live vaccines listed below within 30 days of Screening are excluded from the study and cannot be enrolled.

Vaccine	Trade Name	Manufacturer	Type / Route
Adenovirus	Adenovirus Type 4 & Type 7	Barr Labs Inc.	Live Viral / Oral (tablets)
Herpes Zoster (Shingles)	Zostavax	Merck	Live Attenuated Viral / SC
Influenza	FluMist®	Medimmune	Live Attenuated Viral / Intranasal (spray)
Measles, Mumps, Rubella	M-M-R® II	Merck	Live Attenuated Viral / SC
Measles, Mumps, Rubella, Varicella	ProQuad®	Merck	Live Attenuated Viral / SC
Rotavirus	RotaTeq®	Merck	Live Viral / Oral (liquid)
	Rotarix®	GlaxoSmithKline	Live Viral / Oral (liquid)
Typhoid	Vivotif®	PaxVax	Live Attenuated Bacterial / Oral (capsules)
Varicella	Varivax®	Merck	Live Attenuated Viral / SC
Varicella	Suduvax®	Green Cross	Live Attenuated Viral / SC
Vaccinia (Smallpox)	ACAM2000®	sanofi	Live Attenuated Viral / Percutaneous
Yellow Fever	YF-Vax®	sanofi	Live Attenuated Viral / SC
BCG for Tuberculosis		[multiple manufacturers]	Live attenuated / SC

APPENDIX 3: MOORE'S CRITERIA FOR DETERMINING PROGNOSIS IN CERVICAL CANCER

Source: Moore DH et al., 2010

All study participants should be categorized as low-risk, mid-risk or high-risk based upon the criteria and instructions below.

Criterion	Risk Factor	
	1 point each	**0 points each**
Race	Black	Non-Black
GOG Performance Status*	1 or 2	0
Site of Disease	Pelvis	Non-pelvis
Prior Platinum Agent as a Radiosensitizer?	Yes	No
1st Recurrence within 1 year since diagnosis?	Yes	No
Add number of risk factors, or points, to obtain the Total Risk Score		

Total Score	Risk Category
0-1	**Low-Risk**
2-3	**Mid-Risk**
4-5	**High-Risk**

***GOG Performace Status**

GOG Score	Activity Level
0	Fully active, unrestricted activities of daily living
1	Ambulatory, but restricted in strenuous activity
2	Ambulatory, and capable of self care. Unable to work. Out of bed for greater than 50% of waking hours
3	Limited self care, or confined to bed or chair 50% of waking hours. Needs special assistance
4	Completely disabled, and no self care
5	Dead

APPENDIX 4. CLINICAL LABORATORY TESTS

CLINICAL LABORATORY TESTS RESULTS WITHIN 4 WEEKS (8 WEEKS FOR SEROLOGY) PRIOR TO THE START OF STUDY TREATMENT WILL BE CONSIDERED AS ELIGIBLE TEST RESULTS FOR SCREENING PROCEDURES.

Hematology (Peripheral Blood Sample)

- Hemoglobin and hematocrit
- RBC count
- White blood cell count with differential
- Platelet count

Coagulation Tests

- PT, aPTT and INR

Serum Chemistry-Comprehensive Metabolic Panel (Peripheral Blood Sample)

- Sodium
- Potassium
- Chloride
- CO_2
- Calcium
- Magnesium
- Phosphorus
- Glucose[1]
- Blood urea nitrogen
- Creatinine
- Total protein
- Albumin
- Total and direct bilirubin[2]
- Aspartate aminotransferase (AST)
- Alanine aminotransferase (ALT)
- Alkaline phosphatase (AP)

[1] Fasting glucose is not required. Values considered abnormal must be interpreted in the context of a non-fasting state as clinically appropriate

[2] Direct bilirubin is only required if Total Bilirubin is above the upper limit of normal.

