IOVANCE BIOTHERAPEUTICS

ADVANCING IMMUNO-ONCOLOGY

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

PROTOCOL NUMBER:	C-145-04
IND NUMBER:	CCI
EU CT NUMBER:	2024-510634-41-00
SPONSOR:	Iovance Biotherapeutics, Inc. 825 Industrial Road San Carlos, CA 94070 United States
PROTOCOL AMENDMENT:	Version 10.0 14 Aug 2025
MEDICAL MONITOR:	PPD

SPONSOR SIGNATURE PAGE

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By my signature, I acknowledge my review and approval of this protocol.

PPD

Signature

Date

PPD

INVESTIGATOR PROTOCOL SIGNATURE PAGE

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I agree to conduct the study as detailed in the protocol and in compliance with International Conference on Harmonisation Guidelines for Good Clinical Practice.

I acknowledge that I am responsible for overall study conduct, and I agree to personally conduct or supervise the described clinical study.

I agree to ensure that all associates, colleagues, and employees assisting in the conduct of the study are informed about their obligations. Mechanisms are in place to ensure that site staff receives the appropriate information throughout the study.

_____ _____

Principal Investigator Signature Date

_____

Principal Investigator Printed Name

_____

Institution

RATIONALE FOR PROTOCOL AMENDMENT

Version 10.0 (14 Aug 2025)

This amendment is considered to be substantial based on the criteria set forth in Article 2(13) of Regulation (EU) 536/2014 of the European Parliament and the Council of the European Union.

Overall Rationale for the Amendment:

The protocol has been revised principally to update the primary and secondary objectives and endpoints to reflect that all tumor assessments will be conducted by the Investigator and no assessments will be conducted by an Independent Review Committee due to changes in the Iovance clinical development strategy for LN-145. Substantial changes to the protocol are described in the summary of changes document. All changes, including nonsubstantial changes, are shown in the redlined version of this amended protocol.

PROTOCOL SYNOPSIS

Protocol Title	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
Protocol Number	C-145-04
Study Type	Phase 2
Indication	Treatment of patients with recurrent, metastatic, or persistent carcinoma of the cervix
Investigational Agent	LN-145: autologous tumor infiltrating lymphocytes (TIL) derived from the patient's own tumor
Study Objectives	**Cohort 1 – LN-145 monotherapy in patients who have progressed during or following systemic therapy for recurrent, metastatic, or persistent disease and Cohort 2 – LN-145 monotherapy in patients previously treated with an anti-programmed cell death protein-1 (PD-1) or anti-programmed death-ligand 1 (PD-L1) checkpoint inhibitor:** **Primary Objective** • 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 **Secondary Objectives** • 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 **Exploratory Objectives** • 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) **Cohort 3 – LN-145 in combination with pembrolizumab (US only):** **Primary Objective** • To characterize the safety profile of LN-145 in combination with pembrolizumab in patients with recurrent, metastatic, or persistent cervical

carcinoma

Secondary Objectives

- 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 per RECIST 1.1, as assessed by the Investigator
- To evaluate OS in patients with recurrent, metastatic, or persistent cervical carcinoma

Exploratory Objectives

- To explore the persistence of LN-145 and immune correlates of response, survival, toxicity of treatment, and HPV status
- To explore efficacy based on irRECIST criteria, as assessed by the Investigator
- To assess HRQoL
- To assess quality-adjusted time without symptoms of disease or toxicity of treatment (Q-TWiST)

Cohort 4 – LN-145 previously enrolled patients:

Primary Objective

- To explore the efficacy and safety profile for previously enrolled patients with recurrent, metastatic, or persistent cervical carcinoma treated with LN-145

Cohort 5 – LN-145 re-treated patients:

Primary Objective

- To explore the efficacy and safety profile for re-treated patients with recurrent, metastatic, or persistent cervical carcinoma treated with LN-145 in Cohorts 1 and 2

Study Design

This is a Phase 2, multicenter, multicohort, prospective, open-label, interventional study using autologous TIL infusion (LN-145) with or without pembrolizumab followed by interleukin-2 (IL-2) after a non-myeloablative lymphodepletion (NMA-LD) preparative regimen.

Doses and Treatment Schedule

Cohorts 1, 2, 4, and 5

Cohorts 1, 2, 4, and 5 Treatment Administration	Post-resection	Study Day CCI
Cyclophosphamide		
Mesna		
Fludarabine		
LN-145 infusion		
IL-2		

The adoptive cell therapy (ACT) used in this study involves patients receiving an NMA-LD preparative regimen, consisting of daily intravenous (IV) cyclophosphamide CCI [redacted] ollowed by daily fludarabine CCI [redacted]
Infusion of LN-145 is given on Day 0 (CCI [redacted] and is followed by administration

	of IL-2 at CCI Patients in Cohort 5 (Re-treatment Cohort) may have a second tumor resection, if needed, especially when new lesions are available and feasible for resection. The decision for enrollment into Cohort 5 will be based on a discussion between the Investigator and the Medical Monitor. **Cohort 3: LN-145 in combination with pembrolizumab** CCI * 200 mg pre-NMA-LD ± a s) ** Investigator's choice: 200 mg Q3W or 400 mg Q6W (± 3 days) post-IL-2 until EOT For patients in Cohort 3, the first dose of pembrolizumab 200 mg IV will be administered following tumor resection and baseline scans but before the initiation of NMA-LD. These patients will then receive the NMA-LD preparative regimen, consisting of daily intravenous (IV) cyclophosphamide CCI followed by daily fludarabine CCI . Infusion of LN-145 is given on Day 0 CCI and is followed by administration of IL-2 at CCI Pembrolizumab administrations will continue no earlier than CCI from the first dose and not until the completion of IL-2 and after patients have recovered (Grade ≤ 2 toxicities) from IL-2-related toxicities. Pembrolizumab dosing (dose 2 forward) will continue at Investigator's choice, 200 mg Q3W or 400 mg Q6W (± 3 days) for ≤ 2 years (24 months) from the first dose, or until disease progression or unacceptable toxicity, whichever occurs first.
Duration of Participation	Overall duration of the study will be approximately 5 years from the last patient enrolled, comprising the following periods: **Screening:** Up to CCI prior to tumor resection. **Enrollment:** Upon tumor resection for TIL generation. **Treatment Period:** **Cohorts 1, 2, 4, and 5**: NMA-LD preparative regimen CCI LN-145 infusion CCI , IL-2 administration CCI Patients will return for safety assessment visits on CCI and CCI CCI corresponds with the end-of-treatment (EOT) visit. **Cohort 3 (US only)**: The treatment period for Cohort 3 is up to CCI , including the NMA-LD preparative regimen CCI LN-145 infusion CCI followed by

Cohort 3 Treatment Administration
Cyclophosphamide
Mesna
Fludarabine
Pembrolizumab
LN-145 infusion
IL-2

	IL-2 administrations 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) 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. The EOT visit may be combined with any scheduled visit occurring within this interval during the assessment period. **Assessment Period:** Efficacy (eg, tumor response) assessments will be performed at CCI post-LN-145 infusion then e CCI Patients will continue to be evaluated for response CCI for up to 5 years from CCI ; LN-145 infusion) or until: • Disease progression • 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 (eg, EOA) and will continue for up to 5 years from Enrollment (tumor resection) or until discontinuation from the study, with telephone contact every CCI to obtain survival status and subsequent anticancer therapy information. Patients who had tumor resection but did not receive LN-145 for any reason will perform an EOA visit and transition directly into the OS Follow-up Period.
Number of Study Sites	Approximately 40 clinical study sites globally
Number of Planned Patients	The total number of planned patients to be infused in this study will be approximately 189. Patients will be counted once even if they receive re-treatment. **Cohort 1 - LN-145 monotherapy**: Approximately 75 patients who have progressed during or following systemic therapy for recurrent, metastatic, or persistent cervical cancer and have been infused with cryopreserved LN-145. Cohort 1 is no longer open for enrollment. **Cohort 2 - LN-145 post-treatment with PD-1/PD-L1 checkpoint inhibitor:** Approximately 75 patients who have progressed during or following systemic chemotherapeutic treatments for recurrent, metastatic, or persistent cervical cancer. In addition, patients must have received at least one prior treatment with a checkpoint inhibitor (ie, PD-1, PD-L1) for recurrent, metastatic, or persistent cervical cancer. **Cohort 3 - LN-145 in combination with pembrolizumab (US only):** Approximately 24 patients with recurrent, metastatic, or persistent cervical cancer who have not received any therapies other than prior chemoradiation or surgery for loco-regional disease. **Cohort 4 - Previously enrolled patients:** Approximately 15 patients who do not meet requirements for inclusion in the other study cohorts. Cohort 4 is not open for enrollment. **Cohort 5 – Retreatment cohort:** Approximately 10 patients who have been previously treated in Cohort 1 or 2 of this study, will be retreated with

	cryopreserved LN-145. These patients may have a second tumor resection, if needed, especially if new lesions are available and feasible for resection. Patients in Cohort 3 are not eligible for re-treatment.
Inclusion Criteria	To be eligible for the study, patients must meet ALL of the following criteria prior to participation: 1. Must be ≥ 18 years of age at the time of consent. Enrollment of patients > 70 years of age may be allowed after consultation with the Medical Monitor. 2. Patients must have the ability to understand the requirements of the study, have provided written informed consent as evidenced by signature on an informed consent form (ICF) approved by an Institutional Review Board/Independent Ethics Committee (IRB/IEC), and agree to abide by the study restrictions and return to the site for the required assessments, including the OS Follow-up Period 3. Must be able and willing to comply to the study visit schedule and protocol requirements 4. Must have recurrent, metastatic, or persistent squamous cell carcinoma (SCC), adenosquamous carcinoma (ASC), or adenocarcinoma (AC) of the cervix that is not amenable to curative treatment with surgery and/or radiation therapy and, in Germany and Switzerland only, for which no other therapies are expected to have significant benefit, in the opinion of the Investigator. 5. At least one resectable lesion (or aggregate of lesions resected) of a minimum 1.5 cm in diameter post-resection to generate TIL; surgical removal with minimal morbidity (defined as any procedure for which expected hospitalization is ≤ 3 days) 6. At least one measurable target lesion, as defined by RECIST v1.1 • Lesions in previously irradiated areas (or other local therapy) should not be selected as target lesions, unless treatment was ≥ 3 months prior to Enrollment, and there has been demonstrated disease progression in that particular lesion • If a lesion is partially resected to generate TIL, and remains visible on the Baseline scan after surgery, then the partially resected lesion can be used for RECIST v1.1 response assessment, but only as a non-target lesion 7. **Cohort 1 and Cohort 2:** Progression during or following at least one, but no more than three, prior systemic chemotherapeutic treatments for recurrent, metastatic, or persistent cervical carcinoma • A line of systemic therapy is defined as any chemotherapy or multiple-agent chemotherapy regimen that was administered for recurrent, metastatic, or persistent SCC, ASC, or AC of the cervix. • A bevacizumab and chemotherapy combination is encouraged as a prior line of treatment. • Neither chemoradiation, nor chemotherapy in the neoadjuvant or adjuvant settings are considered as a prior line of systemic therapy.

	Cohort 2: Must also have previously received treatment with a checkpoint inhibitor (ie, PD-1, PD-L1]) in the setting of recurrent, metastatic, or persistent disease either as monotherapy or in combination (eg, in combination with chemotherapy or another immune agent) **Cohort 3 (United States only):** Must have not received any therapies other than prior chemoradiation or surgery for loco-regional disease 8. Any prior therapy directed at the malignant tumor, including chemotherapy, biologic/targeted agents, and immunologic agents must be discontinued at least 28 days prior to tumor resection. Radiation therapy is permitted as long as the lesions irradiated are not expected to be used for TIL generation or as target lesions and any toxicities have resolved to Grade ≤ 1 at least 2 weeks prior to NMA-LD. 9. Have an Eastern Cooperative Oncology Group (ECOG) performance status of 0 or 1 10. Must meet the following laboratory criteria: • Absolute neutrophil count (ANC) ≥ 1000/mm^3 • Hemoglobin ≥ 8 g/dL or ≥ 4.96 mmol/L • Platelet count ≥ 100,000/mm^3 • Serum alanine transaminase (ALT)/serum glutamic-pyruvic transaminase (SGPT) and aspartate transaminase (AST)/serum glutamic-oxaloacetic transaminase (SGOT) < 3.0 times the upper limit of normal (ULN) Patients with liver metastasis must have liver function tests (LFTs) < 5.0 times the ULN • Total bilirubin ≤ 2.0 mg/dL Patients with Gilbert's syndrome must have a total bilirubin ≤ 3.0 mg/dL • Serum creatinine must be ≤ 1.5 mg/dL • Measured creatinine clearance (CrCl) ≥ 40 mL/min calculated from a 24-hour urine collection 11. Patient has no evidence of any active viral, bacterial, or fungal infection requiring ongoing systemic treatment. Patients must be seronegative for the human immunodeficiency virus (HIV). Patients with acute or chronic hepatitis infections may be enrolled if the viral load by nucleic acid amplification test (NAAT) is undetectable with/without active treatment 12. Patients of childbearing potential must be willing to take the appropriate precaution to avoid pregnancy for the duration of the study and practice an approved, highly effective method of birth control during treatment and for 12 months after receiving the last protocol-related therapy. Approved methods of birth control are as follows: • Combined (estrogen and progesterone containing) hormonal birth control associated with inhibition of ovulation: oral, intravaginal, transdermal • Progesterone-only hormonal birth control associated with inhibition of ovulation: oral, injectable, implantable

	• Intrauterine device (IUD) • Intrauterine hormone-releasing system (IUS) • Bilateral tubal occlusion • Vasectomized partner • True sexual abstinence when this is in line with the preferred and usual lifestyle of the patient. Periodic abstinence (eg, calendar ovulation, symptothermal, post-ovulation methods) is not acceptable 13. Prior to study Enrollment (tumor resection), patient must have documentation of radiological disease progression after the most recent therapy 14. Patients have provided written authorization for use and disclosure of protected health information
Exclusion Criteria	Patients who meet *any* of the following criteria are not eligible for participation in this study: 1. Patients who have received an organ allograft or prior cell transfer therapy except for prior LN-145 therapy in the setting of re-treatment only. 2. Patients who require systemic steroid therapy (> 10 mg/day of prednisone or other steroid equivalent dose). Patients receiving steroids as replacement therapy for adrenocortical insufficiency at ≤ 10 mg/day of prednisone or other steroid equivalent may be eligible. 3. Patients who currently have prior therapy-related toxicities Grade > 1 according to National Cancer Institute (NCI) Common Terminology Criteria for Adverse Events (CTCAE) v5.0 (eg, uveitis); except for peripheral neuropathy, alopecia, or vitiligo prior to Enrollment (tumor resection) • Patients with a history of uveitis must have an eye examination performed by a trained eye specialist at Screening to rule out active uveitis that requires treatment. Patients who have active uveitis that requires active treatment will be excluded. • If toxicities have resolved to Grade ≤ 1, a minimum of 2 weeks must elapse prior to Enrollment (tumor resection) • Patients may not have any pre-planned procedures within 2 weeks prior to the start of NMA-LD preparative regimen **Cohort 2:** Patients with documented Grade ≥ 2 diarrhea or colitis as a result of previous treatment with a PD-1/PD-L1 checkpoint inhibitor(s) must have been asymptomatic for at least 6 months or had a normal colonoscopy post-checkpoint inhibitor treatment, by visual assessment, prior to tumor resection. **Cohort 2**: Patients with immunotherapy-related endocrinopathies stable for at least 6 weeks (eg, hypothyroidism, stable on hormonal substitution) and controlled with hormonal replacement, are allowed. 4. No longer applicable 5. Patients who have a history of hypersensitivity to any component or excipient of LN-145 or other study drugs:

	• NMA-LD preparative regimen (cyclophosphamide, mesna, and fludarabine) • Antibiotics (ABX) of the aminoglycoside group (ie, streptomycin, gentamicin); except those who are skin-test negative for gentamicin hypersensitivity • Any component of the LN-145 infusion product formulation including dimethyl sulfoxide (DMSO), human serum albumin (HSA), IL-2, and dextran-40 6. Patients who have active systemic infections, coagulation disorders, or other active major medical illness(es) of the cardiovascular, respiratory, or immune system, including evidence in the medical history of urinary tract obstruction, a positive cardiac stress test, myocardial infarction, cardiac arrhythmia, obstructive or restrictive pulmonary disease, or other conditions that in the opinion of the Investigator would increase the risk of participation • Patients with corrected (ie, percutaneous nephrostomy tubes) urinary tract obstruction must have negative surveillance cultures from externalized tubes within 7 days prior to the start of NMA-LD preparative regimen. Asymptomatic patients with chronic colonization of indwelling urinary diversion tubes may be eligible after active urinary infection is ruled out and discussion with the Medical Monitor. • Patients with evidence of any uncontrolled or active systemic infection requiring ongoing treatment cannot proceed to NMA-LD. Prophylactic anti-infection therapy is acceptable. 7. Patients with symptomatic and/or untreated brain metastases (of any size and any number) • Patients with definitively treated brain metastases may be considered for Enrollment, and must be stable for ≥ 14 days prior to beginning the NMA-LD preparative regimen 8. Patients who have any form of primary immunodeficiency (such as severe combined immunodeficiency [SCID] or acquired immunodeficiency syndrome [AIDS]) 9. Patients who have a diagnosis of end-stage renal disorder requiring hemodialysis 10. Patients who have a left ventricular ejection fraction (LVEF) < 45% or who are New York Heart Association (NYHA) Class 2 or higher. Patients ≥ 60 years of age or who have a history of ischemic heart disease, chest pain, or clinically significant atrial and/or ventricular arrhythmias must have a cardiac stress test (or equivalent local standard stress test): • Patients with an abnormal cardiac stress test may be enrolled if they have adequate ejection fraction (≥ 45%) and cardiology clearance after consultation with the Medical Monitor • Patients with any irreversible wall movement abnormalities are excluded 11. Patients who have a documented forced expiratory volume in 1 second (FEV1) of ≤ 60%

	12. Patients who have had another primary malignancy within the previous 3 years (except for curatively treated localized malignancy that has not required treatment for > 1 year, and in the judgement of the Investigator, does not pose a significant risk of recurrence including, but not limited to, non-melanoma skin cancer or bladder cancer) 13. Patients who are of the following protected classes will be excluded, including: • Pregnant, parturient, or breastfeeding women • Persons who are hospitalized without consent or those deprived of liberty because of a judiciary or administrative decision • Patients with a legal protection measure or a person who cannot express his/her consent • Patients in emergency situations who cannot consent to the study 14. Patients who have received a live or attenuated vaccine within 28 days prior to beginning the NMA-LD preparative regimen 15. Patients whose cancer requires immediate attention or who would otherwise suffer a disadvantage by participating in this study 16. **Cohort 1 and Cohort 3**: Patients who have received prior treatment with immunotherapy (eg, PD-1, PD-L1, or anti-cytotoxic T lymphocyte-associated antigen-4 [CTLA-4] antibodies) 17. Patients who have Grade ≥ 2 hemorrhage within 14 days prior to Enrollment (tumor resection) 18. **Cohort 3**: Patients may not have active or prior documented autoimmune or inflammatory disorders (including pneumonitis, inflammatory bowel disease [eg, colitis or Crohn's disease], diverticulitis [with the exception of diverticulosis], systemic lupus erythematosus, sarcoidosis syndrome, or Wegener syndrome [granulomatosis with polyangiitis, Graves' disease, rheumatoid arthritis, hypophysitis, uveitis, etc.]). The following are exceptions to this criterion: • Patients with vitiligo or alopecia • Patients with hypothyroidism (eg, following Hashimoto syndrome) stable on hormone replacement • Patients with any chronic skin condition that does not require systemic therapy • Patients with celiac disease controlled by diet alone
Criteria for Early Discontinuation from Treatment:	**<u>From TIL Regimen Administration</u>:** • Patient has become ineligible for study participation after tumor resection CCI and prior to the NMA-LD preparative regimen, LN-145 infusion, or IL-2 administration • TIL product not available and the patient is ineligible for or does not wish to undergo another tumor resection • Withdrawal of consent to treatment (partial and full withdrawal) o Every effort should be made to continue OS Follow-up, when applicable

	• Grade ≥ 3 drug-related immune adverse events (AEs) that involve vital organs (heart, kidneys, brain, eye, liver, colon, adrenal gland, lungs) with symptoms emerging following LN-145 infusion • Grade ≥ 3 allergic reaction including bronchospasm or generalized urticaria that does not resolve after medical management in the opinion of the Investigator • Meeting criteria for permanent discontinuation of IL-2 treatment (must have received at least one dose of IL-2) • Determination by the Investigator that continued treatment is not in the best interest of the patient • Administration of prohibited concomitant medications/start of new anti-cancer therapy • Pregnancy • Death • Study terminated by Sponsor **From Pembrolizumab Administration (Cohort 3 only):** • Any toxicity that states pembrolizumab permanent discontinuation per dose modification guidelines or per pembrolizumab prescribing information • Pregnancy • Death • Withdrawal of consent • Study terminated by Sponsor
Criteria for Discontinuation from the Study:	• Withdrawal of consent • Lost to follow-up • Death • Study terminated by the Sponsor
Efficacy Assessments	**Cohorts 1 and 2:** Calculated from CCI [redacted]). The statistical analysis of ORR, DOR, DCR, and PFS will be provided for the patients infused with cryopreserved TIL to determine the potential efficacy of LN-145, as assessed by the Investigator per RECIST v1.1. Estimation of OS will depend on the date of death or the last known alive status. **Cohort 3:** The following efficacy parameters for LN-145 in combination with pembrolizumab will be investigated: ORR, DOR, DCR, PFS. These parameters will be assessed by the Investigator per RECIST v1.1. OS will also be measured. **Cohorts 4 and 5:** Because of the small sample size, results will be reported as appropriate by descriptive statistics.
Safety Assessments	At each scheduled visit to the clinical site, AEs/serious AEs (SAEs) will be collected and graded as per CTCAE v5.0, starting from signing the ICF until the end of the study. Analyses will include all study periods.

