CLINICAL PROTOCOL

A Phase 2 Study to Evaluate the Safety, Tolerability and Efficacy of Cell Transfer Therapy Using Autologous Tumor Infiltrating Lymphocytes (LN-145) followed by IL-2 in Patients with Recurrent and/or Metastatic Squamous Cell Carcinoma of the Head and Neck

PROTOCOL NUMBER:	C-145-03
SPONSOR:	Lion Biotechnologies, Inc. 112 West 34th Street, 17th Floor New York, NY 10120
ORIGINAL PROTOCOL VERSION / DATE:	Version 1.0; 16 August 2016
IND NUMBER:	[redacted]
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SPONSOR SIGNATURE PAGE

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Protocol Version and Date:	Version 1.0; 16 August 2016

[redacted] [redacted]

Signature **Date**

[redacted]

By my signature, I indicate I have reviewed this protocol and find its content to be acceptable.

INVESTIGATOR PROTOCOL SIGNATURE PAGE

Protocol Title:	A Phase 2 Study to Evaluate the Safety, Tolerability and Efficacy of Cell Transfer Therapy Using Autologous Tumor Infiltrating Lymphocytes (LN-145) followed by IL-2 in Patients with Recurrent and/or Metastatic Squamous Cell Carcinoma of the Head and Neck
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I agree to conduct the study as detailed in the protocol and in compliance with ICH Guidelines for Good Clinical Practice.

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

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

_____ _____

Principal Investigator Signature Date

_____

Principal Investigator Printed Name

_____

Institution

PROTOCOL SYNOPSIS

Protocol Title	A Phase 2 Study to Evaluate the Safety, Tolerability and Efficacy of Cell Transfer Therapy Using Autologous Tumor Infiltrating Lymphocytes (LN-145) followed by IL-2 in 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 recurrent and/or Metastatic Squamous Cell Carcinoma of the Head and Neck (HNSCC)
Investigational Agents	• Non-Myeloablative (NMA) lymphodepletion (Cyclophosphamide and Fludarabine) • LN-145: autologous tumor infiltrating lymphocytes (TILs) derived from the patient's own tumor • Interleukin-2
Study Objectives	**Primary Objectives** • To evaluate the safety and tolerability of lymphodepletion, LN-145, and IL-2 in patients with recurrent and/or metastatic HNSCC. • To evaluate the efficacy of therapy using the overall response rate (ORR) in patients with recurrent and/or metastatic HNSCC. **Secondary Objectives** • To evaluate other efficacy parameters such as complete response (CR) rate, the duration of response (DOR), progression-free survival (PFS), and overall survival (OS) in patients with recurrent and/or metastatic HNSCC. **Exploratory Objectives** • To explore persistence of TILs and immune correlates of response, survival, toxicity of the treatment.
Number of Study Sites	Approximately 20 clinical study sites globally.
Number of Planned Patients	Forty-seven (47) patients completing treatment. Complete treatment is defined as successful infusion with non-myeloablative lymphodepletion, followed by LN-145, then at least one dose of IL-2.

Duration of Participation	The study will consist of 3 phases:
	• Pre-Treatment Phase (approximately 50 days)
	  ○ Screening Visit (~28 days)
	  ○ Tumor Resection Visit (1 day)

	○ LN-145 Pre-Manufacturing period (~21 days) • Treatment Phase (approximately 92 days) ○ NMA lymphodepletion regimen (7 days) ○ LN-145 Infusion (1 day) ○ IL-2 Infusion (~4 days) and other required concomitant therapies (~80 days) • Long Term Follow Up Phase (approximately 588 days) ○ Safety and Efficacy evaluations up to Year 2
Study Design	This is a Phase 2, multicenter prospective, open label, interventional study evaluating adoptive cell therapy (ACT) with autologous TIL infusion (LN-145) followed by IL-2 after a non-myeloablative (NMA) lymphodepletion preparative regimen.
Doses and Treatment Schedule	NMA Lymphodepletion Regimen – Visits 4 through 10 (Days -7 through -1) Cyclophosphamide 60 mg/kg IV with Mesna 15 mg/kg (see Section 5.27.1 for drug preparation instructions) infused over 2 hours at Visit 4 (Day -7) and Visit 5 (Day -6). A Mesna infusion will continue at a rate of 3 mg/kg/hour over 22 hours after each cyclophosphamide dose. • Fludarabine 25 mg/ m^2 to be given IV over approximately 30 minutes once daily for 5 days on Visits 6 through 10 (Days -5 through -1). ○ Note: If the patient's BMI > 30.0 kg/m^2, dosages for cyclophosphamide and fludarabine will be calculated using practical weight (see Section 16.3 for determination of practical weight). • Further supportive treatment to prevent infection during neutropenia Autologous TILs (LN-145) – Visit 11 (Day 0) • LN-145 up to [redacted] High-dose IL-2– Visits 12 through 15 (Days 1 through 4) • IL-2 600,000 IU/kg starting approximately 12 to 24 hours after TIL infusion and repeated every 8 to 12 hours (as tolerated) for up to 6 doses during Visits 12 through 15 (Days 1 through 4) only.
Inclusion Criteria	To be eligible for the study, Patients must meet ALL of the following criteria prior to enrollment in the study: 1. Must be greater than 18 and less than 65 years of age at the time of consent. • Patients greater than or equal to 65 years of age may be allowed in the study after discussion between the Principal Investigator and Medical Monitor regarding the patient's ability to tolerate the study treatment regimen. 2. Must understand and voluntarily sign an informed consent document prior to any study related assessments/procedures being conducted.

	3. Able to adhere to the study visit schedule and other protocol requirements. 4. Must have persistent, recurrent or metastatic squamous cell carcinoma, histologic documentation of the primary tumor is required via the pathology report. Requirements regarding the lesion are as follows: • CT scans of the head, neck and chest (scans of additional anatomical locations with suspected disease may be done as determined by the PI) is required and may have been done within 28 days prior to screening. • Patients must have one lesion that is resectable for TIL manufacturing. The ideal resected lesion should be least 1.5 cm in diameter and no greater than 4.0 cm in diameter after prosection. The resection must entail minimal morbidity (as determined by the study PI and surgical team). 5. Must have a remaining measurable target lesion as defined by RECIST version 1.1 following the surgical resection. • Measurable lesions must not have been in a previously irradiated field. 6. Must have had at least 1 prior systemic chemotherapeutic regimen for management of persistent, recurrent or metastatic carcinoma of the head or neck. Patients must not have any curative therapy options, or be intolerant of, or decline standard of care therapy for persistent, recurrent or metastatic disease. 7. Any prior therapy directed at the malignant tumor, including radiation therapy, chemotherapy, biologic/targeted agents and immunologic agents must be discontinued at least 21 days prior to tumor resection for preparing TIL therapy. 8. Have an Eastern Cooperative Oncology Group (ECOG) performance status of 0 or 1. 9. Must meet the following laboratory criteria: • Absolute neutrophil count (ANC) > 1000/mm^3 • Hemoglobin > 8.0 g/dL • Platelet count > 80,000/mm^3 • ALT/SGPT and AST/SGOT < 3.0 x the upper limit of normal (ULN) ○ Patients with liver metastases may have LFT ≤ 3.0 x ULN) • Calculated creatinine clearance ≥ 50.0 mL/min • Total bilirubin ≤ 2.0 mg/dL ○ Patients with Gilbert's Syndrome must have a total bilirubin < 3.0 mg/dL. 10. Patients must be seronegative for the HIV antibody, hepatitis B antigen,

	and hepatitis C antibody or antigen. • Note: Patients with a positive test for hepatitis B virus surface antigen (HBsAg) or hepatitis C virus ribonucleic acid (HCV antibody) indicating acute or chronic infection may be enrolled if the viral load by PCR is undetectable with/without active treatment. 11. Patients must be EBV viral capsid antigen (VCA) IgG positive and/or Epstein Barr nuclear antigen (EBNA) IgG positive, and have no clinical evidence of active EBV infection. 12. 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 lymphodepletion regimen. Patients who are of child bearing potential must agree to practice an approved method of birth control from the start of the study until one year after the completion of all study treatment regimens. Approved methods of birth control are as follows: • Total abstinence • Hormonal contraception (i.e. birth control pills, injection, implant, transdermal patch, vaginal ring) • Intrauterine device (IUD) • Tubal Ligation • Male partner's vasectomy • Implantable or injectable contraceptives • Use of a male or female condom • Cervical Cap or contraceptive sponge with spermicide
Exclusion Criteria	Patients who meet ANY of the following criteria will be excluded from the study: 1. Patients who are on a systemic steroid therapy (greater than 10 mg of prednisone or equivalent) within 28 days prior to Visit 2. 2. Patients who currently have prior therapy-related toxicities greater than Grade 1 according to Common Toxicity Criteria for Adverse Events (CTCAE) v4.03; (see Appendix Section 16.4), except for alopecia or vitiligo prior to enrollment. • Note: Patients may have undergone minor surgical procedures not involving general anesthesia within three weeks prior to Visit 2 as long as all toxicities have recovered to Grade 1 or less or as specified in the eligibility criteria. 3. Patients who have had immunotherapy-attributable AE: • Which led to discontinuation, or • Have had an ophthalmologic or neurologic AE of any grade, or • Actively receiving any immunosuppressive agents for the treatment

	of toxicity related to prior immunotherapy. 4. Patients with documented Grade 2 or greater diarrhea or colitis as a result of previous immunotherapy within six months from screening. • Note: Patients that have a colonoscopy that demonstrates the visual appearance of the absence of inflammation are not excluded. 5. History of severe immediate hypersensitivity reaction to cyclophosphamide, fludarabine, or IL-2. 6. Patients with active systemic infections, coagulation disorders or other active major medical illnesses of the cardiovascular, respiratory or immune system. 7. Have any form of primary immunodeficiency, such as severe combined immunodeficiency disease or acquired immune deficiency syndrome (AIDS). 8. Diagnosis of end-stage renal disorder requiring hemodialysis. 9. Patients who have a left ventricular ejection fraction (LVEF) < 45%. 10. Patients who have a FEV1 (forced expiratory volume in one second) of less than or equal to 60 % of normal. 11. Patients with unresolved uveitits. 12. Have had another primary malignancy within the previous 3 years (with the exception of a history of 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	Response will be determined according to RECIST criteria version 1.1. A descriptive summary of the overall response rate (ORR), time to response, and progression-free survival (PFS) will be used to determine the potential efficacy of LN-145.
Safety Assessment	Treatment-emergent adverse events (TEAEs), clinical laboratory data assessment, and serious adverse events (SAEs) will be evaluated for the duration of the study.

Overview of Statistical Plan	The sample size is based on number of patients who receive NMA lymphodepletion, LN-145 therapy and at least 1 dose of IL-2. The Simon's two-stage optimal design with one-sided alpha level=0.025 and 80% power is adopted for comparing an ORR of 5% versus 20%. In this study, 15 patients would be treated at the first stage and if 1 or fewer patients respond, the study will terminate. Otherwise the study will expand to a total of 47 patients in Stage 2. The study would demonstrate that lymphodepletion + LN-145 + IL2 is clinically meaningful if 6 or more patients respond in Stages 1 and 2. The assessment of safety data will be based on the summarization of treatment-emergent adverse events (AEs) including, serious AE, AEs leading to discontinuation from the study, and clinical laboratory tests. The primary efficacy endpoint (ORR) and the secondary endpoint of CR as a best overall response (%) will be reported including a 95% confidence interval. The secondary efficacy endpoints (DOR, PFS, and OS) will be summarized by Kaplan-Meier analyses with estimated means, medians and ranges reported in months.
DSMB Safety Assessments	The DSMB will evaluate safety data when 3 patients have completed the Treatment Phase. Enrollment shall not be halted and will continue while under review. Additional evaluations will be specified in the charter.
Discontinuation of Treatment	The Investigator will document on the appropriate eCRF page the reasons/circumstances for discontinuation. A patient may be removed from further study drug administration for the following medical or administrative reasons: • Withdrawal of consent. • 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. • Pregnancy • Lost to Follow-up

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LIST OF ABBREVIATIONS

Term	Definition
ACT	Adoptive Cell Therapy
AE	Adverse event
ALT	Alanine transaminase
ANC	Absolute neutrophil count
AST	Aspartate transaminase
CBC	Complete blood count
CFR	Code of Federal Regulations
CMV	Cytomegalovirus
CNS	Central nervous system
CR	Complete response
CRO	Contract Research Organization
CT	Computed tomography
CTCAE v4.03	Common Terminology Criteria for Adverse Events Version 4.03
ECHO	Echocardiogram
ECOG	Eastern Cooperative Oncology Group
eCrCl	Estimated creatinine clearance
eCRF	Electronic case report form
EDC	Electronic data capture
EKG	Electrocardiogram
EOS	End of Study
FDA	Food and Drug Administration
FEV1	Forced Expiratory Volume in the first second
GCP	Good Clinical Practice
HIPAA	Health Insurance Portability and Accountability Act of 1996
HNSCC	Squamous Cell Carcinoma of the Head and Neck
ICH	International Conference on Harmonization
IL-2	Interleukin-2 (aldesleukin)
IRB	Institutional Review Board
IV	Intravenous
LVEF	Left ventricular ejection fraction
MRI	Magnetic resonance imaging
MUGA	Multiple gated acquisition scan
NCI	National Cancer Institute
NMA	Non-myeloablative
NE	Not evaluable
ORR	Overall response rate
OS	Overall survival
PBMC	Peripheral Blood Mononuclear Cells
PD	Progressive disease
PFS	Progression-free survival
PI	Principal Investigator
PO	Per Os (by mouth)
PR	Partial response

Term	Definition
Pre-REP	Expansion of TILs from tumor fragments prior to REP
QD	(Taken) once daily
RECIST	Response Evaluation Criteria in Solid Tumors
REP	Rapid Expansion Protocol
SAE	Serious adverse event
SD	Stable disease
TIL	Tumor Infiltrating Lymphocyte
Treg	Regulatory T cells
TSH	Thyroid stimulating hormone
ULN	Upper limit normal

1. INTRODUCTION

1.1. Head and Neck Cancer

Squamous cell cancers of the head and neck cancer (HNSCC) comprise malignancies of the nasal cavity, paranasal sinuses, nasopharnyx, oral cavity, oropharynx, hyopopharynx, larynx, salivary glands, and head and neck paraganglial tissues (1). The majority of these tumors occur in older individuals who have a history or smoking or high alcohol use (more than 4 drinks per day), and are more frequent in men than in women (2, 3). The HNSCC subset of oropharyngeal cancer (OPC) appears to be a distinct disease, with different risk associations than other HNSCC (4). OPC prevalence among HNSCC has increased worldwide over the last two decades; in the US, the rate increased from 18% of all HNSCC in 1973 to 31% in 2004 (5). HPV-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 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). While HPV vaccines approved for marketing over the last decade can prevent the development of precancerous cervical lesions (15), the effect of HPV vaccine on oral lesions or OPC is unknown and the HPV vaccines now is use were not available for the majority of current subjects with OPC.

The current standard treatment for HNSCC typically involves combinations of surgery, radiation, and chemotherapy, typically with cisplatin (16). Surgery can be minimally invasive in order to preserve organ function. Radiation with hyperfractionation and accelerated fractionation has been found to improve survival (17), but has been associated with swallowing dysfunction (18). Five-year survival has significantly increased for all sites over the past 20 years from 54.7% in 1992 to 1996, to 65.9% in 2002 to 2006 (19). By site, estimated 5-year survival rates remain ≤ 63% for all sites other than the tongue or lip (20). Notably, outcome for subjects with HPV-positive tumors is better than outcome for HPV-negative HNSCC [(6, 21, 22), with reported 2- and 3-year survival rates of approximately 95% and 80%, respectively (6, 21). The improved outcome of subjects harboring HPV-positive tumors may be a result of enhanced activity of TILs at the tumor site (17).

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 (23) 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 (24) Recurrence is higher in HPV-negative than in HPV-positive OPC (3-year recurrence rates of 65.1% vs. 13.6%; P<.001). Additionally, the 3-year rates of second primary malignancy were 14.6% vs. 5.9% (P =.02) in these groups (6).

Outcome for recurrent HNSCC is poor across a variety of therapeutic modalities (25-27), although Strnad et al (28) 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 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<.001) (29).

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 transfer of tumor infiltrating lymphocytes represents a potentially effective treatment for patients with a variety of solid tumors. The method involves the recovery and *ex vivo* expansion of autologous antitumor lymphocytes that have infiltrated a patient's tumor. The basic concept of using lymphoid cells for the immunotherapy of cancer arose from animal experiments that demonstrated, by histologic analysis, the presence of T-lymphocytes within the microenvironment of most solid tumors and their metastases (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 overall survival (OS) and progression-free survival (PFS) in patients with melanoma (15-18), lung cancer (19-22), ovarian cancer (23-25), squamous cell cancers (26, 27), triple-negative breast cancer and basal-like breast cancer (28-35), and colorectal cancer (36-39). Notably, one study found that an increased $Foxp3^+$ Treg/$CD8^+$ ratio and the presence of intra-tumoral high $Foxp3^+$ Tregs predicted worse overall survival (40). In addition, gene expression studies using DNA microarrays have indirectly correlated so-called "immune signature" genes and T-cell associated gene expression (e.g., CD3, CD8, CD4, inducible costimulator (ICOS), granzyme B (GRZB), DC-LAMP and chemokine and chemokine receptors) with improved OS and PFS in both primary and metastatic tumor settings (18, 36, 37, 41-43). 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 to proceed to very high cell numbers in the absence of suppressive factors, such as Treg, that are present in the tumor microenvironment (44-46); allowing re-infusion of much higher numbers of tumor-reactive T-cells than is possible with other approaches. Second, the TIL product potentially recognizes a

wider array of tumor antigens, such as mutated tumor neoantigens (47-50). Preparation of the host patient with lymphodepletion immediately prior to the transfer of the antitumor cells also eliminates potentially suppressive influences (such as regulatory T cells 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 showed that metastatic melanoma tumor 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 when small cut tumor fragments are placed in culture. TIL can be cultured in the presence of IL-2 and can be grown to very large numbers using standardized protocols (≥ 1 x 10^8 cells) (12, 14, 53, 54). 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, 53, 54). Further studies established that the efficacy of infusions of large numbers of TIL was enhanced by treating the tumor-bearing animal with cyclophosphamide to induce a non-toxic transient drop in endogenous lymphocytes in the host and IL-2. With this combination, mice could be cured of advanced hepatic metastases (12). These findings set the stage for NCI clinical trials of TIL in patients with metastatic melanoma using a non-myeloablative (NMA) consisting of fludarabine and cyclophosphamide preconditioning regimen before TIL infusion, combined with high-dose IL-2 following TIL Infusion. Such studies have consistently demonstrated high objective response rates (ORR), from 49% to 72%, with long-term durable and potentially curative CR rates of up to 25%.