Serology

- HIV Ag/Ab
- HAV Ab (IgM)
- HBV Ab
- HBV sAg
- HCV Ab
- HCV RNA (HCV realtime PCR)

Urinalysis

- Protein
- Glucose
- Ketones
- Bilirubin
- Hemoglobin/myoglobin
- Nitrite
- Leukocyte esterase
- pH
- Specific gravity
- Urobilinogen
- Microscopic evaluation (only when protein, esterase or hemoglobin dipstick is positive)

APPENDIX 5: RECIST CRITERIA VERSION 1.1

Source: Eisenhauer et al., 2009

Sponsor's Note: Confirmatory scans are required approximately 4 weeks after any scan that indicates either an objective response or disease progression

MEASURABILITY OF TUMOR AT BASELINE

Definitions

At baseline, tumor lesions will be categorized measurable or non-measurable as follows.

Measurable tumor lesions

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

- 10 mm by CT scan (CT scan slice thickness no greater than 5 mm)
- 10 mm by caliper measurement (lesions which cannot be accurately measured with calipers should be recorded as non-measurable)
- 20 mm by chest X-ray

Malignant lymph nodes: To be considered pathologically enlarged and measurable, a lymph node must be ≥ 15 mm in short axis when assessed by CT scan (CT scan slice thickness recommended to be no greater than 5 mm). At baseline and in follow-up, only the short axis will be measured and followed. See also section below on 'Baseline documentation of target and non-target lesions' for information on lymph node measurement.

Non-measurable tumor lesions

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

Special considerations regarding lesion measurability

Bone lesions, cystic lesions, and lesions previously treated with local therapy require particular comment:

Bone lesions:

- Bone scan, PET scan or plain films are not considered adequate imaging techniques to measure bone lesions. However, these techniques can be used to confirm the presence or disappearance of bone lesions.

- Lytic bone lesions or mixed lytic-blastic lesions, **with identifiable soft tissue components**, that can be evaluated by cross sectional imaging techniques such as CT or MRI can be considered as measurable lesions if the soft tissue component meets the definition of measurability described above.
- Blastic bone lesions are non-measurable.

Cystic lesions:

- Lesions that meet the criteria for radiographically defined simple cysts should not be considered as malignant lesions (neither measurable nor non-measurable) since they are, by definition, simple cysts.
- 'Cystic lesions' thought to represent cystic metastases can be considered as measurable lesions, if they meet the definition of measurability described above. However, if non-cystic lesions are present in the same patient, these are preferred for selection as target lesions.

Lesions with prior local treatment:

- Tumor lesions situated in a previously irradiated area, or in an area subjected to other loco-regional therapy, are usually not considered measurable unless there has been demonstrated progression in the lesion.

SPECIFICATIONS BY METHODS OF MEASUREMENTS

Measurement of lesions

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

Method of assessment

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

Clinical lesions: Clinical lesions will only be considered measurable when they are superficial and ≥ 10 mm diameter as assessed using calipers (e.g., skin nodules). For the case of skin lesions, documentation by color photography including a ruler to estimate the size of the lesion is suggested. As noted above, when lesions can be evaluated by both clinical exam and imaging, imaging evaluation should be undertaken since it is more objective and may also be reviewed at the end of the study.

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

If prior to enrolment it is known that a patient is not able to undergo CT scans with IV contrast due to allergy or renal insufficiency, the decision as to whether a non-contrast CT or MRI (with or without IV contrast) will be used to evaluate the subject at baseline and follow-up, should be guided by the tumor type under investigation and the anatomic location of the disease. For patients who develop contraindications to contrast after baseline contrast CT is done, the decision as to whether non-contrast CT or MRI (enhanced or non-enhanced) will be performed, should also be based on the tumor type, anatomic location of the disease and should be optimized to allow for comparison to the prior studies if possible. Each case should be discussed with the radiologist to determine if substitution of these other approaches is possible and, **if not, the patient should be considered not evaluable from that point forward**.

FDG-PET: While FDG-PET response assessments need additional study, it is sometimes reasonable to incorporate the use of FDG-PET scanning to complement CT scanning in assessment of progression (particularly possible 'new' disease). New lesions on the basis of FDG-PET imaging can be identified according to the following algorithm:

a. Negative FDG-PET at baseline, with a positive* FDG-PET at follow-up is a sign of PD based on a new lesion.

b. No FDG-PET at baseline and a positive FDG-PET at follow-up: If the positive FDG-PET at follow-up corresponds to a new site of disease confirmed by CT, this is PD. If the positive FDG-PET at follow-up is not confirmed as a new site of disease on CT, additional follow-up CT scans are needed to determine if there is truly progression occurring at that site (if so, the date of PD will be the date of the initial abnormal FDG-PET scan). If the positive FDG-PET at follow-up corresponds to a pre-existing site of disease on CT that is not progressing on the basis of the anatomic images, this is not PD.