Overview of Statistical Plan	**Sample Size Consideration** The total number of patients planned to be infused with LN-145 in this study is approximately 189. Patients will be counted once even if they receive re-treatment. **Cohort 1**: 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 ≤ CCI and alternative hypothesis of ORR > CCI will be tested. The sample size of 75 patients will result in more than CCI power to demonstrate superiority to the ORR of CCI using a conservative assumption for TIL therapy of CCI **Cohort 2:** 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 ≤ CCI and alternative hypothesis of ORR > CCI will be tested. The sample size of 75 patients will result in more than CCI power to demonstrate superiority to the ORR of CCI using an assumption for TIL therapy of CCI **Cohort 3**: 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 CCI **Cohort 4**: Approximately 15 patients are planned to have been enrolled and treated with LN-145 alone but do not meet requirement for inclusion in the other study cohorts. **Cohort 5**: Approximately 10 patients who have been previously treated in Cohort 1 or 2 of this study may rescreen for a second administration of the TIL product. These patients may have a second tumor resection, if needed; especially when new lesions are available and feasible for resection. **Statistical Plan** The statistical analysis will be based on the estimation of efficacy and safety parameters and will be performed by cohort, unless otherwise specified. There is no planned statistical comparison between cohorts. Two separate formal statistical hypothesis tests are planned for the primary endpoint in Cohort 1 and Cohort 2, respectively. For all other cohorts, the statistical analysis is based on the use of descriptive methods; no formal hypothesis testing is planned. Patients meeting RECIST v1.1 criteria for a confirmed complete response (CR) or partial response (PR) as assessed by the Investigator will be classified as responders in the analysis of ORR. The ORR will be analyzed using a point estimate and its two-sided 95% confidence limits based on the Clopper-Pearson exact method. All other binary endpoints will be analyzed similarly as the primary endpoint. All time-to-event efficacy endpoints will use the Kaplan-Meier method to summarize the data. The time origin for all such analyses (except for response

	duration) will be the date on which patients received LN-145 infusion[redacted] The assessment of safety data will be descriptive and based on 1) the summarization of treatment-emergent adverse events (TEAEs), SAEs, AEs leading to discontinuation from the study, and 2) vital signs and clinical laboratory tests.
Data Safety Monitoring Board	An independent Data Safety Monitoring Board (DSMB) will evaluate safety data in Cohort 1 when the [redacted] and when up to a total of [redacted] have completed [redacted] of assessments post-LN-145 infusion. Enrollment will continue while under review. The DSMB will also review safety data from the [redacted] in Cohort 2 and [redacted] in Cohort 3, who received TIL.
Independent Data Monitoring Committee	An Independent Data Monitoring Committee (IDMC) composed of a group of clinicians appointed by Iovance will provide oversight of this clinical trial to ensure quality and consistency of study conduct as well as data collection and analysis across international study sites. The IDMC will review the study data when up to a total of [redacted] have completed [redacted] of assessments post-LN-145 infusion. Enrollment will continue while data is under review. The IDMC will also review the study data from Cohort 1 after up to a total of [redacted] have completed [redacted] of assessments post-LN-145 infusion. The IDMC will also review the study data from Cohort 2 after up to a total of [redacted] have received LN-145 infusion, and completed [redacted] of assessments post-LN-145 infusion.

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LIST OF ABBREVIATIONS

Term	Definition
ABX	Antibiotic
AC	Adenocarcinoma
ACT	adoptive cell therapy
AE	adverse event
AESI	adverse event of special interest
AIDS	acquired immunodeficiency syndrome
ALC	absolute lymphocyte count
ALT	alanine transaminase
ANC	absolute neutrophil count
anti-HBc	hepatitis B core antibody
aPTT	activated partial thromboplastin time
ASC	adenosquamous carcinoma
AST	aspartate transaminase
β-HCG	beta-human chorionic gonadotropin
BMI	body mass index
BSA	body surface area
BUN	blood urea nitrogen
CBC	complete blood count
CFR	Code of Federal Regulations
CI	confidence interval
CK	creatine kinase
CLS	capillary leak syndrome
CMV	cytomegalovirus
CO_2	carbon dioxide
CPS	combined positive score
CR	complete response
CrCl	creatinine clearance
CRO	contract research organization
CT	computed tomography
CTCAE v5.0	Common Terminology Criteria for Adverse Events V 5.0
CTLA-4	cytotoxic T lymphocyte-associated antigen-4
CY	cyclophosphamide

Term	Definition
D5W	5% dextrose in water
DC-LAMP	dendritic cell-lysosomal associated membrane glycoprotein
DCR	disease control rate
DMAP	damage-associated molecular pattern
DMSO	dimethyl sulfoxide
DNA	deoxyribonucleic acid
DOR	duration of response
DS	double strength
DSMB	Data Safety Monitoring Board
EES	Efficacy Evaluable Set
EBV	Epstein-Barr virus
ECG	Electrocardiogram
ECHO	Echocardiogram
ECOG	Eastern Cooperative Oncology Group
eCRF	electronic case report form
EDC	electronic data capture
EEG	Electroencephalogram
EMA	European Medicines Agency
EOA	End-of-Assessment
EORTC QLQ-C30	European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire-C30 v 3.0 questionnaire
EOT	End-of-Treatment
EU	European Union
FAS	Full Analysis Set
FDA	Food and Drug Administration
FEV1	forced expiratory volume in 1 second
FLU	fludarabine
FFPE	formalin-fixed, paraffin-embedded
FNA	fine needle aspiration
FSH	follicle-stimulating hormone
GCP	Good Clinical Practice
GDPR	General Data Protection Regulation
GMP	Good Manufacturing Practice
GOG	Gynecologic Oncology Group

Term	Definition
Hb	Hemoglobin
HBsAg	hepatitis B virus surface antigen
Hct	Hematocrit
HCV Ab	hepatitis C virus antibody
HIPAA	Health Insurance Portability and Accountability Act
HIT	heparin-induced thrombocytopenia
HIV	human immunodeficiency virus
HLA	human leukocyte antigen
HPV	human papillomavirus
HRQoL	health-related quality of life
hsa	human serum albumin
HSV	herpes simplex virus
IB	Investigator's Brochure
ICF	informed consent form
ICH	International Conference on Harmonisation
ICOS	inducible T-cell costimulator or CD278
ICU	intensive care unit
IDMC	Independent Data Monitoring Committee
IEC	Independent Ethics Committee
IgM	immunoglobulin M
IL-2	interleukin-2 (aldesleukin)
INR	international normalized ratio
IRB	Institutional Review Board
irRECIST	immune-related Response Evaluation Criteria in Solid Tumors
IU	international unit
IUD	intrauterine device
IUS	intrauterine hormone-releasing system
IV	Intravenous
LDH	lactate dehydrogenase
LFT	liver function tests
LVEF	left ventricular ejection fraction
mAb	monoclonal antibody
MCV	mean corpuscular volume

Term	Definition
MRI	magnetic resonance imaging
NAAT	nucleic acid amplification test
NaCl	sodium chloride
NCI	National Cancer Institute
NCCN	National Comprehensive Cancer Network
NE	not evaluable
NMA-LD	non-myeloablative lymphodepletion
NYHA	New York Heart Association
OKT3	muromonab CD3, a murine monoclonal antibody to human CD3
ORR	objective response rate
OS	overall survival
PBMC	peripheral blood mononuclear cell
PCR	polymerase chain reaction
PD	progressive disease
PD-1	programmed cell death protein-1
PD-L1	programmed death-ligand 1
PE	physical examination
PET	positron emission tomography
PFS	progression-free survival
PHI	personal health information
PO	per os (by mouth)
PR	partial response
PRBC	packed red blood cells
PTT	prothrombin time
Q-TWiST	quality-adjusted time without symptoms of disease or toxicity of treatment
RBC	red blood cell
RECIST	Response Evaluation Criteria in Solid Tumors
REP	Rapid Expansion Protocol
RPR	rapid plasma reagin
RSI	Reference Safety Information
SAE	serious adverse event
SAP	Statistical Analysis Plan
SCC	squamous cell carcinoma

Term	Definition
SCID	severe combined immunodeficiency
SD	stable disease
SGOT	serum glutamic-oxaloacetic transaminase
SGPT	serum glutamic-pyruvic transaminase
SmPC	Summary of Product Characteristics
SMX	Sulfamethoxazole
SoD	sum of diameters
SOP	Standard Operating Procedure
SUSAR	suspected unexpected serious adverse reaction
TEAE	treatment-emergent adverse event
TH	tumor harvested
TIL	tumor infiltrating lymphocyte
TMP	Trimethoprim
TMTB	total measured tumor burden
T_{reg}	regulatory T cell
TSH	thyroid stimulating hormone
ULN	upper limit of normal
US	United States
USPI	United States prescribing information
VDRL	venereal disease research laboratory
WBC	white blood cell

1. INTRODUCTION

1.1. Disease Background

Cervical cancer is a common malignancy in women worldwide [Torre 2015] and is a leading cause of cancer-related death in women [Tewari 2012, Zsiros 2015]. In the United States (US) in 2017, approximately 12,800 new cases of invasive cervical cancer were predicted to be diagnosed and about 4210 women were expected to die from this disease (American Cancer Society 2017). In the European Union (EU), an estimated 58,345 new cases were diagnosed and 24,397 deaths from invasive cervical cancer occurred in 2012 (International Agency for Research on Cancer and World Health Organization 2012).

As noted by Piersma (Piersma 2011), previous studies have shown that virtually all cervical tumors are positive for human papillomavirus (HPV) and that HPV infection is necessary and sufficient to cause cervical tumors [Bosch 2002, Walboomers 1999]. High-risk HPV types 16 and 18 account for approximately 65% of cervical cancers, and the E6 and E7 oncoproteins encoded by the HPV genome are thought to drive cervical cancer formation (Piersma 2011).

1.2. Current Standard Therapy

Early stage cervical cancer is treated successfully with surgery, radiation, chemoradiation, or a combination thereof with cure rates of approximately 90% [Monk 2009]. Those patients with persistent or recurrent disease following platinum-containing therapy, as well as those with metastatic disease, have historically had poor outcomes with modest response rates [Long 2005, Long 2007, Monk 2009]. The addition of bevacizumab to first-line chemotherapy doublets (cisplatin + paclitaxel or topotecan + paclitaxel) was investigated in the phase 3 Gynecologic Oncology Group (GOG) 240 study and demonstrated an objective response rate (ORR) of 48%, a median progression-free survival (PFS) of 8.2 months, and a median overall survival (OS) of 16.8 months [Tewari 2017]. Pembrolizumab in combination with chemotherapy, with or without bevacizumab, is approved in the US and the EU for the treatment of cervical cancer whose tumors express PD-L1 (combined positive score [CPS] ≥1). The KEYNOTE-826 study showed significantly longer OS (24 months estimate of patients alive, 53.0% vs 41.7%; HR 0.64) and PFS (median 10.4 vs 8.2 months; HR 0.65) in patients with PD-L1 CPS ≥1 (Colombo 2021).

In the US, full approval was also given for the single-agent use of pembrolizumab in the second-line setting for cervical carcinoma patients whose tumors express PD-L1 (CPS ≥1). The ORR was 14.3% (95% CI, 7.4 to 24.1%) for patients with PD-L1 CPS ≥1 who had received one or more lines of chemotherapy for recurrent or metastatic disease. Median duration of response was not reached (range, ≥4.1 to ≥18.6 months) (Chung 2019). Tisotumab vedotin received accelerated approval in the US in September 2021 for the second-line setting in patients with recurrent or metastatic cervical cancer with disease progression on or after chemotherapy. The ORR was 24% (95% CI 16 to 33%), with 7 (7%) CR and 17 (17%) PR with median follow up of 10 months (Coleman 2021). However, regular eye exams by an ophthalmologist are required as part of the toxicity management.

Although the National Comprehensive Cancer Network (NCCN) guideline lists pembrolizumab (KEYTRUDA®) as the preferred therapy for patients whose tumors express programmed death-ligand 1 (PDL1), pembrolizumab's use is limited to biomarker-positive patients. There remains

an unmet medical need for those with CPS <1, or for patients who have failed ICI either as part of initial treatment or as second-line therapy. Treatment guidelines will be updated to reflect this change in the standard of care for cervical cancer.

1.3. Clinical Experience with Autologous Tumor Infiltrating Lymphocyte Therapy of Cervical Cancer

Adoptive cell transfer of tumor infiltrating lymphocytes (TIL) represents a potentially effective treatment for patients with a variety of solid tumors. The method involves the recovery and *ex vivo* expansion of autologous antitumor lymphocytes that have infiltrated a patient's tumor. The basic concept of using lymphoid cells for the immunotherapy of cancer arose from animal experiments that demonstrated, by histologic analysis, the presence of T-lymphocytes within the microenvironment of most solid tumors and their metastases [Rosenberg 1986, Vose 1985, Yron 1980]. Recent findings have clearly shown a predictive relationship between the frequency and phenotype of TIL in solid tumors (especially $CD8^+$ T cells) and an increased OS and PFS in patients with melanoma [Azimi 2012, Erdag 2012, Haanen 2006, Ladanyi 2007], lung cancer [Horne 2011, Kilic 2011, Liu 2012a, Ruffini 2009], ovarian cancer [Hagemann 2011, Milne 2012, Webb 2014], squamous cell carcinomas (SCCs) [Balermpas 2014, Wang 2014], triple-negative breast cancer, HER2-positive breast cancer [Luen 2017], basal-like breast cancer [Ali 2014, Ibrahim 2014, Liu 2012b, Luen 2017, Mahmoud 2011, Mahmoud 2012a, Mahmoud 2012b, West 2013], and colorectal cancer [Galon 2006, Galon 2014, Pages 2005, Pages 2009]. Notably, one study found that an increased $Foxp3^+$ regulatory T cells (T_{reg})/$CD8^+$ ratio and the presence of intra-tumoral high $Foxp3^+$ T_{reg} predicted worse OS (Shen 2010). In addition, gene expression studies using deoxyribonucleic acid (DNA) microarrays have indirectly correlated so-called "immune signature" genes and T-cell associated gene expression (eg, CD3, CD8, CD4, inducible T-cell costimulator [ICOS], granzyme B, dendritic cell-lysosomal associated membrane glycoprotein [DC-LAMP], chemokines, and chemokine receptors) with improved OS and PFS in both primary and metastatic tumor settings [Bindea 2013, Erdag 2012, Galon 2006, Galon 2014, Mlecnik 2014, Stoll 2014]. These findings support the development of therapies based on the isolation and expansion of autologous TIL cells as a therapeutic agent against solid tumors.

Adoptive cell therapy (ACT) has several theoretical and practical advantages over active immunization and nonspecific immune stimulation. First, the *ex vivo* environment allows expansion to proceed to very high cell numbers in the absence of suppressive factors, such as T_{reg}, that are present in the tumor microenvironment [Cao 2007, Martin-Orozco 2010, Strauss 2007], allowing re-infusion of much higher numbers of tumor-reactive T-cells than is possible with other approaches. Second, the TIL product potentially recognizes a wider array of tumor antigens, such as mutated tumor neoantigens rather than a single target [Kvistborg 2013, Robbins 2013, Tran 2014b, van Rooij 2013]. Preparation of the host patient with lymphodepletion immediately prior to the transfer of the antitumor cells also eliminates potentially suppressive influences (such as regulatory T cells acting as cytokine sinks) to provide an optimal milieu for the transferred TIL to proliferate and become activated in vivo.

The feasibility of TIL preparation was demonstrated by early studies showing that metastatic melanoma tumors can be excised and placed in tissue culture under conditions in which tumor cells do not survive but any TIL contained within the excised tumor tissue can survive and

proliferate. TIL can be cultured in the presence of interleukin-2 (IL-2) and can be grown to very large numbers using standardized protocols (≥ 1 x 10^8 cells) [Besser 2006, Rosenberg 1986, Spiess 1987, Yron 1980]. These TIL were then shown to have the capacity to kill tumor cells *in vitro* and promote durable antitumor effects in vivo when infused back into the original tumor donor [Besser 2006, Rosenberg 1986, Spiess 1987, Yron 1980]. Additional studies have established that the efficacy of infusing large numbers of TIL can be enhanced by pretreatment of tumor-bearing animals with cyclophosphamide to induce a transient drop in host endogenous lymphocytes and followed by IL-2 administration. With this treatment sequence, mice were cured of advanced hepatic metastases (Rosenberg 1986). These findings set the stage for US National Cancer Institute (NCI) clinical studies using TIL therapy for patients with metastatic melanoma that includes a non-myeloablative lymphodepletion (NMA-LD) preparative regimen consisting of fludarabine and cyclophosphamide followed by IL-2 post-TIL infusion. Such studies have consistently demonstrated high ORR, from 49–72%, with long-term durable and potentially curative complete response (CR) rates of up to 25% [Ghosh 1992, Goff 2016, Rosenberg 2011].

Steven Rosenberg's research team at the US NCI National Institutes of Health has published extensively on preclinical and clinical research supporting the development of TIL-based therapies for cancer.

1.3.1. TIL for Cervical Cancer

The rationale for investigating TIL to treat cervical cancer is based on the overall low survival rates for patients with recurrent disease following standard combinations of surgery, adjuvant chemotherapy, and radiation therapy. Furthermore, as described above for other solid tumors, a positive correlation between the presence of TIL in cervical tumor specimens and patient outcome has been reported. For example, Shah et al. [Shah 2011] reported lower 5-year survival rates in subsets of patients whose cervical tumors had lower numbers of tumor-infiltrating $CD4^+$ T-cells, a decreased $CD4^+/CD8^+$ T-cell ratio, or increased percentages of T_{reg}. de Vos van Steenwijk et al. [de Vos van Steenwijk 2013] reported that levels of $CD14^+CD33^-CD163^-$ mature M1 macrophages and the intraepithelial $CD8^+$ T-cell: T_{reg} ratio were independent positive prognostic factors for survival. These findings suggest that the expansion of potentially active TIL outside the tumor environment could yield a potent individualized antitumor therapeutic.

In addition, both cervical tumors and lymph node metastases have been found to harbor immunosuppressive environments. Piersma et al. [Piersma 2007] reported patients with negative lymph nodes had higher $CD8^+$ counts, $CD8^+$:$CD4^+$ ratios, and $CD8^+$:T_{reg} ratios in cervical tumor specimens compared with findings from patients with lymph node metastases. Furthermore, the highest levels of $CD8^+$ cells were in lymph node-negative patients who had circulating HPV-specific T-cells. Heeren et al. [Heeren 2015] reported a higher presence of T_{reg} cells and IL-10 as well as $CD8^+$ cells with increased surface activation markers and lower $CD4^+$ cells in tumor-positive lymph nodes compared with the cellularity of normal lymph nodes in patients with cervical cancer. Hou et al. [Hou 2012] reported higher proportions of negative regulatory Th17 cells and Foxp3-expressing T cells, as well as higher levels of anti-inflammatory cytokines such as IL-6, TGF-β, and IL-10 in cervical tumor specimens versus healthy cervical tissue. In addition, Adurthi et al. [Adurthi 2012] reported that while Th1 and Th2 $CD4^+$ T effector cells were present in the microenvironment of cervical carcinomas and were capable of being activated, they were inhibited by the presence of T_{reg}.

Several early studies demonstrated the feasibility of expanding TIL from cervical tumors [Ghosh 1992, Hilders 1994]. Hilders et al. (Hilders 1994) successfully expanded TIL from a patient with cervical cancer and found that all cells were $CD3^+/CD8^+$, had heterogeneous CD56 expression, and were cytolytic against autologous tumor cells. Thus, characterization of early TIL preparations revealed similar phenotypes as those TIL isolated and expanded from melanoma tumors.

TIL isolated from human cervical tumors and expanded ex vivo had antitumor activity in mice harboring xenografted human cervical tumors (Li 2010). To date, only one published study, by Stevanovic et al. [Stevanovic 2015], has investigated the use of autologous TIL for the treatment of cervical cancer. In that study, nine women with metastatic cervical cancer who had received prior platinum-based chemotherapy were treated with a single infusion of autologous TIL that had been selected for expansion based on HPV-reactivity, rapid growth, T-cell purity, and proportion of $CD8^+$ T-cells. Of the nine patients, three had adenocarcinoma (AC), two had adenosquamous carcinoma (ASC), and four had SCC; six had received prior cisplatin and other agents and three had received cisplatin with concomitant radiation. Patients underwent a lymphodepletion regimen prior to the TIL infusion and received IL-2 after the TIL infusion. The ORR was 33%, comprising two CRs and one partial response (PR). Among those who progressed on study, the time to progression was 1–3 months. The CRs were of durations of 15+ and 22+ months at the time of the analysis. One CR was in a patient with SCC and the other was in a patient with AC. These CRs have persisted for 46 and 54 months, respectively (Stevanovic 2017). The range of TIL infused was 33×10^9 to 152×10^9. A higher percentage of HPV-reactive TIL in the infusion as well as the frequency of HPV-reactive T-cells in peripheral blood 1 month following the infusion was associated with response. Notably, of the two patients with a CR, the infused TIL were predominantly $CD8^+$ cells for one patient and predominantly $CD4^+$ for the other patient. Adverse events (AEs) were primarily related to the lymphodepletion regimen and IL-2 therapy; no acute toxicity was associated with the TIL infusion.

In summary, current methods for the expansion of autologous TIL from excised tumors are well-established and are robust to ensure a high degree of success in consistently generating sufficient numbers of high-quality therapeutic cells, as described above. Furthermore, clinical studies in melanoma have demonstrated that the effects of the TIL persist in patients for weeks to months and even years after infusion, thereby mediating highly durable complete remissions more than other current immunotherapies or standard therapies, as noted above. The large body of data from these studies justifies the development of adoptive TIL therapy as an approved therapeutic in other solid tumors, such as cervical carcinoma.

1.3.1.1. Rationale for Combination of TIL and Pembrolizumab for Treatment of Solid Tumors

Initial functional programmed cell death protein-1 (PD-1)/PD-L1 axis studies suggest roles in inhibiting both initial T-cell migration and activation, as well as in suppressing effector T-cell generation/function and cytokine production and cytotoxicity [Francisco 2009, Hirano 2005]. This dampening effect of T-cell effector function was postulated to prevent excessive damage mediated in an adaptive immune response by controlling inflammation and promoting tissue tolerance [Blank 2004, Keir 2006]. It has recently been demonstrated that reduced cytotoxicity is a key mechanism by which tumor PD-L1 suppresses antitumor recognition, confirming that

tumor PD-L1 is more than simply a marker of a suppressed antitumor immune system [Juneja 2017].

Following PD-1 blockade, TIL from mouse tumors exhibit increased polyfunctionality (ie, characterized by the production of multiple cytokines or cytotoxic molecules) compared with controls [Gubin 2014, Spranger 2013]. In cancer patients, clinical responses to PD-1 immunotherapy positively correlate with tumor PD-L1 expression, along with other predictive biomarkers such as preexisting $CD8^+$ T-cell infiltration, and the mutational/neoantigen makeup of the tumor [Herbst 2014, Tumeh 2014]. This supports the concept that PD-L1 on tumor cells may act as a molecular shield to protect from T-cell lysis (Zou 2016).

In a murine breast cancer model, pretreatment with anti-PD-1 improves reactive T-cell infiltration and activation, possibly allowing enhanced expansion of tumor-specific T cells following their infiltration into tumors [Karyampudi 2014]. These studies demonstrate that using an anti-PD-1 antibody in combination with a multipeptide vaccine (ie, in breast cancer–bearing mice) prolonged the vaccine-induced increase in the number of Tc1 and Tc2 CD8 T cells (ie, with the $CD27^+IL\text{-}7R^{hi}T\text{-}bet^{lo}$ memory precursor phenotype) and the PFS period (Kodumudi 2016).

Continued pembrolizumab treatment following TIL infusion will likely perpetuate this protection from the suppressive tumor microenvironment, allowing for optimal engraftment and potency of the infused TIL (LN-145) cellular product.

