CLINICAL PROTOCOL

A Phase 2, Multicenter Study to Assess the Efficacy and Safety of Autologous Tumor Infiltrating Lymphocytes (LN-144) for Treatment of Patients with Metastatic Melanoma

PROTOCOL NUMBER:	C-144-01
SPONSOR:	Iovance Biotherapeutics, Inc. 999 Skyway Rd, Suite 150 San Carlos, CA 94070 United States
PROTOCOL VERSION:	Final Version 7.0 (Incorporating Amendments 1 through 6)
PROTOCOL DATE:	23 March 2018
IND NUMBER:	16317
EudraCT NUMBER:	2017-000760-15

This study will be conducted in compliance with the protocol, Good Clinical Practice (CGP) and all other applicable regulatory requirements, including the archiving of essential documents.

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

SPONSOR PROTOCOL SIGNATURE PAGE

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

PPD

PPD

PPD

Date

INVESTIGATOR PROTOCOL SIGNATURE PAGE

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I agree to conduct the study as detailed in the protocol and in compliance with ICH Guidelines for Good Clinical Practice. I received a copy of the Investigator's Brochure.

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.

_____
Investigator Printed Name

_____ _____
Investigator Signature Date

SPONSOR MEDICAL MONITOR / EMERGENCY CONTACT INFORMATION

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PROTOCOL SYNOPSIS

Protocol Title:	A Phase 2, Multicenter Study to Assess the Efficacy and Safety of Autologous Tumor Infiltrating Lymphocytes (LN-144) for Treatment of Patients with Metastatic Melanoma
Study Type:	Phase 2
Indication:	Treatment of patients with metastatic melanoma who have progressed or not responded following prior systemic therapy
Investigational Agent:	LN-144: Autologous tumor infiltrating lymphocytes (TIL) derived from the patient's tumor
Study Objectives:	**Primary Objective** • To evaluate the efficacy of LN-144 in patients with metastatic melanoma using the objective response rate (ORR) as assessed by the Investigator per Response Evaluation Criteria in Solid Tumors (RECIST) 1.1. **Secondary Objectives** • To evaluate the efficacy endpoints of duration of response (DOR), disease control rate (DCR), and progression-free survival (PFS) as assessed by the Investigator per RECIST 1.1 • To further evaluate efficacy of LN-144 therapy in patients with metastatic melanoma by assessing ORR, DOR, DCR, and PFS as assessed by the Independent Review Committee (IRC) per RECIST 1.1 • To evaluate overall survival (OS) • To characterize the safety profile of LN-144 therapy in patients with metastatic melanoma **Exploratory Objectives** • To explore the persistence of LN-144 and potential immune correlates of response, outcome, and toxicity of the treatment • To explore efficacy based on immune-related RECIST (irRECIST) criteria, as assessed by the IRC • To assess health-related quality of life (HRQoL)
Study Design:	Prospective, interventional multicenter study evaluating adoptive cell therapy (ACT) with autologous TIL infusion (LN-144) followed by interleukin-2 (IL-2) after a nonmyeloablative lymphodepletion (NMA-LD) preparative regimen.
Dose and Treatment Schedule:	The cell transfer therapy used in this study involves patients receiving a NMA-LD preparative regimen, consisting of cyclophosphamide intravenous (IV) (60 mg/kg × 2 doses) with mesna 15 mg/kg and fludarabine IV (25 mg/m^2 × 5 doses), followed by infusion of tumor-derived autologous TIL (LN-144) and administration of IL-2 at 600,000 international units [IU]/kg approximately every 8 to 12 hours for up to a maximum of 6 doses, starting approximately 3 to 24 hours after completion of LN-144 infusion.

	Patients will receive 1 course of LN-144 treatment in Cohort 1 (noncryopreserved product or Gen 1) and Cohort 2 (cryopreserved product or Gen 2). Patients may enter Cohort 3 (retreatment cohort) if in the opinion of the Investigator they may benefit from the second treatment with TIL regimen and they meet protocol-specified criteria to receive retreatment. As of December 2017, the Sponsor has selected Gen 2 manufacturing as the method of choice and enrollment in Cohort 1 is closed, with all patients moving forward to be enrolled for initial LN-144 therapy in Cohort 2 only.
Duration of Study Participation:	**Screening:** Up to 4 weeks (28 days) from signing of the informed consent form (ICF) **Enrollment**: Upon tumor resection for TIL generation (1 day) **Treatment Period:** Up to 12 days, including NMA-LD (7 days) and LN-144 infusion followed by IL-2 (up to 4 days) **Response Assessment Period**: Patients will be evaluated for response at Week 6 (Day 42 ± 3 days) following the LN-144 infusion and every 6 weeks thereafter, for up to 6 months (Week 26) post-LN-144 infusion. After this 6-month period, patients will be evaluated for response assessment every 3 months (12 weeks) until the following criteria are met: • Disease progression • Start of a new anticancer therapy • Withdrawal of consent • Lost to Follow-Up • Death **Overall Survival Follow-Up Period**: Overall survival (OS) follow-up will start after completion of the Response Assessment Period and will continue with telephone contact every 3 months to obtain survival status and subsequent anticancer therapy information for up to 5 years for each patient from the last study treatment.
Number of Study Centers:	Approximately 60 clinical sites in the United States (US) and Europe
Number of Planned Patients:	The total number of patients to be enrolled across all cohorts will be approximately 85. A minimum of 60 patients who receive Gen 2 cryopreserved LN-144 infusion product manufactured at Good Manufacturing Practices (GMP) facilities in the US and Europe and who complete treatment. Treatment completion is defined as having received LN-144 infusion followed by at least 1 dose of IL-2. Patients who participate in initial TIL therapy in Cohort 1 or Cohort 2 may enter a third treatment cohort (Cohort 3) in which approximately 10 patients will be retreated with a second manufacturing/administration of LN-144 (TIL therapy).

Study Population: Diagnosis and Main Criteria for Inclusion:	a. Patients with unresectable or metastatic melanoma (Stage IIIc or Stage IV) who progressed following ≥ 1 lines of prior systemic therapy, including immune checkpoint inhibitor (eg, anti-PD-1), and if BRAF mutation-positive, after BRAF inhibitor systemic therapy. Patients must have no other therapy options that are expected to have significant benefit in the opinion of the Investigator and must have: • At least 1 measurable target lesion, as defined by RECIST 1.1. Lesions in previously irradiated areas should not be selected as target lesion, unless treatment was ≥ 3 months prior, and there has been demonstrated disease progression in the lesion • At least 1 resectable target lesion to generate TIL of a minimum 1.5 cm in diameter post-resection; surgical removal with minimal morbidity (defined as any procedure for which expected hospitalization is ≤ 3 days) b. Patients must be ≥ 18 years and ≤ 70 years of age at the time of consent. Enrollment of patients > 70 years of age may be allowed after consultation with the Medical Monitor c. Patients must have an Eastern Cooperative Oncology Group (ECOG) performance status of 0 or 1 and an estimated life expectancy of ≥ 3 months d. In the opinion of the Investigator, patient must be able to complete all study-required procedures e. Patients of childbearing potential or their partners of childbearing potential must be willing to practice an approved method of birth control during treatment and for 12 months after receiving last protocol-related therapy Approved methods of birth control are as follows: • Combined (estrogen and progestogen containing) hormonal birth control associated with inhibition of ovulation: oral; intravaginal; transdermal • Progestogen-only hormonal birth control associated with inhibition of ovulation: oral; injectable; implantable • Intrauterine device (IUD) • Intrauterine hormone-releasing system (IUS) • Bilateral tubal occlusion • Vasectomized partner • True sexual abstinence when this is in line with the preferred and usual lifestyle of the patient. Periodic abstinence (eg, calendar ovulation, symptothermal, post-ovulation methods) is not acceptable. f. Patients must have the following hematologic parameters: • Absolute neutrophil count (ANC) ≥ 1000/mm^3 • Hemoglobin ≥ 9.0 g/dL • Platelet count ≥ 100,000/mm^3 g. Patients must have adequate organ function: • Serum alanine transaminase (ALT)/ serum glutamic-pyruvic transaminase (SGPT) and aspartate transaminase (AST)/serum glutamic oxaloacetic transaminase (SGOT) ≤ 3 times the upper

