IOVANCE BIOTHERAPEUTICS

ADVANCING IMMUNO-ONCOLOGY

CLINICAL PROTOCOL

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

PROTOCOL NUMBER:	C-145-03
IND NUMBER:	[redacted]
EudraCT NUMBER	2016-003446-86
SPONSOR:	Iovance Biotherapeutics, Inc. 999 Skyway Rd, Suite 150 San Carlos, CA 94070
PROTOCOL AMENDMENT:	Protocol Amendment, Version 3.0, Dated 17 August 2018
SUPERSEDES:	Protocol Amendment, Version 2.0, Dated 30 August 2017 Original Protocol, Version 1.0, Dated 16 August 2016
MEDICAL MONITOR:	[redacted] Sr. Vice President, Clinical [redacted]

SPONSOR SIGNATURE PAGE

Protocol Title:	A Phase 2, Multicenter Study to Evaluate the Efficacy and Safety of Autologous Tumor Infiltrating Lymphocytes (LN-145) for the Treatment of Patients with Recurrent and/or Metastatic Squamous Cell Carcinoma of the Head and Neck
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Protocol Version and Date:	Protocol Amendment, Version 3.0, 17 August 2018

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

[redacted] [redacted]

Signature **Date**

[redacted] **Senior VP Clinical, Iovance Biotherapeutics, Inc.**

INVESTIGATOR PROTOCOL SIGNATURE PAGE

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

PROTOCOL SYNOPSIS

Protocol Title	A Phase 2, Multicenter Study to Evaluate the Efficacy and Safety of Autologous Tumor Infiltrating Lymphocytes (LN-145) 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	• Nonmyeloablative lymphodepletion (NMA-LD) (cyclophosphamide and fludarabine) • LN-145: autologous tumor infiltrating lymphocytes (TIL) derived from the patient's own tumor • Interleukin-2 (IL-2, aldesleukin, Proleukin®)
Study Objectives	**Primary Objective** • To evaluate the efficacy of LN-145 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 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 in patients with metastatic and/or recurrent HNSCC **Exploratory Objectives** • To explore the persistence of LN-145 and immune correlates of response, survival, toxicity of the treatment, and the human papillomavirus (HPV) status of the tumor • To explore efficacy based on RECIST v1.1 and immune-related RECIST (irRECIST) criteria—as assessed by independent review • To assess health-related quality of life (HRQoL) • To assess quality-adjusted time without symptoms of disease or toxicity of treatment (Q-TWiST)
Study Design	This is a Phase 2, multicenter, prospective, open-label, interventional study using autologous TIL infusion (LN-145) 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, as tolerated), followed by the infusion of autologous TIL (LN-145) (see Section 2.2) 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 LN-145 infusion, continuing for up to a maximum of 6 doses, as tolerated. Patients may be eligible for retreatment if they relapse or do not respond following LN-145 therapy or had a TIL manufacturing failure. Patients will be evaluated for response at approximately 4 weeks (Day 28), 8 weeks (Day 56), 12 weeks (Day 84), 18 weeks (Day 126), 6 months, 9 months, 12 months, 15 months, 18 months, 21 months, and 24 months following LN-145 therapy.
Duration of Participation	The study will consist of 3 phases: • **Pretreatment Phase (approximately 8 weeks)** o Screening visit (up to 28 days) o Tumor resection visit (1 day) o LN-145 manufacturing period (approximately 3 to 5 weeks) • **Treatment Phase (approximately 2 weeks)** o NMA-LD regimen (7 days) o LN-145 infusion (1 day) o IL-2 infusion (1 to 4 days) • **Assessment Phase (minimum 3 years)** o Efficacy follow-up for safety and efficacy evaluations (24 months) o Long-term Overall Survival Follow-up to assess disease status on durable responders and survival until the last patient is followed for 3 years
Number of Study Sites	Approximately 15 clinical study sites
Number of Planned Patients	Approximately 47 patients who are evaluable for efficacy (see Section 13.2.2)
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. 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 (or aggregate of lesions resected) should yield at least 1.5 cm in diameter post-resection of tumor tissue and can be surgically removed with minimal morbidity (defined as any operation for which expected hospitalization is ≤ 3 days). 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 progressed after radiation therapy. An aggregate of ≥ 1.5 cm in diameter from multiple lesions is permitted. 6. Must have measurable disease as defined by RECIST v1.1 following the surgical resection. If measurable target lesion(s) are in previously irradiated areas, irradiation must have occurred at least 3 months prior to tumor resection and the lesions must have demonstrated evidence of progression since irradiation. 7. Patients must have recurrent and/or metastatic carcinoma of the head or neck and have received at least 1 and no more than 3 lines of prior systemic immunotherapy and/or chemotherapeutic treatments for HNSCC. Patients must have disease progression while receiving or after the completion of the most recent prior treatment. 8. Any prior therapy directed at the malignant tumor, including radiation therapy, chemotherapy, biologic/targeted agents, and immunologic agents must be discontinued at least 28 days prior to lymphodepletion. Radiation therapy may have been received up to 28 days prior to lymphodepletion for lesions not expected to be used for TIL generation or target lesions. 9. Have an Eastern Cooperative Oncology Group (ECOG) performance status of 0 or 1 and an estimated life expectancy of ≥ 3 months. 10. Must meet the following laboratory criteria: • 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 • Serum creatinine ≤ 1.5 mg/dL • An estimated creatinine clearance (eCrCl) ≥ 40 mL/min using the Cockcroft-Gault formula at screening 11. Patients must be seronegative for the human immunodeficiency virus (HIV). 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. 13. Male and female patients of childbearing potential 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 • Sexual abstinence
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, except for prior LN-145. Prior LN-145 therapy must have occurred at least 3 months prior to retreatment tumor resection. 2. Patients who are on a systemic steroid therapy > 10 mg of prednisone or other steroid equivalent daily. • A short course of higher dose steroid therapy is allowed in cases of exacerbation of known disease or for treatments of new acute symptoms 3. Patients who currently have prior therapy-related toxicities greater than Grade 1 per National Cancer Institute (NCI) Common Terminology Criteria for Adverse Events (CTCAE) Version 4.03; except for neuropathy, dysphagia, alopecia, or vitiligo prior to tumor resection. Immunotherapy-related endocrinopathies stable for at least 1 month, and controlled with hormonal replacement, are not excluded. • If toxicities have resolved to Grade 1 or less, 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 or greater 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 been asymptomatic for at least 6 months or had a normal colonoscopy post anti-PD-1/anti-PD-L1 treatment with uninflamed mucosa by visual assessment, 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) • 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, dysphagia, 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 for enrollment after discussion with the Sponsor's Medical Monitor/designee, must be stable for at least 2 weeks, and 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 diagnosis of end-stage renal disease requiring hemodialysis 10. Patients who have a left ventricular ejection fraction (LVEF) < 45% or who are New York Heart Association (NYHA) Class 2 or higher. 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 11. Patients who have a forced expiratory volume in one second (FEV1) of less than 60% of predicted normal. • If a patient is not able 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 demonstrates evidence of hypoxia at any point during the test (SpO2 < 90%), are excluded 12. Patients who have had another primary malignancy within the previous 3 years (except for curatively treated localized malignancy that has not required treatment for greater than 1 year, and in the judgment of the Investigator, does not pose a significant risk of recurrence including, but not limited to, non-melanoma skin cancer or superficial bladder cancer). 13. Patients who are of the following protected classes will be excluded including: a. Pregnant, parturient, or breastfeeding women b. Persons who are hospitalized without consent or those deprived of liberty because of a judiciary or administrative decision c. Patients with a legal protection measure or a person who cannot express his/her consent d. Patients in emergency situations who cannot consent to the study. 14. Patients who have received a live or attenuated vaccine within 28 days of the NMA-LD regimen. 15. Patients whose cancer requires immediate treatment or who would otherwise suffer a disadvantage by participating in this study.
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	Death due to any cause, 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 sequalae. See Section 11.2.1.

Statistical Considerations	The sample size is based on number of treated patients who receive the NMA-LD regimen, any amount of LN-145 therapy, and at least 1 dose of IL-2. A Simon 2-stage optimal design will be employed to have 80% power to detect an ORR difference from 5% versus 20% using a 1-sided alpha of 0.025. The first stage will consist of 15 treated patients. If 1 or fewer patients respond within 3 months (either a partial response [PR] or complete response [CR]), the study will be terminated. Otherwise, the study will continue to enroll for a total of 47 treated patients in Stage 2. The study would demonstrate a clinically meaningful response if 6 or more patients demonstrate an objective response. Patients meeting RECIST v1.1 criteria for CR or PR will be classified as responders in the analysis of the ORR. This rate will be summarized using both a point estimate and its 2-sided 95% confidence limits. The assessment of safety data will be based on the summarization of TEAEs, SAEs, AEs leading to discontinuation from study treatment or Efficacy Follow-up, 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
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
EAV	End of Assessment visit
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
EKG	electrocardiogram

Term	Definition
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
HRQoL	health-related quality of life
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
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
PIK3CA	phosphatidylinositol 3-kinase, catalytic subunit alpha
PR	partial response
pre-REP	expansion of TIL from tumor fragments prior to REP

Term	Definition
PTT	partial thromboplastin time
Q-TWiST	quality-adjusted time without symptoms of disease or toxicity of treatment
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 [Adelstien 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 N 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]. More recently, 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 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].