1.3. TILs 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 subjects with recurrent disease following standard combinations of surgery and adjuvant chemotherapy, radiation therapy. Further, as was described above for other solid tumors, a positive correlation between the presence of TIL in HNSCC tumor specimens and subject outcome has been reported by a number of 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 (DMFS), but not local failure-free survival (LFFS) in multivariate analysis (45). Similarly, low CD8+ T-cell infiltration in the tumors of patients with laryngeal SCC was correlated with decreased survival (84). TIL has shown prognostic value in both human papilloma virus (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 (85), whereas, Wansom et al (86) and Ward et al. (87) found that higher numbers of CD8+ cells in tumors were positively correlated survival in patients with HPV-positive HNSCC or HPV-positive oropharyngeal cancer (OPC). An additional report by Wansom et al found that among patients with advanced OPC, CD8+ cells, as well as Treg cells (FoxP3) and total T-cell number all were positively correlated with OS and DFS,

independently of the tumor's HPV status (88). 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 (89) demonstrated the successful expansion of TIL bulk cultures were expanded in 12/15 (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 were able to kill HLA-A-matched tumor cell lines. Additional characterization showed that the TIL expanded from an HNSCC were phenotypically similar to those from melanomas, ie. CD3+/CD8+ and were similar before and after rapid expansion (90). Moudgil et al (91) reported a success rate of 50% for generation of TIL (33 of 63 cultures initiated). Of 22 tested TIL, 20 secreted IFN-gamma in response to co-culture 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 (92).

To date, a single report has described use of TIL for treatment of a subject with HNSCC. In this report, Leidner et al (93) infused autologous TIL in conjunction with DC-targeted microvessicle DPV-001 intradermal vaccine (Dribbles) to a heavily pretreated 22-year-old subject with recalcitrant HNSCC of the lateral tongue. Prior to TIL therapy, the subject had under gone partial glossectomy followed within 12 weeks by adjuvant intensity modulated radiation therapy at 60 Gy in the ipsilateral neck and 54 Gy in the contralateral neck. Bilateral recurrence in the neck was observed at month 6. During months 7 to 10, the subject received two multi-drug regimens (cisplatin/cetuximab/5FU, carboplatin/ docetaxel), but progressed locally in the neck. The subject was then enrolled on a Phase Ib trial of combination anti-PD-1/anti-KIR (BMS CA223-001, Nivolumab/Lirilumab) during months 11 to 14, but again progressed locally in the neck. At month 15, under an individual subject compassionate treatment protocol, the subject underwent a reduced-intensity lymphodepletion regimen followed by adoptive transfer of expanded autologous TIL in conjunction with Dribbles and imiquimod adjuvant, with high-dose IL-2 support. The expanded TIL had demonstrated tumor-induced IFNγ production in culture. Analysis of peripheral blood showed evidence of lymphocyte recovery, in particular, increases in T-gamma-delta cells, suggesting that TIL had engrafted. Further, immunohistochemical analysis of tumor biopsy specimens showed a decrease in expression of PD-L1 in the tumor microenvironment. Despite evidence of TIL engraftment and some in vivo effects, the subject died at month 18.

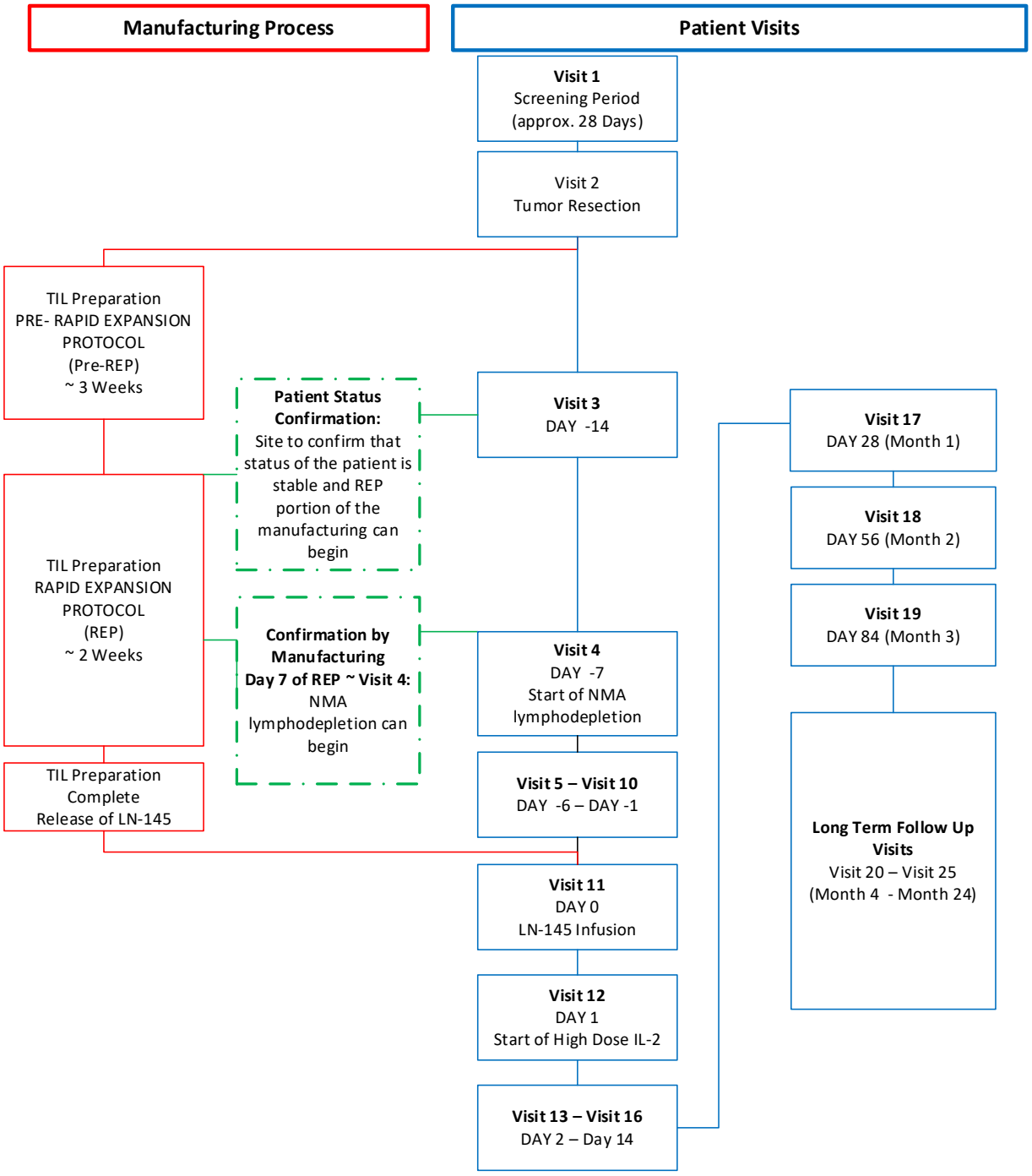
In summary, current methods for the expansion of autologous TIL from excised tumors are well-established and are robust enough to ensure a high degree of success in consistently generating sufficient numbers of high-quality therapeutic cells, as described above. Further, clinical studies in melanoma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

2. STUDY DESIGN

2.1. Overview

This is a prospective single-arm interventional study evaluating patients with HNSCC receive adoptive cell therapy (ACT) with LN-145 (autologous TIL). The TIL therapy to be used in this study is almost identical to that developed for melanoma-derived TIL by Dr. Steven Rosenberg and colleagues at the National Cancer Institute (NCI). Melanoma-derived TIL have demonstrated efficacy in the treatment of Stage IV melanoma, and Phase 2 clinical trials evaluating this product have shown an objective response rate of 49% or more (55-58), exceeding rates reported by other immunotherapies in metastatic melanoma.
Protocols for the tumor harvest and LN-145 administration for the current study are provided in separate operating manuals. TIL therapy comprises multiple interdependent phases: tumor resection for TIL harvest; *ex vivo* expansion of TIL; NMA lymphodepletion, infusion of TIL, and infusion of high-dose IL-2. A study flow chart is shown in **Figure 1.**

Figure 1. Study Flow Chart



2.2. Production and Expansion of Tumor Infiltrating Lymphocytes

Generating LN-145 involves resecting a tumor deposit [redacted] and culturing tumor fragments in media containing IL-2 to expand them *in vitro* **Figure 2.**

Appropriately expanded TIL cultures should reach several million cells (combined) in 2 to 3 weeks. In this trial, TIL cultures will be selected on the basis of better growth and a higher proportion of [redacted] TIL. TIL initially expanded from the tumor fragments then undergo a rapid expansion protocol (REP) using the [redacted] resulting in billions of cells for re-infusion into the patient.

Figure 2. LN-145 Manufacturing Process

TIL production requires approximately 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:

- Surgical removal of autologous metastatic tumor and shipment to the sponsor-designated manufacturing facility
- Initial TIL Culture (Pre-REP) of up to 3 weeks
- REP culture for 14 days

On Day 7 of the 2-week REP protocol, the number of TILs successfully expanded in the initial culture phase, will be determined. If the number of TILs is sufficient for administration, approval by the sponsor will be granted to start the cyclophosphamide/fludarabine lymphodepletion regimen at Visit 4 (Day -7).

2.3. Non-myeloablative (NMA) Lypmphodepletion, TIL and IL-2 Therapy

The lymphodepletion protocol used in the current study (2 days of cyclophosphamide plus mesna, followed by 5 days of fludarabine) is based on the method developed and tested by the NCI (55, 56, 58, 64, 65, 77) and is also the most often used. Patients then will receive up to [redacted] LN-145. The upper limit of the range for infusion [redacted] viable cells) is based on the

known published upper limit safely infused where a clinical response has been attained (64). TIL infusion will be followed by the administration of a regimen of high-dose IL-2 (600,000 IU/kg) every 8 hours starting approximately 12 to 24 hours after the completion of the LN-145 infusion and continuing for up to 6 doses. Patients will be evaluated for response using RECIST version 1.1 at Visits 17, 18 and 19 (Days 28, 56 and 84). Patients who experience stable disease (SD), a partial response (PR), or a complete response (CR), as defined by RECIST version 1.1 at Visit 19 (Day 84) will continue to be evaluated for response and survival will continue to the Long Term Follow Up Phase. Survival status follow-up will continue to the Long Term Follow Up Phase for all treated patients. 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 Objectives

- To evaluate the safety and tolerability of lymphodepletion, LN-145, and IL2 in patients with recurrent and/or metastatic HNSCC.
- To evaluate the efficacy of therapy using the overall response rate (ORR) in patients with recurrent and/or metastatic HNSCC.

3.1.2. Secondary Objective

- To evaluate efficacy parameters such as complete response (CR) rate, the duration of response (DOR), progression-free survival (PFS), and overall survival (OS) in patients with recurrent and/or metastatic HNSCC.

3.1.3. Exploratory Objectives

- To explore potential immune correlates of response, survival, toxicity of the treatment.

3.2. Study Endpoints

3.2.1. Primary Endpoints

- Incidence of treatment-emergent AEs (TEAEs), including SAEs, therapy-related AEs, AEs leading to early discontinuation of treatment or withdrawal from the study or death.
- Overall Response Rate (ORR)

3.2.2. Secondary Endpoints

- Complete Response (CR) rate
- Duration of Response (DOR)
- Progression-Free Survival (PFS)
- Overall Survival (OS)

3.2.3. Exploratory Endpoints

- Evaluation of immune correlates with respect to response, survival, toxicity of the treatment, and HPV status of the tumor.

4. SELECTION OF PATIENT POPULATION

Patients greater than 18 years of age, with a diagnosis of metastatic or recurrent HNSCC who have undergone at least one prior immunotherapy or chemotherapy regimen will be selected for this study.
Details concerning specific benefits and risks for patients participating in this clinical trial may be found in the accompanying Investigator's Brochure and Informed Consent documents.

4.1. Inclusion Criteria

To be eligible for the study, Patients must meet ALL of the following criteria prior to enrollment in the study:

1. Must be greater than 18 and less than 65 years of age at the time of consent.
    - Patients greater than or equal to 65 years of age may be allowed in the study after discussion between the Principal Investigator and Medical Monitor regarding the patient's ability to tolerate the study treatment regimen.
2. Must understand and voluntarily sign an informed consent document prior to any study related assessments/procedures being conducted.
3. Able to adhere to the study visit schedule and other protocol requirements.
4. Must have persistent, recurrent or metastatic HNSCC; histologic documentation of the primary tumor is required via the pathology report. Requirements regarding the lesion are as follows:
    - CT scans of the head, neck and chest (scans of additional anatomical locations with suspected disease may be done as determined by the PI) is required and may have been done within 28 days prior to screening.
    - Patients must have one lesion that is resectable for TIL manufacturing. The ideal resected lesion should be least 1.5 cm in diameter and no greater than 4.0 cm in diameter after prosection. The resection must entail minimal morbidity (as determined by the study PI and surgical team).
5. Must have a remaining measurable target lesion outside the irradiated field as defined by RECIST version 1.1 following the surgical resection.
    - Measurable lesions must not have been in a previously irradiated field.
6. Must have had at least 1 prior systemic chemotherapeutic regimen for management of persistent, recurrent or metastatic HNSCC. Patients must not have any curative therapy options, or be intolerant of, or decline standard of care therapy for persistent, recurrent

or metastatic disease.

7. Any prior therapy directed at the malignant tumor, including radiation therapy, chemotherapy, biologic/targeted agents and immunologic agents must be discontinued at least 21 days prior to tumor resection for preparing TIL therapy.

8. Have an Eastern Cooperative Oncology Group (ECOG) performance status of 0 or 1.

9. Must meet the following laboratory criteria:

   - Absolute neutrophil count (ANC) > 1000/mm^3
   - Hemoglobin > 8.0 g/dL
   - Platelet count > 80,000/mm^3
   - ALT/SGPT and AST/SGOT < 3.0 x the upper limit of normal (ULN)
     - Patients with liver metastases may have LFT ≤ 3.0 x ULN)
   - Calculated creatinine clearance ≥ 50.0 mL/min
   - Total bilirubin ≤ 2.0 mg/dL
     - Patients with Gilbert's Syndrome must have a total bilirubin < 3.0 mg/dL.

10. Patients must be seronegative for the HIV antibody, hepatitis B antigen, and hepatitis C antibody or antigen.

    - Note: Patients with a positive test for hepatitis B virus surface antigen (HBsAg) or hepatitis C virus ribonucleic acid (HCV antibody) indicating acute or chronic infection may be enrolled if the viral load by PCR is undetectable with/without active treatment.

11. Patients must be EBV viral capsid antigen (VCA) IgG positive and/or Epstein Barr nuclear antigen (EBNA) IgG positive, and have no clinical evidence of active EBV infection.

12. Female patients of childbearing potential must be willing to practice birth control starting at the time of informed consent and for 1 year after the completion of the lymphodepletion regimen.

    Approved methods of birth control are as follows:

    - Total abstinence
    - Hormonal contraception (i.e. birth control pills, injection, implant, transdermal patch, vaginal ring)
    - Intrauterine device (IUD)
    - Tubal Ligation
    - Male partner's vasectomy
    - Implantable or injectable contraceptives
    - Use of a male or female condom
    - Cervical Cap or contraceptive sponge with spermicide

4.2. Exclusion Criteria

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

1. Patients who are on a systemic steroid therapy (greater than 10 mg of prednisone or equivalent) within 28 days prior to Visit 2.
2. Patients who currently have prior therapy-related toxicities greater than Grade 1 according to Common Toxicity Criteria for Adverse Events (CTCAE) v4.03; (see Appendix Section 16.4), except for alopecia or vitiligo prior to enrollment.
   - Note: Patients may have undergone minor surgical procedures not involving general anesthesia within three weeks prior to Visit 2 as long as all toxicities have recovered to Grade 1 or less or as specified in the eligibility criteria.
3. Patients who have had immunotherapy-attributable AE:
   - Which led to discontinuation, or
   - Have had an ophthalmologic or neurologic AE of any grade, or
   - Actively receiving any immunosuppressive agents for the treatment of toxicity related to prior immunotherapy.
4. Patients with documented Grade 2 or greater diarrhea or colitis as a result of previous immunotherapy within six months from screening.
   - Note: Patients that have a colonoscopy that demonstrates the visual appearance of the absence of inflammation are not excluded.
5. History of severe immediate hypersensitivity reaction to cyclophosphamide, fludarabine, or IL-2.
6. Patients with active systemic infections, coagulation disorders or other active major medical illnesses of the cardiovascular, respiratory or immune system.
7. Have any form of primary immunodeficiency, such as severe combined immunodeficiency disease or acquired immune deficiency syndrome (AIDS).
8. Diagnosis of end-stage renal disorder requiring hemodialysis.
9. Patients who have a left ventricular ejection fraction (LVEF) < 45%.
10. Patients who have a FEV1 (forced expiratory volume in one second) of less than or equal to 60 % of normal.
11. Patients with unresolved uveitis.
12. Have had another primary malignancy within the previous 3 years (with the exception of a history of 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

The study is primarily planned to assess efficacy and safety for 47 patients who receive treatment with LN-145 followed by at least one dose of IL-2.
Patients who meet all of the inclusion criteria and do not meet any of the exclusion criteria will be enrolled in the study. Patients who sign an ICF and fail to meet the inclusion and/or exclusion criteria are defined as screen failures.
Patients who fail the initial screening process may be re-screened for eligibility. The Principal Investigator and Medical Monitor will discuss the patient prior to any rescreening procedures.

