ADVANCING IMMUNO-ONCOLOGY

CLINICAL PROTOCOL

A Phase 2, Multicenter Study to Evaluate the Efficacy and Safety of Autologous Tumor Infiltrating Lymphocytes (LN-145/LN-145-S1) for the Treatment of Patients with Recurrent and/or Metastatic Squamous Cell Carcinoma of the Head and Neck

PROTOCOL NUMBER:	C-145-03
EudraCT NUMBER	2016-003446-86
SPONSOR:	Iovance Biotherapeutics, Inc. 999 Skyway Rd, Suite 150 San Carlos, CA 94070
PROTOCOL VERSION:	Version 4.0, 25 Nov 2019
SUPERSEDES:	Version 3.0, 17 Aug 2018 Version 2.0, 30 Aug 2017 Version 1.0, 16 Aug 2016
MEDICAL MONITOR:	[redacted] Medical Director [redacted] [redacted]

SPONSOR SIGNATURE PAGE

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Protocol Number:	C-145-03
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Protocol Version and Date:	Protocol Amendment, Version 4.0, 25 Nov 2019

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

DocuSigned by:
[redacted]
Signer Name: [redacted]
Signing Reason: I approve this document
Signing Time: 25-Nov-2019 | 12:01:42 PST
Signature: 8DEF353D7B93431CB5507442AFF1B992

25-Nov-2019 | 12:01:49 PST

Signature **Date**

[redacted]

INVESTIGATOR PROTOCOL SIGNATURE PAGE

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I agree to conduct the study as detailed in the protocol and in compliance with ICH 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 STATEMENT

Below is a review of the substantive changes made to amend Protocol C-145-03 from Version 3.0 to 4.0.

- Addition of a study cohort that will receive LN-145-S1. LN-145-S1 is manufactured using a [redacted] LN-145-S1 is thus a subset of the LN-145 TIL product that will be evaluated in patients with recurrent and/or metastatic squamous cell carcinoma of the head and neck.
- Patients will be grouped into cohorts according to LN-145 TIL manufacturing process and a re-treatment cohort. Some additional information on each manufacturing process has been added to the background for clarity. Five cohorts have been defined as follows:
    - Cohort 1 (closed to enrollment): Treatment with LN-145, Generation 1 (Gen 1), non-cryopreserved TIL
    - Cohort 2: Treatment with LN-145, Generation 2 (Gen 2), cryopreserved TIL (22-day manufacturing process)
    - Cohort 3: Treatment with LN-145, Generation 3 (Gen 3), cryopreserved TIL (≤ 17-day manufacturing process)
    - Cohort 4: Treatment with LN-145-S1, [redacted] cryopreserved TIL
    - Cohort 5: Re-treatment with LN-145 cryopreserved/LN-145-S1[redacted] cryopreserved TIL
- The total number of patients has been increased to approximately 55 to reflect the addition of the LN-145-S1 cohort.
- The sample size justification has been updated for a multiple cohort design for different TIL products.
- Clarifications were made to the eligibility criteria to improve clinical parameters for appropriate patient selection.
    - Updated pulmonary function testing (PFT) parameters to better reflect risk parameters for TIL
    - Updated Screening/Baseline radiographic imaging to avoid unnecessary repetition of scans prior to treatment phase
    - Updated text for patients with asymptomatic brain metastasis
    - Inclusion of disease progression parameters when a therapy with curative intent (eg, neo/adjuvant, chemoradiotherapy) may be considered as a prior line of therapy
    - Inclusion of new text for specific guidance on measurable disease after tumor resection:

    - Lesions that are partially resected for TIL generation and are still measurable per RECIST may be selected as non-target lesions but cannot serve as target lesions for response assessment.
  - Updated text to clarify that patients with prior transplant history are excluded only if it is within the past 20 years
- General non-substantive revisions to improve clarity and enhance overall protocol compliance
- The Schedule of Activities has been updated for clarity and consistency.

PROTOCOL SYNOPSIS

Protocol Title	A Phase 2, Multicenter Study to Evaluate the Efficacy and Safety of Autologous Tumor Infiltrating Lymphocytes (LN-145/LN-145-S1) for the Treatment of Patients with Recurrent and/or Metastatic Squamous Cell Carcinoma of the Head and Neck
Protocol Number	C-145-03
Study Type	Phase 2
Indication	Treatment of patients with recurrent and/or metastatic squamous cell carcinoma of the head and neck (HNSCC)
Investigational Agents	• LN-145/LN-145-S1: autologous tumor infiltrating lymphocytes (TIL) derived from the patient's own tumor
Study Objectives	**Primary Objective** • To evaluate the efficacy of LN-145/LN-145-S1 in patients with recurrent and/or metastatic HNSCC based on the objective response rate (ORR) using Response Evaluation Criteria in Solid Tumors (RECIST) v1.1 as assessed by the Investigator **Secondary Objectives** • To evaluate the efficacy parameters of LN-145/LN-145-S1 in patients with recurrent and/or metastatic HNSCC such as duration of response (DOR), disease control rate (DCR), and progression-free survival (PFS) using RECIST v1.1 as assessed by the Investigator • To evaluate overall survival (OS) in patients with recurrent and/or metastatic HNSCC • To characterize the safety profile of LN-145/LN-145-S1in patients with metastatic and/or recurrent HNSCC **Exploratory Objectives** • To identify clinical biomarkers of LN-145/LN-145-S1 • To explore efficacy based on immune-related RECIST (irRECIST) criteria as assessed by independent review initiated at the Sponsor's discretion
Study Design	This is a Phase 2, multicenter, prospective, open-label, interventional study using autologous TIL infusion (LN-145/LN-145-S1) followed by IL-2 after an NMA-LD pretreatment regimen.
Doses and Treatment Schedule	The adoptive cell therapy (ACT) used in this study consists of administering an NMA-LD preparative regimen consisting of cyclophosphamide intravenous (IV) (60 mg/kg × 2 doses) with mesna and fludarabine IV (25 mg/m^2 × 5 doses), followed by the infusion of autologous TIL (LN-145/LN-145-S1) and administration of IL-2 (600,000 IU/kg) every 8 to 12 hours, starting between 3 and 24 hours after the completion of the TIL infusion, continuing for up to a maximum of 6 doses, as tolerated. Patients will be evaluated for response at approximately 4 weeks (Day 28), 8 weeks (Day 56), 12 weeks (Day 84), 18 weeks (Day 126),

<table>
<tr><td></td><td>6 months, 9 months, 12 months, 15 months, 18 months, 21 months, and 24 months following TIL therapy.
<table>
<tr><th rowspan="2">Treatment Administration</th><th colspan="12">Study Day</th></tr>
<tr><th>-7</th><th>-6</th><th>-5</th><th>-4</th><th>-3</th><th>-2</th><th>-1</th><th>0</th><th>1</th><th>2</th><th>3</th><th>4</th></tr>
<tr><td>Cyclophosphamide 60 mg/kg</td><td>X</td><td>X</td><td></td><td></td><td></td><td></td><td></td><td></td><td></td><td></td><td></td><td></td></tr>
<tr><td>Mesna</td><td>X</td><td>X</td><td></td><td></td><td></td><td></td><td></td><td></td><td></td><td></td><td></td><td></td></tr>
<tr><td>Fludarabine 25 mg/m^2/day</td><td></td><td></td><td>X</td><td>X</td><td>X</td><td>X</td><td>X</td><td></td><td></td><td></td><td></td><td></td></tr>
<tr><td>TIL infusion</td><td></td><td></td><td></td><td></td><td></td><td></td><td></td><td>X</td><td></td><td></td><td></td><td></td></tr>
<tr><td>IL-2 600,000 IU/kg</td><td></td><td></td><td></td><td></td><td></td><td></td><td></td><td></td><td>X</td><td>X</td><td>X</td><td>X</td></tr>
</table></td></tr>
<tr><td>Number of Study Sites</td><td>Approximately 25-30 clinical study sites</td></tr>
<tr><td>Number of Planned Patients</td><td>Approximately 55 patients who are evaluable for efficacy</td></tr>
<tr><td>Inclusion Criteria</td><td>Patients must meet the following inclusion criteria prior to enrollment in the study:
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. Patient (or a legally authorized representative) must understand and voluntarily sign informed consent prior to any study-related assessments/procedures being conducted.
3. Must be able and willing to comply to the study visit schedule and protocol requirements.
4. Must have recurrent and/or metastatic HNSCC. Histologic diagnosis of the primary tumor is required via the pathology report.
5. Must have at least 1 lesion that is resectable for TIL generation. The resected TIL-generating lesion should yield at least 1.5 cm in diameter post-resection of tumor tissue and can be surgically removed with minimal morbidity. An aggregate of ≥ 1.5 cm in diameter from multiple lesions is permitted.
• If the lesion is within a previously irradiated field, the irradiation must have occurred at least 3 months prior to resection and the lesion must have had radiologically documented progression after radiation therapy.
6. Must have measurable disease as defined by RECIST v1.1 following the tumor resection for TIL manufacturing.
• Lesions in previously irradiated areas must not be selected as target lesions unless there has been demonstrated radiographic progression in those lesions.
• Lesions that are partially resected for TIL generation and are still measurable post-resection per RECIST may be selected as non-target lesions but cannot serve as target lesions for response assessment.
7. Must have received at least 1 and no more than 3 lines of prior systemic immunotherapy and/or chemotherapeutic treatments for</td></tr>
</table>

	HNSCC. • Patients must have radiologically documented disease progression while receiving or after the completion of the most recent prior treatment. • Prior systemic therapy in the adjuvant or neoadjuvant setting or as part of definitive chemoradiotherapy will be counted as a line of therapy if the disease progressed during or within 12 months of the completion of such therapy. 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 lymphodepletion, except for localized palliative radiation therapy. 9. Must have an Eastern Cooperative Oncology Group (ECOG) performance status of 0 or 1 and an estimated life expectancy of ≥6 months in the opinion of the Investigator 10. Must meet the following laboratory criteria independent of transfusion and/or blood product support for at least 5 days prior to laboratory testing: • Absolute neutrophil count (ANC) > 1000/mm^3 • Hemoglobin > 9.0 g/dL • Platelet count > 100,000/mm^3 • Alanine aminotransferase (ALT) and aspartate aminotransferase (AST) < 3.0 × upper limit of normal (ULN) o Patients with liver metastases must have liver function tests (LFTs) < 5.0 × ULN • Total bilirubin ≤ 2.0 mg/dL o Patients with Gilbert's Syndrome must have a total bilirubin ≤ 3.0 mg/dL • An estimated creatinine clearance (eCrCl) ≥ 40 mL/min at screening using the Cockcroft-Gault formula 11. Patients must be seronegative for the human immunodeficiency virus (HIV1 and HIV2). 12. Patients seropositive for hepatitis B virus surface antigen (HBsAg), hepatitis B core antibody (anti-HBc), or hepatitis C virus (anti-HCV) indicating acute or chronic infection may be enrolled if the viral load by polymerase chain reaction (PCR) is undetectable with/without active treatment. Additional serology testing may be required depending on local prevalence of certain viral exposures. 13. Patients of childbearing potential and patients whose sexual partners are of childbearing potential must be willing to practice an approved method of highly effective birth control with their partners starting at the time of informed consent and for 1 year after the completion of the study treatment regimen. Approved methods of birth control are as follows: • Combined (estrogen and progesterone containing) hormonal contraception associated with inhibition of ovulation (eg, oral, intravaginal, transdermal)

	• Progesterone-only hormonal contraception associated with inhibition of ovulation (eg, oral, injectable, implantable) • Intrauterine device (IUD) • Intrauterine hormone-releasing system (IUS) • Bilateral tubal occlusion • Vasectomized partner • True absolute 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. 14. Pulmonary function requirement Patients having any of the following require pulmonary function testing (PFT) with post-bronchodilator values of forced expiratory volume (FEV1)/forced vital capacity (FVC) > 0.7 and FEV1 > 50%: • History of cigarette smoking of ≥ 20 pack-years and still smoking, • Ceased smoking within the past 2 years • History of chronic obstructive pulmonary disease (COPD) • Any signs or symptoms of respiratory dysfunction If a patient is unable to perform reliable spirometry due to abnormal upper airway anatomy (ie, tracheostomy), a 6-minute walk test may be used to assess pulmonary function. Patients who are unable to walk a distance of at least 80% predicted for age and sex **or** who demonstrate evidence of hypoxia at any point during the test (SpO2 < 90%) are excluded.
Exclusion Criteria	Patients who meet ANY of the following criteria will be excluded from the study: 1. Patients who have received an organ allograft or prior cell transfer therapy that included a non-myeloablative or myeloablative chemotherapy regimen within the past 20 years. Note: This criterion is applicable for patients undergoing re-treatment with TIL, with the exception that they will have had a prior NMA-LD regimen with their prior TIL treatment. 2. Patients who are on a systemic steroid therapy > 10 mg of prednisone or other steroid equivalent daily. • Patients receiving steroids as replacement therapy for adrenocortical insufficiency at < 10 mg of prednisone or other steroid equivalent daily may be eligible. 3. Patients with prior therapy-related toxicities Grade >1 per National Cancer Institute (NCI) Common Terminology Criteria for Adverse Events (CTCAE) Version 4.03; except for neuropathy, dysphagia, alopecia, or vitiligo. Immunotherapy-related endocrinopathies stable for at least 1 month, and controlled with hormonal replacement, are not excluded. • If toxicities have resolved to Grade <1, a minimum of 4 weeks must elapse prior to enrollment (tumor resection)

	• Patients may not undergo preplanned procedures within 2 weeks of the start of NMA-LD. 4. Patients with documented Grade ≥2 diarrhea or colitis due to previous immunotherapy (eg, ipilimumab, tremelimumab, anti-programmed cell death protein 1 [PD-1 or anti-programmed cell death-ligand 1 [PD-L1] antibodies) within 6 months from screening • Patients who have had a normal colonoscopy post anti-PD-1/anti-PD-L1 treatment with uninflamed mucosa by visual assessment, or who have been asymptomatic for ≥6 months, are not excluded. 5. Patients who have a contraindication to or history of hypersensitivity reaction to any component or excipients of the TIL therapy and the other study drugs: • NMA-LD (cyclophosphamide, mesna, and fludarabine) • IL-2 • Antibiotics of the aminoglycoside group (ie, gentamicin or streptomycin; excluding those who are skin-test negative for gentamicin hypersensitivity) • Any component of the TIL infusion product formulation including dimethyl sulfoxide (DMSO), human serum albumin (HSA), IL-2, and dextran-40 6. Patients with active systemic infections (eg, syphilis), coagulation disorders or other active major medical illnesses of the cardiovascular, respiratory, or immune system, including evidence in the medical history of a positive cardiac stress test, myocardial infarction, cardiac arrhythmia, obstructive or restrictive pulmonary disease, uveitis, or other conditions that in the opinion of the Investigator would significantly increase the risk of participation. 7. Patients with symptomatic and/or untreated brain metastases (of any size and any number). • Patients with definitively treated brain metastases may be eligible after discussion with the Sponsor's Medical Monitor/designee, must be stable for at least 2 weeks and must be asymptomatic prior to the start of treatment (NMA-LD) 8. Patients who have any form of primary or acquired immunodeficiency syndrome, such as severe combined immunodeficiency disease or acquired immune deficiency syndrome (AIDS). 9. Patients who have a left ventricular ejection fraction (LVEF) < 45% or who are New York Heart Association (NYHA) Class 2 or higher. A cardiac stress test demonstrating any irreversible wall movement abnormality in any patient ≥ 60 years of age or in patients who have history of ischemic heart disease, chest pain, or clinically significant atrial and/or ventricular arrhythmias. • Patients with an abnormal cardiac stress test may be enrolled if they have adequate ejection fraction and cardiology clearance with approval of the Sponsor's Medical Monitor

	10. Patients who have had another primary malignancy within the previous 3 years (except for those who do not require treatment or have been curatively treated >1 year ago, and in the judgment of the Investigator, do not pose a significant risk of recurrence; including, but not limited to, non-melanoma skin cancer, ductal carcinoma in situ [DCIS] or lobular carcinoma in situ [LCIS], or prostate cancer Gleason score ≤6.). 11. Patients who are of the following protected classes will be excluded: • 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. 12. Patients who have received a live or attenuated vaccine within 28 days of the NMA-LD regimen.
Efficacy Assessment	A descriptive summary of the ORR, DOR, DCR, and PFS per RECIST v1.1 and OS will be used to summarize the efficacy results.
Safety Assessment	Treatment-emergent adverse events (TEAEs), clinical laboratory data assessments, serious adverse events (SAEs), and adverse events (AEs) that are related to the study treatment (from the time of enrollment/tumor resection) will be collected and evaluated for the duration of the study until resolution or permanent sequelae.
Overview of Statistical Plan	<u>Sample Size Consideration</u> The sample size is based on the number of treated patients who receive the NMA-LD regimen and any amount of LN-145/LN-145-S1 therapy. The total number of patients planned to be infused with LN-145/LN-145-S1 in this study is approximately 55. Patients will be counted once even if they receive re-treatment. All cohorts are intended for signal seeking; no formal hypothesis testing is planned. Cohort 1: Approximately 8 patients were infused with LN-145 Generation 1 (Gen 1) product. The enrollment is closed for this cohort. Cohort 2: Approximately 17 patients are planned to be infused with LN-145 Generation 2 (Gen 2) product. This sample size provides an estimated ORR with a half-width 95% confidence interval of < 0.21 by the Clopper-Pearson exact method. Cohort 3: Up to 15 patients are planned to be infused with LN-145 Generation 3 (Gen 3) product. This sample size provides an estimated ORR with a half-width 95% confidence interval of < 0.23 by the Clopper-Pearson exact method. Cohort 4 (LN-145-S1): Up to 15 patients are planned to be infused with LN-145-S1 product. This sample size provides an estimated ORR with a half-width 95% confidence interval of < 0.23 by the Clopper-Pearson exact method. Cohort 5 (Re-treatment cohort): Patients who have been previously treated in Cohort 1, 2, 3, or 4 of this study may rescreen for a second

	administration of TIL product. These patients may have a second tumor resection, if needed; this is recommended when new lesions are available and feasible for resection. <u>Statistical Plan</u> The statistical analysis will be based on the estimation of efficacy and safety parameters and will be performed by cohort. There is no planned statistical comparison between cohorts. Data from each cohort will be evaluated for efficacy and safety separately. For all 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 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/LN-145-S1 infusion (Day 0). The assessment of safety data will be descriptive and based on 1) the summarization of TEAEs, SAEs, and 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 after the first 5 patients complete Week 4 (Day 28). An additional evaluation will be completed when the first 15 patients complete Week 4 (Day 28). Safety data in this study will be reviewed by the Sponsor on an ongoing basis to identify any potential new safety risks. Enrollment will continue while under review.

