STATISTICAL ANALYSIS PLAN

PROTOCOL NO. GX-188E-005

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

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VERSION NUMBER AND DATE: FINAL V 1.1, 05SEP2022

STATISTICAL ANALYSIS PLAN SIGNATURE PAGE

Statistical Analysis Plan V1.1 (Dated 05Sep2022) for Protocol v4.0 dated 29Aug2022.

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Upon review of this document, the undersigned approves this version of the Statistical Analysis Plan, authorizing that the content is acceptable for the reporting of this study.

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MODIFICATION HISTORY

Unique Identifier for this Version	Date of the Document Version	Author	Significant Changes from Previous Authorized Version
1.0	14Jul2022	Xin Wang	Not Applicable – First Version
1.1	05Sep2022	Xin Wang	Protocol final v4.0 is released on 29Aug2022. SAP is updated accordingly.

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1. INTRODUCTION

This document describes the rules and conventions to be used in the presentation and analysis of efficacy and safety data for Protocol GX-188E-005. It describes the data to be summarized and analyzed, including specifics of the statistical analyses to be performed.

This statistical analysis plan (SAP) is based on protocol version V4.0, dated 29Aug2022. The exploratory objectives of this study (described in SAP section 2.3) are not in IQVIA Biostatistics work scope and analysis methods for exploratory objectives are not included in this SAP.

2. STUDY OBJECTIVES

This study is separated into Parts A, B and C. Part A is the evaluation of safety and tolerability of GX-188E + Pembrolizumab (P) in patients with HPV 16+ and/or 18+ Advanced Cervical Cancer and will establish the recommended Phase 2 regimen for the investigational treatment. Part B is using 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. Part C is the efficacy evaluation in larger number of patients.

2.1. PRIMARY OBJECTIVES

The primary objectives are:

- Part A: To establish the safety and tolerability of GX-188E +P and to identify the recommended Phase 2 treatment regimen.
- Part B: To evaluate Objective Response Rate within 24 weeks (ORR_{24}) by Response Evaluation Criteria in Solid Tumor (RECIST) 1.1. Response determinations from the blinded, independent central reviewers (BICR) will be used for the primary endpoint.
- Part C: To evaluate ORR_{24} by RECIST 1.1. Response determinations from the BICR will be used for the primary endpoint.

2.2. SECONDARY OBJECTIVES

The secondary objectives of Part A are to evaluate:

- Objective Response Rate within 24 weeks (ORR_{24}) by RECIST 1.1 and Response Evaluation Criteria in Solid Tumors for Immunotherapeutics (iRECIST).
- Best Overall Response Rate (BORR), Time-to-Best Response, Duration of Response (DOR), Progression-Free Survival (PFS) and Overall Survival (OS).

The secondary objectives of Parts B and C are to evaluate:

- Safety and tolerability.
- BORR by RECIST v1.1 and iRECIST.
- Progression-Free Survival (PFS): 6-month PFS rate (Probability that the progression has not occurred by 6 months), median PFS time
- Overall Survival (OS): 6-month OS rate (Probability of being alive just before 6 months), Median OS time
- Disease Control Rate (DCR)
- Duration of Response (DOR)
- Time-to-Best Response (TTR)

2.3. EXPLORATORY OBJECTIVES

The exploratory objectives of this study are as follows:

- 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.

3. STUDY DESIGN

3.1. GENERAL DESCRIPTION

This is a Phase Ib/II open-label trial to evaluate the safety and efficacy of GX-188E plus pembrolizumab, (GX-188E + P) in patients with advanced HPV-16+ or HPV-18+ cervical cancer. This study is separated into three 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 2 mg (1 mg/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 patient 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 adverse event (AE) that is not clearly due to progression of the patient's malignancy, that occurs within the first 3 weeks (prior to week 4 Day 1 visit) of treatment initiation, and that meets at least one of the non-hematologic or hematologic criteria.

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.

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 $\leqslant$ 1 patient of 6 enrolled patients experiences DLT, enrolment 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 enrolment will begin at a reduced frequency treatment schedule.

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.

Sample Size for 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 enrolment into the study will be discontinued.

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.

Sample Size for Part B: Part B follows a 1-sided Simon 2-Stage minimax 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 with HPV 16 or 18 positive advanced cervical cancer will be included in the first stage analysis. If 3 or more objective responses (Partial response 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 (partial response or better) to reject the null hypothesis. If a patient's response could not be confirmed, that patient will not be included in the primary efficacy analysis for ORR_{24}.

Part C. Efficacy Evaluation in Larger Number of Patients

If at least 8 of the 28 patients enrolled in Part B, experience an objective response who are considered evaluable for efficacy, it will be considered that objective response rate (ORR) satisfies the criteria for study expansion and additional 17 patients (at least) will be enrolled in Part C to

evaluate efficacy further in larger patient population (N=60). If only 7 or fewer patients in Part B experience an objective response, enrollment to Part C will not open.

Sample Size for 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 $\geq$ 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 0.05.

3.2. SCHEDULE OF EVENTS

Schedule of events can be found in appendix 1 of the protocol. The End of Study (EOS) visit must occur within 28 days of treatment discontinuation/completion and prior to initiation of any new anti-cancer therapy/regimen.

3.3. CHANGES TO ANALYSIS FROM PROTOCOL

No immunogenicity analyses are planned for the Exploratory/Biomarker objectives while the protocol mentioned.

For the efficacy endpoint overall survival, it was decided to present 6-month OS rate with median OS time.

4. PLANNED ANALYSES

One interim analysis and one final analysis will be performed for this study.

4.1. SAFETY MONITORING COMMITTEE (SMC)

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.

Analysis for SMC review is not in IQVIA Biostatistics work scope and the relevant analysis methods for SMC review are not included in this SAP.

4.2. INTERIM ANALYSIS

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

4.3. 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).

5. ANALYSIS POPULATIONS

Agreement and authorization of patients included/ excluded from each analysis population will be conducted prior to Database Lock.

5.1. ALL PATIENTS SCREENED POPULATION

The all patients screened population will contain all patients who provide informed consent for this study.