*A 'positive' FDG-PET scan lesion means one which is FDG avid with an uptake greater than twice that of the surrounding tissue on the attenuation corrected image.

TUMOR RESPONSE EVALUATION

Assessment of overall tumor burden and measurable disease

To assess objective response or future progression, it is necessary to estimate the overall tumor burden at baseline and use this as a comparator for subsequent measurements. Only patients with measurable disease at baseline will be enrolled into this study.

Measurable disease is defined by the presence of at least one measurable lesion.

Baseline documentation of 'target' and 'non-target' lesions

When more than one measurable lesion is present at baseline, all lesions up to a maximum of five lesions total (and a maximum of two lesions per organ) representative of all involved organs should be identified as target lesions and will be recorded and measured at baseline.

This means in instances where patients have only one or two organ sites involved a maximum of two (one site) and four lesions (two sites), respectively, will be recorded. Other lesions in that organ will be recorded as non-measurable lesions (even if size is greater than 10 mm by CT scan).

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

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

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

All other lesions (or sites of disease) including pathological lymph nodes should be identified as non-target lesions and should also be recorded at baseline. Measurements are not required and these lesions should be followed as 'present', 'absent', or in rare cases 'unequivocal progression.' In addition, it is possible to record multiple non-target lesions involving the same organ as a single item on the case report form (e.g., 'multiple enlarged pelvic lymph nodes' or 'multiple liver metastases').

RESPONSE CRITERIA

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

Evaluation of Target Lesions

- Complete Response (CR): Disappearance of all target lesions. Any pathological lymph nodes (whether target or non-target) must have reduction in short axis to < 10 mm.
- Partial Response (PR): *At least a 30% decrease* in the sum of diameters of target lesions, taking as reference the baseline sum diameters.
- Progressive Disease (PD): *At least a 20% increase* in the sum of diameters of target lesions, taking as reference the smallest sum on study (this includes the baseline sum if that is the smallest on study). In addition to the relative increase of 20%, the sum must

also demonstrate an absolute *increase of at least 5 mm*. (Note: the appearance of one or more new lesions is also considered progression).

- Stable Disease (SD): Neither sufficient shrinkage to qualify for PR nor sufficient increase to qualify for PD, taking as reference the smallest sum diameters while on study.

Special notes on the assessment of target lesions

Lymph nodes: Lymph nodes identified as target lesions should always have the actual short axis measurement recorded (measured in the same anatomical plane as the baseline examination), even if the nodes regress to below 10 mm on study. This means that when lymph nodes are included as target lesions, the 'sum' of lesions may not be zero even if complete response criteria are met, since a normal lymph node is defined as having a short axis of < 10 mm. Case report forms or other data collection methods may therefore be designed to have target nodal lesions recorded in a separate section where, in order to qualify for CR, each node must achieve a short axis < 10 mm. For PR, SD, and PD, the actual short axis measurement of the nodes is to be included in the sum of target lesions.

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

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

This default value is derived from the 5 mm CT slice thickness (but should not be changed with varying CT slice thickness). The measurement of these lesions is potentially non-reproducible, therefore providing this default value will prevent false responses or progressions based upon measurement error.

To reiterate, however, if the radiologist is able to provide an actual measure, that should be recorded, even if it is below 5 mm and in that case BML should not be ticked. (BML is equivalent to a less than sign <)

Lesions that split or coalesce on treatment: When non-nodal lesions 'fragment', the longest diameters of the fragmented portions should be added together to calculate the target lesion sum. Similarly, as lesions coalesce, a plane between them may be maintained that would aid in

obtaining maximal diameter measurements of each individual lesion. If the lesions have truly coalesced such that they are no longer separable, the vector of the longest diameter in this instance should be the maximal longest diameter for the 'coalesced lesion'.

Evaluation of non-target lesions

This section provides the definitions of the criteria used to determine the tumor response for the group of non-target lesions. While some non-target lesions may actually be measurable, they need not be measured and instead should be assessed only qualitatively at the time points specified in the protocol.

