Statistical Analysis Plan

A Phase 2, Multicenter Study to Evaluate the Efficacy and Safety Using Autologous Tumor Infiltrating Lymphocytes (LN-145) in Patients with Recurrent, Metastatic, or Persistent Cervical Carcinoma

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LIST OF ABBREVIATIONS AND TERMS

Term	Definition
AE	Adverse event
BMI	Body mass index
BOR	Best overall response
CI	Confidence interval
CR	Complete response
CRF	Case report form
CPS	Combined positive score
CSR	Clinical study report
CTCAE	Common Terminology Criteria for Adverse Events
DCR	Disease control rate
DOR	Duration of response
ECOG	Eastern Cooperative Oncology Group
EMA	European Medicines Agency
EOA	End of assessment
EORTC QLQ-C30	European Organization for Research and Treatment of Cancer Quality of Life Questionnaire-C30 v 3.0 questionnaire
EOT	End of treatment
FAS	Full Analysis Set
FDA	Food and Drug Administration
FWER	Family-wise Type I error rate
HLGT	High-level group term
HLT	High-level term
HPV	Human papillomavirus
HRQoL	Health-related quality of life
ICF	Informed consent form
ICI	Immune checkpoint inhibitor
IL-2	interleukin-2
irRECIST	immune-related Response Evaluation Criteria in Solid Tumors
KM	Kaplan-Meier
LDH	Lactate dehydrogenase
LLOQ	Lower limit of quantification
LLT	Low-level term
MedDRA	Medical Dictionary for Regulatory Activities
NCCN	National Comprehensive Cancer Network
NCI	National Cancer Institute

Term	Definition
NE	Not evaluable
NMA-LD	Nonmyeloablative lymphodepletion
ORR	Objective response rate
OS	Overall survival
PD	Progressive disease
PD-1	Programmed cell death protein-1
PD-L1	Programmed death-ligand 1
PFS	Progression-free survival
PR	Partial response
PT	Preferred term
Q3W	Every 3 weeks
Q6W	Every 6 weeks
Q-TWiST	Quality-adjusted time without symptoms of disease or toxicity of treatment
RECIST	Response Evaluation Criteria in Solid Tumors
SAE	Serious adverse event
SAP	Statistical Analysis Plan
SAS	Statistical Analysis System
SD	Stable disease
SI Units	International System of Units
SOC	System organ class
TEAE	Treatment-emergent adverse event
TH	Tumor harvested
TIL	Tumor-infiltrating lymphocyte
ULOQ	Upper limit of quantification
WHO	World Health Organization

1 INTRODUCTION

The purpose of this Statistical Analysis Plan (SAP) is to provide a comprehensive and detailed description of methods for the data analyses outlined in Protocol C-145-04 Version 10.0 (dated 14AUG2025), and to prespecify the statistical approaches to the analysis of study data prior to database lock. This SAP will be finalized and signed prior to the clinical database lock. All statistical analyses detailed in this SAP will be conducted using Statistical Analysis System (SAS®) Version 9.4 or higher.

Results obtained from the analyses described in this document will provide the basis of the Clinical Study Report (CSR) for this study. Analysis Sets and methods specified in this document take precedence over those described in the protocol should there be any difference due to timing of finalization of each document.

2 DESCRIPTION OF THE STUDY

Study C-145-04 is a Phase 2, multicenter, prospective, open-label, interventional study evaluating patients who receive adoptive cell therapy via autologous tumor-infiltrating lymphocytes (TIL) infusion (LN-145) followed by interleukin-2 (IL-2) after a nonmyeloablative lymphodepletion (NMA-LD) preparative regimen.

The following cohorts will be studied in patients with recurrent, metastatic, or persistent cervical carcinoma:

Cohort 1: LN-145 monotherapy in patients who have progressed during or following at least one, but no more than three prior systemic chemotherapies for recurrent, metastatic, or persistent cervical carcinoma

Cohort 2: LN-145 monotherapy in patients who have also previously received a programmed cell death protein-1 (PD-1)/programmed death-ligand 1 (PD-L1) checkpoint inhibitor in addition to at least one, but no more than three prior systemic chemotherapies

Cohort 3: LN-145 in combination with pembrolizumab in patients who have not received any therapies other than prior chemoradiation or surgery for loco-regional disease

Cohort 4: LN-145 monotherapy in previously enrolled patients who do not meet requirements for inclusion in the other study cohorts. CCI [redacted] Patients will not be actively enrolled in this cohort.

Cohort 5: LN-145 monotherapy as a re-treatment

Notably, patients in Cohort 5 must have received treatment only in Cohort 1 or 2 and may have a second tumor resection based on a discussion between the Investigator and the Medical Monitor.

The overall duration of the study will be approximately 5 years from the last patient enrolled, comprising the following periods:

Screening: Up to CCI [redacted] prior to tumor resection.

Enrollment: Upon tumor resection for TIL generation.