5.2. SAFETY POPULATION

The 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.

5.3. 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).

5.4. EFFICACY EVALUABLE POPULATION

All patients who complete the study will be included into the efficacy evaluable population. These patients will be identified by using the “Subject's status?” with answer “Completed trial” from end of study page of CRF.

All patients who discontinue the study treatment regimen early due to treatment-related toxicity will be considered evaluable for efficacy. These patients will be identified as those with DLT. 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 on protocol treatment to be considered evaluable for efficacy. Patients who discontinue study due to disease-related death will be identified by using the “Primary reason for premature discontinuation from study” with answer “Death” from end of study page of CRF and the “Was death disease related” with answer “Yes” from death details page of CRF. Patients who discontinue study due to unequivocal tumor progression will be identified by using “Primary reason for premature discontinuation from study” with answer “Disease Relapse or Progression” from end of study page of CRF. Patients who discontinue study with at least 1 post-baseline tumor assessment will be identified as those with at least one RECIST/iRECIST Overall Response data on RECIST/iRECIST Overall Response page of CRF after screening visit. Patients in Part B and Part 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 Part C. The following table provides further, more specific details.

Table 1. Determination of Patients to be Included in Efficacy Evaluable Population

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 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 Part 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 Part 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 Part C	Toxicity^	Not applicable	Yes, included in Efficacy Evaluable Population

**RP2 regimen = Recommended Phase 2 regimen of GX-188E*
^ Toxicity = Any dose limiting toxicity (DLT).

6. GENERAL CONSIDERATIONS

6.1. REFERENCE START DATE AND STUDY DAY

Study Day will be calculated from the reference start date and will be used to show start/ stop day of assessments and events.

Reference start date is defined as the day of the first dose of study medication (either GX-188E or P, whichever occurred first), Day 1 is the day of the first dose of study medication and will appear in every listing where an assessment date or event date appears.

- If the date of the event is on or after the reference date, then:

  Study Day = (date of event – reference date) + 1.

- If the date of the event is prior to the reference date, then:

  Study Day = (date of event – reference date).

In the situation where the event date is partial or missing, study day, and any corresponding durations will appear partial or missing in the listings.

6.2. BASELINE

Unless otherwise specified, baseline is defined as the last non-missing measurement (including unscheduled assessments) taken prior to reference start date and time. Reference start date and time is defined as the date and time of the first dose of study medication (either GX-188E or P, whichever occurred first). In the case where the time is unknow and last non-missing measurement and the reference start date coincide, that measurement will be considered pre-baseline, but AEs and medications commencing on the reference start date will be considered post-baseline.

6.3. RETESTS, UNSCHEDULED VISITS AND EARLY TERMINATION DATA

In general, for by-visit summaries, data recorded at the nominal visit will be presented. Unscheduled measurements will not be included in by-visit summaries but will contribute to the best/worst case value where required (e.g. shift table).

In the case of a retest (same visit number assigned), the latest available measurement for that visit will be used for by-visit summaries.

Listings will include scheduled, unscheduled, retest and early discontinuation data.

6.4. STATISTICAL TESTS

The default significance level will be 5% 2-sided; confidence intervals will be 95% (2-sided), unless otherwise specified in the description of the analyses.

6.5. COMMON CALCULATIONS

For quantitative measurements, the following formulates will be used if applicable:

- Change from baseline =Test Value at Visit X – Baseline Value
- Percentage change from Baseline (%) = (Test Value at Visit X – Baseline Value) / Baseline Value × 100

6.6. SOFTWARE VERSION

All analyses will be conducted using SAS version 9.4 or higher.

7. STATISTICAL CONSIDERATIONS

7.1. ADJUSTMENTS FOR COVARIATES AND FACTORS TO BE INCLUDED IN ANALYSES

No adjustment for covariates and factors will be used in the analyses.

7.2. MULTICENTER STUDIES

This study will be conducted by multiple investigators at multiple centres. Because a small

number of patients are expected at each center, data from all centers will be pooled and no center effect will be investigated.

7.3. MISSING DATA

Generally, missing data will not be imputed.

For death date, if year and month of death date are known but the day of date is unknown, day will be imputed as 1. For example, if a patient is reported to die on Dec 2016, the death date will be imputed as 01Dec 2016.

Imputed dates will NOT be presented in the listings.

Partial dates of adverse events and prior/concomitant medication will be handled as described in Appendix 2.

7.4. MULTIPLE COMPARISONS/ MULTIPLICITY

No multiple comparisons and multiplicity adjustment will be performed.

7.5. EXAMINATION OF SUBGROUPS

(1) In Part C, ORR_{24}, BORR and DCR will be assessed and described in the following subgroups:

- Age
  o Less than 50 years
  o ⩾50 to < 65
  o Equal to or more than 65 years
- HPV type
  o HPV-16
  o HPV-18 or both
- Histology type
  o Squamous cell carcinoma
  o Adenocarcinoma

- Prior bevacizumab
  o Yes
  o No

- Eastern Cooperative Oncology Group (ECOG) Performance Status at baseline
  o 0
  o 1

- PD-L1 status at baseline
  o Positive (≥1 CPS)
  o Negative (<1 CPS)

  In Part C, DOR, TTR, PFS and OS by PD-L1 status, HPV type, and Histologic type subgroups will be summarized. Kaplan-Meier curve of BICR/investigator-assessed PFS according to RECIST v1.1 stratified by PD-L1 result, or HPV type, or Histologic type will be displayed. Kaplan-Meier curve of overall survival stratified by PD-L1 result or HPV type, or Histologic type will also be displayed.

(2) Using pain killer or local anaesthetic as a premedication to control the pain may affect Pain assessments. A subset of the safety population (who used pain killer or local anaesthetic to control the pain before GX-188E administration using electroporator) will be used for sensitivity analysis. The following summaries will be made based on the subset of safety population.

- Pain Assessments Summary

8. OUTPUT PRESENTATIONS

Appendix 1 shows conventions for presentation of data in outputs.

The mock up TFLs shell provided with this SAP describe the presentations for this study and therefore the format and content of the summary tables, figures, and listings to be provided by IQVIA Biostatistics.