Complete Response (CR): Disappearance of all non-target lesions and normalization of tumor marker level. All lymph nodes must be non-pathological in size (< 10 mm short axis).

Non-CR/Non-PD: Persistence of one or more non-target lesion(s) and/or maintenance of tumor marker level above the normal limits.

Progressive Disease (PD): Unequivocal progression of existing non-target lesions. (Note: the appearance of one or more new lesions is also considered progression).

Special notes on assessment of progression of non-target disease

The concept of progression of non-target disease requires additional explanation as follows:

When the patient also has measurable disease: **In this setting, to achieve 'unequivocal progression' on the basis of the non-target disease, there must be an overall level of substantial worsening in non-target disease in a magnitude that, even in presence of SD or PR in target disease, the overall tumor burden has increased sufficiently to merit discontinuation of therapy.** A modest 'increase' in the size of one or more non-target lesions is usually not sufficient to qualify for **unequivocal progression** status. The designation of overall progression solely on the basis of change in non-target disease in the face of SD or PR of target disease will therefore be extremely rare.

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

New lesions

The appearance of new malignant lesions denotes disease progression; therefore, some comments on detection of new lesions are important. There are no specific criteria for the identification of new radiographic lesions; however, the finding of a new lesion should be unequivocal: i.e., not attributable to differences in scanning technique, change in imaging modality or findings thought to represent something other than tumor (for example, some 'new' bone lesions may be simply healing or flare of pre-existing lesions). This is particularly important when the patient's baseline lesions show partial or complete response. For example, necrosis of a liver lesion may be reported on a CT scan report as a 'new' cystic lesion, which it is not.

A lesion identified on a follow-up study in an anatomical location that was not scanned at baseline is considered a new lesion and will indicate disease progression. An example of this is the patient who has visceral disease at baseline and while on study has a brain CT or MRI ordered which reveals metastases. The patient's brain metastases are considered to be evidence of PD even if he/she did not have brain imaging at baseline.

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

Time point response

It is assumed that at each protocol specified time point (i.e., radiographic evaluation of tumor burden), a response assessment occurs. Table A provides a summary of the timepoint response status calculation at each time point for patients who have measurable disease at baseline.

Table A: Time Point Response: Patients with Targets (+/- Non-Target) Disease

Target Lesions	Non-Target Lesions	New Lesions	Overall Response [at time point]
CR	CR	No	CR
CR	Non-CR/non-PD	No	PR
CR	Not evaluated	No	PR
PR	Non-PD or not all evaluated	No	PR
SD	Non-PD or not all evaluated	No	SD
Not all evaluated	Non-PD	No	NE
PD	Any	Yes or No	PD
Any	PD	Yes or No	PD
Any	Any	Yes	PD

1. Note: CR = complete response, PR = partial response, SD = stable disease, PD = progressive disease, NE = inevaluable.

Missing assessments and not-evaluable designation

When no imaging/measurement is done at all at a particular time point, the patient is not evaluable at that time point. If only a subset of lesion measurements are made at an assessment, usually the case is also considered not evaluable at that time point, unless a convincing argument can be made that the contribution of the individual missing lesion(s) would not

change the assigned time point response. This would be most likely to happen in the case of PD.

For example, if a patient had a baseline sum of 50 mm with three measured lesions and at follow-up only two lesions were assessed, but those gave a sum of 80 mm, the patient will have achieved PD status, regardless of the contribution of the missing lesion.

If one or more target lesions were not assessed either because the scan was not done, or could not be assessed because of poor image quality or obstructed view, the Response for Target Lesions should be "Unable to Assess" since the patient is not evaluable. Similarly, if one or more non-target lesions are indicated as 'not assessed', the response for non-target lesions should be "Unable to Assess" (except where there is clear progression). Overall response would be "Unable to Assess" if either the target response or the non-target response is "Unable to Assess" (except where this is clear evidence of progression) as this equates with the case being not evaluable at that time point.

Special notes on response assessment

When nodal disease is included in the sum of target lesions and the nodes decrease to 'normal' size (< 10 mm), they may still have a measurement reported on scans. This measurement should be recorded even though the nodes are normal in order not to overstate progression should it be based on increase in size of the nodes. As noted earlier, this means that patients with CR may not have a total sum of 'zero' on the case report form (CRF).