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LIST OF ABBREVIATIONS

Term	Definition
ACT	adoptive cell therapy
AE	adverse event
AIDS	acquired immune deficiency syndrome
ALT	alanine aminotransferase
ANC	absolute neutrophil count
anti-HBc	hepatitis B core antibody
anti-HCV	hepatitis C virus antibody
aPTT	activated partial thromboplastin time
AST	aspartate aminotransferase
BMI	body mass index
BSA	body surface area
CBC	complete blood count
CFR	Code of Federal Regulations
CI	confidence interval
CMO	contract manufacturing organization
CMV	cytomegalovirus
CR	complete response
CRO	Contract Research Organization
CT	computed tomography
CTCAE	Common Terminology Criteria for Adverse Events
DCIS	ductal carcinoma in situ
DCR	disease control rate
DOR	duration of response
DS	double strength
DMSO	Dimethyl sulfoxide
DNA	deoxyribonucleic acid
DSMB	data safety monitoring board
EBNA	Epstein Barr nuclear antigen
EOA	End of Assessment
EBV	Epstein Barr virus
ECG	electrocardiogram
ECHO	echocardiogram
ECOG	Eastern Cooperative Oncology Group
eCrCl	estimated creatinine clearance
eCRF	electronic case report form
EDC	Electronic Data Capture

Term	Definition
EKG	electrocardiogram
FACS	fluorescent-activated cell sorting
FDA	Food and Drug Administration
FEV1	forced expiratory volume in 1 second
GCP	Good Clinical Practice
HBsAg	hepatitis B surface antigen
HCV	hepatitis C virus
HIPAA	Health Insurance Portability and Accountability Act of 1996
HLA	human leukocyte antigen
HPV	human papillomavirus
HNSCC	head and neck squamous cell carcinoma
HSV	herpes simplex virus
ICF	informed consent form
ICH	International Council on Harmonisation
ICOS	inducible T-cell costimulator or CD278
IFN-γ	interferon-gamma
IL-2	interleukin-2 (aldesleukin)
IEC	independent ethics committee
IRB	institutional review board
irRECIST	immune-related Response Evaluation Criteria in Solid Tumors
IV	intravenous
LCIS	lobular carcinoma in situ
LFT	liver-function test
LVEF	left ventricular ejection fraction
MRI	magnetic resonance imaging
NCI	National Cancer Institute
NMA-LD	nonmyeloablative lymphodepletion
NE	not evaluable
OPC	oropharyngeal cancer
ORR	objective response rate
OS	overall survival
PBMC	peripheral blood mononuclear cells
PCR	polymerase chain reaction
PD	progressive disease
PET	positron emission tomography
PFS	progression-free survival
PFT	pulmonary function test

Term	Definition
PIK3CA	phosphatidylinositol 3-kinase, catalytic subunit alpha
PR	partial response
pre-REP	expansion of TIL from tumor fragments prior to REP
PTT	partial thromboplastin time
RECIST	Response Evaluation Criteria in Solid Tumors
REP	rapid expansion protocol
SAE	serious adverse event
SAP	statistical analysis plan
SD	stable disease
SoD	sum of longest diameters
SMX	sulfamethoxazole
SUSAR	suspected unexpected serious adverse reaction
TH	tumor harvested
TIL	tumor infiltrating lymphocytes
TEAE	treatment-emergent adverse event
TMP	trimethoprim
T_{reg}	regulatory T cell
TSH	thyroid stimulating hormone
ULN	upper limit of normal
US	United States

1. INTRODUCTION

1.1. Head and Neck Cancer

Squamous cell cancers of the head and neck (HNSCC) comprise malignancies of the nasal cavity, paranasal sinuses, nasopharynx, oral cavity, oropharynx, hypopharynx, larynx, salivary glands, and head and neck paraganglial tissues [Sidransky 1997]. Most of these tumors occur in older individuals who have a history of smoking or high alcohol use (more than 4 drinks per day) and are more frequent in men than in women [Guo 2016; Rettig 2015]. The oropharyngeal cancer (OPC) subset of HNSCC appears to be a distinct disease with different risk associations (such as human papillomavirus [HPV] infection) than other HNSCC [Gillison 2008]. OPC prevalence among HNSCC has increased worldwide over the last 2 decades; in the United States (US), the rate increased from 18% of all HNSCC in 1973 to 31% in 2004 [Adelstein 2009]. HPV-positivity also has increased over the same period, reaching an estimated 72% prevalence in OPC between 2005 and 2009 [Ang 2010; Chaturvedi 2011; Mehanna 2013]. By contrast, fewer than 20% of other HNSCC are positive for HPV [Lingen 2013; Mehanna 2013]. The increase in incidence of OPC is 4-fold greater in males than females, and among men, is associated with those < 60 years of age and white race [Gillison 2015; Rettig 2015]. Of the many strains of HPV, type 16 (HPV16) has been found in more than 90% of HPV-positive OPC [Gillison 2015]. Notably, genetic mutations in HPV-negative HNSCC appear to be more frequent and distinct from those in HPV-positive tumors [Guo 2016]. For example, mutations of p53, a key tumor suppressor gene, were almost always associated with an HPV-negative tumor [Agrawal 2011; Cancer Genome Atlas 2015], consistent with the known association between smoking and p53 mutations in patients with HNSCC [Brennan 1995]. By contrast, activating mutations and amplifications of phosphatidylinositol 3-kinase, catalytic subunit alpha (PIK3CA) were more common in HPV-positive tumors [Nichols 2013]. As most HPV oral infections are sexually acquired, the increase in HPV-positive OPC is thought to be associated with changes in sexual behavior over time [Rettig 2015].

The current standard treatment for HNSCC typically involves combinations of surgery, radiation, and chemotherapy, typically with cisplatin [Jones 2014]. Radiation with hyperfractionation and accelerated fractionation has been found to improve survival [Maxwell 2016], but has been associated with swallowing dysfunction [Patterson 2014]. Five-year survival has significantly increased for all HNSCC sites over the past 20 years from 54.7% in 1992-1996 to 65.9% in 2002-2006 [Pulte 2010]. By tumor site, estimated 5-year survival rates remain ≤ 63% for all sites other than the tongue or lip [Howlader 2018]. Notably, the outcome for patients with HPV-positive tumors is better than the outcome for HPV-negative HNSCC [Ang 2010; Fakhry 2008; O'Rorke 2012] with reported 2- and 3-year survival rates of approximately 95% and 80%, respectively [Ang 2010; Fakhry 2008]. The improved outcome of patients harboring HPV-positive tumors may be a result of enhanced activity of TIL at the tumor site [Maxwell 2016].

The rates of occurrence of a second primary tumor or recurrence of tumors is high in HNSCC, particularly among smokers, likely due to the “field cancerization” effect of tobacco-induced malignancy, whereby genetic alterations may be induced throughout the upper aerodigestive

mucosa [Rettig 2015]. Argiris et al. [Argiris 2008] estimated a recurrence rate of 50% for patients in remission following treatment of a locally advanced HNSCC, and Chuang et al. estimated that 36% of patients would develop a second primary tumor within 20 years [Chuang 2008]. Recurrence is higher in HPV-negative than in HPV-positive OPC (3-year recurrence rates of 65.1% versus 13.6%; $P < 0.001$). Additionally, the 3-year rates of second primary malignancy were 14.6% versus 5.9% ($P = 0.02$) in these groups [Ang 2010].

Outcome for recurrent HNSCC is poor across a variety of therapeutic modalities [Hsieh 2015; Machiels 2015; Vargo 2015], although Strnad et al. [Strnad 2015] reported long-term high rates of local control of recurrent disease using interstitial pulsed-dose-rate brachytherapy combined with chemotherapy in a selected patient population. HPV-positive recurrent OPC disease has a higher overall survival (OS) rate than HPV-negative recurrent OPC: 2-year OS rates were 54.6% for patients with HPV-positive tumors and 27.6% for those with HPV-negative tumors ($P < 0.001$) [Fakhry 2014]. Immune checkpoint inhibitors have been approved for use in the recurrent setting following progression of a platinum-containing regimen. Nivolumab, an anti-PD-1 inhibitor, demonstrated a superior median OS of 7.5 months versus 5.1 months with standard therapy ($P = 0.01$) [Ferris 2016]. However, the progression-free survival (PFS) was similar in both groups (2.0 versus 2.3 months for nivolumab and standard chemotherapy, respectively) and the objective response rate (ORR) was only 13% [Ferris 2016]. Likewise, pembrolizumab has demonstrated some efficacy in this post-platinum progression setting that had PD-L1-positive tumors including an ORR of only 18% [Seiwert 2016]. More recently, pembrolizumab was approved for the first-line treatment in combination with platinum and fluorouracil (FU) for all patients and as a single agent for patients whose tumors express PD-L1 (combined positive score [CPS] ≥1) [Pembrolizumab PI]. Pembrolizumab plus chemotherapy demonstrated significant improvement in OS in the overall population when compared with cetuximab plus chemotherapy: median OS was 13.0 months for the pembrolizumab plus chemotherapy arm versus 10.7 months for the cetuximab plus chemotherapy. Although these results were encouraging, the response and OS rates remained low indicating an urgent need for improved treatment options in this patient population.

1.2. Adoptive Cell Transfer of Tumor Infiltrating Lymphocytes as Cancer Immunotherapy

Adoptive cell therapy (ACT) using tumor infiltrating lymphocytes (TIL) represents an effective treatment and has the potential to induce a durable complete response (CR) for patients with a variety of solid tumors [Geukes Foppen 2015]. The treatment involves the isolation and ex vivo expansion of autologous 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. Subsequent findings have shown a predictive relationship between the frequency and phenotype of TIL in solid tumors and an increased OS and progression-free survival (PFS) in patients with melanoma [Haanen 2006; Ladanyi 2007; Azimi 2012; Erdag 2012], lung cancer [Horne 2011; Kilic 2011; Liu 2012a; Ruffini 2009], ovarian cancer [Hagemann 2011; Milne 2012; Webb 2014], squamous cell

carcinomas [Wang 2014; Balermpas 2014], triple-negative breast cancer, HER2-positive breast cancer [Ali 2014; Ibrahim 2014], basal-like breast cancer [Ali 2014; Liu 2012b; Mahmoud 2012a; Mahmoud 2012b; Mahmoud 2011; West 2013], colorectal cancer [Galon 2006], and HNSCC [Balermpas 2014; Wang 2014; Xu 2017; de Ruiter 2017]. 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 costimulator [ICOS], granzyme B, chemokines, and chemokine receptors) with improved OS and PFS in both primary and metastatic tumor settings [Erdag 2012; Hagemann 2011; Horne 2011; Webb 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.

ACT has several theoretical and practical advantages over active immunization and nonspecific immune stimulation. First, the ex vivo environment allows expansion of $CD8^+$ cytotoxic T cells to proceed to very high cell numbers in the absence of suppressive factors, such as $CD4^+$ T_{reg} ($CD4^+$ $Foxp3^+$) that inhibit adaptive immune responses in the tumor microenvironment [Ali 2014; Chacon 2013; West 2013] allowing infusion of much higher numbers of tumor-reactive TIL than is possible with other approaches. Second, the TIL product potentially recognizes a wider array of tumor antigens, such as mutated tumor neoantigens and viral-associated antigens, rather than a single target [Robbins 2013; Tran 2014; Kvistborg 2013; van Rooij 2013]. Preparation of the host patient with nonmyeloablative lymphodepletion (NMA-LD) immediately prior to the transfer of the antitumor cells also temporarily eliminates potentially suppressive influences (such as regulatory T cells that act as pro-inflammatory cytokine sinks) to provide an optimal milieu for the transferred TIL to proliferate and maintain activation in vivo.

The feasibility of TIL preparation was demonstrated by early studies showing that metastatic melanoma (MM) tumors can be excised and placed in tissue culture under conditions in which tumor cells do not survive, but 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 ($\geq 1 \times 10^8$ cells) [Rosenberg 1986; 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 [Rosenberg 1986; Yron 1980; Kvistborg 2013; van Rooij 2013]. Additional studies have established that the efficacy of infusing large numbers of TIL can be enhanced by pretreatment of the tumor-bearing animals with cyclophosphamide to induce a transient drop in host endogenous lymphocytes followed by IL-2 administration. With this treatment sequence, mice were cured of advanced hepatic metastases [Rosenberg 1986]. These findings set the stage for the United States (US) National Cancer Institute (NCI) clinical studies using TIL therapy for patients with metastatic melanoma that includes an NMA-LD preconditioning regimen consisting of cyclophosphamide and fludarabine, followed by IL-2 post TIL Infusion. Across clinical studies conducted by the NCI, immunotherapy of patients with advanced melanoma with autologous TIL therapy has induced durable ORRs by Response Evaluation Criteria in Solid Tumors (RECIST) Version 1.0 criteria in 56% (52/93) of patients, including heavily pretreated patients, with 24 of the

101 patients (24%) achieving a CR. Nineteen of the 24 CRs were ongoing beyond 3 years of follow-up [Goff 2016; Rosenberg 2011].

1.3. LN-145-S1: PD-1-selected TIL

Multiple lines of evidence support neoantigen recognition followed by tumor-cell killing as the primary mechanism of action of TIL, suggesting that a TIL product selected for neoantigen recognition may have increased tumor-reactivity [Schumacher and Schreiber 2015]. Tumor-reactive T cells obtained from tumors have been shown to express PD-1 [Inozume 2010], an activation-induced modulator (suppressor) of T-cell function that is specifically expressed in response to recent antigen encounter [Chikuma 2009; Barber 2006]. PD-1 expressing (PD-1+) TIL have been reported in most tumor types [Inozume 2010; Gros 2014; Kansy 2017; Thommen 2018; Shang 2018; McGranahan 2016] and appear to contain the key subpopulation of neoantigen-specific T cells [Gros 2014; Thommen 2018]. For example, tumor-specific CD8+ T cells in melanoma tumor digests were exclusively found in the PD-1-expressing subset of TIL [Gros 2014]. Similar findings were reported by Thommen et al. in CD8+ T-lymphocyte populations from non-small cell lung cancer patients [Thommen 2018].

Anti-tumor activity of expanded PD-1+ TIL has been demonstrated in mouse models of solid tumors [Fernandez-Poma 2017]. Importantly, this anti-tumor activity was shown to be significantly better than that of TIL expanded from sorted PD-1-negative (PD-1-) TIL. Furthermore, the efficacy of the PD-1+ TIL was enhanced with anti-PD-1 treatment in vivo. Comparable results were obtained using a murine multiple myeloma model. PD-1+ displayed greater tumor reactivity ex vivo and in vivo with regard to efficacy than expanded PD-1- TIL [Jing 2017]. The expanded PD-1+ TIL were shown to persist post-infusion and to provide a long-term myeloma response [Jing 2017].

Therefore, selection for PD-1+ TIL in the TIL manufacturing process prior to ex vivo expansion is expected to enrich for neoantigen-specific T cells, while preserving TIL diversity and therefore the potential to recognize an array of tumor neoantigens. This strategy represents a promising means to further optimize the TIL product for ACT.

Based on the research cited above, PD-1-selected TIL are expected to be enriched for the tumor-reactive fraction present in unselected TIL and, as such, may enhance the ability of TIL to initiate a potent and effective anti-tumor effect upon administration to patients for recurrent and/or metastatic HNSCC.

