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 2.0, Dated 30 August 2017
SUPERSEDES:	Original Protocol, Version 1.0, Dated 16 August 2016
MEDICAL MONITOR:	[redacted] Executive Medical Director, Clinical Science [redacted]

This study will be conducted in compliance with the protocol, Good Clinical Practice (CGP) and all other applicable regulatory requirements, including the archiving of essential documents. The specific contact details of the Iovance Biotherapeutics legal/regulatory entity within the relevant country are provided within the clinical trial agreement with the Investigator/Institution and in the Clinical Trial Application with the Competent Authority.

SPONSOR SIGNATURE PAGE

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

[redacted] [redacted]

Signature **dd-mon-yyyy**

[redacted] **Executive Medical Director Clinical Science, Iovance Biotherapeutics, Inc.**

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INVESTIGATOR PROTOCOL SIGNATURE PAGE

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I agree to conduct the study as detailed in the protocol and in compliance with ICH Guidelines for Good Clinical Practice.

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

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

Principal Investigator Signature Date

Principal Investigator Printed Name

Institution

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) consisting of 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 using the objective response rate (ORR) as assessed by investigators per Response Evaluation Criteria in Solid Tumors version 1.1 (RECIST v1.1) **Secondary Objectives** • To characterize the safety profile of LN-145 in patients with metastatic and/or recurrent HNSCC • To evaluate efficacy of LN-145 in patients with recurrent and/or metastatic HNSCC such as complete response (CR) rate, duration of response (DOR), disease control rate (DCR), and progression-free survival (PFS) by investigators' review per RECIST v1.1, and overall survival (OS) **Exploratory Objectives** • To explore the persistence of LN-145 and immune correlates of response, survival, toxicity of the treatment • To explore efficacy based on immune-related RECIST (irRECIST) 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 a NMA-LD pretreatment regimen.

Doses and Treatment Schedule	The adoptive cell therapy (ACT) used in this study consists of administering a 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) and administration of IL-2 (600,000 IU/kg) every 8 to 12 hours, starting between 3 and 24 hours of 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, 18 months, and 24 months following the 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 7 weeks) • **Treatment Phase (approximately 2 weeks)** o NMA lymphodepletion regimen (7 days) o LN-145 infusion (1 day) o IL-2 infusion (1 to 4 days) • **Follow-Up Phase (3 years)** o Efficacy follow-up for safety and efficacy evaluations (24 months) o Overall survival follow-up to assess disease status and survival (12 months)
Number of Study Sites	Approximately 15 clinical study sites in the United States
Number of Planned Patients	Approximately 47 patients who complete treatment. Complete treatment is defined as having received LN-145 post-NMA-LD followed by at least 1 dose of IL-2.
Inclusion Criteria	Patients must meet all of the following inclusion criteria: 1. Must be ≥18 years of age at the time of consent 2. 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 be least 1.5 cm^3 in diameter after resection 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. 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 enrollment (tumor resection) and the lesions must have demonstrated evidence of progression since irradiation. 7. Patients must have relapsed or refractory (no response) recurrent and/or metastatic carcinoma of the head or neck and have received at least 1 line of prior systemic immunotherapy and/or chemotherapeutic 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 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 HIV antibody 12. Patients seropositive for hepatitis B virus surface antigen (HBsAg) or hepatitis C virus (HCV) indicating acute or chronic infection must have a negative (undetectable) viral load by polymerase chain reaction (PCR) with/without active treatment 13. Patients of childbearing potential must be willing to practice an approved method of birth control starting at the time of informed consent and for 1 year after the completion of the study treatment regimen
Exclusion Criteria	1. Patients who have received 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 equivalent daily) **Note**: 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 alopecia or vitiligo prior to enrollment/tumor resection

- If toxicities have resolved to Grade 1 or less, a minimum of 4 weeks must elapse prior to enrollment (tumor resection)

Note: Patients may undergo preplanned procedures if not within 2 to 3 weeks prior to 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

   Note: 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 with history of severe immediate hypersensitivity reaction to cyclophosphamide, fludarabine, IL-2, or aminoglycosides (eg, gentamicin or streptomycin)
6. Patients with active systemic infections (eg, syphilis), coagulation disorders or other active major medical illnesses of the cardiovascular, respiratory or immune system that, in the opinion of the Investigator would significantly increase the risk of participation. Examples of concerning conditions include, but are not limited to, history of a positive thallium stress test, myocardial infarction, cardiac arrhythmia, obstructive or restrictive pulmonary disease, or uveitis.
7. Patients with symptomatic and/or untreated brain metastases (of any size and any number)

   - Patients with definitive treated brain metastases, may be considered for enrollment after discussion with the sponsor's medical monitor/designee, and must be stable for 2 to 4 weeks and asymptomatic prior to the start of treatment (NMA-LD)
8. Patients who have any form of primary immunodeficiency, 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% as determined by an echocardiogram (ECHO) or multiple gated acquisition scan (MUGA); and patients > 60 years of age or those with a history of ischemic heart disease, chest pain, or clinically significant atrial and/or ventricular arrhythmias who have a positive stress thallium test are excluded. Patients with an abnormal stress test may be enrolled following cardiology clearance and approval of the medical monitor
11. Patients who have a forced expiratory volume in one second (FEV1) of less than or equal to 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 bladder cancer) 13. Patients who are pregnant or breastfeeding
Efficacy Assessment	The descriptive summary of the ORR, CR rate, DOR, DCR, PFS will be used to describe efficacy by investigator's review per RECIST v1.1. Estimation of OS will depend on the date of death or the last known alive status date.
Safety Assessment	Treatment-emergent adverse events (TEAEs), clinical laboratory data assessment, and serious adverse events (SAEs) will be collected and evaluated for 6 months after last dose of IL-2 infusion, and AEs that are related to the study treatment (from the time of enrollment/tumor resection) will be collected for the duration of the study until resolution or permanent sequalae.
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% to 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 PR or 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	A 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). A limited analysis may also be conducted reviewing all data available from these patients as specified in the DSMB charter. 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
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
DSMB	data safety monitoring board
EBNA	Epstein Barr nuclear antigen
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
ETV	Early Termination visit
FDA	Food and Drug Administration
FEV1	forced expiratory volume in 1 second
GCP	Good Clinical Practice

Term	Definition
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 cancer
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
MUGA	multiple gated acquisition scan
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
PTT	partial thromboplastin time
Q-TWiST	quality-adjusted time without symptoms of disease or toxicity of treatment