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 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 results. The efficacy analysis will be conducted on the Efficacy Evaluable Population, and the safety analysis will be performed on the Safety Population.

Data listings will be created to support each table and to present all data collected.

9. DISPOSITION AND WITHDRAWALS

All patients who provide informed consent will be accounted for in this study. Patient disposition and withdrawals will be presented for all patients enrolled population. Patient disposition and withdrawals include information about patients enrolled, patients who received study medication, patients who completed/withdrew from study medication/study, reason for study medication withdrawal and study early termination. The breakdown of patients into the analysis sets will be presented.

A listing of inclusion/exclusion criteria deviations and reason for screen failure will be provided for screen failure patients.

Additionally, IQVIA clinical trial management system (CTMS) protocol deviation (PD) will be used. Any protocol deviations identified during the course of the study will be listed and the number and percentage of patients in each type of protocol deviations will be summarized for the SAF.

Follow-up time (months) is the time between a specified event (death, end of the study, follow-up date or completion/ last contact date, whichever occurred later) and the date of first dose.

- Follow-up time (months) = (the date of event-the date of first dose +1)/30.4375

Follow-up time will be summarized for safety population.

10. DEMOGRAPHIC AND OTHER BASELINE CHARACTERISTICS

Demographic data and other baseline characteristics will be presented for the DLT evaluable population, safety population and efficacy evaluable population.

Descriptive statistics will be used for summarizing the patients' characteristics. No statistical testing will be carried out for demographic or other baseline characteristics.

The following demographic and other baseline characteristics will be summarized for this study. Individual data will also be listed.

- Age (years) - calculated relative to date of consent
- Childbearing potential
- Race
- Ethnicity
- Weight (kg)
- BMI (kg/m^2)
- ECOG Performance Status
- Moore's criteria for determining prognosis in cervical cancer
- PD-L1 test result

10.1. DERIVATIONS

- BMI (kg/ m^2) = weight (kg)/ height $(m)^2$
- Age (years) = Year of informed consent (IC) – Year of birth, if month of IC is later than month of birth, or if month of IC is equal to month of birth but day of informed consent is later than or equal to day of birth;

  Age (years) = Year of informed consent – Year of birth – 1, otherwise.

  In this case, if one patient is more than 45 years old but less than 46 years old, then this patient will be presented as age 45.

11. MEDICAL HISTORY

Medical History information will be presented for the safety population.

General Medical History will be coded using Medical Dictionary for Regulatory Activities (MedDRA), Version 21.1 or higher. Data captured on the "Medical History – General" form of the Case Report Form (CRF) will be presented in frequency table by System Organ Class (SOC) and Preferred Term (PT) in descending order of total frequency. For SOCs or PTs with the same total frequency, categories will be sorted alphabetically.

Medical History data captured on the “Medical History – Cancer and HPV” will be presented. The following information will be summarized:

- Medical History Term by SOC and PT (HPV and Advanced inoperable or metastatic cervical cancer)
- Histologic Type at diagnosis
- Stage of disease at diagnosis
- Stage of disease at enrolment
- HPV Variant (HPV 16+/ HPV 18+/ Other)
- Type of anti-cancer therapy (Prior oncologic drugs and biologics / Prior oncologic surgery and procedures / Prior oncologic radiation)
- Target Lesion(s) at time of screening (Uterus, Lymph node, Liver, Lung, Spleen, Bone, Adrenal Gland, Tubes, Ovaries, Vagina, Bladder, Urethra, Rectum, Others)
- Non-Target Lesion(s) at time of screening (Uterus, Lymph node, Liver, Lung, Spleen, Bone, Adrenal Gland, Tubes, Ovaries, Vagina, Bladder, Urethra, Rectum, Others)

Medical history data will be listed.

12. MEDICATIONS AND PROCEDURES

12.1. PRIOR AND CONCOMITANT MEDICATIONS AND NON-DRUG TREATMENT

All concomitant medications received by the patient within 28 days prior to the first dose through the end of the patient’s study participation should be recorded on the “Prior and Concomitant Medications” page of CRF. Prior medications are those medications that were stopped prior to first study treatment. Concomitant medications are medications taken at least once after first study treatment. Medications stopped on the same day as first study treatment will be considered as prior medication only.

Prior and concomitant medications will be coded using the World Health Organization Drug Dictionary. The PT will be used for tabulation. The summary tables will show the number and percentage of patients by PT, for each part and overall. Pre and concomitant medications will be summarized separately. The descriptive summaries for pre and concomitant medications will be

presented for the safety population. Missing or partial dates for medications will be handled according to Appendix 2 of this analysis plan. In the case where it is not possible to define a medication as prior or concomitant, the medication will be classified by the worst case; i.e. concomitant. For the summaries of concomitant medications, patients who take the same medication (in terms of the PT), more than once will only be counted once for that medication. The detailed information of prior and concomitant medication use including medication name, indication, dose, start date, end date, ongoing or not, frequency and route of administration, etc. will be listed.

Non-Drug treatment will be collected on the "Prior and Concomitant Non-Drug Treatment" form of CRF including procedure name, indication, start date, end date and ongoing or not. Non-Drug treatment name will be coded using MedDRA Version 21.1 or higher version. Non-Drug treatment information will be summarized by SOC and PT. Non-Drug treatment will be listed for safety population.

12.2. PRIOR ANTI-CANCER THERAPIES

Information collected on the "Prior Oncologic Drugs and Biologics", "Prior Oncologic Surgery and Procedure", and "Prior Oncologic Radiation" pages of CRF will be summarized descriptively.

12.3. SUBSEQUENT ANTI-CANCER THERAPIES

Subsequent new anti-cancer therapy after the end of the study will be listed.

13. STUDY MEDICATION EXPOSURE

Exposure data will be presented for the safety population.

The date of first study medication administration will be taken from the CRF "Exposure – GX-188E" and "Exposure – Pembrolizumab" form. The date of last study medication will be taken from the "Date of last administration" on "End of Treatment" page of CRF for GX-188E and Pembrolizumab.