4.4. Patient Discontinuation

Patients who discontinue for any reason will be required to complete the early termination visit.

5. STUDY ASSESMENTS, PROCEDURES AND TREATMENTS

5.1. Informed Consent

An Informed Consent Document 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). The patient's source documents must support her qualifications for the study.

5.3. Demographic Data

The demographic data will include (but not be limited to) the patient's initials (as allowed per local regulations), date of birth (as allowed per local regulations), age, gender, and race/ethnic origin.

5.4. Medical History

Relevant medical history shall be recorded, including previous relevant surgeries at the Visit 1 (Screening).

5.5. Documentation of Confirmation of Diagnosis

Patients must have documented diagnosis of metastatic or recurrent HNSCC.

5.6. Documentation of HPV status

Patients must have documented HPV status prior to Visit 2. If documentation is not available, testing for HPV status may be determined at the time of tumor resection at Visit 2, if a sufficient sample is available.

5.7. Physical Examination

Physical examination will be conducted for all visits except for Visit 2 and shall include gastrointestinal (abdomen, liver), cardiovascular, extremities, head, eyes, ears, nose, and throat, respiratory system, skin, psychiatric (mental status), general nutrition. PE conducted during follow-up will be symptom directed. Adverse changes in the PE shall be recorded as adverse events**.**

5.8. Vital Signs

Vital signs shall include height, weight, pulse, respirations, blood pressure and temperature. Height will be measured at Visit 1, Screening only. All other vital signs will be measured at every visit.
BSA and BMI shall be calculated at Visit 4 (Day -7) only.
On Visit 11, Day 0 (LN-145 infusion), vital signs will be monitored every 30 minutes during infusion then hourly (+/-15 minutes) for four hours and then routinely (every four to six hours), unless otherwise clinically indicated, for up to approximately 24 hours post LN-145 infusion.

5.9. Eastern Cooperative Oncology Group (ECOG) performance status

An ECOG performance status will be assessed at Visits 1 through 4, 11, and 17 through 25.

5.10. Safety Blood and Urine Tests

The following safety blood and urine tests will be collected at every visit.

- Chemistry - sodium, potassium, chloride, total CO_2, or bicarbonate, creatinine, glucose, BUN, albumin, calcium, magnesium, phosphorus, alkaline phosphatase, ALT/SGPT, AST/SGOT, total bilirubin, direct bilirubin, LDH, total protein, total CK, uric acid
- Hematology - CBC with differential
- Thyroid panel inclusive of TSH and free T4 shall be done only at Visit 1 (Screening) and Visit 19 (Day 84, Month 3) or as clinically indicated.
- Urinalysis dipstick will be completed at every visit. Abnormal, clinically significant findings shall be recorded as an adverse event. A complete urine culture shall be done if clinically indicated.

5.11. ß-HCG Serum Pregnancy Test

Serum pregnancy test for all women of child-bearing potential at Visit 1 (Screening) and Visit 3 (Day -14).

5.12. Virus Testing

Blood samples will be collected for the following Virus testing at Visit 1 (Screening) only.

- HIV antibody titer;
- Hepatitis - HBsAG determination (HSV-1 IgG and HSV-2 IgG) and anti HCV;
- HSV serology
- Anti-CMV (IgG) antibody titer

- EBV 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 Visit 2 (Tumor Resection Visit).

5.13. Human Leukocyte Antigen (HLA) Typing

Sample collection for HLA typing shall be conducted during Visit 1 (Screening) and analyzed by the central laboratory. Refer to the Laboratory Manual for details.

5.14. HPV Subtype Serotype

Sample collection for HPV subtype serotyping will be collected at Visit 2 (Tumor Resection Visit) and sent to the central laboratory. Refer to the Laboratory Manual for details.

5.15. CMV Antigen Assay

CMV antigen assay shall be completed at Visit 1 (Screening) and at every visit starting at Visit 4 (Day -7) through Visit 25 (Month 24) only if clinically indicated.

5.16. Estimated Creatinine Clearance

The creatinine clearance shall be calculated using the Cockcroft-Gault formula at every visit.

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

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

5.17. Eye Exam

Slit lamp eye exam will be completed at Visit 1 (Screening).

5.18. Cardiac Evaluations

All cardiac evaluations will be performed during Visit 1 (Screening).

5.18.1. Stress Thallium

A stress thallium test will be done for all patients >= 60 years of age who have a history of ischemic heart disease, chest pain or clinically significant atrial and/or ventricular arrhythmias.

5.18.2. Echocardiogram (ECHO) or Multigated Acquisition Scan (MUGA)

An ECHO or MUGA shall be performed. Patients resulting in a LVEF <45% are excluded from the study.

5.18.3. Electrocardiogram

A 12-lead ECG will be performed after the patient has been supine for at least 3 minutes. Sites are to use their own, local ECG machines for the study and the ECG readings will be interpreted by the Investigator by clinically correlating with the patient's condition.

The Investigator's interpretation will be recorded in the ECG eCRF as: normal; abnormal, not clinically significant; or abnormal, clinically significant.

5.19. Pulmonary Function Tests

Pulmonary evaluation will be completed at Visit 1 (Screening).

5.20. Colonoscopy

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

5.21. Tumor Assessments

Tumor assessment by conventional or spiral CT scans of the head, neck and chest will be conducted at Visit 1 (Screening), Visit 3 (Day -14) and Visits 17 through 25 (Days 28 through 672, Months 1 through 24).
CT scans of additional anatomical locations will be conducted at the above referenced visits if prior or suspected disease is clinically indicated. Assessments should be made and recorded by the Investigator or an individual authorized by the Investigator.
MRI or PET scans will be allowed for patients who have an intolerability to contrast media. The imaging modality used must be uniform for the duration of the study.

5.22. Response Assessments

Tumor response will be evaluated starting Visit 17 (Day 28) and at every visit thereafter. Response and progression will be evaluated using the RECIST version 1.1 criteria (95).
CT scans will be forwarded to a central imaging facility for review. Data generated by central laboratories and evaluations done by the central reviewers will prevail over locally generated information in the evaluation of the patient's efficacy results. An independent central response adjudication committee will perform an assessment of tumor responses. These data will be used in the final study analysis and the assessment will be included in the Clinical Study Report (CSR).

5.23. Prior and Concomitant Medications

All medications and therapies (prescription, and non-prescription, including herbal supplements) taken by the patient up to 28 days prior to Visit 1 should be recorded, 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.

5.24. Adverse Events

All patients will have AE assessment by NCI CTCAE Version 4.03 performed during all visits once the ICF is signed.

5.25. Tumor Harvest for TILs

LN-145 is an autologous product which is procured and delivered by means which 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 according to a strict protocol to ensure optimal quality of the specimen and minimum transport time to and from the processing facility, as well as to ensure the unique identification of the specimen at all times including injection back into the patient.

At Visit 2 (Tumor Resection Visit), following confirmation of patient eligibility, the medical monitor, or designee, will provide approval patient for enrollment into the clinical trial.
If enrolled, tumor resection is expected to occur approximately 44 days prior to the LN-145 infusion at Visit 11 (Day 0) and is dependent on the rate of cell growth at the central TIL manufacturing facility.
A detailed Tumor Procurement Manual will be provided to each clinical site and training will be performed on the procedures for harvest, prosection, transport, and shipping of the tumor to the sponsor-designated central TIL Manufacturing Facility.

5.26. Six paraffin embedded slides from resected tumor

Six paraffin-embedded tumor section slides will be prepared for biomarker analysis Visit 2 (Tumor Resection). Whole exome sequencing may be performed with consent.

5.27. Peripheral Blood Mononuclear Cells (PBMC) for genetic sequencing

Whole exome sequencing of normal cells may be performed with consent to enable identification of mutations in the tumor specimen at Visit 2 (Tumor Resection).

5.28. Non-myeloablative (NMA) lymphodepletion Regimen

The NMA lymphodepletion regimen is scheduled to start on Visit 4 (Day -7) which is in conjunction with Day 7 of the 2-week REP protocol. Approval from the sponsor is required to start the NMA lymphodepletion regimen in order to ensure that the number of TILs cultured is adequate. The regimen comprises 2 days of cyclophosphamide followed by 5 days of fludarabine, as follows:

5.28.1. Preparation of Cyclophosphamide

The dose is 60 mg/kg. Reconstitute cyclophosphamide per institutional standard to deliver calculated dose in a final concentration of 20 mg/mL. Add dextrose 5% in 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, do not add D5W, and the total volume will be infused.

Note: if the Patient is obese (BMI > 30.0 kg/m^2), the dose of cyclophosphamide will be calculated using practical weight as described in Appendix Section 16.3. Infuse with Mesna as described below.

5.28.2. Preparation of Mesna

The dose is 15 mg/kg. Actual weight should be used to calculate the Mesna dose, even if the Patient's BMI > 30.0 kg/m^2. Dilute the volume of Mesna injection per institutional standard, or in any of the following fluids (per Mesna prescribing information, dated 9/2015) 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

5.28.3. 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 Visits 4 and 5 (Days -7 and -6). Mesna infusion will continue at a rate of 3 mg/kg/hour over 22 hours after each cyclophosphamide dose during Visits 4 and 5 (Days -7 and -6).

5.28.4. Fludarabine

The fludarabine dose is 25 mg/ m^2 administered by IV over approximately 30 minutes once daily for 5 days during Visits 6 through 10 (Days -5 through -1)
Note: If the Patient is obese (BMI > 30.0 kg/m^2) fludarabine dosage will be calculated using practical weight as described in Appendix 163.3.

5.29. LN-145 Infusion

Upon completion of the manufacturing process the product will be labeled with a patient specific label and shipped overnight by courier to the clinical site pharmacy. The product will be shipped under quarantine and received by the appropriate clinical pharmacy for the particular patient. Additional details for handling and administration of the investigational product can be found in the Pharmacy and Administration Manual.
If not already hospitalized, the patient will be admitted 1-2 days prior to planned LN-145 administration and prepared for study drug administration. Patients will remain hospitalized until the completion of the IL-2 therapy, as per institutional standards.

5.29.1. Description

LN-145 is a cell product comprising a live cell suspension of autologous tumor-infiltrating lymphocytes derived from the patient's own tumor. The overall process of

tumor shipping, TIL manufacturing, and TIL product shipping, and infusion was described above in Section 5.25 and summarized in Figure 2.

Each dose contains up to [redacted] total viable lymphocytes. The total volume to be infused will be dependent on cell concentrations.

The lower limit of viable cells is used to define the minimum number of cells needed on day 7 of the 14-day REP in order to make a decision to lymphodeplete the patient using NMA lymphodepletion regimen. At the time of the day 14 harvest, all available cells will be provided in the final product. Once lymphodepletion has begun based on this minimal attained cell number on day 7, the treatment of the patient is based on the number TILs generated at the conclusion of the 14-day REP. The upper limit of the range for infusion[redacted] viable cells) is based on the known published upper limit safely infused where a clinical response has been attained (64). There is no evidence that moving beyond this upper limit will have more clinical benefit.

5.29.2. Composition

The active product is autologous, viable, tumor infiltrating lymphocytes. The quantitative composition is shown in **Table 1.**

[redacted]

[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]

5.29.3. Transport

Each dose of the live suspension LN-145 will be shipped/sent by courier to the clinical site from the TIL Manufacturing Facility the day before administration using a method that is intended to support 24-hour delivery. Additional details will be specified in the Pharmacy and Administration Manual.

5.29.4. Receipt at Clinical Site and Administration

The dose of 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, verification,

and labelling with the clinical sites' specific labels at the pharmacy, the investigational product, LN-145, will be transferred to the patient bedside. Clinical investigators will be instructed to administer autologous LN-145 as soon as feasible. Administration is recommended within 36 hours from the time of manufacture but no later than 48 hours. The product is infused by gravity within 45 minutes. If interruption of infusion is required for medical reasons, the product infusion should complete within 3 hours of beginning infusion. Refer to the Pharmacy and Administration Manual for additional details.

5.30. Interleukin-2

Please see Section 16.5.3.1.1 for aldesleukin prescribing information.
The high-dose IL-2 infusion will begin approximately 12 to 24 hours after completion of the LN-145 infusion. IL-2 will be administered at a dose of 600,000 IU/kg (based on total body weight) and will be administered by intravenous infusion at a frequency not greater than every 8 hours as per institutional standard of care and continued for up to a maximum of six doses. IL-2 doses will be skipped if patient experiences a Grade 3 or 4 toxicity due to IL-2 with the exception of 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. Management of IL-2 toxicity is detailed in **Table 7**. 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.

5.31. Required Concomitant Medications

5.31.1. TMP/SMX DS

Prophylactic antibiotics such as TMP/SMX DS 160 mg/800 mg PO should be given per standard of care starting from Visit 11 (Day 0) through Visit 19 (Day 84/Month 3).

5.31.2. Filgrastim

Filgrastim is administered as per standard of care, or institutional protocol. Doses ranging from 5 µg/kg/day to > 300 µg/kg/day are administered by subcutaneous injection. Filgrastim is administered each day until the absolute neutrophil count reaches >1000/mm^3 for three consecutive days.

5.31.3. Fluconazole

Fluconazole 400 mg PO daily. This should be administered each day until the absolute neutrophil count reaches >1000/mm^3.

5.31.4. Anti-Viral

Antiviral treatment for herpes infection will be initiated in patients positive for HSV. Valacyclovir PO or acyclovir IV will be administered daily, and continued until CD4 > 200 cells/mm^3.

5.32. Immune Monitoring

Blood for biomarker analysis will be drawn on Visits 2, 4, and every visit starting visit 12 through 25. Samples drawn on Visit 4 (Day -7) will be considered a baseline value. Refer to the study Laboratory Manual for the complete procedure details.

6. PERMITTED AND PROHIBITED CONCOMITANT MEDICATIONS

6.1. Permitted Medications

Current medications for conditions other than HNSCC are permitted.

- Cetuximab is permitted up until approximately 2 weeks prior to start of NMA lymphodepletion regimen. No other anti-tumor therapy is permitted during participation in the study.
- Systemic steroid therapy greater than 10 mg/day of prednisone or equivalent is discouraged unless absolutely medically indicated.

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

6.2. Prohibited Medications and Prior Treatment Washout

6.2.1. Prohibited Medications

The following treatments are prohibited during the study:

- Systemic therapies and radiation intended to treat HNSCC are not permitted while the patient is on study.
- Other investigational drugs

6.2.2. Prior Treatment Washout

Patients will enter a washout period prior to enrollment and must stop prior therapy as follows:

- Cetuximab: approximately 2 weeks before initiation of NMA lymphodepletion regimen.
- All other chemotherapy or radiation therapy must have been discontinued 21 days prior to Visit 2 (Tumor Resection Visit).

7. EXPECTED TOXICITIES AND THEIR MANAGEMENT

Expected toxicities with use of the NMA lymphodepletion regimen, the LN-145 infusion, and high dose IL-2; and treatment guidelines for such toxicities, are described in Section 16.5. General

toxicity management for cyclophosphamide, fludarabine, and IL-2 are provided in Section 7.1. Full prescribing information for cyclophosphamide, fludarabine and IL-2 are provided in Appendix Sections 16.5.

7.1. General Toxicity Management

7.1.1. Empiric Antibiotics

Patients will start on broad-spectrum antibiotics, either a 3rd or 4th generation cephalosporin or a quinolone for fever – defined as 38.3°C once, or two temperature recordings of 38.0°C or above at least one hour apart, AND an ANC <500/mm^3. Infectious disease consultation will be obtained for all patients with unexplained fever or any infectious complications.

7.1.2. Blood Product Support

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

7.1.3. Renal Toxicity

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

7.1.4. Infection Prophylaxis

Prophylactic antibiotics such as TMP/SMX DS 160 mg/800 mg may be given as clinically indicated, per standard of care.
Note: Other anti-infective agents may be substituted at the discretion of the treating Investigator.

7.1.5. Pneumocystis Jiroveci Pneumonia

All patients will receive the fixed combination of trimethoprim (TMP) and sulfamethoxazole [SMX] as double strength (DS) tab (DS tabs = TMP 160 mg/tab, and SMX 800 mg/tab) (PO) daily three times a week on non-consecutive days, beginning on the first Monday, Wednesday, or Friday on or after the first dose of chemotherapy. Pentamidine will be substituted for TMP/SMX DS in patients with sulfa allergies. It will be administered aerosolized at 300 mg per nebulizer within one week prior to receiving study treatment and continued monthly until CD4 count is above 200/mm^3 and for at least six months post chemotherapy, or as Investigator deems appropriate.

Pneumonia prophylaxis will continue for six months post chemotherapy. If the CD4 count is less than 200/mm^3 at six months post chemotherapy, or as Investigator deems appropriate, prophylaxis will continue until the CD4 count is greater than 200/mm^3.

7.1.6. Herpes Virus Prophylaxis

Patients with positive HSV serology will be given valacyclovir orally at a dose of 500 mg daily the day after chemotherapy ends, or acyclovir, 250 mg/m2 IV every 12 hours if the patient is not able to take medication by mouth. Reversible renal insufficiency has been reported with IV but not oral acyclovir. Neurologic toxicity including delirium, tremors, coma, acute psychiatric disturbances, and abnormal EEGs has been reported with higher doses of acyclovir. Should this occur, a dosage adjustment will be made or the drug will be discontinued. Acyclovir will not be used concomitantly with other nucleoside analogs which interfere with DNA synthesis, e.g. ganciclovir. In renal disease, the dose is adjusted as per product labeling.

Herpes prophylaxis will continue for six months post-chemotherapy, or as long as Investigator deems necessary. If the CD4 count is less than 200/mm^3 at six months post chemotherapy, prophylaxis will continue until the CD4 count is greater than 200/mm^3.