1.4. TIL for Head and Neck Cancer

The rationale for investigating the use of TIL for treatment of HNSCC is based on the high rate of recurrence and overall low survival rates for patients with recurrent disease following standard combinations of surgery, adjuvant chemotherapy, radiation therapy, and immunotherapy. Furthermore, as described above for other solid tumors, a positive correlation between the presence of TIL in HNSCC tumor specimens and patient outcome has been reported by several Investigators. For example, Balermpas et al. reported that among patients with HNSCC, those

with high immunohistochemical CD3 and CD8 expression had significantly increased OS, PFS, and distant metastasis-free survival, but not local failure-free survival in multivariate analysis [Balermpas 2014]. Similarly, low CD8+ T-cell infiltration in the tumors of patients with laryngeal squamous cell cancer was correlated with decreased survival [Ogino 2006]. TIL has shown prognostic value [Xu 2017; de Ruiter 2017] in both HPV-positive and HPV-negative HNSCC tumor specimens. For example, Kong et al. reported a survival benefit for higher CD3+ TIL in tumor specimens only for HNSCC with weak or no expression of HPV [Kong 2009]; whereas, Wansom et al. [Wansom 2010] and Ward et al. [Ward 2014] found that higher numbers of $CD8^+$ cells in tumors were positively correlated with improved survival in patients with HPV-positive HNSCC or HPV-positive OPC. An additional report by Wansom et al. found that among patients with advanced OPC, $CD8^+$ cells, as well as Treg cells ($CD8^+$ FOXP3) and total T-cell number all were positively correlated with improved OS and disease-free survival, independently of the tumor's HPV status [Wansom 2012]. Of relevance to LN-145-S1, levels of PD-1-positive TIL were positively correlated with a favorable clinical outcome for patients with HNSCC [Badoual 2013; Kansy 2017]. These data strongly suggest a beneficial role for TIL in the body's response to HNSCC.

The feasibility of generating TIL from HNSCC has been demonstrated by several investigators. Junker et al. [Junker 2011] demonstrated the successful expansion of TIL bulk cultures in 12 of 15 (80%) evaluable patients. Up to 3500-fold expansion was achieved within 17 days. TIL from 60% of the patients could kill human leukocyte antigen (HLA)-A-matched tumor cell lines. Additional characterization showed that the TIL expanded from HNSCC tumor samples were phenotypically like those from melanomas (ie, $CD3+/CD8^+$), and were similar before and after rapid expansion [Junker 2012]. Moudgil et al. [Mougdil 2015] reported a success rate of 50% for generation of TIL (33 of 63 cultures initiated). Of 22 tested TIL, 20 secreted interferon-gamma (IFN-γ) in response to coculture with the autologous tumor cell target. These findings are consistent with those of a retrospective study that showed that TIL were successfully generated in 677 (86%) of the 787 specimens from 402 patients with melanoma [Goff 2010].

Iovance's recent clinical experience is consistent with a high success rate of LN-145 TIL product manufacturing from a variety of HNSCC samples, while its nonclinical experience predicts an equally successful production of LN-145-S1 TIL product.

1.5. LN-145/LN-145-S1 TIL Therapy Regimen

The LN-145/LN-145-S1 treatment regimen involves a course of the NMA-LD preconditioning using cyclophosphamide and fludarabine for 1 week prior to TIL infusion, and a limited course of IL-2 administration (six doses) following TIL infusion. The NMA-LD preconditioning regimen and IL-2 are included in the regimen to support engraftment, expansion, and activation of the infused TIL.

Several preconditioning regimens have been used in conjunction with TIL therapies. NMA-LD preconditioning regimens have included cyclophosphamide/fludarabine, total body irradiation, and a combination of the two. The NMA-LD preconditioning regimen used in the current study

is based on the method developed and tested by the NCI, which involves 2 days of cyclophosphamide followed by 5 days of fludarabine. Each patient will undergo an NMA-LD preconditioning regimen prior to infusion of LN-145/LN-145-S1.

1.6. Brief Description of LN-145/LN-145-S1

LN-145/LN-145-S1 is a ready-to-infuse, autologous TIL therapy based on the original discovery made at NCI and developed 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 [redacted]
- LN-145-S1 is manufactured using a modification of the LN-145 process in which [redacted] LN-145-S1 is therefore a subset of the LN-145 TIL product.

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 [redacted]

An earlier noncryopreserved product formulation is no longer in development. Patients in Cohort 1 of this study received that noncryopreserved product.

1.7. 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 [redacted] 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.

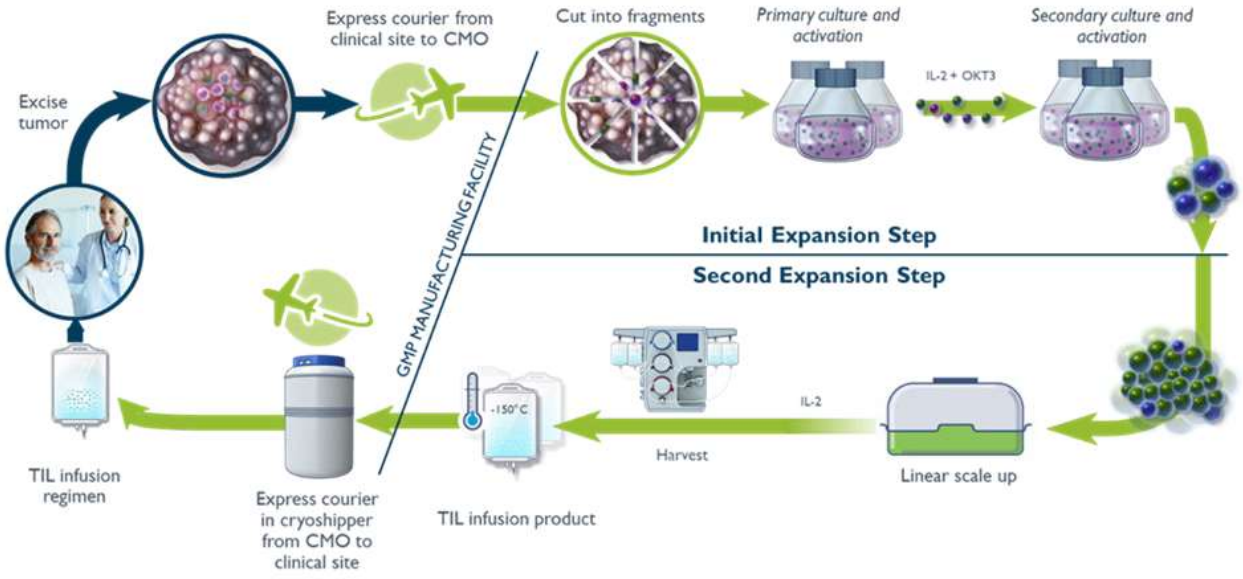
The key manufacturing steps for both LN-145/LN-145-S1 products are identical and include the following:

1. The ex vivo expansion of the TIL (LN-145) or [redacted] TIL (LN-145-S1) present in the [redacted]
2. Further expansion of the TIL (LN-145 and LN-145-S1) via the [redacted]

3. Harvesting and formulation in transport media or cryopreservation media and shipment to the clinical site for infusion.

A diagram of the Iovance TIL manufacturing process is provided in Figure 1.

Figure 1 LN-145/LN-145-S1 Manufacturing Process



Each cryopreservation bag of the LN-145/LN-145-S1 final product is labeled with a patient-specific label. LN-145/LN-145-S1 is shipped from the manufacturing facility to clinical sites for administration to patients as described in the Pharmacy & Administration Manual.

1.8. Safety of the LN-145 Cellular Therapy

AEs observed during LN-145 cellular therapy have been associated primarily with either the lymphodepletion 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 [Rosenberg 2011; Goff 2016; Radvanyi 2012; Dudley 2008; Pilon-Thomas 2012; Sarnaik 2017a; Sarnaik 2017b; Besser 2009; Besser 2010; Ellebaek 2012; Besser 2013; Andersen 2016].

The LN-145 product [redacted] The cryopreserved TIL cellular product contains [redacted]

There are no clinical data to date on LN-145-S1; however, the product is a selected subpopulation of bulk TIL (LN-145), and the formulation of the final infused product is unchanged from LN-145. Thus, there are no anticipated safety differences from LN-145.

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

1.9. Benefit-Risk Assessment of LN-145/LN-145-S1

As noted in the Section 1.4, HNSCC remains a cancer type with significant unmet medical need. LN-145/LN-145-S1 is an experimental treatment that may provide clinical benefit to patients with recurrent and/or metastatic HNSCC. In 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 2014]. The risks associated with TIL therapy include: a delay in treatment due to the need to harvest and grow the cells; a surgical procedure 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 at ≤22 days for manufacturing. 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.

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 6.2.5.

In summary, current methods for the expansion of autologous TIL from excised tumors are well established and are robust enough to ensure a high degree of success in consistently generating sufficient numbers of high-quality therapeutic cells. Further, clinical studies in melanoma and cervical cancer have demonstrated that the effects of the TIL persist in patients for weeks to months and even years after infusion, thereby potentially mediating highly durable complete remissions more than other current immunotherapies or standard therapies. 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 HNSCC.

2. STUDY DESIGN

2.1. Overview

This is a Phase 2, multicenter, multicohort, non-randomized, prospective, open-label, interventional study evaluating patients with HNSCC who receive ACT with LN-145/LN-145-S1 autologous TIL. Instructions for the tumor resection/harvest and LN-145/LN-145-S1 administration for the current study are provided in separate operating manuals. TIL therapy comprises multiple interdependent phases: tumor resection for production of TIL; ex vivo expansion of TIL; NMA-LD; infusion of TIL; and administration of IL-2.

The study is planned to assess efficacy and safety for approximately 55 patients who receive LN-145/LN-145-S1 in the following cohorts:

Cohort 1: Treatment with LN-145, Generation 1 (Gen 1), non-cryopreserved TIL (closed to enrollment; n=8 patients)

Cohort 2: Treatment with LN-145 Generation 2 (Gen 2), cryopreserved TIL, 22-day manufacturing process (approximately 17 patients)

Cohort 3: Treatment with LN-145 Generation 3 (Gen 3), cryopreserved TIL, 16-day manufacturing process (up to 15 patients)

Cohort 4: Treatment with LN-145-S1 PD-1-selected cryopreserved TIL (up to 15 patients)

Cohort 5: LN-145 cryopreserved/LN-145-S1 PD-1-selected cryopreserved TIL re-treatment

TIL product for re-treatment may vary from initial method of manufacturing. Patients treated in the re-treatment cohort may have a second tumor resection if needed. This is recommended 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. Please see Section 6.4.2 for more details.

The study consists of the following periods:

- **Screening and Enrollment Period:** Up to 28 days from signing the informed consent form (ICF)

  Patients are considered enrolled upon confirmation of eligibility and receipt of tumor resection for TIL generation at the CMO.

- **Manufacturing of LN-145/LN-145-S1 Product**: Approximately ≤22 days from tumor resection

- **Treatment Period:** up to 12 days, including:

  - NMA-LD regimen (up to 7 days)
  - LN-145/LN-145-S1 infusion (1 day)

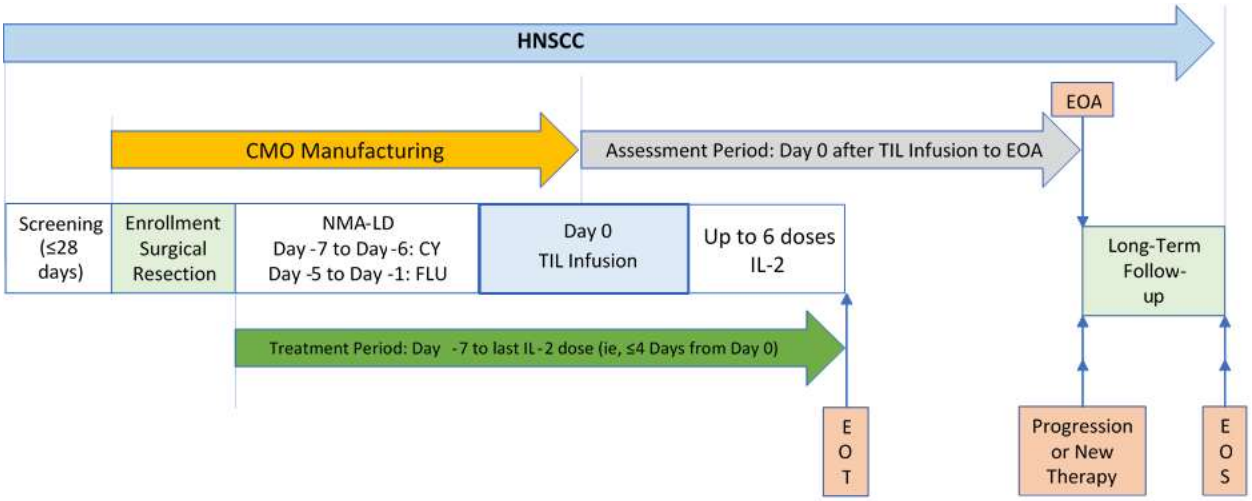
- IL-2 infusion (1 to 4 days)

Treatment is completed once the patient receives his/her last dose of IL-2.

- **Assessment Period**
  - Begins after LN-145/LN-145-S1 infusion on Day 0 and ends upon disease progression, the start of a new anticancer therapy, withdrawal of consent, or after 2 years (Month 24), whichever occurs first. An end-of assessment (EOA) visit should be completed.
- **Long-Term Follow-up Period**
  - Begins after the EOA and stops at the end of study (EOS) , where EOS can be due to death, patient lost to follow-up, withdrawal of consent, study termination by Sponsor, or after 3 years, whichever occurs first. Patients who had tumor resection but did not receive LN-145/LN-145-S1 for any reason will perform an EOA visit and transition directly into the Long-Term Follow-up Period.

The study flow chart is shown in Figure 2.

Figure 2. Study Flow Chart



Abbreviations: Cy=cyclophosphamide; CMO=contract manufacturing organization; EOA=end of assessment visit; EOS=end of study; EOT=end of treatment; Flu=fludarabine; HNSCC=head and neck squamous cell carcinoma IL-2=interleukin-2; NMA-LD=nonmyeloablative lymphodepletion; TIL=tumor infiltrating lymphocytes.

Patients must be hospitalized prior to the planned LN-145/LN-145-S1 infusion for overnight hydration. Patients will remain hospitalized until completion of the IL-2 administration.

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

Response assessments will be conducted by the Investigator following RECIST v1.1.

3. STUDY OBJECTIVES AND ENDPOINTS

3.1. Study Objectives

3.1.1. Primary Objective

- To evaluate the efficacy of LN-145/LN-145-S1 in patients with recurrent and/or metastatic HNSCC based on the ORR using RECIST v1.1 as assessed by the Investigator

3.1.2. Secondary Objectives

- To evaluate the efficacy parameters of LN-145/LN-145-S1 in patients with recurrent and/or metastatic HNSCC such as duration of response (DOR), disease control rate (DCR), and PFS using RECIST v1.1 as assessed by the Investigator
- To evaluate OS in patients with recurrent and/or metastatic HNSCC
- To characterize the safety profile of LN-145/LN-145-S1 in patients with recurrent and/or metastatic HNSCC

3.1.3. Exploratory Objectives

- To identify clinical biomarkers of LN-145/LN-145-S1 activity
- To explore efficacy based on irRECIST criteria—as assessed by independent review initiated at the Sponsor's discretion

3.2. Study Endpoints

3.2.1. Primary Endpoint

- ORR using RECIST v1.1 as assessed by the Investigator

3.2.2. Secondary Endpoints

- DOR using RECIST v1.1 as assessed by the Investigator
- DCR using RECIST v1.1 as assessed by the Investigator
- PFS using RECIST v1.1 as assessed by the Investigator
- OS
- Incidence of TEAEs including SAEs, therapy-related AEs, AEs leading to early discontinuation of treatment or withdrawal from LTFU.

3.2.3. Exploratory Endpoints

- Identification of clinical biomarkers of LN-145/LN-145-S1 activity. Exploratory endpoints aiming at identifying predictive and pharmacodynamic clinical biomarkers of LN-145/ LN-145-S1 activity may include:
    - Phenotypic and functional characterization of the TIL products

  - Immune profile of the tumor tissues, including PD-L1
  - Gene signature of the TIL products, tumor tissues, and/or PBMCs
  - Mutational landscape of the tumors
  - Circulating immune factors
- ORR, DOR, DCR, and PFS as assessed per irRECIST by independent review initiated at Sponsor's discretion

4. SELECTION OF PATIENT POPULATION

Patients who meet the inclusion criteria and do not meet any of the exclusion criteria will be eligible for enrollment into the study.