Treatment Period:

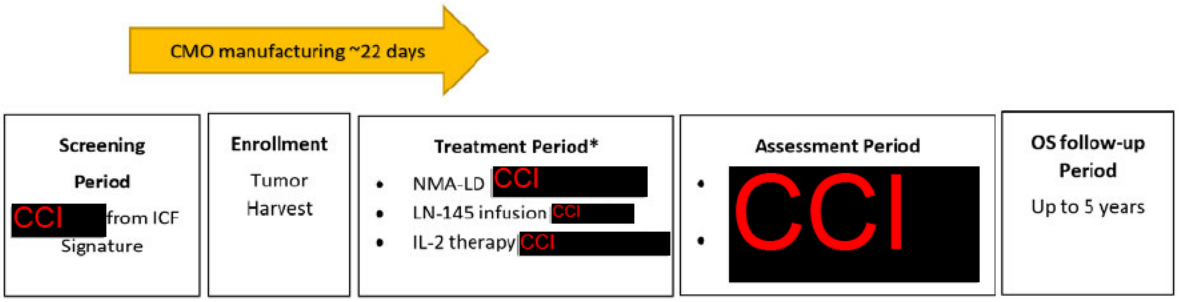
Cohort 1, 2, 4, 5-NMA-LD preparative regimen (up to CCI), LN-145 infusion (CCI), and IL-2 administration (up to CCI). Patients will return for safety assessment visits on CCI and CCI corresponds with the End of Treatment [EOT] visit).

Cohort 3-The treatment period for Cohort 3 is up to CCI, including pembrolizumab, NMA-LD CCI, LN-145 infusion (CCI), and IL-2 administration (CCI). Pembrolizumab treatment starts after tumor resection and baseline scans and before NMA-LD. Patients are treated again with pembrolizumab after IL-2 treatment (and recovery of related toxicities to Grade ≤ 2) 200 mg every 3 weeks (Q3W) or 400 mg every 6 weeks (Q6W) until disease progression or unacceptable toxicity, whichever occurs first. The EOT visit occurs within CCI of the last dose of pembrolizumab or on CCI if the patient does not continue pembrolizumab post-IL-2 for any reason.

Assessment Period: Efficacy (e.g., tumor response) assessments will be performed at CCI post-LN-145 infusion and then will occur CCI. Patients will continue to be evaluated for response CCI starting from CCI up to 5 years or until disease progression or start of a new anticancer therapy. At that time, the End of Assessment (EOA) visit will be completed.

Overall Survival Follow-up Period: Begins after completion of the last study assessment (e.g., EOA) and will continue for up to 5 years from Enrollment (tumor resection) or until discontinuation from the study; with telephone contact CCI to obtain survival status and subsequent anticancer therapy information.

Figure 1 Study Flowchart



*Cohort 3 patients also receive pembrolizumab starting after tumor resection and baseline scans and before NMA-LD. They will continue to be treated with pembrolizumab after IL-2 treatment up to CCI

3 STUDY OBJECTIVES AND ENDPOINTS

3.1 Study Objectives

3.1.1 Primary Objective

The primary objective for each cohort is listed below:

Cohort	Primary Objective
1 and 2	• To evaluate the efficacy of LN-145 in patients with recurrent, metastatic, or persistent cervical carcinoma based on the objective response rate (ORR) as assessed by the Investigator per Response Evaluation Criteria in Solid Tumors (RECIST) v1.1
3	• To characterize the safety profile of LN-145 in combination with pembrolizumab in patients with recurrent, metastatic, or persistent cervical carcinoma
4	• To explore the efficacy and safety profile of previously enrolled patients with recurrent, metastatic, or persistent cervical carcinoma treated with LN-145
5	• To explore the efficacy and safety profile of re-treated patients with recurrent, metastatic, or persistent cervical carcinoma treated with LN-145

3.1.2 Secondary Objectives

The secondary objectives for each cohort are listed below:

Cohort	Secondary Objectives
1 and 2	• To evaluate the efficacy parameters of LN-145 in patients with recurrent, metastatic, or persistent cervical carcinoma by assessing duration of response (DOR), disease control rate (DCR), and progression-free survival (PFS) as assessed by the Investigator per RECIST v1.1 • To evaluate overall survival (OS) in patients with recurrent, metastatic, or persistent cervical carcinoma • To characterize the safety profile of LN-145 in patients with recurrent, metastatic, or persistent cervical carcinoma
3	• To evaluate the efficacy of LN-145 in combination with pembrolizumab in patients with recurrent, metastatic, or persistent cervical carcinoma by assessing ORR, DOR, DCR, and PFS as assessed by the Investigator per RECIST v1.1 • To evaluate OS in patients with recurrent, metastatic, or persistent cervical carcinoma

3.1.3 Exploratory Objectives

The exploratory objectives for each cohort are listed below:

Cohort	Exploratory Objectives
1, 2, and 3	• To explore the persistence of LN-145 and immune correlates of response, survival, toxicity of the treatment, and human papillomavirus (HPV) status • To explore efficacy based on immune-related RECIST (irRECIST) criteria, as assessed by the Investigator • To assess health-related quality of life (HRQoL) • To assess quality-adjusted time without symptoms of disease or toxicity of treatment (Q-TWiST)

3.2 Study Endpoints

3.2.1 Primary Endpoints

- Cohorts 1 and 2: ORR as assessed by the Investigator per RECIST v1.1
- Cohort 3: Incidence of Grade ≥ 3 treatment-emergent adverse events (TEAEs)
- Cohort 4 and 5: Because of the small sample size, results will be reported as appropriate by descriptive statistics