The findings of survival rates of 63% or less among most patients with HPV-negative HNSCC or recurrent HPV-positive HNSCC, and even lower survival rates among patients with recurrent HPV-negative tumors, indicate a need for improved therapeutic options.

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 potentially durable complete response (CR) for patients with a variety of solid tumors. The treatment involves the isolation and ex vivo expansion of autologous antitumor lymphocytes that have infiltrated a patient's tumor. The basic concept of using lymphoid cells for the immunotherapy of cancer arose from animal experiments that demonstrated, by histologic analysis, the presence of T-lymphocytes within the microenvironment of most solid tumors and their metastases [Agrawal 2011; Brennan 1995; Nichols 2013]. Recent findings have shown a predictive relationship between the frequency and phenotype of TIL in solid tumors (especially CD8+ T cells) and an increased OS and progression-free survival (PFS) in patients with melanoma [Di Mario 2015; Jones 2014; Maxwell 2016; Patterson 2014], lung cancer [Fakhry 2008; Howlader N 2018; O'Rorke 2012; Pulte 2010], ovarian cancer [Argiris 2008; Chuang 2008; Hsieh 2015], squamous cell carcinomas [Machiels 2015; Vargo 2015], triple-negative breast cancer, HER2-positive breast cancer [McArthur 2016], basal-like breast cancer [Azimi 2012; Fakhry 2014; Haanen 2006; Ladanyi 2007; Rosenberg 1986; Strnad 2015; Vose 1985; Yron 1980], and colorectal cancer [Erdag 2012; Horne 2011; Kilic 2011; Liu 2012a]. Notably,

one study found that an increased Foxp3$^+$ T_{reg}/CD8$^+$ ratio and the presence of intra-tumoral high Foxp3$^+$ T_{reg} each predicted worse OS [Ruffini 2009]. 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; Milne 2012; Patterson 2014; 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; Balermpas 2014; Wang 2014]; 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 [Chacon 2013; Ibrahim 2014; Liu 2012b] [Mahmoud 2012]. 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 any TIL contained within the excised tumor tissue can survive and proliferate. TIL can be cultured in the presence of interleukin-2 (IL-2) and can be grown to very large numbers using standardized protocols ($\geq 1 \times 10^8$ cells) [Agrawal 2011; Galon 2006; Nichols 2013; West 2013]. 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 [Agrawal 2011; Galon 2006; Nichols 2013; West 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 [Agrawal 2011]. 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. 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 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]. 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 were expanded in 12 of 15 (80%) evaluable patients; tumor specificity of the TIL were shown in 60%. 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 an HNSCC 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].

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, as described above. 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, as noted above. The large body of data from these studies justifies the development of adoptive TIL therapy as an approved therapeutic in other solid tumors, such as HNSCC.

2. STUDY DESIGN

2.1. Overview

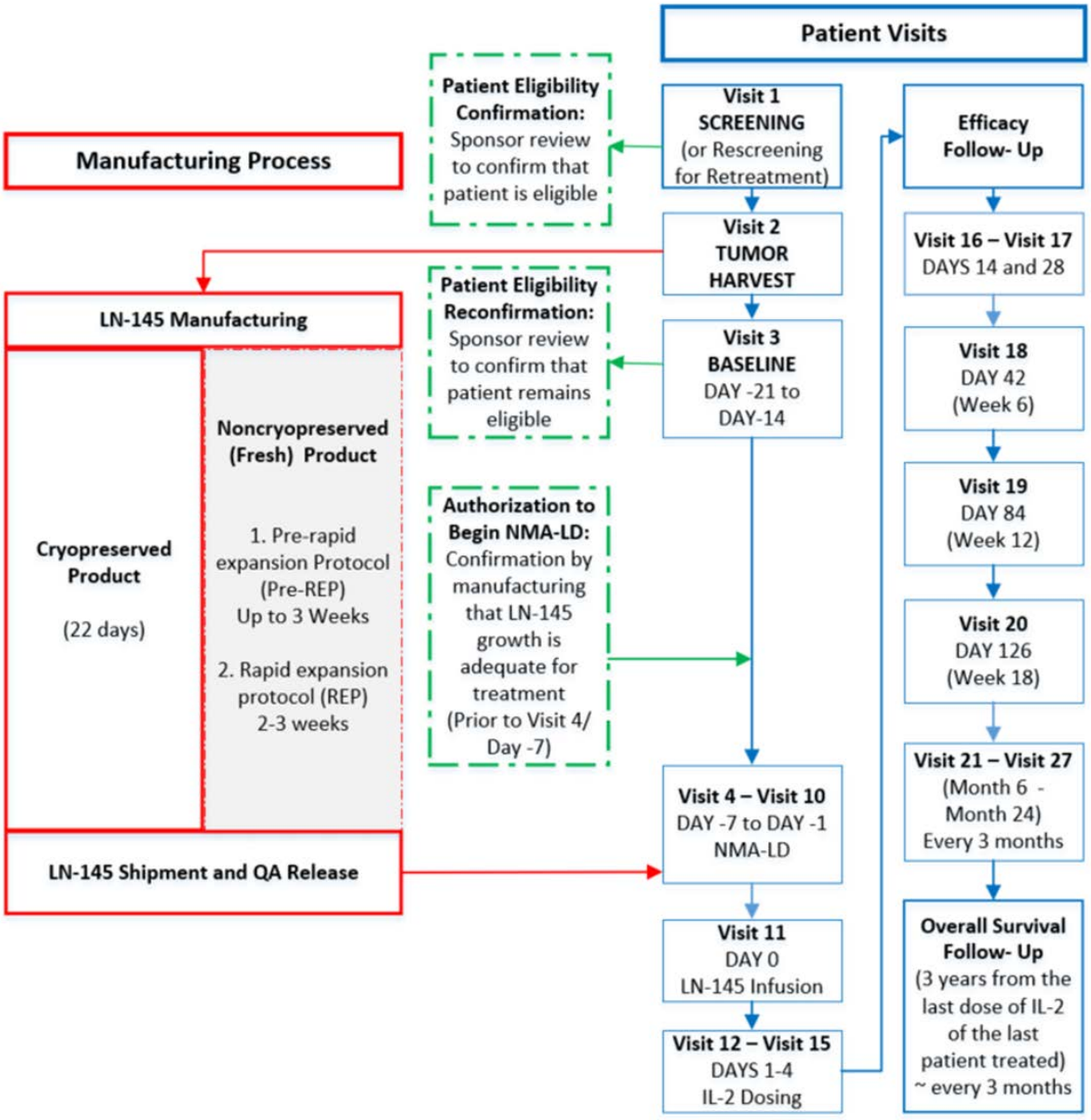
This is a prospective single-arm interventional study evaluating patients with HNSCC who receive ACT with LN-145 (autologous TIL). Instructions for the tumor resection/harvest and LN-145 administration for the current study are provided in separate operating manuals. TIL therapy comprises multiple interdependent phases: tumor resection for production of TIL; ex vivo expansion of TIL; NMA-LD; infusion of TIL; and administration of IL-2. A study flow chart is shown in Figure 1.

The study is primarily planned to assess efficacy and safety for 47 patients who receive LN-145.

The study consists of 3 phases:

- **Pretreatment Phase (approximately 8 weeks)**
  - Screening visit (up to 28 days)
  - Tumor resection visit (1 day)
  - LN-145 manufacturing period (approximately 3 to 5 weeks)
- **Treatment Phase (approximately 2 weeks)**
  - NMA-LD regimen (7 days)
  - LN-145 Infusion (1 day)
  - IL-2 Infusion (1 to 4 days)
- **Assessment Phase (minimum 3 years)**
  - Efficacy Follow-up for safety and efficacy evaluations (24 months)
  - Long-term Overall Survival Follow-up to assess disease status on durable responders and survival until the last patient is followed for 3 years

Figure 1. Study Flow Chart



2.2. Production and Expansion of Tumor Infiltrating Lymphocytes

LN-145 is an autologous cellular investigational product composed of viable TIL derived from an individual patient's own tumor (autologous cell product). The process for manufacturing LN-145 begins following the surgical resection of primary or secondary metastatic tumor material of [redacted] from the patient and the tumor is received at the Good Manufacturing Practice (GMP) manufacturing facility. The tumor specimen(s) is placed in biopreservation transport media and shipped (at [redacted] overnight to the GMP manufacturing facility. Upon arrival at the GMP manufacturing facility, the tumor specimen is dissected into fragments of [redacted], from which TIL are expanded with [redacted] The expanded cells (TIL) are then harvested, washed, and formulated in transport and infusion bags for shipment by courier to the clinical site as either a fresh, chilled [redacted] non-cryopreserved product or a cryopreserved (in [redacted] product. The dosage form of the investigational product is a live cell suspension of TIL for intravenous (IV) infusion into the patient from which they were derived (Figure 2).