4.1. Inclusion Criteria

Patients must meet the following inclusion criteria prior to enrollment in the study:

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. Patient (or a legally authorized representative) must understand and voluntarily sign informed consent prior to any study-related assessments/procedures being conducted.
3. Must be able and willing to comply to the study visit schedule and protocol requirements.
4. Must have recurrent and/or metastatic HNSCC. Histologic diagnosis of the primary tumor is required via the pathology report.
5. Must have at least 1 lesion that is resectable for TIL generation. The resected TIL-generating lesion should yield at least 1.5 cm in diameter post-resection of tumor tissue and can be surgically removed with minimal morbidity. An aggregate of ≥ 1.5 cm in diameter from multiple lesions is permitted.
    - If the lesion is within a previously irradiated field, the irradiation must have occurred at least 3 months prior to resection and the lesion must have had radiologically documented progression after radiation therapy.
6. Must have measurable disease as defined by RECIST v1.1 following the tumor resection for TIL manufacturing.
    - Lesions in previously irradiated areas must not be selected as target lesions unless there has been demonstrated radiographic progression in those lesions.
    - Lesions that are partially resected for TIL generation and are still measurable per RECIST may be selected as non-target lesions but cannot serve as a target lesion for response assessment.
7. Must have received at least 1 and no more than 3 lines of prior systemic immunotherapy and/or chemotherapeutic treatments for HNSCC.
    - Patients must have radiologically documented disease progression while receiving or after completion of the most recent prior treatment.
    - Prior systemic therapy in the adjuvant or neoadjuvant setting, or as part of definitive chemoradiotherapy, will be counted as a line of therapy if the disease progressed during or within 12 months of the completion of such therapy.
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 lymphodepletion except for localized palliative radiation therapy.

9. Must have an Eastern Cooperative Oncology Group (ECOG) performance status of 0 or 1 and an estimated life expectancy of ≥ 6 months in the opinion of the Investigator
10. Must meet the following laboratory criteria independent of transfusion and/or blood product support for at least 5 days prior to laboratory testing:
    - Absolute neutrophil count (ANC) > 1000/mm^3
    - Hemoglobin > 9.0 g/dL
    - Platelet count > 100,000/mm^3
    - Alanine aminotransferase (ALT) and aspartate aminotransferase (AST) < 3.0 × upper limit of normal (ULN)
        - Patients with liver metastases must have liver function tests (LFTs) < 5.0 × ULN
    - Total bilirubin ≤ 2.0 mg/dL
        - Patients with Gilbert's Syndrome must have a total bilirubin ≤ 3.0 mg/dL
    - An estimated creatinine clearance (eCrCl) ≥ 40 mL/min at screening using the Cockcroft-Gault formula
11. Patients must be seronegative for the human immunodeficiency virus (HIV1 and HIV2).
12. Patients seropositive for hepatitis B surface antigen (HBsAg), hepatitis B core antibody (anti-HBc), or hepatitis C virus (anti-HCV) indicating acute or chronic infection may be enrolled if the viral load by polymerase chain reaction (PCR) is undetectable with/without active treatment. Additional serology testing may be required depending on local prevalence of certain viral exposures.
13. Patients of childbearing potential and patients whose sexual partners are of childbearing potential must be willing to practice an approved method of highly effective must be willing to practice an approved method of birth control with their partners; starting at the time of informed consent and for 1 year after the completion of the study treatment regimen. Approved methods of birth control are as follows:
    - Combined (estrogen and progesterone containing) hormonal contraception associated with inhibition of ovulation (eg, oral, intravaginal, transdermal)
    - Progesterone-only hormonal contraception associated with inhibition of ovulation (eg, oral, injectable, implantable)
    - Intrauterine device (IUD)
    - Intrauterine hormone-releasing system (IUS)
    - Bilateral tubal occlusion
    - Vasectomized partner
    - True absolute 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.

14. Pulmonary function requirement

    Patients having any of the following require pulmonary function testing (PFT) with post-bronchodilator values of forced expiratory volume (FEV1)/forced vital capacity (FVC) > 0.7 and FEV1 > 50%:

    - History of cigarette smoking of ≥ 20 pack-years and still smoking,
    - Ceased smoking within the past 2 years
    - History of chronic obstructive pulmonary disease
    - Any signs or symptoms of respiratory dysfunction

    If a patient is unable to perform reliable spirometry due to abnormal upper airway anatomy (ie, tracheostomy), a 6-minute walk test may be used to assess pulmonary function. Patients who are unable to walk a distance of at least 80% predicted for age and sex **or** demonstrate evidence of hypoxia at any point during the test (SpO2 < 90%) are excluded.

4.2. Exclusion Criteria

Patients who meet ANY of the following criteria will be excluded from the study:

1. Patients who have received an organ allograft or prior cell transfer therapy that included a nonmyeloablative or myeloablative chemotherapy regimen within the past 20 years. Note: This criterion is applicable for patients undergoing retreatment with TIL with the exception that they will have had a prior NMA-LD regimen with their prior TIL treatment.
2. Patients who are on a systemic steroid therapy > 10 mg of prednisone or other steroid equivalent daily.
    - Patients receiving steroids as replacement therapy for adrenocortical insufficiency are study eligible.
3. Patients with prior therapy-related toxicities Grade >1 per NCI Common Terminology Criteria for Adverse Events (CTCAE) Version 4.03; (see Appendix 17.4), except for neuropathy, dysphagia, alopecia, or vitiligo. Immunotherapy-related endocrinopathies stable for at least 1 month, and controlled with hormonal replacement, are not excluded.
    - If toxicities have resolved to Grade <1 , a minimum of 4 weeks must elapse prior to enrollment (tumor resection)
    - Patients may not undergo preplanned procedures within 2 weeks of the start of NMA-LD
4. Patients with documented Grade ≥2 diarrhea or colitis due to previous immunotherapy (eg, ipilimumab, tremelimumab, anti-PD-1, or anti-PD-L1) within 6 months from screening.
    - Patients who had a normal colonoscopy post anti-PD-1/anti-PD-L1 treatment with uninflamed mucosa by visual assessment, or who have been asymptomatic for ≥6 months, are not excluded

5. Patients who have a contraindication to or history of hypersensitivity reaction to any component or excipients of the TIL therapy and other study drugs:
   - NMA-LD (cyclophosphamide, mesna, and fludarabine)
   - IL-2
   - Antibiotics of the aminoglycosides group (ie, gentamicin or streptomycin; excluding those who are skin-test negative for gentamicin hypersensitivity)
   - Any component of the TIL infusion product formulation including dimethyl sulfoxide (DMSO), human serum albumin (HSA), IL-2, and dextran-40
6. Patients with active systemic infections (eg, syphilis), coagulation disorders, or other active major medical illnesses of the cardiovascular, respiratory, or immune system; including evidence in the medical history of a positive cardiac stress test, myocardial infarction, cardiac arrhythmia, obstructive or restrictive pulmonary disease, uveitis, or other conditions, that in the opinion of the Investigator, would significantly increase the risk of participation.
7. Patients with symptomatic and/or untreated brain metastases (of any size and any number).
   - Patients with definitively treated brain metastases may be considered eligible after discussion with the Sponsor's Medical Monitor/designee, must be stable for at least 2 weeks and must be asymptomatic prior to the start of treatment (NMA-LD)
8. Patients who have any form of primary or acquired immunodeficiency syndrome, such as severe combined immunodeficiency disease or acquired immune deficiency syndrome (AIDS).
9. Patients who have a left ventricular ejection fraction (LVEF) < 45% or who are New York Heart Association (NYHA) Class 2 or higher. A cardiac stress test demonstrating any irreversible wall movement abnormality in any patient ≥ 60 years of age or any patients who have history of ischemic heart disease, chest pain, or clinically significant atrial and/or ventricular arrhythmias
   - Patients with an abnormal cardiac stress test may be enrolled if they have adequate ejection fraction and cardiology clearance with approval of the Sponsor's Medical Monitor
10. Patients who have had another primary malignancy within the previous 3 years (except for those which do not require treatment or have been curatively treated >1 year ago, and in the judgment of the Investigator, do not pose a significant risk of recurrence; including, but not limited to, non-melanoma skin cancer, ductal carcinoma in situ [DCIS] or lobular carcinoma in situ [LCIS], or prostate cancer Gleason score ≤6)
11. Patients who are of the following protected classes will be excluded:
    - 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

12. Patients who have received a live or attenuated vaccine within 28 days of the NMA-LD regimen

4.3. Eligibility Authorization and Eligibility Re-confirmation

Patients who meet all inclusion criteria and do not meet any of the exclusion criteria may be eligible for the study. Patients must have documented approval from the Sponsor's Medical Monitor or designee on the Patient Eligibility Form.

Patients who sign an ICF and fail to meet the inclusion and/or exclusion criteria are defined as screen failures. Patients who failed the initial Screening process may be re-screened and will be registered as a new patient.

Patients who are otherwise eligible but have a delayed tumor resection for TIL production outside of the 28 days from signing the ICF may continue in the study but will need to re-sign the ICF and be reassessed for eligibility as appropriate.

After the Tumor Resection visit takes place, the patient must continue to meet overall health and performance status-related eligibility criteria prior to initiation of NMA-LD. The NMA-LD preconditioning regimen may not commence without documented Sponsor approval using the 'Patient Eligibility Re-Confirmation Form', completed by the Investigator. The Investigator must confirm the patient's health status based on Baseline assessments (including laboratory values and CT scans) to ensure that the patient is stable to proceed with NMA-LD. Prior to beginning the NMA-LD regimen, the Investigator should assess whether the patient has had any clinical deterioration or new medical findings that would put her/him at increased risk when receiving the NMA-LD and IL-2 administrations. Specifically, the Investigator should consider whether a worsening of ECOG status and/or a deterioration of laboratory values constitutes that the patient no longer meets the inclusion and exclusion criteria. If the patient's deterioration is believed to be irreversible and of sufficient magnitude to increase the risk associated with NMA-LD or IL-2 administration, this patient will not be allowed to proceed with NMA-LD. The 'Patient Eligibility Re-Confirmation Form' is to be completed by the Investigator prior to the start of NMA-LD and TIL infusion and sent to the Sponsor or designee for review. Once the Sponsor certifies that sufficient TIL product is available, the form will be signed and returned to the site. This signed form is required prior to the initiation of the NMA-LD regimen.

5. STUDY ASSESSMENTS

5.1. Informed Consent

The most recently approved ICF(s) must be signed before any study-related assessments are performed (and prior to re-treatment, if applicable).

5.2. Inclusion/Exclusion Criteria

Patients must meet all inclusion criteria (Section 4.1) and must not meet any of the conditions specified in the exclusion criteria (Section 4.2). Patients must continue to meet health-related eligibility criteria until start of NMA-LD pretreatment regimen Day -7.

5.3. Demographic Data

The demographic data will include date of birth (as allowed per local regulations), age, gender, and race/ethnic origin.

5.4. Medical History

Relevant and significant medical/surgical history, including cancer history, and concurrent illnesses will be collected for all patients at Screening and updated as applicable. Any pre-existing conditions that worsen after signing of the ICF must be reported as AEs.

5.5. Documentation of Confirmation of Diagnosis or Progression

Patients must have a documented diagnosis of primary HNSCC via pathology report. Patients must have documentation of radiologic disease progression on or after the most recent therapy.

5.6. Tumor HPV Status/HPV Serotype and PD-L1 Expression Score

The patient's HPV tumor status of HNSCC will be recorded if known. If documentation is not available, testing for HPV status is strongly recommended locally using archival tumor tissue or excess tissue obtained during tumor resection.

PD-L1 expression score will also be recorded if known.

5.7. Concomitant Medications

All medications and therapies (prescription and nonprescription, including herbal supplements) taken by the patient up to 28 days prior to Screening will be collected in the electronic case report form (eCRF), including the stop dates for medications prohibited in the study, at the time of consent. All medications and therapies being taken by the patients, or changes thereof, at any time during the study, must also be recorded.

5.8. Physical Examination

Physical examination (PE) will be conducted at the time points specified in Appendix 17.1. Initial PE will include gastrointestinal (abdomen, liver), cardiovascular, extremities, head, eyes, ears, nose, and throat, respiratory system, skin, and psychiatric (mental status). Subsequent PEs will be symptom directed.

5.9. Vital Signs

Vital signs will be measured at the time points specified in Appendix 17.1. Vital signs will include height, weight, pulse, respirations, blood pressure, and temperature. Height will be measured at Screening only.

Body surface area (BSA) and Body Mass Index (BMI) will be calculated at Day -7 only.

On Day 0 (TIL infusion), vital signs will be monitored every 30 minutes during infusion, then hourly (+/-15 minutes) for 4 hours and then routinely (every 4 to 6 hours), unless otherwise clinically indicated, for up to approximately 24 hours post TIL infusion.

Pulse oximetry is required during IL-2 administration.

5.10. Eastern Cooperative Oncology Group Performance Status

An ECOG performance status will be assessed at the timepoints in Appendix 17.1.

5.11. Clinical Chemistries

The following safety blood and urine tests will be collected and analyzed locally at the timepoints in Appendix 17.1.

- Serum chemistry – sodium, potassium, chloride, total CO_2 or bicarbonate, serum creatinine, glucose, blood urea nitrogen (or total urea if local laboratory reports urea in lieu of BUN), albumin, calcium, magnesium, phosphorus, alkaline phosphatase, alanine aminotransferase/serum glutamic pyruvic transaminase (ALT/SGPT), aspartate aminotransferase/serum glutamic oxaloacetic transaminase (AST/SGOT), total bilirubin, lactate dehydrogenase (LDH), total protein, total creatine kinase (CK), uric acid
- Hematology – complete blood count (CBC) with differential. Differentials are not required to be reported if they were not done due to low overall white blood cell count (typically less than 0.3). Bands are only collected if reported.
- Coagulation panel – prothrombin time /international normalized ratio (PT/INR), and partial thromboplastin time /activated partial thromboplastin time (PTT/aPTT). This is required only at Screening.
- Thyroid panel – thyroid stimulating hormone (TSH) and free T4. This is required only at Screening.

- Urinalysis – a complete urinalysis with microscopy and/or urine culture

5.12. ß-HCG Serum Pregnancy Test

Serum pregnancy test for all women of child-bearing potential at the timepoints in Appendix 17.1. Occasionally, a positive serum beta human chorionic gonadotropin (ß-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).

5.13. Infection Testing

Blood samples will be collected for the following virus testing at Screening only:

- HIV (HIV1 and HIV2) serology as per local standards antibody titer
- Hepatitis serology: hepatitis B surface antigen (HBsAg IgG), hepatitis B core antibody (anti-HBc), and hepatitis C virus antibody (anti-HCV IgG). If any hepatitis serology is positive, a corresponding viral PCR test is required
- Syphilis assay as per local standard (eg, rapid plasma reagent [RPR], venereal disease research laboratory [VDRL], or other)
- HSV serology determination (HSV-1 IgG and HSV-2 IgG)
- Epstein Barr Virus (EBV) Panel: viral capsid antigen immunoglobulin G (VCA-IgG), VCA immunoglobulin M (VCA-IgM), and Epstein Barr nuclear antigen immunoglobulin G (EBNA-IgG) or tests conducted as per local standard to confirm absence of acute or active EBV infection
- Cytomegalovirus (CMV) serology (IgG and IgM)

5.14. Human Leukocyte Antigen Typing

Sample collection for HLA typing will be conducted at Screening and analyzed by the Central Laboratory.

5.15. Estimated Creatinine Clearance

$$C_{Cr} = \frac{(140 - \text{age}) \times \text{weight (kg)}}{72 \times S_{Cr}} \quad [\times 0.85 \text{ if female}]$$

C_{Cr} = creatinine clearance (expressed in mL/min); S_{Cr} = serum creatinine (expressed in mg/dL)

The estimated creatinine clearance will be calculated by the site using the Cockcroft-Gault formula at Screening only.

5.16. Cardiac Evaluations

All cardiac evaluations (NYHA, ECHO or MUGA, ECG, cardiac stress test) will be performed during Screening.

5.16.1. New York Heart Association

The New York Heart Association (NYHA) classification must be determined during Screening.

5.16.2. Echocardiogram or Multigated Acquisition Scan

An ECHO or MUGA must be performed to assess left ventricular function for all patients within Screening. If this has been performed within 6 months prior to Screening, it does not need to be repeated.

5.16.3. Electrocardiogram

A 12-lead electrocardiogram (ECG) will be performed locally. Patients must be supine for the examination for at least 3 minutes. If an ECG has been performed within 2 weeks prior to Screening, it does not need to be repeated.

5.16.4. Cardiac Stress Test

A cardiac stress test will be done for all patients ≥ 60 years of age or any patient with a history of ischemic heart disease, chest pain, clinically significant atrial and/or ventricular arrhythmias, or any other clinically significant cardiac disease. If a cardiac stress test was performed within 6 months prior to Screening, it does not have to be repeated.

Any patient with an abnormal cardiac stress test with a normal LVEF requires clearance by a cardiologist and the Sponsor's Medical Monitor to enter the study.

5.17. Pulmonary Function Tests

For patients requiring PFTs, spirometry will be completed during Screening. See Section 4.1 for spirometry criteria.

Patients who are unable to conduct reliable pulmonary function test measurements due to abnormal upper airway anatomy (ie, tracheostomy) may undergo a 6-minute walk test to assess pulmonary function. Patients who are unable to walk a distance of at least 80% predicted for age and sex or who demonstrate evidence of hypoxia at any point during the test (SpO2 <90%) are excluded.

5.18. Colonoscopy

Colonoscopy is only required for patients who have had a documented Grade ≥2 diarrhea or colitis due to previous immunotherapy within 6 months of Screening.