The variables relevant to the extent of exposure listed as below will be summarized for safety population. Individual exposure data recorded in "Exposure – GX-188E" and "Exposure – Pembrolizumab" as well as the derived variables will also be listed.

- Duration of exposure of GX-188E

- Number of Doses of GX-188E
- Percentage of Patients with GX-188E interruption
- Duration of exposure of Pembrolizumab
- Number of Doses of Pembrolizumab
- Percentage of Patients with Pembrolizumab interruption

The information of the overdose, abuse and accidental exposure of GX-188E and Pembrolizumab will be collected in “Overdose, Abuse, Accidental Exposure – GX-188E” and “Overdose, Abuse, Accidental Exposure – Pembrolizumab” form in CRF. The overdose, abuse and accidental exposure data will be listed for safety population.

13.1. DERIVATIONS

- Duration of exposure to GX-188E (weeks)= (Last dose date of GX-188E – First dose date of GX-188E +1) / 7

  When the start or stop date is missing, then the exposure will be treated as missing. Interruptions, compliance, and dose changes are not taken into account for duration of exposure.
- Number of Doses of GX-188E (times) = Count total numbers from “Exposure – GX-188E Vaccination” CRF page with response of “Yes” to the question “Was GX-188E administered at this visit?”
- Duration of exposure to Pembrolizumab (weeks)= (Last dose date of Pembrolizumab – First dose date of Pembrolizumab +1) / 7

  When the start or stop date is missing, then the exposure will be treated as missing. Interruptions, compliance, and dose changes are not taken into account for duration of exposure.
- Number of Doses of Pembrolizumab (times) = Count total numbers from “Exposure – Pembrolizumab” CRF page with response of “Yes” to the question “Was Pembrolizumab administered at this visit? “

14. STUDY MEDICATION COMPLIANCE

Compliance with study medication—based on the drug exposure data—will be calculated as the amount taken divided by the prescribed amount expressed as a percentage. “Per Visit” Compliance to GX-188E, Overall Compliance to GX-188E, “Per Visit” Compliance to Pembrolizumab and Overall Compliance to Pembrolizumab will be calculated.

The compliance will also be summarized by categories as below:

- < 80%
- 80 – 120%
- > 120%

The variables relevant to compliance to study medication will be presented in summary table for the safety population. Individual data will be listed.

14.1. DERIVATIONS

- “Per Visit” Compliance to GX-188E (%) = (Dose in mg administrated at location 1+Dose in mg administrated at location 2)/Planned dose in mg per day*100, presented to 1 decimal place.

  Planned dose per day is total of 2 mg per vaccination day.
- Overall Compliance to GX-188E (%) = Actual Number of Doses of GX-188E / Planned Number of Doses of GX-188E Injection

  Planned number of doses of GX-188E (times) = 6
- “Per Visit” Compliance to Pembrolizumab (%) =Dose in mg per administration /Planned dose in mg per administration *100, presented to 1 decimal place.
- Overall Compliance to Pembrolizumab (%) = Actual Number of Doses of Pembrolizumab / Planned number of doses of Pembrolizumab

  Planned number of doses of Pembrolizumab (times) = 35

15. EFFICACY OUTCOMES

Tumor response to treatment will be evaluated using both RECIST v1.1 and iRECIST. For each patient with objectively measurable disease and who meet the criteria for inclusion in the Efficacy Evaluable population, response to therapy will be calculated. The analysis of ORR_{24}, BORR and DCR per RECIST v1.1 will also be performed in safety population as sensitivity analysis.

RECIST 1.1 will be used by 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 will be evaluated and categorized using RECIST 1.1. Confirmatory scans are required for all determinations of objective response [Partial response (PR) or Complete response (CR)], Stable disease (SD) and disease progression (PD). Confirmatory scans must be performed at least 4 weeks later.

Investigator assessment of tumor response based upon RECIST v1.1 will be analyzed in the same way as the corresponding BICR-assessed endpoints (except Kaplan-Meier curves which will only be presented for BICR assessment). Concordance between BICR and Investigator assessments will be summarized at a patient level for BOR.

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 of protocol. 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.

Efficacy endpoints are as follows.

- Objective Response Rate within 24 weeks (ORR_{24})
- Best Overall Response Rate (BORR)
- Progression-Free Survival including 6-month PFS rate and median PFS time
- Overall Survival including 6-month OS rate and median OS time
- Disease Control Rate
- Duration of Response
- Time to Best Response

15.1. PRIMARY EFFICACY ENDPOINTS

The primary efficacy variable is BICR-assessed ORR_{24} by RECIST 1.1 in Part B and C.

Best overall response within 24 weeks (BOR_{24}) is the best objective response achieved within the first 24 weeks of treatment prior to study discontinuation. All available response designations will contribute to the BOR_{24} determination. If a patient's BOR_{24} could not be confirmed, that patient will not be included in the primary efficacy population for ORR_{24}. Additional patients will be enrolled to meet the study hypothesis. Any CR or PR must be confirmed by a sequential assessment that is at least 4 weeks apart. The confirmation rule is defined in Table 2 (please refer to RECIST 1.1 [1]). The confirmed response will be determined before analysis. The number and percentage of patients in each category of best overall response CR, PR, SD, PD or Not Evaluable (NE) will be provided.

ORR_{24} is the proportion of efficacy evaluable patients who achieve an objective response (PR or CR) within 24 weeks prior to study discontinuation. The number and percentage of patients who achieve best overall response of PR or CR will be summarized.

If the first responses can be confirmed by the second response within 24 weeks of treatment, they will be included as responses for ORR_{24}. Also, If the first response within 24 weeks is confirmed by the second response after 24 weeks of treatment, the first response should be included as response for ORR_{24}.