	limit of normal [ULN]), patients with liver metastasis ≤ 5 times ULN • An estimated creatinine clearance (eCl_{Cr}) ≥ 40 mL/min using the Cockcroft-Gault formula at Screening • Total bilirubin ≤ 2 mg/dL o Patients with Gilbert's syndrome must have a total bilirubin ≤ 3 mg/dL h. Patients must be seronegative for the human immunodeficiency virus (HIV) antibody, hepatitis B antigens, and hepatitis C antibody or antigen i. Patients must have recovered from all prior therapy-related adverse events (AEs) to ≤ Grade 1 (per Common Terminology Criteria for Adverse Events [CTCAE] v4.03), except for alopecia or vitiligo, prior to enrollment (tumor resection), with a washout period from prior anticancer therapy(ies) to the start of planned NMA-LD of a minimum duration detailed as follows: • Targeted therapy: prior targeted therapy with a MEK/BRAF or other-directed agent, is allowed provided the washout period is a ≥ 21 days or 5 half-lives, whichever is longer prior to the start of NMA-LD • Chemotherapy: adjuvant, neoadjuvant or definitive chemotherapy/ chemoradiation is allowed provided the washout period is ≥ 21 days or 5 half-lives, whichever is longer prior to the start of NMA-LD • Immunotherapy: prior checkpoint-targeted therapy with an anti-CTLA-4/anti-PD-1, other monoclonal antibody (mAb), or vaccine is allowed if disease progression is confirmed prior to or within the washout period of ≥ 21 days before the start of NMA-LD • Palliative radiation therapy is permitted between biopsy and NMA-LD if it does not involve lesions being selected as target or nontarget • Patients may undergo preplanned procedures if within 2 to 3 weeks prior to the start of NMD-LD j. Patients with documented Grade 2 or higher diarrhea or colitis as a result of previous treatment with immune checkpoint inhibitor(s) must have been asymptomatic for at least 6 months and/or had a normal colonoscopy post immune checkpoint inhibitor treatment by visual assessment, prior to planned tumor resection k. Patients must have the ability to understand the requirements of the study, have provided written informed consent, as evidenced by signature on an informed consent form (ICF) approved by an Institutional Review Board/Independent Ethics Committee (IRB/IEC), and agree to abide by the study restrictions and return to the site for the required assessments l. Patients have provided written authorization for use and disclosure of protected health information

Main Criteria for Exclusion:	a. Patients with melanoma of uveal/ocular origin b. Patients who have received an organ allograft or prior cell transfer therapy that included a nonmyeloablative or myeloablative chemotherapy regimen (not applicable for patients in the retreatment Cohort 3) c. Patients with symptomatic and/or untreated brain metastases (of any size and any number) • Patients with definitively treated brain metastases may be considered for enrollment after discussion with the Medical Monitor, and must be stable for ≥ 2 weeks prior to the start of NMA-LD d. Patients who are pregnant or breastfeeding e. Patients who are on a systemic steroid therapy at a dose of > 10 mg of prednisone or equivalent per day • A short course of higher-dose steroid therapy is allowed in cases of exacerbation of known disease or for treatments of new acute symptoms f. Patients who have active medical illness(es) that in the opinion of the Investigator would pose increased risk for study participation that may include active systemic infections, such as syphilis, or any other infections requiring antibiotics, coagulation disorders, or other active major medical illnesses of the cardiovascular, respiratory, or immune system g. Patients who have any form of primary immunodeficiency (such as severe combined immunodeficiency disease [SCID] or acquired immunodeficiency syndrome [AIDS]) h. Patients who have a history of hypersensitivity to any component or excipient of the TIL therapy and other study drugs: • NMA-LD (cyclophosphamide, mesna, and fludarabine) • IL-2 • Antibiotics of the aminoglycoside group (ie, streptomycin, gentamicin) • Any component of the TIL infusion product formulation including dimethyl sulfoxide [DMSO], human serum albumin [HSA], IL-2, and dextran-40 i. Patients who have a left ventricular ejection fraction (LVEF) < 45% or New York Heart Association (NYHA) functional classification > Class 1 at Screening. All patients must have echocardiogram (ECHO) or multiple gated acquisition scan (MUGA) at Screening. For patients ≥ 60 years or patients who have a history of ischemic heart disease, chest pain, or clinically significant atrial and/or ventricular arrhythmias, a cardiac stress tests must be performed showing LVEF ≥45%, and if any wall movement abnormalities, they must be reversible. j. Patients who have obstructive or restrictive pulmonary disease and have a documented FEV_1 (forced expiratory volume in 1 second) of ≤ 60%