3.2.2 Secondary Endpoints

Cohorts 1 and 2

- DOR, DCR, and PFS as assessed by the Investigator per RECIST v1.1
- ORR, DOR, DCR, and PFS as assessed by the Investigator per RECIST v1.1
- OS
- Incidence of severity, seriousness, relationship to study treatment, and characteristics of TEAEs, including serious AEs (SAEs), therapy related AEs, and AEs leading to early discontinuation from treatment or withdrawal from the Assessment Period or death

Cohort 3

- ORR, DOR, DCR, and PFS as assessed by the Investigator per RECIST v1.1
- OS

Cohorts 4 and 5

- Because of the small sample size, results will be reported as appropriate by descriptive statistics

3.2.3 Exploratory Endpoints

Cohorts 1, 2 and 3

- Immune correlates CCI [redacted] will be determined by immunological and molecular assays
- ORR, DOR, DCR, and PFS as assessed by the Investigator per irRECIST
- Patient-reported outcomes for HRQoL as assessed per European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire-C30 v 3.0 Questionnaire (EORTC QLQ-C30)
- Q-TWiST using Investigators' assessments of disease symptoms and reported safety events prior to the next systemic anticancer therapy

Cohorts 4 and 5

- Because of the small sample size, results will be reported as appropriate by descriptive statistics

4 GENERAL METHODOLOGY AND CONVENTIONS

4.1 Analysis Sets

Four analysis sets are defined for the statistical analysis and presentation of the data. The Full Analysis Set (FAS) will be the primary set for the analysis of efficacy data. The Safety Analysis Set will be the primary set for the analysis of safety data. Additional analyses of AE data and some safety data will be conducted using the Safety Population and/or Tumor Harvested (TH) Set.

Analysis Set	Cohort	Description
CCI [redacted]		

[redacted]

4.2 Sample Size Determination

The total number of patients who will receive TIL infusions in this study - cryopreserved and non-cryopreserved - is approximately 189. Patients who are re-treated will be counted only once.

Cohort 1 LN-145 monotherapy: Approximately 75 patients are planned to be infused and receive cryopreserved LN-145 product. The prospectively defined hypothesis for the primary endpoint of ORR as assessed by the Investigator as per RECIST v1.1 based on the null hypothesis of ORR [redacted] and alternative hypothesis of ORR [redacted] will be tested. The sample size of 75 patients will result in more than [redacted] power to demonstrate superiority to the ORR of [redacted] using a conservative assumption for TIL therapy of [redacted]

Cohort 2 LN-145 post-treatment with a PD-1/PD-L1 checkpoint inhibitor: Approximately 75 patients are planned to be infused with cryopreserved LN-145. The prospectively defined hypothesis for the primary endpoint of ORR as assessed by the Investigator as per RECIST v1.1 based on the null hypothesis of ORR ≤ [redacted] and alternative hypothesis of ORR > [redacted] will be tested. The sample size of 75 patients will result in more than [redacted] power to demonstrate superiority to the ORR of [redacted] using an assumption for TIL therapy of [redacted]

Cohort 3 LN-145 in combination with pembrolizumab: Approximately 24 patients are planned to be infused with cryopreserved LN-145 in combination with pembrolizumab. This cohort is intended for signal seeking; no formal hypothesis testing is planned. This sample size will provide an estimated ORR and Grade ≥ 3 TEAE rate with a half-width [redacted]

Cohort 4 previously enrolled patients: Approximately 15 patients are planned to have been enrolled and treated with LN-145 alone but do not meet requirements for inclusion in the other study cohorts.

Cohort 5 Retreatment cohort: Approximately 10 patients who have been previously treated in Cohort 1 or 2 of this study may rescreen for a second administration of TIL product. These patients

may have a second tumor resection, if needed; especially when new lesions are available and feasible for resection.

4.3 Hypothesis Testing and Multiplicity Adjustment

One hypothesis for the Cohort 1 patient population with respect to ORR will be tested at a 2-sided significance level of 0.05. No multiplicity adjustment is needed.

Hypothesis in Cohort 1: H_{01}: ORR [redacted] vs. H_{a1}: ORR > [redacted].

This is to test the null hypothesis of ORR of ≤ [redacted] in patients with recurrent, metastatic, or persistent cervical carcinoma with disease progression on or after chemotherapy.

For other cohorts, the statistical analyses will be performed using descriptive methods and no formal hypothesis testing is planned.

4.4 Justification for Null Hypothesis

Justification for the null hypothesis of ORR ≤ [redacted] in Cohort 1: The preferred regimen for second-line systemic therapy of recurrent or metastatic disease is pembrolizumab for patients whose tumors express PD-L1 as determined by a Food and Drug Administration (FDA) approved test. [redacted] excluding [redacted] The patient population across levels of PD-L1 matches the population enrolled into Cohort 1 of Study C-145-04. Therefore, the same null hypothesis of [redacted] ORR will be used for this cohort.

4.5 Timing of Analysis

The final analysis for the CSR will be performed after all patients complete 5 years of follow-up from enrollment unless discontinued or the study is terminated by the Sponsor, whichever occurs first.