7.1.7. Fungal Prophylaxis (Fluconazole)

Patients will start fluconazole 400 mg (PO) the day after chemotherapy concludes and continue until the absolute neutrophil count is greater than 1000/mm^3. The drug may be given IV at a dose of 400 mg in 0.9% sodium chloride USP daily in patients unable to take it orally.

8. COMPLETION/DISCONTINUATION AND WITHDRAWAL OF PATIENTS

8.1. Treatment Completion

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

8.2. Study Completion

Study completion for an individual patient is defined as reaching Visit 25 (Day 672/Month 24).

8.3. Criteria for Early Termination from Study (Removal from Treatment)

The Investigator will document on the appropriate eCRF page the reasons/circumstances for discontinuation and complete an Early Termination Visit. A patient may be removed from further study drug administration for the following medical or administrative reasons:

- Withdrawal of consent
  - Patients may voluntarily withdraw at any time during the course of the study
  - The patient may withdraw consent to treatment but continue consent for follow-up evaluations and/or survival status

- 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.
- Determination by the PI that continued treatment is not in the best interest of the patient.
- Death
- Study Terminated by sponsor
- Pregnancy
- Lost to Follow-up

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.

8.4. Criteria for Removal from the Long Term Follow-Up Phase

Patients will be removed from the Long Term Follow Up phase of the study in the following situations:

- The patient voluntarily withdraws (the reason patient withdraws consent will be collected).
- There is significant noncompliance with protocol required activities.
- General or specific changes in the patient's condition render continued participation the patient unacceptable for further participation in the judgment of the Investigator.
- Death
- Lost to Follow-Up
- Study Terminated by Sponsor

8.5. Study Discontinuation (Study or Site Termination)

Conditions may arise during the study that could prompt the study to be stopped or a study site to be closed. Conditions that may prompt such considerations include, but are not limited to the following:

- The discovery of unexpected, serious, or unacceptable risk to patients enrolled in the study;
- A decision on the part of the Sponsor to suspend, discontinue, or shorten the study;
- Study conduct at a study site may warrant termination under conditions that include the following:
    - Failure of the Investigator(s) to enroll eligible patients into the study
    - Failure of the Investigator(s) to comply with FDA or country-specific regulations
    - Submission of false information from the research facility to the Sponsor, the Clinical Monitor, or a regulatory authority
    - Insufficient adherence to protocol requirements
    - A conflict of interest on the part of the Investigator, his/her institution, or site personnel that would negatively impact the integrity of the clinical trial

- Institution or IRB under investigation for cause by a federal agency

9. SAFETY ASSESMENTS

9.1. Data Safety Monitoring Board

The DSMB will perform a safety evaluation of data analyzed when the first 3 patients have completed the Treatment Phase. Enrollment shall not be halted and will continue while under review. Additional evaluations may be specified in the charter.

9.2. Considerations

Adverse events are detailed in Section 10. 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 antigen status, as clinically indicated.
In particular, attention will be made to the expected toxicities of the NMA lymphodepletion regime and the high-dose IL-2 regimens (see Appendix Section 16.5.2).

- Serum chemistry parameters include the following:
- Sodium
- Potassium
- Chloride
- Total CO2, or bicarbonate
- Creatinine
- Glucose
- Bun
- Albumin
- Calcium
- Magnesium
- Phosphorus
- Alkaline phosphatase
- ALT/SGPT
- AST/SGOT
- Bilirubin (total and direct)
- LDH
- Total protein
- Total CK
- Uric acid
- Thyroid panel (including TSH and free T4)

10. 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 the NCI's CTCAE v4.03 dated June 14, 2010 (see Appendix Section 16.4).

10.1. Definitions

10.1.1. Adverse Event

An AE is defined as any untoward medical occurrence that occurs during a clinical investigation regardless of causal relationship with the investigational product. An AE can therefore be any unfavorable and unintended sign (including an abnormal laboratory finding), symptom or disease assessed in eligible Patients after enrollment in the study.

Events meeting the definition of an AE include:

- Adverse event temporally associated with the use of any of the study drugs or TIL treatment whether or not considered related to the use of any of the study drugs or TIL treatment.
- Any abnormal laboratory test results (e.g. hematology, clinical chemistry, or urinalysis) or other safety assessments (e.g., 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 (e.g., endoscopy, appendectomy); the condition that leads to the procedure is an AE.
- Situations where an untoward medical occurrence did not occur (social and/or convenience admission to a hospital).
- 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.

10.1.2. 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
- In-Patient hospitalization or prolongation of an existing hospitalization
- A persistent or significant incapacity or substantial disruption of the ability to conduct normal life functions
- A congenital anomaly/birth defect

Important medical events that may not directly result in death, be life-threatening, or require hospitalization 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 a serious adverse event.

Any pregnancy that occurs while on the study must be reported to the Sponsor or their representative. The pregnancy must be followed up until discharge following delivery or premature termination to determine outcome and status of mother and child. Pregnancy complications and elective terminations for medical reasons must be reported as an AE or SAE. Spontaneous abortions must be reported as an SAE. Any SAE occurring in association with a pregnancy, brought to the Investigator's attention after the Patient has completed the study and considered by the Investigator as possibly related to the investigational product, must be promptly reported to the Sponsor or their representative. In addition, the Investigator must attempt to collect pregnancy information on any female partners of male study Patients who become pregnant while the Patient is enrolled in the study. Pregnancy information must be reported to the Sponsor or their representative.

10.2. Reporting Procedures for Adverse Events

10.2.1. All Adverse Events

All AEs occurring after enrollment in the study and either observed by the Investigator or reported by the patient (whether or not attributed to the use of IL-2 or LN-145), will be reported on the eCRF. Monitoring and reporting AEs will be conducted through the last on-study visit.

Medically significant AEs considered related to the study treatment by the Investigator or the Sponsor will be followed until resolved or resolved with sequelae. The Investigator shall categorize the cause of the AE as chemotherapy, LN-145, IL-2 or other and must assign the following attributes: description; dates of onset and resolution; severity; assessment of relatedness to investigational product, and action taken. The Investigator may be asked to provide follow-up information.

If any patient should die while on the study, the Investigator will inform the Sponsor as

soon as possible. (Note: Death due to disease progression should not be reported as a SAE unless it is deemed to be related to the use of study treatment.) The cause of death should be recorded in detail on the SAE Report Form.

Each site will be responsible for reporting SAEs occurring at the site to the applicable IRB per the IRB's reporting guidelines.

It will be left to the Investigator's clinical judgment whether or not an AE is of sufficient severity to require the patient's removal from the study treatment. A patient may also voluntarily discontinue treatment due to what he or she perceives as an intolerable AE. This should be captured in the eCRF. If 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 a safety Follow-up visit. If the patient was permanently removed from the study or investigational product due to an SAE, this information must be included in either the initial or follow-up SAE Report Form and in the eCRF.

10.2.2. Relationship to Study Drug

The following categories and definitions of causal relationship to study treatment should be considered:

- **Definite:** There is a known causal relationship between the study drug and the AE/SAE. The event responds to withdrawal of study drug (de-challenge), and recurs with re-challenge when clinically feasible. (>95% certainty of relatedness).
- **Probable**: There is reasonable causal relationship between the study drug and the AE/SAE. The event responds to de-challenge. Re-challenge is not required. (65%-95% probability of relatedness).
- **Possible:** There is reasonable causal relationship between the study drug and the AE/ SAE. De-challenge information is lacking or unclear. (35%-65% probability of relatedness).
- **Not likely:** There is temporal relationship to study drug administration, but there is not a reasonable causal relationship between the study drug and the AE/SAE. (5-35% probability of relatedness).
- **Not related:** There is not a temporal relationship to study drug administration (too early, or late, or study drug not taken), or there is known causal relationship between the AE/SAE and another drug, concurrent disease, or other circumstance. (<5% chance of relatedness).

10.2.3. 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 v 4.03 (see Section 16.4). In the event the CTCAE v 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

10.3. Reporting Procedures for Serious Adverse Events

10.3.1. Investigator Reporting to Sponsor

All SAEs, regardless of relationship to study treatment, must be collected while on the study. In addition, the Investigator must notify the Sponsor of any SAE that may occur after this time period which (s)he believes to be certainly, probably, or possibly related study treatment.

SAE terminology and severity grading will be based on the NCI's CTCAE v4.03 guidelines.

All SAEs that occur during the course of the investigation 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 is possible with the information available and include the Investigator's assessment of whether there is a reasonable possibility that the study drug caused the event. SAE reports will be reported to Chiltern International, Inc. via EDC system, MERGE eCOS. Paper SAE forms can be used as back up and send via GlobalSAEinbox@chiltern.com or fax (1-888-726-8416). Reporting to Regulatory Agencies and Institutional Review Boards (IRBs).

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

The Investigator is responsible for reporting serious adverse events to their IRBs

In addition, the Sponsor must submit expedited reports of an increased rate of occurrence of serious adverse events over that listed in the protocol or Investigational Brochure. Sponsor will notify participating sites of any serious adverse events which occur during trial.

11. Efficacy ASSESSMENTS

11.1. Tumor Response Criteria

Clinical response will be determined using RECIST version 1.1.

11.1.1. Evaluation of Target Lesions[1]

- Complete Response (CR): Disappearance of all target lesions. Any pathological lymph nodes (whether target or non-target) must have a reduction in short axis to <10 mm).
- Partial Response (PR): At least a 30% decrease in the sum of the diameter of target lesions taking as reference the baseline sum diameters.
- 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 one 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.

11.1.2. Evaluation of Non-Target Lesions[2]

- Complete Response (CR): Disappearance of all non-target lesions and normalization of tumor marker level. All lymph nodes must be non-pathological in size (<10 mm short axis).
- Non-Complete Response: Persistence of one or more non-target lesion(s) and/or maintenance of tumor marker level above normal limits.
- Progressive Disease (PD): Unequivocal progression of existing non-target lesions. (Note: the appearance of one or more new lesions is also considered progression)

11.1.3. Determination of Best Response for Each Patient

The best response for each patient is determined once all the data for the patient is known. The best overall response is the best response recorded from the start of treatment until disease progression/recurrence, the initiation of new anti-cancer therapy, death or 24 months whichever comes first. The patient's best response assignment will depend on the achievement

[1] All measurable lesions up to a maximum of two lesions per organ and five lesions in total, representative of all involved organs should be identified as **target lesions** and recorded and measured during screening. A sum of the diameters (longest for non-nodal lesions, short axis for nodal lesions) for all target lesions will be calculated and reported as the baseline sum diameters. The baseline sum diameters will be used as reference by which to characterize any objective tumor regression in the measurable dimension of the disease. If lymph nodes are to be included in the sum, only the short axis will contribute.

[2] All other lesions (or sites of disease) should be identified as **non-target lesions** and should also be recorded at baseline.

of both measurement and confirmation criteria. The assignment of response for an individual patient, based on both target and non-target 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 with Target (± Non-target) Disease

Target Lesions at the indicated Time point	Non-Target Lesions at the indicated Time point	New Lesions at the indicated Time point	Overall Response at the indicated Time point
CR	CR	No	CR
CR	Non-CR/Non-PD	No	PR
CR	Not evaluated	No	PR
PR	Non-PD or not all evaluated	No	PR
SD	Non-PD or not all evaluated	No	SD
Not all evaluated	Non-PD	No	NE
PD	Any	Yes or No	PD
Any	PD	Yes or No	PD
Any	Any	Yes	PD

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

11.2. Overall Response Rate (ORR)

The ORR will be based on the best overall response for each patient. The ORR rate is the percentage of patients who achieved a best response of CR or PR among those successfully undergone NMA lymphodepletion and infused with LN-145 and at least one dose of IL-2.

11.3. Confirmatory Measurement/Duration of Response

11.3.1. Confirmation

To be assigned a status of PR or CR changes in tumor measurements must be confirmed by repeat studies that should be performed at least 4 weeks after the criteria for response are first met.

11.3.2. Duration of Overall Response

The duration of overall complete response is measured from the time measurement criteria are first met for CR until the first date that recurrent disease is objectively documented.

12. STATISTICAL ANALYSIS PLAN

12.1. 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 non-missing data (N), mean, standard deviation, median, minimum, and maximum values. Categorical data will be summarized as counts and their related percentages, where applicable. Estimation of 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).

12.2. Analysis Populations

Three analysis populations will be defined to summarize the data. The resected population will consist of all patients with resection of tumor for TIL harvest. The treated population consists of the resected patients who have been successfully infused with lymphodepletion, LN-145 followed by at least 1 dose of IL-2. Separately, the untreated population also represents the other subset of the resected population who did not receive the study treatment.
The efficacy analysis is performed among patients in the treated population. The responder population comprises those patients achieving a CR or PR as a best overall response. The responder population will be used to summarize the duration of response.

12.3. Sample Size Justification

The planned sample size for this single arm study is 47 patients. A Simon's optimal two-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 interim analysis of Stage 1. If at least 6 patients respond to therapy, the study therapy would be considered to have met its statistical goal. This two-stage design has 80% power to detect a difference of an ORR of 5% versus 20% using a one-sided 0.025 alpha level test.

12.4. Baseline Demographic and Clinical Characteristics

[redacted] Age will be derived as a function of the date of informed consent. Patients among the resected, untreated population will be summarized by the primary reason of not receiving the treatment together with the safety events.

12.5. Safety and Efficacy Analysis

12.5.1. Primary Endpoint

The assessment of safety data will be descriptive and based on the summarization of treatment-emergent adverse events including serious adverse events, adverse events

leading to discontinuation from the study, and clinical laboratory tests. Adverse event summaries will be based on patient incidence counts and their related percentages; the number of events will be displayed as appropriate. In additional to an overall summary of adverse events, separate displays will be made by intensity (grades by CTCAE) and relationship. These toxicity grade summaries will also be provided separately for applicable laboratory parameters.

A separate safety summary will be provided for patients in the resected treated population until the lymphodepletion therapy and resected untreated population.

The primary efficacy endpoint is the overall response rate (CR+PR) as assessed by a central imaging reader. The ORR is defined as the proportion of patients who achieve either a PR or CR as best response as assessed by investigators according to the RECIST version 1.1 Criteria. Objective response will be evaluated per each disease assessment and the ORR will be calculated for the Safety population. The corresponding 95% two-sided confidence interval will be derived.

12.5.2. Secondary Endpoints

12.5.2.1. Additional Measures of Efficacy

- The CR rate is based on responders (patients with ORR) who achieved CR as a best overall response, as assessed by investigators.
- PFS is defined as the time (in months) [redacted] o PD, or death due to any cause, whichever event is earlier. Patients not experiencing PD or 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 (in months) from the [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.
- Duration of overall response is measured from the first time response criteria are met until the first date that recurrent or progressive disease occurs. Patients not experiencing PD or death 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.
- PFS, OS, durations of any response will be subjected to right censoring. Kaplan-Meier methods will apply.

12.5.3. Exploratory Analyses

Correlations of immune factors with response, survival, and toxicity will be explored.

13. ADMINISTRATIVE REQUIREMENTS

13.1. 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 Good Clinical Practice (GCP), as described in International Conference on Harmonization (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/EC 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.

13.2. 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 approval, except where necessary to eliminate immediate hazards to the patients or when the change(s) involves only logistical or administrative aspects of the trial (e.g., change in monitor[s], change of telephone number[s]). Responsibilities for reporting protocol amendments to any Regulatory Authority (if applicable) and/or IRB are further described in the Ethical Aspects section 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.

13.3. Regulatory Documentation

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

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

- A copy of the IRB approved informed consent and other adjunctive materials (e.g., advertising) to be used in the study, including written documentation of IEC approval of these items.
- Name and address of any local laboratory conducting tests for the study, a dated copy of the laboratory reference values for tests to be performed during the study and a copy of the certification or other documentation establishing adequacy of the facility.
- Required financial agreement.
- In addition to the documents required prior to the study, other documentation may be required during the course of the study.

13.4. 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.

13.5. Data Quality Assurance

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 and direct transmission of clinical laboratory data from a central laboratory into the database. Electronic CRFs will be reviewed for accuracy and completeness by Clinical Research Monitors during on- site monitoring visits and after their return from the site, and any discrepancies will be resolved with the Investigator or designees, as appropriate. The data will be verified for accuracy.

Agreements made by the Sponsor with the Investigator/Institution and any other parties involved in the clinical trial will be in writing as a separate agreement. On-Site Audits Representatives of the Sponsor's Clinical Quality Assurance department may visit the site to carry out an audit of the study in compliance with regulatory guidelines and company policy. Such audits will require access to all study records, including source documents, for inspection

and comparison with the eCRFs. Patient privacy must, however, be respected. Sufficient prior notice will be provided to allow the Investigator to prepare properly for the audit.
Similar auditing procedures may also be conducted by agents of any regulatory body reviewing the results of this study in support of a Licensing Application. The Investigator should immediately notify the Sponsor if they have been contacted by a regulatory agency concerning an upcoming inspection.

13.6. Data Handling and Recordkeeping

13.6.1. Electronic Data

When using electronic data handling, the Sponsor or their designee will ensure that systems comply with 21CFR Part 11 requirements. Documentation regarding the electronic data systems used in this protocol is located in the study-specific plans or SOPS for that particular task.

13.6.2. Electronic Case Report Form (eCRF) Completion

Electronic data capture (EDC) will be used for this study. The site will be suitably trained on the use of the eCRF and appropriate site personnel will be provided electronic signatures. Data must be entered into the eCRF screens in English. The eCRFs are to be completed at the time of the patient's visit, with the exception of results of tests performed outside the Investigator's office, so that they always reflect the latest observations on the patients participating in the trial.
Data must be recorded first on a source document that can be verified before it is entered in the EDC system. Completed eCRFs are to be signed off by the Investigator as per the data completion guidelines written for this trial.
All eCRF corrections are to be made by the Investigator or other authorized study site personnel. The Investigator must authorize changes to the recorded safety and efficacy data.
Completed eCRFs will be submitted according to the Sponsor's instructions, and reviewed by the Sponsor to determine their acceptability. If necessary, Data Correction Requests will be generated for resolution by the study site.