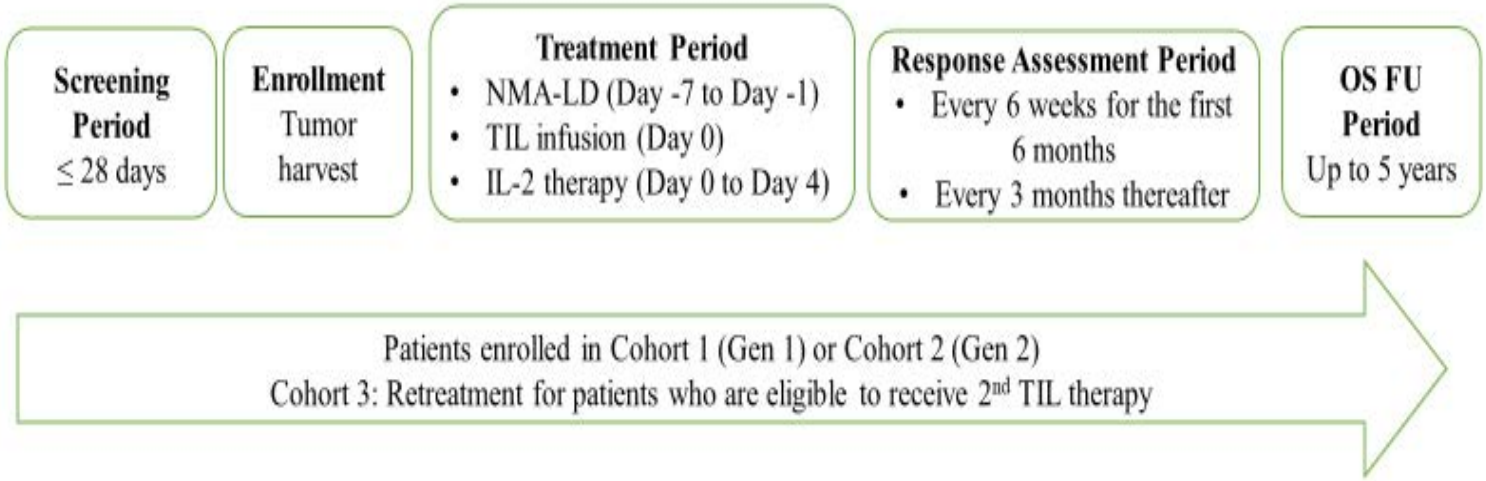
	k. Patients who have had another primary malignancy within the previous 3 years (with the exception of carcinoma in situ of the breast, cervix, or bladder, localized prostate cancer and nonmelanoma skin cancer that has been adequately treated) l. Patients who have been shown to be BRAF mutation positive (V600), but have not received prior systemic therapy with a BRAF-directed kinase inhibitor m. Patients who have received a live or attenuated vaccine within 28 days of the start of NMA-LD n. Patients whose cancer requires immediate attention or who would otherwise suffer a disadvantage by participating in this trial o. Patients protected by the following constraints: • Hospitalized persons without consent or persons deprived of liberty because of a judiciary or administrative decision • Adult persons with a legal protection measure or persons who cannot express their consent • Patients in emergency situations who cannot consent to participate in the trial
Treatment Cohorts:	LN-144 (autologous TIL) infusion is preceded by a NMA-LD preparative regimen of cyclophosphamide and fludarabine, and followed by IL-2, as an open-label treatment **Cohort 1:** LN-144 process without cryopreservation of the final TIL product (Gen 1 infusion product) **Cohort 2:** LN-144 process with cryopreservation of the final TIL product (Gen 2 infusion product) **Cohort 3:** Retreatment cohort: patients from Cohort 1 or Cohort 2 may rescreen for a second TIL regimen therapy if they meet all Inclusion and Exclusion Criteria (except exclusion criterion b). These patients may have a second tumor resection, especially when new lesions are available and feasible for resection. The decision for enrollment in Cohort 3 will be based on discussion between Principal Investigator and a Medical Monitor. As of December 2017, all patients receiving retreatment in Cohort 3 will receive the Gen 2 LN-144 infusion product.
Discontinuation from Treatment:	Criteria for discontinuation from treatment: • Grade 3 or greater drug-related immune AEs that involve vital organs (heart, kidneys, brain, eye, liver, colon, adrenal gland, lungs) with symptoms emerging following LN-144 infusion • Grade 3 or greater allergic reaction including bronchospasm or generalized urticaria that does not resolve after medical management in the opinion of the Investigator • Meeting criteria for permanent discontinuation of IL-2 treatment • Determination by the Investigator that continued treatment is not in the best interest of the patient • Administration of prohibited concomitant medication

Discontinuation from the Study	Criteria for discontinuation from the study at any time:
	• Full withdrawal of consent by patient
	  o Every effort should be made to continue overall survival follow-up
	• Administration of any other anticancer therapy(ies)
	  o Every effort should be made to continue overall survival follow-up
	• Lost to follow-up after 3 documented attempts to contact the patient
	• Death
	• Study terminated by the Sponsor

Efficacy Assessment:	The descriptive summary of the ORR, DOR, DCR, and PFS per cohort will be used to determine the potential efficacy of LN-144, as assessed by the Investigator per RECIST 1.1. Estimation of OS will depend on the date of death or the last known alive status.
Safety Assessment:	Adverse events (AEs) of any attribution will be collected from the time the patient signs the ICF up until completion of the response assessment period and/or the start of a new anticancer therapy. All AEs attributed to treatment will be collected from signing of the ICF from the start of a new anticancer therapy, lost to follow-up, or withdrawal of consent, whichever occurs first. Treatment-emergent adverse events (TEAEs), defined from the LN-144 infusion to 30 days thereafter, and clinical laboratory data will be evaluated to assess the safety of this treatment.
Overview of Statistical Plan	The primary statistical plan of analysis is based on estimation of efficacy and safety parameters will be performed by cohort. There is no planned statistical comparison among cohorts. Patients meeting RECIST 1.1 criteria for a confirmed complete (CR) or partial (PR) response and will be classified as responders in the analysis of the ORR. The best overall response result will be summarized using a point estimate and its 2-sided 95% confidence limits. All time-to-event efficacy endpoints will use the Kaplan-Meier method to summarize the data. The time origin for all such analyses (except for response duration) will be the date on which patients began treatment with LD. The assessment of safety data will be descriptive and based on the summarization of TEAEs, AEs, and serious AEs (SAEs), leading to discontinuation from treatment and the study, vital signs, physical examinations, and clinical laboratory tests. Patients who are retreated with LN-144 therapy (Cohort 3) will have their safety and efficacy data tabulated separately. Patients who received LN-144 for the first time in Cohort 3 due to a previous manufacturing failure or other reason, will be included in the original cohort for efficacy and safety analyses. There will be no formal comparisons among cohorts.

Sample Size Consideration:	The planned number of patients is approximately 85 including 60 patients in the Efficacy Analysis set who received either US or European manufactured Gen 2 LN-144 infusion product in Cohort 2. The lower 95% confidence limit for ORR is estimated per the Wilson Score method. The maximum half width of the 2-sided confidence limit is less than 12.3% when ORR is expected to range from 20% to 50%. The primary analysis will occur when more than 60 patients have been followed for a minimum of 6 months. This allows sufficient time for disease-controlled patients (SD or better) to demonstrate emergence and durability of response.
DSMB Safety Assessments:	An independent Data Safety Monitoring Board (DSMB) will evaluate cumulative safety data on the first 3 patients completing 12 weeks of assessment in Cohort 1 and Cohort 2, respectively. Enrollment will continue while under DSMB review. As of November 2017, the DSMB had reviewed the data from Cohort 1 and Cohort 2 and recommended to continue enrollment without any changes to the clinical study protocol. Additional evaluations of safety data may be specified in the DSMB charter.