4.6 General Convention

The statistical analysis will be performed by cohort, unless otherwise specified. There is no planned statistical comparison between cohorts. The data from Cohort 1 and 2 are to evaluate [redacted] LN-145 product in the treatment of patients who have progressed during or following systemic therapy for recurrent, metastatic, or persistent cervical cancer. A separate analysis for data from

Cohort 3 will evaluate the efficacy and safety for the combination therapy of pembrolizumab and LN-145. Due to the exploratory objectives and small number of patients, the statistical analysis for Cohort 2, 3, and 4 will be based on the use of descriptive methods. The data from Cohort 5 for patients who received LN-145 as a re-treatment will be listed separately.

Patients who did not receive LN-145 treatment following the initial screening with or without initial tumor harvest (due to screen failure, manufacturing failure, or other reasons) may be re-screened and may receive LN-145 if they meet eligibility criteria at the second screening. These patients will be included in the analysis sets corresponding to the cohort in which they received LN-145 treatment.

Continuous data will be summarized as the number of patients with non-missing data (N), mean, standard deviation, median, minimum, and maximum values. Categorical data will be summarized as counts and their related percentages, where applicable. Estimation of CIs will use the CCI [redacted] with a two-sided 95% criterion unless otherwise specified. The formula to estimate “duration” in days is provided for relevant endpoints and will be converted to months divided by 30.4375, when applicable.

5 PATIENT CHARACTERISTICS AND TREATMENT EXPOSURE

5.1 Patient Disposition

The patient disposition will be summarized by cohort using frequency and percentage for each of the categories listed below:

- All screened patients and the reason for not enrolling
- CCI
- Patients who received 2 courses of LN-145

For Cohort 3, the reason for pembrolizumab discontinuation will also be summarized.

A summary of patients enrolled by site and geographic region will be provided. A listing for patients in Cohort 4 that includes the reasons for being assigned to Cohort 4 will also be provided.

5.2 Protocol Deviations

The protocol deviations are identified and assessed by the Sponsor clinical research associate or designee following company standard operational procedure. Patients with important protocol deviations will be summarized by categories of deviations. All protocol deviations will be listed.

5.3 Demographics and Baseline Disease Characteristics

5.3.1 Demographics

The following demographic characteristics will be summarized descriptively: age, age categories (< 40, ≥ 40 to < 65, and ≥ 65), sex, race, ethnicity, weight, body mass index (BMI, kg/m^2), geographic region (United States, Europe), and country.

5.3.2 Baseline Disease Characteristics

The following baseline disease characteristics will be summarized:

All Cohorts except Cohort 5:

- screening and baseline Eastern Cooperative Oncology Group (ECOG) performance status,
- histologic cell type,
- stage at initial diagnosis,
- disease metastasis at study entry,
- HPV status of primary tumor,
- resected tumor anatomic site,
- number of baseline target and non-target lesions,
- sum of diameter (SOD) of all measured lesions at screening (> 2 cm or ≤ 2cm),
- baseline target lesion SOD,
- number and category of adjudicated prior anticancer therapies,
- prior radiotherapy radiation site,
- time from tumor harvest to LN-145 infusion,
- time from last therapy to tumor harvest,
- PD-L1 combined positive score,
- time from first diagnosis of cervical cancer to study entry.

Cohort 1, 2, 4 only:

- prior bevacizumab (Yes or No),
- number of adjudicated prior systemic chemotherapies,
- duration of time on prior chemotherapy,
- duration of time on prior immune checkpoint inhibitor (ICI, for Cohort 2 only),
- progressive disease for at least one prior chemotherapy,
- progressive disease for the last prior chemotherapy before study entry,
- progressive disease for at least one prior chemotherapy/ICI (for Cohort 2 only).

Cohort 3 only:

- prior curative/therapeutic surgery (Yes or No),
- prior radiotherapy only (Yes or No),
- prior chemoradiation (Yes or No).

Continuous variables will be summarized descriptively by number of patients, mean, standard deviation, median, minimum, and maximum values. Categorical variables will be summarized by number and percentage of patients in each category. Individual patient listings will be provided to support the summary tables.

5.4 Medical History

A summary of medical history will be presented by system organ class (SOC) and preferred term (PT) using Medical Dictionary for Regulatory Activities (MedDRA) Version 28.1. A patient data listing of medical history and prior cancer-related surgery will also be provided.

5.5 Prior and Concomitant Medications

Prior and concomitant medications will be coded using the World Health Organization (WHO) Drug Global B3 September 2025. Prior medications are defined as any medications that are stopped before the first dose of NMA-LD (or the date of the first infusion of pembrolizumab for Cohort 3), not including the study regimen or prior anticancer systemic therapy. Concomitant medications for Cohorts 1, 2, 4, and 5 are defined as medications that are either initiated before and continued after the first dose of NMA-LD or initiated after the first dose of NMA-LD through CCI s post LN-145 infusion, not including the study regimen. For Cohort 3 concomitant medications are defined as medications that are either initiated before and continued after the first infusion of pembrolizumab or initiated after the first infusion of pembrolizumab CCI the last infusion of pembrolizumab (or LN-145 if pembrolizumab is never given or only given the first dose). The number and percentage of patients who take prior medications and concomitant medications will be summarized for the Safety Analysis Set.

New anticancer therapies received during survival follow-up will also be summarized similarly.

All medications recorded on the case report form (CRF) will be listed.