Figure 2. LN-145 Manufacturing Process

TIL production requires approximately 3 to 5 weeks following excision of tumor specimens. The TIL product is manufactured ex vivo using autologous tumor as starting material. The key manufacturing steps include the following:

- Surgical removal of autologous metastatic tumor and shipment to the Sponsor-designated manufacturing facility
- Fresh product
  - Initial TIL culture (pre-Rapid Expansion Protocol [pre-REP] of up to 3 weeks)
  - Rapid Expansion Protocol (REP) of approximately 2 weeks

- Cryopreserved product
  - Single expansion process of approximately 3 weeks

On protocol Day -8, the number of TIL successfully expanded will be determined. If the number of TIL is sufficient for administration, approval by the Sponsor will be granted to begin the NMA-LD regimen.

The lymphodepletion protocol is based on the method developed and tested by the NCI [Besser 2009; Cao 2007; Galon 2014; Pages 2005; Robbins 2013; Shen 2010]. Following lymphodepletion, patients will receive up to [redacted] cells of LN-145. The upper limit of the range for infusion (approximately [redacted] viable cells) is based on the known published upper limit safely infused where a clinical response has been attained [Itzhaki 2011; Radvanyi 2012].

The lower limit of [redacted] viable cells is based upon the approximate number of tumor antigen-specific [redacted] T-cells within a physiologic range expected to exert an anti-tumor effect. To date, in patients treated during the Sponsor's clinical studies, a clinically-meaningful response has been observed with a total cell count in this range [redacted]. In addition, the specified range of total viable cell count is consistent with manufacturing procedures developed at the NCI, and their clinical experience in treating more than 100 patients with advanced MM and cervical cancer [Goff 2016; Stevanovic 2015].

The LN-145 infusion will be followed by the administration of IL-2 (600,000 IU/kg) every 8 to 12 hours starting between 3 and 24 hours after the completion of the LN-145 infusion and continuing for up to 6 doses as tolerated. Patients will be evaluated for response using RECIST v1.1. All responses are required to be confirmed with a follow-up assessment. See Section 5.24 and Appendix 17.1 for specific time points.

Patients who complete the Treatment Phase will continue to be evaluated for safety and efficacy during Efficacy Follow-up visits (24 months following treatment). Once the patients complete the Efficacy Follow-up or discontinue for any reasons indicated under Section 9.4.1, they will be followed in Long-term Overall Survival Follow-up with quarterly telephone contact for 12 months to assess disease status and subsequent anticancer therapy as described in Section 9.4.2. Radiologic assessment of disease may also be performed at additional time points at the discretion of the Investigator.

3. STUDY OBJECTIVES AND ENDPOINTS

3.1. Study Objectives

3.1.1. Primary Objective

- To evaluate the efficacy of LN-145 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 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 in patients with recurrent and/or metastatic HNSCC

3.1.3. Exploratory Objectives

- To explore the persistence of LN-145 and immune correlations of response, survival, toxicity of the treatment, and HPV status of the tumor
- To explore efficacy based on RECIST v1.1 and immune-related RECIST (irRECIST) criteria—as assessed by independent review
- To assess health-related quality of life (HRQoL)
- To assess the quality-adjusted time without symptoms of disease or toxicity of treatment (Q-TWiST)

3.2. Study Endpoints

3.2.1. Primary Endpoint

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

3.2.2. Secondary Endpoints

- Duration of Response (DOR) using RECIST v1.1 as assessed by the Investigator
- Disease Control Rate (DCR) using RECIST v1.1 as assessed by the Investigator
- PFS using RECIST v1.1 as assessed by the Investigator
- Overall Survival (OS)
- Death due to any cause, incidence of treatment-emergent adverse events (TEAEs), including serious adverse events (SAEs), therapy-related AEs, AEs leading to early discontinuation of treatment or withdrawal from Efficacy Follow-up

3.2.3. Exploratory Endpoints

- Immune correlations with respect to response, survival, toxicity of the treatment, and HPV status of the tumor
- ORR, DOR, DCR, and PFS as assessed per RECIST v1.1 and irRECIST by independent review
- HRQoL as assessed per European Organisation for Research and Treatment of Cancer (EORTC) Quality of Life Questionnaire (QLQ)-C30 v3.0 questionnaire
- Q-TWiST [Sherrill 2013] using investigators' assessments of disease symptoms and reported safety events prior to the next systemic anti-cancer therapy for PFS

4. SELECTION OF PATIENT POPULATION

Patients with a diagnosis of recurrent and/or metastatic HNSCC who have undergone at least 1 and no more than 3 prior systemic immunotherapy or chemotherapy regimens will be selected for this study.

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

Patients may be eligible for retreatment if they have progressed or have incomplete response to a prior treatment on this protocol with LN-145. A minimum of 3 months must have elapsed from the last infusion of LN-145 to be eligible.

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.
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 (or aggregate of lesions resected) should yield at least 1.5 cm in diameter post-resection of tumor tissue and can be surgically removed with minimal morbidity (defined as any operation for which expected hospitalization is ≤ 3 days). 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 progressed after radiation therapy. An aggregate of ≥ 1.5 cm in diameter from multiple lesions is permitted.
6. Must have measurable disease as defined by RECIST v1.1 following the surgical resection. If measurable target lesion(s) are in previously irradiated areas, irradiation must have occurred at least 3 months prior to tumor resection and the lesions must have demonstrated evidence of progression since irradiation.
7. Patients must have recurrent and/or metastatic carcinoma of the head or neck and have received at least 1 and no more than 3 lines of prior systemic immunotherapy and/or chemotherapeutic treatments for HNSCC. Patients must have disease progression while receiving or after completion of the most recent prior treatment.
8. Any prior therapy directed at the malignant tumor, including radiation therapy, chemotherapy, biologic/targeted agents, and immunologic agents must be discontinued at least 28 days prior to lymphodepletion. Radiation therapy may have been received up to 28 days prior to lymphodepletion for lesions not expected to be used for TIL generation or target lesions.
9. Have an Eastern Cooperative Oncology Group (ECOG) performance status of 0 or 1 and an estimated life expectancy of ≥ 3 months.

10. Must meet the following laboratory criteria:
    - 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
    - Serum creatinine ≤ 1.5 mg/dL
    - An estimated creatinine clearance (eCrCl) ≥ 40 mL/min using the Cockcroft-Gault formula at screening
11. Patients must be seronegative for the human immunodeficiency virus (HIV).
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.
13. Male and female patients of childbearing potential 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
    - Sexual abstinence

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, prior cell transfer therapy, except for prior LN-145. Prior LN-145 therapy must have occurred at least 3 months prior to retreatment tumor resection.

2. Patients who are on a systemic steroid therapy > 10 mg of prednisone or other steroid equivalent daily.
    - A short course of higher dose steroid therapy is allowed in cases of exacerbation of known disease or for treatments of new acute symptoms
3. Patients who currently have prior therapy-related toxicities greater than 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 prior to enrollment/tumor resection. Immunotherapy-related endocrinopathies stable for at least 1 month, and controlled with hormonal replacement, are not excluded.
    - If toxicities have resolved to Grade 1 or less, 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 or greater diarrhea or colitis due to previous immunotherapy (eg, ipilimumab, tremelimumab, anti-PD-1, or anti-PD-L1) within 6 months from screening.
    - Patients who have been asymptomatic for at least 6 months or had a normal colonoscopy post anti-PD-1/anti-PD-L1 treatment with uninflamed mucosa by visual assessment 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).
    - 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, dysphagia, 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 who may be considered for enrollment after discussion with the Sponsor's Medical Monitor/designee, must be stable for at least 2 weeks and 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 diagnosis of end-stage renal disease requiring hemodialysis.
10. Patients who have a left ventricular ejection fraction (LVEF) < 45% or who are New York Heart Association (NYHA) Class 2 or higher. 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
11. Patients who have a forced expiratory volume in 1 second (FEV1) < 60% of predicted normal.
    - If a patient is not able 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** demonstrates evidence of hypoxia at any point during the test (SpO2 < 90%) are excluded
12. Patients who have had another primary malignancy within the previous 3 years (except for curatively treated localized malignancy that has not required treatment for greater than 1 year, and in the judgment of the Investigator, does not pose a significant risk of recurrence including, but not limited to, non-melanoma skin cancer or superficial bladder cancer).
13. 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
14. Patients who have received a live or attenuated vaccine within 28 days of the NMA-LD regimen.
15. Patients whose cancer requires immediate treatment or who would otherwise suffer a disadvantage by participating in this study.

4.3. Patient Enrollment and Re-Screening

Patients who meet all inclusion criteria and do not meet any of the exclusion criteria may be enrolled in the study. Enrollment is defined as patients who began or completed tumor resection

procedure. Patients cannot enroll in the study without documented approval from the Sponsor's Medical Monitor or designee on the Patient Eligibility Form.

Patients who sign an informed consent form (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 for enrollment and will be registered as a new patient. The Investigator and Sponsor's Medical Monitor will discuss the patient's status prior to any re-screening procedures.