1.3.1.2. Rationale for TIL and Pembrolizumab in Cervical Cancer

The rationale for the addition of a TIL in combination with pembrolizumab cohort is to explore safety and efficacy of LN-145 with another immunotherapy agent as a first line of treatment for patients with recurrent, metastatic, or persistent cervical cancer.

Not all patients respond to or experience long-term benefit from the standard chemotherapy regimen currently used in this setting. Tawari et al. [Tewari 2017], for example, reported a 48% ORR in the front-line metastatic cervical patient population. Therefore, there remains an unmet need in this patient group for novel treatment options, especially treatment incorporating cancer immunotherapy agents that have the potential for long-term benefit and cure.

The LN-145 regimen has demonstrated encouraging efficacy (ORR=44.4%; n=27) and safety in cervical cancer patients who have progressed on or after prior chemotherapy regimens (Jazaeri 2019).

Similarly, pembrolizumab has shown benefit (ORR=11.2%) and has received accelerated approval in the second-line setting in recurrent or metastatic cervical cancer .

The combination of LN-145 with pembrolizumab as explored in this study is expected to have antitumor activity that is at least as good or better than antitumor activity in later lines of treatment and/or the activity of LN-145 or pembrolizumab alone and has the potential to address an unmet medical need.

Furthermore, we anticipate the landscape of care for cervical cancer to change to utilization of checkpoint therapy in earlier lines of care as has been the case in other solid tumor indications. In anticipation of this new emerging landscape, it is important to explore combination therapy in earlier lines of treatment to possibly offer patients deeper and/or more durable response or offer

non-chemotherapeutic options. In addition, the toxicity profile of adding TIL to checkpoint therapy has not shown additive toxicities as noted by Rosenberg (personal communication) and Creelan and colleagues (Creelan 2018).

1.4. LN-145 TIL Therapy Regimen

The LN-145 treatment regimen involves a course of the NMA-LD preparative regimen using cyclophosphamide and fludarabine for one week prior to TIL infusion, and a limited course of IL-2 administration CCI following the TIL infusion. The NMA-LD preparative regimen and IL-2 are included in the regimen to support the engraftment, expansion, and activation of the transferred TIL.

Several preparative regimens have been used in conjunction with TIL therapies. NMA-LD preparative regimens have included cyclophosphamide/fludarabine, total body irradiation, or the combination of the two. CCI [redacted] Each patient will undergo an NMA-LD preparative regimen prior to infusion of LN-145.

1.5. Brief Description of the Product

LN-145 is a ready-to-infuse, autologous TIL therapy based on that developed by Dr. Rosenberg and colleagues at the NCI and further optimized by Iovance.

LN-145 is composed of autologous TIL, which are obtained from an individual patient's tumor and expanded ex vivo through cell culture in the presence of the cytokine IL-2 and muromonab CD3, a murine monoclonal antibody (mAb) to human CD3 (OKT3).

The final drug product is a cryopreserved live-cell suspension that is formulated for intravenous (IV) infusion. The ex vivo expanded autologous TIL are formulated in CCI [redacted]

1.6. Production and Expansion of TIL

The manufacturing process begins at the clinical site with the surgical resection of a tumor lesion containing viable tumor material of ≥ 1.5 cm. An aggregate of multiple separate lesion biopsies may also be resected from the patient and is encouraged if patient safety allows. The tumor specimen is placed in transport media and shipped express at 2–8°C to the Good Manufacturing Practices (GMP) manufacturing facility. CCI [redacted] cells are then harvested, washed, and formulated in a blood transport/infusion bag for shipment by courier to the clinical site.

A diagram of the manufacturing process for LN-145 is provided in Figure 1.

Figure 1 LN-145 Manufacturing Process

Each cryopreservation bag of the LN-145 final product is labeled with a patient-specific label. LN-145 is shipped from the manufacturing facility to clinical sites for administration to patients as described in the Pharmacy & Investigational Product Administration Manual.

1.7. Safety of TIL LN-145 Cellular Therapy

Overall, toxicities and AEs observed during TIL LN-145 cellular therapy have been associated primarily with either the lymphodepletion preparative regimen or the IL-2 administration given after TIL infusion. Few infusion-related AEs have been documented following the TIL infusion itself, with Grade ≥ 3 events rarely observed [Andersen 2016, Besser 2009, Besser 2010, Besser 2013, Dudley 2008, Goff 2016, Pilon-Thomas 2012, Radvanyi 2012, Rosenberg 2011, Sarnaik 2017a, Sarnaik 2017b].

The LN-145 product contains tumor infiltrating lymphocytes (TIL); CCI

Hypersensitivity events, including severe allergic reactions or anaphylaxis, have occurred during infusion with LN-144 (melanoma-specific TIL) and LN-145; this may be anticipated because hypersensitivity reactions have been associated with at least one of the aforementioned formulation components. Patients who have a known history of hypersensitivity to any component or excipient of the TIL treatment regimen and the other study drugs will be excluded from this study. See Section 8.2.1 for more details.

Uveitis has been observed in studies of patients with melanoma who have received treatment with autologous TIL products. Uveitis in patients in Iovance studies was mostly mild to moderate in intensity; associated with symptoms such as blurred vision, eye pain, nyctalopia, photopsia, retinal hemorrhage, and/or vitreous floaters; and often improved with local corticosteroid therapy. If untreated or not appropriately treated, acute inflammation can develop into chronic, sight-threatening inflammation; therefore, those presenting with symptoms must be evaluated by a trained eye specialist and managed according to current treatment guidelines in order to prevent any severe long-term effects. See Section 8.2.2 for more details.

Vitiligo has been observed in studies of patients with melanoma who have received treatment with Iovance's autologous TIL product. All reports of vitiligo in these patients were mild to moderate in intensity. For patients who develop vitiligo, a thorough history should be taken including the site and type of vitiligo (segmental, nonsegmental), disease extent (affected body surface area), disease stability, and speed of onset. Topical corticosteroids (medium or high potency) are recommended for localized vitiligo (<10% of body surface area) and may be used at Investigator discretion. Specialized dermatology consultation is recommended for appropriate management in all cases unless vitiligo is self-limited, localized, and non-progressive.

Details concerning specific risks for patients participating in this clinical study may be found in the accompanying LN-144/LN-145 Investigator's Brochure (IB), informed consent documents, and each of the following currently approved local prescribing information for these components: cyclophosphamide, mesna, fludarabine, and IL-2 (Proleukin®).

1.7.1. Safety of the Combination of TIL Therapy and Checkpoint Inhibitors

Clinical trials combining pembrolizumab with chemotherapy showed no increase in AEs, and pembrolizumab in combination with TIL is also not expected to have a clinically significant impact on patient safety. Lymphodepletion of the patient prior to pembrolizumab dosing would reduce the potential targets of pembrolizumab administration to only the anti-tumor TIL found in the LN-145 product. As for potential impact on IL-2 toxicity, studies conducted at the NCI have not demonstrated increased toxicity due to IL-2 when given in combination with anti-PD-1 treatment [Brayer 2014, Siebert 2017] or concurrently with pembrolizumab .

As pembrolizumab is a monoclonal antibody (mAb), it is expected to be metabolized into peptides and amino acids via catabolic pathways (Longoria 2016); whereas TIL are thought to be eliminated through apoptosis and programmed cell death as seen with lymphocytes (Gupta 2005). The individual and unique mechanisms of clearance for TIL therapy (TIL LN-145) and pembrolizumab indicate that the chance for increased safety risk is low with the combination of TIL therapy (LN-145) and pembrolizumab due to minimum overlapping mechanisms of clearance.

1.8. Pembrolizumab Background

The nonclinical and clinical experience with pembrolizumab is fully described in the current approved local prescribing information.

Pembrolizumab is a human mAb of the immunoglobulin G (IgG) 4 kappa subclass that inhibits binding of PD-L1 and has been developed by Merck for use in the treatment of various cancers (Scapin 2015). As pembrolizumab is an engineered mAb, it does not induce antibody-dependent cellular cytotoxicity or complement-dependent cytotoxicity.

Pembrolizumab has been marketed as KEYTRUDA in the US since September 2014 and in Europe since July 2015 and has been used to treat a large number of patients.

1.8.1. Rationale for Pembrolizumab Fixed Dosing

A fixed dosing approach is currently the recommended dosing schedule for these indications per the FDA label and is preferred by the prescribing community due to ease of use and reduced dosing errors. As such, a fixed dose of IV pembrolizumab at either 200 mg Q3W or 400 mg Q6W (± 3 days) is included in the current study.

1.8.2. Potential Risks of Pembrolizumab Administration

1.8.2.1. General Risks

Monoclonal antibodies directed against immune checkpoint proteins, such as PD-1 and those directed against PD-L1 or CTLA-4, aim to boost endogenous immune responses directed against tumor cells by stimulating the immune system; however, there is the potential for adverse effects on other tissues.

Most adverse drug reactions reported with immune checkpoint inhibitors are thought to be due to the effects of inflammatory cells on specific tissues. These immune-mediated risks are generally events with a potential inflammatory mechanism that may require more frequent monitoring and/or unique interventions such as immunosuppressants (eg, corticosteroids) and/or endocrine replacement therapy. These risks include gastrointestinal AEs, such as colitis and diarrhea; pneumonitis/interstitial lung disease (ILD); renal AEs, such as nephritis and increases in creatinine; hepatic AEs, such as hepatitis and liver enzyme elevations; skin events, such as rash and dermatitis; myocarditis; endocrinopathies, such as hypo- and hyperthyroidism, hypophysitis, adrenal insufficiency, diabetes mellitus type I, and diabetes insipidus; and neurotoxicities, such as myasthenia gravis and Guillain-Barre syndrome (Haanen 2017).

1.8.2.2. Specific Risks

Pembrolizumab administration increases the risk of the following immune-mediated adverse drug reactions: pneumonitis, colitis, hepatitis, endocrinopathies, nephritis, and renal dysfunction. Pembrolizumab administration also increases the risk of immune-mediated skin adverse reactions, infusion-related reactions, and other immune-mediated adverse reactions. Information on these risks can be found in the current approved local prescribing information.

Monotherapy clinical studies included AEs such as fatigue, musculoskeletal pain, decreased appetite, pruritus, diarrhea, nausea, rash, pyrexia, cough, dyspnea, constipation, pain, abdominal pain, and hypothyroidism.

The majority of treatment-related AEs were manageable with dose delays, symptomatic treatment, and in the case of events suspected to have an immune basis, the use of established treatment guidelines for immune-mediated toxicity.

A detailed summary of pembrolizumab monotherapy and combination-therapy AE data can be found in the current approved local prescribing information.

1.9. Benefit-Risk Assessment of LN-145

Cervical cancer is a leading cause of cancer-related death in women. As noted, in the US in 2017, approximately 12,800 new cases of invasive cervical cancer were expected to be diagnosed and about 4210 women were expected to die from this disease (American Cancer Society 2017). As noted, in the EU, an estimated 58,345 new cases were diagnosed and 24,397 deaths from invasive cervical cancer occurred in 2012 (International Agency for Research on Cancer and World Health Organization 2012).

LN-145 is an experimental treatment that may provide clinical benefit to patients with treatment-refractory unresectable or metastatic cervical cancer—although only limited clinical data are available today in this patient population. In even heavily-pretreated patients, cell transfer therapy with autologous TIL appears able to mediate durable responses, and in some cases, CRs in patients with advanced solid tumors [Goff 2016, Rosenberg 2011, Tran 2014a]. As noted, in a study of TIL therapy in nine patients with advanced cervical cancer, the ORR per Response Evaluation Criteria in Solid Tumors (RECIST) v1.1 was 33%, comprising two CRs and one PR. The CRs were of 46+ and 54+ months duration at the most recent analysis [Stevanovic 2015, Stevanovic 2017]. More recently, the LN-145 regimen has demonstrated encouraging efficacy (ORR=44.4%; n=27) and safety in cervical cancer patients who have progressed on or after prior chemotherapy regimens (Jazaeri 2019).

The risks associated with TIL therapy include: a delay in treatment due to the need to harvest and grow the cells; a surgical procedure (possibly major) to obtain tumor for the cell product; the possibility that a cell product cannot be generated; and the toxicities known to be associated with the NMA-LD preparative regimen and IL-2 administration. However, current methods for the expansion of autologous TIL from excised tumors are shorter than previously used for TIL. These methods are well established with over 90% success rates for manufacturing and are sufficiently robust to ensure a high degree of success in consistently generating adequate numbers of high-quality therapeutic cells from resected melanoma lesions.

Hypersensitivity events, including severe allergic reactions or anaphylaxis, have occurred during infusion with LN-144 (melanoma-specific TIL) and LN-145; this may be anticipated because hypersensitivity has been associated with at least one of the above-mentioned formulation components. Patients who have a known history of hypersensitivity to any component or excipient of the TIL regimen therapy and the other study drugs are excluded from this study. Premedication and supportive therapy instructions are provided in Section 6.1.2.6. Uveitis and vitiligo have been observed in studies of patients with melanoma who received TIL, likely due to TIL activity in the normal melanocytes of these patients. All reports of vitiligo and most reports of uveitis in these patients were mild to moderate in intensity, and uveitis often improved with local corticosteroid therapy.

Pembrolizumab has demonstrated benefit in cervical cancer patients as a single agent and has a well-characterized safety profile enabling appropriate guidance for monitoring and management of pembrolizumab toxicity. The addition of pembrolizumab to TIL is not expected to lead to a safety profile with relevant differences from the safety profiles of the individual treatments.

Overall, the risk-benefit balance for Study C-145-04 should be viewed as favorable considering the following:

- Substantial clinical experience with TIL in the treatment of advanced melanoma and other solid tumors has demonstrated the capacity to induce clinically meaningful responses in patients with progressive disease (PD) following PD-1 blocking antibodies who had also received targeted therapy, if indicated.
- First reports on TIL therapy for patients with cervical cancer demonstrate encouraging activity.
- The combination of LN-145 with pembrolizumab is expected to have antitumor activity that is at least as good or better than antitumor activity in later lines of treatment and/or the activity of LN-145 or pembrolizumab alone is expected to have an acceptable safety profile. Thus, this arm has a benefit/risk profile appropriate for an exploratory cohort.
- Furthermore, the landscape of care for cervical cancer is anticipated to change to utilization of checkpoint therapy in earlier lines of care as has been the case in other solid tumor indications. It is important to explore combination therapy in earlier lines of treatment to possibly offer patients deeper and/or more durable response or offer non-chemotherapeutic options.
- The toxicity profile of adding TIL to checkpoint therapy has not shown additive toxicities.
- Safety monitoring is incorporated into this C-145-04 study protocol.

In summary, ACT with TIL represents a one-time treatment, with the possibility of offering a durable treatment option for patients with cancer, especially those with advanced metastatic disease who have limited to no treatment options after the failure of available conventional therapies (eg, immune checkpoint inhibitors or targeted therapies).

2. STUDY DESIGN

2.1. Description of the Study

This is a Phase 2, prospective, multicenter, multicohort, open-label interventional study evaluating patients with recurrent, metastatic, or persistent cervical carcinoma who receive ACT with LN-145 (autologous TIL) with or without pembrolizumab. Protocols for the tumor resection and LN-145 administration for the current study are provided in separate operating manuals. All patients will receive an NMA-LD preparative regimen, then a single infusion of LN-145, followed by the administration of a regimen of IL-2. A study flow chart is shown in Figure 2.

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 systemic therapy; this cohort is no longer open for enrollment.

Cohort 2: LN-145 monotherapy in patients who have previously received a PD-1/PD-L1 checkpoint inhibitor either as monotherapy or combination therapy.

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; this cohort is not open for enrollment.

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

Patients treated in the re-treatment cohort may have a second tumor resection if needed, especially when new lesions are available and feasible for resection. The decision for enrollment into Cohort 5 will be based on a discussion between the Investigator and the Medical Monitor. Patients in Cohort 5 must previously have received treatment only in Cohort 1 or 2.

The study consists of the following periods:

- **Screening:** Up to CCI prior to tumor resection
- **Enrollment:** Upon tumor resection for TIL generation
- **Treatment Period:**

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

  Cohort 3 - The treatment period for Cohort 3 is up to CCI, including NMA-LD (CCI), LN-145 infusion CCI followed by 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 Q3W or 400 mg 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. The EOT visit may be combined with any scheduled visit occurring within this interval during the assessment period.

- **Assessment Period:** Efficacy (eg, 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 for up to 5 years from CCI LN-145 infusion) or until:
  - Disease progression
  - 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 (eg, 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. Patients who had tumor resection but did not receive LN-145 for any reason will perform an EOA visit and transition directly into the OS Follow-up Period

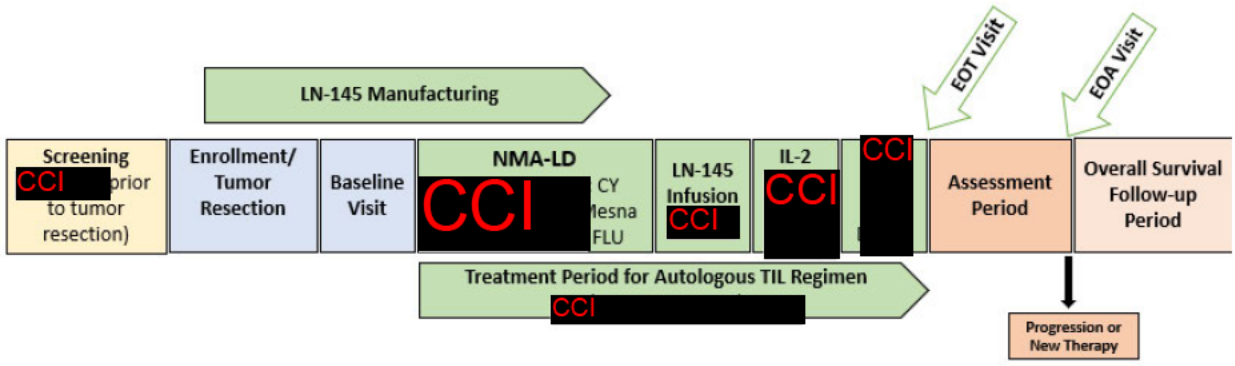
Patients may be hospitalized prior to the planned LN-145 infusion for hydration. Patients will remain hospitalized until completion of the IL-2 administration, or as per institutional standards.

Patients may also require hospitalization for tumor resection, NMA-LD preparative regimen, and treatment recovery, as per institutional guidelines.

All visits following LN-145 infusion, except OS Follow-up, are calculated from LN-145 infusion CCI .

Response assessments will be conducted by the Investigator following both RECIST v1.1 and immune-related RECIST (irRECIST).

Figure 2 Study Flow Chart for TIL Regimen



Abbreviations: CY=cyclophosphamide; EOA=End-of-Assessment; EOT=End-of-Treatment; FLU=fludarabine; IL=interleukin; NMA-LD=non-myeloablative lymphodepletion

NOTE: For Cohort 3 only, pembrolizumab is administered post-resection/pre-NMA-LD and then either Q3W or Q6W post-IL-2 for ≤ 2 years (24 months) from the first dose, or until disease progression or unacceptable toxicity, whichever occurs first.

3. STUDY OBJECTIVES AND ENDPOINTS

3.1. Study Objectives

3.1.1. Cohorts 1 and 2 – LN-145 monotherapy

3.1.1.1. Primary Objective

- 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

3.1.1.2. Secondary Objectives

- 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

3.1.1.3. Exploratory Objectives

- 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)

3.1.2. Cohort 3 – LN-145 in combination with pembrolizumab (US only) who have not received any therapies other than prior chemoradiation or surgery for loco-regional disease

3.1.2.1. Primary Objective

- To characterize the safety profile of LN-145 in combination with pembrolizumab in patients with recurrent, metastatic, or persistent cervical carcinoma

3.1.2.2. Secondary Objectives

- 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

3.1.2.3. Exploratory Objectives

- To explore the persistence of LN-145 and immune correlates of response, survival, toxicity of treatment, and HPV status
- To explore efficacy based on irRECIST criteria, as assessed by the Investigator
- To assess HRQoL
- To assess quality-adjusted time without symptoms of disease or toxicity of treatment (Q-TwiST)

3.1.3. Cohort 4 – LN-145 previously enrolled patients

3.1.3.1. Primary Objectives

- To explore the efficacy and safety profile of previously enrolled patients with recurrent, metastatic, or persistent cervical carcinoma treated with LN-145

3.1.4. Cohort 5– LN-145 re-treated patients

3.1.4.1. Primary Objectives

- To explore the efficacy and safety profile of re-treated patients with recurrent, metastatic, or persistent cervical carcinoma treated with LN-145

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)
- **Cohorts 4 and 5**: Because of the small sample size, results will be reported as appropriate by descriptive statistics.

3.2.2. Secondary Endpoints

3.2.2.1. Cohorts 1 and 2

- 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 treatment-emergent adverse events (TEAEs), including serious AEs (SAEs), therapy-related AEs, and AEs leading to early discontinuation from treatment or withdrawal from the Assessment Period or death

3.2.2.2. Cohort 3

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

3.2.2.3. Cohorts 4 and 5

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

3.2.3. Exploratory Endpoints

3.2.3.1. Cohorts 1, 2, and 3

- Immune correlates of response, survival, toxicity of treatment, HPV status, and TIL persistence in the peripheral blood 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 (Sherrill 2013) using Investigators' assessments of disease symptoms and reported safety events prior to the next systemic anticancer therapy

3.2.3.2. Cohorts 4 and 5

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

4. SELECTION OF PATIENT POPULATION

4.1. Inclusion Criteria

To be eligible for the study, patients must meet ALL of the following criteria prior to participation:

1. Must be ≥ 18 years of age at the time of consent

   Enrollment of patients > 70 years of age may be allowed after consultation with the Medical Monitor

2. Patients must have the ability to understand the requirements of the study, have provided written informed consent as evidenced by signature on an informed consent form (ICF) approved by an Institutional Review Board/Independent Ethics Committee (IRB/IEC), and agree to abide by the study restrictions and return to the site for the required assessments, including the OS Follow-up Period
3. Must be able and willing to comply to the study visit schedule and protocol requirements
4. Must have recurrent, metastatic, or persistent squamous cell carcinoma (SCC), adenosquamous carcinoma (ASC), or adenocarcinoma (AC) of the cervix that is not amenable to curative treatment with surgery and/or radiation therapy and, in Germany and Switzerland only, for which no other therapies are expected to have significant benefit, in the opinion of the Investigator
5. At least one resectable lesion (or aggregate of lesions resected) of a minimum 1.5 cm in diameter post-resection to generate TIL; surgical removal with minimal morbidity (defined as any procedure for which expected hospitalization is ≤ 3 days)
6. At least one measurable target lesion, as defined by RECIST v1.1
   - Lesions in previously irradiated areas (or other local therapy) should not be selected as target lesions, unless treatment was ≥ 3 months prior to Enrollment, and there has been demonstrated disease progression in that particular lesion
   - If a lesion is partially resected to generate TIL, and remains visible on the Baseline scan after surgery, then the partially resected lesion can be used for RECIST v1.1 response assessment, but only as a non-target lesion
7. **Cohort 1 and Cohort 2:** Progression during or following at least one, but no more than three prior systemic chemotherapeutic treatments for recurrent, metastatic, or persistent cervical carcinoma
   - A line of systemic therapy is defined as any chemotherapy or multiple-agent chemotherapy regimen that was administered for recurrent, metastatic, or persistent SCC, ASC, or AC of the cervix
   - A bevacizumab and chemotherapy combination is encouraged as a prior line of treatment
   - Neither chemoradiation, nor chemotherapy in the neoadjuvant or adjuvant settings are considered as a prior line of systemic therapy

Cohort 2: Must also have previously received treatment with a checkpoint inhibitor (ie, PD-1, PD-L1) in the setting of recurrent, metastatic, or persistent disease either as monotherapy or in combination (eg, in combination with chemotherapy or another immune agent).