5.6 Treatment Exposure

Study treatment and extent of exposure summaries will be provided for the patients in the Safety Population. The total viable cells infused and relative infusion for LN-145 will be calculated and summarized descriptively. The relative infusion is calculated as the actual infused viable cells divided by the total manufactured and released viable cells.

The exposure to the NMA-LD regimen (cyclophosphamide and fludarabine) and IL-2 will be summarized based on the number of patients who received the agent, total number of infusions received, total cumulative dose, and relative dose intensity. Relative dose intensity (RDI) is defined as the actual dose intensity divided by the planned dose intensity where dose intensity refers to the cumulative dose of the above agents divided by the corresponding protocol planned number of doses (i.e., CCI).

For Cohort 3 only, the exposure to pembrolizumab will be summarized based on the number of patients who received pembrolizumab, total number of infusions received, total cumulative dose, and relative dose intensity. The treatment duration (in months) for pembrolizumab will also be summarized using descriptive statistics. The pembrolizumab treatment duration is defined as the time (in months) from the first dose date to the end of the last pembrolizumab treatment cycle, which is the minimum of the last dose date of pembrolizumab CCI for patients who are on the CCI dosing schedule for the last prescribed dose, the death date, or data cutoff date, or the minimum of the last dose of pembrolizumab CCI for patients who are on the CCI dosing schedule for the last prescribed dose, the death date, or the data cutoff date.

6 EFFICACY ANALYSIS

Efficacy analysis will be performed for patients in the FAS.

6.1 Primary Efficacy Endpoint

The primary efficacy endpoint in Cohorts 1 and 2 is the ORR as assessed by the Investigator as per RECIST v1.1. It is derived as the number of patients who have the best overall response (BOR) of CR or PR as assessed by the Investigator divided by the number of patients in the FAS×100%. In order for the BOR to be categorized as CR or PR, a confirmatory evaluation is required CCI or more apart after the first CR or PR. To determine BOR, all tumor response assessments up to the first PD per RECIST v1.1 should be considered. Any further tumor response assessments after the first PD or after the start of a new anticancer therapy are not considered. Patients without any baseline or any post-baseline measurements are considered not evaluable (NE).

ORR is expressed as a binomial proportion and will be summarized using a point estimate and its two-sided 95% confidence intervals based on the CCI

6.2 Secondary Efficacy Endpoints

Derivation of confirmed BOR based on two consecutive tumor assessment visits CCI or more apart per RECIST v1.1 is provided in Table 1.

Table 1 - General Rule to Derive BOR per RECIST v1.1

Overall response first timepoint	Overall response subsequent timepoint	BOR per RECIST v1.1
CR	CR	CR
CR	PR	SD, PD, or PR[a]
CR	SD	SD provided minimum criteria for SD duration are met, otherwise PD
CR	PD	SD provided minimum criteria for SD duration are met, otherwise PD
CR	NE	SD provided minimum criteria for SD duration met, otherwise NE
PR	CR [b]	PR
PR	PR	PR
PR	SD	SD

PR	PD	SD provided minimum criteria for SD duration are met, otherwise PD
PR	NE	SD provided minimum criteria for SD duration are met, otherwise NE
SD	CR[b]	SD
SD	PR[b]	SD
SD	SD	SD
SD	PD	SD provided minimum criteria for SD duration are met, otherwise PD
SD	NE	SD provided minimum criteria for SD duration are met, otherwise NE
NE	NE	NE
PD		PD

Note: BOR = best overall response; CR = complete response; NE = not evaluable; PD = progressive disease PR = partial response; SD = stable disease.

The minimum criteria for SD duration is 4 weeks from LN-145 infusion.

[a] If a CR is truly met at the 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 the 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.

[b] Subsequent assessments should be conducted to confirm the CR/PR.

DOR, DCR, and **PFS** will be analyzed per RECISIT v1.1 as assessed by the Investigator. For time-to-event endpoints such as DOR, PFS, and OS, CCI will be used to estimate the survivorship function. Median time to event and two-sided 95% CI based on log-log transformation will be obtained. The event-free rates for appropriate time points including CCI be provided for PFS and OS depending on the maturity of the study data at the time of the planned analysis.

DOR is defined as the time (in months) from the time point at which the initial measurement criteria per RECIST v1.1 are met for a CR or PR, whichever response is observed first, until the first date that PD is objectively documented, or the patient dies. Patients not experiencing PD or who have not died prior to the time of data cut will have their event times censored at the last adequate tumor assessment. For patients who received new anticancer therapies, DOR will be censored at the date of last tumor response assessment prior to the start of new anticancer therapies. For patients with PD or death after two or more consecutive missing tumor assessment visits, the DOR will be censored at the last adequate tumor assessment prior to the missing tumor assessments.

DOR (day) = Date of PFS event (PD or death) or censoring – Date of first overall response + 1

The median DOR and its 95% CI will be obtained using the Kaplan-Meier method for patients achieving a response (CR or PR).