Patients who do not have a tumor resection within 28 days of signing the ICF are thus not enrolled. However, they may re-sign the ICF and be reassessed for eligibility following a discussion between the Investigator and Sponsor's Medical Monitor to agree on which screening procedures need to be redone.

Once the patient is approved to enroll in the study, the patient must continue to meet eligibility criteria after completion of Baseline procedures (Day -28 to Day -10; Visit 3). Patients cannot begin NMA-LD without documented approval from the Sponsor's Medical Monitor or designee on the Patient Eligibility Re-Confirmation Form.

Patients may rescreen for a second tumor resection and LN-145 treatment if patients meet all requirements on the Re-Treatment Form (including all inclusion and exclusion criteria). These patients may have a second tumor harvest and TIL (LN-145) therapy. In some cases, if cells are available from the prior manufacturing process, these cells may be used for generating a second LN-145 product.

Examples of patients who may be eligible for retreatment are prior responders to LN-145 who relapse, nonresponders, and harvested patients who did not receive TIL due to any reason. Patients cannot be approved for re-treatment without documented approval from the Sponsor's Medical Monitor or designee on the Re-Treatment Form. Prior to enrollment for retreatment, patients must undergo an abbreviated Screening (Visit 1) procedure, which includes all assessments and procedures for initial Screening with the exception of Demographics, Medical History, Documentation of Diagnosis, HLA, and Documentation of HPV status. The Medical Monitor will have authority to adjudicate enrollment for re-treatment (second TIL therapy).

5. STUDY ASSESSMENTS/PROCEDURES

5.1. Informed Consent

The applicable and 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 have any of the conditions specified in the exclusion criteria (Section 4.2). Patients must continue to meet eligibility criteria until start of NMA-LD pretreatment regimen Day -7 (Visit 4).

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 and concurrent illnesses will be collected for all patients at screening (Visit 1) and updated as applicable. Any worsening from pre-existing conditions should be reported as AEs. All AEs occurring after the patient has consented, but before enrollment (prior to tumor resection), will be collected on the medical history eCRF unless the event is new and attributed to protocol-mandated procedures and assessments.

5.5. Documentation of Confirmation of Diagnosis

Patients must have a documented diagnosis of primary HNSCC via pathology report.

5.6. Tumor HPV Status and HPV Serotype

Patients must have documented HPV tumor status of HNSCC. If documentation is not available, testing for HPV status must be performed locally using archival tumor tissue or excess tissue obtained during tumor resection.

HPV serotype testing should be done on either archival HNSCC cancer tissue or on excessive tumor collected at Tumor Resection (Visit 2).

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 (Visit 1) 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. Adverse Events

All AEs for all patients will be assessed as per NCI CTCAE Version 4.03 [US Department of Health and Human Services 2010]. Any AEs occurring after Screening (Visit 1), but prior to enrollment/tumor resection, will be recorded as medical history in the eCRF. Any events occurring after enrollment/tumor resection will be captured as AEs in the eCRF until Day 168 (Visit 21/Month 6) or until the first dose of the subsequent anti-cancer therapy, whichever occurs first. All AEs attributed to protocol-required procedures or treatment will be collected through Visit 27/Month 24. Additional safety reporting requirements are described under Section 11.

5.9. HRQoL Questionnaire – EORTC QLQ-30 Version 3.0

The HRQoL Questionnaire is to be performed as the first procedure at Baseline (Day -28 to Day -10; Visit 3) and at the timepoints specified in Appendix 17.1.

5.10. Physical Examination

Physical examination (PE) will be conducted for all visits except for the tumor resection visit (Visit 2) and shall include gastrointestinal (abdomen, liver), cardiovascular, extremities, head, eyes, ears, nose, and throat, respiratory system, skin, and psychiatric (mental status). PE conducted during the Follow-up Phase will be symptom-directed. Clinically significant changes in the physical examination findings will be recorded as AEs**.**

5.11. Vital Signs

Vital signs shall include height, weight, pulse, respirations, blood pressure, and temperature. Height will be measured at screening (Visit 1) only. All other vital signs will be measured at every visit up to Visit 27/Month 24.

Body surface area (BSA) and Body Mass Index (BMI) will be calculated at Day -7 (Visit 4) only.

On Day 0 (Visit 11/LN-145 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 LN-145 infusion.

Pulse oximetry is required during IL-2 administration.

5.12. Eastern Cooperative Oncology Group Performance Status

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

5.13. Safety Blood and Urine Tests

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

- Chemistry – sodium, potassium, chloride, total CO_2 or bicarbonate, serum creatinine,

glucose, blood urea nitrogen, 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 – measurement of prothrombin time /international normalized ratio (PT/INR), and partial thromboplastin time /activated partial thromboplastin time (PTT/aPTT).
- Thyroid panel – thyroid stimulating hormone (TSH) and free T4.
- Urinalysis dipstick – A complete urinalysis with microscopy and/or urine culture shall be performed as clinically indicated

Safety labs collected for the subsequent visits include:

- Chemistry – as above (Visits 3–21)
- Hematology – as above (Visits 3–21)
- Urinalysis dipstick – as above (Visits 3–21), and as clinically indicated

5.14. 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).

5.15. Infection Testing

Blood samples will be collected for the following virus testing at screening (Visit 1) only:

- HIV 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)
- Cytomegalovirus (CMV) serology (IgG and IgM)

Blood samples must be collected within 7 days following Tumor Resection (Visit 2) for the following virus testing:

- HIV serology as per local standards
- Hepatitis serology (HBsAg, anti-HBc, and anti-HCV). If positive, a viral PCR test is required.
- Syphilis assay as per local standard (eg, RPR, VDRL, or other)

5.16. Human Leukocyte Antigen Typing

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

5.17. HPV Subtype Serotype

Tumor sample (obtained at Visit 2) collection for HPV subtype serotyping will be managed by the central laboratory if not done locally. Refer to the Laboratory Manual for details.

5.18. Estimated Creatinine Clearance

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

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

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

5.19. Eye Examination

For patients with a history of uveitis, a slit-lamp eye examination is required within 28 days of screening (Visit 1) to rule out active uveitis.

5.20. Cardiac Evaluations

All cardiac evaluations (NYHA, ECHO, ECG, cardiac stress test) will be performed within 28 days of Screening (Visit 1).

5.20.1. New York Heart Association

The New York Heart Association (NYHA) classification must be determined during Screening (Visit 1).

5.20.2. Echocardiogram (ECHO)

An ECHO must be performed to assess left ventricular function for all patients within screening. These may have been performed up to 60 days prior to signing of ICF.

5.20.3. Electrocardiogram

A 12-lead electrocardiogram (ECG) will be performed locally. Patients must be supine for the examination.

5.20.4. 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.

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.

5.21. Pulmonary Function Tests

Pulmonary evaluation using spirometry will be completed within 28 days from Screening (Visit 1). Evaluations completed within 1 month prior to Screening (Visit 1) will be accepted except for patients with known pulmonary metastases or clinically significant pulmonary disease.

Patients who are unable to conduct reliable pulmonary function test measurements due to abnormal upper airway anatomy may undergo a 6-minute walk test to assess pulmonary function.

5.22. Colonoscopy

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

5.23. 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.

5.24. Radiographic Assessments

Radiographic assessments by CT scans with contrast of the head/neck, chest, and abdomen are required for all patients for tumor assessments. CT scans are performed at Screening (Visit 1; or within 30 days prior to consent if collected as standard of care), Baseline (Day -28 to Day -10; Visit 3), and at the additional timepoints in Appendix 17.1, or until disease progression.

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

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

The same method of assessment (CT or MRI) and the same technique for acquisition of radiographic images should be used to characterize each identified and reported lesion at Baseline (Day -28 to Day -10; Visit 3) and then each subsequent assessment throughout the course of the study. Patients will be evaluated for response at approximately every 4 weeks from LN-145 administration for the first 3 months, and at 4.5 months, 6 months, 9 months, 12 months, 15 months, 18 months, 21 months, and 24 months. Additional radiological 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.

All patients should have radiographic tumor measurements performed at the participating study center or an acceptable alternate imaging facility using an identical imaging protocol and similar equipment that has been qualified by a central imaging vendor. The same imaging equipment and parameters should be utilized for all scans throughout the study.

5.25. Tumor Resection / Harvest

Prior to tumor resection (Visit 2), following confirmation of patient eligibility, the Sponsor's Medical Monitor or designee will provide approval for patient enrollment 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 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). 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.

Tumor specimens must undergo intraoperative frozen section examination by a pathologist to ensure that viable tumor is present. This must occur at the Tumor Resection (Visit 2) prior to the tumor specimen for TIL generation being shipped to the 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.

Refer to the **Tumor Procurement & Shipping Manual** for details.

5.25.1. Additional Tumor Tissue from Resected Tumor

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

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.

The tumor tissue sent to the Central Laboratory will be analyzed for 1) immunohistochemistry to identify individual immune cell populations and for patients who sign the optional sub-study consent (ie, Research Substudy ICF) 2) isolation of DNA and RNA, which will be used for PCR-based genoming sequencing and transcriptomic evaluation.