Term	Definition
RECIST	Response Evaluation Criteria in Solid Tumors
REP	rapid expansion protocol
SAE	serious adverse event
SAP	statistical analysis plan
SD	Stable Disease
SLD	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 (HNSCCs) comprise malignancies of the nasal cavity, paranasal sinuses, nasopharynx, oral cavity, oropharynx, hypopharynx, larynx, salivary glands, and head and neck paraganglial tissues (1). 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 (2, 3). 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 (4). 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 (5). Human papillomavirus-positivity also has increased over the same period, reaching an estimated 72% prevalence in OPC between 2005 and 2009 (6-8). By contrast, fewer than 20% of other HNSCC are positive for HPV (8, 9). The increase in incidence of OPC is 4-fold greater in males than females, and among men, is associated with age less than 60 years and white race (3, 10). Of the many strains of HPV, type 16 (HPV16) has been found in more than 90% of HPV-positive OPC (10). Notably, genetic mutations in HPV-negative HNSCC appear to be more frequent and distinct from those in HPV-positive tumors (2). For example, mutations of p53, a key tumor suppressor gene, were almost always associated with an HPV-negative tumor (11, 12), consistent with the known association between smoking and p53 mutations in subjects with HNSCC (13). By contrast, activating mutations and amplifications of phosphatidylinositol 3-kinase, catalytic subunit alpha (PIK3CA) were more common in HPV-positive tumors (14). 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 (3). The current standard treatment for HNSCC typically involves combinations of surgery, radiation, and chemotherapy, typically with cisplatin (15). Surgery can be minimally invasive to preserve organ function. Radiation with hyperfractionation and accelerated fractionation has been found to improve survival (16) but has been associated with swallowing dysfunction (17). 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 (18). By tumor site, estimated 5-year survival rates remain ≤ 63% for all sites other than the tongue or lip (19). Notably, outcome for subjects with HPV-positive tumors is better than outcome for HPV-negative HNSCC (6, 20, 21), with reported 2- and 3-year survival rates of approximately 95% and 80%, respectively (6, 20). The improved outcome of subjects harboring HPV-positive tumors may be a result of enhanced activity of TIL at the tumor site (16).

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 (3). Argiris et al. (22) estimated a recurrence rate of 50% for subjects in remission following treatment of a locally advanced HNSCC, and Chuang et al. estimated that 36% of subjects would develop a second primary tumor within 20 years (23). 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 (6).

Outcome for recurrent HNSCC is poor across a variety of therapeutic modalities (24-26), although Strnad et al. (27) reported long-term high rates of local control of recurrent disease using interstitial pulsed-dose-rate brachytherapy combined with chemotherapy in a selected subject 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 subjects with HPV-positive tumors and 27.6% for those with HPV-negative tumors ($p < 0.001$) (28).

The findings of survival rates of 63% or less among most subjects with HPV-negative HNSCC or recurrent HPV-positive HNSCC, and even lower survival rates among subjects with recurrent HPV-negative tumors, indicates 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 (12-14). Recent findings have clearly shown a predictive relationship between the frequency and phenotype of TIL in solid tumors (especially CD8+ T cells) and an increased OS and progression-free survival (PFS) in patients with melanoma (15-17, 29), lung cancer (18-21), ovarian cancer (22-24), squamous cell carcinomas (25, 26), triple-negative breast cancer, HER2-positive breast cancer (30), basal-like breast cancer (27, 28, 31-36), and colorectal cancer (37-40). 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 (41). In addition, gene expression studies using 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, DC-LAMP and chemokine and chemokine receptors) with improved OS and PFS in both primary and metastatic tumor settings (17, 37, 38, 42-44). 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 antitumor immune responses in the tumor microenvironment (45-47); 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, rather than a single target (48-50) (51). 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 and cytokine sinks) to provide an optimal milieu for the transferred TIL to proliferate and become activated in vivo.

The feasibility of TIL preparation was demonstrated by early studies showing that metastatic melanoma tumors can be excised and placed in tissue culture under conditions in which tumor cells do not survive, but any TIL contained within the excised tumor tissue can survive and proliferate. TIL can be cultured in the presence of interleukin-2 (IL-2) and can be grown to very large numbers using standardized protocols ($\geq 1 \times 10^8$ cells) (12, 14, 52, 53). 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 (12, 14, 52, 53). Further studies established that the efficacy of infusions of large numbers of TIL were enhanced by pretreatment of the tumor-bearing animals with cyclophosphamide to induce a transient drop in endogenous lymphocytes in the host and followed by IL-2 administration. With this combination, mice could be cured of advanced hepatic metastases (12). These findings set the stage for National Cancer Institute (NCI) clinical trials using TIL therapy for patients with metastatic melanoma that includes a NMA-LD preconditioning regimen consisting of fludarabine and cyclophosphamide combined with IL-2 following TIL Infusion. Across clinical studies conducted by the NCI, immunotherapy of patients with advanced melanoma with autologous TIL therapy has induced durable objective response rates (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 (54, 55).

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, and radiation therapy. 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 (46). Similarly, low CD8+ T-cell infiltration in the tumors of patients with laryngeal squamous cell cancer was correlated with decreased survival (56). 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 (57); whereas, Wansom et al. (58) and Ward et al. (59) 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 (60). 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. (61) demonstrated the successful expansion of TIL bulk cultures were expanded in 12 of 15 (80%) evaluable subjects; tumor specificity of the TIL were shown in 60%. Up to 3500-fold expansion was achieved within 17 days. TIL from 60% of the subjects 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 (62). Moudgil et al. (63) 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 that TIL were successfully generated in 677 (86%) of the 787 specimens from 402 subjects with melanoma (64).

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). The TIL therapy to be used in this study is similar to that developed for melanoma-derived and cervical cancer-derived TIL by Dr. Steven Rosenberg and colleagues at the NCI. Melanoma-derived TIL have demonstrated efficacy in the treatment of Stage IV melanoma, and Phase 2 clinical studies evaluating this product have shown an ORR of 56% or more (54, 55), exceeding rates reported by other immunotherapies in metastatic melanoma. In addition, long-term durable CRs of 24% in melanoma and 22% in cervical cancer patients were observed (54, 55, 65, 66).

Protocols 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 will assess efficacy and safety for 47 patients who receive LN-145 treatment followed by at least 1 dose of IL-2.