5.19. Immune Monitoring

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

Blood for immune monitoring will be collected at the time points listed in Appendix 17.1.

5.20. Radiographic Assessments

Radiographic assessments by CT scans with contrast are required for all patients and must include head (not brain), neck, chest and abdomen. CT scans are performed at Screening (or historical scans collected within 30 days prior to consent). Baseline scans are to be completed within 14 days of the scheduled LD initiation, preferably as close to the beginning of NMA-LD as possible, and at the protocol-specified timepoints in Appendix 17.1.

Radiographic assessments of additional anatomic locations (eg, brain) will be conducted at the protocol-specified or unscheduled visits as clinically indicated. Response assessments should be evaluated and documented by a qualified Investigator participating in the study.

Magnetic resonance imaging (MRI) or CT positron emission tomography (CT-PET) combined scans of the chest, and abdomen in lieu of CT scans may be allowed for patients who have an intolerability to contrast media or if deemed more clinically appropriate, as described in the Image Acquisition Guidelines.

The same method of assessment (eg, CT, MRI) and the same technique for acquisition of radiographic images should be used to characterize each identified and reported lesion. Patients will be evaluated for response approximately every 4 weeks from LN-145/LN-145-S1 administration for the first 3 months, then at approximately 4.5 and 6 months post-TIL infusion, then approximately every 3 months thereafter until the patient experiences PD per RECIST v1.1 (or if the patient withdraws full consent). Additional radiologic assessments may be performed per the Investigator's discretion.

Although response for primary analysis will be per the Investigator's assessment, imaging will be collected for evaluation by a central imaging service to provide independent review per the Sponsor's discretion.

5.21. Tumor Resection/Harvest

Following confirmation of patient eligibility, the Sponsor's Medical Monitor or designee will provide approval for patient eligibility into the clinical study and subsequent tumor resection. Ideally, the targeted tumor should be in a visceral location (sterile site) and have not been previously irradiated. Prior irradiation of the resected tumor is allowed if at least 3 months have elapsed between irradiation and resection and the tumor has radiographically demonstrated growth during that interim. The tumor to be resected may be from the primary site, regional lymph nodes, or be a distant metastasis. The selection of the tumor to be resected should consider the expected morbidity of the surgery, the amount of potential viable tumor available, and the

potential for contamination/colonization (eg, those with exposure to the aerodigestive tract or skin).

Whenever possible, resection from multiple tumors for TIL generation should be obtained if it would not significantly increase the potential morbidity of the surgical procedure. The compiled aggregate of tumor tissue, however should not exceed 4.0 cm in diameter, or 10 g in weight, due to the limited quantity of the bio-preservation media present in the transport bottle.

Tumor specimens must undergo intraoperative frozen section examination by a pathologist to ensure that viable tumor is present. This must occur at tumor resection prior to the tumor specimen for TIL generation being shipped to the contract manufacturing organization (CMO). A fine needle aspiration may be performed on the planned resected tumor if appropriate.

The patient specimens must be procured and handled to ensure optimal quality of the specimen and minimum transport time to the processing CMO facility, as well as to ensure the appropriate identification of the study product at all times.

All concomitant medications administered for the tumor resection must be recorded and entered into the eCRF.

Refer to the Tumor Procurement & Shipping Manual for details.

5.21.1. Additional Tumor Tissue from Resected Tumor

To improve knowledge of TIL therapy and tumor biology, additional material is collected to be sent to the research facility. Preferably, this material will be obtained at the same time and from the same anatomic location as the material harvested for TIL generation. If additional material cannot be obtained for any reason, the patient is still eligible for study participation. This material enables the pursuit of the exploratory biomarker objectives.

Provision of adequate amount of tumor tissue for TIL manufacturing sent to the CMO takes priority over the collection of additional tumor tissue that is sent to the central laboratory. However, every effort should be made to obtain adequate tumor tissue for both TIL manufacturing and additional analysis.

If there is an excess of tumor tissue post-resection for TIL manufacturing, then the study site should prepare both a fresh sample and a formalin-fixed, paraffin-embedded (FFPE) block using the tissue and send to a designated Central Laboratory.

The FFPE tumor tissues sent to the Central Laboratory may be analyzed for 1) immune cell populations and specific protein expression, 2) specific oncogenic mutations, 3) HPV status, 4) gene expression profile, and, 5), for patients who sign the optional sub-study consent (ie, Research Substudy ICF) for tumor mutational burden.

The fresh tumor samples sent to the Sponsor’s Research laboratory may be analyzed for 1) TIL content, 2) LN-145/LN-145-S1 reactivity, and 3) gene expression profile.

5.22. Post-Treatment Biopsy

Exploratory endpoints may include those studied on baseline and post-treatment biopsies.

A post-treatment (post-LN-145/LN-145-S1 infusion) biopsy (fresh and FFPE) of at least one lesion will be collected, if feasible, on Day 28 (+3 days) after the Day 28 tumor assessment scans. See Appendix 17.1. Post-treatment biopsies must be collected from a lesion distinct from those used as target or non-target for tumor response assessment.

6. STUDY TREATMENT

The investigational product used in this study is listed in Table 1.

Table 1 List of Investigational Products

Therapy Type	Investigational Product	Dosage Form and Strength	Manufacturer
TIL regimen consisting of NMA-LD, TIL LN-144/ LN-145, and aldesleukin (IL-2)	TIL LN-145/145-S1	[redacted] total viable lymphocytes	Iovance

6.1. Nonmyeloablative Lymphodepletion Regimen

The NMA-LD regimen is scheduled to start on Day -7. Patient eligibility re-confirmation and documented subsequent approval from the Sponsor is required to start the NMA-LD preconditioning regimen.

Verification of sufficient LN-145/LN-145-S1 viable cell expansion will be confirmed by the Sponsor and the site will receive the authorization to begin the NMA-LD preconditioning regimen. Eligibility re-confirmation will be completed prior to the start of LD.

Patients may remain hospitalized until the completion of the lymphodepletion regimen for close monitoring of toxicity and hematologic parameters. If indicated by daily hematologic parameters, any modification of the lymphodepletion regimen must be discussed with, and approved by, the Sponsor's Medical Monitor.

The NMA-LD regimen includes **single daily doses** of cyclophosphamide on Day -7 and Day -6 for a total of 2 doses followed by **single daily doses** of fludarabine on Day -5 through Day -1 for a total of 5 doses and should be administered as per institutional protocol/standards for nonmyeloablative chemotherapy. Guidelines for preparation and administration are described below. For consistency in dosing, all patients (including obese patients) should be dosed using actual weight or institutional practice.

6.1.1. Preparation of Cyclophosphamide

The dose of cyclophosphamide is 60 mg/kg. Reconstitute cyclophosphamide per institutional standard to deliver calculated dose in a final concentration of no more than 20 mg/mL.

Cyclophosphamide must be infused with mesna as described in Section 6.1.3.

Actual weight should be used to calculate the cyclophosphamide dose (even if the patient's BMI > 35.0 kg/m^2) or per institutional guidelines.

Please refer to the current appropriate Package Insert.

6.1.2. Preparation of Mesna

Mesna is administered to reduce the risk of hemorrhagic cystitis related to cyclophosphamide administration. Mesna should be administered per institutional guidelines.

6.1.3. Infusion of Cyclophosphamide and Mesna

Cyclophosphamide (60 mg/kg) in a total volume of 250 mL (or greater if required), plus mesna (15 mg/kg) are to be infused together over 2 hours on Day -7 and -6 (Visits 4 and 5). Mesna administration will then continue as per institutional guidelines after each cyclophosphamide dose during Days -7 and -6. The total dose administered must be at least 1.3 times that of the dose of cyclophosphamide to prevent hemorrhagic cystitis. Refer to the current PI/SmPC for mesna dosing.

6.1.4. Fludarabine

The fludarabine dose of 25 mg/m^2 is administered by IV over approximately 30 minutes (or per institutional standard) once daily for 5 consecutive days during Days -5 through -1 (Visits 6 through 10).

Approval from the Sponsor's Medical Monitor is required prior to the administration of TIL if more than 4 days have elapsed from the last dose of fludarabine.

Fludarabine dose will be adjusted according to eCrCl as follows:

- eCrCl 50-79 mL/min: Reduce dose to 20 mg/m^2
- eCrCl 40-49 mL/min: Reduce dose to 15 mg/m^2

Dose hold or discontinuation of fludarabine will only be allowed in the case of toxicity described in the package insert. Refer to the current appropriate package insert for fludarabine full prescribing information, or per institutional standard.

Actual weight should be used to calculate the fludarabine dose (even if the patient's BMI > 35.0 kg/m^2) or per institutional guidelines.

Fludarabine has been reported to cause skin toxicity consisting primarily of skin rashes. If this or other fludarabine-related toxicity event occurs, consultation with Sponsor's Medical Monitor is recommended prior to administration of LN-145/LN-145-S1.

6.2. LN-145/LN-145-S1

6.2.1. Description of LN-145/LN-145-S1

The investigational product, LN-145/LN-145-S1, is a ready-to-infuse therapy composed of autologous TIL derived from the patient's own tumor.

Each dose contains between [redacted] (minimum dose) and [redacted] (maximum dose) total viable lymphocytes. The total volume to be infused will be dependent on total cell dose (approximately 250 mL to 500 mL). The patient is to receive the full dose of TIL product provided.

At the time of completion of TIL manufacturing, the appropriate number of cells will be harvested and provided in the final investigational product.

6.2.2. Composition of LN-145/LN-145-S1

Both non-cryopreserved and cryopreserved formulations of LN-145 have been developed for use in clinical studies.

The cryopreserved investigational TIL product is a [redacted] Refer to the Pharmacy & Investigational Product Administration Manual for details on thawing and administering the cryopreserved TIL product.

The non-cryopreserved product is no longer being used.

6.2.3. Transport of LN-145/LN-145-S1

Each dose of the live suspension LN-145/LN-145-S1 will be shipped/sent by courier to the clinical site from the CMO at least the day before planned administration using a method that is intended to support 24-hour delivery and expected to arrive on the morning of scheduled infusion (Day 0).

The cryopreserved LN-145/LN-145-S1 investigational product will be shipped to the clinical site [redacted] The product is stored in [redacted] until the patient is ready for infusion.

6.2.4. Receipt of LN-145/LN-145-S1

LN-145/LN-145-S1 will be received at the clinical site prior to administration while awaiting the Release for Infusion from the Sponsor. Receipt is defined as the moment the LN-145/LN-145-S1 shipper is signed for by site personnel and released from the courier's custody.

After receiving, inspecting, verifying, and re-labeling with the clinical sites' specific labels, the investigational product, LN-145/LN-145-S1, will be transferred to the patient bedside, preferably in its original shipping container [redacted] product) for administration.

6.2.5. Administration of LN-145/LN-145-S1

6.2.5.1. Pre-LN-145/LN-145-S1 Infusion

Within 24 hours prior to administering LN-145/LN-145-S1, the patient must be hospitalized and prepared with IV hydration, as needed, to ensure good hydration status. Patients must be premedicated with acetaminophen/paracetamol 650 mg PO and diphenhydramine 25 to 50 mg IV (or other histamine H1 antagonist) between 30 and 60 minutes prior to administration of LN-145/LN-145-S1.

In addition, emergency anaphylaxis medications must be available at bedside (eg, epinephrine and diphenhydramine; corticosteroids should only be given in a life-threatening situation).

Additional supportive therapy may include:

- Acetaminophen (650 mg Q4H)
- Indomethacin (50 to 75 mg Q6H)
- Ranitidine (150 mg Q12H)
- Meperidine (25 to 50 mg) or other medications per institutional standards may be given IV if severe rigors/chills develop

6.2.5.2. LN-145/LN-145-S1 Infusion

At least 24 hours must have elapsed between the last dose of fludarabine and the administration of LN-145/LN-145-S1. If fludarabine is discontinued due to an AE, LN-145/LN-145-S1 may be given after resolution of that AE or with approval of the Sponsor's Medical Monitor. Approval of the Sponsor's Medical Monitor is required prior to administration of LN-145/LN-145-S1 if more than 4 days have elapsed from the last dose of fludarabine.

LN-145/LN-145-S1 is to be infused by gravity beginning at a rate of 1 mL/min for the first 5 minutes. If no adverse reaction is observed, the rate can then increase to between 5 and 10 mL/min as clinically appropriate for the completion of the infusion. Infusion rates should not exceed 10 mL/min. Multiple cryopreserved bags are thawed and administered sequentially. If the infusion is interrupted for medical reasons, the TIL infusion bags not yet thawed should be kept in the cryoshipper and any thawed TIL product should be infused within 3 hours of being thawed. The Pharmacy & Investigational Product Administration Manual should be consulted.

Continuous supervision of the patient by site medical staff is required until completion of infusion of the first bag of TIL to monitor for potential signs and symptoms (eg, of a severe hypersensitivity reaction, such as anaphylaxis) that may require immediate medical attention and treatment.

Refer to the Pharmacy & Investigational Product Administration Manual for details. For details on LN-145/LN-145-S1 toxicities, see Section 1.8 and the LN-145 IB.

6.3. Interleukin-2

The IL-2 infusion will begin between 3 and 24 hours after completion of the LN-145/LN-145-S1 infusion. IL-2 will be administered at a dose of 600,000 IU/kg based on total body weight recorded Day 0 and will be administered by IV infusion over 15 minutes at a frequency of every 8 to 12 hours following the initial dose and continued for up to a maximum of 6 doses as tolerated.

If the first dose is not administered within 24 hours, this first dose will be marked as "skipped" and the next dose must be administered within 36 hours of the end of LN-145/LN-145-S1 infusion. If 36 hours elapse from the end of LN-145/LN-145-S1 infusion without a dose of IL-2 being administered due to an AE or other toxicity, no IL-2 will be given and therapy will have been completed.

- IL-2 dosing is allowed for up to 4 days post-LN-145/LN-145-S1 infusion to allow for proper management of any IL-2 toxicities.
- If toxicities can be easily reversed within 24 hours by supportive measures, the additional doses of IL-2 (up to the protocol-defined maximum of six doses) may be given.
- IL-2 dosing may be held or stopped at the discretion of the Investigator.
- IL-2 AEs and toxicities/management are described in Appendix 17.5.

Skipping IL-2 doses is allowed if patient experiences a Grade 3 or Grade 4 toxicity (Appendix 17.5). If two consecutive doses of IL-2 are skipped, then IL-2 administration will be discontinued.

Dosing administration and dose modification details can be found in the current United States Food and Drug Administration-approved Package Insert (USPI) for Proleukin® (eg, bolus IV dosing). Refer to interleukin-2/aldesleukin (Proleukin®) current USPI for additional information including contraindications, monitoring parameters, and contraindicated medications, as applicable.

6.4. Repeat Tumor Resection and Re-treatment

6.4.1. Repeat Tumor Resection

Harvested patients who did not receive TIL generated from the initial harvest, or for whom TIL cannot be generated from the initial harvest due to any reason, can be reharvested and infused if all inclusion and exclusion criteria are met, but will not be considered "re-treated."

6.4.2. Re-Treatment

Patients may rescreen for a second tumor resection and TIL treatment if they meet all inclusion and exclusion criteria. These patients may have a second tumor resection and LN-145/LN-145-S1 therapy. In some cases, if cells are available from the prior manufacturing process, these cells may be used for generating a second TIL product.

Examples of patients who may be eligible for retreatment attempts are prior responders to TIL who relapse and non-responders. Patients cannot be approved for re-treatment without documented approval from the Sponsor's Medical Monitor or designee on the Patient Eligibility Form.

Prior to enrollment for re-treatment, patients must reconsent and undergo an abbreviated Screening visit procedure that includes all assessments and procedures for initial Screening, with the exception of demographics, medical history, documentation of diagnosis, and documentation of HPV status (oropharyngeal disease only) and PD-L1 expression, which do not need to be performed again.

7. PERMITTED AND PROHIBITED CONCOMITANT MEDICATIONS

7.1. Permitted Medications

- Current medications for conditions other than HNSCC are permitted.
- Palliative radiation therapy is permitted if it does not involve anatomic areas containing target or non-target lesions.
- Use of systemic steroid therapy that is ≤ 10 mg/day of prednisone or equivalent is permitted. Topical or inhaled steroids are permitted.

Any changes in concomitant medications will be recorded in the site's source documentation and the patient's eCRF throughout the study.

7.2. Prohibited Medications and Prior Treatment Washout

7.2.1. Prohibited Medications

The following treatments are prohibited during the study:

- Systemic therapies and radiation intended to treat HNSCC or any medications that may have an anti-tumoral effect. Palliative radiation may be allowed if it is not directed at any target or non-target lesions. Prior discussion with the Medical Monitor is strongly encouraged before initiating palliative radiation therapy to avoid inadvertent protocol deviations.
- Other investigational drugs
- Live or attenuated vaccines administered within 28 days prior to the start of NMA-LD and for at least 3 months following the last dose of IL-2 and/or until ANC is ≥ 1000/mm^3, whichever is longer.