Cohort 3 (United States only) Must have not received any therapies other than prior chemoradiation or surgery for loco-regional disease.

8. Any prior therapy directed at the malignant tumor, including chemotherapy, biologic/targeted agents, and immunologic agents must be discontinued at least 28 days prior to tumor resection. Radiation therapy is permitted as long as the lesions irradiated are not expected to be used for TIL generation or as target lesions and any toxicities have resolved to Grade ≤ 1 at least 2 weeks prior to NMA-LD.
9. Have an Eastern Cooperative Oncology Group (ECOG) performance status of 0 or 1
10. Must meet the following laboratory criteria:
    - Absolute neutrophil count (ANC) ≥ 1000/mm^3
    - Hemoglobin ≥ 8 g/dL or ≥ 4.96 mmol/L
    - Platelet count ≥ 100,000/mm^3
    - Serum alanine transaminase (ALT)/serum glutamic-pyruvic transaminase (SGPT) and aspartate transaminase (AST)/serum glutamic-oxaloacetic transaminase (SGOT) < 3.0 times the upper limit of normal (ULN)
        - Patients with liver metastasis must have liver function tests (LFTs) < 5.0 times the ULN
    - Total bilirubin ≤ 2.0 mg/dL
        - Patients with Gilbert's syndrome must have a total bilirubin ≤ 3.0 mg/dL
    - Serum creatinine must be ≤ 1.5 mg/dL
    - Measured creatinine clearance (CrCl) ≥ 40 mL/min calculated from a 24-hour urine collection
11. Patient has no evidence of any active viral, bacterial, or fungal infection requiring ongoing systemic treatment. Patients must be seronegative for the human immunodeficiency virus (HIV). Patients with acute or chronic hepatitis infections may be enrolled if the viral load by nucleic acid amplification test (NAAT) is undetectable with/without active treatment.
12. Patients of childbearing potential must be willing to take the appropriate precaution to avoid pregnancy for the duration of the study and practice an approved, highly effective method of birth control during treatment and for 12 months after receiving the last protocol-related therapy. Approved methods of birth control are as follows:
    - Combined (estrogen and progesterone containing) hormonal birth control associated with inhibition of ovulation: oral, intravaginal, transdermal

- Progesterone-only hormonal birth control associated with inhibition of ovulation: oral, injectable, implantable
- Intrauterine device (IUD)
- Intrauterine hormone-releasing system (IUS)
- Bilateral tubal occlusion
- Vasectomized partner
- True sexual abstinence when this is in line with the preferred and usual lifestyle of the patient. Periodic abstinence (eg, calendar ovulation, symptothermal, post-ovulation methods) is not acceptable

13. Prior to study Enrollment (tumor resection), patient must have documentation of radiological disease progression after the most recent therapy
14. Patients have provided written authorization for use and disclosure of protected health information

4.2. Exclusion Criteria

Patients who meet *any* of the following criteria are not eligible for participation in this study:

1. Patients who have received an organ allograft or prior cell transfer therapy except for prior LN-145 therapy in the setting of re-treatment only
2. Patients who require systemic steroid therapy (> 10 mg/day of prednisone or other steroid equivalent dose).

   Patients receiving steroids as replacement therapy for adrenocortical insufficiency at ≤ 10 mg/day of prednisone or another steroid equivalent dose may be eligible.
3. Patients who currently have prior therapy-related toxicities Grade > 1 according to National Cancer Institute (NCI) Common Terminology Criteria for Adverse Events (CTCAE) v5.0 (eg, uveitis); except for peripheral neuropathy, alopecia, or vitiligo prior to Enrollment (tumor resection)Patients with a history of uveitis must have an eye examination performed at Screening to rule out active uveitis that requires treatment. Patient who has active uveitis that requires active treatment will be excluded.

   - If toxicities have resolved to Grade ≤ 1, a minimum of 2 weeks must elapse prior to Enrollment (tumor resection)
   - Patients may not have any pre-planned procedures within 2 weeks prior to the start of the NMA-LD preparative regimen

   Cohort 2: Patients with documented Grade ≥ 2 diarrhea or colitis as a result of previous treatment with a PD-1/PD-L1 checkpoint inhibitor(s) must have been asymptomatic for at least 6 months or had a normal colonoscopy post- checkpoint inhibitor treatment, by visual assessment, prior to tumor resection.

   Cohort 2: Patients with immunotherapy-related endocrinopathies stable for at least 6 weeks (eg, hypothyroidism, stable on hormonal substitution) and controlled with hormonal replacement, are allowed.

4. No longer applicable
5. Patients who have a history of hypersensitivity to any component or excipient of LN-145 or other study drugs:
    - NMA-LD preparative regimen (cyclophosphamide, mesna, and fludarabine)
    - Antibiotics (ABX) of the aminoglycoside group (ie, streptomycin, gentamicin); except those who are skin-test negative for gentamicin hypersensitivity
    - Any component of the LN-145 infusion product formulation including DMSO, HSA, IL-2, and dextran-40
6. Patients who have active systemic infections, coagulation disorders, or other active major medical illness(es) of the cardiovascular, respiratory, or immune system, including evidence in the medical history of urinary tract obstruction, a positive cardiac stress test, myocardial infarction, cardiac arrhythmia, obstructive or restrictive pulmonary disease, or other conditions that in the opinion of the Investigator would increase the risk of participation
    - Patients with corrected (ie, percutaneous nephrostomy tubes) urinary tract obstruction must have negative surveillance cultures from externalized tubes within 7 days prior to the start of the NMA-LD preparative regimen. Asymptomatic patients with chronic colonization of indwelling urinary diversion tubes may be eligible after active urinary infection is ruled out and discussion with the Medical Monitor.
    - Patients with evidence of any uncontrolled or active systemic infection requiring ongoing treatment cannot proceed to NMA-LD.
7. Patients with symptomatic and/or untreated brain metastases (of any size and any number)
    - Patients with definitively treated brain metastases may be considered for Enrollment, and must be stable for ≥ 14 days prior to beginning the NMA-LD preparative regimen
8. Patients who have any form of primary immunodeficiency (such as severe combined immunodeficiency [SCID] or acquired immunodeficiency syndrome [AIDS])
9. Patients who have a diagnosis of end-stage renal disorder requiring hemodialysis
10. Patients who have a left ventricular ejection fraction (LVEF) < 45% or who are New York Heart Association (NYHA) Class 2 or higher. Patients ≥ 60 years of age or who have a history of ischemic heart disease, chest pain, or clinically significant atrial and/or ventricular arrhythmias must have a cardiac stress test (or equivalent local standard stress test):
    - Patients with an abnormal cardiac stress test may be enrolled if they have adequate ejection fraction (≥ 45%) and cardiology clearance after consultation with the Medical Monitor
    - Patients with any irreversible wall movement abnormalities are excluded
11. Patients who have a documented forced expiratory volume in 1 second (FEV1) of ≤ 60%

12. Patients who have had another primary malignancy within the previous 3 years (except for curatively treated localized malignancy that has not required treatment for > 1 year, and in the judgment of the Investigator, does not pose a significant risk of recurrence including, but not limited to, non-melanoma skin cancer or bladder cancer)
13. Patients who are of the following protected classes will be excluded, including:
    - Pregnant, parturient, or breastfeeding women
    - Persons who are hospitalized without consent or those deprived of liberty because of a judiciary or administrative decision
    - Patients with a legal protection measure or a person who cannot express his/her consent
    - Patients in emergency situations who cannot consent to the study
14. Patients who have received a live or attenuated vaccine within 28 days prior to beginning the NMA-LD preparative regimen
15. Patients whose cancer requires immediate attention or who would otherwise suffer a disadvantage by participating in this study
16. **Cohort 1 and Cohort 3**: Patients who have received prior treatment with immunotherapy (eg, anti-PD-1, anti-PD-L1, or anti-cytotoxic T lymphocyte-associated antigen-4 [CTLA-4] antibodies)
17. Patients who have Grade ≥ 2 hemorrhage within 14 days prior to Enrollment (tumor resection)
18. **Cohort 3**: Patients may not have active or prior documented autoimmune or inflammatory disorders (including pneumonitis, inflammatory bowel disease [eg, colitis or Crohn's disease], diverticulitis [with the exception of diverticulosis], systemic lupus erythematosus, sarcoidosis syndrome, or Wegener syndrome [granulomatosis with polyangiitis, Grave's disease, rheumatoid arthritis, hypophysitis, uveitis, etc.]). The following are exceptions to this criterion:
    - Patients with vitiligo or alopecia
    - Patients with hypothyroidism (eg, following Hashimoto syndrome) stable on hormone replacement
    - Any chronic skin condition that does not require systemic therapy
    - Patients with celiac disease controlled by diet alone

4.3. Definition of Screening and Patient Enrollment

Screening assessments must be performed within CCI prior to the tumor harvest unless otherwise indicated in Section 5. Patients will then be approved to proceed to Enrollment in the study.

- Enrollment will occur upon tumor resection.

- If a patient does not meet the eligibility criteria, then they will be defined as a screen failure
- Patients who meet inclusion criteria and do not receive LN-145 (eg, due to a manufacturing failure) may be re-screened after consultation with the Medical Monitor

4.3.1. Screen Failure

Patients who do not meet eligibility criteria will need to have the reason for the screen failure documented. Any SAEs occurring in such patients after signing the ICF until study discontinuation (the day of screen failure) will also be documented/reported in the Electronic Data Capture (EDC) system. Patients who do not meet the criteria for participation in this study (screen failure) may be rescreened. Rescreened patients will be assigned a new patient identification number for every screening/rescreening event.

4.3.2. Rescreening for Re-treatment Cohort (Cohort 5)

Patients treated in Cohort 5 may receive a second administration of LN-145. Patients who in the opinion of the Investigator and the Medical Monitor will benefit from a second LN-145 treatment regimen must be rescreened and meet the eligibility criteria as described in Sections 4.1 and 4.2. Patients in Cohort 5 must have previously received treatment in only Cohorts 1 or 2.

5. STUDY ASSESSMENTS/PROCEDURES

5.1. Informed Consent

An ICF must be signed before any study-related assessments are performed (and prior to re-treatment, if applicable).

The ICF will be signed at Screening CCI

5.2. Inclusion/Exclusion Criteria

Patients must meet all inclusion criteria (Section 4.1) and must not have any of the conditions specified in the exclusion criteria (Section 4.2). Patients must continue to meet eligibility criteria until start of NMA-LD preparative regimen CCI).

Inclusion/exclusion criteria will be reviewed at Screening CCI Eligibility criteria will be reconfirmed at, or prior to, CCI prior to the start of the NMA-LD preparative regimen.

5.3. Demographic Data

The demographic data will include year of birth, age, sex, and race/ethnic origin.

Demographic data will be obtained at Screening CCI).

5.4. Medical History

Relevant and significant medical/surgical history, including tumor PD-L1 expression status as determined by a validated test using CPS (http://www.fda.gov/CompanionDiagnostics or consult with the Sponsor) prior to any previous checkpoint inhibitor treatment as applicable, and concurrent illnesses will be collected for all patients at Screening CCI and updated as applicable. Any pre-existing condition that worsens after signing of ICF must be reported as an AE.

Medical history will be collected at Screening CCI

For Cohort 2, all patients must provide one of the following;

- Results of PD-L1 expression: CPS as determined by a validated test (http://www.fda.gov/CompanionDiagnostics or consult with the Sponsor)
- An archival tumor sample available: formalin-fixed, paraffin-embedded (FFPE) block or slides to be used for future central PD-L1 testing
- New tumor tissues taken at the time of tumor resection and processed for future central PD-L1 testing

If PD-L1 results determined by a validated test are not available, an archival tumor sample (an FFPE block under 5 years old or 3 to 5 slides less than 5 months from the time of sectioning if stored at 2-8ºC or less than 1 month if stored at 25ºC) must be sent to a designated central laboratory. If neither local PD-L1 results nor archival tumor samples are available, study sites should agree to provide new tumor tissues taken at the time of tumor resection and processed to an FFPE block for central PD-L1 testing (Refer to Section 5.26 and the Laboratory Manual for details on utilization, processing, and shipping of excess tumor tissue).

5.5. Documentation of Confirmation of Diagnosis

Patients must have documented diagnosis of recurrent, metastatic, or persistent cervical carcinoma via a pathology report.

Diagnosis confirmation will be documented at Screening CCI

Prior to study Enrollment (tumor resection; CCI patient must have documentation of radiological disease progression after the most recent therapy.

5.6. Tumor HPV Status and HPV Serotype

Patients must have documented HPV status and serotyping (HPV16/18) of cervical carcinoma. If documentation is not available, testing for HPV status and serotype should be performed locally using excess tissue obtained during tumor resection (after completion of preparation of tumor tissue for LN-145 manufacturing) or archival tumor tissue. If local testing is not possible, tumor tissue should be sent to the Central Laboratory for HPV testing. Refer to Section 5.25.1 and the Laboratory Manual for details on utilization, processing, and shipping of excess tumor tissue.

5.7. HRQoL Questionnaire – EORTC QLQ-30 Version 3.0

HRQoL questionnaire is to be performed as the first procedure at Baseline (CCI

HRQoL questionnaire will be performed at CCI

5.8. Physical Examination

Physical examinations (PE) will be conducted for all visits except for Enrollment (tumor resection; CCI and shall include gastrointestinal (abdomen, liver), cardiovascular, extremities, head, eyes, ears, nose, throat, respiratory system, skin, and psychiatric (mental status). PE will be symptom directed at all visits.

Clinically relevant changes will be recorded on the electronic case report form (eCRF) AE page.

5.9. Vital Signs

Vital signs shall include height, weight, heart rate, respirations, blood pressure, and temperature. Height will be measured at Screening CCI only. All other vital signs will be measured at every visit up to Month 60 CCI

Body surface area (BSA) and body mass index (BMI) will be calculated at CCI only, as described in Appendix 17.6.

On CCI LN-145 infusion), vital signs will be monitored every 30 minutes (± 5 minutes) during infusion, then hourly (± 15 minutes) for 4 hours, and then routinely (every 4–6 hours), unless otherwise clinically indicated, for up to approximately CCI post-LN-145 infusion.

Pulse oximetry should be monitored as per institutional standards to direct supportive care and monitoring of AEs.

5.10. Skin Test for Hypersensitivity

Patients with a history of hypersensitivity to any drugs of the aminoglycoside group (eg, streptomycin, gentamicin) are excluded (Section 4.2). These patients may be eligible if current hypersensitivity has been excluded.

5.11. Eastern Cooperative Oncology Group Performance Status

An ECOG performance status evaluation will be performed at Screening CCI Visits CCI , and at the EOA visit.

5.12. Safety Blood and Urine Tests

Safety blood and urine tests will be collected and analyzed locally.

Safety labs collected for the tumor resection CCI may be collected up to 24 hours prior to tumor resection.

- Chemistry – sodium, potassium, chloride, total carbon dioxide (CO_2) or bicarbonate, serum creatinine, glucose, blood urea nitrogen (BUN), albumin, calcium total, magnesium total, phosphorus, alkaline phosphatase, ALT/SGPT, AST/SGOT, total bilirubin, direct bilirubin, lactate dehydrogenase (LDH), total protein, total creatine kinase (CK), uric acid
  - Chemistry will be collected at Screening CCI), Visits CCI EOA visit, and as clinically indicated
- Hematology – complete blood count (CBC) with differentials, when available.
  - White blood cell (WBC) count with differentials (neutrophils, lymphocytes, monocytes, eosinophils, and basophils), red blood cell (RBC) count, Hb, hematocrit (Hct), mean corpuscular volume (MCV), platelet count
  - Hematology will be collected at Screening (CCI Visits CCI , EOA visit, and as clinically indicated
- Coagulation – International Normalized Ratio (INR) or prothrombin time (PTT) and activated partial thromboplastin time (aPTT)
  - Coagulation will be collected at Screening (CCI and CCI prior to tumor resection, and as clinically indicated
- Thyroid panel – thyroid stimulating hormone (TSH) and free T4
  - Thyroid panel will be collected at Screening (CCI , at the EOA visit, and as clinically indicated
- Urinalysis dipstick – A complete urinalysis with microscopy and/or urine culture shall be done as clinically indicated
  - Urinalysis dipstick will be collected at Screening (CCI and as clinically indicated

5.13. β-HCG Serum Pregnancy Test

Serum pregnancy test is required for all women of child-bearing potential. Occasionally, a positive serum beta-human chorionic gonadotropin (β-HCG) may be encountered even in a patient who is rendered sterile by prior cancer therapy. In such circumstances, additional tests will be conducted to ensure that the patient is not pregnant (eg, to prove menopause via follicle-stimulating hormone [FSH] and/or estradiol levels).

For all women of childbearing potential, β-HCG serum pregnancy tests will be conducted at CCI

5.14. Infection Testing

Blood samples will be collected for the following infection testing at Screening (Visit 1):

- HIV-1 and HIV-2 antibody titer, as per local standard
- Hepatitis serology (HBsAg, anti-HBc, and HCV Ab). If any hepatitis serology is consistent with active or chronic infection, a corresponding NAAT assay is required. Patients with acute or chronic hepatitis infections may be enrolled if the viral load by NAAT is undetectable with/without active treatment.
- Syphilis assay as per local standard (eg, rapid plasma reagin [RPR] or venereal disease research laboratory [VDRL] test)

Repeat serology testing only for tumor samples acquired in Europe are to be done on the day of the tumor resection CCI or within CCI after the resection. Patients with evidence of any uncontrolled or active systemic infection requiring ongoing treatment cannot proceed to NMA-LD. Prophylactic anti-infection therapy is acceptable; refer to Section 7.1.

5.15. Human Leukocyte Antigen Typing

Sample collection for human leukocyte antigen (HLA) typing will be conducted at Screening (Visit 1) and analyzed by the Central Laboratory.

5.16. Measured Creatinine Clearance

The measured CrCl (creatinine clearance) must be calculated from a 24-hour urine collection (time, volume, and creatinine concentration) and plasma creatinine and corrected for BSA at Screening CCI at Baseline (CCI). If more than 14 days pass from the last measured CrCl to the start of the NMA-LD preparative regimen CCI the measured CrCl must be repeated prior to the start of NMA-LD preparative regimen.

5.17. Eye Examination

For patients with a history of uveitis, a slit lamp eye examination by a trained eye specialist is required within CCI of Screening CCI to rule out uveitis. Eye examination performed within CCI prior to signing the ICF is allowed.

5.18. Cardiac Evaluations

All cardiac evaluations (NYHA, echocardiogram [ECHO], cardiac stress test) will be performed during Screening CCI

5.18.1. New York Heart Association

The NYHA classification must be determined during Screening CCI

5.18.2. Echocardiogram

An ECHO must be performed to assess left ventricular function during Screening CCI

- For patients ≥ 60 years of age and for any patient with a history of ischemic heart disease, chest pain, or clinically significant atrial and/or ventricular arrhythmias, a cardiac stress test (or equivalent local standard stress test) must be performed showing no irreversible wall movement abnormalities.
- Patients with an abnormal cardiac stress test and adequate ejection fraction (≥ 45%) may be enrolled with clearance with a cardiologist after discussion with the Medical Monitor.

5.19. Electrocardiogram

Electrocardiogram (ECG) will be performed at Screening CCI as clinically indicated. If an ECG was performed within CCI prior to signing the ICF, and considered normal, it does not have to be repeated.

5.20. Pulmonary Function Tests

Spirometry will be completed during Screening CCI Evaluations completed within CCI prior to Screening CCI will be accepted, except for evaluations of patients with known pulmonary metastases or clinically significant pulmonary disease.

5.21. Immune Monitoring

Peripheral blood will be collected for immune monitoring (biomarker analysis) to test cellular and soluble factors.

Immune monitoring samples will be collected at CCI

5.22. Radiographic Assessments

Computed tomography (CT) of chest, abdomen, pelvis, and additional anatomic regions (eg, extremities, neck) per disease history and clinical symptoms are required for all patients:

- High-resolution CT with PO/IV contrast or contrast-enhanced MRI is the preferred imaging modality for assessing radiographic tumor response. If a patient has a known allergy to CT contrast material, please use the alternate modality. In cases where contrast is strictly contraindicated, a non-contrast scan is acceptable.

- Previous CT/MRI/PET scans performed within CCI prior to signing the ICF can be used for Screening CCI

Additional radiological assessments may be performed per Investigator's discretion. All imaging, including scheduled and unscheduled scans, must be assessed by the Investigator and the assessment recorded in the eCRF.

All patients should have radiographic tumor measurements performed at the participating study center or an acceptable alternate imaging facility using an identical imaging protocol. The same imaging modality should be used for all scans being done for tumor assessment purposes throughout the study.

Tumor assessments are planned for: CCI .

5.23. Concomitant Medications

Use of all medications taken by the patient CCI prior to signing the ICF will be recorded in the eCRF. All medications taken by the patient, or any changes in medications will also be recorded throughout the course of the study until the EOA visit, including those taken as part of the tumor resection procedure.

Concomitant medication taken by the patient will be collected at all visits, including the EOA visit.

5.24. Adverse Events

AEs will be collected and reported according to Section 11.2.

All AEs for all patients will be graded as per NCI CTCAE Version 5.0.

5.25. Tumor Harvest and Processing Procedure

If the patient has only one identified target lesion at Screening CCI then another lesion needs to be identified and used for TIL generation.

The detailed CCI Manual will be provided to each clinical site and training will be conducted on the procedures for collecting and shipping of the tumor to the LN-145 manufacturing facility. The resected tumor specimen for LN-145 manufacturing should be viable solid tumor tissue (or aggregate of lesions resected) that is ≥ 1.5 cm, but no more than 4.0 cm in diameter. Viable solid tumor tissue is tissue that has all portions of necrotic, hemorrhagic, and fatty tissue removed. Biopsy from multiple different lesions is encouraged.

Tumor specimens must undergo intraoperative frozen section (or fine needle aspiration [FNA]) examination by a pathologist to ensure that tumor cells are present. In addition, at the time of tumor resection, the surgeon and/or pathologist must use their best judgement to evaluate the results of the frozen section (or FNA), incorporating visual inspection of the specimen. This is done to ensure that viable tumor specimens are being shipped for TIL. The pathologist and surgeon must perform these assessments in parallel prior to shipping the tumor specimen for TIL generation.