DCR is defined as the proportion of patients who have the BOR of CR or PR or SD. The BOR of SD must be at least CCI from LN-145 infusion. DCR is expressed as a binomial proportion and will be summarized using a point estimate and its two-sided 95% CI based on CCI

PFS is defined as the time (in months) from the date of LN-145 infusion (or from the first infusion of pembrolizumab for Cohort 3) to PD or death due to any cause, whichever occurs earlier. Patients not experiencing PD or not having died at the time of the data cut will have their event times censored at the last adequate tumor assessment. The PFS censoring rules and definition of progression date follow the FDA "Guidance for Industry Clinical Trial Endpoints for the Approval of Cancer Drugs and Biologics (2018)". For patients who received new anticancer therapies, the PFS will be censored at the date of last tumor response assessment prior to the start of new anticancer therapies. For patients with PD or death after two or more consecutive missing tumor assessment visits, the PFS will be censored at the last adequate tumor assessment prior to the missing tumor assessments.

PFS (day) = Date of PFS event (PD or death) or censoring – Date of LN-145 infusion (or first dose of pembrolizumab for Cohort 3) + 1

The median PFS with its 95% CI and PFS at appropriate time points (e.g., CCI will be obtained using the KM method.

OS is defined as the time (in months) from the date of LN-145 infusion (or from the first infusion of pembrolizumab for Cohort 3) to death due to any cause. Patients having not died at the time of data cut will have their event times censored on the last date of their known survival status. The date of last known alive will be derived as the latest among dosing records, safety, and any other assessment dates indicating that a patient is alive. The median OS with its 95% confidence interval and OS at appropriate time points (e.g., CCI will be obtained using the KM method.

OS (day) = Date of death or last known alive – Date of LN-145 infusion (or first dose of pembrolizumab for Cohort 3) + 1

6.3 Other Planned Efficacy Analyses

The following analysis may be performed for patients in the FAS unless otherwise specified.

- Time to first response will be calculated and summarized descriptively based on patients with a confirmed PR or CR as assessed by the Investigator.

7 SAFETY ANALYSIS

Safety analysis will be performed for patients in the Safety Analysis Set for all cohorts except Cohort 5. Additional analysis for AEs and SAEs will be conducted using the CCI [redacted] The assessment of safety data will be descriptive and based on the summarization of adverse events, vital signs, and clinical laboratory tests.

7.1 Adverse Events

Adverse events will be coded using the MedDRA version 28.1. SOC, high-level group term (HLGT), high-level term (HLT), PT, and lower-level term (LLT) will be provided in the AE dataset. The severity of each adverse event will be graded by the Investigator using Common Terminology Criteria for Adverse Events (CTCAE) version 4.03 or higher version specified in the protocol.

Related AEs are based on 3 out of the 5 categories of causal relationship to study drug reported by Investigator: "Definite," "Probable," and "Possible." The causal relationship of "Not Likely" and "Not Related" will be categorized as unrelated. Adverse events will be identified and captured as SAEs if they meet the definition for an SAE.

7.1.1 Analysis Periods for Adverse Events

Three analysis periods are defined below for AE analyses. The focus of the AE summarization will be based on the treatment-emergent adverse events (TEAEs) CCI [redacted]

Tumor-Harvest Adverse Events include AEs that occur from tumor harvest and up to the start of any component of the study regimen. For patients who did not receive any component of the study regimen, AEs up to CCI [redacted] from tumor harvest will be included.

Treatment-Emergent Adverse Events (TEAEs): For Cohort 1, 2, 4, and 5, TEAEs include AEs that occur after the start of the LN-145 infusion and up to CCI [redacted] after the LN-145 infusion. For Cohort 3, TEAEs include AEs that occur after the first dose of pembrolizumab or LN-145 infusion (whichever is earlier) and up to CCI [redacted] after last dose of pembrolizumab or LN-145 infusion (whichever is later) or up to the start of a new anticancer therapy, whichever is earlier.

Regimen-Emergent Adverse Events (REAEs): For Cohort 1, 2, 4 and 5, REAEs include AEs that occur from the first dose of the TIL regimen (including NMA-LD, LN-145, and IL-2) and up to CCI after the last dose of the TIL regimen, the start of new anticancer therapy, or the data cutoff date, whichever is earlier. For Cohort 3, REAEs include AEs that occur after the first dose of pembrolizumab or the TIL regimen (whichever is earlier) and up to CCI after the last dose of pembrolizumab or the TIL regimen (whichever is later) or up to the start of a new anticancer therapy, whichever is earlier.

Tabular summaries including numbers and percentages of patients with the adverse events described in Table 2 will be presented by SOC and PT. In addition, AE summaries will be presented by PT only for TEAEs, and treatment-emergent SAEs.

For AE summaries by PT, cytopenia AEs will be grouped based on PTs and presented as leukopenia (including white blood cell count decreased and leukopenia), lymphopenia (including lymphocyte count decreased and lymphopenia), neutropenia (including neutrophil count decreased and neutropenia), thrombocytopenia (including platelet count decreased and thrombocytopenia), and anaemia (including haemoglobin decreased, red blood cell count decreased, and anaemia). These grouped cytopenia PTs belong to different SOCs: Blood and lymphatic system disorders or Investigations. For AE summaries by SOC and PT, for analysis purposes, they will be summarized under the SOC of Blood and lymphatic system disorders.

All grade AEs, Grade 3 AEs, Grade 4 AEs and Grade 5 AEs will be presented in separate columns. The most severe grade will be used for those AEs that occur more than once in an individual patient.