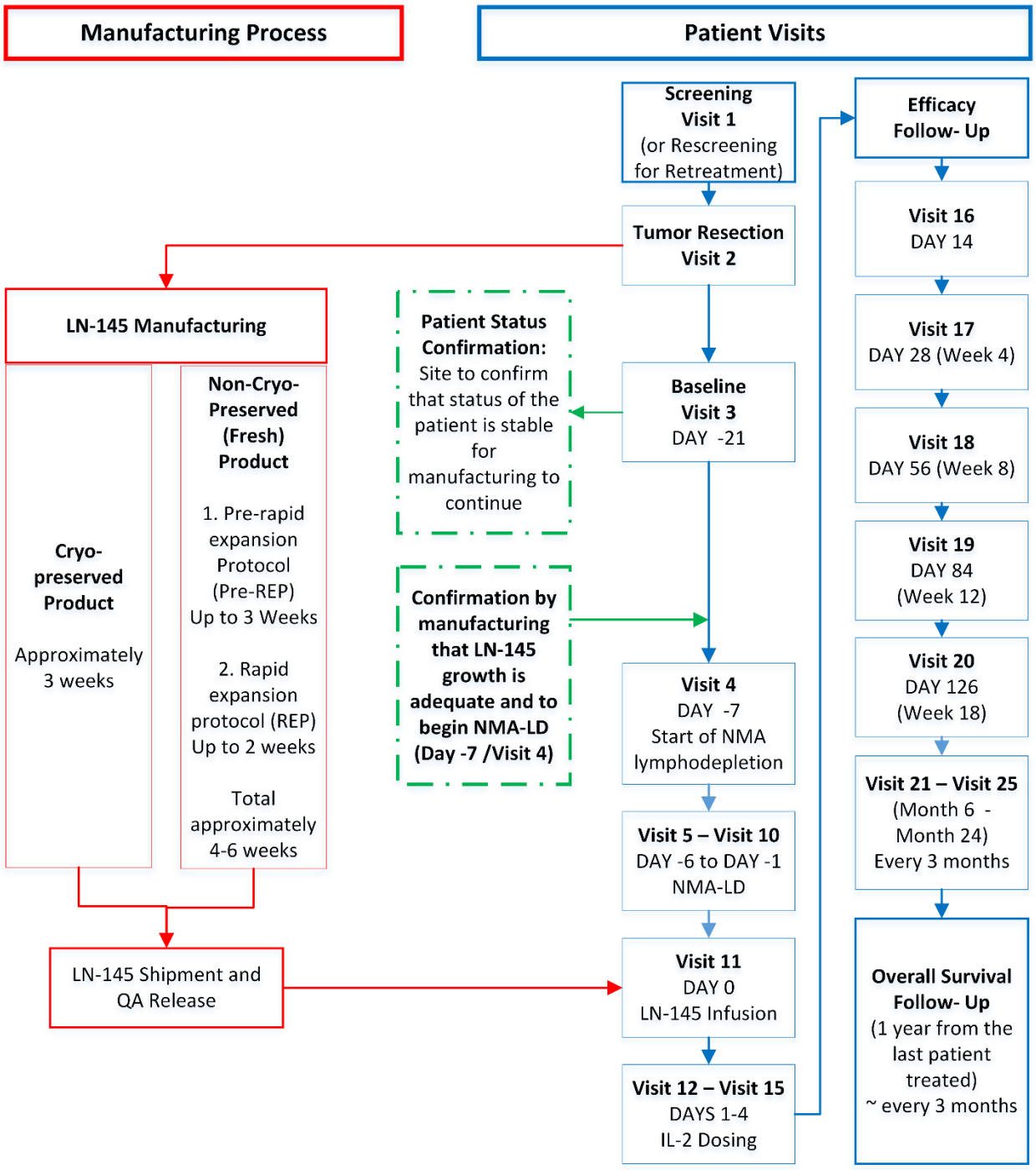
The study consists of 3 phases:

- **Pretreatment Phase (approximately 8 weeks)**
  - Screening visit (up to 28 days)
  - Tumor resection visit (1 day)
  - LN-145 manufacturing period (approximately 3 to 7 weeks)

- **Treatment Phase (approximately 2 weeks)**
  - NMA-LD regimen (7 days)
  - LN-145 Infusion (1 day)
  - IL-2 Infusion (1 to 4 days)

- **Follow-Up Phase (3 years)**
  - Efficacy follow-up for safety and efficacy evaluations (24 months)
  - Overall survival follow-up to assess disease status and survival (12 months)

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 at the clinical site with the surgical resection of primary or secondary metastatic tumor material of [redacted] from the patient. The tumor specimen(s) is placed in biopreservation transport media and shipped (at [redacted] overnight to a Good Manufacturing Practice (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 blood transport and infusion bags for shipment by courier to the clinical site as either a fresh, chilled [redacted] non-cryopreserved product or a cryopreserved [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 6 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 (67-72). 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 (73, 74).

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 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 using the ORR as assessed by investigators per RECIST v1.1

3.1.2. Secondary Objectives

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

3.1.3. Exploratory Objectives

- To explore the persistence of LN-145 and immune correlations of response, survival, toxicity of the treatment
- To explore efficacy based on immune-related RECIST (irRECIST) (75) 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 as assessed by investigator per RECIST v1.1

3.2.2. Secondary Endpoints

- Incidence of treatment-emergent adverse events (TEAEs), including serious adverse events (SAEs), therapy-related adverse events (AEs), AEs leading to early discontinuation of treatment or withdrawal from efficacy follow-up or death
- CR rate
- DOR
- DCR
- PFS
- OS

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 irRECIST by independent review
- HRQoL as assessed per EORTC QLQ-C30 questionnaire
- Q-TWiST (76) using investigators' assessments for PFS

4. SELECTION OF PATIENT POPULATION

Patients with a diagnosis of recurrent and/or metastatic HNSCC who have undergone at least 1 prior systemic immunotherapy or chemotherapy regimen will be selected for this study.

Details concerning specific benefits and risks for patients participating in this clinical study may be found in the accompanying Investigator's Brochure and informed consent documents.

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 to be eligible.

4.1. Inclusion Criteria

1. Must be ≥18 years of age at the time of consent
2. 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 be least 1.5 cm^3 in diameter after resection, 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.
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 enrollment (tumor resection) and the lesions must have demonstrated evidence of progression since irradiation
7. Patients must have relapsed or refractory (no response) recurrent and/or metastatic carcinoma of the head or neck and have received at least 1 line of prior systemic immunotherapy and/or chemotherapeutic 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.
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 HIV antibody
12. Patients seropositive for hepatitis B surface antigen (HBsAg) or hepatitis C virus (HCV) indicating acute or chronic infection must have a negative (undetectable) viral load by polymerase chain reaction (PCR) with/without active treatment
13. Patients of childbearing potential must be willing to practice an approved method of birth control 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:

    - Total abstinence
    - Hormonal contraception (ie, birth control pills, injection, implant, transdermal patch, vaginal ring)
    - Intrauterine device (IUD)
    - Tubal ligation
    - Vasectomy
    - Implantable or injectable contraceptives
    - Use of a male or female condom with spermicide
    - Cervical cap or contraceptive sponge with spermicide

4.2. Exclusion Criteria

1. Patients who have received 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 equivalent daily).
   - **Note**: 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 alopecia or vitiligo prior to enrollment/tumor resection.
    - If toxicities have resolved to Grade 1 or less, a minimum of 4 weeks must elapse prior to enrollment (tumor resection).
    - Patients may undergo preplanned procedures if not within 2 to 3 weeks prior to 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 with history of severe immediate hypersensitivity reaction to cyclophosphamide, fludarabine, IL-2, or aminoglycosides (eg, gentamicin or streptomycin).
6. Patients with active systemic infections (eg, syphilis), coagulation disorders or other active major medical illnesses of the cardiovascular, respiratory or immune system that, in the opinion of the investigator, would significantly increase the risk of participation. Examples of concerning conditions include, but are not limited to, history of a positive thallium stress test, myocardial infarction, cardiac arrhythmia, obstructive or restrictive pulmonary disease, or uveitis.
7. Patients with symptomatic and/or untreated brain metastases (of any size and any number).
    - Patients with definitive treated brain metastases may be considered for enrollment after discussion with the sponsor's medical monitor/designee, and must be stable for 2 to 4 weeks and asymptomatic prior to the start of treatment (NMA-LD).
8. Patients who have any form of primary immunodeficiency, 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% as determined by an echocardiogram (ECHO) or multiple gated acquisition scan (MUGA); and patients > 60 years of age or those with a history of ischemic heart disease, chest pain, or clinically significant atrial and/or ventricular arrhythmias who have a positive stress thallium test are excluded. Patients with an abnormal stress test may be enrolled following cardiology clearance and approval of the medical monitor.
11. Patients who have a forced expiratory volume in 1 second (FEV1) of less than or equal to 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 bladder cancer).