Patients with a global deterioration of health status requiring discontinuation of treatment without objective evidence of disease progression at that time should be reported as 'symptomatic deterioration'. Every effort should be made to document objective progression even after discontinuation of treatment. Symptomatic deterioration is not a descriptor of an objective response: it is a reason for stopping study therapy. The objective response status of such patients is to be determined by evaluation of target and non-target disease.

Conditions that define 'early progression, early death, and non-evaluability are study specific and should be clearly described in each protocol (depending on treatment duration, treatment periodicity).

In some circumstances it may be difficult to distinguish residual disease from normal tissue. When the evaluation of complete response depends upon this determination, it is recommended that the residual lesion be investigated (fine needle aspirate/biopsy) before assigning a status of complete response. FDG-PET may be used to upgrade a response to a CR in a manner similar to a biopsy in cases where a residual radiographic abnormality is thought to represent fibrosis or scarring. The use of FDG-PET in this circumstance should be prospectively described in the protocol and supported by disease specific medical literature for the indication. However, it must be acknowledged that both approaches may lead to false positive CR due to limitations of FDG-PET and biopsy resolution/sensitivity.

For equivocal findings of progression (e.g., very small and uncertain new lesions; cystic changes or necrosis in existing lesions), treatment may continue until the next scheduled

assessment. If at the next scheduled assessment, progression is confirmed, the date of progression should be the earlier date when progression was suspected.

Evaluation of best overall response

The best overall response is the best response recorded from the start of the study treatment until the end of treatment taking into account any requirement for confirmation. The patient's best overall response assignment will depend on the findings of both target and non-target disease, will also take into consideration the appearance of new lesions and will depend upon confirmatory scans. For this study, determinations of either CR, PR or PD require a confirmatory scan at least 4 weeks later. This is described further in Table B below.

Table B.Best Overall Response

Target Lesions	Non-Target Lesions	New Lesions	Overall Response	Best Response for this Category Also Requires
CR	CR	No	CR	≥4 weeks confirmation
CR	Non-CR/ Non-PD	No	PR	≥4 weeks confirmation
PR	Non-PD	No	PR	
SD	Non-PD	No	SD	documented at least once ≥4 weeks from baseline
PD	Any	Yes or No	PD	no prior SD, PR or CR
Any	PD*	Yes or No	PD	
Any	Any	Yes	PD	

* In exceptional circumstances, unequivocal progression in non-target lesions may be accepted as disease progression

APPENDIX 6: DESCRIPTION OF THE iRECIST PROCESS FOR ASSESSMENT OF DISEASE STATUS AND DISEASE PROGRESSION

iRECIST Assessment of Disease

Source: Seymour L et al. 2017

The RECIST Working Group recently published iRECIST to provide a standard approach to the evaluation of solid tumors with measurements and assessment of the disease burden in trials that incorporate one or more immunotherapies. iRECIST follows similar recommendations provided by RECIST 1.1 in terms of methods of lesion measurement and size criteria, and the methodology of determining response is also comparable. However, there are some key differences between iRECIST and RECIST v1.1 that are highlighted in the table below. These differences take into account tumor shrinkage or disappearance following an initial RECIST v1.1. progression. Disease progression by iRECIST requires confirmation at a subsequent assessment, 4-8 weeks after the initial RECIST v1.1. PD determination. Additionally, iRECIST categorizes new lesions as Target or Non-Target. Importantly, the time point response and best overall response by iRECIST may be different from RECIST v1.1 and should be recorded separately.

The following table was modified from EORTC iRECIST Training slides: http://recist.eortc.org/irecist/

	iRECIST
Definitions of measurable, non-measureable diseases	Same as RECIST v1.1
Definitions of Target and Non-Target lesions	Same as RECIST v1.1
Measurement and management of nodal disease	Same as RECIST v1.1
Calculation of the sum-of-measurement (SOM)	Same as RECIST v1.1
Definitions of CR, PR, and SD, and their duration	Same as RECIST v1.1
Confirmation of CR and PR	Same as RECIST v1.1
Definition of progression in Target and Non-Target lesions	First RECIST v1.1 PD is considered unconfirmed for iRECIST, termed i-Unconfirmed Progression (iUPD)
Management of new lesions	Assessed using RECIST 1.1 principles: • Classified as measurable or non-measurable