13.7. Study Completion/Termination

13.7.1. Study Completion

The Investigator will complete the study and submit all eCRFs in satisfactory compliance with the protocol after study completion.

13.8. Monitoring

On-site monitoring visits will be performed by the Sponsor as frequently as necessary. Visits are usually made at intervals of at least four to twelve weeks. The dates of the visits will be recorded by the monitor in a trial center visit log to be kept at the site. The first post-initiation visit will usually be made as soon as possible after enrollment has begun. At these visits the

monitor will compare the data entered into the eCRFs with the hospital or clinic records (source documents). At a minimum, source documentation must be available to substantiate proper informed consent procedures, adherence to protocol procedures, adequate reporting and follow-up of adverse events, administration of concomitant medication, drug receipt/dispensing/return records, and study drug administration information. Specific items required as source documents will be reviewed with the Investigator prior to the study. Findings from this review of eCRFs and source documents will be discussed with the Investigator. The Sponsor expects that, during monitoring visits, the Investigator (and as appropriate the Study Coordinator) will be available, the source documentation will be available, and a suitable environment will be provided for review of study-related documents.

14. INVESTIGATOR REGULATORY OBLIGATIONS

14.1. Institutional Review Boards

This trial will be undertaken only after full approval of the protocol and addenda has been obtained from an IRB and a copy of this approval has been received by the Sponsor. The IRB must be informed of all subsequent protocol amendments issued by the Sponsor. Reports on, and reviews of, the trial and its progress will be submitted to the IRB by the Investigator at intervals stipulated in their guidelines.
The IRB must meet all regulatory requirements governing IRBs (CFR, Title 21, Part 56).

14.2. 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. The informed consent should be in accordance with the current revision of the Declaration of Helsinki, current International Conference on Harmonization (ICH) and Good Clinical Practice (GCP) guidelines, and the Sponsor's policies.
The Investigator must explain to potential patients or their legal representatives the aims, methods, reasonably anticipated benefits and potential hazards of the trial, and any discomfort it may entail. Patients will be informed 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 that personal information 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 should receive a signed and dated copy of the informed consent. The informed consent process should be documented in the patient's medical record.

In accordance with HIPAA, the written Informed Consent Form 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 access to patient's medical information that includes all hospital records relevant to the study, including a patient's medical history.

14.3. Patient Data Protection

The Principal Investigator at each site and designees, employees, and agents involved with this study will comply with relevant state and federal laws relating to the confidentiality, privacy, and security of patient's personal health information (PHI). They will only create, maintain, use, or disclose any data that is generated by this study or other information disclosed to the Principal Investigator or their employees or agents during the course of the study to the Sponsor, IRB, FDA, 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 records are only to be identified by initials and patient ID numbers.

14.4. Adverse Event Reporting

The Investigator agrees to report all AEs to the Sponsor as described in the Adverse Events section. Furthermore, the Investigator is responsible for ensuring that any co-Investigator or sub-Investigator promptly bring AEs to the attention of the Investigator. If applicable, the Investigator also is responsible for informing the participating IRB/IEC of any SAEs.

14.5. Investigator

The Investigator will permit study-related monitoring, audits, IEC/IRB 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.

14.6. 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 (e.g., 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.

14.7. 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 to journals or professional societies without the prior written approval of the Sponsor.

15. REFERENCES

1. Sidransky, D., Schantz, S., Harrison, L., Forastiere, A., and Sessions, R. 1997. Cancer of the Head and Neck. In Cancer: Principles and Practice of Oncology. V.J. Devita, S. Helman, and S. Rosenberg, editors. Philadelphia: Lippincott-Raven.
2. Guo, T., Rettig, E., and Fakhry, C. 2015. Understanding the impact of survival and human papillomavirus tumor status on timing of recurrence in oropharyngeal squamous cell carcinoma. Oral Oncol.
3. Rettig, E.M., and D'Souza, G. 2015. Epidemiology of head and neck cancer. Surg Oncol Clin N Am 24:379-396.
4. Gillison, M.L., D'Souza, G., Westra, W., Sugar, E., Xiao, W., Begum, S., and Viscidi, R. 2008. Distinct risk factor profiles for human papillomavirus type 16-positive and human papillomavirus type 16-negative head and neck cancers. J Natl Cancer Inst 100:407-420.
5. Adelstien, D. 2009. NCI Stat Bite: Oropharyngeal Cancers are an Increasing Proportion of All Head and Neck Cancers. In National Cancer Institute State of the Science Meeting. N.C. Institute, editor. Washington, DC: Oxfod University Press.
6. Ang, K.K., Harris, J., Wheeler, R., Weber, R., Rosenthal, D.I., Nguyen-Tan, P.F., Westra, W.H., Chung, C.H., Jordan, R.C., Lu, C., et al. 2010. Human papillomavirus and survival of patients with oropharyngeal cancer. N Engl J Med 363:24-35.
7. Chaturvedi, A.K., Engels, E.A., Pfeiffer, R.M., Hernandez, B.Y., Xiao, W., Kim, E., Jiang, B., Goodman, M.T., Sibug-Saber, M., Cozen, W., et al. 2011. Human papillomavirus and rising oropharyngeal cancer incidence in the United States. J Clin Oncol 29:4294-4301.
8. Mehanna, H., Beech, T., Nicholson, T., El-Hariry, I., McConkey, C., Paleri, V., and Roberts, S. 2013. Prevalence of human papillomavirus in oropharyngeal and nonoropharyngeal head and neck cancer--systematic review and meta-analysis of trends by time and region. Head Neck 35:747-755.
9. Lingen, M.W., Xiao, W., Schmitt, A., Jiang, B., Pickard, R., Kreinbrink, P., Perez-Ordonez, B., Jordan, R.C., and Gillison, M.L. 2013. Low etiologic fraction for high-risk human papillomavirus in oral cavity squamous cell carcinomas. Oral Oncol 49:1-8.
10. Gillison, M.L., Chaturvedi, A.K., Anderson, W.F., and Fakhry, C. 2015. Epidemiology of Human Papillomavirus-Positive Head and Neck Squamous Cell Carcinoma. J Clin Oncol 33:3235-3242.
11. 2015. Comprehensive genomic characterization of head and neck squamous cell carcinomas. Nature 517:576-582.
12. Agrawal, N., Frederick, M.J., Pickering, C.R., Bettegowda, C., Chang, K., Li, R.J., Fakhry, C., Xie, T.X., Zhang, J., Wang, J., et al. 2011. Exome sequencing of head and neck squamous cell carcinoma reveals inactivating mutations in NOTCH1. Science 333:1154-1157.
13. Brennan, J.A., Boyle, J.O., Koch, W.M., Goodman, S.N., Hruban, R.H., Eby, Y.J., Couch, M.J., Forastiere, A.A., and Sidransky, D. 1995. Association between cigarette smoking and mutation of the p53 gene in squamous-cell carcinoma of the head and neck. N Engl J Med 332:712-717.

14. Nichols, A.C., Palma, D.A., Chow, W., Tan, S., Rajakumar, C., Rizzo, G., Fung, K., Kwan, K., Wehrli, B., Winquist, E., et al. 2013. High frequency of activating PIK3CA mutations in human papillomavirus-positive oropharyngeal cancer. JAMA Otolaryngol Head Neck Surg 139:617-622.
15. Di Mario, S., Basevi, V., Lopalco, P.L., Balduzzi, S., D'Amico, R., and Magrini, N. 2015. Are the Two Human Papillomavirus Vaccines Really Similar? A Systematic Review of Available Evidence: Efficacy of the Two Vaccines against HPV. J Immunol Res 2015:435141.
16. Jones, T.M. 2014. Tumour-infiltrating lymphocytes in the risk stratification of squamous cell carcinoma of the head and neck. Br J Cancer 110:269-270.
17. Maxwell, J.H., Grandis, J.R., and Ferris, R.L. 2015. HPV-Associated Head and Neck Cancer: Unique Features of Epidemiology and Clinical Management. Annu Rev Med.
18. Patterson, J.M., McColl, E., Carding, P.N., Hildreth, A.J., Kelly, C., and Wilson, J.A. 2014. Swallowing in the first year after chemoradiotherapy for head and neck cancer: clinician- and patient-reported outcomes. Head Neck 36:352-358.
19. Pulte, D., and Brenner, H. 2010. Changes in survival in head and neck cancers in the late 20th and early 21st century: a period analysis. Oncologist 15:994-1001.
20. Howlader, N., Noone, A.M., Krapcho, M., Garshell, J., Miller, D., Altekruse, S.F., Kosary, C.L., Yu, M., Ruhl, J., Tatalovich, Z., et al. 2014. SEER Cancer Statistics Review, 1975-2011. National Cancer Institute. Bethesda, MD.
21. Fakhry, C., Westra, W.H., Li, S., Cmelak, A., Ridge, J.A., Pinto, H., Forastiere, A., and Gillison, M.L. 2008. Improved survival of patients with human papillomavirus-positive head and neck squamous cell carcinoma in a prospective clinical trial. J Natl Cancer Inst 100:261-269.
22. O'Rorke, M.A., Ellison, M.V., Murray, L.J., Moran, M., James, J., and Anderson, L.A. 2012. Human papillomavirus related head and neck cancer survival: a systematic review and meta-analysis. Oral Oncol 48:1191-1201.
23. Argiris, A., Karamouzis, M.V., Raben, D., and Ferris, R.L. 2008. Head and neck cancer. Lancet 371:1695-1709.
24. Chuang, S.C., Scelo, G., Tonita, J.M., Tamaro, S., Jonasson, J.G., Kliewer, E.V., Hemminki, K., Weiderpass, E., Pukkala, E., Tracey, E., et al. 2008. Risk of second primary cancer among patients with head and neck cancers: A pooled analysis of 13 cancer registries. Int J Cancer 123:2390-2396.
25. Hsieh, M.J., Lin, C.W., Chiou, H.L., Yang, S.F., and Chen, M.K. 2015. Dehydroandrographolide, an iNOS inhibitor, extracted from Andrographis paniculata (Burm.f.) Nees, induces autophagy in human oral cancer cells. Oncotarget 6:30831-30849.
26. Machiels, J.P., Haddad, R.I., Fayette, J., Licitra, L.F., Tahara, M., Vermorken, J.B., Clement, P.M., Gauler, T., Cupissol, D., Grau, J.J., et al. 2015. Afatinib versus methotrexate as second-line treatment in patients with recurrent or metastatic squamous-cell carcinoma of the head and neck progressing on or after platinum-based therapy (LUX-Head & Neck 1): an open-label, randomised phase 3 trial. Lancet Oncol 16:583-594.
27. Vargo, J.A., Ferris, R.L., Ohr, J., Clump, D.A., Davis, K.S., Duvvuri, U., Kim, S., Johnson, J.T., Bauman, J.E., Gibson, M.K., et al. 2015. A prospective phase 2 trial of reirradiation with stereotactic body radiation therapy plus cetuximab in patients with previously irradiated

recurrent squamous cell carcinoma of the head and neck. Int J Radiat Oncol Biol Phys 91:480-488.

28. Strnad, V., Lotter, M., Kreppner, S., and Fietkau, R. 2015. Reirradiation for recurrent head and neck cancer with salvage interstitial pulsed-dose-rate brachytherapy: Long-term results. Strahlenther Onkol 191:495-500.
29. Fakhry, C., Zhang, Q., Nguyen-Tan, P.F., Rosenthal, D., El-Naggar, A., Garden, A.S., Soulieres, D., Trotti, A., Avizonis, V., Ridge, J.A., et al. 2014. Human papillomavirus and overall survival after progression of oropharyngeal squamous cell carcinoma. J Clin Oncol 32:3365-3373.
30. Rosenberg, S.A., Spiess, P., and Lafreniere, R. 1986. A new approach to the adoptive immunotherapy of cancer with tumor-infiltrating lymphocytes. Science 233:1318-1321.
31. Vose, B.M., and Moore, M. 1985. Human tumor-infiltrating lymphocytes: a marker of host response. Semin Hematol 22:27-40.
32. Yron, I., Wood, T.A., Jr., Spiess, P.J., and Rosenberg, S.A. 1980. In vitro growth of murine T cells. V. The isolation and growth of lymphoid cells infiltrating syngeneic solid tumors. J Immunol 125:238-245.
33. Haanen, J.B., Baars, A., Gomez, R., Weder, P., Smits, M., de Gruijl, T.D., von Blomberg, B.M., Bloemena, E., Scheper, R.J., van Ham, S.M., et al. 2006. Melanoma-specific tumor-infiltrating lymphocytes but not circulating melanoma-specific T cells may predict survival in resected advanced-stage melanoma patients. Cancer Immunol Immunother 55:451-458.
34. Ladanyi, A., Kiss, J., Somlai, B., Gilde, K., Fejos, Z., Mohos, A., Gaudi, I., and Timar, J. 2007. Density of DC-LAMP(+) mature dendritic cells in combination with activated T lymphocytes infiltrating primary cutaneous melanoma is a strong independent prognostic factor. Cancer Immunol Immunother 56:1459-1469.
35. Azimi, F., Scolyer, R.A., Rumcheva, P., Moncrieff, M., Murali, R., McCarthy, S.W., Saw, R.P., and Thompson, J.F. 2012. Tumor-infiltrating lymphocyte grade is an independent predictor of sentinel lymph node status and survival in patients with cutaneous melanoma. J Clin Oncol 30:2678-2683.
36. Erdag, G., Schaefer, J.T., Smolkin, M.E., Deacon, D.H., Shea, S.M., Dengel, L.T., Patterson, J.W., and Slingluff, C.L., Jr. 2012. Immunotype and immunohistologic characteristics of tumor-infiltrating immune cells are associated with clinical outcome in metastatic melanoma. Cancer Res 72:1070-1080.
37. Horne, Z.D., Jack, R., Gray, Z.T., Siegfried, J.M., Wilson, D.O., Yousem, S.A., Nason, K.S., Landreneau, R.J., Luketich, J.D., and Schuchert, M.J. 2011. Increased levels of tumor-infiltrating lymphocytes are associated with improved recurrence-free survival in stage 1A non-small-cell lung cancer. J Surg Res 171:1-5.
38. Kilic, A., Landreneau, R.J., Luketich, J.D., Pennathur, A., and Schuchert, M.J. 2011. Density of tumor-infiltrating lymphocytes correlates with disease recurrence and survival in patients with large non-small-cell lung cancer tumors. J Surg Res 167:207-210.
39. Liu, H., Zhang, T., Ye, J., Li, H., Huang, J., Li, X., Wu, B., Huang, X., and Hou, J. 2012. Tumor-infiltrating lymphocytes predict response to chemotherapy in patients with advance non-small cell lung cancer. Cancer Immunol Immunother 61:1849-1856.

40. Ruffini, E., Asioli, S., Filosso, P.L., Lyberis, P., Bruna, M.C., Macri, L., Daniele, L., and Oliaro, A. 2009. Clinical significance of tumor-infiltrating lymphocytes in lung neoplasms. Ann Thorac Surg 87:365-371; discussion 371-362.
41. Hagemann, A.R., Hagemann, I.S., Cadungog, M., Hwang, W.T., Patel, P., Lal, P., Hammond, R., Gimotty, P.A., Chu, C.S., Rubin, S.C., et al. 2011. Tissue-based immune monitoring II: multiple tumor sites reveal immunologic homogeneity in serous ovarian carcinoma. Cancer Biol Ther 12:367-377.
42. Milne, K., Alexander, C., Webb, J.R., Sun, W., Dillon, K., Kalloger, S.E., Gilks, C.B., Clarke, B., Kobel, M., and Nelson, B.H. 2012. Absolute lymphocyte count is associated with survival in ovarian cancer independent of tumor-infiltrating lymphocytes. J Transl Med 10:33.
43. Webb, J.R., Milne, K., Watson, P., Deleeuw, R.J., and Nelson, B.H. 2014. Tumor-infiltrating lymphocytes expressing the tissue resident memory marker CD103 are associated with increased survival in high-grade serous ovarian cancer. Clin Cancer Res 20:434-444.
44. Wang, J., Jia, Y., Wang, N., Zhang, X., Tan, B., Zhang, G., and Cheng, Y. 2014. The clinical significance of tumor-infiltrating neutrophils and neutrophil-to-CD8+ lymphocyte ratio in patients with resectable esophageal squamous cell carcinoma. J Transl Med 12:7.
45. Balermpas, P., Michel, Y., Wagenblast, J., Seitz, O., Weiss, C., Rodel, F., Rodel, C., and Fokas, E. 2014. Tumour-infiltrating lymphocytes predict response to definitive chemoradiotherapy in head and neck cancer. Br J Cancer 110:501-509.
46. Ali, H.R., Provenzano, E., Dawson, S.J., Blows, F.M., Liu, B., Shah, M., Earl, H.M., Poole, C.J., Hiller, L., Dunn, J.A., et al. 2014. Association between CD8+ T-cell infiltration and breast cancer survival in 12,439 patients. Ann Oncol 25:1536-1543.
47. Chacon, J.A., Wu, R.C., Sukhumalchandra, P., Molldrem, J.J., Sarnaik, A., Pilon-Thomas, S., Weber, J., Hwu, P., and Radvanyi, L. 2013. Co-stimulation through 4-1BB/CD137 improves the expansion and function of CD8(+) melanoma tumor-infiltrating lymphocytes for adoptive T-cell therapy. PLoS One 8:e60031.
48. Ibrahim, E.M., Al-Foheidi, M.E., Al-Mansour, M.M., and Kazkaz, G.A. 2014. The prognostic value of tumor-infiltrating lymphocytes in triple-negative breast cancer: a meta-analysis. Breast Cancer Res Treat.
49. Liu, S., Lachapelle, J., Leung, S., Gao, D., Foulkes, W.D., and Nielsen, T.O. 2012. CD8+ lymphocyte infiltration is an independent favorable prognostic indicator in basal-like breast cancer. Breast Cancer Res 14:R48.
50. Mahmoud, S.M., Lee, A.H., Paish, E.C., Macmillan, R.D., Ellis, I.O., and Green, A.R. 2012. Tumour-infiltrating macrophages and clinical outcome in breast cancer. J Clin Pathol 65:159-163.
51. Mahmoud, S.M., Lee, A.H., Paish, E.C., Macmillan, R.D., Ellis, I.O., and Green, A.R. 2012. The prognostic significance of B lymphocytes in invasive carcinoma of the breast. Breast Cancer Res Treat 132:545-553.
52. Mahmoud, S.M., Paish, E.C., Powe, D.G., Macmillan, R.D., Grainge, M.J., Lee, A.H., Ellis, I.O., and Green, A.R. 2011. Tumor-infiltrating CD8+ lymphocytes predict clinical outcome in breast cancer. J Clin Oncol 29:1949-1955.