Concurrent treatment for malignancy under study is not permitted between enrollment and TIL infusion, respectively, with the following exceptions:

- Palliative radiation therapy is permitted between tumor resection and lymphodepletion if target or non-target lesions are excluded from the radiation treatment beam paths.
- Local surgery of isolated lesions for palliative intent is acceptable if no target or non-target lesions are affected.
- Patients may undergo minor preplanned procedures (ie, port placement) within 2 to 3 weeks prior to the start of NMA-LD with recovery from any procedure related AEs to Grade 1 or Baseline.

7.2.2. Prior Treatment Washout

Patients will enter a washout period prior to NMA-LD and must stop treatments as follows:

- All chemotherapy or biologic therapy must have been discontinued 28 days prior to start of NMA-LD.

8. TOXICITIES MANAGEMENT GUIDELINES

8.1. NMA-LD Regimen Toxicity Management

The use of the NMA-LD regimen (cyclophosphamide with mesna and fludarabine) prior to cell administration is expected to lead to myelosuppression in all patients. Therefore, a high index of suspicion for occult bacteremia should be maintained until marrow recovery.

Refer to the current appropriate cyclophosphamide and fludarabine package insert for additional information.

8.1.1. Infection Prophylaxis

8.1.1.1. Pneumocystis *jirovecii* Pneumonia (PJP)

All patients must receive appropriate *pneumocystis jirovecii* pneumonia (PJP) prophylaxis per institutional standard of care for patients receiving chemotherapy-induced immunosuppression. Such prophylaxis may include any of the following (below) and must begin by Day 14 or as the Investigator deems appropriate and continue until the ALC is > 1000 cells/mm^3 (approximately 3–6 months) or as per institutional standard of care.

One acceptable regimen includes trimethoprim (TMP) and sulfamethoxazole (SMX) as double strength (DS) tab (DS tabs = TMP 160 mg/tab, and SMX 800 mg/tab) by mouth twice daily 3 times a week on nonconsecutive days, beginning on the first Monday, Wednesday, or Friday.

Pentamidine may be substituted for TMP/SMX DS in patients with sulfa allergies and may be administered either IV or aerosolized monthly using standard doses indicated for PJP prophylaxis.

Other appropriate PJP prophylactic schedules or agents may be substituted at the discretion of the treating Investigator.

8.1.1.2. Herpes Virus Prophylaxis

Patients with positive HSV serology must begin herpes reactivation (typically valacyclovir or acyclovir) by Day 14 or as the Investigator deems appropriate and continue until the ALC is > 1000/mm^3 (approximately 3–6 months), or as per institutional standard of care.

Other appropriate viral prophylactic agents may be substituted at the discretion of the treating Investigator.

8.1.1.3. Fungal Prophylaxis (Fluconazole)

Patients must start fluconazole 400 mg (by mouth) from Day 1 and continue until the ANC is > 1000/mm^3. Another suitable fungal prophylaxis regimen as per standard of care at the treating institution may also be used for the duration of grade 3 neutropenia.

8.1.2. Hemorrhagic Cystitis Risk Reduction

To reduce the risk of cyclophosphamide-associated hemorrhagic cystitis, patients will receive mesna in addition to IV fluids. Mesna infusion is per institutional guidelines.

Mesna can interfere with some tests causing a false positive for urinary ketones and a false negative for CPK activity. In addition, it has been associated with hypersensitivity reactions and skin changes. Please refer to the current appropriate package insert for more details.

8.1.3. Febrile Neutropenia

Patients are expected to become neutropenic following the lymphodepletion regimen. Furthermore, IL-2 causes neutrophil migration dysfunction putting patients at risk for pseudomonas infection as well as severe occult bacteremia. Therefore, for FIRST fever > 38.3 °C (or 38.0 °C or above at least 1 hour apart) at any point following lymphodepletion (from Day 0 onward), patients must be started on empiric broad-spectrum antibiotics with adequate pseudomonas coverage (as per local institutional antibiogram) regardless of neutrophil count. Empiric antibiotics should continue at least until the neutrophil count becomes > 500 cells/mm^3 even if no blood-stream infectious agent is identified. If a blood-stream agent is identified, broad-spectrum antibiotics 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.

8.1.3.1. Filgrastim

Patients will receive filgrastim or biosimilar 5 mcg/kg/day (recommended maximum dose of 300 mcg/day or higher as per institutional standard) subcutaneously daily starting from Day 1 until the ANC is > 1000/mm^3 for 3 consecutive days, or as per standard of care at the treating institution.

8.1.4. Blood Product Support

Using daily CBC as a guide, the patient should receive platelets and packed red blood cells as clinically indicated. As a general guideline, patients may be transfused to maintain:

- Hemoglobin ≥ 7.5 g/dL
- Platelets ≥ 10,000/mm^3

Patients may be transfused for different parameters as clinically indicated, such as: an increased risk for bleeding (eg, from an invasive procedure, or presence of metastatic lesion likely to bleed [such as in the brain]), high-grade fever, or sepsis.

All blood products must be irradiated. Leukocyte filters will be utilized for all blood and platelet transfusions to decrease sensitization to transfused white blood cells and decrease the risk of CMV infection.

8.2. LN-145/LN-145-S1 Toxicity Management

Toxicities related to the infusion of LN-145/LN-145-S1 (those which may be seen immediately following TIL 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/LN-145-S1 product.

8.2.1. Expected Toxicities with LN-145/LN-145-S1

Hypersensitivity events, including severe allergic reactions and life-threatening anaphylaxis, have occurred during infusion with the LN-145 investigational product. Premedication and supportive therapy instructions are provided in Section 6.2.5. Avoid prophylactic use of systemic corticosteroids, as it may interfere with the activity of LN-145/LN-145-S1. Corticosteroids should only be used to treat life-threatening conditions.

Allergic reactions 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. More severe reactions, including anaphylaxis, have occurred and require immediate treatment with emergency medications. During infusion of the LN-145/LN-145-S1 product, appropriate emergency medications (eg, epinephrine, diphenhydramine, and corticosteroids) should be available at bedside during administration and institutional guidelines should be followed for the treatment of anaphylaxis. A more severe reaction is less likely but may occur and may require treatment with an injection of epinephrine, steroids, and inhaled bronchodilators.

Rarely, severe breathing problems, known as anaphylaxis, developed. If these symptoms do occur, they must be treated immediately with the medications listed above.

Details concerning specific risks for patients participating in this clinical study may be found in the accompanying LN-145 Investigator's Brochure.

8.3. Interleukin-2 Toxicity Management

IL-2 (Proleukin, aldesleukin) can affect nearly every organ system, but essentially every abnormality will most often normalize following discontinuation of IL-2 dosing. Below is a list of the commonly seen toxicities. Appendix 17.5 has further details for suggested management as well as decision for holding (skipping a dose) and discontinuing IL-2 therapy.

8.3.1. Neurologic Toxicity

Decreased mental status may occur and can range from somnolence to obtundation. IL-2 should be discontinued for any significant mental status changes or hallucinations. Agitation may be observed due to mild hallucinations. Appropriate psychiatry consultation should be considered for guidance in management.

8.3.2. Renal Toxicity

Renal toxicity defined by rapid rise in serum creatinine levels or clinical symptoms is a risk that is commonly observed (1.5 to 2.0 x ULN for mild elevation, or greater than 3.0 x ULN for marked elevation). If patients exhibit signs or symptoms of renal toxicity, manage as per institutional standard of care (and may include low-dose dopamine to improve perfusion or continuous veno-venous hemofiltration). Hemodialysis should be reserved for life-threatening renal failure such as prolonged anuria, hyperkalemia, and profound uremia.

8.3.3. Capillary Leak Syndrome and Weight Gain

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

8.3.4. Cardiac Arrhythmias and Myocarditis

All new cardiac arrhythmias should be promptly evaluated and continuously monitored with intensive management.

8.3.5. Pulmonary

TIL can remain in the pulmonary circulation for 24 to 48 hours following infusion and may cause transient shortness of breath. In addition, pulmonary edema is commonly observed with IL-2 dosing. Supplemental oxygen may be administered as needed. Subsequent IL-2 dosing should be delayed until supplemental oxygen has been weaned or is minimal (< 2 L/min per nasal cannula). If hypoxia persists or is significant, IL-2 should be discontinued.

8.3.6. Sepsis/Febrile Neutropenia during IL-2

Sepsis can mimic IL-2 side effects. Fever symptoms may be masked during IL-2 dosing due to scheduled indomethacin and acetaminophen. In neutropenic patients exhibiting hypotension or oliguria unresponsive to IV fluids, a high degree of suspicion for infection should be entertained and broad-spectrum antibiotics should be initiated.

8.3.7. Heparin-induced Thrombocytopenia

Heparin-induced thrombocytopenia has been observed with IL-2 administration. To minimize this risk, heparin flushes should be avoided or minimized, if possible, during IL-2 dosing.

Refer to **Interleukin-2/aldesleukin (Proleukin®) current package insert** for additional information.

8.4. Concomitant Medications to Control Side Effects

Nausea/vomiting

Nausea and vomiting should be controlled with ondansetron or similar medication. Other second and third line medications (eg, prochlorperazine, promethazine, lorazepam, scopolamine, and aprepitant) can be used per institutional guidelines.

Fever

Premedication for fever should be initiated as per institutional standard of care and may begin the night prior to TIL administration (Day -1) and continue throughout IL-2 treatment. Medications may include indomethacin 50 mg every 8 hours and/or acetaminophen every 4 to 6 hours. Indomethacin 75 mg may be used for persistently febrile patients.

Rigors

IL-2 associated rigors can routinely be treated with meperidine/pethidine. An initial dose of 25 mg can be initiated and followed with an additional 25 mg 15 minutes later if rigors persist or as per institutional standards of care. Prophylactic use of meperidine is discouraged.

Diarrhea

IL-2 associated diarrhea may be observed. Anti-motility agents, such as loperamide and lomotil, may be used as per institutional standards of care (after testing for infectious etiologies such as *Clostridium difficile*, if present).

9. COMPLETION/WITHDRAWAL OF PATIENTS

9.1. Definition of Treatment Completion

Patients will be considered to have completed treatment if they complete the LN-145/LN-145-S1 infusion.

9.2. Non-initiation or Early Discontinuation from Treatment Regimen

Some patients may undergo tumor resection but may not receive infusion of LN-145/LN-145-S1, as follows:

- Patients who initiate NMA-LD but do not receive LN-145/LN-145-S1 will perform an EOA visit and then transition to the LTFU Period.
- Patients who do **not** initiate the NMA-LD therapy and do not receive LN-145/LN-145-S1 will transition directly to the LTFU Period.

Patients may not initiate treatment or may discontinue the study regimen early. Reasons for non-initiation or early discontinuation include:

- Patient has become ineligible for study participation after tumor resection and prior to lymphodepletion.
- TIL are not available, and the patient is ineligible for or does not wish to undergo reharvest.
- Grade ≥ 3 autoimmunity that involves vital organs (heart, kidneys, brain, eye, liver, colon, adrenal gland, lungs) with symptoms emerging prior to study treatment completion
- Grade ≥ 3 allergic reaction including bronchospasm or generalized urticaria that does not resolve after medical management in the opinion of the Investigator
- Grade ≥ 3 toxicity due to IL-2 that does not decrease to Grade 2 or less within 96 hours of management
- Investigator's decision: determination by the Investigator that continuation of treatment is not in the best interest of the patient
- Administration of prohibited concomitant medications/start of new anticancer therapy
- Withdrawal of consent (reasons, if provided, must be documented in patient's source documents):
  - Partial withdrawal of consent: The patient may withdraw from receiving study treatment but agree to continue all or some safety and/or efficacy follow-up evaluations.
  - Full withdrawal of consent: No additional assessments to be performed.
- Pregnancy
- Lost to follow-up

- Death
- Study terminated by Sponsor

9.3. Assessment Completion/End of Assessment

All patients will be assessed for up to 2 years from Day 0 or, until disease progression or the start of new anticancer therapy, whichever occurs first.

9.4. Patient End of Study

The EOS is 3 years after enrollment. The maximum time any patient will remain on the study is 3 years.

9.5. Patient Withdrawal from Study

Patients may discontinue early from the study at any time, for any reasons, without prejudice to further treatment.

Patients may be withdrawn from the study for any of the following reasons, but may be followed up for safety until resolution or permanent sequalae of all toxicities attributable to the investigational product (if applicable):

- Withdrawal of consent by patient (if provided, the reasons must be documented in patient's source documents)
- Lost to follow-up
- Study terminated by Sponsor
- Death

9.6. Early Termination of Study/Center Closure

The study may be terminated at any time by the Sponsor.

9.7. Study Completion

The study is expected to be completed approximately 3 years after the last patient completes enrollment, the time point all patients have exited the study for any reasons, or study termination at the Sponsor's discretion, whichever occurs first.

10. TUMOR RESPONSE ASSESSMENTS

10.1. Response Criteria

Response assessment will be evaluated using RECIST v1.1 with a modification to require confirmation of progressive disease (if clinically indicated). Refer to Table 2 for RECIST v1.1 response criteria definitions [Eisenhauer 2009].

10.2. Documentation of Target and Non-target Lesions

Baseline scans of all lesions are to be completed within 14 days prior to planned initiation of NMA-LD, and as close as possible to the start of NMA-LD. If the initiation of NMA-LD is delayed by more than 3 weeks, Baseline scans must be repeated prior to the initiation of NMA-LD. Measurable disease is defined as the presence of at least 1 measurable non-nodal lesion of ≥ 10 mm in longest diameter by CT scan or ≥ 15 mm in short diameter for nodal lesions. When more than 1 measurable lesion is present at Baseline, all lesions up to a maximum of 5 lesions total (and a maximum of 2 lesions per organ) should be identified as target lesions and will be recorded and measured at Baseline.

Target lesions should be selected based on their size (lesions with the longest diameter) and be representative of all involved organs. All other lesions should be listed as non-target lesions.

Lesions that are partially resected for TIL generation and are still measurable per RECIST may be selected as non-target lesions but cannot serve as target lesions for response assessment.

Pathological lymph nodes which are defined as measurable may be identified as target lesions and must meet the criterion of a short axis diameter of ≥ 15 mm by CT scan. Only the short axis of these nodes will contribute to the Baseline sum. All other pathological nodes (those with short axis ≥ 10 mm but < 15 mm) should be considered non-target lesions. Nodes that have a short axis < 10 mm are considered nonpathological and should not be recorded or followed.

Radiographic assessments by CT/MRI scans with contrast of the head, neck, chest, and abdomen are required for all patients for tumor assessments and will be performed every 4 weeks between Day 28 and Day 84, every 6 weeks until Month 6, and every 3 months through Month 24 or until the patient develops PD as per RECIST v1.1 (or if the patient withdraws full consent).

A sum of the longest diameters (SoD) at Baseline (long axis for non-nodal target lesions and short axis for nodal target lesions) for all target lesions will be calculated and reported as the Baseline SoD. The Baseline SoD will be used as reference to evaluate changes in the measurable dimension of the disease, and thus, response assessment as per RECIST v1.1 guidelines.

All other lesions (or sites of disease), including pathological lymph nodes, should be identified as non-target lesions and should also be recorded at Baseline. Measurements are not required, and these lesions should be assessed as “present.”

10.3. Evaluation of Target Lesions

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

Complete Response (CR)	Disappearance of all target lesions. Any pathological lymph nodes (whether target or non-target) must have a reduction in short axis to < 10 mm).
Partial Response (PR)	At least a 30% decrease in the SoD of target lesions taking as reference the Baseline SoD.
Progressive Disease (PD)	At least a 20% increase in the sum of diameters of target lesions taking as reference the smallest sum on study (this includes the Baseline sum if that is the smallest on study). In addition to the relative increase of 20%, the sum must also demonstrate an absolute increase of at least 5 mm. (The appearance of 1 or more new lesions is also considered progression).
Stable Disease (SD)	Neither sufficient shrinkage to qualify for PR nor sufficient increase to qualify for PD taking as references the smallest sum diameters while on study.

10.4. Evaluation of Non-target Lesions

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

Complete Response (CR)	Disappearance of all non-target lesions. All lymph nodes must be nonpathological in size (< 10 mm short axis).
Non-Complete Response/ Non-Progressive Disease	Persistence of 1 or more non-target lesion(s).
Progressive Disease (PD)	Unequivocal progression of existing non-target lesions. (The appearance of 1 or more new lesions is also considered progression).

10.5. Evaluation of New Lesions

The finding of a new lesion should be unequivocal, ie, not attributable to differences in scanning technique, change in imaging modality or findings thought to represent something other than tumor (for example, some ‘new’ bone lesions may be simply healing or flare of pre-existing lesions). This is particularly important when the patient’s Baseline lesions show PR or CR. For example, necrosis of a liver lesion may be reported on a CT scan report as a ‘new’ cystic lesion, which it is not.

If a new lesion is equivocal, for example because of its small size, continued therapy and follow-up evaluation will clarify if it represents truly new disease. If repeat scans confirm a definite new lesion, then progression should be declared using the date of the initial scan (see Section 10.7.1).

10.6. Evaluation of Overall Response

The best overall response for each patient is the best response recorded from the start of treatment until disease progression/recurrence, the initiation of subsequent anticancer therapy, death or 24 months post-treatment, whichever occurs first (taking reference for PD the smallest measurements recorded since the treatment started). The patient's best response assignment will depend on the achievement of both measurement and confirmation criteria. 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.