5.25.1. Additional Resected Tumor Tissue at Tumor Harvest CCI

Mandatory tumor sample collection

For Cohort 2, if local PD-L1 results determined by a validated test or archival tumor samples for central PD-L1 testing are not available, every effort should be made to collect additional resected tumor tissue to be prepared as a formalin-fixed paraffin-embedded (FFPE) block for central PD-L1 testing. Ensure that this biopsy does not bring the final tumor tissue for TIL generation to < 1.5 cm. If no excess tumor tissue is available, then a single 2-mm punch biopsy from the center of the resected tumor can be collected. If excess viable tumor tissue and punch biopsy are not available, then excess viable tumor tissue can be resected from an additional lesion (if available). Note that this excess tumor tissue cannot originate from a target lesion. FFPE specimens should be prepared using standard methods of tissue processing and sent to a designated central laboratory.

For all cohorts including Cohort 2, patients must have documented HPV status and serotyping (HPV16/18) of cervical carcinoma. If documentation is not available, testing for HPV status and serotype should be performed locally using excess tissue obtained during tumor resection (after completion of preparation of tumor tissue for LN-145 manufacturing) or archival tumor tissue. Ensure that this biopsy does not bring the final tumor tissue for TIL generation to < 1.5 cm. If no excess tumor tissue is available, then a single 2-mm punch biopsy from the center of the resected tumor can be collected. If excess viable tumor tissue and punch biopsy are not available, then excess viable tumor tissue can be resected from an additional lesion (if available). Note that this excess tumor tissue cannot originate from a target lesion. If local testing is not possible, tumor tissue prepared as a FFPE block or 3 to 5 slides should be sent to the Central Laboratory for HPV testing.

Optional tumor sample collection

For all patients who did not provide mandatory FFPE samples, if a portion of the tumor tissue is still available after completion of preparation of tumor tissue for LN-145 manufacturing, then the excess tumor tissue will be utilized for exploratory biomarker analysis.-Specimens should be prepared as an FFPE block using standard methods and shipped to a designated central laboratory.

For all patients, if tumor tissue is still in excess of that required for TIL manufacturing and preparation of an FFPE sample, then this excess tissue should be prepared as a viable (non-fixed) tissue sample and shipped overnight to the Sponsor's laboratory. Fresh tumor sample analysis may include 1) T cell content and characterization, 2) TIL infusion product reactivity, 3) protein levels and/or 4) gene mutations in properly consented patients.

Please refer to the Tumor Procurement and Laboratory Manual for details on collection, processing, and shipping of samples.

5.25.2. Optional Post-Treatment Core Biopsy

Every effort should be made to obtain an on-study, post-treatment (post-LN-145 infusion) core biopsy at CCI following the first post-Baseline tumor response assessment scans and if patient consent is provided and there is minimal risk to the patient. Two to six post-treatment core biopsies should be collected from a lesion distinct from those used as target or non-target for tumor response assessment.

Refer to the CCI Manual for details on collection, processing, and shipment to the Central Laboratory.

While this post-treatment core biopsy is optional, the importance of this biopsy cannot be overstated to better characterize potential predictive markers of response.

5.26. Assessment Period

Efficacy/imaging (eg, tumor response) assessments will be performed at CCI window. Subsequent assessments will CCI 5 years from CCI ; LN-145 infusion), or until disease progression or start of new anticancer therapy. Subsequently, patients will perform the EOA visit and begin the OS Follow-up Period (Section 5.27).

5.27. Overall Survival Follow-up Period

The OS Follow-up Period will begin when a patient completes the EOA visit (last efficacy assessment) and will continue for up to 5 years from Enrollment (tumor resection) or until discontinuation from the study (eg, withdrawal of consent to the study, lost to follow up, death, or study terminated by the Sponsor).

Patients who had tumor resection but did not receive LN-145 for any reason will perform an EOA visit and transition directly into OS Follow-up Period.

OS Follow-up will consist of telephone calls (or other means of contact) with the patient or designee every CCI for survival and subsequent anticancer therapy.

5.28. Hospitalization

Patients may be hospitalized prior to the planned LN-145 infusion for hydration (CCI

Patients may also require hospitalization as per institutional guidelines (tumor resection; NMA-LD preparative regimen; and treatment recovery). However, if the institutional guidelines mandate a required hospitalization longer than the protocol, this pre-planned hospitalization event will not be considered as an SAE.

All dates of hospitalization, regardless if required per protocol, including intensive care unit (ICU) stays, must be collected and recorded in the Hospitalization eCRF through CCI

6. STUDY TREATMENT

The investigational products used in this study are listed in Table 1.

Table 1 List of Investigational Products

Investigational Product	Dosage Route of Administration
LN-145	CCI total viable lymphocytes administered by IV infusion (single treatment)
Pembrolizumab	200 mg Q3W or 400 mg Q6W administered by IV infusion (Investigator choice).

6.1. LN-145 Treatment Regimen

6.1.1. Non-myeloablative Lymphodepletion Preparative Regimen

The NMA-LD preparative regimen is scheduled to start on CCI Based on baseline assessments CCI the Investigator will assess whether the patient has had any clinical deterioration or new medical findings that would put the patient at increased risk when receiving the TIL treatment regimen (NMA-LD, LN-145, and IL-2 administrations). If the patient continues to be stable to proceed with administration of the TIL treatment regimen, this will be documented on the CCI Form, which must be sent to the Medical Monitor or designee for review..

Verification of sufficient LN-145 viable cell expansion will be confirmed by the Sponsor and the site will receive the CCI form prior to beginning the NMA-LD preparative regimen.

- Authorization for the NMA-LD preparative regimen must be received by the site from the Sponsor or designee prior to beginning the NMA-LD preparative regimen (with a planned start on CCI

Full resolution of any active infection should be documented by clinical evaluation and/or laboratory studies (eg, serology, cultures, or NAAT) prior to start of the NMA-LD preparative regimen (Section 8.5.1). The NMA-LD preparative regimen is comprised of **single daily doses** of cyclophosphamide on CCI and CCI followed by **single daily doses** of fludarabine on CCI For consistency in dosing, obese patients (patients with a BMI $\geq$ 35.0 kg/m^2) should be dosed using actual weight unless the standard of practice at the clinical site demands using practical weight (Section 17.6.3).

Use of systemic corticosteroids (>10 mg prednisone or equivalent) is not allowed starting CCI prior to beginning the NMA-LD preparative regimen, through treatment, and up to CCI post-LN-145 infusion except for adrenal replacement doses and not > 10 mg/day of prednisone or equivalent; such medications should only be used to treat immediately life-threatening conditions or conditions potentially leading to major irreversible morbidity. The Medical Monitor must be consulted or informed as soon as reasonably possible after use of higher doses of steroids (>10 mg/day of prednisone or equivalent).

6.1.1.1. Preparation of Cyclophosphamide

The dose of cyclophosphamide is CCI after consultation with the Medical Monitor]. Reconstitute cyclophosphamide as per institutional standard to deliver calculated dose in a final concentration not to exceed CCI

Cyclophosphamide must be infused with mesna as described in Section 6.1.1.3.

For patients with a history of pelvic irradiation or history of prolonged neutropenia with prior therapy, the dose of cyclophosphamide may be reduced to CCI after consultation with the Medical Monitor.

For consistency in dosing, obese patients (patients with a BMI ≥ 35.0 kg/m^2) should be dosed using actual weight unless the standard of practice at the clinical site demands using practical weight.

Please refer to the current approved local prescribing information for cyclophosphamide.

6.1.1.2. Preparation of Mesna

Mesna is administered to reduce the risk of hemorrhagic cystitis related to cyclophosphamide administration. Mesna will be administered as a continuous infusion or per institutional standards.

The total dose of mesna is not adjusted if the amount of cyclophosphamide is reduced. Dilute the volume of mesna injection or infusion per institutional standard.

6.1.1.3. Infusion of Cyclophosphamide and Mesna

Cyclophosphamide CCI in a total volume of 250 mL or 500 mL (eg, 5% dextrose in water [D5W] or 0.9 % sodium chloride [NaCl]).

Mesna CCI may be infused over approximately 2 hours with cyclophosphamide, then at a rate of 3 mg/kg/hour for the remaining 22 hours in a suitable diluent over 24 hours starting concomitantly with each cyclophosphamide dose. Alternatively, mesna may be administered as per institutional standards. This will be repeated for each cyclophosphamide dose.

The total dose administered must be at least 1.3 times that of the dose of cyclophosphamide. Higher or continued doses of mesna can be administered for prevention of hemorrhagic cystitis. Refer to the current approved local prescribing information for mesna.

6.1.1.4. Fludarabine

Fludarabine (CCI) is to be given IV over approximately 30 minutes, once daily, for consecutive days from CCI

Fludarabine dose will be adjusted according to measured CrCl as follows:

- CrCl 50-79 mL/min: Reduce dose to CCI
- CrCl 40-49 mL/min: Reduce dose to CCI

Please refer to the current approved local prescribing information for fludarabine.

For consistency in dosing, if the patient is obese (BMI > 35.0 kg/m^2), fludarabine dosage will be calculated using actual weight unless the standard of practice at the clinical site demands using practical weight.

Fludarabine has been reported to cause skin toxicity consisting primarily of skin rashes. If this or other fludarabine-related toxicity event occurs, consultation with Medical Monitor is recommended.

6.1.2. LN-145

Qualitative Composition of LN-145

The product is composed of autologous TIL obtained from an individual patient through surgical resection of tumor and expanded ex vivo through cell culture in the presence CCI [redacted]

6.1.2.1. Manufacturing Process

An overview of the manufacturing process for cryopreserved product from tumor resection through infusion of LN-145 product is provided in Figure 1.

LN-145 is manufactured *ex vivo* using autologous tumor as starting material. The key steps to manufacturing drug substance and drug product are:

Drug Substance

- CCI [redacted]
- [redacted]
- [redacted]

Drug Product

- [redacted]
- [redacted]

6.1.2.2. Final Investigational Product Container

Cryopreserved LN-145 is packaged in up to four cryopreservation bags containing CCI [redacted] of viable cells. Each bag of product is labeled with patient-specific information.

6.1.2.3. Shipping/Transport of Investigational Product

LN-145 is shipped by express courier to the clinical site in a shipping container qualified to maintain a temperature of < -150ºC for cryopreserved product. Additional details are specified in the Pharmacy & Investigational Product Administration Manual.

6.1.2.4. Receipt of Investigational Product at Clinical Site

LN-145 will be received by the clinical site's pharmacy or designee prior to, or on, the day of infusion (CCI). The date and time that possession of the product transfers from the courier to the clinical site will be documented on, and determined by, the courier's shipping paperwork. Please refer to the CCI Manual for specific TIL receipt and handling instructions.

6.1.2.5. LN-145 Infusion Procedures

Patients may be hospitalized prior to the planned LN-145 infusion for hydration and will remain hospitalized until completion of the IL-2 administration, or as per institutional standards.

6.1.2.6. Pre-LN-145 Infusion

The following medications will be administered to the patient prior to LN-145 infusion as follows or as per institutional standards:

- Within 24 hours, hydration
- Within 30–60 minutes, premedicate the patient with acetaminophen (650 mg) or equivalent, and diphenhydramine (25–50 mg IV), or another H1 histamine antagonist
  - Prophylactic use of systemic corticosteroids (>10 mg prednisone or equivalent) is not allowed except for adrenal replacement doses and not > 10 mg/day of prednisone or equivalent; such medications should only be used to treat immediately life-threatening conditions or conditions potentially leading to major irreversible morbidity. The Medical Monitor must be consulted or informed as soon as reasonably possible after use of higher doses of steroids (>10 mg/day of prednisone or equivalent).
- During infusion of LN-145, appropriate emergency medications (eg, epinephrine and diphenhydramine) should be available at bedside, and institutional emergency guidelines should be followed as needed. Additional supportive therapy may include:
  - Continued acetaminophen (650 mg q4h) or equivalent
  - Indomethacin (50–75 mg q6h)
  - Ranitidine (150 mg q12h)
  - Meperidine (25–50 mg)
  - Other medications as per institutional standards

6.1.2.7. LN-145 Infusion

LN-145 should be infused as soon as practically possible, after CCI following the last dose of fludarabine. If CCI have elapsed between the last fludarabine dose and LN-145 infusion, the ALC should be measured and there should be a discussion with the Medical Monitor.

Each cryobag of LN-145 will be thawed at 37ºC using a water bath or other thawing device, one at a time, for sequential infusion.

LN-145 will be administered by IV and infused by gravity beginning at a rate of 1 mL/minute for the first 5 minutes. If no adverse reaction is observed, the infusion rate can then increase to between 5 and 10 mL/minute for the completion of the infusion. During periods of infusion interruption, any remaining cryobags of LN-145 should be kept in the cryoshipper. Refer to the LN-145 Pharmacy & Investigational Product Administration Manual for details on the thawing and administration procedure.

All visits following LN-145 infusion are calculated from CCI forward.

6.1.3. Interleukin-2 Dosing and Dose Adjustments

The first IL-2 administration will begin approximately CCI after the completion of LN-145 infusion at a dose of approximately CCI (based on actual body weight recorded at CCI unless the standard of practice at the clinical site demands using practical weight). IL-2 is administered by IV at a frequency of approximately CCI Continue for up to a maximum of CCI

- IL-2 dosing is allowed for up to CCI post-LN-145 infusion to allow for proper management of any IL-2 toxicities
- If toxicities can be easily reversed within 24 hours by supportive measures, then the additional doses of IL-2 (up to the protocol-defined maximum of CCI may be given
- IL-2 dosing may be held or stopped at the discretion of the Investigator

Skipping IL-2 doses is allowed if patient experiences a Grade 3 or Grade 4 toxicity. If two consecutive doses of IL-2 are skipped, then IL-2 administration will be discontinued.

- IL-2 AEs and toxicities/management are described in Section 8.3 and the aldesleukin current approved local prescribing information

6.2. Pembrolizumab

6.2.1. Preparation of Pembrolizumab

Pembrolizumab will be supplied as per available locally-approved drug formulation.

Standard infusion time is 30 minutes. If interruptions occur during pembrolizumab infusion, the total allowed time should not exceed 6 hours at room temperature. Any unused portion must be discarded.

See the Pharmacy Manual for information regarding reconstitution and preparation.

6.2.2. Infusion of Pembrolizumab

For Cohort 3, patients will receive the first dose of pembrolizumab 200 mg, administered as an IV infusion over 30 minutes following tumor resection for TIL production and baseline imaging but before NMA-LD.

Patients must have recovered (Grade ≤ 2) from all IL-2-related toxicities prior to the second dose of pembrolizumab.

Pembrolizumab administrations will continue no earlier than 3 weeks from the first dose and not until the completion of IL-2 and after patients have recovered (Grade ≤ 2 toxicities) from IL-2-related toxicities. Pembrolizumab will continue Q3W (± 3 days) at 200 mg or Q6W (± 3 days) at 400 mg for ≤ 2 years (24 months) from the first dose of pembrolizumab, or until disease progression or unacceptable toxicity, whichever occurs first.

If TIL infusion is delayed for any reason, consult with the Medical Monitor about further dosing of pembrolizumab prior to TIL infusion.

Refer to the pembrolizumab current approved local prescribing information for additional information.

6.2.3. Monitoring of Pembrolizumab Dose Administrations

Patients will be monitored as per the pembrolizumab dosing instructions found in the current approved local prescribing information. Monitoring will be undertaken before, during, and after the pembrolizumab administration with assessment of vital signs at the times specified in the Schedule of Assessments. Patients are monitored (pulse rate, blood pressure) every 15 minutes (± 5 minutes) during the 30-minute pembrolizumab infusion period (including times where infusion rate is slowed or temporarily stopped).

In the event of a Grade ≤ 2 infusion-related reaction, the infusion rate of pembrolizumab may be decreased by 50% or interrupted until resolution of the event (up to 4 hours) and re-initiated at 50% of the initial rate until completion of the infusion. For patients with a Grade ≤ 2 infusion-related reaction, subsequent infusions may be administered at 50% of the initial rate. Acetaminophen and/or an antihistamine (eg, diphenhydramine) or equivalent medications per institutional standard may be administered.

If the infusion-related reaction is Grade 3 or higher in severity, pembrolizumab will be discontinued. The standard infusion time is 30 minutes, however if there are interruptions during infusion, the total allowed time from infusion start to completion of infusion should not exceed 6 hours (otherwise new infusion preparation is required). For management of patients who experience an infusion reaction, please refer to the pembrolizumab current approved local prescribing information, and in certain circumstances pembrolizumab should be permanently discontinued.

7. CONCOMITANT MEDICATIONS AND NON-DRUG THERAPIES

7.1. Concomitant Medications

Use of all medications taken by the patient CCI prior to signing the ICF will be recorded in the eCRF. All medications taken by the patient, or any changes in medications will also be recorded throughout the course of the study until the EOA visit, including those taken as part of the tumor resection procedure.

7.2. Prohibited and Permitted Medications During Study Treatment

7.2.1. Prohibited Treatment

- Systemic therapies intended to treat cervical cancer or any medications that may have an antitumor effect
- **Use of systemic corticosteroids (> 10 mg prednisone or equivalent) is not allowed** starting CCI prior to beginning the NMA-LD preparative regimen, through treatment, and up to CCI post-LN-145 infusion except for adrenal replacement doses and not > 10 mg/day of prednisone or equivalent; such medications should only be used to treat immediately life-threatening conditions or conditions potentially leading to major irreversible morbidity. The Medical Monitor must be consulted or informed as soon as reasonably possible after use of higher doses of steroids (>10 mg/day of prednisone or equivalent).
- Palliative RT is permitted to specified areas only post tumor resection and before lymphodepletion; see Section 7.3. Palliative radiation is not permitted at any time on study post NMA-LD
- Investigational drugs (other than LN-145)
- Live or attenuated vaccine within CCI prior to beginning the NMA-LD preparative regimen or within 3 months after the last dose of IL-2 (CCI until ANC is $\geq 1000/mm^3$

7.3. Permitted Medications

Concurrent medications for conditions other than patients' cervical cancer are permitted.

Palliative radiation therapy is permitted between the time of tumor resection and initiation of the NMA-LD preparative regimen, if it does not involve target or non-target lesions.

Refer to the Information for Use package insert provided with all drugs used in this study to understand the contraindications, precautions, and warnings relative to a specific drug.

7.3.1. Prior Treatment Washout

Patients will enter a washout period prior to Enrollment (tumor resection) and must stop treatments as follows:

- All chemotherapy, biologic/targeted agents, and immunologic agents must have been discontinued CCI prior to Enrollment (tumor resection; CCI

- Radiation therapy is permitted as long as the lesions irradiated are not expected to be used for TIL generation or as target lesions and any toxicities have resolved to Grade ≤ 1 at least CCI prior to NMA-LD.

7.4. Pembrolizumab Drug–Drug Interactions

To date, no formal nonclinical or clinical pharmacokinetic drug–drug interaction studies have been found with pembrolizumab treatment. As pembrolizumab is a mAb and therefore a protein, it will be degraded to small peptides and amino acids and will be eliminated by renal and reticuloendothelial clearance. It is therefore not expected that pembrolizumab will induce or inhibit the major drug-metabolizing cytochrome P450 pathways. As a result, no pharmacokinetic drug–drug interactions are expected. The mechanism of action of pembrolizumab involves binding to PD-1, and, therefore, significant pharmacodynamic drug interactions with the commonly administered concomitant medications are not expected.

7.5. Blood Donations

Patients should not donate blood while receiving study treatment and for at least 90 days following the last study treatment.

8. EXPECTED TOXICITIES AND TREATMENT GUIDELINES

The following sections present information for common adverse effects. For more details on side effects, refer to the Investigator's Brochure (IB) and relevant prescribing information.

An overdose is not applicable for LN-145. In the event of cyclophosphamide, fludarabine, or IL-2 overdose, refer to the package insert for details on management (Section 11.1.1.1).

8.1. Cyclophosphamide and Fludarabine Toxicities

Expected toxicities with cyclophosphamide and fludarabine administration, as well as supportive care and management of toxicities are listed in the package inserts. Treatment will be given as per institutional standards.

In general, the use of the NMA-LD preparative regimen (cyclophosphamide and fludarabine) prior to LN-145 administration can lead to myelosuppression. Therefore, a high index of suspicion for occult bacteremia should be maintained until marrow recovery.

Additional guidelines for toxicity management are outlined below.

8.1.1. Hemorrhagic Cystitis Prophylaxis

To reduce the risk of cyclophosphamide-associated hemorrhagic cystitis, patients will receive continuous infusion of mesna in addition to IV fluids. Higher doses of mesna are allowed if the institutional standards recommend. Refer to treatment guidelines for recommended mesna dosing.

8.1.2. Fludarabine Hypersensitivity

Fludarabine has been reported to cause skin toxicity consisting primarily of skin rashes. If this or other fludarabine-related toxicity events occur, consultation with the Medical Monitor is recommended prior to administration of LN-145.

8.1.3. Febrile Neutropenia

Patients are expected to become neutropenic following the NMA-LD preparative regimen. See Section 8.5.3.1 for guidance.

8.1.4. Filgrastim

Patients will receive filgrastim or biosimilar 5 mcg/kg/day (recommended maximum dose of 300 mcg/day) subcutaneously daily starting from CCI [redacted] until the ANC is > 1000/mm^3 for 3 consecutive days. Alternative dosing schedules and regimens may be used as per standard of care at the treating institution but must continue until neutropenia is resolved.

8.1.5. Blood Product Support

Using daily CBCs as a guide, the patient may receive platelets and packed red blood cells (PRBCs) as needed or as per institutional standards. Attempts will be made to keep Hb > 7.5 g/dL, and platelets > 10,000/mm^3. All blood products must be irradiated. Leukocyte filters will be utilized for all blood and platelet transfusions to decrease sensitization to transfused WBCs and decrease the risk of CMV infection.

8.2. LN-145 Toxicity Management

Toxicities related to the infusion of LN-145 (those which may be seen immediately following LN-145 infusion and prior to IL-2 administration) are generally mild and include fevers, chills, headache, and malaise. Dysgeusia may occur and should be limited to the duration of infusion. It also is possible that patients may experience severe allergic reaction including anaphylaxis that can be life threatening during infusion of LN-145 product. Uveitis, which can lead to develop into chronic, sight-threatening inflammation if not managed appropriately, also has been observed in studies of patients with melanoma who have received treatment with the LN-145 product. Additional guidance is provided below for hypersensitivity reactions (Section 8.2.1) and uveitis (Section 8.2.2). Details on the specific toxicities and risks may be found in the IB.

8.2.1. Hypersensitivity Reactions, Including Severe Allergic Reactions and Anaphylaxis

Allergic reactions to components of the cryopreserved LN-145 product may present with symptoms such as rash, low blood pressure, shortness of breath, swelling of the face or throat, cough, chest tightness, and/or wheezing. These symptoms can usually be reversed promptly using an inhaled bronchodilator. Hypersensitivity events, including severe allergic reactions or anaphylaxis have occurred during infusion with LN-145 because hypersensitivity has been associated with at least one of the above-mentioned formulation components. Rarely have severe allergic reactions, such as anaphylaxis, developed. If anaphylaxis does occur, it will be treated immediately with an injection of epinephrine, steroids, and inhaled bronchodilators.