Figure 1 Study Flowchart (All Cohorts)



Abbreviations: NMA-LD = nonmyeloablative lymphodepletion; TIL = tumor infiltrating lymphocytes; IL-2 = interleukin-2; OS = overall survival; FU = follow up; Gen 1 = generation 1; Gen 2 = generation 2

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LIST OF ABBREVIATIONS

ABX	antibiotics
ACT	adoptive cell therapy
AE	adverse event
AIDS	acquired immune deficiency syndrome
ALC	absolute lymphocyte count
ALT	alanine transaminase
ANC	absolute neutrophil count
APC	antigen presenting cell
AST	aspartate transaminase
BMI	body mass index
BRAF	proto-ongcogene B-Raf
BSA	body surface area
BUN	blood urea nitrogen
CBC	complete blood count
$CD4^+/CD8^+$	cluster of differentiation 4/8
CFR	Code of Federal Regulations
CK	creatinine clearance
ClCr	clearance creatinine
CLS	capillary leak syndrome
CMO	Contract Manufacturing Organization
CMV	cytomegalovirus
CNS	central nervous system
CO_2	carbon dioxide
CR	complete response
CT	computed tomography
CTL	cytotoxic T lymphocyte
CTLA	cytotoxic T lymphocyte-associated antigen
CTCAE v4.03	Common Terminology Criteria for Adverse Events Version 4.03
CY	cyclophosphamide
DC	dendritic cell
DCR	disease control rate
DNA	deoxyribonucleic acid
DOR	duration of response
DSMB	Data Safety Monitoring Board
EBV	Epstein-Barr virus
ECHO	echocardiogram
eClCr	estimated creatinine clearance using Cockroft-Gault formula
ECOG	Eastern Cooperative Oncology Group
eCRF	electronic case report form
EDC	electronic data capture
EKG	electrocardiogram
EORTC	European Organization for Research and Treatment of Cancer
EORTC QLQ-C30	European Organisation for Research and Treatment of Cancer Quality-of-Life Questionnaire - Core 30 instrument
EOS	end of study

ETV	early termination visit
EU	European Union
FDA	Food and Drug Administration
FDG-PET	flurodeoxyglucose positron emission tomography
FEV_1	forced expiratory volume in 1 second
FFPE	formalin-fixed, paraffin-embedded
FU	follow up
GCP	Good Clinical Practice
GDPR	General Data Protection Regulation
Gen	generation
GMP	Good Manufacturing Practices
Gp100	glycoprotein 100
HBcAg	hepatitis B core antibody (IgM)
HBsAg	hepatitis B surface antigen
β-HCG	β human chorionic gonadotropin
HIPAA	Health Insurance Portability and Accountability Act of 1996
HIT	heparin-induced thrombocytopenia
HIV	human immunodeficiency virus
HRQoL	health related quality of life
HSA	human serum albumin
HSV-1	herpes simplex virus-1
ICF	informed consent form
ICH	International Conference on Harmonization
ICU	intensive care unit
IEC	Independent Ethics Committee
IgG	immunoglobulin G
IgM	immunoglobulin M
IL-2	interleukin-2 (also known as “aldesleukin”)
IND	Investigational New Drug (Application)
IP	investigational product
IRB	Institutional Review Board
IRC	Independent Review Committee
irRECIST	immune-related Response Evaluation Criteria in Solid Tumors
IU	international unit
IUD	intrauterine device
IUS	intrauterine hormone-releasing system
IV	intravenous
LD	lymphodepletion
LDH	lactate dehydrogenase
LN-144	autologous tumor infiltrating lymphocytes
LPLD	last patient last dose
LVEF	left ventricular ejection fraction
mAb	monoclonal antibody
MART-1	myristylated Akt
MAGE	melanoma antigen gene
MEK	mitogen-activated extracellular signal-regulated kinase

MNC	mononucleated cells
MRI	magnetic resonance imaging
mRNA	messenger RNA (ribonucleic acid)
MUGA	multiple gated acquisition scan
NCCN	National Comprehensive Cancer Network
NCI	National Cancer Institute
NMA	nonmyeloablative
NY-ESO-01	immunogenic cancer testis antigen
OKT	muromonab CD3
ORR	objective response rate
OS	overall survival
PBMC	peripheral blood mononuclear cell
PD	progressive disease
PET	positron emission tomography
PFS	progression-free survival
PFT	pulmonary function test
PO	per Os (by mouth)
PR	partial response
PRBC	packed red blood cells
QD	(taken) once daily
RECIST	Response Evaluation Criteria in Solid Tumors
REP	rapid expansion protocol
RPR	rapid plasma reagin
SAE	serious adverse event
SAP	statistical analysis plan
SCID	severe combined immunodeficiency disease
SD	stable disease
SEER	Surveillance, Epidemiology, and End Results Program
SGOT	serum glutamic-oxaloacetic transaminase
SGPT	serum glutamic-pyruvic transaminase
SmPC	Summary of Product Characteristics
TCR	T-cell antigen receptor
TEAE	treatment-emergent adverse event
TH	tumor harvested patient population
TIL	tumor infiltrating lymphocyte
TME	tumor microenvironment
TMP-SMX DS	trimethoprim-sulfamethoxazole double strength
TRP-1	tyrosine-related protein-1
TSH	thyroid-stimulating hormone
UK	United Kingdom
ULN	upper limit of normal
US	United States
VCA	viral capsid antigen
VDRL	venereal disease research laboratory

1 INTRODUCTION

1.1 Background

An estimated 232,000 newly diagnosed cases of melanoma skin cancers occur globally each year, making it the fifth most common malignancy in men and sixth most common malignancy in women. [1] Unlike other malignancies, the incidence of melanoma is increasing by more than 3.2% and 2.4% per year in males and females, respectively. [2] Globally, the incidence rate varies with 20 to 30 new melanoma cases per 100,000 people in the United States (US), compared to ≤10 to 25 new melanoma cases per 100,000 people in the European Union (EU), and with the highest incidence of 50 to 60 per 100,000 inhabitants in Australia. [3] One estimate predicts 112,000 new cases of invasive melanoma in 2030 if the current trend continues, showing relative increases in new melanoma cases in ranging from 291% in Australia to 585% in the United Kingdom (UK). [4, 5] Of interest, individuals under the age of 45 years account for 25% of all new melanoma cases. [1]

The National Cancer Institute's Surveillance, Epidemiology, and End Results uptake (SEER) Program estimates that 9,730 deaths due to melanoma have occurred in 2017 in the US, despite the approvals of ipilimumab in 2011, pembrolizumab and nivolumab in 2014, and the rapid uptake of these immunotherapeutic agents. [2] The 5-year survival depends on the stage at diagnosis. Between 2005 and 2011, 98% of patients with local disease survived 5 years as opposed to 63% with regional lymph node disease and 17% with distant spread at the time of diagnosis. [4]

Current melanoma treatment guidelines are similar in Europe, the US, Canada, Australia, and New Zealand. [6] Approved first-line treatments for metastatic melanoma include immunotherapeutic strategies blocking PD-1 (pembrolizumab, nivolumab), or combining nivolumab- with the CTLA-4 blocker ipilimumab, or chemotherapy with agents targeting specific activating mutations in the BRAF pathway (eg, vemurafenib, dabrafenib, trametinib). Following disease progression, patients can receive additional treatment with anti-PD1 monotherapy; ipilimumab combination therapy; ipilimumab monotherapy; BRAF and/or MEK inhibitors, if BRAF mutant; high-dose aldesleukin (interleukin-2;

IL-2); chemotherapy [eg, dacarbazine, temozolomide, paclitaxel, cisplatin, carboplatin, vinblastine; or imatinib for KIT-mutant melanoma] (NCCN Guidelines Version 2.2016). [7] In 2015, talimogene laherparepvec, a live oncolytic virus therapy, was approved for the local treatment of unresectable cutaneous, subcutaneous, and nodal lesions in patients with melanoma recurrent after initial surgical excision. This product has not been shown to improve overall survival or to have an effect on visceral metastases. [8]