5.26. Post-Treatment Biopsy

A post-treatment (post-LN-145 infusion) biopsy (fresh and FFPE) of at least one target lesion will be collected, if feasible, on Day 28 (+7 days) (Visit 17) after the Day 28 tumor assessment scans. See Appendix 17.1.

6. STUDY TREATMENT

6.1. Nonmyeloablative Lymphodepletion Regimen

The NMA-LD regimen is scheduled to start on Day -7 (Visit 4). Eligibility confirmation to proceed and subsequent approval from the Sponsor is required to start the NMA-LD regimen and should be completed at Baseline (Day -28 to -10; Visit 3). Patients are typically hospitalized for administration of the cyclophosphamide due to concomitant mesna administration. Hospitalization for the rest of NMA-LD is at the discretion of the Investigator. Modification of the lymphodepletion regimen is allowed as clinically indicated and should be guided by daily hematological parameters as described below for fludarabine in patients with a history of irradiation or delayed hematologic recovery with prior chemotherapy.

The NMA-LD regimen comprises of 2 daily doses of cyclophosphamide (with continuous mesna) followed by 5 daily doses of fludarabine. For consistency in dosing, obese patients (defined as having a BMI > 35.0 kg/m^2) should be dosed as recommended in this protocol (See Appendix 17.3).

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.

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 as a continuous infusion unless approved by the Sponsor's Medical Monitor.

Actual weight should be used to calculate the mesna dose, even if the patient's BMI > 35.0 kg/m^2. Dilute the volume of mesna injection per institutional standard.

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 at a rate of 3 mg/kg/hour over 22 hours after each cyclophosphamide dose during Days -7 and -6 (Visits 4 and 5). The total dose administered must be at least 1.3 times that of the dose of cyclophosphamide; higher doses of mesna may be administered as per local standards.

6.1.4. Fludarabine

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

Hematological parameters (CBC and differential) are to be reviewed daily during lymphodepletion. If after a minimum of 3 doses of fludarabine, the absolute lymphocyte count (ALC) falls below 100 cells/mm^3, the remaining dose(s) of fludarabine should be omitted.

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

Please refer to the current appropriate package insert for fludarabine.

Actual weight should be used to calculate the fludarabine dose, even if the patient's BMI > 35.0 kg/m^2.

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.

6.2. LN-145

6.2.1. Description of LN-145

LN-145 is a cellular investigational product comprising a live cell suspension of autologous TIL derived from the patient's own tumor that is shipped either as a non-cryopreserved product or as a cryopreserved product. A summary of the TIL manufacturing process is described in Figure 2.

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).

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

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

The cryopreserved investigational TIL product is a sterile product formulated in [redacted]

[redacted]

6.2.3. Transport of LN-145

Each dose of the live suspension LN-145 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 investigational product will be shipped to the clinical site [redacted] The product is stored in vapor phase liquid nitrogen until the patient is ready for infusion.

The non-cryopreserved product is shipped in a temperature-controlled and -monitored shipping container. Additional details are specified in the Pharmacy & Investigational Product Administration Manual.

6.2.4. Receipt of LN-145

LN-145 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 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, will be transferred to the patient bedside, preferably in its original shipping container [redacted] for administration.

6.2.5. Administration of LN-145

At least 24 hours must have elapsed from the last dose of fludarabine and the administration of LN-145. If fludarabine is discontinued due to a low ALC, then LN-145 may be administered 24 hours after the last dose of fludarabine given. If fludarabine is discontinued due to an AE, LN-145 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 if more than 4 days has elapsed from the last dose of fludarabine.

Within 24 hours prior to administering LN-145, 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. In addition, emergency anaphylaxis medications must be available at bedside (eg, epinephrine,

diphenhydramine, and corticosteroids). Prophylactic use of systemic corticosteroids should be avoided, as it may interfere with the activity of LN-145. 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

LN-145 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 for the completion of the infusion. Multiple cryopreserved bags are thawed and administered sequentially. If the infusion is interrupted for medical reasons, the LN-145 infusion bags not yet thawed should be kept in the cryoshipper and any thawed LN-145 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-144/LN-145 toxicities, see Section 1.1.

6.3. LN-145 Toxicity Management

Both noncryopreserved and cryopreserved TIL product formulations contain 0.5% human serum albumin (HSA), 300 IU/mL of interleukin-2 (IL-2), and potentially low residual amounts of gentamycin and streptomycin, which belong to the aminoglycoside group of antibiotics. The cryopreserved Gen 2 TIL product formulation includes the cryopreservation medium CryoStor® CS10, which contains the cryoprotectants DMSO and dextran-40.

Hypersensitivity events, including severe allergic reactions and life-threatening anaphylaxis, have occurred during infusion with the LN-144/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-144/LN-145. 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-144/LN-145 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 will 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.

6.4. Interleukin-2

The IL-2 infusion will begin between 3 and 24 hours after completion of the LN-145 infusion. IL-2 will be administered at a dose of 600,000 IU/kg (based on total body weight), 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.

The first dose of IL-2 should be administered between 3 and 24 hours following the completion of the LN-145 infusion. 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 infusion. If 36 hours elapse from the end of LN-145 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 doses will be skipped if a patient experiences a Grade 3 or 4 toxicity due to IL-2, except for reversible Grade 3 toxicities common to IL-2 such as diarrhea, nausea, vomiting, hypotension, skin changes, anorexia, mucositis, dysphagia, or constitutional symptoms and laboratory changes. Suggested management of IL-2 toxicity is detailed in Section 8.2 and Appendix 17.5. If these toxicities can be easily reversed within 24 hours by supportive measures, then additional doses may be given. If 2 sequential doses of IL-2 are skipped (meaning more than 24 hours elapses since the previous dose), no further doses will be given, and therapy will have been completed. If greater than 2 non-sequential doses of IL-2 are skipped, IL-2 administration will be stopped. In addition, dosing may be held or stopped at the discretion of the treating Investigator.

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.

6.5. Re-Treatment

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

Examples of patients who may be eligible for retreatment are prior responders to LN-145 who relapse, nonresponders, and harvested patients who did not receive TIL due to any reason. 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 retreatment, patients must undergo an abbreviated Screening (Visit 1) procedure, which includes all assessments and procedures for initial Screening with the exception of Demographics, Medical History, Documentation of Diagnosis, HLA, and Documentation of HPV status.

7. PERMITTED AND PROHIBITED CONCOMITANT MEDICATIONS

7.1. Permitted Medications

- Current medications for conditions other than HNSCC are permitted.
- Antitumor therapy is permitted up until 4 weeks prior to start of NMA lymphodepletion regimen. No other subsequent antitumor therapy is permitted during participation in the study.
- Palliative radiation therapy is permitted between the time of tumor resection and initiation of NMA-LD if it does not involve target or nontarget lesions.
- Patients may undergo preplanned procedures if 2 weeks prior to the start of NMA-LD.
- Use of systemic steroid therapy that is less than 10 mg/day of prednisone or equivalent is permitted.
    - Use of > 10 mg/day of prednisone or equivalent is permitted in cases of exacerbation of known disease or for treatment of new symptoms on study per Investigator's discretion.

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

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 must have been discontinued or completed at least 28 days prior to start of NMA-LD. Further therapies are not permitted thereafter while the patient remains on study. Palliative radiation may be allowed if it is not directed at any target or nontarget lesions.
- Other investigational drugs
- Live or attenuated vaccines administered within 4 weeks of the start of NMA-LD and for at least 3 months following the last dose of IL-2 (Day 84) are not permitted.

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 (Day -7/Visit 4).
- Radiation therapy must have been completed at least 3 months prior to enrollment (tumor harvest). Radiation therapy administered after tumor resection must be completed at least 28 days prior to NMA-LD.
- Systemic steroid therapy (> 10 mg of prednisone or equivalent) within 28 days prior to tumor resection (Visit 2) is prohibited. Patients weaned from a higher dose of steroid

therapy must be ≤ 10 mg of prednisone or equivalent for at least 28 days prior to enrollment (tumor resection).

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 should 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 should begin by Day 14 (Visit 16), 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 should begin herpes reactivation (typically valacyclovir or acyclovir) by Day 14 (Visit 16), 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 will start fluconazole 400 mg (by mouth) 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.

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. Please refer to treatment guidelines for recommended mesna dosing. Continuous mesna infusion is encouraged, however, alternative dosing regimens of mesna may be allowed if the dose is greater than what is suggested in this protocol per institutional standard of care and Investigator discretion with approval of the Sponsor's Medical Monitor.

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 (Visit 12) until the ANC is > 1000/mm^3 for 3 consecutive days, or as per standard of care at the treating institution, but must continue until neutropenia is resolved.

8.1.4. Blood Product Support

Using daily CBC as a guide, the patient will 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.

For infusion of LN-145 please refer to the Pharmacy & Investigational Product Administration Manual for specific infusion instructions. Overall, toxicities or AEs during the LN-145 infusion have almost entirely been associated with either the NMA-LD regimen or the IL-2 therapy given after TIL infusion. The following AEs have been observed in published studies that treated patients with TIL products prepared by a process like that being used to prepare LN-145:

- Short-term, transient/reversible effects of TIL infusion include fever, chills, shortness of breath, increased heart rate, hypotension (prolonged hypotension necessitating pressor treatment has been reported) [Goff 2016] following TIL infusion.