Table 2. Best overall response when confirmation of CR and PR is required per RECIST 1.1 Guideline

Overall response **First time point**	**Overall response** **Subsequent time point**	**Best overall response**
CR	CR	CR
CR	PR	PR, or SD provided at least 28 days' duration, otherwise PD[a]
CR	SD	SD provided at least 28 days' duration, otherwise PD

CR	PD	SD provided at least 28 days' duration, otherwise PD
CR	NE	SD provided at least 28 days' duration, otherwise NE
PR	CR	PR
PR	PR	PR
PR	SD	SD
PR	PD	SD provided at least 28 days' duration, Otherwise PD
PR	NE	SD provided at least 28 days' duration, Otherwise NE
NE	NE	NE

Note: CR = complete response, PR = partial response, SD = stable disease, PD = progressive disease, and NE = not evaluable.

[a] *If a CR is truly met at first time point, then any disease seen at a subsequent time point, even disease meeting PR criteria relative to baseline, makes the disease PD at that point (since disease must have reappeared after CR). Best response would depend on whether minimum duration for SD was met. However, sometimes 'CR' may be claimed when subsequent scans suggest small lesions were likely still present and in fact the patient had PR, not CR at the first time point. Under these circumstances, the original CR should be changed to PR and the best response is PR.*

In the case of best response equal to SD, the minimum duration for SD should be met. In other words, there will be at least once overall response being SD or CR or PR after 28 days from the first dose of study medication. For example, if the first overall response is CR evaluated less than 28 days from the first dose, with subsequent overall response as PD, then the best overall response should be PD. If the first overall response is CR evaluated on or more than 28 days from the first dose, with subsequent overall response as PD, then the best overall response should be SD.

In the case of only one tumor assessment post dosing, if PD reported, the best overall response will be PD. Otherwise, if less than 28 days from the first dose, the best overall response should

be NE. If the only post dosing tumour assessment is 28 or more days from the first dose and overall response equal to CR or PR or SD, the best overall response will be SD, otherwise NE.

BICR-assessed ORR_{24} by RECIST v1.1 will be displayed for Part B and Part C.

In Part C, BICR-assessed ORR_{24} by RECIST v1.1 will be calculated for patients overall. 95% confidence interval for ORR_{24} will be estimated using exact Clopper-Pearson method. In Part C, 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 0.05.

15.2. SECONDARY EFFICACY ENDPOINTS

- BORR

BORR in Parts A, B and C is one of the secondary efficacy endpoints. Both BICR-assessed BORR and Investigator-assessed BORR by RECIST 1.1 or iRECIST in Parts A, B and C will be calculated.

BICR-assessed BORR by iRECIST and investigator-assessed BORR by RECIST 1.1 or iRECIST in Parts B and C will be calculated.

Overall responses evaluated according to iRECIST will be used for analysis. iRECIST defines i-Unconfirmed Progression (iUPD) on the basis of RECIST 1.1 principles; however, iUPD requires confirmation, which is done on the basis of observing either a further increase in size (or in the number of new lesions) in the lesion category in which progression was first identified in (ie, target or non-target disease), or progression (defined by RECIST 1.1) in lesion categories that had not previously met RECIST 1.1 progression criteria. However, if progression is not confirmed, but instead tumour shrinkage occurs (compared with baseline), which meets the criteria of iCR, iPR, or iSD, then the bar is reset so that iUPD needs to occur again (compared with nadir values) and then be confirmed (by further growth) at the next assessment for i-Confirmed Progression (iCPD) to be assigned. If no change in tumour size or extent from iUPD occurs, then the timepoint response would again be iUPD. This approach allows atypical responses, such as delayed responses that occur after pseudo progression, to be identified, further understood, and better characterised. The iBOR is the best time-point response recorded from the start of the study treatment until death or lost to follow up before the end of the study, whichever occurs first, taking into account any requirement for confirmation. Confirmation of iCR and iPR is the same as that in Table 2 per RECIST v1.1. Confirmation of progression is also required per iRECIST.

BORR will be summarized by number of patients and percentages. The BORR and its 95% confidence interval will be presented. The 95% (exact) confidence interval will be calculated

based on the Clopper-Pearson method. PROC FREQ procedure of SAS will be used to calculate 95% (exact) confidence interval by the Clopper-Pearson method.

- ORR_{24}

24 weeks ORR in Part A is one of the secondary efficacy endpoints. Both BICR-assessed ORR_{24} and Investigator-assessed ORR_{24} by RECIST 1.1 or iRECIST in Part A will be calculated.

ORR_{24} will be summarized by number of patients and percentages. The ORR_{24} and its 95% confidence interval will be presented. The 95% (exact) confidence interval will be calculated based on the Clopper-Pearson method.

- DCR

DCR is defined as the percentage of patients who had a CR, PR or Stable Disease. 95% confidence interval of DCR will be calculated using the Clopper-Pearson method.

DCR in Parts A, B and C is one of the secondary efficacy endpoints. Both BICR-assessed DCR and Investigator-assessed DCR by RECIST 1.1 or iRECIST in Parts A, B and C will be calculated.

- DOR

Duration of response only applies to the subgroup of patients in efficacy evaluation population whose best overall response is CR or PR according to RECIST v1.1. Median DOR time is the timepoint at which the probability of disease progression equals 50% after documented objective tumor response (PR or CR).

Subject continuing without disease progression or death will be censored and the censoring date will be the date of the last evaluable tumor assessment prior to data cut-off/start of subsequent anti-cancer therapy. In case of progression or death after two or more consecutive missed tumor assessments, censoring will be done at last evaluable tumor assessment date prior to the missed tumor assessments. Reason of censoring will be summarized.

The Kaplan-Meier method will be used to estimate the median DOR time, and 2-sided 95% CI for the median will be provided. BICR-assessed DOR and investigator-assessed DOR by RECIST v1.1 will be displayed for Part A, Part B and Part C. Kaplan-Meier curve for BICR-assessed DOR will be presented.

- TTR

TTR is time from treatment initiation to the best objective response achieved (i.e., PR or CR whichever occurs earlier). This endpoint is only determined for patients who have a PR or CR by RECIST v1.1. Median TTR is the timepoint from treatment initiation to the best objective response achieved in 50% of patients. Median TTR will be calculated using descriptive statistics

in efficacy evaluation population restricted to patients with the best objective response. BICR-assessed TTR and investigator-assessed TTR by RECIST v1.1 will be displayed for Part A, Part B and Part C.