13. Patients who are pregnant or breastfeeding.

4.3. Patient Enrollment and Re-Screening

Patients who meet all inclusion criteria and do not meet any of the exclusion criteria will be enrolled in the study. Enrollment is defined as patients who began or completed tumor resection/tumor harvest 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 or do not have a tumor resection/harvest within 28 days of signing the informed consent 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 medical monitor will discuss the patient's status prior to any re-screening procedures.

Once the patient is approved to enroll in the study, the patient must continue to meet eligibility criteria until the NMA-LD visit (Day -7/Visit 4). The investigator must confirm the patient's health status based at baseline (Day -21/Visit 3) laboratory values and computed tomography (CT) scans to ensure the patient is stable to proceed with NMA-LD.

Patients may rescreen for a second tumor resection and LN-145 treatment if they meet all inclusion and exclusion Criteria. These patients will have a second tumor harvest and TIL (LN-145) therapy. Examples of patients who may be eligible for retreatment are prior responders to LN-145 who relapse, nonresponders, and patients with manufacturing failures. The medical monitor will have authority to adjudicate enrollment for retreatment (second TIL therapy).

5. STUDY ASSESMENTS/PROCEDURES

5.1. Informed Consent

The applicable and approved ICF(s) must be signed before any study related assessments are performed.

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.

5.5. Documentation of Confirmation of Diagnosis

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

5.6. Documentation of HPV Tumor Status

Patients must have documented HPV tumor status prior to tumor resection (Visit 2).
If documentation is not available, testing for HPV status of the tumor may be determined locally or at Iovance at the time of 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 during all visits once the ICF is signed. Any events occurring after screening, but prior to enrollment/tumor resection, will be recorded as medical history in the eCRF, unless the events are related to protocol-mandated procedures. Any events occurring after enrollment/tumor resection will be captured as

AEs in the eCRF until Day 168 (Visit 21/Month 6) and as clinically indicated. Additional safety reporting requirements are described under Section 11.

5.9. HRQoL Questionnaire – EORTC QLQ-30 Version 3.0

The HRQoL Questionnaire will be conducted at baseline (Day -21/Visit 3) and be performed as the first procedure on the subsequent visits. See Appendix 17.1 for specific time points.

5.10. Physical Examination

Physical examination 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, psychiatric (mental status), and general nutritional status. Physical examination conducted during follow-up 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 applicable time points. See Appendix 17.1.

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.

5.12. Eastern Cooperative Oncology Group Performance Status

An ECOG performance status will be assessed at screening (Visit 1) through Visits 4, 11, and 17 through 25 (see Appendix 17.1).

5.13. Safety Blood and Urine Tests

The following safety blood and urine tests will be collected and analyzed locally at every visit:

- Chemistry - sodium, potassium, chloride, total CO_2 or bicarbonate, serum creatinine, glucose, blood urea nitrogen, albumin, calcium, magnesium, phosphorus, alkaline phosphatase, ALT, AST, total bilirubin, direct bilirubin, lactate dehydrogenase, total protein, total creatine kinase, uric acid
- Hematology – complete blood count (CBC) with differential
- Coagulation - Measurement of prothrombin time (PT)/international normalized ratio (INR), and partial thromboplastin time (PTT)/activated PTT will be performed at screening only and analyzed locally.

- Thyroid panel inclusive of thyroid stimulating hormone (TSH) and free T4 shall be done only at screening (Visit 1) and Day 84 (Visit 19/Week 12) or as clinically indicated.
- Urinalysis dipstick will be completed at every visit. Abnormal, clinically significant findings shall be recorded as AEs. A complete urine culture shall be performed if clinically indicated.

5.14. ß-HCG Serum Pregnancy Test

All women of childbearing potential will have serum pregnancy tests at screening (Visit 1) and baseline (Day -21/Visit 3).

5.15. Infection Testing

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

- HIV antibody titer;
- Hepatitis - HBsAg IgG and anti-HCV IgG
- Syphilis assay (as per local standard; eg, rapid plasma reagent, venereal disease research laboratory, or other) at screening, and thereafter as clinically indicated;
- Herpes simplex virus (HSV) serology determination (HSV-1 IgG and HSV-2 IgG)
- Cytomegalovirus (CMV) serology (IgG and IgM)
- Epstein Barr virus (EBV) panel (VCA-IgG, and/or EBNA IgG [tests conducted to confirm absence of acute or active EBV infection] may have been done within 3 months prior to tumor resection [Visit 2]).

5.16. Human Leukocyte Antigen Typing

Sample collection for HLA typing will be conducted at screening (Visit 1) and analyzed by the central laboratory. Refer to the Laboratory Manual for details.

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

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

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

The 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) or up to 30 days prior to consent signing to rule out active uveitis.

5.20. Cardiac Evaluations

All cardiac evaluations (Echo/MUGA and electrocardiogram) will be performed during screening (Visit 1). Evaluations completed within 6 months prior to screening (Visit 1) will be accepted.

5.20.1. Stress Thallium

A stress thallium test will be done for all patients ≥ 60 years of age or any patient with a history of ischemic heart disease, chest pain, or clinically significant atrial and/or ventricular arrhythmias.

5.20.2. Echocardiogram or Multigated Acquisition Scan

An ECHO or MUGA will be done 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.

5.21. Pulmonary Function Tests

Pulmonary evaluation will be completed within 28 days from screening (Visit 1). Evaluations completed within 6 months prior to screening (Visit 1) will be accepted.

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 and Peripheral Blood Mononuclear Cells

Peripheral blood mononuclear cells (PBMC), serum, and plasma will be collected to test for cellular and soluble factors.

Blood for immune monitoring will be drawn at tumor resection (Visit 2) and subsequent collections will be drawn at applicable time points (see Appendix 17.1).

Blood draw for PBMC biomarker analysis is only to be collected at tumor resection (Visit 2).

Refer to the study Laboratory Manual for details.

5.24. Radiographic Assessments

Radiographic assessments by CT scans with contrast of the chest, abdomen, and pelvis are required for all patients for tumor assessments. CT scans are performed throughout the study until progressive disease by investigator assessment per RECIST v1.1 is noted (or if the patient withdraws full consent).

Radiographic assessments of additional anatomical locations will be conducted at the protocol-specified or unscheduled visits (see Appendix 17.1 for specific time points) 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.

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 Day -21 to Day -14 (Visit 3/baseline) 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, 18 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 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. If it has been previously irradiated, then the tumor must have demonstrated growth over the last 3 months since the last dose of radiation. If enrolled, tumor resection is expected to occur approximately 3 to 6 weeks prior to the LN-145 infusion at Day 0 (Visit 11) and is dependent on the rate of cell growth of TIL at the sponsor-designated contracted manufacturing organization (CMO) facility.

LN-145 is an autologous investigational product which is procured and administered by means that have more in common with autologous blood product delivery than those of traditional drug production.

It is imperative that only the patient's own (autologous) study treatment (LN-145) be administered to the same individual patient. For these reasons, the patient specimen must be procured and handled per a strict protocol to ensure optimal quality of the specimen and minimum transport time to and from the processing CMO facility, as well as to ensure the appropriate identification of the study product at all times including infusion back into the patient.

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 after resection for TIL manufacturing, then a portion of the remaining viable tumor tissue is to be sent to the central laboratory as outlined in the Tumor Procurement & Shipping Manual.