Table 2 – Summary of AE analyses

Summary	Population	Cohorts[a]
Tumor-harvest AEs	CCI	1+2,3,4
TEAEs		1+2,3,4
TEAEs related to LN-145		1+2,3,4
TEAEs leading to LN-145 discontinuation		1+2,3,4
TEAEs leading to pembrolizumab discontinuation		3
Treatment-emergent SAEs		1+2,3,4
Treatment-emergent SAEs related to LN-145		1+2,3,4
Tumor-harvest SAEs		1+2,3,4
REAEs		1+2,3,4
Regimen-emergent SAEs		1+2,3,4

REAEs related to any component of the study regimen	CCI	1+2,3,4
REAEs leading to any component of the TIL regimen discontinuation		1+2,3,4
REAEs leading to pembrolizumab discontinuation		3
Deaths that occur after tumor harvest prior to receiving the LN-145 infusion		1+2,3,4
Deaths that occur after LN-145 infusion		1+2,3,4

[a] "1+2" refers to combined Cohorts 1 and 2. The tabular summary has columns for individual Cohort 1 and 2, along with the column for combined data from Cohorts 1 and 2.

In addition to the summaries described above, a histogram plot of AE frequency over time will be provided with different colors for different toxicity grades. All occurrences will be counted if a patient experiences the same AE, but multiple records are reported on the CRF due to a toxicity grade increase. If multiple records are reported on the CRF for the same episode due to a toxicity grade decrease when the event is resolving, it will be counted once with the highest grade displayed on the histogram plot.

Patient data listings will also be provided for AE and death data.

7.2 Laboratory Evaluations

The laboratory assessments are conducted by local laboratories in this study. All laboratory values will be converted to and reported in the SI units and classified as low, normal, or high based on the reference ranges provided by the local laboratory. All laboratory data will be listed with a variable indicating whether the event is treatment emergent. Descriptive statistics will be provided to summarize laboratory parameters.

7.2.1 Analysis Periods for Laboratory Abnormalities

Analysis periods by cohort are defined below for the laboratory abnormality analysis. All laboratory data will be listed. The focus of the laboratory data summarization will be based on the treatment-emergent laboratory abnormalities.

The **NMA-LD period** includes the laboratory results that are collected after the start of NMA-LD and before the start of LN-145 infusion for all cohorts. The NMA-LD period is part of the Treatment-Emergent Period for Cohort 3.

The **Treatment-emergent Period** for Cohorts 1, 2, 4, and 5 includes the laboratory results that are collected from LN-145 infusion and through CCI post LN-145 infusion. For Cohort 3, the treatment-emergent period includes laboratory results that are collected from the first dose of pembrolizumab or LN-145 infusion (whichever is earlier) and up to CCI after last dose of pembrolizumab or LN-145 infusion (whichever is later).

The **Post-treatment-emergent Period** includes the laboratory results that are collected after the treatment-emergent period through the end of the assessment period or until the start of a new anti-cancer therapy, whichever occurs first.

7.2.2 Graded Laboratory Results

Applicable hematology and chemistry lab parameters severity data will be graded according to NCI-CTCAE, Version 5.0. Grade 0 includes all nonmissing values that do not meet criteria for an abnormality of at least Grade 1. Some laboratory tests have criteria for both increased and decreased levels; analyses for each direction (i.e., increased, decreased) will be presented separately.

The baseline CTCAE severity grade, and the maximum grade during each analysis period will be summarized using number and percentage of patients in each category. Patients will be categorized according to the most severe abnormality grade.

The number and percentage of patients with Grade 3 or 4 laboratory toxicity will be summarized for baseline, and each post-baseline visit.

Shift tables will be presented by showing the change in CTCAE severity grade from baseline to each analysis period. For parameters for which a CTCAE severity scale does not exist, shift tables will be presented showing the change in results from the baseline value (low, normal, and high) to each analysis period (decreased, normal, and high). Summaries of laboratory abnormalities will also be provided for worsening of ≥ 2 grades from baseline to each analysis period (i.e., shift from baseline Grade 0 to post-baseline Grade 2, 3 or 4, from baseline Grade 1 to post-baseline Grade 3 or 4, or from baseline Grade 2 to post-baseline Grade 4), as well as for worsening from baseline Grade 0-2 to post-baseline Grade 3-4.

7.2.3 Numeric Laboratory Results

Summaries of numeric laboratory data will be based on observed data and will be reported using SI units. Baseline, measurements after baseline, and changes from baseline at each post-treatment visit will be summarized using descriptive statistics for each laboratory parameter. The by-visit plot for

mean ± standard error of the mean will be provided for parameters of hemoglobin, neutrophils, leukocytes, platelets, and lymphocytes for baseline and each post-baseline visit.

7.3 Vital Signs

Descriptive statistics for vital signs parameters (i.e., body weight, pulse rate, respiration rate, blood pressure, and temperature) and changes from baseline will be presented by visit.

8 OTHER PLANNED ANALYSES

There are no other planned analyses for this study.

9 DEFINITONS AND DATA HANDLING CONVENTIONS

9.1 Definitions and Computations

The study day is the day relative to the LN-145 infusion. It will be calculated from the date of LN-145 infusion and derived as: assessment date - LN-145 infusion date. CCI [redacted]

For tumor assessments, the baseline value will be based on imaging data from the scheduled baseline visit (CCI [redacted]).