- PFS

PFS is defined as the time from treatment initiation until documented disease progression or death from any cause. If the patient progresses or dies after two or more consecutive missed tumor assessment visits, the patient will be censored at the time of the latest evaluable RECIST v1.1 assessment. Two consecutive missed/non-evaluable tumor assessment visits is defined as no evaluable tumor assessment within 126 days (2*9 weeks) of first dose or the previous evaluable RECIST 1.1 measurement. If the patient has no evaluable tumor assessment visits after first dose or does not have evaluable baseline tumor assessment data, the patient will be censored on the date of first dose. Table 3 defines the censoring rules for PFS.

Table 3. Censoring Rules for Analysis of Progression-Free Survival

Description	Event/Censor	Date of Event/Censor
Documented progression before two consecutive missed tumor assessment visits	Event	Date of documented disease progression
Death (without progression) before two consecutive missed tumor assessment	Event	Date of death
Death or progression after two or more consecutive missed tumor assessments	Censor	Date of last evaluable tumor assessment prior to the consecutive missed tumor assessment visits
Progression or death after subsequent anti-cancer therapy	Censor	Date of the last evaluable tumor assessment prior to start of subsequent anti-cancer therapy
No evaluable baseline or post-baseline tumor assessment	Censor	Date of first dosing of study medication

No progression and no death before end of study or data cut-off	Censor	Date of last evaluable tumor assessment

Median PFS time (months) is the timepoint at which the probability of progression-free survival equals 50% in the efficacy evaluable population.

6-month PFS rate is the proportion of efficacy evaluable patients without evidence of disease progression and who are alive 6 months after treatment initiation.

Kaplan-Meier method will be used to estimate median PFS and the corresponding 95% CI. Kaplan-Meier curves will be constructed to provide a visual presentation of the BICR assessed PFS rate change with time. The PFS rate and 95% CI at 6 months will also be summarized.

BICR-assessed PFS and investigator-assessed PFS by RECIST v1.1 will be displayed for Part A, Part B and Part C.

- OS

Overall survival is defined as the time from treatment initiation until death from any cause. Median OS time (months)l is the timepoint at which the probability of survival equals 50% in the efficacy evaluable population. Patients developing no event will be censored on the last known survival date. Patients providing no follow-up information will be censored on the day of first dosing. Kaplan-Meier method will be used to estimate median OS and the corresponding 95% CI. Kaplan-Meier curves will be constructed to provide a visual presentation of the OS rate change with time.

6-month OS rate is the proportion of efficacy evaluable patients who are alive 6 months after treatment initiation. The OS rate and 95% CI at 6 months will also be summarized.

OS will be displayed for Part A, Part B and Part C.

- Waterfall, Spider, Swim-lane and forest Plots

A waterfall plot will be prepared to visually present the best percentage change from baseline in sum of diameters in target lesions for each patient grouped by PD-L1 status, HPV type, and histologic type.

A Spider Plot will be used to visualize changes in sum of diameters in target lesions with best overall response by BICR according to RECIST 1.1. With a Spider Plot, post-baseline measurements are compared to the baseline. Thus, the data plotted is the percent change from baseline over the period of patient evaluation. Each leg of the “spider” represents a unique patient.

Swim-lane Plot for Tumor Response will be presented to show tumor assessment by at each

visit. Specifically, the Swim-lane plot will show total time to tumor response, whether the response was complete or partial, when the response started/ended and censoring information of the patient grouped by PD-L1 status, HPV type, and Histologic type.

These plots will be displayed only for Part C.

In Part C, a forest plot will be used to display BICR Assessed BORR according to RECIST v1.1 across subgroups.

15.3. EXPLORATORY EFFICACY ENDPOINTS

Not Applicable.

16. SAFETY OUTCOMES

Safety variables to be analyzed are AEs, laboratory test results (e.g., hematology, coagulation, serum chemistry, thyroid function tests, and urinalysis), vital signs and others.

All outputs for safety outcomes will be based on the safety population. The results will be presented for Part A, Part B Part C and overall except for DLT.

16.1. ADVERSE EVENTS

An adverse event 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. AEs will be coded using MedDRA 21.1 or higher.

See Appendix 2 for handling of partial dates for AEs. In the case where it is not possible to define an AE as treatment emergent or not, the AE will be classified by the worst case; i.e. treatment emergent.

An overall summary of number and percentage of patients and number of adverse events within each of the categories described in the section below except for DLT, will be provided.

Listings will include both TEAEs and Non-TEAEs. Tables will include TEAEs.

16.1.1. ALL TREATMENT EMERGENT ADVERSE EVENTS

Treatment emergent adverse events are defined as AEs that started or worsened on or after the

first dose of study medication. In the case where it is not possible to define an AE as treatment emergent or not, the AE will be classified by the worst case; i.e. treatment emergent.

Incidence of TEAEs will be presented by SOC and PT and also broken down further as shown in the following sections.

16.1.1.1. Severity

The severity of all TEAEs shall be graded according to 5 grades (Grade 1 to Grade 5) in accordance with the national cancer institute common terminology criteria for adverse event (NCI CTCAE) V4.0 or the most recent version.

If a patient reports a TEAE more than once within that SOC/ PT, the AE with the worst-case severity will be used in the corresponding severity summaries.

16.1.1.2. Relationship

Relationship to study medications, as indicated by the Investigator, is classed as" Probably related", "Possibly related", "Unlikely related" and "Unrelated" (decreasing in severity of relationship).

If a patient reports the same AE more than once within that SOC/ PT, the AE with the worst-case relationship to study medications will be used in the corresponding relationship summaries.

16.1.2. Treatment Related Adverse Events (TRAE)

TRAE is defined as an AE with relationship to study medications as "Probably related" or "Possibly related" to GX-188E and/or Pembrolizumab. TRAEs with a missing relationship to study medication will be regarded as "Probably related" to study medication.

Summary tables for all TRAEs will be tabulated together. TRAEs with Relationship to GX-188E and TRAEs with Relationship to Pembrolizumab will be also summarized separately.