53. West, N.R., Kost, S.E., Martin, S.D., Milne, K., Deleeuw, R.J., Nelson, B.H., and Watson, P.H. 2013. Tumour-infiltrating FOXP3(+) lymphocytes are associated with cytotoxic immune responses and good clinical outcome in oestrogen receptor-negative breast cancer. Br J Cancer 108:155-162.
54. Galon, J., Costes, A., Sanchez-Cabo, F., Kirilovsky, A., Mlecnik, B., Lagorce-Pages, C., Tosolini, M., Camus, M., Berger, A., Wind, P., et al. 2006. Type, density, and location of immune cells within human colorectal tumors predict clinical outcome. Science 313:1960-1964.
55. Galon, J., Mlecnik, B., Bindea, G., Angell, H.K., Berger, A., Lagorce, C., Lugli, A., Zlobec, I., Hartmann, A., Bifulco, C., et al. 2014. Towards the introduction of the 'Immunoscore' in the classification of malignant tumours. J Pathol 232:199-209.
56. Pages, F., Berger, A., Camus, M., Sanchez-Cabo, F., Costes, A., Molidor, R., Mlecnik, B., Kirilovsky, A., Nilsson, M., Damotte, D., et al. 2005. Effector memory T cells, early metastasis, and survival in colorectal cancer. N Engl J Med 353:2654-2666.
57. Pages, F., Kirilovsky, A., Mlecnik, B., Asslaber, M., Tosolini, M., Bindea, G., Lagorce, C., Wind, P., Marliot, F., Bruneval, P., et al. 2009. In situ cytotoxic and memory T cells predict outcome in patients with early-stage colorectal cancer. J Clin Oncol 27:5944-5951.
58. Shen, Z., Zhou, S., Wang, Y., Li, R.L., Zhong, C., Liang, C., and Sun, Y. 2010. Higher intratumoral infiltrated Foxp3+ Treg numbers and Foxp3+/CD8+ ratio are associated with adverse prognosis in resectable gastric cancer. J Cancer Res Clin Oncol 136:1585-1595.
59. Bindea, G., Mlecnik, B., Tosolini, M., Kirilovsky, A., Waldner, M., Obenauf, A.C., Angell, H., Fredriksen, T., Lafontaine, L., Berger, A., et al. 2013. Spatiotemporal dynamics of intratumoral immune cells reveal the immune landscape in human cancer. Immunity 39:782-795.
60. Mlecnik, B., Bindea, G., Angell, H.K., Sasso, M.S., Obenauf, A.C., Fredriksen, T., Lafontaine, L., Bilocq, A.M., Kirilovsky, A., Tosolini, M., et al. 2014. Functional network pipeline reveals genetic determinants associated with in situ lymphocyte proliferation and survival of cancer patients. Sci Transl Med 6:228ra237.
61. Stoll, G., Enot, D., Mlecnik, B., Galon, J., Zitvogel, L., and Kroemer, G. 2014. Immune-related gene signatures predict the outcome of neoadjuvant chemotherapy. Oncoimmunology 3:e27884.
62. Strauss, L., Bergmann, C., Szczepanski, M., Gooding, W., Johnson, J.T., and Whiteside, T.L. 2007. A unique subset of CD4+CD25highFoxp3+ T cells secreting interleukin-10 and transforming growth factor-beta1 mediates suppression in the tumor microenvironment. Clin Cancer Res 13:4345-4354.
63. Martin-Orozco, N., Li, Y., Wang, Y., Liu, S., Hwu, P., Liu, Y.J., Dong, C., and Radvanyi, L. 2010. Melanoma cells express ICOS ligand to promote the activation and expansion of T-regulatory cells. Cancer Res 70:9581-9590.
64. Cao, X., Cai, S.F., Fehniger, T.A., Song, J., Collins, L.I., Piwnica-Worms, D.R., and Ley, T.J. 2007. Granzyme B and perforin are important for regulatory T cell-mediated suppression of tumor clearance. Immunity 27:635-646.
65. Robbins, P.F., Lu, Y.C., El-Gamil, M., Li, Y.F., Gross, C., Gartner, J., Lin, J.C., Teer, J.K., Cliften, P., Tycksen, E., et al. 2013. Mining exomic sequencing data to identify mutated antigens recognized by adoptively transferred tumor-reactive T cells. Nat Med 19:747-752.

66. Tran, E., Turcotte, S., Gros, A., Robbins, P.F., Lu, Y.C., Dudley, M.E., Wunderlich, J.R., Somerville, R.P., Hogan, K., Hinrichs, C.S., et al. 2014. Cancer immunotherapy based on mutation-specific CD4+ T cells in a patient with epithelial cancer. Science 344:641-645.
67. Kvistborg, P., van Buuren, M.M., and Schumacher, T.N. 2013. Human cancer regression antigens. Curr Opin Immunol 25:284-290.
68. van Rooij, N., van Buuren, M.M., Philips, D., Velds, A., Toebes, M., Heemskerk, B., van Dijk, L.J., Behjati, S., Hilkmann, H., El Atmioui, D., et al. 2013. Tumor exome analysis reveals neoantigen-specific T-cell reactivity in an ipilimumab-responsive melanoma. J Clin Oncol 31:e439-442.
69. Sim, G.C., Chacon, J., Haymaker, C., Ritthipichai, K., Singh, M., Hwu, P., and Radvanyi, L. 2014. Tumor-infiltrating lymphocyte therapy for melanoma: rationale and issues for further clinical development. BioDrugs 28:421-437.
70. Wu, R., Forget, M.A., Chacon, J., Bernatchez, C., Haymaker, C., Chen, J.Q., Hwu, P., and Radvanyi, L.G. 2012. Adoptive T-cell therapy using autologous tumor-infiltrating lymphocytes for metastatic melanoma: current status and future outlook. Cancer J 18:160-175.
71. Besser, M.J., Treves, A.J., Itzhaki, O., Hardan, I., Nagler, A., Papa, M.Z., Catane, R., Winkler, E., Shalmon-Zifroni, B., and Schachter, J. 2006. Adoptive cell therapy for metastatic melanoma patients: pre-clinical development at the Sheba Medical Center. Isr Med Assoc J 8:164-168.
72. Spiess, P.J., Yang, J.C., and Rosenberg, S.A. 1987. In vivo antitumor activity of tumor-infiltrating lymphocytes expanded in recombinant interleukin-2. J Natl Cancer Inst 79:1067-1075.
73. Dudley, M.E., Wunderlich, J.R., Yang, J.C., Sherry, R.M., Topalian, S.L., Restifo, N.P., Royal, R.E., Kammula, U., White, D.E., Mavroukakis, S.A., et al. 2005. Adoptive cell transfer therapy following non-myeloablative but lymphodepleting chemotherapy for the treatment of patients with refractory metastatic melanoma. J Clin Oncol 23:2346-2357.
74. Dudley, M.E., Yang, J.C., Sherry, R., Hughes, M.S., Royal, R., Kammula, U., Robbins, P.F., Huang, J., Citrin, D.E., Leitman, S.F., et al. 2008. Adoptive cell therapy for patients with metastatic melanoma: evaluation of intensive myeloablative chemoradiation preparative regimens. J Clin Oncol 26:5233-5239.
75. Dudley, M.E., Gross, C.A., Langhan, M.M., Garcia, M.R., Sherry, R.M., Yang, J.C., Phan, G.Q., Kammula, U.S., Hughes, M.S., Citrin, D.E., et al. 2010. CD8+ enriched "young" tumor infiltrating lymphocytes can mediate regression of metastatic melanoma. Clin Cancer Res 16:6122-6131.
76. Rosenberg, S.A., Yang, J.C., Sherry, R.M., Kammula, U.S., Hughes, M.S., Phan, G.Q., Citrin, D.E., Restifo, N.P., Robbins, P.F., Wunderlich, J.R., et al. 2011. Durable complete responses in heavily pretreated patients with metastatic melanoma using T-cell transfer immunotherapy. Clin Cancer Res 17:4550-4557.
77. Besser, M.J., Shapira-Frommer, R., Treves, A.J., Zippel, D., Itzhaki, O., Schallmach, E., Kubi, A., Shalmon, B., Hardan, I., Catane, R., et al. 2009. Minimally cultured or selected autologous tumor-infiltrating lymphocytes after a lympho-depleting chemotherapy regimen in metastatic melanoma patients. J Immunother 32:415-423.
78. Besser, M.J., Shapira-Frommer, R., Treves, A.J., Zippel, D., Itzhaki, O., Hershkovitz, L., Levy, D., Kubi, A., Hovav, E., Chermoshniuk, N., et al. 2010. Clinical responses in a phase II study using

adoptive transfer of short-term cultured tumor infiltration lymphocytes in metastatic melanoma patients. Clin Cancer Res 16:2646-2655.

79. Ellebaek, E., Iversen, T.Z., Junker, N., Donia, M., Engell-Noerregaard, L., Met, O., Holmich, L.R., Andersen, R.S., Hadrup, S.R., Andersen, M.H., et al. 2012. Adoptive cell therapy with autologous tumor infiltrating lymphocytes and low-dose Interleukin-2 in metastatic melanoma patients. J Transl Med 10:169.
80. Besser, M.J., Shapira-Frommer, R., Itzhaki, O., Treves, A.J., Zippel, D.B., Levy, D., Kubi, A., Shoshani, N., Zikich, D., Ohayon, Y., et al. 2013. Adoptive transfer of tumor-infiltrating lymphocytes in patients with metastatic melanoma: intent-to-treat analysis and efficacy after failure to prior immunotherapies. Clin Cancer Res 19:4792-4800.
81. Anderson, A., Donia, M., Holz-Borch, T., Ellebaek-Steensgaard, E., Zeeeberg-Iversen, T., Kongsted, P., Anderson, M.H., Straten, P.T., and Svane, I.M. 2014. Adoptive cell therapy with tumor infiltrating lymphocytes and intermediate dose IL-2 for metastatic melanoma. 29th Annual Meeting of the Society for the Immunotherapy of Cancer (SITC).
82. Radvanyi, L.G., Bernatchez, C., Zhang, M., Fox, P.S., Miller, P., Chacon, J., Wu, R., Lizee, G., Mahoney, S., Alvarado, G., et al. 2012. Specific lymphocyte subsets predict response to adoptive cell therapy using expanded autologous tumor-infiltrating lymphocytes in metastatic melanoma patients. Clin Cancer Res 18:6758-6770.
83. Pilon-Thomas, S., Kuhn, L., Ellwanger, S., Janssen, W., Royster, E., Marzban, S., Kudchadkar, R., Zager, J., Gibney, G., Sondak, V.K., et al. 2012. Efficacy of adoptive cell transfer of tumor-infiltrating lymphocytes after lymphopenia induction for metastatic melanoma. J Immunother 35:615-620.
84. Ogino, T., Shigyo, H., Ishii, H., Katayama, A., Miyokawa, N., Harabuchi, Y., and Ferrone, S. 2006. HLA class I antigen down-regulation in primary laryngeal squamous cell carcinoma lesions as a poor prognostic marker. Cancer Res 66:9281-9289.
85. Kong, C.S., Narasimhan, B., Cao, H., Kwok, S., Erickson, J.P., Koong, A., Pourmand, N., and Le, Q.T. 2009. The relationship between human papillomavirus status and other molecular prognostic markers in head and neck squamous cell carcinomas. Int J Radiat Oncol Biol Phys 74:553-561.
86. Wansom, D., Light, E., Worden, F., Prince, M., Urba, S., Chepeha, D.B., Cordell, K., Eisbruch, A., Taylor, J., D'Silva, N., et al. 2010. Correlation of cellular immunity with human papillomavirus 16 status and outcome in patients with advanced oropharyngeal cancer. Arch Otolaryngol Head Neck Surg 136:1267-1273.
87. Ward, M.J., Thirdborough, S.M., Mellows, T., Riley, C., Harris, S., Suchak, K., Webb, A., Hampton, C., Patel, N.N., Randall, C.J., et al. 2014. Tumour-infiltrating lymphocytes predict for outcome in HPV-positive oropharyngeal cancer. Br J Cancer 110:489-500.
88. Wansom, D., Light, E., Thomas, D., Worden, F., Prince, M., Urba, S., Chepeha, D., Kumar, B., Cordell, K., Eisbruch, A., et al. 2012. Infiltrating lymphocytes and human papillomavirus-16--associated oropharyngeal cancer. Laryngoscope 122:121-127.
89. Junker, N., Andersen, M.H., Wenandy, L., Dombernowsky, S.L., Kiss, K., Sorensen, C.H., Therkildsen, M.H., Von Buchwald, C., Andersen, E., Straten, P.T., et al. 2011. Bimodal ex vivo

expansion of T cells from patients with head and neck squamous cell carcinoma: a prerequisite for adoptive cell transfer. Cytotherapy 13:822-834.

90. Junker, N., Kvistborg, P., Kollgaard, T., Straten, P., Andersen, M.H., and Svane, I.M. 2012. Tumor associated antigen specific T-cell populations identified in ex vivo expanded TIL cultures. Cell Immunol 273:1-9.
91. Mougdil, T., Paustian, C., Feng, Z., Leidne, r.R., Dubay, C., Curti, B., Hu, H.-M., Bifulco, C., Fox, B., and Bell, B. 2015. An Evaluation of autologous tumor-reactive TIL generation from head and neck squamous cell cancers. J ImmunoTherapy of Cancer 3 37.
92. Goff, S.L., Smith, F.O., Klapper, J.A., Sherry, R., Wunderlich, J.R., Steinberg, S.M., White, D., Rosenberg, S.A., Dudley, M.E., and Yang, J.C. 2010. Tumor infiltrating lymphocyte therapy for metastatic melanoma: analysis of tumors resected for TIL. J Immunother 33:840-847.
93. Leidner, R., BD, C., Payne, R., Urba, W., Bahjat, K., Koguchi, Y., Nelson, K., Moore, J., Crittenden, M., Ying, Y., et al. 2015. Adoptive TIL in HPV-negative Oral SCCA. J ImmunoTherapy of Cancer 3:26.
94. Dudley, M.E., Wunderlich, J.R., Robbins, P.F., Yang, J.C., Hwu, P., Schwartzentruber, D.J., Topalian, S.L., Sherry, R., Restifo, N.P., Hubicki, A.M., et al. 2002. Cancer regression and autoimmunity in patients after clonal repopulation with antitumor lymphocytes. Science 298:850-854.
95. Eisenhauer EA, et al. New response evaluation criteria in solid tumours: revised RECIST guideline (version 1.1). Eur J Cancer. 2009 Jan;45(2):228-47.