The tumor tissue sent to the central laboratory will be analyzed for 1) immunohistochemistry to identify individual immune cell populations, 2) mRNA extraction for profiling of immune and tumor gene expression, 3) isolation of DNA which will be used for "exome" (not whole genome) sequencing for neoepitope interrogation, and 4) HPV typing as necessary.

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 analyses. The patient may be requested to sign the substudy consent (eg, Genetic Research Substudy ICF) for additional tumor tissue and specimen collected during the study.

Refer to the Laboratory Manual for details.

6. STUDY TREATMENT

6.1. Nonmyeloablative Lymphodepletion Regimen

The NMA-LD regimen is scheduled to start on Day -7 (Visit 4). Approval from the sponsor is required to start the NMA-LD regimen. 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.

The NMA-LD regimen comprises 2 daily doses of cyclophosphamide (with continuous mesna) followed by 5 daily doses of fludarabine and should be administered as per institutional protocol/standards for nonmyeloablative chemotherapy. Guidelines for preparation and administration are described below. For consistency in dosing, obese patients (defined as having a BMI > 35 kg/m^2) should be dosed as recommended in this protocol (using Practical Weight, Appendix 17.3.3).

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 20 mg/mL. Add dextrose 5% water (D5W) to the required volume of cyclophosphamide to reach a total infusion volume of 250 mL. If the volume of reconstituted cyclophosphamide is > 250 mL, additional D5W is not necessary.

If the patient is obese (BMI > 35.0 kg/m^2), the dose of cyclophosphamide will be calculated using practical weight as described in Appendix 17.3.3. Infuse with mesna as described below.

6.1.2. Preparation of Mesna

Mesna is administered to prevent the occurrence of hemorrhagic cystitis related to cyclophosphamide. Mesna may be administered per local protocol or as per the following regimen (15 mg/kg). 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, or in any of the following fluids (per mesna current prescribing information) to obtain a final concentration of 20 mg/mL:

- 5% Dextrose Injection, USP
- 5% Dextrose and 0.2% Sodium Chloride Injection, USP
- 5% Dextrose and 0.33% Sodium Chloride Injection, USP
- 5% Dextrose and 0.45% Sodium Chloride Injection, US
- 0.9% Sodium Chloride Injection, USP
- Lactated Ringer's Injection, USP

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 infusion will continue as per institutional standards or at a rate of 3 mg/kg/hour over 22 hours after each cyclophosphamide dose during Days -7 and -6 (Visits 4 and 5) to prevent hemorrhagic cystitis. Higher doses of mesna can be administered as per local standards for the prevention of hemorrhagic cystitis.

6.1.4. Fludarabine

The fludarabine dose of 25 mg/m^2 is administered intravenously over approximately 30 minutes once daily for 5 consecutive days during Days -5 through -1 (Visits 6 through 10). Effort should be made to administer the fifth dose of fludarabine by 10 AM on Day -1 to ensure 24 hours elapse before infusion of LN-145.

Hematological parameters (CBC and differential) are to be reviewed daily during lymphodepletion. If after 3 or 4 doses of fludarabine, the absolute lymphocyte count falls below 100 cells/mm^3 the remaining dose(s) of fludarabine may be omitted following discussion with the sponsor's medical monitor.

Note: If the patient is obese (BMI > 35.0 kg/m^2), fludarabine dosage will be calculated using practical weight as described in Appendix 17.3.3.

6.2. LN-145 Infusion

Upon completion of the manufacturing process, the investigational product will be labeled with a patient-specific label (including subject ID and manufacturing number) and shipped overnight by courier to the clinical site. The product will be shipped under quarantine and received by the appropriate clinical staff at the site. Additional details for handling and administration of the investigational product can be found in the Investigational Product Administration Manual.

If not already hospitalized, the patient will be admitted the day prior to planned LN-145 administration and prepared with overnight intravenous hydration prior to the investigational product administration. Patients will remain hospitalized until the completion of the IL-2 therapy, as per institutional standards.

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. For details about tumor handling, see Tumor Procurement and Shipping Manual.

Each dose contains up to [redacted] total viable lymphocytes. The total volume to be infused will be dependent on total cell dose (generally between 250 mL and 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. The upper limit of the number of cells for infusion [redacted] viable cells) is based on the known published upper limit safely infused where a clinical response has been attained (73, 74). There is no evidence that moving beyond this upper limit will have more clinical benefit.

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 non-cryopreserved investigational product (fresh) is a live cell suspension that is formulated in [redacted]

The cryopreserved investigational TIL product is a sterile product formulated i [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 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). Additional details are specified in the Pharmacy & Investigational Product Administration Manual.

The cryopreserved LN-145 investigational product will be shipped to the clinical site in a [redacted] temperature monitoring device will be used to continuously monitor the product temperature during shipment. The product is shipped to the clinical site by expedited courier, and is stored in [redacted] until the patient is ready for infusion.

6.2.4. Receipt of LN-145 and Administration

A single LN-145 dose is given intravenously approximately 24 hours after lymphodepletion chemotherapy followed by IL-2 therapy every 8 to 12 hours for up to 6 doses beginning 3 to 24 hours after LN-145 infusion.

LN-145 will be received at the clinical site in the pharmacy on the day of administration. LN-145 will be shipped to clinical sites under quarantine while awaiting results of release tests. Receipt is defined as the moment the LN-145 package is signed for by site personnel and released from courier's custody.

After receiving, verifying, and re-labeling with the clinical sites' specific labels at the pharmacy, the non-cryopreserved investigational product, LN-145, will be transferred to the patient bedside in its original shipping container [redacted] Prior to administration, the cryopreserved LN-145 investigational product is to be thawed according to the detailed instructions provided in the Pharmacy & Investigational Product Administration Manual.

Patients may be premedicated with antihistamines and non-steroidal anti-inflammatory medications (eg, indomethacin and diphenhydramine) prior to administration of LN-145. Clinical investigators will be instructed to administer autologous LN-145 as soon as feasible but at least approximately 24 hours since the last dose of fludarabine. Administration of LN-145 is recommended within 24 hours from the time of manufacture but no later than 48 hours. The investigational product is infused by gravity within 45 minutes as tolerated and can be slowed as clinically appropriate. If the infusion is slowed or interrupted for medical reasons, the product infusion should be completed within 3 hours of the start of the infusion. Refer to the Pharmacy & **Investigational Product Administration Manual** for details.

6.3. Interleukin-2

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 at a frequency of every 8 to 12 hours following the initial dose as per institutional standard of care 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 a dose is not administered within 24 hours, this first dose will be marked as "skipped" and the next dose will 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, no IL-2 will be given and therapy will have been completed.

IL-2 doses will be skipped if 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 8.3 and Appendix 17.5. If these toxicities can be easily reversed within 24 hours by supportive measures, then additional doses may be given. If greater than 2 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.

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

6.4. Retreatment

Patients may rescreen for a second tumor resection and LN-145 treatment if they meet all inclusion and exclusion criteria. These patients will have a second tumor harvest and TIL (LN-145) therapy. Examples of patients who may be eligible for retreatment are prior responders to LN-145 who relapse, nonresponders, and patients with manufacturing failures. The medical monitor will have authority to adjudicate enrollment for retreatment (second TIL therapy). Prior to enrollment for retreatment, patients must undergo an abbreviated screening procedure.