Until recently, high-dose aldesleukin was the only Food and Drug Administration (FDA)-approved systemic therapy for metastatic melanoma capable of inducing durable objective cancer responses, with an overall objective response rate (ORR) of 16% and durable complete responses (CRs) observed in up to 6% of treated patients. [9]
The recently approved PD-1 immune checkpoint inhibitors pembrolizumab and nivolumab approximately double the rate of durable responses in metastatic melanoma relative to IL-2 treatment. [10, 11] In previously treated patients, the ORR for nivolumab is 32%, with higher and more durable responses correlated with higher levels of PD-1 ligand expression by tumors; and the ORR for pembrolizumab following prior therapy with ipilimumab is 21%. In treatment-naïve patients, durable objective responses are achieved in 50% of patients when nivolumab and ipilimumab are administered in combination, although the CR rate remains low at 8.9%. [Opdivo® (nivolumab) Label, FDA, October 2016] Retreatment of patients who progressed post anti-PD-1 therapy with additional checkpoint inhibitors is often selected as a treatment option; however, overall response rates of 16% and 21% are the best reported for the ipilimumab or ipilimumab plus nivolumab, respectively. [12]

Use of the immune checkpoint inhibitors is associated with a spectrum of immune-related adverse events (AEs), including pneumonitis, colitis, hepatitis, nephritis, and renal dysfunction. [13, 14] Increased toxicity is observed in patients treated with nivolumab and ipilimumab combination therapy: Treatment-related adverse events leading to discontinuation of therapy occurred in 36.4%, 7.7%, and 14.8% of patients receiving the combination therapy, nivolumab alone, or ipilimumab alone, respectively. [10, 14]

Although the targeted therapies and immune checkpoint inhibitors can achieve dramatic responses in patients with metastatic melanoma, death rates for this cancer are projected to remain stable through 2030. The overall age-adjusted melanoma death rate was 2.7 per 100,000 in 2011 and remained at this level in 2015. [15]

Cell transfer therapy with autologous tumor-infiltrating lymphocyte (TIL) appears able to mediate durable complete responses in patients with metastatic melanoma and other solid tumors, irrespective of prior treatment, so that even heavily pretreated patients can show dramatic and durable responses. [16-18] present, however, only a limited number of clinical centers in the US with access to suitable Good Manufacturing Practice (GMP) manufacturing facilities are able to offer investigational therapy with autologous TIL. Furthermore, each institution follows its own procedure for production of TIL distinct from other institutions. Iovance Biotherapeutics, Inc. is utilizing the TIL manufacturing method developed by Dr. Steven A. Rosenberg's team at the National Cancer Institute (NCI) as a starting point in developing a robust GMP process for the production of LN-144, and in parallel, to execute a clinical development program designed to evaluate the efficacy and safety of LN-144 in the treatment of double-refractory melanoma.

The scientific and pharmacologic rationale for developing adoptive transfer of TIL as an anticancer therapeutic is based on observations that 1) the immune system is adept at producing antigen-specific anti-tumor cytotoxic T-cell responses that have demonstrated antitumor reactivity both in vitro and in vivo, the latter having also demonstrated therapeutic efficacy; 2) such autologous cellular therapies represent the terminal engagement of antigen-specific effector mechanisms mediated by the pro-inflammatory immunologic cascade, which are subject to significantly fewer adverse autoimmune sequalae than more broad-spectrum, nonspecific, upstream immunologic interventions, such as checkpoint blockade; 3) T cells isolated and expanded from the tumor microenvironment (TME), as opposed to elsewhere in the body, are enriched for reactivity against tumor cells; [1, 2][19, 20] 4) increased frequencies of TIL in the TME of melanoma and other solid tumors are correlated with improved prognosis both at the primary tumor stage setting as well as in later stage metastatic disease settings; [21-23]

and 5) while the TME appears to limit the capacity of TIL to overcome tumor cell growth, TIL isolated from the patient's TME, expanded to large numbers (10^9 to 10^{11}) ex vivo, and then infused back into the patient have demonstrated potent anti-tumor activity. [17]

TIL isolated from melanoma and other solid tumors are a heterogeneous mixture primarily consisting of $CD4^+$ and $CD8^+$ T cells at different stages of differentiation. $CD8^+$ cytotoxic T lymphocytes (CTL) comprise the most numerous and the most active component with anti-tumor cell killing properties. [24-26] Antigens recognized by TIL result from the overexpression of genes that are either specific to melanoma, or members of oncogene, growth factor gene, or signaling gene families, or from the expression of neo-epitopes resulting from mutated genes in the tumor cell. [27] The latter are now thought to be the key type of antigen recognized by TIL mediating enhanced tumor eradication during TIL therapy. [28] In addition, TIL are expected to facilitate a pro-inflammatory environment conducive to increased trafficking of dendritic cells (DCs) and other antigen-presenting cells (APCs) to further drive anti-tumor responses by taking up antigen from dying tumor cells and stimulating other T-cell clones in the infused or endogenous T cells. [29-33]

Ex vivo expansion of TIL is key to the development of a product with therapeutic value. Protocols have varied somewhat across treatment centers. The current procedure used in LN-144 production follows the most widely adopted process per the NCI's publications, whereby TIL are sourced from cut tumor fragments then expanded in 2 stages. Iovance Biotherapeutics, Inc. has worked closely with Dr. Rosenberg's team in understanding and recreating the details of the TIL growth process and further in transferring the procedure to our own GMP manufacturing facilities. In both processes, the TIL first undergo an initial culture in the presence of IL-2, termed the pre-rapid expansion protocol (pre-REP), then they are further cultured within a REP protocol that includes IL-2 the OKT3 (anti-CD3 monoclonal antibody) and irradiated peripheral blood mononuclear cells (PBMC; as feeder cells).

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. Key advances in TIL therapy include the introduction of a more intensive, 2-agent NMA-LD preparative regimen, post-infusion IL-2 (up to a maximum of 6 doses), and the use of minimally cultured ("young") TIL that undergo REP without selection for particular attributes.

The NCI has contributed a substantial body of preclinical and clinical research that supports the development of TIL-based therapies for cancer. Across clinical studies conducted by the NCI, immunotherapy of patients with advanced melanoma with autologous TIL infusion has induced durable objective responses (ORs) by Response Evaluation Criteria in Solid Tumors (RECIST) in 54% (54/101) of patients, including heavily pretreated patients, with 24 of the 101 patients (24%) achieving a complete response (CR). Nineteen of the 24 CRs were ongoing beyond 3 years of follow-up. [14, 34]

1.2 Overview of Adoptive Cell Transfer for Metastatic Melanoma

The efficacy of IL-2 therapy in the treatment of patients with advanced melanoma revealed that manipulation of the immune response could alter the clinical course of the disease. [35] The induction of tumor regression by IL-2 is believed to be related to its immune regulatory effects, including the expansion of T lymphocytes following activation by specific antigen and NK cells. [36-38] T-cell recognition leading to tumor cell killing and/or the release of helper and other cytokines is due to the presence of specifically recognized antigens present on the tumor cells. [39, 40] In the case of melanoma, a number of antigens have now been identified that can be recognized by both $CD8^+$ cytotoxic T cells and $CD4^+$ T-helper cells, including myristylated Akt (MART-1), glycoprotein 100 (gp100), melanoma associated antigen (MAGE-1), tyrosinase, tyrosine-related protein (TRP-1), TRP-2 and immunogenic cancer testis antigen (NY-ESO-1). [39, 41] The presence of these antigens on melanoma tumor cells has led to immunotherapy regimens that focused on the ability of effector T cells to

mediate tumor destruction specially the development of adoptive cell transfer regimens using TIL.