Table 2. Response at Each Assessment Time Point for Patients

Target Lesions	Non-target Lesions	New Lesions	Overall Response [a]
CR	CR	No	CR
CR	Non-CR/Non-PD	No	PR
CR	Not evaluated	No	PR
PR	Non-PD or not evaluated	No	PR
SD	Non-PD or not evaluated	No	SD
Not evaluated	Non-PD	No	NE
PD	Any	Yes or No	PD
Any	PD	Yes or No	PD
Any	Any	Yes	PD

CR = complete response; NE = not evaluable; PD = progressive disease; PR = partial response; SD = stable disease

[a] 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.

10.7. Confirmation of Tumor Assessments

10.7.1. 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 ≥ 4 weeks apart after the criteria for response are first met. If the confounding factor/tumor flare is considered at subsequent assessment points, as the previous assessment was stable disease (SD) or PR, then the response should be SD or PR, until proven otherwise. 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 not evaluable (eg, scan was not done).

10.7.2. Confirmation of Progressive Disease

Disease progression should be confirmed by an additional scan ≥ 4 weeks after the initial assessment of disease progression as clinically appropriate.

11. ADVERSE EVENTS

Toxicities will be recorded as AEs and SAEs in the patient's source documents and on the Adverse Events eCRF and must be graded using NCI CTCAE Version 4.03 dated 14 June 2010 (see Appendix 17.4).

11.1. Definitions

11.1.1. Adverse Event

An AE as defined by International Council on Harmonisation (ICH)-Good Clinical Practice (GCP) is any untoward medical occurrence in a patient for which a medicinal/investigational product was administered, and which does not necessarily have a causal relationship with this 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 considered related to the medicinal/investigational product or not.

Events meeting the definition of an AE include:

- Adverse event(s) temporally associated with the use of any of the investigational products or TIL treatment whether or not considered related to the use of any of the investigational products or TIL treatment
- Any abnormal laboratory test results (eg, hematology, clinical chemistry, or urinalysis) or other safety assessments (eg, ECGs, radiological scans, vital signs measurements, physical examination), led to hospitalization or prolongation of hospitalization, required 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 either an increase in frequency and/or intensity of the condition
- New conditions detected or diagnosed after investigational product administration
- Signs, symptoms, or the clinical sequelae of a suspected interaction with investigational product
- Signs, symptoms, or the clinical sequelae of a suspected overdose of either investigational product or a concomitant medication

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

- Any clinically significant abnormal laboratory finding or other abnormal safety assessments 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
- Overdose without clinical sequelae (see Section 11.4)

- Situations where an untoward medical occurrence did not occur (social and/or convenience admission to a hospital)
- Anticipated day-to-day fluctuations of pre-existing disease(s) or condition(s) present or detected at the start of the study that do not worsen

11.1.2. Serious Adverse Event

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

- Death
- Is life-threatening
- 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
- Important medical events that may not directly result in death, be life-threatening, or require hospitalization but may be considered serious when, based on Investigator decision, they may jeopardize the patient and may require intervention to prevent one of the above outcomes as listed in this definition.

Hospitalization including admission to a telemetry unit or intensive care unit specifically for administration of study treatment is not considered an SAE.

An AE meeting the above criteria, even if expected, must be reported as an SAE.

11.1.3. Relationship to the Investigational Product

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 investigational product and the AE/SAE. The event responds to withdrawal of study treatment (de-challenge) and recurs with re-challenge when clinically feasible.
- **Probable**: There is reasonable causal relationship between the investigational product and the AE/SAE. The event responds to de-challenge.
- **Possible**: There is reasonable causal relationship between the investigational product and the AE/ SAE. De-challenge information is lacking or unclear.
- **Not likely**: There is temporal relationship to the investigational product 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 investigational product administration (too early, or late, or investigational product not administered), 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 equals as related and reportable to Health Authorities; Not likely and Not related equals unrelated and not reportable to Health Authorities

11.1.4. Severity

The severity of an event describes the degree of impact and/or the need for medical care necessary to treat an event. Severity of an AE does not equal seriousness of the AE, and is required for the collection of the AEs in the clinical database

AE grading will be defined by the CTCAE Version 4.03 [US Department of Health and Human Services 2010]. In the event the CTCAE Version 4.03 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.
- Death: Outcome of AE is death.

11.2. Reporting Procedures for Adverse Events

AEs/SAEs will be assessed by the Investigator and must be recorded on the appropriate eCRF. All AEs of any attribution will be reported starting immediately after the patient has been consented and continue until 30 days after the end of treatment.

All AEs attributable to the investigational product must be followed until resolution or permanent sequelae is determined by the Investigator.

All AEs attributed to protocol-required procedures or treatment will be collected through the EOA visit.

If any patient should die while on the study or within 30 days after the last dose of study treatment, the Investigator will inform the Sponsor within 24 hours of awareness. The clinical signs and symptoms leading to death should be reported as an SAE with an outcome of death. The cause of death should be recorded in detail on the SAE Report Form. Disease progression is not unexpected in this study population and should not be reported as an AE. Clinical signs and

symptoms that represent the manifestation of the disease progression should be reported as AEs if they occur during AE reporting period.

Each site will be responsible for reporting SAEs occurring at the site to the applicable institutional review board (IRB)/independent ethics committee (IEC) per the IRB's/IEC's reporting guidelines. Sites that are required to utilize a local IRB/IEC will be responsible for their own local IRB/IEC submissions.

It will be left to the Investigator's clinical judgment whether 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 as patient withdraw of consent to treatment. If the patient was permanently removed from the study or LN-145/LN-145-S1 due to an AE or SAE, this information must be included in either the initial or follow-up SAE Report Form and in the eCRF.

11.3. Reporting Procedures for Serious Adverse Events

11.3.1. Investigator Reporting to Sponsor

All SAEs, regardless of relationship to study treatment, must be collected while on the study (from patient signing of informed consent through 30 days after the end of treatment). All AEs/SAEs attributed to protocol-required procedures or treatment will be collected through the EOA visit. If the Investigator learns of any SAEs that occur after the AE reporting period as defined above 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 designated Safety contract research organization (CRO).

All SAEs that occur during the study 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 treatment causality, as defined in Section 11.1.3.

Severity grading will be based on the NCI-CTCAE v4.03 [US Department of Health and Human Services 2010] guidelines. All AEs and SAEs will be recorded in the eCRF within the timelines outlined in the eCRF completion guideline.

Each site is responsible for reporting SAEs occurring at the site to the applicable IRB/IEC per the IRB/IEC's reporting requirements.

All SAEs will also be reported on the SAE report form and submitted by email or fax within 24 hours of knowledge of the event to the attention of the CRO contact below.

CRO	Contact Information for Submission of SAE Report Form
Synteract	**E-mail: SafetyFax@Synteract.com** **Fax: 760-268-6500**

11.4. Special Situations Reporting

11.4.1. Definitions 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. The special situation reports will be reported as an SAE but not considered an AE/SAE unless associated with an AE/SAE.

Medication error is any unintentional error in the prescribing, dispensing, or administration of a medicinal product while in the control of the health care provider, patient, or consumer.

An overdose is defined as an accidental or intentional administration of a quantity of a medicinal product given per administration or cumulatively, which is above the maximum recommended dose as per protocol or in the product labeling (as it applies to the daily dose of the medicinal product in question).

Product complaint is defined as complaints arising from potential deviations in the manufacture, packaging, or distribution of the medicinal product.

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

11.4.2. Reporting Procedures for Special Situations

11.4.2.1. Pregnancy Reporting

Any pregnancy (including those of female partners of male patients) that occurs while on the study through 12 months from the last dose of IL-2 or until the first dose of the subsequent anticancer therapy, whichever comes first, must be reported using the Pregnancy Report 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 11.3.

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 Sponsor or delegate using the Pregnancy Outcome form. Any SAE occurring in association with a pregnancy, brought to the Investigator's attention after the patient has completed the study treatment and Efficacy 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. 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 the investigational product, must be promptly reported to the Sponsor or their representative.

11.4.3. Other Special Situations Reporting

All other special situation reports involving the study treatment must be reported to the Safety CRO using the SAE report form within 24 hours of becoming aware of the situation. 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.

11.5. 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 the Sponsor using reference safety information in the Investigator's Brochure and relevant prescribing information, as applicable.

In addition, the Sponsor must submit expedited reports of potential serious risks from clinical studies or any other source based on relevant local legislation or regulations, including the applicable US FDA Code of Federal Regulations (or other controlling authorities) and relevant updates. The Sponsor will notify participating sites of relevant SUSAR reports and other applicable serious safety findings which occur during the study including the Efficacy Follow-up Phase. The Investigator should notify the IRB or IEC of SUSAR reports as soon as is practical where required by local regulatory agencies and in accordance with the local institutional policy.

12. SAFETY ASSESSMENTS

12.1. Data Safety Monitoring Board

An independent DSMB will monitor the patient safety during the study. The DSMB will evaluate safety data after the first 5 patients and up to a total of 15 patients completing 28 days of assessments. An additional evaluation will be completed when the first 15 patients complete Week 4 (Day 28). Safety data in this study will be reviewed by the Sponsor on an ongoing basis to identify any potential new safety risks. Enrollment will continue while under review.

12.2. Considerations

AEs are detailed in Section 11. Other measures of safety include the following: physical exam including weight (calculated BSA and BMI), ECOG performance status, vital signs (heart rate, respirations, blood pressure and temperature), blood and urine tests (prior to cyclophosphamide administration), hematology (CBC with differential), serum chemistry, urinalysis (complete urine culture if indicated), pulse oximetry, and ongoing assessment of CMV infection, as clinically indicated.

The expected toxicities of the NMA-LD pre-treatment regimen and IL-2 administration will be closely monitored by Sponsor or Sponsor delegate.

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. There is no planned statistical comparison between cohorts. Data from each cohort will be evaluated for efficacy and safety separately. For all 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

Two analysis sets are defined for the statistical analysis and presentation of the data. [redacted] Additional analysis for the primary efficacy endpoint and adverse events will be conducted using the Enrolled Set.

13.2.1. Full Analysis Set

[redacted]

13.2.2. Enrolled Set (for All Cohorts)

[redacted]

13.2.3. Sample Size Justification

The total number of patients who will receive LN-145/LN-145-S1 infusions in this study—Gen 1, Gen 2, Gen 3, and [redacted]—is approximately 55. Patients who are re-treated will only be counted once. All cohorts are intended for signal seeking; no formal hypothesis testing is planned.

Cohort 1: Approximately 8 patients are planned to be infused with LN-145 Gen 1 product. The enrollment is closed for this cohort.

Cohort 2: Approximately 17 patients are planned to be infused with LN-145 Gen 2 product. The planned enrollment is closed for this cohort. This sample size will provide an estimated ORR with a half-width 95% confidence interval of < 0.21 by the Clopper-Pearson exact method.

Cohort 3: Up to 15 patients are planned to be infused with LN-145 Gen 3 product. This sample size will provide an estimated ORR with a half-width 95% confidence interval of < 0.23 by the Clopper-Pearson exact method.

Cohort 4: Up to 15 patients are planned to be infused with LN-145-S1 TIL product. This sample size will provide an estimated ORR with a half-width 95% confidence interval of < 0.23 by the Clopper-Pearson exact method.

Cohort 5 (Re-treatment cohort): Patients who have been previously treated in Cohort 1, 2, 3, or 4 of this study may rescreen for a second administration of TIL products. These patients may have a second tumor resection if needed, especially when new lesions are available and feasible for resection.

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

[redacted]

Age will be derived as a function of the date of informed consent. 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 all cohorts is the ORR as assessed by 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 Clopper-Pearson exact method. Patients without any baseline or any post-baseline measurements are considered non-evaluable.

13.5.2. Secondary Endpoints

The secondary efficacy endpoints for each cohort 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 radiologic 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) [redacted] 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/LN-145-S1 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 [redacted] 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: 6 months, 12 months, 18 months, and 24 months from the date on which patients received LN-145/LN-145-S1 infusion (Day 0), depending on the maturity of the study data at the time of analysis.

13.6. 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. [redacted] 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 v4.03 for each measure under consideration (eg, ANCs for neutropenia; platelets for thrombocytopenia; see Appendix 17.4).

[redacted]

13.7. Exploratory Analyses

Correlation of immune factors (cellular and soluble factors; eg, cytokines; LDH; neutrophil lymphocyte ratios), biochemical, genetic, or phenotypic sample data, HPV status, PD-L1, and serotype 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 independent review initiated at Sponsor's discretion.

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 E6 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.

14.2. Protocol Modifications

The Investigator will not modify this protocol without obtaining the concurrence of the Sponsor. 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 study (eg, change in 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 in Section 15 of the protocol.

In situations requiring a departure from the protocol, the Investigator or other physician in attendance will contact the Sponsor or its representative for approval prior to any intended departure from the protocol.

14.3. Regulatory Approval and Documentation

Documents that must be provided to the Sponsor prior to investigational product shipment are as follows:

- Up-to-date curriculum vitae for each Investigator
- Signed and dated Investigator agreement
- Applicable local regulatory documentation (eg, Form FDA 1572)
- Signed financial disclosure Form
- A copy of the formal written notification to the Investigator regarding approval of the protocol by the IRB/IEC is required. 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 (Clinical Study Agreement).
- In addition to the documents required prior to the study, other documentation may be required during the study.

14.4. Record Retention

In compliance with the ICH Guideline E6, 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 study documents as specified in Essential Documents for the Conduct of a Clinical Study 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 the investigational product. 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.

14.5. Data Quality Assurance

This study 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).

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, periodic monitoring visits by the Sponsor or designee and direct transmission of clinical study data into the database.

Agreements made by the Sponsor with the Investigator/institution and any other parties involved in the clinical study will be in writing as a separate agreement. Representatives of the Sponsor 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.

14.6. Data Processing and Recordkeeping

14.6.1. Electronic Data

When using electronic data processing, the Sponsor or their designee will ensure that systems comply with 21CFR 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 described in the relevant study-specific plans or standard operating procedures.

14.6.2. Electronic Case Report (eCRF) Form Completion

Electronic data capture (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 in English. The eCRFs are to be completed within the agreed time frame after the patient's visit, except for the results of tests performed outside the Investigator's office, so that they always reflect the latest observations on the patients participating in the study.

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 eCRF 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, and changes must reflect in source documents.

14.6.3. Study Monitoring

In accordance with 21 CFR Part 312.56, the clinical monitor will periodically inspect all eCRFs, study documents, research facilities, and clinical laboratory facilities associated with this study at mutually convenient times during and after completion of the study. As required by 21 CFR Part 312, Subpart D: Responsibilities of Sponsors and Investigators, the monitoring visits provide the Sponsor with the opportunity to evaluate the progress of the study; verify the accuracy and completeness of eCRFs against source documentation; ensure that all protocol requirements, applicable to FDA regulations, and Investigator’s obligations are being fulfilled; and resolve any inconsistencies in the study records. This includes inspection of all documents and records related to the study that are required to be maintained by the Investigator, including

but not limited to medical records (office, clinic, or hospital) and investigational pharmacy records for the patients participating in this study. The names and identities of all research patients will be kept in strict confidence and will not appear on eCRFs or other records provided to or retained by the Sponsor. The IND regulations also require the Investigator to allow authorized representatives of Sponsor, the FDA or regulatory authorities to access all study records and source documentation and inspect and make copies of the same records. The Investigator should immediately notify the Sponsor if they have been contacted by a regulatory agency concerning an upcoming inspection. The names and identities of the patients need not be divulged to the Sponsor; however, the records must nevertheless be inspected. This can be accomplished by blacking out the patient's name and replacing the name with the patient's study identification (ID) number. If these requirements conflict with the local regulatory restrictions or institutional requirements, the Investigator must inform the Sponsor of these restrictions before initiation of the study.

14.6.4. Clinical Trial Insurance

In the event of a side effect or injury, appropriate medical care as determined by the Investigator/designee will be provided.

Clinical trial insurance has been undertaken according to the laws of the countries where the study will be conducted.

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) and international regulations (ICH E6 GCP Guidelines), the protocol and ICF 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 federal 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 study. Amendments to the protocol will be subject to the same requirements as the original protocol.

Reports on, and reviews of, the study and its progress will be submitted to the IRB/IEC by the Investigator at intervals stipulated in their guidelines.

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 International Council on Harmonisation (ICH) and Good Clinical Practice (GCP) guidelines, Directive 2001/20/EC (and when in force EU Regulation 536/2014), and Regulation 2016/679 (GDPR), 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 that they 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. Finally, they will be told that their records may be examined by competent authorities and authorized persons, but their personal data will be treated as strictly confidential and will not be publicly available. Patients must be given the opportunity to ask questions. 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 or her legally designated representative to consider his or her decision to participate in the study.

In accordance with 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.

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 regulations 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 study to the Sponsor, IRB/IEC, FDA, EMA, regulatory agencies, or other authorized recipients as appropriate for the execution, analysis, review, and reporting of this study. Such information shall not be used for any other purposes and will remain confidential. Patient will not be individually identified but will be referred to in records by the study-assigned number and patient initials (if applicable by local regulations).