16. APPENDICIES

16.1. Schedule of Assessments

	Pre Treatment 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 -14**	**Day -7**	**Day -6**	**Days -5, -4, -3, -2, -1**	**Day 0 (LN-145 Infusion Visit)**
Visit Window	up to 4 weeks (28 days)	N/A	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						
Physical Exam [1]	X		X	X	X	X	X
Vital Signs [2]	X	X	X	X	X	X	X [3]
ECOG performance status	X	X	X	X			X
Safety blood and urine tests [4]	X	X	X	X	X	X	X
ß-HCG Serum Pregnancy Test	X		X				
Virus testing [5]	X						
HLA typing [6]	X						
HPV Serotype		X					
CMV Antigen Assay [7]	X			X	X	X	X
Estimated Creatinine Clearance [8]	X	X	X	X	X	X	X
Eye Exam	X						
Cardiac Evaluations [9]	X						
Pulmonary function tests [10]	X						
Colonoscopy [11]	X						
Tumor Assessments [12]	X		X				
Response Assessments (RECIST v. 1.1)							
Concomitant Meds	X	X [13]	X	X	X	X	X
Adverse events	X	X	X	X	X	X	X
Tumor Harvest for TIL [14]		X					
Slides from resected tumor		X					
PBMC genetic sequencing		X					
NMA lymphodepletion [15]				X	X	X	
LN-145 Infusion [16]							X
IL-2 600,000 IU/kg [17]							
TMP/SMX DS [18]							X
Filgrastim [19]							
Fluconazole [20]							
Anti-viral [21]							
Immune Monitoring [22]		X		X			

	Treatment Phase				
	Visits 12, 13, 14, 15	**Visit 16**	**Visit 17**	**Visit 18**	**Visit 19**
Visit Name	**Days 1, 2, 3, 4**	**Day 14**	**Day 28 (Month 1)**	**Day 56 (Month 2)**	**Day 84 (Month 3)**
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					
Physical Exam [1]	X	X	X	X	X
Vital Signs [2]	X	X	X	X	X
ECOG performance status			X	X	X
Safety blood and urine tests [4]	X	X	X	X	X
ß-HCG Serum Pregnancy Test					
Virus testing [5]					
HLA typing [6]					
HPV Serotype					
CMV Antigen Assay [7]	X	X	X	X	X
Estimated Creatinine Clearance [8]	X	X	X	X	X
Eye Exam					
Cardiac Evaluations [9]					
Pulmonary function tests [10]					
Colonoscopy [11]					
Tumor Assessments [12]			X	X	X
Response Assessments (RECIST v 1.1)			X	X	X
Concomitant Meds	X	X	X	X	X
Adverse events	X	X	X	X	X
Tumor Harvest for TIL [14]					
Slides from resected tumor					
PBMC genetic sequencing					
NMA lymphodepletion [15]					
LN-145 Infusion [16]					
IL-2 600,000 IU/kg [17]	X				
TMP/SMX DS [18]	X	X	X	X	X
Filgrastim [19]	X	X	X	X	X
Fluconazole [20]	X	X	X	X	X
Anti-viral [21]	X	X	X	X	X
Immune Monitoring [22]	X	X	X	X	X

	Long Term Follow Up Phase						
	Visit 20	**Visit 21**	**Visit 22**	**Visit 23**	**Visit 24**	**Visit 25**	**ETV [23]**
Visit Name	**Day 112 (Month 4)**	**Day 168 (Month 6)**	**Day 252 (Month 9)**	**Day 336 (Month 12)**	**Day 504 (Month 18)**	**Day 672 (Month 24)**	**Early Termination Visit**
Visit Window	(+/- 7 days)	(+/- 7 days)	(+/- 7 days)	(+/- 7 days)	(+/- 21 days)	(+/- 21 days)	(+/- 3 days)
Informed Consent							
Inclusion/Exclusion							
Demographic Data							
Medical History							
Documentation of diagnosis							
Documentation of HPV status							
Physical Exam [1]	X	X	X	X	X	X	X
Vital Signs [2]	X	X	X	X	X	X	X
ECOG performance status	X	X	X	X	X	X	X
Safety blood and urine tests [4]	X	X	X	X	X	X	X
ß-HCG Serum Pregnancy Test							
Virus testing [5]							
HLA typing [6]							
HPV Serotype							
CMV Antigen Assay [7]	X	X	X	X	X	X	X
Estimated Creatinine Clearance [8]	X	X	X	X	X	X	X
Eye Exam							
Cardiac Evaluations [9]							
Pulmonary function tests [10]							
Colonoscopy [11]							
Tumor Assessments [12]	X	X	X	X	X	X	X
Response Assessments (RECIST 1.1)	X	X	X	X	X	X	X
Concomitant Meds	X	X	X	X	X	X	X
Adverse events	X	X	X	X	X	X	X
Tumor Harvest for TIL [14]							
Slides from resected tumor							
PBMC genetic sequencing							
NMA lymphodepletion [15]							
LN-145 Infusion [16]							
IL-2 600,000 IU/kg [17]							
TMP/SMX DS [18]							
Filgrastim [19]							
Fluconazole [20]							
Anti-viral [21]							
Immune Monitoring [22]	X	X	X	X	X	X	X

[1] Physical examination (PE) will include gastrointestinal (abdomen, liver), cardiovascular, extremities, head, eyes, ears, nose, and throat, respiratory system, skin, psychiatric (mental status), general nutrition. PE conducted during follow-up will be symptom directed.
[2] Vital signs will include height, weight, heart rate, respiratory rate, blood pressure, and temperature. Height will be measured at Screening only. BSA and BMI shall be Calculated at Visit 4 (Day -7) only.
[3] On Day 0 (LN-145 infusion), vital signs will be monitored every 30 minutes during infusion then hourly (+/-15 minutes) for four hours and then routinely (every four to six hours), unless otherwise clinically indicated, for up to approximately 24 hours post TIL infusion.
[4] Chemistry: sodium, potassium, chloride, total CO2, or bicarbonate, creatinine, glucose, BUN, albumin, calcium, magnesium, phosphorus, alkaline phosphatase, ALT/SGPT, AST/SGOT, total bilirubin, direct bilirubin, LDH, total protein, total CK, uric acid. Thyroid panel (to include TSH and Free T4) is to be done at Visits 1 and 19 or as clinically indicated.
Hematology: CBC with differential
Urinalysis Dipstick: A complete urine culture shall be conducted if indicated
[5] HIV antibody titer; Hepatitis - HbsAG determination (HSV-1 IgG and HSV-2 IgG) and anti HCV; CMV antigen assay; Anti-CMV antibody titer; HSV serology; EBV viral capsid antigen (VCA) IgG and/or Epstein Barr nuclear antigen (EBNA) IgG (may be within previous 3 months to Visit 2).
[6] HLA typing by central laboratory. .
[7] CMV assay to be completed at Screening and every other specified visit only if clinically indicated
[8] Estimated CrCl based on the Cockcroft-Gault calculation.
[9] Cardiac Evaluations consist of Stress Thallium, ECHO or MUGA and ECG. See section 5.17 for further descriptions.
[10] Pulmonary evaluation using spirometry will be completed for all patients.
[11] Colonoscopy only required for documented Grades 2 or greater diarrhea or colitis as a result of previously immunotherapy within six months from screening. Patients who have had a previous colonoscopy within six months from Visit 2 and demonstrate the visual appearance of the absence of inflammation will not need to repeat the colonoscopy.
[12] CT Scans of head, neck and chest, are required at the indicated time points. Additional anatomical locations may be scanned if clinically indicated. Scans will be read centrally. MRI or PET scans will be allowed for patients who have an intolerability to contrast media. The imaging modality used must be uniform for the duration of the study.
[13] Include only medications that are NOT part of the tumor harvest procedure.
[14] See Section 5.25.
[15] Cyclophosphamide with mesna for 2 days followed by fludarabine for 5 days. See Section 5.27.
[16] LN-145 infusion is to be done 1 to 2 days after the last dose of agent in the NMA lymphodepletion regimen. See Section 5.28
[17] Initiate IL-2 at 600,000 IU/kg within approximately 12 to 24 hours after LN-145 infusion and continue every eight hours for up to six doses. See Section 5.29.
[18] Prophylactic antibiotics such as TMP/SMX DS 160 mg/800 mg may be given as clinically indicated, per standard of care.
[19] Filgrastim 5 µg/kg/day SC; this will be administered each day until the absolute neutrophil count reaches >1000/mm3 for three consecutive days. Filgrastim at doses > 300 µg per day is allowed if this is the institutional standard protocol
[20] Fluconazole 400 mg PO daily. This should be administered each day until the absolute neutrophil count reaches >1000/mm3.
[21] Anti-viral treatment will be initiated in Patients positive for HSV. Valacyclovir PO or acyclovir IV will be administered daily, and continued until CD4 > 200 cells/mm3.
[22] 50 mL of blood drawn using vacutainers; refer to the Laboratory Manual. Site should make best effort should be made to collect follow-up samples at Months 4 and 6.
[23] The Early Termination Visit is completed if discontinuation from the study occurs for at any time after Visit 2 and before Visit 25.

16.2. 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 (e.g., 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.

16.3. 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 > 30.0 kg/m^2), the practical weight will be used.

16.3.1. BMI

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

16.3.2. BSA

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

16.3.3. 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 > 30.0 kg/m^2.
Note: Practical weight will NOT be used in the calculation of dose for IL-2.

16.3.3.1.1. 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

16.4. Common Terminology Criteria for Adverse Events

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

16.5. Expected Toxicities

16.5.1. LN-145

Overall, toxicities or adverse events during the LN-145 infusion have almost entirely been associated with the either the non-myeloablative lymphodepletion regimen or the high-dose IL-2 therapy given after TIL infusion. The following adverse events have been observed in published studies that treated patients with TIL products prepared by a process highly similar to 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) (8) following TIL infusion.
- Autoimmune melanocyte destruction resulting in conditions such as vitiligo and uveitis have been reported.

In addition, it should be noted that 2 deaths have been reported in conjunction with the lymphodepletion/TIL/IL-2 protocol. One patient died of cardiac failure caused by cyclophosphamide before receiving the TIL infusion (10), and the other patient developed an EBV lymphoproliferative disease 4 months after treatment and died of this lymphoma 8 months later (3).

16.5.2. NMA Lymphodepletion

The use of the NMA lymphodepletion regimen (cyclophosphamide and fludarabine) prior to cell administration increases the toxicity of this treatment as profound myelosuppression occurs in all Patients. A summary of risks expected with use of each of these agents is provided below. Full prescribing information for cyclophosphamide and fludarabine are provided in Section 16.5.2.1.1 and Section 16.5.2.2.1 , respectively.

16.5.2.1. Cyclophosphamide

16.5.2.1.1. Package Insert for Cyclophosphamide

http://www.accessdata.fda.gov/drugsatfda_docs/label/2013/012141s090,012142s112lbl.pdf

16.5.2.1.2. Contraindications

Hypersensitivity

Cyclophosphamide is contraindicated in patients who have a history of severe hypersensitivity reactions to it, any of its metabolites, or to other components of the product. Anaphylactic reactions including death have been reported with cyclophosphamide. Possible cross-sensitivity with other alkylating agents can occur.

Urinary Outflow Obstruction

Cyclophosphamide is contraindicated in patients with urinary outflow obstruction.

16.5.2.1.3. Warning and Precautions

Myelosuppression, Immunosuppression, Bone Marrow Failure and Infections

Cyclophosphamide can cause myelosuppression (leukopenia, neutropenia, thrombocytopenia and anemia), bone marrow failure, and severe immunosuppression which may lead to serious and sometimes fatal infections, including sepsis and septic shock. Latent infections can be reactivated.

Monitoring of complete blood counts is essential during cyclophosphamide treatment so that the dose can be adjusted, if needed. Cyclophosphamide should not be administered to patients with neutrophils ≤1,500/mm3 and platelets < 50,000/mm3. Cyclophosphamide treatment may not be indicated, or should be interrupted, or the dose reduced, in patients who have or who develop a serious infection. G-CSF may be administered to reduce the risks of neutropenia complications associated with cyclophosphamide use. For additional information, see Section 5.1 of Full Prescribing Information.

Urinary Tract and Renal Toxicity

Hemorrhagic cystitis, pyelitis, ureteritis, and hematuria have been reported with cyclophosphamide. Urotoxicity can occur with short-term or long-term use of cyclophosphamide and can be fatal.

Discontinue cyclophosphamide therapy in case of severe hemorrhagic cystitis. Urotoxicity (bladder ulceration, necrosis, fibrosis, contracture and secondary cancer) may require interruption of cyclophosphamide treatment or cystectomy.

Before starting treatment, exclude or correct any urinary tract obstructions [see Contraindications]. Urinary sediment should be checked regularly for the presence of erythrocytes and other signs of urotoxicity and/or nephrotoxicity. Cyclophosphamide should be used with caution, if at all, in patients with active urinary tract infections. Aggressive hydration with forced diuresis and frequent bladder emptying can reduce the frequency and severity of bladder toxicity. Mesna has been used to prevent severe bladder toxicity.

Cardiotoxicity

Myocarditis, myopericarditis, pericardial effusion including cardiac tamponade, and congestive heart failure, which may be fatal, have been reported with cyclophosphamide therapy.

Supraventricular arrhythmias (including atrial fibrillation and flutter) and ventricular arrhythmias (including severe QT prolongation associated with ventricular tachyarrhythmia) have been reported after treatment with regimens that included cyclophosphamide.

Monitor patients with risk factors for cardiotoxicity and with pre-existing cardiac disease.
For additional information, see Section 5.3 of Full Prescribing Information.

Pulmonary Toxicity

Pneumonitis, pulmonary fibrosis, pulmonary veno-occlusive disease and other forms of pulmonary toxicity leading to respiratory failure have been reported during and following treatment with cyclophosphamide. Late onset pneumonitis (greater than 6 months after start of cyclophosphamide) appears to be associated with increased mortality. Pneumonitis may develop years after treatment with cyclophosphamide.
Monitor patients for signs and symptoms of pulmonary toxicity.

Secondary Malignancies

Cyclophosphamide is genotoxic (see 13.1 [Nonclinical Toxicology] of Full Prescribing Information). Secondary malignancies (urinary tract cancer, myelodysplasia, acute leukemias, lymphomas, thyroid cancer, and sarcomas) have been reported in patients treated with cyclophosphamide-containing regimens.

Veno-occlusive Liver Disease

Veno-occlusive liver disease (VOD) including fatal outcome has been reported in patients receiving cyclophosphamide-containing regimens. A cytoreductive regimen in preparation for bone marrow transplantation that consists of cyclophosphamide in combination with whole-body irradiation, busulfan, or other agents has been identified as a major risk factor. For additional information, see Section 5.6 of Full Prescribing Information.

Embryo-Fetal Toxicity

Cyclophosphamide can cause fetal harm when administered to a pregnant woman (see Section 8.1 [Use in Specific Populations] of Full Prescribing Information). Exposure to cyclophosphamide during pregnancy may cause birth defects, miscarriage, fetal growth retardation, and fetotoxic effects in the newborn. Cyclophosphamide is teratogenic and embryo-fetal toxic in mice, rats, rabbits and monkeys.
Advise female patients of reproductive potential to avoid becoming pregnant and to use highly effective contraception during treatment and for up to 1 year after completion of therapy.

Infertility

Male and female reproductive function and fertility may be impaired in patients being treated with cyclophosphamide. Cyclophosphamide interferes with oogenesis and spermatogenesis. It may cause sterility in both sexes. Development of sterility appears to depend on the dose of cyclophosphamide,

duration of therapy, and the state of gonadal function at the time of treatment. Cyclophosphamide-induced sterility may be irreversible in some patients. Advise patients on the potential risks for infertility.

Wound Healing

Cyclophosphamide may interfere with normal wound healing. See Section 5.9 of Full Prescribing Information.

Hyponatremia

Hyponatremia associated with increased total body water, acute water intoxication. A syndrome resembling syndrome of inappropriate secretion of antidiuretic hormone (SIADH), which may be fatal, has been reported.

16.5.2.1.4. Common Adverse Events

Hematopoietic system

Neutropenia occurs in patients treated with cyclophosphamide. The degree of neutropenia is particularly important because it correlates with a reduction in resistance to infections. Fever without documented infection has been reported in neutropenic patients.

Gastrointestinal system

Nausea and vomiting occur with cyclophosphamide therapy. Anorexia and, less frequently, abdominal discomfort or pain and diarrhea may occur. There are isolated reports of hemorrhagic colitis, oral mucosal ulceration and jaundice occurring during therapy.

Skin

Alopecia occurs in patients treated with cyclophosphamide. Skin rash occurs occasionally in patients receiving the drug. Pigmentation of the skin and changes in nails can occur.

16.5.2.1.5. Post-Marketing Experience

The following adverse reactions have been identified from clinical trials or post-marketing surveillance. Because they are reported from a population from unknown size, precise estimates of frequency cannot be made.

Cardiac

Cardiac arrest, ventricular fibrillation, ventricular tachycardia, cardiogenic shock, pericardial effusion (progressing to cardiac tamponade), myocardial hemorrhage, myocardial infarction, cardiac failure (including fatal outcomes), cardiomyopathy, myocarditis, pericarditis, carditis, atrial fibrillation, supraventricular arrhythmia, ventricular arrhythmia, bradycardia, tachycardia, palpitations, QT prolongation.

Congenital, Familial and Genetic

Intra-uterine death, fetal malformation, fetal growth retardation, fetal toxicity (including myelosuppression, gastroenteritis).

Ear and Labyrinth

Deafness, hearing impaired, tinnitus.

Endocrine

Water intoxication.

Eye

Visual impairment, conjunctivitis, lacrimation.

Gastrointestinal

Gastrointestinal hemorrhage, acute pancreatitis, colitis, enteritis, cecitis, stomatitis, constipation, parotid gland inflammation.

General Disorders and Administrative Site Conditions

Multi-organ failure, general physical deterioration, influenza-like illness, injection/infusion site reactions (thrombosis, necrosis, phlebitis, inflammation, pain, swelling, erythema), pyrexia, edema, chest pain, mucosal inflammation, asthenia, pain, chills, fatigue, malaise, headache.

Hematologic

Myelosuppression, bone marrow failure, disseminated intravascular coagulation and hemolytic uremic syndrome (with thrombotic microangiopathy).

Hepatic

Veno-occlusive liver disease, cholestatic hepatitis, cytolytic hepatitis, hepatitis, cholestasis; hepatotoxicity with hepatic failure, hepatic encephalopathy, ascites, hepatomegaly, blood bilirubin increased, hepatic function abnormal, hepatic enzymes increased.

Immune

Immunosuppression, anaphylactic shock and hypersensitivity reaction.

Infections

The following manifestations have been associated with myelosuppression and immunosuppression caused by cyclophosphamide: increased risk for and severity of pneumonias (including fatal outcomes), other bacterial, fungal, viral, protozoal and, parasitic infections; reactivation of latent infections, (including viral hepatitis, tuberculosis), Pneumocystis jiroveci, herpes zoster, Strongyloides, sepsis and septic shock.

Investigations

Blood lactate dehydrogenase increased, C-reactive protein increased.

Metabolism and Nutrition

Hyponatremia, fluid retention, blood glucose increased, blood glucose decreased.

Musculoskeletal and Connective Tissue

Rhabdomyolysis, scleroderma, muscle spasms, myalgia, arthralgia.

Neoplasms

Acute leukemia, myelodysplastic syndrome, lymphoma, sarcomas, renal cell carcinoma, renal pelvis cancer, bladder cancer, ureteric cancer, thyroid cancer.

Nervous System

Encephalopathy, convulsion, dizziness, neurotoxicity has been reported and manifested as reversible posterior leukoencephalopathy syndrome, myelopathy, peripheral neuropathy, polyneuropathy, neuralgia, dysesthesia, hypoesthesia, paresthesia, tremor, dysgeusia, hypogeusia, parosmia.

Pregnancy

Premature labor.

Psychiatric

Confusional state.

Renal and Urinary

Renal failure, renal tubular disorder, renal impairment, nephropathy toxic, hemorrhagic cystitis, bladder necrosis, cystitis ulcerative, bladder contracture, hematuria, nephrogenic diabetes insipidus, atypical urinary bladder epithelial cells.

Reproductive System

Infertility, ovarian failure, ovarian disorder, amenorrhea, oligomenorrhea, testicular atrophy, azoospermia, oligospermia.