For the cryopreserved LN-145 product only, patients may experience severe allergic reaction (anaphylaxis) due to DMSO contained therein. Thus, appropriate emergency medications (eg, epinephrine and diphenhydramine) should be available at bedside during time of administration. High-dose systemic steroids should be avoided if at all possible.

Refer to current LN-145 Investigator's Brochure for additional information.

8.2. 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.

8.2.1. 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 would be warranted for guidance in management.

8.2.2. 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.

8.2.3. 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.

8.2.4. Cardiac Arrhythmias and Myocarditis

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

8.2.5. 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.

8.2.6. 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.

8.2.7. 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.

8.3. 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. Steroids, such as dexamethasone may be used as an antiemetic only during cyclophosphamide administration and must be discontinued a minimum of 3 days prior to administration of LN-145.

Fever

Premedication for fever should be initiated as per institutional standard of care and may begin the night prior to LN-145 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. Treatment Completion

Patients will be considered to have completed treatment if they complete the tumor resection and receive the NMA-LD regimen and LN-145 infusion.

9.2. Study Completion

The study is expected to be completed approximately 3 years after the last patient completes the last dose of IL-2, the time point all patients have exited the study for any reasons, or study termination at the Sponsor's discretion, whichever occurs first.

9.3. Criteria for Discontinuation Prior to or From Study Treatment

Patients who discontinue prior to receiving the study treatment (NMA-LD) or from the study treatment for any reasons are to complete the End of Assessment visit (EAV). EAV is not required if the same procedures are done within 2 weeks from the previous visit. See Appendix 17.1.

A patient will be discontinued prior to or from further investigational product administration for the following reasons:

- Patient has become ineligible for study participation after tumor resection (Visit 2) and prior to lymphodepletion, LN-145 infusion, or IL-2 administration
- Sufficient number of TIL are not produced, and the patient is not eligible for or does not wish to undergo retreatment
- Grade 3 or greater autoimmunity that involves vital organs (heart, kidneys, brain, eye, liver, colon, adrenal gland, lungs) with symptoms emerging prior to first IL-2 administration
- Grade 3 or greater allergic reaction including bronchospasm or generalized urticaria that does not resolve after medical management in the opinion of the Investigator
- Grade 3 or greater toxicity due to IL-2 that does not decrease to Grade 2 or less within 96 hours of management
- Investigator's decision
- Withdrawal of consent (reasons must be documented in patient's source documents):
    - Partial withdrawal of consent: The patient may withdraw from receiving study treatment but agree to continue for safety and efficacy follow-up evaluations.
    - Full withdrawal of consent: No additional data to be collected.
- Pregnancy
- Death
- Study terminated by Sponsor

9.4. Follow-up

9.4.1. Efficacy Follow-up

Once the patient discontinues/completes the Treatment Phase, the patient will enter Efficacy Follow-up and continue efficacy assessments and continued safety monitoring beginning on Day 14 (Visit 16)

The patient will discontinue the Efficacy Follow-up at any time for any of the following reasons. Appropriate reasons must be documented in the patient's source documentation and eCRF page:

- Disease progression
- Receipt of prohibited therapy (eg, another anti-cancer treatment)
- Investigator's decision
- Withdrawal of consent (reasons must be documented in patient's source documents):
    - Partial withdrawal of consent: The patient may withdraw to in-clinic visits but agree to be contacted via phone for disease and survival status assessment
    - Full withdrawal of consent: No additional data to be collected
- Study terminated by Sponsor
- Death

In the event of a patient's full withdrawal of consent from the Efficacy Follow-up, the Investigator will promptly notify the Sponsor's Medical Monitor or designee and will make every effort to complete the EAV as appropriate.

9.4.2. Long-term Overall Survival Follow -Up

Approximately every 3 months following the discontinuation/completion of Efficacy Follow-up, patients will be contacted (eg, via phone) to assess disease status and subsequent (current) anticancer therapies. Durable responders will continue to have response assessments during Long-term Overall Survival until the last patient is followed for 3 years. Disease progression occurring during Long-term Overall Survival Follow-up will only be assessed if the patient did not progress during the Efficacy Follow-up. Quarterly follow-ups will continue until death, full withdrawal of consent by patient, lost to follow-up, or study termination by the Sponsor, but not more than 5 years following the last dose of IL-2.

Efforts will be made to follow all patients who are lost to follow-up. Patients can only be considered lost to follow-up after 3 documented attempts to contact the patient.

9.5. Patient Withdrawal from Study

Patients may discontinue 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 (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.

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 1 and Table 2 for RECIST v1.1 response criteria definitions [Eisenhauer 2009].

10.1.1. Documentation of Target and NonTarget Lesions

Baseline documentation of all lesions will occur from Day -28 to Day -10 (Visit 3). 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.

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 nontarget 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 thereafter through Visit 27/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 nontarget lesions and should also be recorded at Baseline. Measurements are not required, and these lesions should be assessed as “present”, “absent”, or “unequivocal progression”.

10.1.2. 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 nontarget) 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.

10.1.3. Evaluation of Nontarget Lesions

This section provides the definitions of the criteria used to determine the tumor response for the group of nontarget lesions. While some nontarget 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 nontarget lesions. All lymph nodes must be nonpathological in size (< 10 mm short axis).
Non-Complete Response / Non-Progressive Disease	Persistence of 1 or more nontarget lesion(s).
Progressive Disease (PD)	Unequivocal progression of existing nontarget lesions. (The appearance of 1 or more new lesions is also considered progression).

10.1.4. Evaluation of New Lesions

New measurable lesions may be identified if the new lesions meet criteria as defined for Baseline target lesion selection and meet the same minimum RECIST v1.1 size requirements of 10 mm in long diameter for non-nodal lesions and a minimum of 15 mm in short axis for nodal lesions. New measurable lesions shall be prioritized according to size with the largest lesions selected as new measured lesions.

All new lesions not selected as new measurable lesions (eg, new nodal lesions < 15 mm in short diameter) are considered new nonmeasurable lesions and are followed qualitatively. Only an unequivocal progression of new nonmeasurable (eg, nodal enlargement to > 15 mm in short diameter) lesions leads to an overall assessment of PD for that time point.

The finding of a new lesion should be unequivocal: i.e. not attributable to differences in scanning technique, change in imaging modality or findings thought to represent something other than tumor (for example, some 'new' bone lesions may be simply healing or flare of pre-existing lesions). This is particularly important when the patient's Baseline lesions show 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 10.2.1).

10.1.5. 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 nontarget lesions, *at each assessment time point* is shown in Table 1. The Best Overall Response for each patient is determined as shown in Table 2.

Table 1. Response at Each Assessment Time Point for Patients

Target Lesions	Nontarget 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.

Table 2. Examples of Best Overall Response for Each Patient Across All Assessments

Overall Response at Time point 1	Overall Response at Time point 2	Overall Response at Time point 3	Best Overall Response Across Assessment Time Points
CR	CR	CR	CR

PR	PR	CR	PR
SD	SD	PR	SD
SD	PR	SD	SD
SD	SD	PD	SD

10.2. Confirmation of Tumor Assessments

10.2.1. Confirmation of Response (PR or CR)

Confirmation of response (either PR or CR) is required. Changes in tumor measurements must be confirmed by repeat assessments that should be performed ≥ 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).

10.2.2. Confirmation of Stable Disease

A minimum of 4 weeks from the treatment start date is required to assess SD.

10.2.3. Confirmation of Progressive Disease

All PD assessed by the Investigator must be confirmed by objective measures per RECIST v1.1.

For patients with a minimal increase of over 20% in the sum of diameters of target lesions taking as reference the smallest sum on study or for nontarget or new nonmeasurable lesions, a confirmation scan is recommended by the Sponsor at least 4 weeks after the first PD assessment.

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), will be reported as AEs only if they are felt to be clinically significant; 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.

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.

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

11.2.1. All Adverse Events

AEs/SAEs will be assessed by the Investigator and must be recorded on the appropriate eCRF. Adverse events will be reported starting immediately after the patient has been consented.

All AEs occurring after the patient has consented, but before enrollment (prior to tumor resection), will be collected on the medical history eCRF unless the event is new and attributed to protocol-mandated procedures and assessments. All AEs occurring on or after enrollment/ tumor resection in the study, and either observed by the Investigator or reported by the patient (whether attributed to the use of lymphodepletion drugs, LN-145 or IL-2 or not), must be reported on the AE eCRF.

All AEs attributable to the investigational product may be followed until resolution or permanent sequelae even if discontinued from the study. The final outcome of AEs ongoing at the time of the EAV will be captured as “Not Recovered/Not Resolved.”

Monitoring and reporting AEs/SAEs, regardless of cause or relationship, will be conducted through Day 168 (Visit 21/Month 6) from the last dose of IL-2 or until the first dose of the subsequent anticancer therapy, whichever occurs first. All AEs attributed to protocol-required procedures or treatment will be collected through Visit 27/Month 24 study visit. AEs that occur

after the treatment and Follow-up Phase with a reasonable possibility that the event may have been caused by the study treatment may be reported at the Investigator's discretion.