The identification of melanoma-specific antigens that are recognized by T cells, and the ability to isolate and expand the tumor-reactive T cell population in vitro has led to the development of adoptive cell transfer (ACT) regimens for the treatment of metastatic melanoma. TIL derived from resected melanoma tumors and expanded in vitro are capable of specifically recognizing tumor antigens, particularly MART-1, in over two-thirds of melanoma patients. [42, 43] In addition, recent studies have shown that TIL from melanoma tumors can recognize antigens derived from mutated gene products in the cancer cells recognized as “neo-antigens” by the T cells.

The initial efficacy reported for IL-2 therapy in patients with advanced melanoma and the discovery of tumor antigens recognized by TIL inspired the first attempts to expand lymphocytes from isolated tumor fragments and re-infuse these expanded cells as a potential therapeutic back into the patient. Some of the first clinical trials performed in individual centers in the US and Europe, such as the NCI, used TIL expanded ex vivo for a number of weeks from tumor tissue with IL-2 alone followed by re-infusion into patients. This was followed up by low-dose IL-2 infusion or subcutaneous IL-2 administration. [44-47] Although these protocols were found to be feasible, they had inconsistent and widely varying response rates ranging from 0% to 66%, with the caveat that some of these trials were only conducted on small numbers (<10) of patients. [47]

During this time, the Surgery Branch at the National Cancer Institute (Bethesda, MD) also embarked on performing TIL trials for metastatic melanoma using a similar expansion method for TIL with IL-2 alone. The NCI however included a preparative chemotherapy regimen using low-dose cyclophosphamide (CY) before TIL infusion that resulted in a partial and transient depletion of host lymphocytes. IL-2 was administered after TIL infusion. This led to more promising response rates in small pilot clinical trials of 30% to 60%. [48-50] This prior CY preconditioning approach resulted from work on murine tumor models at the NCI showing that the host immune environment may significantly impact the efficacy of adoptive T-cell therapy. In these studies, an improved

persistence and anti-tumor activity of transferred TIL expanded from implanted murine tumors was found when host mice were treated with CY or non-lethally irradiated to deplete endogenous lymphocytes. [19, 50] Furthermore, this prior LD preconditioning regimen with CY was also later found to remove suppressive $CD4^+$ regulatory cells (CD4-Foxp3 of cancer patients have also been cells) that inhibit anti-tumor immune responses in mice. Higher T-regulatory cell frequencies in the blood of cancer patients have also been correlated with an unfavorable prognosis. [51-54] Alternatively, prior depletion of lymphocytes may create 'space' for the adoptively transferred cells within the lymphocyte compartment. [55] Under this model, homeostatic lymphocyte survival may result in increased proliferation and enhanced survival of transferred T-cells, perhaps through a mechanism involving increased access to endogenous cytokines, IL-7, IL-15, and IL-21. [56] The success of prior LD in animal models and the use of single agent CY preconditioning in initial TIL therapy trials, led to testing of more intensive preconditioning regimens yielding a complete depletion of host lymphocytes for a longer window of time than the prior CY monotherapy regimens.

The NCI first reported a study on 35 patients including this more intense lymphodepleting conditioning regimen to adoptive cell transfer therapy in patients with metastatic melanoma. [57, 58] Patients received a lymphodepleting chemotherapy regimen consisting of high-dose cyclophosphamide and standard doses of fludarabine before administration of selected, expanded, tumor reactive TIL and IL-2. The LD step resulted in a transient myelosuppression and the elimination of all circulating lymphocytes for approximately 1 week, after which time patients recovered endogenous marrow function and reconstituted their lymphocyte compartments towards normal levels within 2 to 3 weeks. [57, 58]

Published clinical trials evaluating TIL therapy from several institutions using similar protocols as the NCI are reporting reproducible and promising results. Across clinical studies conducted by the NCI, immunotherapy of patients with advanced melanoma with autologous TIL therapy has induced durable ORRs by Response Evaluation Criteria in Solid Tumors (RECIST) 1.0 criteria in 54 of 101 (54%) patients, including heavily

pretreated patients 24 of whom (24%) achieved a CR. Nineteen of the 24 CRs were ongoing beyond 3 years of follow-up. [10, 11]

1.3 LN-144 TIL Therapy

LN-144 is an autologous, ready-to-infuse TIL, therapy that is comparable to that developed by Dr. Steven A. Rosenberg and colleagues at the NCI.

Several preconditioning regimens have been used in conjunction with TIL therapy. Lymphodepleting regimens have included cyclophosphamide/fludarabine, total body irradiation or the combination of the two. The NMA-LD regimen used in the current study is based on the method developed and tested by the NCI. It involves 2 days of cyclophosphamide followed by 5 days of fludarabine as a lymphodepleting pretreatment. The TIL therapy includes infusion with LN-144 (investigational product [IP]) followed by IL-2. Details for the tumor resection and LN-144 administration are provided in the Tumor Procurement & Shipping Manual and Pharmacy & Administration Manual.

The final IP will be available for administration in one of several volumes for infusion, as described in the Pharmacy & Administration Manual.

1.4 Production and Expansion of Tumor Infiltrating Lymphocytes

The LN-144 active biologic is composed of viable TIL derived from an individual patient's own tumor (autologous cell product). The process for manufacturing LN-144 begins at the clinical site with the surgical resection of primary or secondary metastatic tumor material of ≥ 1.5 cm from the patient. The tumor specimen is placed in biopreservation transport media and shipped (at 2 °C to 8 °C), by overnight transport to a GMP manufacturing facility. Upon arrival at the GMP manufacturing facility, the tumor specimen is dissected into fragments of 2 mm^3 to 3 mm^3, which are cultured in a pre-REP with human recombinant IL-2 (Proleukin®) to generate a suitable number of viable cells to move into the REP phase. In the Gen 1 process, pre-REP cells are cryopreserved allowing for flexibility in the subsequent scheduling of TIL therapy administration into the patient from which they were originally derived. In the shorter Gen 2 process,

pre-REP cells are taken directly into the REP. The REP further expands the cells in the presence of IL-2 and OKT3 (muromonab-CD3, murine monoclonal antibody to human CD3) with irradiated allogenic mononuclear cells as feeder cells. The REP-expanded cells (TIL) are then harvested, washed, and formulated in a blood transport/infusion bag for shipment by courier to the clinical site. The dosage form of the IP is a live cell suspension of either noncryopreserved (Gen 1, Cohort 1) or cryopreserved (Gen 2, Cohort 2) autologous TIL for intravenous infusion into the patient from which they were derived.

During the TIL manufacturing process at a timepoint that coincides with protocol study Day -8, the number of TIL successfully expanded will be determined. If the number of TIL is sufficient for administration ($\geq 250 \times 10^6$ cells), approval by the Sponsor will be granted to begin the NMA-LD regimen (2 days of cyclophosphamide at Day -7 and Day 6) followed by 5 days of fludarabine at Day -5 through Day -1. Beyond the point for NMA-LD approval, the cell number continues to increase for the duration of culture of the TIL product. Clinical experience to date with LN-144 indicates that as few as 1×10^9 cells can induce an antitumor response.