Respiratory

Pulmonary veno-occlusive disease, acute respiratory distress syndrome, interstitial lung disease as manifested by respiratory failure (including fatal outcomes), obliterative bronchiolitis, organizing pneumonia, alveolitis allergic, pneumonitis, pulmonary hemorrhage; respiratory distress, pulmonary hypertension, pulmonary edema, pleural effusion, bronchospasm, dyspnea, hypoxia, cough, nasal congestion, nasal discomfort, oropharyngeal pain, rhinorrhea.

Skin and Subcutaneous Tissue

Toxic epidermal necrolysis, Stevens-Johnson syndrome, erythema multiforme, palmar-plantar erythrodysesthesia syndrome, radiation recall dermatitis, toxic skin eruption, urticaria, dermatitis, blister, pruritus, erythema, nail disorder, facial swelling, hyperhidrosis.

Tumor lysis syndrome

Similar to other cytotoxic drugs, cyclophosphamide may induce tumor-lysis syndrome and hyperuricemia in patients with rapidly growing tumors.

Vascular

Pulmonary embolism, venous thrombosis, vasculitis, peripheral ischemia, hypertension, hypotension, flushing, hot flush.

16.5.2.2. Fludarabine (FLUDARA for INJECTION)

16.5.2.2.1. Package Insert for Fludarabine

http://www.accessdata.fda.gov/drugsatfda_docs/label/2009/020038s032lbl.pdf

16.5.2.2.2. Warning

BOXED WARNING

WARNING: FLUDARA FOR INJECTION should be administered under the supervision of a qualified physician experienced in the use of antineoplastic therapy. FLUDARA FOR INJECTION can severely suppress bone marrow function. When used at high doses in dose-ranging studies in patients with acute leukemia, FLUDARA FOR INJECTION was associated with severe neurologic effects, including blindness, coma, and death. This severe central nervous system toxicity occurred in 36% of patients treated with doses approximately four times greater (96 mg/m2/day for 5-7 days) than the recommended dose. Similar severe central nervous system toxicity has been rarely (≤0.2%) reported in patients treated at doses in the range of the dose recommended for chronic lymphocytic leukemia. Instances of life-threatening and sometimes fatal autoimmune hemolytic anemia have been reported to occur after one or more cycles of treatment with FLUDARA FOR INJECTION. Patients undergoing treatment with FLUDARA FOR INJECTION should be evaluated and closely monitored for hemolysis. In a clinical investigation using FLUDARA FOR INJECTION in combination with pentostatin (deoxycoformycin) for the treatment of refractory chronic lymphocytic leukemia (CLL), there was an unacceptably high incidence of fatal pulmonary toxicity. Therefore, the use of FLUDARA FOR INJECTION in combination with pentostatin is not recommended.

16.5.2.2.3. Precautions

General: FLUDARA FOR INJECTION is a potent antineoplastic agent with potentially significant toxic side effects. Patients undergoing therapy should be closely observed for signs of hematologic and non-hematologic toxicity. Periodic assessment of peripheral blood counts is recommended to detect the development of anemia, neutropenia and thrombocytopenia.

Tumor lysis syndrome associated with FLUDARA FOR INJECTION treatment has been reported in CLL patients with large tumor burdens. Since FLUDARA FOR INJECTION can induce a response as early as the first week of treatment, precautions should be taken in those patients at risk of developing this complication.

There are inadequate data on dosing of patients with renal insufficiency. FLUDARA FOR INJECTION must be administered cautiously in patients with renal insufficiency. The total body clearance of 2-fluoro-ara-A has been shown

to be directly correlated with creatinine clearance. Patients with moderate impairment of renal function (creatinine clearance 30-70 mL/min/1.73 m2) should have their Fludara dose reduced by 20% and be monitored closely. Fludara is not recommended for patients with severely impaired renal function (creatinine clearance less than 30 mL/min/1.73 m2). For additional precautions in special populations, refer to the Full Prescribing Information in Section 16.9.

16.5.2.2.4. Adverse Events

The most common adverse events include myelosuppression (neutropenia, thrombocytopenia and anemia), fever and chills, infection, and nausea and vomiting. Other commonly reported events include malaise, fatigue, anorexia, and weakness. Serious opportunistic infections have occurred in CLL patients treated with FLUDARA FOR INJECTION. Non-hematoglic AEs observed in two clinical trials of fludarabine in patients with chronic lymphocytic leukemia are shown in Table 4.

Table 4. Percent of Patients with Refractory CLL Reporting Non-Hematologic Adverse Events

Adverse Events	MDAH (N=101) %	SWOG (N=32) %
Any Adverse Event	88	91
Body as a Whole	72	84
Fever	60	69
Chills	11	19
Fatigue	10	38
Infection	33	44
Pain	20	22
Malaise	8	6
Diaphoresis	1	13
Alopecia	0	3
Anaphylaxis	1	0
Hemorrhage	1	0
Hyperglycemia	1	6
Dehydration	1	0
Neurological	21	69
Weakness	9	65
Paresthesia	4	12
Headache	3	0
Visual Disturbance	3	15
Hearing Loss	2	6

Adverse Events	MDAH (N=101) %	SWOG (N=32) %
Sleep Disorder	1	3
Depression	1	0
Cerebellar Syndrome	1	0
Impaired Mentation	1	0
Pulmonary	35	69
Cough	10	44
Pneumonia	16	22
Dyspnea	9	22
Sinusitis	5	0
Pharyngitis	0	9
Upper Respiratory Infection	2	16
Allergic Pneumonitis	0	6
Epistaxis	1	0
Hemoptysis	1	6
Bronchitis	1	0
Hypoxia	1	0
Gastrointestinal	46	63
Nausea/Vomiting	36	31
Diarrhea	15	13
Anorexia	7	34
Stomatitis	9	0
GI Bleeding	3	13
Esophagitis	3	0
Mucositis	2	0
Liver Failure	1	0
Abnormal Liver Function Test	1	3
Cholelithiasis	0	3
Constipation	1	3
Dysphagia	1	0
Cutaneous	17	18
Rash	15	15
Pruritus	1	3
Seborrhea	1	0
Genitourinary	12	22
Dysuria	4	3
Urinary Infection	2	15
Hematuria	2	3

Adverse Events	MDAH (N=101) %	SWOG (N=32) %
Renal Failure	1	0
Abnormal Renal Function Test	1	0
Proteinuria	1	0
Hesitancy	0	3
Cardiovascular 12 38	12	38
Edema	8	19
Angina	0	6
Congestive Heart Failure	0	3
Arrhythmia	0	3
Supraventricular Tachycardia	0	3
Myocardial Infarction	0	3
Deep Venous Thrombosis	1	3
Phlebitis	1	3
Transient Ischemic Attack	1	0
Aneurysm	1	0
Cerebrovascular Accident	0	3
Musculoskeletal	7	16
Myalgia	4	16
Osteoporosis	2	0
Arthralgia	1	0
Tumor Lysis Syndrome	1	0

Source: FLUDARA INJECTION Full Prescribing Information, October 2014.

The most frequently reported adverse events and those reactions which are more clearly related to the drug are arranged below according to body system.

Hematopoietic Systems

Hematologic events (neutropenia, thrombocytopenia, and/or anemia) were reported in the majority of CLL patients treated with FLUDARA FOR INJECTION. During FLUDARA FOR INJECTION treatment of 133 patients with CLL, the absolute neutrophil count decreased to less than 500/mm^3 in 59% of patients, hemoglobin decreased from pretreatment values by at least 2 grams percent in 60%, and platelet count decreased from pretreatment values by at least 50% in 55%. Myelosuppression may be severe, cumulative, and may affect multiple cell lines. Bone marrow fibrosis occurred in one CLL patient treated with FLUDARA FOR INJECTION.

Several instances of trilineage bone marrow hypoplasia or aplasia resulting in ancytopenia, sometimes resulting in death, have been reported in

postmarketing surveillance. The duration of clinically significant cytopenia in the reported cases has ranged from approximately 2 months to approximately 1 year. These episodes have occurred both in previously treated or untreated patients.

Life-threatening and sometimes fatal autoimmune hemolytic anemia have been reported to occur in patients receiving FLUDARA FOR INJECTION (see WARNINGS section). The majority of patients rechallenged with FLUDARA FOR INJECTION developed a recurrence in the hemolytic process.

Metabolic

Tumor lysis syndrome has been reported in CLL patients treated with FLUDARA FOR INJECTION. This complication may include hyperuricemia, hyperphosphatemia, hypocalcemia, metabolic acidosis, hyperkalemia, hematuria, urate crystalluria, and renal failure. The onset of this syndrome may be heralded by flank pain and hematuria.

Nervous System

(See WARNINGS section) Objective weakness, agitation, confusion, visual disturbances, and coma have occurred in CLL patients treated with FLUDARA FOR INJECTION at the recommended dose. Peripheral neuropathy has been observed in patients treated with FLUDARA FOR INJECTION and one case of wrist-drop was reported.

Pulmonary System

Pneumonia, a frequent manifestation of infection in CLL patients, occurred in 16%, and 22% of those treated with FLUDARA FOR INJECTION in the MDAH and SWOG studies, respectively. Pulmonary hypersensitivity reactions to FLUDARA FOR INJECTION characterized by dyspnea, cough and interstitial pulmonary infiltrate have been observed. In post-marketing experience, cases of severe pulmonary toxicity have been observed with Fludara use which resulted inARDS, respiratory distress, pulmonary hemorrhage, pulmonary fibrosis, and respiratory failure. After an infectious origin has been excluded, some patients experienced symptom improvement with corticosteroids.

Gastrointestinal System

Gastrointestinal disturbances such as nausea and vomiting, anorexia, diarrhea, stomatitis, and gastrointestinal bleeding have been reported in patients treated with FLUDARA FOR INJECTION.

Cardiovascular

Edema has been frequently reported. One patient developed a pericardial effusion possibly related to treatment with FLUDARA FOR INJECTION. No other severe cardiovascular events were considered to be drug related.

Genitourinary System

Rare cases of hemorrhagic cystitis have been reported in patients treated with

FLUDARA FOR INJECTION.

Skin

Skin toxicity, consisting primarily of skin rashes, has been reported in patients treated with FLUDARA FOR INJECTION.

16.5.3. IL-2

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

IL-2 treatment is also associated with impaired neutrophil function (reduced chemotaxis) and with an increased risk of disseminated infection, including sepsis and bacterial endocarditis. Consequently, preexisting bacterial infections should be adequately treated prior to initiation of IL-2 therapy. Patients with indwelling central lines are particularly at risk for infection with gram positive microorganisms. Antibiotic prophylaxis with oxacillin, nafcillin, ciprofloxacin, or vancomycin has been associated with a reduced incidence of staphylococcal infections. IL-2 administration should be withheld in Patients developing moderate to severe lethargy or somnolence; continued administration may result in coma.

The standard approach to the administration of high-dose IL-2 in all studies is to continue dosing until grade 3 or 4 events occur. The most commonly seen grade 4 events are pulmonary and renal impairment, and mental status changes. These toxicities may sometimes require intubation for protection of the Patient's airway. It is important to note that although these Patients require significant supportive measures during this period, all toxicities are reversible and the overwhelming majority of Patients have suffered no long term sequelae following this treatment regimen. However, fatal complications are possible and it is therefore only appropriate to carry out this experimental treatment in the context of life threatening metastatic cancer.

16.5.3.1.1. Package Insert for IL-2 (aldesleukin)

http://www.accessdata.fda.gov/drugsatfda_docs/label/2012/103293s5130lbl.pdf

16.5.3.1.2. Adverse Events

Adverse events reported in > 10% of participants in a clinical trial of IL-2 in 255 patients with metastatic renal cell cancer and 270 patients with metastatic melanoma were reported in the Proleukin® as listed in Table 5. Life-

threatening (Grade 4) AEs reported in the same patient populations are listed in Table 6.

Table 5. Adverse Events Reported in >10% of Patients in Two Clinical Trials of IL-2

Body System/Events	% Patients (N = 525)
Body as a whole	
Chills	52
Fever	29
Malaise	27
Asthenia	23
Infection	13
Pain	12
Abdominal pain	11
Enlarged Abdomen	10
Cardiovascular System	
Hypotension	71
Tachycardia	23
Vasodilation	13
Supraventricular Tachycardia	12
Cardiovascular disorder[a]	11
Arrhythmia	10
Digestive System	
Diarrhea	67
Vomiting	50
Nausea	35
Stomatitis	22
Anorexia	20
Nausea and Vomiting	19
Hematologic and Lymphatic	
Thrombocytopenia	37
Anemia	29
Leukopenia	16
Metabolic and Nutritional Disorders	
Bilirubinemia	40
Creatinine Increase	33
Peripheral Edema	28
SGOT increase	23
Weight gain	16

Body System/Events	% Patients (N = 525)
Edema	15
Acidosis	12
Hypomagnesemia	12
Hypocalcemia	11
Alkaline Phosphatase Increase	10
Nervous System	
Confusion	34
Somnolence	22
Anxiety	12
Dizziness	11
Respiratory System	
Dyspnea	43
Lung Disorder[b]	24
Respiratory Disorder[c]	11
Cough increase	11
Rhinitis	10
Skin and Appendages	
Rash	42
Pruritus	24
Exfoliative dermatitis	18
Urogenital System	
Oliguria	63

a Cardiovascular disorder: fluctuations in blood pressure, asymptomatic ECG changes, CHF.
b Lung disorder: physical findings associated with pulmonary congestion, rales, rhonchi.
c Respiratory disorder: ARDS, CXR infiltrates, unspecified pulmonary changes.
Source: Proleukin® Prescribing Information, January 2015.

Table 6. Life-Threatening (Grade 4) Adverse Events Reported in Patients in Two Clinical Trials of IL-2

Body System/Events	% Patients (N = 525)
	N (%)
Body as a whole	
Fever	5 (1)
Infection	7 (1)
Sepsis	6 (1)
Cardiovascular System	
Hypotension	15 (3)

Body System/Events	% Patients (N = 525)
Supraventricular Tachycardia	3 (1)
Cardiovascular disorder[a]	7 (1)
Myocardial infarct	7 (1)
Ventricular Tachycardia	5 (1)
Cardiac arrest	4 (1)
Digestive System	
Diarrhea	10 (2)
Vomiting	7 (1)
Hematologic and Lymphatic	
Thrombocytopenia	5 (1)
Coagulation disorder[b]	4 (1)
Metabolic and Nutritional Disorders	
Bilirubinemia	13 (2)
Creatinine Increase	5 (1)
SGOT increase	3 (1)
Acidosis	4 (1)
Nervous System	
Confusion	5 (1)
Stupor	3 (1)
Coma	8 (2)
Psychosis	7 (1)
Respiratory System	
Dyspnea	5 (1)
Respiratory Disorder[c]	14 (3)
Apnea	5 (1)
Urogenital System	
Oliguria	33 (6)
Anuria	25 (5)
Acute kidney failure	3 (1)

a Cardiovascular disorder: fluctuations in blood pressure, asymptomatic ECG changes, CHF.

b Lung disorder: physical findings associated with pulmonary congestion, rales, rhonchi.

c Respiratory disorder: ARDS, CXR infiltrates, unspecified pulmonary changes.

Source: Proleukin® Prescribing Information, January 2015.

Table 7. Management of IL-2 Toxicities

Expected toxicity	Expected Grade	Supportive Measures suggested	Stop Cycle*	Stop Treatment **
Chills	3	IV Meperidine 25-50 mg, IV q1h, prn,	No	No
Fever	3	Acetaminophen 650 mg, po, q4h; Indomethacin 50-75 mg, po, q8h	No	No

Expected toxicity	Expected Grade	Supportive Measures suggested	Stop Cycle*	Stop Treatment **
Pruritus	3	Hydroxyzine HCl 10-20 mg po q6h, prn; Diphenhydramine HCl 25-50 mg, po, q4h, prn	No	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 p.r., prn or 10 mg IV q6h prn	No	No
Diarrhea	3	Loperamide 2mg, po, q3h, prn; Diphenoxylate HCl 2.5 mg and atropine sulfate 25 µg, po, q3h, prn; codeine sulfate 30-60 mg, po, q4h, prn	If uncontrolled after 24 hours despite all supportive measures	No
Malaise	3 or 4	Bedrest interspersed with activity	If other toxicities occur simultaneously	No
Hyperbilirubinemia	3 or 4	Observation	If other toxicities occur simultaneously	No
Anemia	3 or 4	Transfusion with PRBCs	If uncontrolled despite all supportive measures	No
Thrombocytopenia	3 or 4	Transfusion with platelets	If uncontrolled despite all supportive measures	No
Edema/Weight gain	3	Diuretics prn	No	No
Hypotension	3	Fluid resuscitation Vasopressor support	If uncontrolled despite all supportive measures	No
Dyspnea	3 or 4	Oxygen or ventilatory support	If requires ventilatory support	No
Oliguria	3 or 4	Fluid boluses or dopamine at renal doses	If uncontrolled despite all supportive measures	No
Increased creatinine	3 or 4	Observation	Yes (Grade 4)	No
Renal failure	3 or 4	Dialysis	Yes	Yes

Expected toxicity	Expected Grade	Supportive Measures suggested	Stop Cycle*	Stop Treatment **
Pleural effusion	3	Thoracentesis	If uncontrolled despite all supportive measures	No
Bowel perforation	3	Surgical intervention	Yes	Yes
Confusion	3	Observation	Yes	No
Somnolence	3 or 4	Intubation for airway protection	Yes	Yes
Arrhythmia	3	Correction of fluid and electrolyte imbalances; chemical conversion or electrical conversion therapy	If uncontrolled despite all supportive measures	No
Elevated Troponin levels	3 or 4	Observation	Yes	If changes in LV function have not improved to baseline by next dose
Myocardial Infarction	4	Supportive care	Yes	Yes
Elevated transaminases	3 or 4	Observation	For Grade 4 without liver metastases	If changes have not improved to baseline by next dose
Electrolyte imbalances	3 or 4	Electrolyte replacement	If uncontrolled despite all supportive measures	No
Neutropenia	4	Observation	No	No

*Unless the toxicity is not reversed within 12 hours
** Unless the toxicity is not reversed to Grade 2 or less by next re-treatment.