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 tumor resection and lymphodepletion if it does not affect target and nontarget lesions.
- Patients may undergo preplanned procedures if 2 to 3 weeks prior to the start of NMA-LD.
- Use of systemic steroid therapy ≤ 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 trial.

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
- Patients who complete the NMA-LD should not receive a live or attenuated vaccine until ALC is ≥ 1000/mm3

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 following tumor harvest 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 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 cyclophosphamide and fludarabine current package inserts for additional information.

8.1.1. Infection Prophylaxis

8.1.1.1. *Pneumocystis jirovecii* Pneumonia

All patients should receive appropriate *pneumocystis jirovecii* pneumonia (PJP) prophylaxis per institutional standards for patients receiving chemotherapy-induced immunosuppression. This may include any of the following regimens and should begin by Day 14 (Visit 16), or as the investigator deems appropriate and continue until the absolute lymphocyte count is > 1000 cells/mm^3 (typically for at least 6 months) or as per institutional standards.

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 on or after the first dose of chemotherapy.

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.

Note: 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 receive appropriate reactivation prophylaxis with either valacyclovir or acyclovir.

Herpes prophylaxis should begin by Day 14 (Visit 16), or as the investigator deems appropriate and continue until the absolute lymphocyte count is > 1000/mm^3 (typically for at least 6 months) or as per institutional practice.

Note: 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 absolute neutrophil count is >1000/mm^3, or another suitable fungal prophylaxis regimen as per standard of care at the treating institution.

8.1.2. Hemorrhagic Cystitis Prophylaxis

Patients will receive mesna to prevent cyclophosphamide-associated hemorrhagic cystitis in addition to intravenous fluids. Please refer to treatment guidelines for recommended mesna dosing. Alternative dosing regimens of mesna are allowed per institutional standards and investigator discretion.

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 will 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.

8.1.4. Filgrastim

Patients will receive filgrastim 5 mcg/kg/day (recommended maximum dose of 300 mcg/day or 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.

8.1.5. 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

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

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

8.2. LN-145 Toxicity Management

Infusion of LN-145 must occur before the expiration time (recommended within 24 hours, but no later than 48 hours of manufacture). 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) (55) 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.

8.3. Interleukin-2 Toxicity Management

Interleukin-2 (Proleukin, aldesleukin) can affect nearly every organ system, but essentially every abnormality will most often normalize following discontinuation of IL-2 dosing. Please see Appendix 17.5 for suggested management guidelines for the treatment of expected toxicities of IL-2 administration.

8.3.1. Neurologic Toxicity

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

8.3.2. Renal Toxicity

Renal toxicity defined by rapid rise in creatinine levels or clinical symptoms is a risk that is commonly observed (1.5 to 2.0 for mild elevation, or greater than 3.0 for marked elevation). If patients exhibit signs or symptoms of renal toxicity, manage as per institutional standard of care (and may include low-dose dopamine to improve perfusion or continuous veno-venous

hemofiltration). Hemodialysis should be reserved for life-threatening renal failure such as prolonged anuria, hyperkalemia, and profound uremia.

8.3.3. Capillary Leak Syndrome and Weight Gain

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

8.3.4. Cardiac Arrhythmias and Myocarditis

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

8.3.5. Pulmonary

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

8.3.6. Sepsis/Febrile Neutropenia During IL-2

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

8.3.7. Heparin-Induced Thrombocytopenia

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

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

8.4. Concomitant Medications to Control Side Effects

Nausea/vomiting

Nausea and vomiting should be controlled with ondansetron or similar medication. Other second and third line medications (eg, prochlorperazine, promethazine, lorazepam, scopolamine, and aprepitant) can be used per institutional guidelines. Steroids should NOT be used as an antiemetic at any time.

Fever

Premedication for fever should be initiated as per institutional standards. Recommend initiating nonsteroidal anti-inflammatory medication 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. 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. 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 (after testing for infectious etiologies such as *Clostridium difficile*).

9. COMPLETION/WITHDRAWAL OF PATIENTS

9.1. Treatment Completion

Patients will be considered to have completed treatment if they complete the tumor harvest, receive the NMA-LD regimen, LN-145 infusion, and at least 1 dose of IL-2.

9.2. Study Completion

The study is expected to be completed approximately 1 year after the last patient completes the efficacy follow-up (3 years from last patient's 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 Early Termination visit (ETV). ETV is not required if the same procedures are done within 2 weeks from the previous visit (see Appendix 17.1). Appropriate reasons of the discontinuation must be documented in the patient's source documentation and eCRF page.

A patient may 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
- 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 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 undergo efficacy assessments and continued safety monitoring.

The patient may 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
- 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 ETV as appropriate. All AEs attributable to the investigational product may be followed until resolution or permanent sequalae. The final outcome of unrelated AEs ongoing at the time of the ETV will be captured as "Not Recovered/Not Resolved."

9.4.2. 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. Disease progression occurring during OS Follow-up will only be assessed if the patient did not progress during the Efficacy Follow-up. Quarterly follow-up 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 trial 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:

- Full 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. The study may be terminated at a study site if the investigator does not adhere to the protocol.

10. TUMOR RESPONSE ASSESSMENTS

10.1. Response Criteria

Response assessment will be based on investigator evaluation per RECIST v1.1 with a modification to require confirmation of progressive disease (PD). Refer to Table 1 and Table 2 for RECIST v1.1 response criteria definitions (77).

10.1.1. Baseline Documentation of Target and NonTarget Lesions

Baseline documentation of all lesions will occur with scans occurring at the baseline visit (Day -21). Measurable disease is defined as the presence of at least 1 measurable lesion of ≥ 10 mm in long diameter of nonnodal lesions or ≥ 15 mm in short diameter for lymph node lesions by CT scan. 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.

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.

The sum of the longest diameters (SLD) 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 SLD. The baseline SLD 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 followed as present, absent, or in rare cases 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 SLD of target lesions taking as reference the baseline SLD.

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. (Note: 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. (Note: 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 less than 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 greater than 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 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	CR
SD	SD	PR	PR
SD	PR	SD	PR
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 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 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 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 or clinical trial subject administered a medicinal/investigational product 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, EKGs, radiological scans, vital signs measurements), that worsen from baseline, and are felt to be clinically significant in the medical and scientific judgment of the investigator
- 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: such events 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.

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 (see Section 17.4). 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.

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 Day 672 (Visit 25/Month 24) study visit. AEs that occur after the treatment and follow-up period 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 cause of death should be recorded in details on the SAE Report Form. Disease progression itself is not an AE, but the clinical signs or symptoms leading to death should be reported as an SAE with an outcome of death.

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 post-treatment 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.

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 Month 24 of the study. If the Investigator learns of any SAEs that occur after the follow-up period and there is a reasonable possibility that the event may have been caused by the study treatment, then the SAE should be promptly reported to the Sponsor or designated Safety 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.