The lower limit of 250×10^6 for the TIL manufacturing process has been selected based the following research data. While the lower dose limit of efficacious TIL has not been defined, the normal response to infection by the body is the generation of approximately 30×10^6 to 200×10^6 antigen-specific CD8+ cytotoxic T-cells. [59] Based on this information, a total cell dose of 250×10^6 would include an approximate number of tumor antigen-specific CD8+ T-cells within this physiologic range. To date in patients treated on Iovance-sponsored clinical studies, a clinically meaningful response has been observed with a total cell count on this order (ie, 1.2×10^9). Therefore, following LD, the risk/benefit ratio favors the administration of at least 250×10^6 TIL.

While an upper limit for viable cells administered for TIL infusion has not been established, 150×10^9 viable cells has been chosen as a conservative amount based on the number of cells administered in several studies. [60]

Cohort 1 (LN-144 manufacturing process without final cryopreservation)

This final cellular IP is formulated in a minimum of 50% HypoThermosol™ in Plasma-Lyte A™ (volume/volume) and up to 0.5% HSA (compatible for human infusion) containing 300 IU/mL IL-2:

1) 250 mL (in a 300-mL capacity infusion bag) when the total TIL harvested are $\leq 75 \times 10^9$

or

2) 500 mL (in a 600-mL capacity infusion bag) when the total TIL harvested are $\leq 150 \times 10^9$

Cohort 2 (LN-144 manufacturing process with final cryopreservation).

This final cellular IP is formulated in 50% 10® in Plasma-Lyte A™.

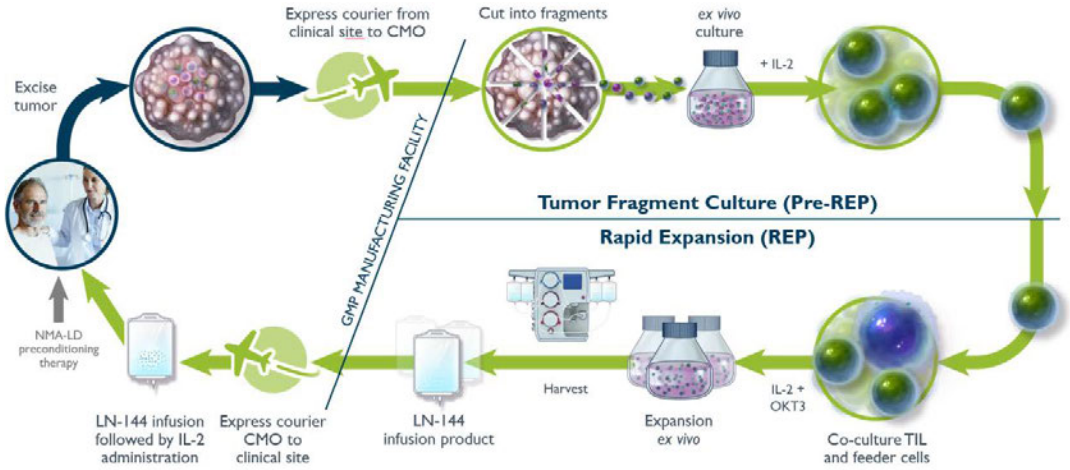
1) Up to 4 infusion bags containing up to approximately 100 to 150 mL of thawed cells. The number of infusion bags is dependent on the total cell count.

As of December 2017, all patients receiving retreatment in Cohort 3 will receive the Gen 2 cryopreserved LN-144 infusion product.

A diagram of the production process for the LN-144 IP is provided in Figure 2.

Upon completion of the manufacturing process, the IP, LN-144, will be labeled with a patient specific label. The IP will then be shipped from the manufacturing facility to the respective clinical site for infusion, as described in the Pharmacy & Administration Manual.

Figure 2 LN-144 Manufacturing Process



2 STUDY DESIGN

2.1 Description of the Study

This is a prospective, multicenter interventional study evaluating patients who receive ACT with LN-144 (autologous TIL). Patients will receive a single infusion of LN-144, followed by the administration of a regimen of IL-2 at 600,000 IU/kg approximately every 8 to 12 hours starting approximately 3 hours to 24 hours after the LN-144 infusion and continuing for up to 6 doses. All visit dates following the LN-144 infusion (Day 0) are calculated from this date forward. Patients will be evaluated for objective response 6 weeks following the LN-144 infusion for the first 6 months and every 3 months thereafter (see Appendix 1 and Appendix 2). Formal response evaluations by an Independent Review Committee (IRC) will follow RECIST 1.1 criteria. [61]

Overall Survival (OS) Follow-Up will continue for up to 5 years for each patient after the last study treatment. Patients who do not receive LN-144 will enter into OS Follow-Up to collect survival status and subsequent anticancer therapy.

2.2 Description of the Study Centers

Patients may be seen at the Investigators' private offices or affiliated medical centers for evaluations prior to enrollment and during follow-up. Patients will require hospitalization during the mesna administration in the NMA-LD pretreatment regimen and then also just prior to the LN-144 infusion through IL-2 administration. All dates of hospitalization(s) must be recorded in the electronic case report form (eCRF).

3 STUDY OBJECTIVES AND ENDPOINTS

3.1 Study Objectives

3.1.1 Primary Objective

- To evaluate the efficacy of LN-144 in patients with metastatic melanoma using the ORR as assessed by the Investigator per RECIST 1.1

3.1.2 Secondary Objectives

- To evaluate the efficacy endpoints of duration of response (DOR), disease control rate (DCR), and progression free survival (PFS) as assessed by the Investigator per RECIST 1.1
- To further evaluate efficacy of LN-144 therapy in patients with metastatic melanoma by assessing ORR, DOR, DCR, and PFS as assessed by the Independent Review Committee (IRC) per RECIST 1.1
- To evaluate overall survival (OS)
- To characterize the safety profile of LN-144 therapy in patients with metastatic melanoma

3.1.3 Exploratory Objectives

- To explore the persistence of LN-144 and potential immune correlates of response, outcome, and toxicity of the treatment
- To explore efficacy based on immune-related Response Evaluation Criteria in Solid Tumors (irRECIST) criteria, [62] as assessed by the IRC

- To assess health-related quality of life (HRQoL)

3.2 Study Endpoints

3.2.1 Primary Endpoints

- Objective response rate (ORR) as assessed by the Investigator per RECIST 1.1 criteria

3.2.2 Secondary Endpoints

- The DOR, DCR, and PFS per RECIST 1.1 criteria [61] as assessed by the Investigator
- The ORR, DOR, DCR, PFS, per RECIST 1.1 criteria [61] as assessed by the IRC
- Overall survival (OS)
- Incidence, severity, seriousness, relationship to study treatment, and characteristics of treatment-emergent adverse events (TEAEs), including AEs leading to early discontinuation from treatment or withdrawal from the Response Assessment Period study follow-up, and AEs resulting in deaths