16.1.3. TEAEs Leading to Discontinuation or Interruption of Study Medication

TEAEs leading to drug interruption of GX-188E will be identified by using the "Action Taken with GX-188E" with answer "Drug Interrupted" from the AE page of the CRF. TEAEs leading to drug interruption of pembrolizumab will be identified by using the "Action Taken with pembrolizumab" with answer "Drug Interrupted" from the AE page of the CRF.

TEAEs leading to permanent discontinuation of GX-188E will be identified by using the "Action Taken with GX-188E" with answer "Drug withdrawn" from the AE page of the CRF. TEAEs leading to permanent discontinuation of pembrolizumab will be identified by using the "Action

Taken with pembrolizumab" with answer "Drug withdrawn" from the AE page of the CRF.

For TEAEs leading to discontinuation or interruption of study medication, summaries of incidence rates (frequencies and percentages) by SOC and PT will be prepared.

16.1.4. AEs Leading to Study Discontinuation

TEAEs leading to study discontinuation will be identified by using the "Did this event lead to withdrawal from the study?" with answer "Yes" from the AE page of the CRF.

For TEAEs leading to study discontinuation, summaries of the number and percentage of patients by SOC and PT will be prepared. For TRAEs leading to study discontinuation will be summarized in the same way.

16.1.5. AEs Leading to Death

TEAEs leading to death are those events which are recorded as "Fatal" on the Adverse Events page of the CRF.

A summary of TEAEs and TRAEs leading to death by SOC and PT will be prepared.

16.1.6. Serious Adverse Events

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.

SAEs will be identified as those events recorded as "Serious" on the Adverse Events page of

the CRF.

Summaries of all SAEs and SAEs Related to study medications by SOC, PT and Maximum CTCAE Grade will be prepared.

16.1.7. Dose Limiting Toxicity (DLT)

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 or the most recent version) AE of ≥ Grade 3 treatment-related non-hematological toxicity except for the following:

o nausea, vomiting, or diarrhea lasting ≤ 72 hr

o Grade 3 fatigue lasting ≤ 7 days

o hypersensitivity reactions lasting ≤ 72 hrs

o Grade 3 hyperglycemia lasting ≤ 72 hr with standard anti-diabetic therapy

o 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)

o 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:

o Grade 4 neutropenia (ANC < 0.5 $x10^9$/L)

o Grade 3 febrile neutropenia (ANC < 1.0 x 10^9/L with temperature ≥ 38.3°C)

o Grade 4 thrombocytopenia (platelet count < 25.0 x 10^9/L) lasting > 4 days or that requires platelet transfusion

o Grade ≥ 3 thrombocytopenia (platelet count < 50.0 x 10^9/L) associated with Grade ≥ 3 bleeding

o 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:

o Any toxicity leading to more than one missed dose of either GX-188E or pembrolizumab during the DLT-evaluation period

o Any toxicity leading to > 2 weeks delay in initiation of the 2nd cycle of pembrolizumab.

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 will be identified on “Adverse Events” form of CRF with the response of “Yes” to the question “Is this AE considered as a DLT (Dose-Limiting Toxicities)?”.

Summaries of DLTs by DLT Category, SOC, PT and Maximum CTC Grade will be prepared for DLT evaluable population in Part A.

16.1.8. Adverse Events of Clinical Interest

Adverse Events of Clinical Interest (AECI) 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.

Adverse Events of Clinical Interest are those events recorded as “Yes” for the question of “Is this an AE of Clinical Interest?” on the Adverse Events page of the CRF. AECI categories based on AE page of CRF are as follows: overdose, abuse, accidental exposure and elevated liver enzymes. A summary of AECIs by AECIs category and by SOC and PT will be prepared.

16.1.9. 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.

irAEs will be identified as those events which are recorded as “Yes” for the question of “Is this an immune-related AE?” on the Adverse Events page of the CRF. A summary of irAE by SOC

and PT will be prepared.

16.2. DEATHS

If any patients die during the study as recorded on the “death details” page of the CRF, the information will be presented in a summary table and a data listing.

16.3. LABORATORY EVALUATIONS

Results from the local laboratory will be included in the reporting of this study for Hematology, Coagulation, Blood Chemistry, Urinalysis, Thyroid function tests, TA4 and CEA.

Presentations will use SI Units.

Quantitative laboratory measurements reported as “< X”, i.e. below the lower limit of quantification (BLQ), or “> X”, i.e. above the upper limit of quantification (ULQ), will be converted to X for the purpose of quantitative summaries, but will be presented as recorded, i.e. as “< X” or “> X” in the listings.

The following summaries will be provided for laboratory data:

- Actual and change from baseline by visit (for quantitative measurements)
- Incidence of abnormal values according to normal range criteria
- Incidence of abnormal values according to clinical judgement.
- Shift from baseline according to clinical judgement
- Listing of individual laboratory data

16.3.1. LABORATORY REFERENCE RANGES

Quantitative laboratory measurements will be compared with the relevant laboratory reference ranges in SI units and categorized as:

- Low: Below the lower limit of the laboratory reference range.
- Normal: Within the laboratory reference range (upper and lower limit included).
- High: Above the upper limit of the laboratory reference range.

16.3.2. CTCAE GRADING FOR LABORATORY DATA

Laboratory measurements will be graded using the Common Terminology Criteria for Adverse Events (CTCAE) grading system as defined in the following link:

https://www.eortc.be/services/doc/ctc/CTCAE_4.03_2010-06-14_QuickReference_5x7.pdf

Laboratory CTCAE Grade by Scheduled Visit will be summarized. Shift from baseline to worst CTCAE grade according to CTC grading system for parameters whose CTCAE scale is available will be provided.

16.4. ELECTROCARDIOGRAM (ECG) EVALUATIONS

ECG will be measured at screening visit only. Results from the 12-Lead ECG will be listed.