Patients who have known allergies to ABX of the aminoglycoside group are excluded from studies of LN-145 (except those who are skin-test negative for gentamicin). Premedication and supportive therapy instructions are provided in Section 6.1.2.6.

During infusion of LN-145, appropriate emergency medications (eg, epinephrine and diphenhydramine) are to be available at bedside, and institutional emergency guidelines should be followed as needed (Section 6.1.2.6).

8.2.2. Uveitis

Uveitis, or inflammation of the uvea (which consists of the iris, ciliary body, and choroid), has been observed with mostly mild to moderate intensity in patients who have received the TIL investigational product for the treatment of metastatic melanoma. Uveitis in these patients was associated with symptoms such as blurred vision, eye pain, nyctalopia, photopsia, retinal hemorrhage, and/or vitreous floaters, and often improved with local corticosteroid therapy.

Uveitis may be caused by a number of different etiologies; therefore, diagnosis and treatment of the underlying disease are imperative not only to treat the disease but also to preserve vision and potentially uncover underlying systemic diseases. If untreated or not appropriately treated, acute inflammation can develop into chronic, sight-threatening inflammation. Thus, when a patient participating in this study presents with clinical signs and symptoms that may be associated with uveitis (eg, blurry vision; dull, aching, or throbbing pain in the temple or periorbital region; photophobia; circumlimbal injection; anterior chamber cells and flare; altered intraocular pressure), the Investigator should refer the patient to a trained eye specialist for further evaluation. Once an etiology has been established, appropriate treatment should be commenced

and customized to each patient as suboptimal treatment may lead to complications and loss of vision.

8.3. IL-2 Toxicity

The most commonly seen Grade 4 events are pulmonary and renal impairment and mental status changes. These toxicities may sometimes require intubation for protection of the patient's airway. It is important to note that although patients require significant supportive measures during this period, almost all toxicities are reversible, and most patients have experienced no long-term sequelae following this treatment regimen. However, fatal complications are possible. Subcutaneous administration of IL-2 is not permitted.

Refer to the prescribing information for IL-2.

8.3.1. Expected Toxicities with IL-2

8.3.1.1. Decreased Mental Status with IL-2

IL-2 can result in decreased mental status, which can range from somnolence to obtundation; continued administration may result in coma. Agitation may also be observed due to mild hallucinations. Administration of IL-2 should be withheld or permanently discontinued in patients with decreased mental status. Refer to the aldesleukin current approved local prescribing information for IL-2 AEs and toxicity management guidelines.

8.3.1.2. Pulmonary Risk

LN-145 can remain in the pulmonary circulation for 24–48 hours following infusion and may cause transient shortness of breath. In addition, pulmonary edema is commonly observed with IL-2 treatment. Supplemental oxygen should be administered as needed. Subsequent IL-2 dosing should be delayed until supplemental oxygen has been weaned or is minimal (< 2 L/minute per nasal cannula). If hypoxia persists or is significant, then IL-2 should be withheld or stopped. Refer to the aldesleukin current approved local prescribing information for IL-2 AEs and toxicity management guidelines.

8.3.1.3. Cardiac Arrhythmias and Myocarditis

All new cardiac arrhythmias should be promptly evaluated and continuously monitored with intensive management. Upon patient recovery from the cardiac event, continuation of IL-2 administration is per the Investigator's discretion.

8.3.1.4. Capillary Leak Syndrome

Administration of IL-2 has been associated with capillary leak syndrome (CLS), which is characterized by a loss of vascular tone and extravasation of plasma proteins and fluid into the extravascular space. CLS results in hypotension and reduced organ perfusion, which may be severe and can result in death. CLS may be associated with cardiac arrhythmias (supraventricular and ventricular), angina, myocardial infarction, respiratory insufficiency requiring intubation, gastrointestinal bleeding or infarction, renal insufficiency, edema, and mental status changes.

Resultant intravascular volume depletion should be managed with IV fluids. Diuresis should be initiated as tolerated following completion of IL-2 treatment. Hypotension not responsive to IV fluids should raise suspicion for occult bacteremia and associated sepsis.

8.3.1.5. Heparin-Induced Thrombocytopenia

Heparin-induced thrombocytopenia (HIT) has been observed with IL-2 administration. To minimize this risk, heparin flushes should not be used during IL-2 treatment.

8.3.1.6. Renal Toxicity

Renal toxicity, defined by a rapid rise in creatinine levels or clinical symptoms, is a risk. If patients exhibit signs or symptoms of renal toxicity, manage as per institutional standards.

8.4. Pembrolizumab Toxicity Management

Guidelines for the management of immune-mediated reactions, infusion-related reactions, and nonimmune-mediated reactions for pembrolizumab monotherapy are provided in the pembrolizumab current approved local prescribing information. Pembrolizumab dose may be delayed for up to a maximum of 12 weeks due to AEs related to IL-2 or pembrolizumab treatment if the following discontinuation criteria are not met.

Patients should be thoroughly evaluated, and appropriate efforts should be made to rule out neoplastic, infectious, metabolic, toxin, or other etiologic causes of the immune-mediated AE. Serologic, immunologic, and histologic (biopsy) data, as appropriate, should be used to support an immune-mediated AE diagnosis. In the absence of a clear alternative etiology, events should be considered potentially immune related.

In addition, there are certain circumstances in which pembrolizumab should be permanently discontinued (see additional information in the pembrolizumab current approved local prescribing information.

Permanently discontinue pembrolizumab for any of the following:

- Grade 3 or Grade 4 adverse reactions that are life threatening. Endocrinopathies that can be medically treated do not require treatment discontinuation
- Grade 3 or Grade 4 pneumonitis, or recurrent Grade 2 pneumonitis
- Grade 3 or Grade 4 nephritis
- Grade 3 or 4 colitis
- Severe immune-mediated adverse skin reactions: Stevens-Johnson Syndrome and toxic epidermal necrolysis
- AST or ALT ≥ 5 times ULN or total bilirubin ≥ 3 times ULN
- For patients with liver metastasis who begin treatment with Grade 2 AST or ALT, if AST or ALT increases by greater than or equal to 50% relative to Baseline and lasts for at least 1 week
- Grade 3 or 4 myocarditis, encephalitis, or Guillain-Barré syndrome

- Grade 3 or Grade 4 infusion-related reactions
- Persistent Grade 2 or Grade 3 adverse reactions that do not recover to Grade 0 or Grade 1 within 12 weeks after last dose of pembrolizumab
- Any severe or Grade 3 treatment-related adverse reaction that recurs
- Pregnancy

Following the first dose of pembrolizumab, subsequent administration of pembrolizumab can be modified based on toxicities observed as described in the pembrolizumab current approved local prescribing information. These guidelines have been prepared by the manufacturer to assist the Investigator in the exercise of his/her clinical judgment in treating these types of toxicities. These guidelines apply to AEs considered causally related to pembrolizumab by the reporting Investigator.

Pembrolizumab may be administered at 200 mg Q3W or 400 mg Q6W per Investigator preference (per pembrolizumab prescribing information). Dose reductions of pembrolizumab are not permitted. In case of doubt, the Investigator should consult with the Iovance Medical Monitor.

Interruptions for intercurrent non-toxicity related events

Pembrolizumab dose interruptions for conditions other than toxicity resolution should be kept as short as possible and discussed with the Medical Monitor.

8.5. Infection Prophylaxis

8.5.1. Active Infection Prior to NMA-LD

Patients with evidence of any uncontrolled or active systemic infection requiring ongoing treatment cannot proceed to NMA-LD. Prophylactic anti-infection therapy is acceptable.

Those with HSV infection should receive treatment doses of anti-HSV medications as per institutional standards until documented resolution. Similarly, patients with clinically significant CMV viremia detected on NAAT should receive anti-CMV therapy per institutional standards until resolution of viremia. Full resolution of infection should be documented by clinical evaluation and/or NAAT prior to the start of the NMA-LD preparative regimen.

8.5.2. Infectious Disease Prophylaxis

8.5.2.1. *Pneumocystis Jirovecii* Pneumonia Prophylaxis

Pneumocystis jirovecii pneumonia (PJP) prophylaxis should begin on CCI [redacted] and may be administered per institutional standards. Recommended agents include TMP-SMX, atovaquone, dapsone, and inhaled pentamidine. PJP prophylaxis will continue for a minimum of 6 months and until a peripheral blood CD4 count >200/mm^3 is achieved. If the CD4 count is ≤200/mm^3 at 6 months post-chemotherapy, prophylaxis will continue until the CD4 count is >200/mm^3.

8.5.2.2. Fungal Infection Prophylaxis

Systemic antifungal prophylaxis should begin on CCI for all patients and may be administered per institutional standards. Recommended prophylaxis is fluconazole 400 mg daily PO or IV. Appropriate alternative antifungal prophylaxis may include any approved systemic antifungal agents including azoles and echinocandins. Topical antifungal therapy (eg, nystatin) by itself is not appropriate. Antifungal prophylaxis should be continued until the ANC is >1000/mm^3.

8.5.2.3. HSV and Varicella Prophylaxis

All patients irrespective of serology will be placed on HSV and varicella prophylaxis starting with NMA-LD CCI as per institutional standards. Minimum prophylaxis should include valacyclovir 500 mg PO daily or acyclovir 400 mg PO BID or equivalent alternative agent for at least 3 months following NMA-LD. Patients with evidence or suspicion of HSV infection should receive treatment doses of anti-HSV medications as per institutional standards. Full resolution of infection should be documented by clinical evaluation and/or NAAT prior to the start of the NMA-LD preparative regimen.

Reversible renal insufficiency has been reported with IV, but not oral acyclovir. Neurologic toxicity including delirium, tremors, coma, acute psychiatric disturbances, and abnormal electroencephalogram (EEG) has been reported with higher doses of acyclovir. If this occurs, then the acyclovir dose should be adjusted or discontinued. Acyclovir cannot be used concomitantly with other nucleoside analogs, which interfere with DNA synthesis (eg, ganciclovir). In renal disease, the dose is adjusted as per product labeling.

8.5.2.4. Anti-bacterial Infection Prophylaxis

Treatment with IL-2 is associated with impaired neutrophil function (reduced chemotaxis) and an increased risk of disseminated infection, including sepsis and bacterial endocarditis. Pre-existing bacterial infections should be adequately treated to resolution prior to the start of the IL-2 administration. Patients with indwelling central lines are particularly at risk for infection with Gram-positive microorganisms. Antibiotic prophylaxis with oxacillin, nafcillin, ciprofloxacin, or vancomycin has been associated with a reduced incidence of staphylococcal infections. Antibacterial prophylaxis including the choice of anti-infective agents will be as per institutional standards starting with the onset of neutropenia and continued until the ANC is >500/mm^3.

8.5.3. Infection Management

8.5.3.1. Treatment of Febrile Neutropenia

Patients are expected to become neutropenic following the NMA-LD preparative regimen. Furthermore, IL-2 causes neutrophil migration dysfunction putting patients at significant risk for bacteremia and sepsis including *Pseudomonas* infections. For any documented fevers, empiric broad spectrum antibiotic with adequate *Pseudomonas* coverage is necessary as per institutional standards and local antibiogram. Aminoglycosides should be avoided unless there is clear evidence of worsening sepsis.

After febrile neutropenia, empiric broad spectrum antibiotics should continue until the neutrophil count is >500 cells/mm^3 even if no bloodstream infectious agent is identified. If a bloodstream

infectious agent is identified, the antibiotic may be tailored to treat the infection as per institutional standard of care. Infectious disease consultation will be obtained for all patients with unexplained fever, any infectious complications, or as per standard of care at the treating institution.

8.5.3.2. Treatment of Sepsis

Sepsis can mimic IL-2 side effects. Fever may be masked during IL-2 administration due to scheduled indomethacin and acetaminophen or equivalent. Neutropenic patients exhibiting hypotension or oliguria that is unresponsive to IV fluids should be evaluated for infection and broad-spectrum antibiotics should be initiated.

9. COMPLETION/DISCONTINUATION AND WITHDRAWAL OF PATIENTS

9.1. Treatment Completion

For Cohorts 1, 2, and 5, the Treatment Period is from CCI 4; start of NMA-LD preparative regimen) to CCI ; EOT visit). For Cohort 3, the Treatment Period lasts for up to CCI beginning at the first dose of pembrolizumab and continuing until the last dose of pembrolizumab.

For Cohorts 1, 2, and 5, treatment completion is defined as having received LN-145 infusion. For Cohort 3, treatment completion is the final dose of pembrolizumab.

9.2. Criteria for Early Discontinuation from TIL Treatment Regimen

Some patients may undergo tumor resection but may not receive infusion of LN-145. Such patients will perform an EOA visit and transition directly into the OS Follow-up Period of the study.

Patients may discontinue any component of the study regimen. Criteria for discontinuation from treatment:

- Patient has become ineligible for study participation after tumor resection CCI and prior to the NMA-LD preparative regimen, LN-145 infusion, or IL-2 administration
- TIL product not available, and the patient is ineligible for or does not wish to undergo another tumor resection
- Withdrawal of consent to treatment (partial and full withdrawal).Every effort should be made to continue OS Follow-up, when applicable)
- Grade ≥ 3 drug-related immune AEs that involve vital organs (heart, kidneys, brain, eye, liver, colon, adrenal gland, lungs) with symptoms emerging following LN-145 infusion
- Grade ≥ 3 allergic reaction including bronchospasm or generalized urticaria that does not resolve after medical management in the opinion of the Investigator
- Meeting criteria for permanent discontinuation of IL-2 treatment (must have received at least one dose of IL-2; refer to the aldesleukin current approved local prescribing information)
- Determination by the Investigator that continued treatment is not in the best interest of the patient
- Administration of prohibited concomitant medications/start of new anti-cancer therapy
- Pregnancy
- Death
- Study terminated by Sponsor

9.3. Criteria for Early Discontinuation from Pembrolizumab Administration (Cohort 3 only)

- Grade 3 or 4 adverse reactions that are life-threatening. Endocrinopathies that can be medically treated do not require treatment discontinuation.
- Grade 3 or 4 pneumonitis or recurrent Grade 2 pneumonitis
- Grade 3 or 4 nephritis
- Grade 3 or 4 colitis
- Severe immune-mediated adverse skin reactions: Stevens-Johnson Syndrome and toxic epidermal necrolysis
- AST or ALT ≥ 5 times ULN or total bilirubin ≥ 3 times ULN
  - For patients with liver metastasis who begin treatment with Grade 2 AST or ALT, if AST or ALT increases by ≥ 50% relative to Baseline and lasts for at least 1 week
- Grade 3 or 4 myocarditis, encephalitis, or Guillain-Barré syndrome
- Grade 3 or 4 infusion-related reactions
- Persistent Grade 2 or 3 adverse reactions that do not recover to Grade 0 or 1 within 12 weeks after the last dose of pembrolizumab
- Any severe or Grade 3 treatment-related adverse reaction that recurs
- Pregnancy
- Disease progression
- Death
- Withdrawal of consent
- Study terminated by Sponsor

9.4. Assessment Completion/End of Assessment

All patients will be assessed for up to 5 years from CCI [redacted] or until disease progression or the start of new anticancer therapy.

9.5. Discontinuation from the Study

Patients will be discontinued from the study after 5 years from Enrollment (tumor resection), withdrawal of consent to the study, lost to follow-up, death, or if the study is terminated by the Sponsor.

9.6. Study Completion

The study is expected to be completed approximately 5 years (60 months) from Enrollment (tumor resection) of the last patient. This is the time point when all patients have exited the study for any reason, or study is terminated by the Sponsor, whichever occurs first.

10. RESPONSE ASSESSMENTS

10.1. Tumor Response Assessments

Tumor response assessments will be performed by clinical examination and by conventional or spiral CT scans of the chest, abdomen, pelvis, and additional anatomic regions (eg, extremities, neck) per disease history and clinical symptoms. Tumor response assessments are planned for: [redacted] until the EOA visit has been completed.

CT scans of additional anatomical locations will be conducted at the above referenced visits if prior or suspected disease is clinically indicated. Additional radiological assessments may be performed per Investigator's discretion. All imaging, including scheduled and unscheduled scans, must be assessed by the Investigator and the assessment recorded in the eCRF.

High-resolution CT with PO/IV contrast or contrast-enhanced MRI is the preferred imaging modality for assessing radiographic tumor response. If a patient has a known allergy to CT contrast material, please use the alternate modality. In cases where contrast is strictly contraindicated, a non-contrast scan is acceptable. All patients should have radiographic tumor measurements performed at the participating study center or an acceptable alternate imaging facility using an identical imaging protocol. **The same imaging modality should be used for all scans throughout the study.**

10.1.1. Response Criteria

Tumor response will be determined using RECIST v1.1 with a modification to require confirmation of PD per irRECIST performed at least [redacted] from the last date of progression, as clinically indicated, as assessed by the Investigator. Refer to Table 2 for RECIST v1.1 definitions and Table 3 for irRECIST definitions. Images (CT scans and/or MRI scans) obtained at Baseline visit [redacted] are to be utilized for RECIST v1.1 response assessments throughout the study.

Tumor response assessments performed at the site should be used for clinical treatment decisions and may include photographic/caliper measurement of superficial dermal and subcutaneous lesion.

All locally-obtained images will be forwarded to a central imaging facility for storage.

10.1.1.1. Definition of Target and Non-Target Lesions

Patients should have at least one measurable target lesion as defined by RECIST v1.1. If the patient has only one identified target lesion at Screening [redacted] then another lesion needs to be identified and harvested for TIL generation. If a lesion was partially resected to generate TIL, and remains visible on the Baseline scan after surgery, then the partially resected lesion can be used for RECIST v1.1 response assessment, but only as a non-target lesion.

Baseline target lesions should have also been measured at Screening [redacted] to understand the tumor dynamics and potentially identify hyperprogressors.

Lesions in previously irradiated areas (or other local therapy) should not be selected as target lesions unless treatment was ≥ 3 months prior to Screening CCI and there has been demonstrated disease progression of the lesion.

10.1.1.2. Evaluation of Overall Response

The best overall response is the best response recorded from the first post-Baseline tumor assessment at CCI until disease progression or the start of a new anticancer therapy. The patient's best response assignment will depend on target lesion sum of diameters (SoD), non-target lesion status, absence of a new lesion, and the confirmation criteria. The best overall response is determined once all the data for the patient is known. The assignment of Overall Response for an individual patient, based on both target and non-target lesions, at each assessment time point is shown in Table 2 for RECIST v1.1 definitions and Table 3 for irRECIST definitions.

Table 2 Response at each Assessment Time Point for Patients

Target Lesions	Non-Target Lesions	New Lesions	Overall Response*
CR	CR	No	CR
CR	Non-CR/Non-PD	No	PR
CR	Not evaluated	No	PR
PR	Non-PD or not all evaluated	No	PR
SD	Non-PD or not all evaluated	No	SD
Not evaluated	Non-PD	No	Not evaluable
PD	Any	Yes or No	PD
Any	PD	Yes or No	PD
Any	Any	Yes	PD

Abbreviations: CR=complete response; PD=progressive disease; PR=partial response; SD=stable disease
*If Investigator's Response Assessment is difficult to determine due to presence of confounding factors (ie, tumor flare), then overall response should be SD until proven otherwise.

Table 3 irRECIST Overall Tumor Assessment

TMTB	Non-Target Lesions	New Non-Measured Lesions	Overall Tumor Assessment
irCR	None/irCR	No	irCR
	None	Yes	irPR
	irNN	Yes/No	irPR
	irNE	Yes/No	irPR
	irPD	Yes/No	irPD
	None/irCR/irNN/irNE	Unequivocal Progression	irPD
irPR	None/irCR/ irNN/irNE	Yes/No	irPR
	None/irCR/irNN/irNE	Unequivocal Progression	irPD
irSD	None/irCR/ irNN/irNE	Yes/No	irSD
	None/irCR/irNN/irNE	Unequivocal Progression	irPD
irPD	None/irCR/irNN/irNE	Yes/No/Unequivocal Progression	irPD
irNE	None/irCR/irNN/irNE	Yes/No	irNE
	None/irCR/irNN/irNE	Unequivocal Progression	irPD
None	irCR	No	irCR
	irCR	Yes	irNN
	None/irCR/irNN/irNE	Unequivocal Progression	irPD
	irNN	Yes/No	irNN
	irPD	Yes/No/Unequivocal Progression	irPD
	irNE	Yes/No	irNE
	None	No	irND
	None	Yes	irNN
	None	Unequivocal Progression	irPD

Abbreviations: irCR=immune-related complete response; irNE=immune-related not evaluable; irNN=immune-related non-complete response/non-partial response; irPD=immune-related progressive disease; irPR=immune-related partial response; irSD=immune-related stable disease; TMTB=total measured tumor burden
NOTE: Worsening of non-target and/or new non-measured lesions must be massive to drive an overall irPD by itself.

10.2. Confirmation of Tumor Assessments

10.2.1. Confirmation of Response (PR or CR)

Confirmation of response (either PR or CR) is required. Changes in tumor measurements must be confirmed by repeat assessments that should be performed ≥CCI apart after the criteria for response are first met. The response assessment should be updated, if needed, based on the consecutive observation. 'Not Evaluable (NE)' should only be selected if the response was truly NE (eg, scan was not done).

10.2.2. Confirmation of Progressive Disease

If PD is assessed, then this must be confirmed by objective measures per irRECIST (as clinically indicated) suggesting unambiguous evidence of disease progression.

For patients with a minimal increase of over 20% in the SoD of target lesions taking as reference the smallest sum on study or for non-target or new non-measurable lesions, a confirmation scan is necessary at CCI after the first PD assessment.

10.3. Biomarkers

Immune-monitoring samples (blood) and tumor specimens will be collected as detailed in the SOA (Sections 17.1 and 17.2) to identify biomarkers of LN-145. Immune-monitoring samples will be processed as peripheral blood mononuclear cells (PBMC), serum, and plasma for cellular, molecular, and genetic assessments. TCR repertoire analyses carried out on PBMC will potentially inform the composition and in vivo persistence of the product T cells. Levels of circulating immune modulators and effectors such as cytokines, chemokines, and enzymes will potentially be measured by immunoassays on plasma and/or serum samples. Plasma cell-free DNA can be an additional source of information about tumor burden, as assessed by PCR-based sequencing methods.

Excess tumor tissue collected during CCI (described in Section 5.25) and at the posttreatment core biopsy collected during CCI (described in Section 5.25.2) will be a) assessed for gene mutations and gene expression profiles by molecular assays, b) assessed for the presence of different immune cell subsets by immunohistochemistry, and c) utilized in antigen-specific T-cell reactivity assays. A substudy consent will be obtained if required.

Excess tumor tissue collected during CCI (described in Section 5.25) will also be tested for PD-L1 status.