	• Up to 5 (2 per site) measured (but not included in the SOM of target lesions identified at baseline) and recorded as new lesions target (NL-T) with an i-sum of measurements (iSOM) • Other new lesions (measurable/non-measurable) are recorded as new lesions non-target (NL-NT) • New lesions do not have to resolve for subsequent iSD or iPR providing that the next assessment did not confirm progression
Time point response after RECIST 1.1 progression	There can be iSD, iPR or iCR after RECIST 1.1 PD • First RECIST 1.1 PD is "unconfirmed" for iRECIST – termed iUPD • iUPD must be confirmed at the next assessment (4-8 weeks) • If confirmed, termed iCPD Time point response is dynamic and based on • Change from baseline (for iCR, iPR, iSD) or change from nadir (for PD) • The last i-response
Confirmation of progression required	First RECIST 1.1 PD is "unconfirmed" for iRECIST; disease progression must be confirmed at the next assessment (4-8 weeks later Treatment past RECIST 1.1 PD is permitted if patient clinically stable • No worsening of performance status • No clinically relevant ↑ in disease related symptoms • No requirement for intensified management of disease related symptoms (analgesics, radiation, palliative care)
Collection of reason why progression cannot be confirmed	Record the reason iUPD not confirmed • Not stable • Treatment stopped but patient not reassessed/imaging not performed • iCPD never occurs • Patient has died

Assessment at Screening and Prior to RECIST 1.1 Progression

Until radiographic disease progression based on RECIST 1.1, there is no distinct iRECIST assessment.

Assessment and Decision at RECIST 1.1 Progression

For participants who show evidence of radiological PD by RECIST 1.1 as determined by the Investigator, the Investigator will decide whether to continue a participant on study treatment

until repeat imaging is obtained (using iRECIST for participant management (see Table 6 and Figure 5). This decision by the Investigator should be based on the participant's overall clinical condition.

Clinical stability is defined as the following:

- Absence of symptoms and signs indicating clinically significant progression of disease
- No decline in ECOG performance status
- No requirements for intensified management, including increased analgesia, radiation, or other palliative care

Any participant deemed **clinically unstable** should be discontinued from study treatment at site-assessed first radiologic evidence of PD, and is not required to have repeat tumor imaging for confirmation of PD by iRECIST.

If the Investigator decides to continue treatment, the participant may continue to receive study treatment and the tumor assessment should be repeated 4 to 8 weeks later to confirm PD by iRECIST, per Investigator assessment. Images should continue to be sent in to the central imaging vendor for potential retrospective BICR.

Tumor flare may manifest as any factor causing radiographic progression per RECIST 1.1, including:

- Increase in the sum of diameters of target lesion(s) identified at baseline to ≥20% and ≥5 mm from nadir
    - Note: the iRECIST publication uses the terminology "sum of measurements", but "sum of diameters" will be used in this protocol, consistent with the original RECIST 1.1 terminology.
- Unequivocal progression of non-target lesion(s) identified at baseline
- Development of new lesion(s)

iRECIST defines new response categories, including iUPD (unconfirmed progressive disease) and iCPD (confirmed progressive disease). For purposes of iRECIST assessment, the first visit showing progression according to RECIST 1.1 will be assigned a visit (overall) response of iUPD, regardless of which factors caused the progression.

At this visit, target and non-target lesions identified at baseline by RECIST 1.1 will be assessed as usual.

New lesions will be classified as measurable or non-measurable, using the same size thresholds and rules as for baseline lesion assessment in RECIST 1.1. From measurable new lesions, up to 5 lesions total (up to 2 per organ), may be selected as New Lesions – Target. The sum of diameters of these lesions will be calculated, and kept distinct from the sum of diameters for target lesions at baseline. All other new lesions will be followed qualitatively as New Lesions – Non-target.

Assessment at the Confirmatory Imaging

On the confirmatory imaging, the participant will be classified as progression confirmed (with an overall response of iCPD), or as showing persistent unconfirmed progression (with an overall response of iUPD), or as showing disease stability or response (iSD/iPR/iCR).