16.5. VITAL SIGNS

The following Vital Signs measurements will be reported for this study:

- Systolic Blood Pressure (mmHg)
- Diastolic Blood Pressure (mmHg)
- Heart Rate (bpm)
- Respiratory Rate (resp/min)
- Body Temperature (ºC)
- Weight (kg)

The following summaries will be provided for vital signs data:

- Actual and change from baseline by visit
- Incidence of markedly abnormal values
- Shift from baseline to worst post baseline according to markedly abnormal criteria
- Listing of individual vital sign data

16.5.1. VITAL SIGNS MARKEDLY ABNORMAL CRITERIA

Markedly abnormal quantitative Vital Signs measurements will be identified in accordance with the following predefined markedly abnormal criteria:

Variable	Unit	Low	High
SBP	mmHg	≤ 90 mmHg AND change from baseline ≤ -20 mmHg	≥ 180 mmHg AND change from baseline ≥ 20 mmHg
DBP	mmHg	≤ 50 mmHg AND change from ≤ -15 mmHg	≥ 105 mmHg AND change from baseline ≥ 15 mmHg
Heart rate	Bpm	≤ 50 bpm AND change from baseline ≤ -15 bpm	≥ 120 bpm AND change from baseline ≥ 15 bpm
Body temperature	˚C	NA	≥ 38.3 ˚C AND change from baseline ≥ 1.1 ˚C
Weight	Kg	percentage change from baseline ≤ -7.0 %	percentage change from baseline ≥ 7.0 %

16.6. PHYSICAL EXAMINATION

Physical examination results will be listed.

16.7. OTHER EXAMINATIONS

ECOG of Performance Status will be reported for the study. The following summaries will be provided for the ECOG data.

- Worst post-baseline result
- Baseline and post-baseline by visit summary table

- Shift from baseline to worst post-baseline table

Individual ECOG data will be listed.

Device malfunction information collected on “Device Malfunction” page of CRF will be listed.

Tumor Biopsy Sample collected on “Tumor Biopsy Sample” page of CRF will be listed.

Pregnancy test information will be listed.

Serology results will be listed.

Pain assessment information will be summarized and listed.

A listing will be provided for patients whose trial participation are impacted by COVID-19, including patient number and site number together with a description of the impact. These protocol deviations are documented in IQVIA clinical trial management system,

Research blood collection will be listed.

17. REFERENCES

1. Eisenhauer EA, Therasse P, Bogaerts J, et al. New response evaluation criteria in solid tumours: revised RECIST guideline (version 1.1). Eur. J. Cancer. 2009;45(2):228–247.

APPENDIX 1. PROGRAMMING CONVENTIONS FOR OUTPUTS OUTPUT CONVENTIONS

Outputs will be presented according to the following IQVIA' general guidelines and template for outputs conventions.

DATES & TIMES

Depending on data available, dates and times will take the form DDMMMYYYYThh:mm.

SIGNIFICANT DIGITS OF SUMMARY STATISTICS

1 Summary statistics are displayed with the following digits.

Description	Characteristic	Number of decimal places
Count	n	0
Count corresponding to the number of patients for a cohort	N	0
Mean	Mean	As in source + 1
Standard Deviation	SD	As in source + 1
Confidence Interval	CI	As in source + 1
Minimum	Min	As in source
Median	Median	As in source + 1
Maximum	Max	As in source
Percentage	%	1 *

* Number of decimal places can be two, if necessary.

2 If the source has more than 5 significant digits, the above would be replaced with the corresponding number of significant digits.

SPELLING FORMAT

English US

PRESENTATION OF STUDY PHASE

For outputs, groups will be represented as follows and in that order:

Group	For Tables and Graphs	For Listings (include if different to tables)
Part A	Part A	Part A
Part B	Part B	Part B
Part C	Part C	Part C

PRESENTATION OF VISITS

For outputs, visits in listings will be represented as follows and in that order:

Long Name (default)	Short Name
Screening	Screening
Week 1 Day 1	W1D1
…	…
End of Treatment	EOT

Long Name (default)	Short Name
End of Study	EOS

CRF visits will be displayed in the listings. Analysis baseline defined in SAP will be flagged and will be identified in the listings as needed. Analysis visits will be displayed in the tables.

LISTINGS

All listings will be ordered by the following (unless otherwise indicated in the template):

- Study part
- Patient ID
- Visit Number or Date (where applicable)

APPENDIX 2. PARTIAL DATE CONVENTIONS

Imputed dates will NOT be presented in the listings.

ALGORITHM FOR TREATMENT EMERGENCE OF ADVERSE EVENTS:

START DATE	STOP DATE	ACTION
Known	Known	If start date < study med start date, then not TEAE If start date >= study med start date, then TEAE
	Partial	If start date < study med start date, then not TEAE If start date >= study med start date, then TEAE
	Missing	If start date < study med start date, then not TEAE If start date >= study med start date, then TEAE
Partial, but known components show that it cannot be on or after study med start date	Known	Not TEAE
	Partial	Not TEAE
	Missing	Not TEAE
Partial, could be on or after study med start date	Known	If stop date < study med start date, then not TEAE If stop date >= study med start date, then TEAE

START DATE	STOP DATE	ACTION
	Partial	Impute stop date as latest possible date (i.e. last day of month if day unknown or 31st December if day and month are unknown), then: If stop date < study med start date, then not TEAE If stop date >= study med start date, then TEAE
	Missing	Assumed TEAE
Missing	Known	If stop date < study med start date, then not TEAE If stop date >= study med start date, then TEAE
	Partial	Impute stop date as latest possible date (i.e. last day of month if day unknown or 31st December if day and month are unknown), then: If stop date < study med start date, then not TEAE If stop date >= study med start date, then TEAE
	Missing	Assumed TEAE

ALGORITHM FOR PRIOR / CONCOMITANT MEDICATIONS:

START DATE	STOP DATE	ACTION
Known/ Partial/ Missing	Known	If stop date <= study med start date, assign as prior If stop date >study med start date, assign as concomitant
	Partial	Impute stop date as latest possible date (i.e. last day of month if day unknown or 31st December if day and month are unknown), then: If stop date <=study med start date, assign as prior If stop date >study med start date, assign as concomitant
	Missing	If stop date is missing could never be assumed a prior medication, assign as concomitant