11. SAFETY MONITORING AND REPORTING

11.1. Adverse Events

Safety events will be recorded as AEs and SAEs in the patient's source documents and on the AE eCRF, and must be graded using the NCI's CTCAE v5.0 dated 27 November 2017 (web address provided in Appendix 17.5).

11.1.1. Definitions

11.1.1.1. Adverse Event

An AE is defined by the International Conference on Harmonisation (ICH) Guidelines for Good Clinical Practice (GCP) as any untoward medical occurrence in a patient or clinical trial patient starting from signing the ICF, which does not necessarily have a causal relationship with LN-145 treatment. An AE can therefore be any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease temporally associated with the use of a medicinal product, whether or not considered related to LN-145.

Events meeting the definition of an AE include:

- AE temporally associated with the use of any of the study drugs, including LN-145 treatment, whether or not considered related to the use of any of the study drugs or LN-145 treatment
- Abnormal laboratory test values or results (eg, hematology, clinical chemistry, urinalysis) or other safety assessments (eg, ECGs, radiological scans, vital sign measurements, significant PE changes) or events related to protocol mandated procedures (eg, incidental patient injury during a procedure), will be reported as AEs only if they are deemed by the Investigator as being clinically significant, led to hospitalization or prolongation of hospitalization, required a change in dosing or treatment of study therapies, or required initiation of concomitant therapy for laboratory abnormalities
- Exacerbation of a chronic or intermittent pre-existing condition including an increase in frequency and/or intensity of the condition
- New conditions detected or diagnosed after LN-145 administration
- Signs, symptoms, or the clinical sequelae of a suspected interaction with LN-145
- Signs, symptoms, or the clinical sequelae of special situations (eg, suspected overdose of either cyclophosphamide, fludarabine, IL-2, or a concomitant medication; medication error; product complaint; or occupational/accidental exposure)

Events that do not meet the definition of an AE include:

- Any clinically significant abnormal laboratory finding or other abnormal safety assessment that is associated with the underlying disease, unless judged by the Investigator to be more severe than expected for the patient's condition

- Medical or surgical procedure (eg, endoscopy, appendectomy). The condition that leads to the procedure is an AE
- Situations where an untoward medical occurrence did not occur (social and/or convenience admission to a hospital)
- Special situations, as described above (eg, overdose from a study medication or concomitant medication; medication error; product complaint; or occupational/accidental exposure) without clinical sequelae (Section 11.2.1)
- Anticipated day-to-day fluctuations of pre-existing disease(s) or condition(s) present (eg, AE grade change from 1 to 2 is an anticipated fluctuation) or detected at the start of the study that do not worsen

During clinical trials, AEs can be spontaneously reported or elicited during open-ended questioning, examination, or evaluation of a patient.

11.1.1.2. Serious Adverse Event

An SAE is considered "serious" if, in the view of either the Investigator or the Sponsor, it results in any of the following outcomes:

- Death
- A life-threatening situation
- Requires inpatient hospitalization or prolongation of an existing hospitalization
- A persistent or significant incapacity or substantial disruption of the ability to conduct normal life functions
- A congenital anomaly/birth defect
- An important medical event or a medically significant event that may not result in death, be immediately life-threatening, or require hospitalization but may be considered serious when, based on appropriate medical judgment, the event may jeopardize the patient or may require medical or surgical intervention to prevent one of the outcomes listed above

  Note: Hospitalization including admission to a telemetry unit or ICU specifically when pre-planned for administration of study treatment is not considered an SAE.

11.1.1.3. Relationship to Study Drug

The Investigator is responsible for assessing the relationship to study treatment using clinical judgement and the following considerations:

Definite: There is a known causal relationship between the study drug and the AE/SAE. The event responds to withdrawal of study drug (de-challenge), and recurs with re-challenge when clinically feasible

Probable: There is reasonable causal relationship between the study drug and the AE/SAE. The event responds to de-challenge

Possible: There is reasonable causal relationship between the study drug and the AE/SAE. De-challenge information is lacking or unclear

Not likely: There is temporal relationship to study drug administration, but there is not a reasonable causal relationship between the study drug and the AE/SAE

Not related: There is not a temporal relationship to study drug administration (too early, too late, or study drug not taken), or there is known causal relationship between the AE/SAE and another drug, concurrent disease, or other circumstance

Note: For regulatory reporting purposes, Definite, Probable, and Possible are submitted as related; Not likely and Not related are submitted as unrelated.

11.1.1.4. Severity

The severity of an event describes the degree of impact and/or the need for medical care necessary to treat an event.

AE grading will be defined by the CTCAE v5.0 (Appendix 17.5). If the CTCAE v5.0 does not apply, the severity descriptions below will be used:

Mild: Asymptomatic, clinical or diagnostic observations only; intervention not indicated

Moderate: Minimal, local, or noninvasive intervention indicated; limiting age-appropriate activities of daily life

Severe: Medically significant but not immediately life-threatening; hospitalization or prolongation of hospitalization may be required; disabling; limiting activities of daily life

Life-threatening: Urgent intervention is required.

11.2. Reporting Procedures for Adverse Events

11.2.1. All Adverse Events

All AEs/SAEs occurring after the patient has signed the ICF will be collected and recorded in the AE eCRFs and graded as per CTCAE v5.0. Disease progression is not considered an AE for the purposes of this study.

AEs will be collected at the temporal intervals described in Section 11.2.1.1.

If a patient dies while on the study, the Investigator will inform the Sponsor within 24 hours and report the cause of death as an SAE. For those SAEs leading to death, the CCI Form should indicate the most plausible cause(s) of death (eg, study disease, pre-existing condition[s], concomitant medication[s], intercurrent illness[es], or study procedure[s]). The clinical event leading to death should be recorded in detail on the CCI Form. Disease progression itself is not an AE, but the clinical signs or symptoms leading to death should be reported as an SAE with an outcome of death. Those deaths that occur greater than CCI after the last dose of Study drugs and that are assessed as not related to any study treatment should only be captured on the CCI eCRF and not on the CCI Form.

On the CCI Form, the cause of death should be recorded as follows:

- If due to an AE, it should be specified from which AE
  - Disease progression is not considered an AE
- If due to sequelae of disease under study, the specific reason should be identified (eg, clinical deterioration, respiratory insufficiency, liver failure, etc.)
- If due to "other" causes, the specific cause should be identified
- For patients who expired during OS Follow-up and medical records were unavailable, the cause of death should be marked as "unknown"

Each site will be responsible for reporting SAEs occurring at the site to the applicable IRB/IEC per the IRB's/IEC's reporting guidelines. Sites that are required to utilize a local IRB will be responsible for their own local IRB/IEC submissions.

It will be left to the Investigator's clinical judgment if an AE is of sufficient severity to require the patient's removal from the study treatment.

A patient may also voluntarily discontinue treatment due to what he or she perceives as an intolerable AE. This should be captured in the eCRF. If the patient was permanently removed from the study or LN-145 due to an SAE, this information must be included in either the initial or follow-up CCI Form and in the eCRF.

11.2.1.1. Investigator Reporting to Sponsor

AEs will be collected and reported according to the following temporal intervals:

- Adverse events and SAEs of any attribution must be reported to the Sponsor from the time of the signed ICF until CCI after the last dose of LN-145 or pembrolizumab (whichever occurs last) or start of new anticancer therapy.
- If a Grade 3 or 4 AE or SAE occurs from CCI after the last dose of LN-145 or pembrolizumab (whichever occurs last), it must be reported to the Sponsor only if considered related to any study drug.
- If any SAE occurs CCI after the last dose of LN-145 and there is a reasonable possibility that the event may have been caused by LN-145, then the SAE should be promptly reported to the Sponsor.

If the Investigator learns of any SAEs that occur after the OS Follow-up Period and there is a reasonable possibility that the event may have been caused by the study treatment, then the SAE should be promptly reported to the Sponsor or designee.

All SAEs that occur during the study period defined above must be reported by the Investigator to the Sponsor or designee within 24 hours of learning of the event. The initial notification should be as complete as possible with the information available and include the Investigator's assessment of study drug relationship, as defined in Section 11.1.1.3. All AEs, regardless of their severity, will be captured in the eCRF within the timelines outlined in the eCRF completion guidelines.

SAE terminology and severity grading will be based on the NCI's CTCAE v5.0 guidelines (Appendix 17.5).

All SAEs will also be reported on the CCI Form and submitted by email within 24 hours of knowledge of the event to:

Email: SCCI

Any additional correspondence or source documents requested by Iovance Safety also should be sent to this email address.

11.2.1.2. Special Situation Reporting

Definition of Special Situations

Special situation reports include: reports of medication error; overdose; AEs associated with product complaints; occupational exposure; and pregnancy reports regardless of an associated AE. Medication error is considered any unintentional error in the prescribing, dispensing, or administration of investigational product while in the control of the health care provider or patient. An overdose is defined as an accidental or intentional administration of a quantity of a medicinal/investigational product given per administration or cumulatively that is above the maximum recommended dose as per protocol.

Product complaints are defined as complaints arising from potential deviations in the manufacture, packaging, or distribution of the medicinal/investigational product.

Occupational exposure is defined as the exposure to a medicinal product as a result of one's professional or nonprofessional occupation.

Special situation reports must be reported to the Sponsor or designee using the CCI Form within 24 hours of becoming aware of the situation and the AE CRF but not considered an SAE unless associated with an SAE (ie, seriousness criteria would only need to be checked if there were an accompanying SAE). Special situations involving concomitant medications do not need to be reported; however, any AE resulting from a special situation should be reported on the AE eCRF page.

11.2.1.3. Pregnancy Reporting

Any pregnancy that occurs while on the study through CCI from the last study treatment or until the first dose of the next anticancer therapy, whichever occurs first, must be reported using the CCI Form within 24 hours of becoming aware of the pregnancy. The pregnancy itself is not considered an AE, nor is an induced abortion to terminate a pregnancy without medical reasons. Any premature termination of pregnancy (eg, a spontaneous abortion, an induced therapeutic abortion due to complications, or other medical reasons), must be reported within 24 hours as an AE or SAE. The underlying medical reason for this procedure should be recorded as the AE or SAE term. A spontaneous abortion is always considered to be an SAE and will be reported as described in Section 11.2.1.2.

The patient should receive appropriate monitoring and care until the conclusion of the pregnancy to determine the outcome and status of the patient and child. The outcome should be reported to the Safety CRO using the CCI Form. Any SAE occurring in association with a pregnancy, brought to the Investigator's attention after the patient has completed the study

treatment and Assessment Period follow-up visits, must be promptly reported to the Sponsor or their representative.

The pregnancy must be followed up until discharge following delivery or premature termination to determine outcome and status of mother and child. Pregnancy complications and elective terminations for medical reasons must be reported as an AE or SAE. Spontaneous abortions must be reported as an SAE. Any SAE occurring in association with a pregnancy, brought to the Investigator's attention after the patient has completed the study, and considered by the Investigator as possibly related to LN-145, must be promptly reported to the Sponsor or their representative.

11.2.1.4. Adverse Events of Special Interest

Uveitis

Uveitis, or inflammation of the uvea (which consists of the iris, ciliary body, and choroid), has been observed in patients who have received LN-145 for the treatment of metastatic melanoma and is considered an adverse event of special interest (AESI). Uveitis in these patients was mild to moderate in intensity, associated with symptoms such as blurred vision, eye pain, nyctalopia, photopsia, retinal hemorrhage, and/or vitreous floaters, and often improved with corticosteroid therapy.

Uveitis may be caused by a number of different etiologies; therefore, diagnosis and treatment of the underlying disease are imperative not only to treat the disease but also to preserve vision and potentially uncover underlying systemic diseases. If untreated or not appropriately treated, acute inflammation can develop into chronic, sight-threatening inflammation. Thus, when a patient presents with clinical signs and symptoms that may be associated with uveitis (eg, blurry vision; dull, aching, or throbbing pain in the temple or periorbital region; photophobia; circumlimbal injection; anterior chamber cells and flare; altered intraocular pressure), the Investigator should refer the patient to a trained eye specialist for further evaluation. Once an etiology has been established, appropriate treatment should be initiated and customized to each patient, as suboptimal treatment may lead to complications and loss of vision.

All AEs of uveitis, whether considered related or unrelated to TIL or any study treatment, must be recorded on the CCI Form and reported to the Sponsor or designee within 24 hours, even if they are considered nonserious according to the usual regulatory criteria. The Investigator must follow any patient experiencing uveitis until resolution or stabilization of the event, an alternative explanation to study intervention is provided for the event, or the patient is lost to follow-up. The Investigator should submit any further details obtained from follow-up to the Sponsor or designee within 24 hours of it becoming available.

11.2.1.5. Regulatory Reporting Requirements

In the event of a suspected unexpected serious adverse reaction (SUSAR), the Sponsor, or their designee, will notify the appropriate regulatory authorities and all appropriate parties as per the regulations.

Assessment of expectedness for SAEs will be determined by Iovance Biotherapeutics Inc. using reference safety information (RSI) in the IB and relevant prescribing information for TIL, as well as the RSI for cyclophosphamide, fludarabine, and IL-2. Assessment of expectedness based on

local label (USPI) for cyclophosphamide, fludarabine, and IL-2 will apply for reports to the US Food and Drug Administration (FDA).

In addition, the Sponsor must submit expedited reports of potential serious risks from clinical trials or any other source based on relevant local legislation or regulations, including the applicable US FDA Code of Federal Regulations (CFR) and the EU Clinical Trial Directive (2001/20/EC) and relevant updates. The Sponsor will notify participating sites of relevant SUSAR reports and other applicable serious safety findings that occur during the trial including the post-study treatment follow-up phase.

11.2.1.6. Product Complaints

The Sponsor collects product complaints arising from potential deviations in the manufacture, packaging, or distribution of LN-145 and other study drugs in order to ensure the safety of study participants, monitor quality, and facilitate process and product improvements.

All product complaints associated with material packaged, labeled, and released by the Sponsor or its designee will be reported to the Sponsor. All product complaints associated with other study material will be reported directly to the respective manufacturer.

The Investigator or his/her designee is responsible for reporting a complete description of the product complaint via email or other written communication to the Sponsor contact or respective manufacturer as noted in the packaging information. Any AE associated with a product complaint should be reported as described in Section 11.2.

If the Investigator is asked to return the product for investigation, he/she will return a copy of the product complaint communication with the product. Any AE associated with a product complaint should be reported as described in Section 11.2.1.2.

12. SAFETY ASSESSMENTS

12.1. Data Safety Monitoring Board

An independent Data Safety Monitoring Board (DSMB) will evaluate safety data in Cohort 1 when the CCI and when up to a total of CCI have completed CCI assessments post-LN-145 infusion. Enrollment will continue while under review. The DSMB will also review safety data from the CCI in Cohort 2 and CCI in Cohort 3, who received TIL and have completed CCI of assessments post LN-145 infusion.

12.2. Independent Data Monitoring Committee

An Independent Data Monitoring Committee (IDMC) composed of a group of clinicians appointed by Iovance will provide oversight of this clinical trial to ensure quality and consistency of study conduct as well as data collection and analysis across international study sites. The IDMC will review the study data when up to a total of CCI have completed CCI of assessments post-LN-145 infusion. Enrollment will continue while data is under review. The IDMC will also review the study data in Cohort 1 after up to a total of CCI have completed CCI of assessments post-LN-145 infusion. The IDMC will also review the study data from Cohort 2 after up to a total of CCI have received LN-145 infusion and completed CCI assessments post-LN-145 infusion.

13. STATISTICAL AND ANALYTICAL PLANS

13.1. Introduction

The statistical analysis will be based on the estimation of efficacy and safety parameters and 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 support registration of cryopreserved LN-145 product in the treatment of patients who have progressed during or following systemic therapy for recurrent, metastatic, or persistent cervical cancer. Two separate formal statistical hypothesis testing are planned for the primary endpoint in Cohort 1 and Cohort 2, respectively. For all other cohorts, the statistical analysis is based on the use of descriptive methods; no formal hypothesis testing is planned. A more detailed description of the analyses of the data will be provided in the Statistical Analysis Plan (SAP).

13.2. Study 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 analysis for the primary efficacy endpoint and adverse events will be conducted using the Tumor Harvested (TH) Set (also termed Enrolled Set). The primary efficacy endpoint will also be summarized using the Efficacy Evaluable (EE) Set.

Study Analysis Set Definitions

Sample Size Justification

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 only be counted 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 ≤CCI and alternative hypothesis of ORR >CCI will be tested. The sample size of 75 patients will result in more thanCCI power to demonstrate superiority to the ORR of

CCI using a conservative assumption for TIL therapy of CCI

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 ≤ CCI and alternative hypothesis of ORR > CCI will be tested. The sample size of 75 patients will result in more than CCI power to demonstrate superiority to the ORR of CCI using an assumption for TIL therapy of CCI **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 CCI

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.

13.2.1. Hypothesis Testing and Multiplicity Adjustment

Two separate hypotheses, one for Cohort 1 and one for Cohort 2, will be tested in this study. Each hypothesis will be tested at a two-sided significance level of 0.05. Since the two hypotheses will test the primary efficacy endpoint in two different patient population and the statistical inference will be made separately, no multiplicity adjustment is needed.

- Hypothesis in Cohort 1: H_{01}: ORR ≤ CCI vs. H_{a1}: ORR > CCI. This is to test the null hypothesis of ORR of ≤ CCI in recurrent, metastatic, or persistent cervical carcinoma with disease progression on or after chemotherapy.
- Hypothesis in Cohort 2: H_{02}: ORR ≤ CCI vs. H_{a2}: ORR > CCI This is to test the null hypothesis of ORR of ≤ CCI in patients with recurrent, metastatic, or persistent cervical carcinoma with disease progression on or after chemotherapy as well as a PD-1/PD-L1 checkpoint inhibitor.

Justification for Null Hypothesis

Justification for the null hypothesis of ORR≤ CCI 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 an FDA-approved test. CCI excluding CCI. 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 is proposed for this cohort.

Justification for the null hypothesis of ORR ≤ [redacted] in Cohort 2: There is no approved systemic therapy and high unmet medical need in patients who have progressed during or following treatment with frontline chemotherapy and PD-1/PD-L1 checkpoint inhibitor. McLachlan et al. reported that ORRs for advanced cervical cancer patients treated with second and third line therapy were 13.2% and 3.4% respectively [McLachlan 2017]. In this paper, only one patient received anti-PD-L1 treatment within a clinical trial. In the NCCN guidelines, no recommendation is given about the most effective second-line treatment except PD-1 checkpoint inhibitors for PD-L1 positive tumors because most ORRs are low (range 4.5-28.6%) and DOR is short in recurrent setting [Schilder 2005; Garcia 2007; Monk 2009; Look 1996; Alberts 2012; Verschraegen 1997; Miller 2008; Muggia 2004; Bookman 2000]. Tewari, et al reported that in their randomized Phase 3 trial involving patients with recurrent cervical cancer who had disease progression after platinum-containing therapy, the observed ORR for the patients who were treated with Investigator's choice chemotherapy was 6.3% (19/304 patients) [Tewari 2022]. The treatment response in patients who have progressed during or following treatment with PD-1/PD-L1 checkpoint inhibitor is unknown.

Therefore, the null hypothesis of [redacted] ORR is considered clinically meaningful for Cohort 2 with patients who have progressed during or following at least 1, but no more than 3, prior systemic chemotherapeutic treatments and received treatment with a checkpoint inhibitor (ie, PD-1, PD-L1).

13.3. Patient Disposition

Patient disposition will be summarized using frequency and percentage as described in the SAP. A summary of patients enrolled by site will be provided.

13.4. Baseline Demographic and Clinical Characteristics

Baseline [redacted] demographic and clinical (disease) characteristics will be summarized descriptively. Patients among the resected, untreated population will be summarized by the primary reason of not receiving the treatment together with the safety events.

13.5. Study Endpoints and Planned Analyses

13.5.1. Primary Endpoint

The primary endpoint for Cohort 1 and 2 is the ORR as assessed by the Investigator as per RECIST v1.1. It is expressed as binomial proportions and will be summarized for the best overall response using a point estimate and its two-sided 95% confidence limits based on the [redacted] Patients without any baseline or post-baseline measurements are considered non-responders.

13.5.2. Secondary Endpoints

- The secondary efficacy endpoints for each Cohorts 1, 2, and 3 are defined in Section 3.2.2. DOR is measured from the first-time response (PR/CR) criteria are met

until the first date that PD is objectively documented, or the patient expires. Patients not experiencing PD or who have not died prior to the time of data cut or the final database lock will have their event times censored on the last adequate radiological disease assessment before the start of a new anticancer therapy.

- DCR is derived as the sum of the number of patients who achieved confirmed PR/CR or stable disease (SD) tumor responses divided by the number of patients in the Analysis Set ×100%
- PFS is defined as the time (in months) from the time of LN-145 infusion to PD, or death due to any cause, whichever event is earlier. Patients not experiencing PD or not having died at the time of the data cut or the final database lock will have their event times censored on the last date that an adequate assessment of tumor status is made. For patients who received new anticancer therapies, the PFS is measured from the date of LN-145 infusion to the date of last tumor response assessment prior to the start of new anticancer therapies
- OS is defined as the time (in months) from date of LN-145 infusion to death due to any cause. Patients not having died by the time of data cut or the final database lock will have their event times censored on the last date of their known survival status

The DCR is expressed as binomial proportions and will be summarized using both a point estimate and its two-sided 95% confidence limits based on the Clopper-Pearson exact method.

The PFS, OS, and DOR are time-to-event variables subjected to right censoring. Kaplan-Meier probabilities and related summary statistics will be provided for the entire time-to-event curve as well as for the following landmark event-free rates: CCI [redacted] from the date on which patients received LN-145 infusion CCI [redacted] depending on the maturity of the study data at the time of analysis.

13.5.3. Safety Analysis

The assessment of safety data will be descriptive and based on the summarization of TEAEs, SAEs, and AEs leading to discontinuation from the study, vital signs, and clinical laboratory tests. TEAEs include AEs that occur from the start of LN-145 infusion and up to CCI [redacted] after LN-145 infusion for Cohorts 1 and 2. For Cohort 3, TEAEs include AEs that occur from 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 anti-cancer therapy. AE summaries will be based on patient incidence counts and their related percentages. In addition to an overall summary of AEs, separate displays will be made by severity and relationship. Certain safety data will be amenable to summary by use of toxicity grades, and all such analyses will evaluate the worst grade observed per patient during the treatment-emergent period. These toxicity grade summaries will be derived separately based on the current version of CTCAE v5.0 for each measure under consideration (eg, ANCs for neutropenia; platelets for thrombocytopenia; Appendix 17.5).

A separate safety summary will be provided for patients in the TH population starting from the tumor resection for CCI [redacted] (TH nontreated population) or until date of first dose of the study treatment.