For all other assessments, the baseline value will be defined as the last non-missing value on or before the first dose of the study regimen. For patients who did not receive any dose of the study regimen but had tumor harvested, the baseline value will be defined as the assessment from the scheduled baseline visit. If the baseline visit is not performed, the screening assessment will be used unless the screening value is summarized separately.

For time-to-event efficacy endpoints, the interval is calculated as:

- Time to event (in days) = event date or censoring date - start date + 1, or
- Time to event (in months) = (event date or censoring date - start date + 1)/30.4375, or
- Time to event (in years) = (event date or censoring date - start date + 1)/365.25

Calculation of follow-up time for time-to-event endpoints (e.g., OS, DOR) will be performed using the CCI [redacted]

9.2 Missing Data Handling

General handling rule for missing response assessment data

For the derivation of BOR, patients without any baseline or any post-baseline measurements are considered not evaluable (NE). For the BOR to be categorized as CR or PR, a confirmatory evaluation is required 4 weeks or more apart after the first CR or PR.

The censoring rules and the definition of progression date for PFS and DOR follow FDA's guidance documents, i.e., Guidance for Industry Clinical Trial Endpoints for the Approval of Cancer Drugs and Biologics (2018). For patients with PD or death after a single missing tumor assessment visit, the PFS or DOR are considered as having an event at date of progression assessment or death. For patients with PD or death after two or more consecutive missing tumor assessment visits, the PFS or DOR are

censored at the last adequate tumor assessment prior to the missing tumor assessments. The missing response assessments will be ignored if the subsequent assessment shows no progression.

General imputation rules for missing or partial dates

For missing or partial start and end date for AEs, a conservative approach is taken to perform the relevant analyses. If the available information of a date is not enough to judge whether an event occurred on or after initiation of the study treatment, it will be conservatively taken as a treatment-emergent event. In case of a completely missing date, AE start date will not be imputed, and the AE will be treated as treatment emergent. If the partial AE start date is in the same year, or in the same year and month as the LN-145 infusion date (first dose of pembrolizumab or LN-145 infusion, whichever is earlier for Cohort 3), then the AE start date will be imputed as the LN-145 infusion date (first dose of pembrolizumab or LN-145 infusion, whichever is earlier for Cohort 3).

Otherwise, the following general imputation rule is applied for partial start and end dates of AEs. The general rule below may also be applied for partial dates of prior/concomitant medications, or subsequent anticancer therapy for analysis purposes.

- If only day is missing, the 15th of that month will be used.
- If only year is present, June 30th will be used.

If an imputed start date is after the end date, the end date will be used. If an imputed end date is before the start date, the start date will be used. If an imputed end date is after the death date, the death date will be used.

Other missing data handling

Missing height will be imputed using average heights among patients in the same cohort with baseline height in the TH Set.

9.4 Imputation Rules for Laboratory Values Reported with Symbols

Laboratory values that are reported with "<" or "≤" in the database will be imputed by the numeric values × 0.99, and laboratory values that are reported with ">" or "≥" in the database will be imputed by the numeric values × 1.01 for reporting purposes. The original laboratory value will be listed.

9.5 Visit Window

For summarizing data by visit, all scheduled and unscheduled assessments will be assigned to analysis visits according to a visit window schema. Visit windows for laboratory, vital signs, and other assessments are defined as shown in Table 4. If more than 1 assessment is within a given visit window, the assessment closest to the target date will be used. If 2 assessments are equally close to the target day, the earlier assessment will be used. By-visit analysis will not be conducted after Month 24 due to expected small sample size.

Table 4 – Visit Windows for Laboratory and Vital Sign Assessments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10 CHANGES TO THE STATISTICAL ANALYSES SPECIFIED IN THE PROTOCOL

Below are the changes to the statistical analyses specified in the protocol.

- Exploratory analyses listed below will not be conducted.
    - Correlation of immune factors, HPV status, and serotype with efficacy of TIL therapy
    - Evaluation of ORR, DOR, DCR, and PFS as assessed per irRECIST by the Investigator
    - Patient-reported outcomes for HRQoL assessed using the EORTC QLQ-C30 v3.0 instrument and analyzed per the published evaluation manual
    - Q-TWiST calculated as sum of the three health state periods (Toxicity, TWiST, and Relapse) with each multiplied by the appropriate utility score
- Due to the changes in the Iovance clinical development strategy and small sample size, the hypothesis for Cohort 2 patients with respect to ORR will not be conducted.
- Safety Population is added to summarize safety data in patients who received any component of the study regimen.
- Efficacy Evaluable (EE) set will not be defined and used in any analysis.
- Additional analysis for the primary efficacy endpoint using the TH Set will not be conducted.

11 REFERENCE

- Merck. KEYTRUDA® (pembrolizumab) for injection, for intravenous use prescribing information. 2018.
- FDA Guidance for Industry Clinical Trial Endpoints for the Approval of Cancer Drugs and Biologics, December 2018. Available from: https://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM071590.pdf
- NCCN Clinical Practice Guidelines in Oncology: Cervical Cancer Version 3.2019. Available from: https://jnccn.org/view/journals/jnccn/17/1/article-p64.xml

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