Medically significant AEs considered related to the study treatment by the Investigator or the Sponsor will be followed until resolved or resolved with sequelae.

If any patient should die while on the study, the Investigator will inform the Sponsor within 24 hours of awareness and report the cause of death as an SAE. The clinical event 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. Deaths that are attributed by the Investigator to be solely due to disease progression should be recorded only on the Cause of Death eCRF.

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 or not. This should be captured in the eCRF. If either of these occurs, the patient must undergo an early termination visit and be given appropriate care under medical supervision until symptoms cease or the condition becomes stable and returns for Efficacy Follow-up visits. If the patient is removed from the investigational product or Efficacy Follow-up due to an SAE, this information must be included in either the initial or follow-up SAE Report Form and in the eCRF.

If a patient is withdrawn from study treatment due to an AE or SAE, data concerning such event should continue to be collected until resolution or death.

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 6 months from the last dose of IL-2 or until the first dose of the next anticancer therapy, whichever occurs first). All AEs/SAEs attributed to protocol-required procedures or treatment will be collected through Visit 27/Month 24 of the study. If the Investigator learns of any SAEs that occur after the Follow-up Phase 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 Safety CRO 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.

11.4.2.2. 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.

13. STATISTICAL CONSIDERATIONS

13.1. Introduction

The primary statistical plan of analysis is based on use of descriptive methods unless mentioned otherwise. Continuous data will be summarized as the number of patients with nonmissing data (N), mean, standard deviation, median, minimum, and maximum values. Categorical data will be summarized as counts and their related percentages, where applicable. Estimation of confidence limits will use two-sided, 95%. Missing data will not be imputed unless mentioned otherwise.

A more detailed description of the analyses and reporting plan of the data will be provided in the statistical analysis plan (SAP).

13.2. Study Analysis Sets

Three analysis populations will be defined to summarize the data. [redacted] The TH population is further divided into the following analysis populations:

13.2.1. Safety Analysis Set

[redacted]

13.2.2. Efficacy Analysis Set

[redacted] Patients who progressed or expired prior to reaching the first radiological assessment will be included.

13.3. Sample Size Justification

The single-agent treatments currently available for patients with recurrent HNSCC cancer (including PD-1 therapy) have reported ORRs between 5.8% (standard therapy) and 13.3% (nivolumab) with very short OS [Boussios 2016; Ferris 2016]. The sample size is set to rule out the historical ORR of 5% using 95% CI confidence interval assuming that the estimated ORR for TIL is ≥ 20%.

The planned sample size of the treated patients for this single arm study is 47 patients. Given a potential 16% attrition rate, approximately 56 patients will be enrolled/resected. A Simon's optimal 2-stage design will be used to test the null hypothesis that ORR will be ≤ 5% (not considered clinically meaningful). Fifteen patients will be included in the first stage, and if there are 1 or fewer patients responding to therapy, the study will terminate. Expansion into Stage 2 to a total of 47 patients will occur concurrently with the Stage 1 analysis. If at least 6 of those 47 patients respond to therapy, the study therapy would be considered to have met its primary study goal. This 2-stage design has 80% power to detect a difference of an ORR of 5% versus 20% using a 1-sided 0.025 alpha level test.

The sample size is based on the number of patients in the Efficacy Analysis Set, consisting of patients who have received TIL LN-145 infusion and had at least one post-Baseline radiological assessment. Patients who progressed or died prior to reaching the first radiological assessment will be included. The planned analysis will be conducted when the 47th patient has had the opportunity to be followed for a minimum of 6 months. This will allow sufficient time for disease-controlled patients (SD or better) to demonstrate extended durability.

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.

13.5. Study Endpoints and Planned Analyses

13.5.1. Primary Endpoint

13.5.1.1. Efficacy

The ORR is defined as the proportion of patients who achieve either a confirmed PR or CR within 6 months following treatment as best response as assessed by Investigator evaluation per RECIST v1.1 within the Efficacy Analysis Set. Objective response will be evaluated per each disease assessment and the ORR will be calculated with the corresponding Wilson Score 95% two-sided confidence interval (CI).

13.5.2. Secondary Endpoints

13.5.2.1. Safety

The primary safety analysis will be descriptive and based on the summarization of TEAEs including SAEs, AEs leading to discontinuation from the study treatment, and Efficacy Follow-up [redacted] AE summaries will be based on patient incidence counts and percentages per the safety population. In addition to the overall summary of AEs, breakdown summaries will be made by NCI CTCAE grade of severity, and relationship to the study treatment. All laboratory results will be summarized using descriptive statistics. SAEs will also be summarized.

[redacted]

13.5.2.2. Additional Measures of Efficacy

- DOR is measured among responders from the first-time response (PR/CR) criteria are met until the first date that recurrent or PD is objectively documented, or receipt of subsequent anticancer therapy, or the patient expires (whichever is first recorded). Patients not

experiencing PD or have not expired prior to the time of 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.

- DCR is derived as the sum of the number of patients who achieved confirmed PR/CR or sustained SD (at least 4 weeks) divided by the number of patients in the all-treated population × 100%.
- PFS is defined as the time (in months) [redacted] 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.
- OS is defined as the time (in months) [redacted] 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.
- DOR, DCR, PFS, and OS per RECIST v1.1 as assessed by the Investigator, will be subjected to right censoring. Kaplan-Meier methods will apply.

13.5.3. Exploratory Analyses

- Correlation of immune factors (cellular and soluble factors [eg, damage-associated molecular patterns {DAMPs}, cytokines, LDH, neutrophil lymphocyte ratio; tumor HPV status and subtype) with efficacy and safety. The results will be reported in a separate report.
- Evaluation of ORR, DOR, DCR, and PFS as assessed per RECIST v1.1 and irRECIST by independent review.
- HRQoL will be assessed using the EORTC QLQ-C30 instrument and analyzed per the published evaluation manual.
- Q-TWiST will be calculated as sum of the three health state periods (Toxicity, TWiST, and Relapse) [Sherrill 2013] with each multiplied by the appropriate utility score [Beusterien 2009].

13.5.3.1. Stage 1 Analysis

- The Stage 1 analysis will occur when the 15th patient treated has had an opportunity to reach the second tumor assessment (Day 56 assessment). The study will move forward to Stage 2 with 2 or more confirmed responses as assessed by the Investigator evaluation per RECIST v1.1.

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 (R2) and in accordance with the general ethical principles outlined in the Declaration of Helsinki. The study will receive approval from an IRB/IEC prior to commencement. The Investigator will conduct all aspects of this study in accordance with applicable national, state, and local laws of the pertinent regulatory authorities.

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 (R2), 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 R2).

Steps to be taken to assure the accuracy and reliability of data include; the selection of qualified Investigators and appropriate study centers, review of protocol procedures with the Investigator and associated personnel prior to the study, 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. On-site audits 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 at the time of 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, and ICH 6 R2 Section 5.18, 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, and ICH 6 R2 Section 5.18, 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 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.

14.7. 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 [R2] 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, 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 Harmonization (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

	Pretreatment Phase			Treatment Phase					Assessment Phase													Long-term Overall Survival Follow-up (Quarterly Contact)
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 -28 to -10 (Baseline)	Day -7	Day -6	Days -5, -4, -3, -2, -1	Day 0 (LN-145 Infusion Visit)	Days 1, 2, 3, 4	Day 14	Day 28 (Week 4)	Day 56 (Week 8)	Day 84 (Week 12)	Day 126 (Month 4.5/Wk 18)	(Month 6)	Month 9	Month 12	Month 15	Month 18	Month 21	Month 24	EAV[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 and HPV Serotype	X	X																				
HRQoL Questionnaire[b]			X									X		X		X				X		
Physical Examination[c]	X		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	
Vital Signs[d]	X	X	X	X	X	X	X[e]	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[f]	X	X[g]	X	X	X	X	X	X	X	X	X	X	X	X							X	
ß-HCG Serum Pregnancy Test	X		X																			
Infection Testing[h]	X	X																				
HLA Typing[i]	X																					
Serum Creatinine[j]	X	X[g]	X	X	X	X	X	X	X	X	X	X	X	X							X	
Eye Examination	X																					
Cardiac Evaluations[k]	X																					
Pulmonary Function Tests[l]	X																					
Colonoscopy[m]	X																					
Tumor Assessments (CT/MRI)[n]	X		X							X	X	X	X	X	X	X	X	X	X	X	X	X[o]

Response Assessments (RECIST v1.1)										X	X	X	X	X	X	X	X	X	X	X	X	X[o]
Post-treatment core biopsy[p]										X												
Eligibility Confirmation[q]			X																			
Hospitalization[r]		X		X	X		X	X														
Concomitant Medications	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	
Adverse Events[s]	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	
Tumor Resection[t]		X																				
FFPE block collection[u]		X																				
NMA-LD[v]				X	X	X																
LN-145 Infusion[w]							X															
IL-2 600,000 IU/kg[x]								X														
PJP[y]									X	X	X	X	X[y]	X[y]								
Filgrastim[z]								X														
Fungal Prophylaxis[aa]								X	X	X	X	X										
Herpes Virus Prophylaxis[bb]									X	X	X	X	X[bb]	X[bb]								
Immune Monitoring[cc]		X[g]		X				X[cc]	X	X	X	X		X	X	X					X	
Long-term Overall Survival Follow-up[dd]																						X