SAE terminology and severity grading will be based on the NCI CTCAE Version 4.03 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
SynteractHCR	**E-mail: SafetyFax@SynteractHCR.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, subject, 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 subject 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 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 Iovance 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 trials or any other source based on relevant local legislation or regulations, including the applicable US FDA Code of Federal Regulations and the EU Clinical Trial Directive (2001-20/EC) and relevant updates. The sponsor will notify participating sites of relevant SUSAR reports and other applicable serious safety findings which occur during the trial 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 complete Week 4 (Day 28). An additional evaluation will be completed when the first 15 patients complete Week 4 (Day 28). A limited analysis may also be conducted reviewing all data available from these patients as specified in the DSMB charter. Enrollment will continue while under review. Additional roles, responsibilities, and conduct are described in an independent charter.

12.2. Considerations

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

In particular, the expected toxicities of the NMA-LD pre-treatment regimen and IL-2 administration will be closely monitored.

Serum chemistry parameters include the following:

- Sodium
- Potassium
- Chloride
- Total CO2, or bicarbonate
- Creatinine
- Glucose
- Bun
- Albumin
- Calcium
- Magnesium
- Phosphorus
- Alkaline phosphatase
- ALT
- AST
- Bilirubin (total and direct)

- Lactate dehydrogenase
- Total protein
- Creatine kinase
- Uric acid
- Thyroid panel (including TSH and free T4)

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. Analysis Populations

Three analysis populations will be defined to summarize the data. The tumor harvested (TH) population will consist of all patients with resection of tumor for production of TIL. The TH population is further divided into the following analysis populations:

13.2.1. Efficacy Population

Primary: All-treated population that consists of patients in the safety population who have been successfully treated with NMA-LD regimen, any amount of LN-145 followed by IL-2 (at least 1 dose).

Secondary: Efficacy-evaluable population consists of patients in the all-treated population with an adequate baseline and at least one postbaseline radiological assessments by investigators. Patients who are clinically/unequivocally progressed or expired prior to reaching the first radiological assessment will be included.

13.2.2. Safety Population

Primary: Safety population consists of patients in the TH population who have tumor harvested successfully and received at least 1 component of the study treatment; cyclophosphamide, fludarabine, any amount of LN-145 or IL-2.

Secondary: Nontreated population consists of patients who are in the TH population but not a part of the primary safety population.

13.3. Sample Size Justification

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.

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 among the all-treated population. Objective response will be evaluated per each disease assessment and the ORR will be calculated with the corresponding 95% two-sided confidence interval (CI).

13.5.2. Secondary Endpoints

13.5.2.1. Safety

The primary safety data will be descriptive and based on the summarization of TEAEs including SAEs and AEs leading to discontinuation from the study treatment. [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

- CR rate is based on responders who achieved confirmed CR as assessed by investigators.
- 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 6 weeks) divided by the number of patients in the all-treated population × 100%.
- PFS is defined as the time (in months) [redacted] to PD, or death due to any cause, whichever event is earlier. Patients not experiencing PD or not having expired 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 [redacted] due to any cause. Patients not having expired 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 will be subjected to right censoring. Kaplan-Meier methods will apply.

13.5.3. Exploratory Analyses

- Correlations of immune factors with efficacy and safety of the TIL therapy and HPV status of the tumor will be explored. The results will be reported in a separate report.
- Evaluation of ORR, DOR, DCR, and PFS as assessed per irRECIST by independent review.
- 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) (76) with each multiplied by the appropriate utility score (78).

13.5.3.1. Stage I Analysis

- The Stage 1 analysis will occur when the fifteenth treated patient has an opportunity to reach the second tumor assessment (Day 56 assessment). The study will move forward to Stage 2 with 2 or more confirmed response as assessed by 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 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 Trial 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/GCP guidelines, the investigator/institution will be responsible for all information in the eCRF and will maintain the source documents that support the data collected from each patient, and all trial documents as specified in Essential Documents for the Conduct of a Clinical Trial and as specified by the applicable regulatory requirement(s). The investigator/institution will take measures to prevent accidental or premature destruction of these documents. Essential documents must be retained until at least 2 years after the last approval of a marketing application in an ICH region or at least 2 years have elapsed since the formal discontinuation of clinical development of 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 trial 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 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, the clinical monitor will periodically inspect all eCRFs, study documents, research facilities, and clinical laboratory facilities associated with this study at mutually convenient times during and after completion of the study. As required by 21 CFR Part 312, Subpart D: Responsibilities of Sponsors and Investigators, the monitoring visits provide the sponsor with the opportunity to evaluate the progress of the study; verify the accuracy and completeness of eCRFs against source documentation; ensure that all protocol requirements, applicable to FDA regulations, and investigator’s obligations are being fulfilled; and resolve any inconsistencies in the study records. This includes inspection of all documents and records related to the study that are required to be maintained by the investigator, including

but not limited to medical records (office, clinic, or hospital) and investigational pharmacy records for the patients participating in this study. The names and identities of all research patients will be kept in strict confidence and will not appear on eCRFs or other records provided to or retained by the sponsor. The IND regulations also require the Investigator to allow authorized representatives of sponsor, the FDA or regulatory authorities to 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 GCP Guidelines), the protocol and informed consent form 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 trial 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 trial, 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 trial 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 trial, 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 subject or his or her legally designated representative to consider his or her decision to participate in the study.

In accordance with 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 trial 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 subinvestigator promptly bring AEs to the attention of the principle investigator. The investigator 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 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 Trial 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			
	Visit 1	Visit 2	Visit 3	Visit 4	Visit 5	Visits 6, 7, 8, 9, 10	Visit 11
Visit Name	**Screening Visit**	**Tumor Resection Visit**	**Day -21 to -14 (Baseline)**	**Day -7**	**Day -6**	**Days -5, -4, -3, -2, -1**	**Day 0 (LN-145 Infusion Visit)**
Visit window	**Up to 28 days**		**N/A**	**N/A**	**N/A**	**N/A**	**N/A**
Informed consent	X						
Inclusion/exclusion	X						
Demographic data	X						
Medical history	X						
Documentation of diagnosis	X						
Documentation of HPV status	X						
HRQoL Questionnaire[b]			X				
Physical examination[c]	X		X	X	X	X	X
Vital signs[d]	X	X	X	X	X	X	X[e]
ECOG performance status	X	X	X	X			X
Safety blood and urine tests[f]	X	X[g]	X	X	X	X	X
ß-HCG serum pregnancy test	X		X				
Infection testing[h]	X						
HLA typing[i]	X						
HPV serotype		X					
Serum creatinine[j]	X	X[g]	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				
Response assessments (RECIST v1.1)							
Concomitant medications	X	X	X	X	X	X	X
Adverse events[o]	X	X	X	X	X	X	X
Tumor harvest[p]		X					
NMA lymphodepletion[q]				X	X	X	
LN-145 infusion[r]							X
IL-2 600,000 IU/kg[s]							
PJP[t]							
Filgrastim[u]							
Fungal prophylaxis[v]							
Herpes virus prophylaxis[w]							
Immune monitoring & PBMC[x]		X[g]		X			