13.5.4. Exploratory Analyses

- Correlation of immune factors CCI [redacted] with efficacy of TIL therapy will be explored. The results will be reported in a separate report
- Evaluation of ORR, DOR, DCR, and PFS as assessed per irRECIST by the Investigator
- Patient-reported outcomes for HRQoL will be assessed using the EORTC QLQ-C30 v3.0 instrument and analyzed per the published evaluation manual
- Q-TWiST will be calculated as sum of the three health state periods (Toxicity, TWiST, and Relapse) [Sherrill 2013] with each multiplied by the appropriate utility score [Beusterien 2009]

14. ADMINISTRATIVE REQUIREMENTS

14.1. Good Clinical Practice

The procedures set out in this study protocol pertaining to the conduct, evaluation, and documentation of this study are designed to ensure that the Sponsor, its authorized representative, and Investigator abide by GCP, as described in ICH Guideline (ICH E6 R2) and in accordance with the general ethical principles outlined in the Declaration of Helsinki. The study will receive approval from an IRB/IEC prior to commencement. The Investigator will conduct all aspects of this study in accordance with applicable national, state, and local laws of the pertinent regulatory authorities.

The specific contact details of the Iovance Biotherapeutics Inc. legal/regulatory entity within the relevant country are provided within the clinical trial agreement with the Investigator/Institution and in the Clinical Trial Application with the Competent Authority.

14.2. Adherence to the Protocol

The Investigator is responsible for ensuring the study is conducted in accordance with the procedures and evaluations described in the protocol. The Investigator will not deviate from this protocol without obtaining the concurrence of the Sponsor, specifically without discussion with the Medical Monitor. All protocol amendments must be issued by the Sponsor, signed and dated by the Investigator, and should not be implemented without prior IRB/IEC approval, except where necessary to eliminate immediate hazards to the patients or when the change(s) involves only logistical or administrative aspects of the trial (eg, change in Medical Monitor[s], change of telephone number[s]). Responsibilities for reporting protocol amendments to any regulatory authority (if applicable) and/or IRB/IEC are further described per Sponsor or designee operating procedures and delegation of regulatory obligations.

14.3. Record Retention

In compliance with the ICH-GCP guidelines, the Investigator/Institution will be responsible for all information in the eCRF and will maintain the source documents that support the data collected from each patient, and all trial documents as specified in Essential Documents for the Conduct of a Clinical Trial and as specified by the applicable regulatory requirement(s). The Investigator/Institution will take measures to prevent accidental or premature destruction of these documents. Essential documents must be retained until at least 2 years after the last approval of a marketing application in an ICH region or at least 2 years have elapsed since the formal discontinuation of clinical development of LN-145. These documents will be retained for a longer period if required by the applicable regulatory requirements or by an agreement with the Sponsor. It is the responsibility of the Sponsor to inform the Investigator/Institution as to when these documents no longer need to be retained. If the responsible Investigator retires, relocates, or for other reasons withdraws from the responsibility of keeping the study records, custody must be transferred to a person who will accept the responsibility. The Sponsor must be notified in writing of the name and address of the new custodian.

14.4. Data Quality Assurance

This trial shall be conducted in accordance with the provisions of the Declaration of Helsinki (October 2008) and all revisions thereof, and in accordance with FDA regulations (21 CFR Parts 11, 50, 54, 56, and 312, Subpart D – Responsibilities of Sponsors and Investigators) and with the ICH guidelines on GCP (ICH E6 R2).

Steps to be taken to assure the accuracy and reliability of data include: the selection of qualified Investigators and appropriate study centers; review of protocol procedures with the Investigator and associated personnel prior to the study; and periodic monitoring visits by the Sponsor/designee. The eCRFs will be reviewed for accuracy and completeness by Clinical Research Monitors during on-site monitoring visits and after their return from the site, and any discrepancies will be resolved with the Investigator or designees, as appropriate. The data will be verified for accuracy.

Agreements made by the Sponsor with the Investigator/Institution and any other parties involved in the clinical trial will be in writing as a separate agreement.

Representatives of the Sponsor's Clinical Quality Assurance department/designee may visit the site to carry out an audit of the study in compliance with regulatory guidelines and company policy. Such audits will require access to all study records, including source documents, for inspection and comparison with the eCRFs. Patient privacy must, however, be respected. Sufficient prior notice will be provided to allow the Investigator to prepare properly for the audit.

Similar auditing procedures may also be conducted by agents of any regulatory body reviewing the results of this study in support of a Licensing Application. The Investigator should immediately notify the Sponsor if they have been contacted by a regulatory agency concerning an upcoming inspection.

14.5. Data Handling and Recordkeeping

14.5.1. Regulatory Approval and Documentation

Iovance Biotherapeutics Inc. (Sponsor) will determine the appropriate local, national, and/or regional regulatory approvals that need to be obtained to conduct the study.

Documents that must be provided to the Sponsor prior to study-drug shipment are as follows:

- Up-to-date curriculum vitae for each Investigator
- Signed and dated Investigator Agreement
- Applicable local regulatory documentation (eg, FDA 1572 Form)
- A copy of the formal written notification to the Investigator regarding approval of the protocol by an IRB/IEC that is in compliance with regulatory guidelines. The written notification is to be signed by the chairman or authorized designee and must identify the specific protocol. In cases where an IRB/IEC member has a known conflict of interest, abstention of that individual from voting should be documented; an Investigator may be a member of the IRB/IEC, but may not vote on any research in which he or she is involved

- Name and address of the IRB/IEC with a statement that it is organized and operates according to GCP and the applicable laws and regulations, and a current list of the IRB/IEC members. If accompanied by a letter of explanation from the IRB/IEC, a general statement may be substituted for this list
- A copy of the IRB/IEC approved informed consent and other adjunctive materials (eg, advertising) to be used in the study, including written documentation of IRB/IEC approval of these items
- Name and address of any local laboratory conducting tests for the study, a dated copy of the laboratory reference values for tests to be performed during the study and a copy of the certification or other documentation establishing adequacy of the facility
- Required financial agreement
- In addition to the documents required prior to the study, other documentation may be required during the study

14.5.2. Electronic Data

When using electronic data processing, the Sponsor or their designee ensures that systems comply with 21 CFR Part 11, CTR EU No. 536/2014 and General Data Protection Regulation (GDPR), EU 2016/679 requirements, as applicable. Documentation regarding the electronic data systems used in this protocol is located in the study-specific plans or Standard Operating Procedures (SOPs) for that particular task.

14.5.3. Data Handling and Recordkeeping

14.5.3.1. Electronic Case Report Form Completion

EDC will be used for the study. The site will be suitably trained on the use of the eCRF and appropriate site personnel will be provided electronic signatures. Data must be entered into the eCRF screens in English.

Data must be recorded first on a source document that can be verified before it is entered in the EDC system. Completed eCRFs are to be signed off by the Investigator as per the data completion guidelines written for the study.

All eCRF corrections are to be made by the Investigator or other authorized study site personnel. The Investigator must authorize changes to the recorded safety and efficacy data.

Completed eCRFs will be reviewed by the Sponsor/designee to determine their acceptability. If necessary, Data Correction Requests will be generated for resolution by the study site.

14.5.4. Study Completion/Termination

The Sponsor reserves the right to temporarily suspend or terminate the study at any time. Reasons for such action taken by the Sponsor include, but are not limited to:

- The discovery of unexpected, serious, or unacceptable risk to patients enrolled in the study
- A decision on the part of the Sponsor to suspend, discontinue, or shorten the study

Upon completion of the study, the Investigator will ensure that the complete set of source data has been entered into the eCRFs.

14.5.5. Monitoring

On-site monitoring visits will be performed by the Sponsor as frequently as necessary. At these visits, the monitor will compare the data entered into the eCRFs with the hospital or clinic records (source documents). At a minimum, source documentation must be available to substantiate proper informed consent procedures, adherence to protocol procedures, adequate reporting and follow-up of AEs, administration of concomitant medications, drug receipt/dispensing/return records, and study drug administration information. Specific items required as source documents will be reviewed with the Investigator prior to the study. Findings from this review of eCRFs and source documents will be discussed with the Investigator. The source documentation will be available, and a suitable environment will be provided for review of study-related documents.

15. INVESTIGATOR REGULATORY OBLIGATIONS

15.1. Institutional Review Board/Independent Ethics Committee

Before Enrollment of patients into the study, as required by federal regulations (21 CFR 56), international regulations, and ICH-GCP Guidelines, the protocol and ICF(s) must be reviewed and approved by an appropriate IRB/IEC. By signing the FDA Statement of Investigator Form 1572 or the Sponsor's Statement of Investigator Commitments, the Investigator assures that all aspects of the institutional review will be conducted in accordance with current applicable regulations. A letter documenting the IRB/IEC approval with the names and titles of the IRB/IEC members must be received by the Sponsor before the initiation of the trial. Amendments to the protocol will be subject to the same requirements as the original protocol. In other countries, the protocol and any amendments must be approved by the concerned IECs as per the applicable laws and requirements on the national and European level.

15.2. Informed Consent

Each patient (or a legally authorized representative) must give written consent (and sign other locally required documents) according to local requirements after the nature of the study has been fully explained. The consent form must be signed prior to performance of any study-related activity. The consent form that is used must be approved both by the Sponsor and by the reviewing IRB/IEC. The informed consent should be in accordance with the current revision of the Declaration of Helsinki, current ICH and GCP guidelines, Directive 2001/20/EC (and when in force EU Regulation 536/2014), and GDPR 2016/679, as interpreted by the national laws and regulatory bodies, and the Sponsor's policies.

The Investigator must explain to potential patients or their legal representatives the purpose, methods, reasonably anticipated benefits and potential hazards of the study, its duration, and any discomfort it may entail. Patients will be informed in their native language, comprehensive, concise, clear, relevant, and understandable to a layperson, that their participation is voluntary and that they are free not to participate in the study and may withdraw consent to participate at any time. They will be told which alternative treatments are available if they refuse to take part and that such refusal will not prejudice future treatment. They will be told that their records may be examined by competent authorities and authorized persons but that their personal data will be treated as strictly confidential and will not be publicly available. Patients must be given the opportunity to ask questions.

During the consenting process the Investigator or designee will explain to each patient that their coded study data, along with clinical and health data collected as part of this study, may be used for future exploratory cancer research and related treatment options. These data may be used to identify factors predictive of response or resistance to TIL therapy to drive improvement of TIL therapy, identify pharmacodynamic mechanisms important for LN-145 activity, and identify multivariate correlations predicting response or resistance to TIL therapy, as well as mechanisms important for TIL activity and treatment options.

Patients will be told that their unused biological samples may be used for future exploratory cancer research and they are free to refuse to participate and may withdraw their consent at any time for optional use of their leftover samples for any reason during the sample storage period.

Samples provided during the study will continue to be analyzed to study exploratory biomarker objectives and endpoints unless the patient indicates in writing that she/he wishes for her/his samples to be destroyed.

After this explanation and before entry into the study, consent should be appropriately recorded by means of the patient's or his/her legal representative's dated signature. If a patient and his/her legal representative are unable to read, an impartial witness must be present during the entire informed consent discussion. The signature of the impartial witness will certify the patient's consent. The patient and their legally designated representative must receive a signed and dated copy of the informed consent. The informed consent process should be documented in the patient's medical record. Adequate time shall be given for the patient or his/her legally designated representative to consider his/her decision to participate in the study.

In accordance with the Health Insurance Portability and Accountability Act (HIPAA), the written ICF must include a patient authorization to release medical information to the Sponsor or their representative and/or allow the Sponsor or their representative, a regulatory authority, or IRB/IEC access to patient's medical information that includes all hospital records relevant to the study, including a patient's medical history and other data that may identify him/her, including the purpose of this access and data processing connected with it.

15.3. Patient Data Protection

The Investigator at each site and designees, employees, and agents involved with the study will comply with relevant state, federal national, and regional laws relating to the confidentiality, privacy, and security of patient's personal health information (PHI). They will only create, maintain, use, or disclose any data that is generated by the study or other information disclosed to the Investigator or their employees or agents during the course of the study to the Sponsor, the Sponsor's collaborators, IRB/IEC, FDA, European Medicines Agency (EMA), national regulatory authorities, or other authorized recipients as appropriate for the execution, analysis, review, and reporting of the study. Such information shall not be used for any other purposes and will remain confidential. Patients will not be individually identified but will be referred to in records by the study-assigned number.

15.4. Adverse Event Reporting

The Investigator agrees to report all AEs/SAEs to the Sponsor as described in Section 11.2. Furthermore, the Investigator is responsible for ensuring that any co-Investigator or sub-Investigator promptly bring AEs to the attention of the Principal Investigator. The Investigator shall promptly notify the IRB/IEC of any SAEs, or any other information that may affect the safe use of LN-145 during the course of the trial as applicable per the local IRB/IEC requirements.

15.5. Investigator

The Investigator will permit study-related monitoring, audits, IRB/IEC review, and regulatory inspections by providing direct access to source data and documents. The Investigator must notify the Sponsor when contacted by a regulatory authority regarding inspection of her/his study site and document all access to personal data and their transfers covered by this protocol.

All required data will be recorded in the eCRFs in a timely manner. All eCRF data must be submitted to the Sponsor throughout and at the end of the study.

If an Investigator retires, relocates, or otherwise withdraws from conducting the study, the Investigator must notify the Sponsor to agree upon an acceptable storage solution. Regulatory authorities will be notified with the appropriate documentation detailing the person to whom the responsibility has been transferred.

15.6. Confidentiality

Unless otherwise specified in the clinical study agreement, the following process shall occur: the Investigator must assure that patients' anonymity will be maintained and that their identities are protected from unauthorized parties. In the eCRFs or other documents submitted to the Sponsor, patients should not be identified by their names, but by an identification code. The Investigator should keep a site-enrollment log showing codes, names, and addresses. Documents not for submission to the Sponsor (eg, patients' written ICFs) should be maintained by the Investigator in strict confidence, in accordance with all applicable local and national regulations. All information provided to the Investigator prior to the study, as well as all data developed during the study, is confidential and remains the property of the Sponsor. The Investigator agrees that no information based on the conduct of this study (including the protocol, the data resulting from the study, or the fact that the study is/was conducted) will be released without prior written consent of the Sponsor unless this requirement is superseded by local or national regulations.

15.7. Publications

The Sponsor will be responsible for determining when the study results should be published. The Sponsor will work jointly with the Investigators to publish information on study results. An Investigator shall not submit a publication or abstract to journals or scientific meetings without the prior written approval of the Sponsor, except as permitted by the agreed terms of the clinical trial agreement, including after the reporting of the results of this multi-center study by the Sponsor and other institutions.

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17. APPENDICES

17.1. Schedule of Assessments

	Screening, Enrollment, and Baseline Period	Treatment Period	Assessment Period	Overall Survival
CCI				

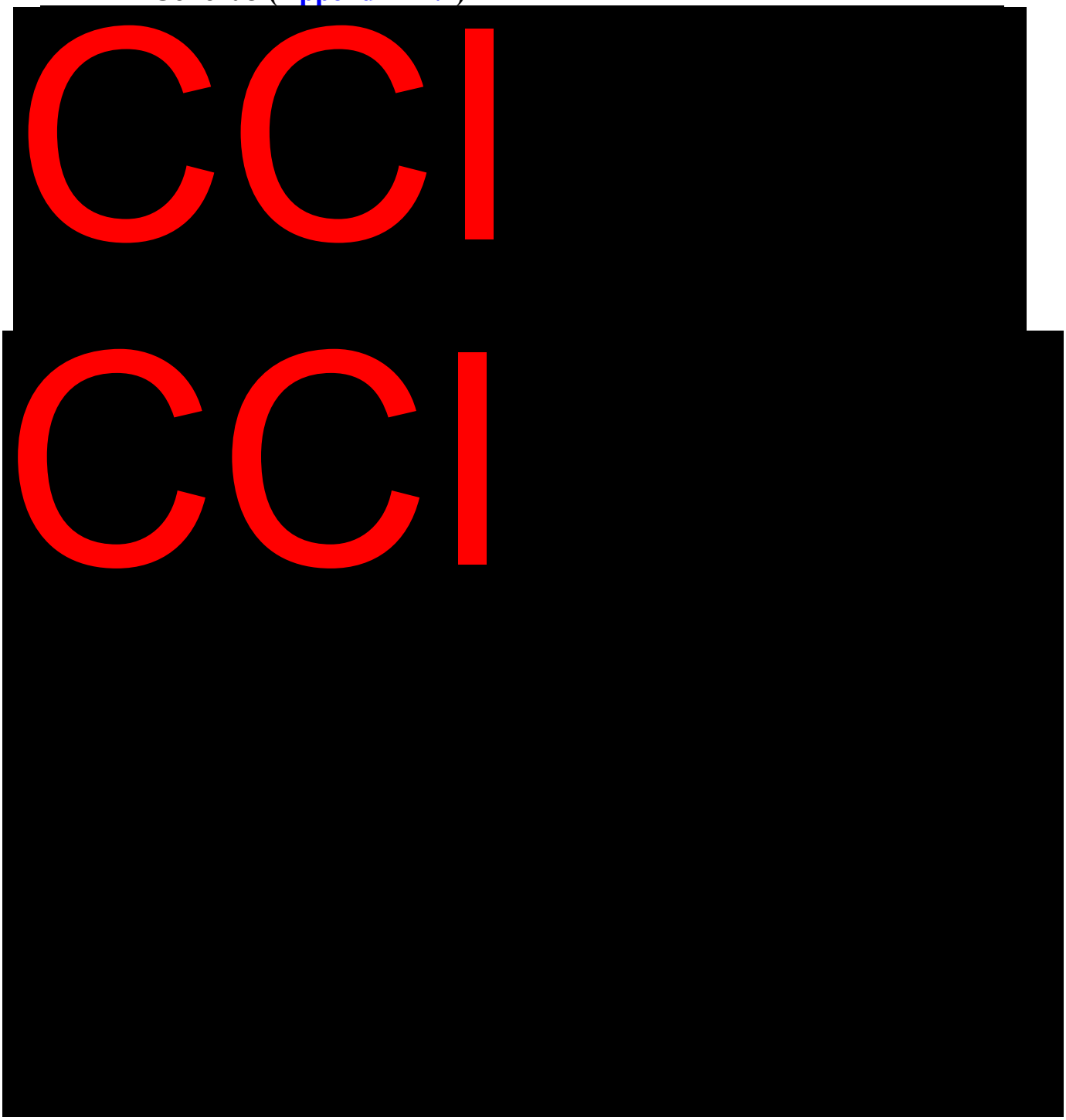
	Screening, Enrollment, and Baseline Period	Treatment Period	Assessment Period	Overall Survival
CCI				

	Screening, Enrollment, and Baseline Period	Treatment Period	Assessment Period	Overall Survival
[redacted]				


CCI


CCI

17.2. Study-Specific Visits as Outlined in the Schedule of Assessments for Cohort 3 (Appendix 17.1)*



17.3. Fédération Internationale de Gynécologie et d'Obstétrique (FIGO) Classifications for Cervical Carcinoma

FIGO STAGES	Surgical-Pathologic Findings
I	Cervical carcinoma confined to the cervix (disregard extension to the corpus)
IA	Invasive carcinoma diagnosed only by microscopy; stromal invasion with a maximum depth of 5.0 mm measured from the base of the epithelium and a horizontal spread of 7.0 mm or less; vascular space involvement, venous or lymphatic, does not affect classification
IA1	Measured stromal invasion ≤ 3.0 mm in depth and ≤ 7.0 mm in horizontal spread
IA2	Measured stromal invasion > 3.0 mm and ≤ 5.0 mm with a horizontal spread ≤ 7.0 mm
IB	Clinical lesions confined to the cervix or preclinical lesions greater than Stage IA. All gross lesions even with superficial invasion are Stage IB cancers.
IB1	Clinically visible lesion ≤ 4.0 cm in greatest dimension
IB2	Clinically visible lesion > 4.0 cm in greatest dimension
II	Cervical carcinoma invades beyond uterus but not to pelvic wall or to lower third of vagina
IIA	Tumor without parametrial invasion. Involvement of up to the upper two-thirds of the vagina.
IIB	Tumor with parametrial invasion, but not into the pelvic sidewall
III	Tumor extends to pelvic wall and/or involves lower third of vagina and/or causes hydronephrosis or nonfunctional kidney
IIIA	Tumor involves lower third of vagina, no extension to pelvic wall
IIIB	Tumor extends to pelvic wall and/or causes hydronephrosis or nonfunctional kidney
IV	Tumor invades mucosa of bladder or rectum and/or extends beyond true pelvis (bullous edema is not sufficient to classify a tumor as T4)
IVA	Tumor invades mucosa of bladder or rectum
IVB	Tumor extends beyond true pelvis
***Regional lymph nodes (N)**	
NX	Regional lymph nodes cannot be assessed
N0	No regional lymph node metastasis
N1	Regional lymph node metastasis
***Distant metastasis (M)**	
M0	No distant metastasis
M1	Distant metastasis (including peritoneal spread; involvement of supraclavicular, mediastinal, or para-aortic lymph nodes; and lung, liver, or bone)

Source: TNM Classification of malignant tumours. L. Sobin and Ch Wittekind (eds.),
UICC International Union against Cancer, Geneva, Switzerland, pp155-157; 6th ed. 2002.
References: [Pecorelli 2009a, Pecorelli 2009b]

17.4. ECOG Performance Status Scale

ECOG Performance Status Scale	
Grade	**Descriptions**
0	Normal activity. Fully active, able to carry on all pre-disease performance without restriction.
1	Symptoms, but ambulatory. Restricted in physically strenuous activity, but ambulatory and able to carry out work of a light or sedentary nature (eg, light housework, office work).
2	In bed < 50% of the time. Ambulatory and capable of all self-care, but unable to carry out any work activities. Up and about more than 50% of waking hours.
3	In bed > 50% of the time. Capable of only limited self-care, confined to bed or chair more than 50% of waking hours.
4	100% bedridden. Completely disabled. Cannot carry on any self-care. Totally confined to bed or chair.
5	Dead.

Adapted from [Oken 1982]

17.5. Common Terminology Criteria for Adverse Events

CTCAE_v5_Quick_Reference_5x7.pdf

17.6. Calculation of BMI, BSA, and Practical Weight

Unless otherwise specified in this protocol, actual body weight is used for dose calculations of treatment agents. In patients who are determined to be obese (BMI > 35.0 kg/m^2), the actual weight will be used unless the standard of practice at the clinical site demands using practical weight.

17.6.1. BMI

BMI = weight (kg)/[height (m)]^2

17.6.2. BSA

The BSA should be calculated using the following formula:

BSA = 0.007184 x height (cm)$^{0.725}$ x weight (kg)$^{0.425}$

Other institutional standard formulas are acceptable.

17.6.3. Practical Weight

Actual body weight recorded at CCI will be used, unless the standard of practice at the clinical site demands using practical weight.

If the standard of practice at the clinical site demands, practical body weight (average of the actual weight and ideal body weight) is to be used when dosing cyclophosphamide and fludarabine in patients who have a BMI > 35.0 kg/m^2.

17.6.4. Ideal Body Weight

Male = 50 kg + 2.3 x (number of inches over 60 inches)
Example: ideal body weight of 5’10’’male
50 + 2.3 x 10 = 73 kg

Female = 45.5 kg + 2.3 x (number of inches over 60 inches)
Example: ideal body weight of 5’3’’female
45.5 + 2.3 x (3) = 57 kg