15.4. Adverse Event Reporting

The Investigator agrees to report all AEs/SAEs to the Sponsor as described in Section 11. Furthermore, the Investigator is responsible for ensuring that any co-Investigator or sub-Investigator promptly bring AEs to the attention of the Principal Investigator (PI). The PI shall promptly notify the IRB/IEC of any SAEs, or any other information that may affect the safe use of the investigational product during the course of the study as applicable per the local and/or central 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.

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 consent forms) 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 this study, or the fact that this 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. The Investigator shall not submit a publication or abstract to journals or professional societies without the prior written approval of the Sponsor, except as permitted by the agreed terms of the Clinical Study Agreement, including after the reporting of the results of this study by the Sponsor and other institutions.

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17. APPENDICES

17.1. Schedule of Assessments

	Screening and Enrollment Period						Treatment Period		Assessment Period													LTFU Period
Visit #	1	2	3	4	5	6, 7, 8, 9, 10	11	12, 13, 14, 15	16	17	18	19	20	21	22	23	24	25	26	27	-	
Visit Name	Screening Visit	Tumor Resection	Day -14 -- (Baseline)	Day -7	Day -6	Days -5, -4, -3, -2, -1	Day 0 (TIL Infusion)	Days 1, 2, 3, 4	Day 14	Day 28 (Week 4)	Day 56 (Week 8)	Day 84 (Week 12)	Day 126 (Month 4.5/ Week 18)	Month 6	Month 9	Month 12	Month 15	Month 18	Month 21	Month 24	EOA Visit [a]	
Visit window	Up to 28 days	Up to 48 hours prior to resection	N/A	N/A	N/A	N/A	N/A	N/A	(+/- 3 days)	(+3 days)	(+/- 3 days)	(+/- 3 days)	(+/- 7 days)	(+/- 7 days)	(+/- 7 days)	(+/- 7 days)	(+/- 21 days)	(+/- 21 days)	(+/- 21 days)	(+/- 21 days)	N/A	(+/- 21 days)
Informed Consent	X																					
Inclusion/Exclusion	X																					
Demographic Data	X																					
Medical History	X																					
Documentation of Diagnosis	X																					
Tumor HPV Status/HPV Serotype and PD-L1 Expression	X	(X)																				
Physical Examination [b]	X		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	
Vital Signs [c]	X	X	X	X	X	X	X [d]	X	X	X	X	X	X	X	X	X	X	X	X	X	X	
Pulse Oximetry								X														
ECOG Performance Status	X	X	X	X			X			X	X	X	X	X	X	X	X	X	X	X	X	
Safety Blood and Urine Tests [e]	X	X [f]	X	X	X	X	X	X	X	X	X	X	X	X							X	
ß-HCG Serum Pregnancy Test	X		X																			
Infection Testing [g]	X																					
HLA Typing [h]	X																					
Estimated Creatinine Clearance [i]	X																				X	
Cardiac Evaluations [j]	X																					
Pulmonary Function Tests [k]	X																					

	Screening and Enrollment Period						Treatment Period		Assessment Period														LTFU Period
Visit #	1	2	3	4	5	6, 7, 8, 9, 10	11	12, 13, 14, 15	16	17	18	19	20	21	22	23	24	25	26	27	-	
Visit Name	Screening Visit	Tumor Resection	Day -14 (Baseline)	Day -7	Day -6	Days -5, -4, -3, -2, -1	Day 0 (TIL Infusion)	Days 1, 2, 3, 4	Day 14	Day 28 (Week 4)	Day 56 (Week 8)	Day 84 (Week 12)	Day 126 (Month 4.5/ Week 18)	Month 6	Month 9	Month 12	Month 15	Month 18	Month 21	Month 24	EOA [a]	
Visit window	Up to 28 days	Up to 48 hours prior to resection	N/A	N/A	N/A	N/A	N/A	N/A	(+/- 3 days)	(+3 days)	(+/- 3 days)	(+/- 3 days)	(+/- 7 days)	(+/- 7 days)	(+/- 7 days)	(+/- 7 days)	(+/- 21 days)	(+/- 21 days)	(+/- 21 days)	(+/- 21 days)	N/A	(+/- 21 days)
Colonoscopy [l]	X																					
Tumor Assessments [m]	X		X							X	X	X	X	X	X	X	X	X	X	X	X	X [n]
Response Assessments (RECIST v1.1)										X	X	X	X	X	X	X	X	X	X	X	X	X [n]
Post-treatment core biopsy [o]										X												
Eligibility Confirmation [p]			X																			
Hospitalization [q]						(X)	X	X														
Concomitant Medications	X	X	X	X	X	X	X	X	X	X												
Adverse Events [r]	X	X	X	X	X	X	X	X	X	X												
Tumor Resection [s]		X																				
Pre-treatment biopsies [t]		X																				
NMA-LD [u]				X	X	X																
TIL Infusion [v]							X															
IL-2 600,000 IU/kg [w]								X														
PJP [x]									X	X	X	X	X [y]	X [y]								
Filgrastim [y]								X														
Fungal Prophylaxis [z]								X	X	X	X	X										
Herpes Virus Prophylaxis [aa]									X	X	X	X	X [aa]	X [aa]								
Immune Monitoring [bb]	X	X [f]		X				X [bb]	X	X	X	X		X	X	X					X	
Survival status and new anti-cancer therapies [cc]																						X

(X)=If applicable.

ß-HCG = beta human chorionic gonadotropin; CT = computed tomography; ECOG = Eastern Cooperative Oncology Group; EOA = End of Assessment visit; HLA = human leukocyte antigen; HPV = human papillomavirus; IL-2 = interleukin-2; MRI = magnetic resonance imaging; N/A = not applicable; NMA = nonmyeloablative; PBMC = peripheral Blood Mononuclear Cells; PJP = *pneumocystis jirovecii* pneumonia; RECIST = Response Evaluation Criteria in Solid Tumors; Wk = Week.

a Assessments for the EOA visit do not need to be repeated if the same assessments were performed within 14 days prior to the EOA visit.

b Initial physical examination will include gastrointestinal (abdomen, liver), cardiovascular, extremities, head, eyes, ears, nose, and throat, respiratory system, skin, and psychiatric (mental status). Subsequent physical examinations will be symptom directed. See Section 5.8.

c Vital signs will include height, body weight, heart rate, blood pressure, and temperature. Height will be measured at Screening only. Body surface area and body mass index will be calculated at Day -7 only with weight collected on Day -7 or within 24 hours thereof. Weight on Day 0 will be used for IL-2 dose calculations. Weight measurement on days -6 through -1 is only required if there is a concern of >10% weight changed from Day -7. All others will be assessed at every visit through Month 24. See Section 5.9.

d On Day 0 (TIL infusion), vital signs will be monitored every 30 minutes during infusion then hourly (+/-15 minutes) for 4 hours and then routinely (every 4 to 6 hours), unless otherwise clinically indicated, for up to approximately 24 hours post TIL infusion. See Section 5.9.

e Safety Blood and Urine Tests
- Chemistry: sodium, potassium, chloride, total CO2, or bicarbonate, creatinine, glucose, BUN, albumin, calcium, magnesium, phosphorus, alkaline phosphatase, ALT, AST, total bilirubin, lactate dehydrogenase, total protein, total creatine kinase, uric acid. See Section 5.11.
- Hematology: CBC with differential. Differentials are not required to be reported if they were not done due to low overall white blood cell count (typically less than 0.3). Bands are only collected if reported.
- Thyroid panel: TSH and free T4 will be done at Screening and as clinically indicated.
- Urinalysis: A complete urinalysis with microscopy and/or urine culture will be done.
- Coagulation: Prothrombin time /international normalized ratio (PT/INR), and partial thromboplastin time/activated partial thromboplastin time (PTT/aPTT) will be performed at Screening only.

f Laboratory samples may be collected within 48 hours prior to the tumor resection visit.

g HIV antibody titer (HIV1 and HIV2); Hepatitis – HBsAg, anti-HBc determination and anti- HCV; CMV serology (IgG and IgM), HSV serology determination (HSV-1 IgG and HSV-2 IgG); EBV viral capsid antigen immunoglobulin G (VCA-IgG), VCA immunoglobulin M (VCA-IgM) and/or Epstein Barr nuclear antigen (EBNA-IgG) (may be within previous 3 months to Tumor Resection/Visit 2). Syphilis testing (VDRL or other). Syphilis screening (as per local standard; eg, Rapid Plasma Reagin [RPR] venereal disease research laboratory [VDRL] or other) at Screening, and thereafter as clinically indicated. See Section 5.13.

h HLA typing will be conducted as Screening and analyzed by central laboratory. See Section 5.14.

i Estimated CrCl is calculated at Screening only and based on the Cockcroft-Gault calculation. See Section 5.15.

j Cardiac Evaluations consist of NYHA, ECHO or MUGA, ECG and cardiac stress test within 28 days prior to Screening. Stress test must show normal LVEF and unimpaired wall movement. If patient is ≥ 60 years of age or with a history of ischemic heart disease, chest pain, or clinically significant atrial and/or ventricular arrhythmias, patient must have had a stress test. See Section 5.16.

k For patients requiring PFTs, spirometry, or equivalent will be completed during Screening. See Section 5.17.

l Colonoscopy is only required for documented Grade ≥ 2 diarrhea or colitis as a result of previous immunotherapy within 6 months from Screening. Patients that have been asymptomatic for at least 6 months from Screening or had a normal colonoscopy post anti-PD-1/anti-PD-L1 treatment, with uninflamed mucosa by visual assessment will not need to repeat the colonoscopy. See Section 5.18.

m CT Scans of the head, neck, chest, and abdomen are required at the indicated time points. Baseline scans of all lesions are to be completed within 14 days prior to initiation of NMA-LD, preferably as close as possible to the start of NMA-LD. Additional radiological assessments may be performed per Investigator's discretion. MRI may be used if patients are intolerable to contrast media. See Section 5.20.

n Tumor assessment and Response assessment are to be performed at LTFU only for patients with stable disease or response (eg, pts who do not progress and continue without further treatment).

o A post-treatment (post TIL infusion) core biopsy of at least one lesion (fresh and FFPE) will be collected, if feasible, on Day 28 (+3 days). The biopsy must occur after the Day 28 tumor assessment scans and from a lesion not being used for RECIST response assessment. See Section 5.22.

p Eligibility re-confirmation completed at Baseline must be approved by Sponsor's Medical Monitor prior to initiation of lymphodepletion.

q Hospitalization is mandatory from the day before TIL infusion through all IL-2 infusions. The length of and reason for hospitalization must be reported on the eCRF for Tumor Resection and study related treatments. In addition, any unscheduled hospitalization due to AE/SAE must also be reported on the eCRF. Patients who are hospitalized for any reason (eg, tumor resection, mandated therapy [chemotherapy, IL-2], AEs, other) will need to complete a Hospitalization Form.

r All AEs will be assessed as per NCI-CTCAE Version 4.03 during treatment period and applicable visits after the ICF is signed and for 30 days after the last treatment, regardless of relationship. Thereafter SAEs that the Investigator assesses as at least possibly related to study treatment or procedures will be collected and followed through resolution. See Section 11.

s At Tumor Resection, all lesions to be resected for TIL harvest must undergo intraoperative frozen section and be analyzed by a pathologist prior to resection. In addition, any excess tumor tissue not sent for TIL generation should be prepared in an FFPE block and sent to the designated Central Laboratory. See Section 5.21.

t If there is an excess of tumor tissue post-resection for TIL manufacturing, then the study site should prepare a FFPE block using the tissue and send to a designated Central Laboratory. See Section 5.21.1.

u Cyclophosphamide with mesna for 2 days at Day -7 and Day -6 followed by 5 days of fludarabine at Day -5 thru Day -1. See Section 6.1.

v TIL infusion is to be done at least 24 hours from last dose of fludarabine. If more than 4 days have elapsed from last dose of fludarabine, Medical Monitor approval is required prior to TIL administration. See Section 6.1.

w Initiate IL-2 at 600,000 IU/kg (based on total body weight at Day 0) between 3 and 24 hours after completion of the LN-145/LN-145-S1 infusion and continue every 8 to 12 hours for up to 6 doses. See Section 6.3.

x PJP prophylaxis must be given by Day 14 or as the Investigator deems appropriate and continue until the absolute lymphocyte count is > 1000 cells/mm^3. See Section 8.1.1.1.

y Filgrastim 5 mcg/kg/day subcutaneous must be administered daily starting from Day 1 (Visit 12) until the absolute neutrophil count is > 1000/mm^3 for 3 consecutive days, or as per institutional standard. See Section 8.1.3.1.

z Fungal prophylaxis (fluconazole 400 mg by mouth daily) must be administered each day starting from Day 1 (Visit 12) and continue until the ANC is > 1000/mm^3. Another suitable fungal prophylaxis regimen as per standard of care at the treating institution may also be used for the duration of grade 3 neutropenia. See Section 8.1.1.3.

aa Herpes prophylaxis must begin by Day 14 or as the Investigator deems appropriate and continue, until ALC is > 1000/mm^3 or as per institutional standard of care. See Section 8.1.1.2. Patients with positive HSV serology will be given valacyclovir or acyclovir for prophylaxis.

bb Blood draw for immune monitoring is to be collected at screening, tumor resection, Day -7, Day 1, Day 4, each scheduled visit Day 14 through Day 84, then at 6, 9, and 12 months and at the EOA visit.

cc The LTFU period begins after the assessment period ends and stops at the EOS, where EOS equals death, lost to follow-up, withdrawal of consent, study termination by Sponsor, or 3 years, whichever occurs first. Patients are to be followed approximately every 3 months to assess OS, disease status and subsequent anticancer therapy. Durable responders will continue to have response assessments.

17.2. 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]

17.3. Calculation of BMI and BSA

Actual body weight is used for dose calculations of treatment agents, even if the patient's BMI > 35.0 kg/m^2.

BMI

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

BSA

The BSA should be calculated using the following formula:

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

Other institutional standard formulas are acceptable.

17.4. Common Terminology Criteria for Adverse Events

https://evs.nci.nih.gov/ftp1/CTCAE/CTCAE_4.03/CTCAE_4.03_2010-06-14_QuickReference_8.5x11.pdf

17.5. Expected Aldesleukin Toxicities and Their Suggested Management

Expected Toxicity	Expected Grade	Supportive Measures	Stop Treatment*
Chills	3	IV Meperidine 25-50 mg, IV q1h, prn	No
Fever	3	Acetaminophen 650 mg, po, q4h; Indomethicin 50-75 mg, po, q8h	No
Pruritis	3	Hydroxyzine HCL 10-20 mg po q6h, prn; Diphenhydramine HCL 25-50 mg, po, q4h, prn	No
Nausea/ Vomiting/ Anorexia	3	Ondansetron 10 mg, IV, q8h, prn; Granisetron 0.01 mg/kg IV daily prn; Droperidol 1 mg, IV q4-6h, prn; Prochlorperazine 25 mg q4h pr, prn or 10 mg IV q6h prn	No
Diarrhea	3	Loperamide 2 mg, po, q3h, prn; Diphenoxylate HCl 2.5 mg and atropine sulfate 25 mcg, po, q3h, prn; codeine sulfate 30-60 mg, po, q4h, prn	If uncontrolled after 24 hours despite all supportive measures
Malaise	3 or 4	Bedrest interspersed with activity	If other toxicities occur simultaneously
Hyperbilirubinemia	3 or 4	Observation	If other toxicities occur simultaneously
Anemia	3 or 4	Transfusion with PRBCs	If uncontrolled despite all supportive measures
Thrombocytopenia	3 or 4	Transfusion with platelets	If uncontrolled despite all supportive measures
Neutropenia	4	Observation	No
Edema/Weight gain	3	Diuretics prn	No
Hypotension	3	Fluid resuscitation; Vasopressor support	If uncontrolled despite all supportive measures
Dyspnea	3 or 4	Oxygen or ventilatory support	If requires ventilatory support
Oliguria	3 or 4	Fluid boluses or dopamine at renal doses	If uncontrolled despite all supportive measures
Increased creatinine	3 or 4	Observation	Yes (grade 4)
Renal failure	3 or 4	Dialysis	Yes
Pleural effusion	3	Thoracentesis	If uncontrolled despite all supportive measures
Bowel perforation	3	Surgical intervention	Yes
Confusion	3	Observation	Yes
Somnolence	3 or 4	Intubation for airway protection	Yes
Arrhythmia	3	Correction of fluid and electrolyte imbalances; chemical conversion or electrical conversion therapy	If uncontrolled despite all supportive measures

Expected Toxicity	Expected Grade	Supportive Measures	Stop Treatment*
Elevated Troponin levels	3 or 4	Observation	Yes
Myocardial infarction	4	Supportive care	Yes
Elevated transaminases	3 or 4	Observation	For Grade 4 without liver metastases
Electrolyte imbalances	3 or 4	Electrolyte replacement	If uncontrolled despite all supportive measures

*Unless the toxicity is not reversed within 12 hours

** Unless the toxicity is not reversed to Grade 2 or less by next retreatment