	Treatment Phase	Efficacy Follow-Up			
	Visits 12, 13, 14, 15	Visit 16	Visit 17	Visit 18	Visit 19
Visit Name	**Days 1, 2, 3, 4**	**Day 14**	**Day 28 (Week 4)**	**Day 56 (Week 8)**	**Day 84 (Week 12)**
Visit window	**N/A**	**(+/- 3 days)**	**(+/- 3 days)**	**(+/- 3 days)**	**(+/- 3 days)**
Informed consent					
Inclusion/exclusion					
Demographic data					
Medical history					
Documentation of diagnosis					
Documentation of HPV status					
HRQoL Questionnaire[b]					X
Physical examination[c]	X	X	X	X	X
Vital signs[d]	X	X	X	X	X
ECOG performance status			X	X	X
Safety blood and urine tests[f]	X	X	X	X	X
ß-HCG serum pregnancy test					
Infection testing[h]					
HLA typing[i]					
HPV serotype					
Serum creatinine[j]	X	X	X	X	X
Eye examination					
Cardiac evaluations[k]					
Pulmonary function tests[l]					
Colonoscopy[m]					
Tumor assessments (CT/MRI)[n]			X	X	X
Response assessments (RECIST v1.1)			X	X	X
Concomitant medications	X	X	X	X	X
Adverse events[o]	X	X	X	X	X
Tumor harvest[p]					
NMA lymphodepletion[q]					
LN-145 infusion[r]					
IL-2 600,000 IU/kg[s]	X				
PJP[t]		X	X	X	X
Filgrastim[u]	X				
Fungal prophylaxis[v]	X	X	X	X	X
Herpes virus prophylaxis[w]		X	X	X	X
Immune monitoring & PBMC[x]		X	X	X	X

	Efficacy Follow-up							Overall Survival Follow-up (Quarterly Contact)
	Visit 20	Visit 21	Visit 22	Visit 23	Visit 24	Visit 25		
Visit Name	Day 126 (Month 4.5/Wk 18)	Day 168 (Month 6)	Day 252 (Month 9)	Day 336 (Month 12)	Day 504 (Month 18)	Day 672 (Month 24)	ETV[a]	
Visit Window	(+/- 7 days)	(+/- 7 days)	(+/- 7 days)	(+/- 7 days)	(+/- 21 days)	(+/- 21 days)		(+/- 21 days)
Informed consent								
Inclusion/exclusion								
Demographic data								
Medical history								
Documentation of diagnosis								
Documentation of HPV status								
HRQoL Questionnaire[b]		X		X		X		
Physical examination[c]	X	X	X	X	X	X	X	
Vital signs[d]	X	X	X	X			X	
ECOG performance status	X	X	X	X	X	X	X	
Safety blood and urine tests[f]	X	X					X	
ß-HCG serum pregnancy test								
Infection testing[h]								
HLA typing[i]								
HPV serotype								
Serum creatinine[j]	X	X					X	
Eye examination								
Cardiac evaluations[k]								
Pulmonary function tests[l]								
Colonoscopy[m]								
Tumor assessments (CT/MRI scans)[n]	X	X	X	X	X	X	X	
Response assessments (RECIST v1.1)	X	X	X	X	X	X	X	
Concomitant medications	X	X					X	
Adverse events[o]	X	X					X	
Tumor harvest[p]								
NMA lymphodepletion[q]								
LN-145 infusion[r]								
IL-2 600,000 IU/kg[s]								
PJP[t]	X[t]	X[t]						
Filgrastim[u]								
Fungal prophylaxis[v]								
Herpes virus prophylaxis[w]	X[w]	X[w]						
Immune monitoring & PBMC[x]		X	X	X			X	
Survival follow-up [y]								X

ß-HCG = beta human chorionic gonadotropin; CT = computed tomography; ECOG = Eastern Cooperative Oncology Group; ETV = Early Termination 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 ETV is completed if discontinuation prior to/from the study treatment or post-treatment follow-up occurs at any time after Visit 2 and before Visit 25.

b HRQoL Questionnaire is to be performed as the first procedure at baseline Day -21 (Visit 3) and be performed as the first procedure on Day 84 (Visit 19/Week 12), Day 168 (Visit 21/Month 6), Day 336 (Visit 23/Month 12), and Day 672 (Visit 25/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, psychiatric (mental status), general nutrition. Physical examinations conducted during follow-up will be symptom directed. See Section 5.10.

d Vital signs will include height, 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. 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 Chemistry: sodium, potassium, chloride, total CO_2, or bicarbonate, creatinine, glucose, BUN, albumin, calcium, magnesium, phosphorus, alkaline phosphatase, ALT, AST, total bilirubin, direct bilirubin, lactate dehydrogenase, total protein, total creatine kinase, uric acid. Thyroid panel (to include TSH and Free T4) is to be done at Visits 1 and 19 or as clinically indicated. See Section 5.13.
Hematology: CBC with differential.
Urinalysis Dipstick: A complete urine culture shall be conducted if indicated.
Coagulation: Measurement of prothrombin time (PT)/international normalized ratio (INR), and partial thromboplastin time (PTT)/activated PTT will be performed at screening only and analyzed locally.

g Laboratory samples may be collected within 2 days prior to the tumor resection visit.

h HIV antibody titer; Hepatitis - HBsAg determination and anti HCV; CMV serology (IgG and IgM), HSV serology determination (HSV-1 IgG and HSV-2 IgG); EBV viral capsid antigen (VCA) IgG 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 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 ECHO or MUGA and ECG, and 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 for all patients. 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 chest, abdomen, and pelvis, are required at the indicated time points. Baseline scans may occur between Day -21 (Visit 3) and Day -7 (Visit 4). 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 Any AEs occurred after screening, 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 25/Month 24). See Section 11.

p See Section 5.25 for tumor harvest for TIL manufacturing and additional tumor tissue to central laboratory.

q 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.

r 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.

s Initiate IL-2 at 600,000 IU/kg within approximately 3 to 24 hours after LN-145 infusion and continue every 8 to 12 hours for up to 6 doses. See Section 6.3.

t 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.

u Filgrastim 5 µg/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.
v Fungal prophylaxis (fluconazole 400 mg by mouth daily) should be administered each day starting from Day 1 (Visit 12) until the absolute neutrophil count is > 1000/mm^3 or as per the institutional standard. See Section 8.1.1.3.
w 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 absolute lymphocyte count is > 1000/mm^3. See Section 8.1.1.2. Patients with positive HSV serology will be given valacyclovir or acyclovir for prophylaxis.
x Blood draw for immune monitoring is to be collected at tumor resection (Visit 2), Day -7 (Visit 4), 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 ETV. Blood draw for PBMC analysis is only to be collected at tumor resection (Visit 2). See Section 5.23 and the Laboratory Manual.
y 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. 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 MM, Creech RH, Tormey DC, et al. Toxicity and Response Criteria of The Eastern Cooperative Oncology Group. Am J Clin Oncol. 1982;5:649-655.

17.3. Calculation of BMI, BSA and Practical Weight

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

17.3.1. BMI

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

17.3.2. BSA

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

17.3.3. Practical Weight

Practical body weight (average of the actual weight and ideal body weight) is to be used when dosing cyclophosphamide and fludarabine in patients who have a BMI > 35.0 kg/m^2.

Note: Practical weight will NOT be used in the calculation of dose for IL-2.

17.3.4. Ideal Body Weight

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

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

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
Pruritis	3	Hydroxyzine HCL 10-20 mg po q6h, prn; Diphenhydramine HCL25-50 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

Expected Toxicity	Expected Grade	Supportive Measures	Stop Treatment*
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
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.