ß-HCG = beta human chorionic gonadotropin; CT = computed tomography; ECOG = Eastern Cooperative Oncology Group; EAV = End of Assessment visit; HLA = human leukocyte antigen; HPV = human papillomavirus; HRQoL = health-related quality of life; 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 The EAV is completed if discontinuation prior to/from the study treatment or Efficacy Follow-up occurs at any time after Visit 2 and before Visit 27. The EAV is not required if assessments were performed within 2 weeks of patient's last visit.

b HRQoL Questionnaire is to be performed as the first procedure at Baseline Day -28 to Day -10 (Visit 3) and as indicated in the Schedule of Assessments through Visit 27/Month 24. See Section 5.9.

c Physical examination will include gastrointestinal (abdomen, liver), cardiovascular, extremities, head, eyes, ears, nose, and throat, respiratory system, skin, and psychiatric (mental status). Physical examinations conducted during follow-up will be symptom directed. See Section 5.10.

d Vital signs will include height, body weight, heart rate, respiratory 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 (Visit 4) only. All others will be assessed at every visit through Visit 27/Month 24. See Section 5.11.

e On Day 0 (LN-145 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 5.11.

f 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. Labs are to be done at Visits 3–21. See Section 5.13.
- Hematology: CBC with differential is to be done at Visits 3–21. 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 is to be done at Visits 1 and 19 or as clinically indicated.
- Urinalysis Dipstick: A complete urinalysis with microscopy and/or urine culture is to be done at Visit 3–21 or as clinically indicated.
- Coagulation: Measurement of prothrombin time /international normalized ratio (PT/INR), and partial thromboplastin time/activated partial thromboplastin time (PTT/aPTT) will be performed at screening only and analyzed locally.

g Laboratory samples may be collected within 48 hours prior to the tumor resection visit. The creatinine clearance will be calculated by the site using the Cockcroft-Gault formula at Screening Visit only.

h HIV antibody titer; 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 5.15.

i HLA typing will be conducted as Screening (Visit 1) and analyzed by central laboratory. See Section 5.16.

j Estimated CrCl is calculated at screening only by site based on the Cockcroft-Gault calculation. See Section 5.18.

k Cardiac Evaluations consist of NYHA, ECHO, ECG and cardiac stress test within 28 days of Screening (Visit 1). Stress thallium 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 thallium test. See Section 5.20.

l Pulmonary evaluation using spirometry or 6-minute walk test will be completed within 28 days from Screening (Visit 1) for all patients. In patients without pulmonary metastases, evaluations completed within 6 months prior to Screening (Visit 1) will be accepted. See Section 5.21.

m Colonoscopy is only required for documented Grades 2 or greater 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 5.22.

n CT Scans of the head/neck, chest, and abdomen are required at the indicated time points. Baseline scans may occur between Day -28 to Day -10 (Visit 3). Additional radiological assessments may be performed per Investigator's discretion. MRI may be used if patients are intolerable to contrast media. See Section 5.24.

o 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).

p A post-treatment (post LN-145 infusion) core biopsy of at least one target lesion (fresh and FFPE) will be collected, if feasible, on Day 28 (+7 days) (Visit 17). The biopsy should occur after the Day 28 tumor assessment scans. See Section 5.26.

q Eligibility confirmation completed at Baseline (Day -28 to -10; Visit 3) must be approved by Sponsor's Medical Monitor prior to initiation of lymphodepletion.

r 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. Hospitalization is mandatory from the day before LN-145 infusion through all IL-2 infusions. Patients who are hospitalized for any reason (eg, tumor resection, mandated therapy [chemotherapy, IL-2], AEs, other) will need to complete a Hospitalization Form.

s Any AEs occurred after Screening (Visit 1), but prior to enrollment/tumor resection, will be recorded as medical history in the eCRF. Any AEs occurred after enrollment/tumor resection will be captured as AEs through Day 168 (Visit 21/Month 6) and as clinically indicated, or until the first dose of the subsequent anticancer therapy, whichever occurs first. All AEs attributed to protocol-required procedures or treatment will be collected through Day 672 (Visit 27/Month 24). See Section 11.

t At Tumor Resection (Visit 2), 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 5.25.

u 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 5.25.1.

v Cyclophosphamide with mesna for 2 days at Day -7 and Day -6 (Visits 4 thru 5) followed by 5 days of fludarabine at Day -5 thru Day -1 (Visits 6 thru 10). See Section 6.1.

w LN-145 infusion is to be done 1 to 2 days after the last dose of agent in the NMA lymphodepletion regimen. See Section 6.2.

x Initiate IL-2 at 600,000 IU/kg between 3 and 24 hours after completion of the LN-145 infusion and continue every 8 to 12 hours for up to 6 doses. See Section 6.2.5.

y PJP prophylaxis should be given by Day 14 (Visit 16) or as the Investigator deems appropriate and continue until the absolute lymphocyte count is > 1000 cells/mm^3. See Section 8.1.1.1.

z Filgrastim 5 mcg/kg/day subcutaneous should 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 8.1.4.

aa Fungal prophylaxis (fluconazole 400 mg by mouth daily) should 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.

bb Herpes prophylaxis should begin by Day 14 or as the Investigator deems appropriate and continue for 6 months post-treatment, or in general, until the is > 1000/mm^3 ALC 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.

cc Blood draw for immune monitoring is to be collected at tumor resection (Visit 2), Day -7 (Visit 4), Day 1 (Visit 12), Day 4 (Visit 15), Day 14 (Visit 16) through Day 84 (Visit 19/Week 12), and Day 168 (Visit 21/Month 6) through Day 336 (Visit 23/Month 12) and EAV.

dd Patients are to be contacted quarterly (approximately every 3 months) after discontinuing/completing the post-treatment Efficacy Follow-up to assess disease status and subsequent anticancer therapy. Durable responders will continue to have response assessments during Long-term Overall Survival Follow-up until the last patient is followed for 3 years. See Section 9.4.2.

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.

17.3.1. BMI

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

17.3.2. BSA

The BSA should be calculated using the following formula:

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

Other institutional standard formulas are acceptable.

17.4. Common Terminology Criteria for Adverse Events

http://evs.nci.nih.gov/ftp1/CTCAE/CTCAE_4.03_2010-06-14_QuickReference_5x7.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

Expected Toxicity	Expected Grade	Supportive Measures	Stop Treatment*
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
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

Expected Toxicity	Expected Grade	Supportive Measures	Stop Treatment*
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

17.6. Summary of Changes (Major/Minor) In Protocol C-145-03 Version 2.0 (Dated 30 August 2017)

The major changes and purposes for revising the C-145-03 protocol are the following:

- Updated and clarified the primary, secondary, and exploratory objectives and endpoints
- Clarified investigational product doses and treatment schedule
- Updated the durations for each of the study phases
- Revised the long-term follow-up to include an overall survival follow-up period
- Revised the number and location of study sites to reflect current study design
- Clarified the planned patient population, including multiple clarifications made to the inclusion and exclusion eligibility criteria
- Revised required diagnosis to primary HNSCC via pathology report
- Allowed for patients who progress or who have an incomplete response to treatment on this protocol to be rescreened and retreated
- Allowed for patients who cannot undergo pulmonary function tests alternatives for pulmonary function assessment
- Allowed for patients to have undergone prior irradiation to persistent lesions
- Allowed for washout period of current treatment to begin closer to treatment rather than from tumor harvest
- Multiple clarifications around study assessments and procedures to be performed and timing for the assessments and procedures
- Updated the description of the production and expansion of TIL for clarity
- Changed the cutoff for obese BMI from > 30.0 kg/m^2 to > 35.0 kg/m^2
- Clarified the sample size calculation and revised the statistical analyses to align with the revised study objectives and endpoints
- Revised the timing of evaluations to be performed by the DSMB
- Clarified permitted and prohibited concomitant medications
- Clarified prophylaxis therapies to be administered
- Added guidance on management of LN-145, NMA-LD, and IL-2 toxicities
- Clarified definitions for study treatment completion and study completion

- Numerous clarifications for safety monitoring
- Added special situations reporting
- Updated the key Sponsor and designee contact information

The minor changes and purposes for revising the C-145-03 protocol are the following:

- Revised protocol title for clarity
- Updated Table of Contents and Introduction
- Revised the study flow chart to reflect the current study design
- Numerous typographical changes were made for clarity and consistency
- Minor administrative changes and additions to clarify operational issues
- Formatting, including additions to the List of Abbreviations and adding hyperlinks for Sections, Tables, Figures, Appendices, and References

A separate Summary of Changes document outlines the noteworthy changes from Version 1.0 to Version 2.0, and includes rationales for the changes.