Confirmation of Progression

Progression is considered confirmed, and the overall response will be iCPD, if ANY of the following occurs:

- Any of the factors that were the basis for the initial iUPD show worsening
  - For target lesions, worsening is a further increase in the sum of diameters of ≥5 mm, compared to any prior iUPD time point
  - For non-target lesions, worsening is any significant growth in lesions overall, compared to a prior iUPD time point; this does not have to meet the "unequivocal" standard of RECIST 1.1
  - For new lesions, worsening is any of these:
    - An increase in the new lesion sum of diameters by ≥5 mm from a prior iUPD time point
    - Visible growth of new non-target lesions
    - The appearance of additional new lesions
- Any new factor appears that would have triggered PD by RECIST 1.1

Persistent iUPD

Progression is considered not confirmed, and the overall response remains iUPD, if:

- None of the progression-confirming factors identified above occurs AND
- The target lesion sum of diameters (initial target lesions) remains above the initial PD threshold (by RECIST 1.1)

Additional imaging for confirmation should be scheduled 4 to 8 weeks from the imaging on which iUPD is seen. This may correspond to the next visit in the original visit schedule. The assessment of the subsequent confirmation imaging proceeds in an identical manner, with possible outcomes of iCPD, iUPD, and iSD/iPR/iCR.

Resolution of iUPD

Progression is considered not confirmed, and the overall response becomes iSD/iPR/iCR, if:

- None of the progression-confirming factors identified above occurs, AND
- The target lesion sum of diameters (initial target lesions) is not above the initial PD threshold.

The response is classified as iSD or iPR (depending on the sum of diameters of the target lesions), or iCR if all lesions resolve.

In this case, the initial iUPD is considered to be pseudo-progression, and the level of suspicion for progression is "reset". This means that the next visit that shows radiographic progression, whenever it occurs, is again classified as iUPD by iRECIST, and the confirmation process is repeated before a response of iCPD can be assigned.

Management Following the Confirmatory Imaging

If repeat imaging does not confirm PD per iRECIST, as assessed by the Investigator, and the participant continues to be clinically stable, study treatment may continue and follow the regular imaging schedule. If PD is confirmed, participants will be discontinued from study treatment.

NOTE: If a participant has confirmed radiographic progression (iCPD) as defined above, but the participant is achieving a clinically meaningful benefit, an exception to continue study treatment may be considered following consultation with the Sponsor. In this case, if study treatment is continued, tumor imaging should continue to be performed following the intervals as outlined in the Schedule of Events (Appendix 1) and submitted to the central imaging vendor.

Detection of Progression at Visits After Pseudo-progression Resolves

After resolution of pseudo-progression (i.e., achievement of iSD/iPR/iCR), iUPD is indicated by any of the following events:

- Target lesions
    - Sum of diameters reaches the PD threshold (≥20% and ≥5 mm increase from nadir) either for the first time, or after resolution of previous pseudo-progression. The nadir is always the smallest sum of diameters seen during the entire trial, either before or after an instance of pseudo-progression.
- Non-target lesions
    - If non-target lesions have never shown unequivocal progression, their doing so for the first time results in iUPD.
    - If non-target lesions have shown previous unequivocal progression, and this progression has not resolved, iUPD results from any significant further growth of non-target lesions, taken as a whole.
- New lesions
    - New lesions appear for the first time
    - Additional new lesions appear
    - Previously identified new target lesions show an increase of ≥ 5 mm in the new lesion sum of diameters, from the nadir value of that sum
    - Previously identified non-target lesions show any significant growth

If any of the events above occur, the overall response for that visit is iUPD, and the iUPD evaluation process (see Assessment at the Confirmatory Imaging above) is repeated. Progression must be confirmed before iCPD can occur.

The decision process is identical to the iUPD confirmation process for the initial PD, with one exception: if new lesions occurred at a prior instance of iUPD, and at the confirmatory imaging

the burden of new lesions has increased from its smallest value (for new target lesions, the sum of diameters is ≥5 mm increased from its nadir), then iUPD cannot resolve to iSD or iPR. It will remain iUPD until either a decrease in the new lesion burden allows resolution to iSD or iPR, or until a confirmatory factor causes iCPD.

Additional details about iRECIST are provided in the iRECIST publication.