3.2.3 Exploratory Endpoints

- TIL persistence in the peripheral blood and immune correlates with respect to response, outcome, and/or toxicity of the treatment will be determined by immunological and molecular assays
- The ORR, DCR, and PFS using irRECIST [62] as assessed by the IRC
- Patient-reported outcomes based on the European Organization for Research and Treatment of Cancer Quality-of-Life Questionnaire – Core 30 Instrument (EORTC QLQ-C30 HRQoL)

4 SELECTION OF PATIENT POPULATION

4.1 Inclusion Criteria

a. Patients with unresectable or metastatic melanoma (Stage IIIc or Stage IV), who progressed following ≥1 line of prior systemic therapy, including immune checkpoint inhibitor (eg, anti-PD-1), and if BRAF mutation-positive, after BRAF inhibitor systemic therapy. Patients must have no other therapy options that are expected to have significant benefit in the opinion of the Investigator and must have:

   - At least 1 measurable target lesion by RECIST 1.1. [61] Lesions in previously irradiated areas should not be selected as target lesion, unless treatment was ≥ 3 months prior, and there has been demonstrated disease progression in the lesion
   - At least 1 resectable target lesion to generate TIL of a minimum 1.5 cm in diameter post-resection; surgical removal with minimal morbidity (defined as any procedure for which expected hospitalization is ≤ 3 days)

b. Patients must be ≥ 18 years and ≤ 70 years of age at the time of consent. Enrollment of patients > 70 years of age may be allowed after consultation with the Medical Monitor

c. Patients must have an Eastern Cooperative Oncology Group (ECOG) performance status of 0 or 1 (Appendix 3) and an estimated life expectancy of ≥ 3 months

d. In the opinion of the Investigator, patient must be able to complete all study-required procedures

e. Patients of childbearing potential or their partners of childbearing potential must be willing to practice an approved method of birth control during treatment and for 12 months after receiving all protocol-related therapy

Approved methods of birth control are as follows:

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

f. Patients must have the following hematologic parameters:

- Absolute neutrophil count (ANC) $\geq 1000/mm^3$
- Hemoglobin ≥ 9.0 g/dL
- Platelet count $\geq 100,000/mm^3$

g. Patients must have adequate organ function:

- Serum alanine transaminase (ALT)/serum glutamic-pyruvic transaminase (SGPT) and aspartate transaminase (AST)/serum glutamic-oxaloacetic transaminase (SGOT) ≤ 3 times the upper limit of normal (ULN); patients with liver metastasis ≤ 5 times ULN
- An estimated creatinine clearance (eCl_{Cr}) ≥ 40 mL/min using the Cockcroft-Gault formula at Screening
- Total bilirubin ≤ 2 mg/dL
  - Patients with Gilbert's syndrome must have a total bilirubin ≤ 3 mg/dL

h. Patients must be seronegative for the human immunodeficiency virus (HIV) antibody, hepatitis B antigens, and hepatitis C antibody or antigen

i. Patients must have recovered from all prior therapy-related AEs to Grade 1 or less (per Common Terminology Criteria for Adverse Events [CTCAE] v4.03), except for alopecia or vitiligo prior to enrollment (tumor resection) with a washout period from prior anticancer therapy(ies) to the start of planned NMA-LD of a minimum duration detailed as follows:

- Targeted therapy: prior targeted therapy with a MEK/BRAF or other-directed agent, is allowed provided the washout period is a ≥ 21 days or 5 half-lives, whichever is longer prior to the start of NMA-LD
- Chemotherapy: adjuvant, neoadjuvant or definitive chemotherapy/ chemoradiation is allowed provided the washout period is ≥ 21 days or 5 half-lives, whichever is longer prior to the start of NMA-LD
- Immunotherapy: prior checkpoint-targeted therapy with an anti-CTLA-4/anti-PD-1, other monoclonal antibody (mAb), or vaccine is allowed if disease progression is confirmed prior to or within the washout period of ≥ 21 days before the start of NMA-LD
- Palliative radiation therapy is permitted between biopsy and NMA-LD if it does not involve lesions being selected as target or nontarget
- Patients may undergo preplanned procedures if within 2 to 3 weeks prior to the start of NMD-LD

j. Patients with documented Grade 2 or higher diarrhea or colitis as a result of previous treatment with immune checkpoint inhibitor(s) must have been asymptomatic for at least 6 months and/or had a normal colonoscopy post immune checkpoint inhibitor treatment, by visual assessment, prior to the start of NMA-LD

k. Patients must have the ability to understand the requirements of the study, have provided written informed consent as evidenced by signature on an informed consent form (ICF) approved by an Institutional Review Board/Independent Ethics Committee (IRB/IEC), and agree to abide by the study restrictions and return to the site for the required assessments

l. Patients have provided written authorization for use and disclosure of protected health information

4.2 Exclusion Criteria

a. Patients with melanoma of uveal/ocular origin

b. Patients who have received an organ allograft or prior cell transfer therapy that included a nonmyeloablative or myeloablative chemotherapy regimen (not applicable for patients in the retreatment Cohort 3)

c. Patients with symptomatic and/or untreated brain metastases (of any size and any number)

- Patients with definitively treated brain metastases may be considered for enrollment after discussion with the Medical Monitor, and must be stable for ≥ 2 weeks prior to the start of treatment NMA-LD

d. Patients who are pregnant or breastfeeding

e. Patients who are on a systemic steroid therapy at a dose of > 10 mg of prednisone or equivalent per day

- A short course of higher-dose steroid therapy is allowed in cases of exacerbation of known disease or for treatments of new acute symptoms

f. Patients who have active medical illness(es) that in the opinion of the Investigator would pose increased risk for study participation that may include active systemic infections, such as syphilis or any other infection(s) requiring antibiotics,

coagulation disorders, or other active major medical illnesses of the cardiovascular, respiratory or immune system

g. Patients who have any form of primary immunodeficiency (such as severe combined immunodeficiency disease [SCID] and acquired immune deficiency disease [AIDS])

h. Patients who have a history of hypersensitivity to any component or excipient of the TIL regimen therapy and other study drugs:

- NMA-LD (cyclophosphamide, mesna, and fludarabine)
- IL-2
- Antibiotics of the aminoglycoside group (ie, streptomycin, gentamicin)
- Any component of the TIL infusion product formulation including dimethyl sulfoxide (DMSO), human serum albumin (HSA), IL-2, and dextran-40

i. Patients who have a left ventricular ejection fraction (LVEF) < 45% or New York Heart Association (NYHA) functional classification > Class 1 at Screening. All patients must have echocardiogram (ECHO) or multiple gated acquisition scan (MUGA) at Screening. For patients ≥ 60 years or patients who have a history of ischemic heart disease, chest pain, or clinically significant atrial and/or ventricular arrhythmias, a cardiac stress tests must be performed showing LVEF ≥45%, and if any wall movement abnormalities, they must be reversible.

j. Patients who have obstructive or restrictive pulmonary disease and a documented FEV_1 (forced expiratory volume in 1 second) of ≤ 60%

k. Patients who have had another primary malignancy within the previous 3 years (with the exception of carcinoma in situ of the breast, cervix, or bladder, localized prostate cancer, and non-melanoma skin cancer that has been adequately treated)

l. Patients who have been shown to be BRAF mutation positive (V600), but have not received prior systemic therapy with a BRAF-directed kinase inhibitor

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

n. Patients whose cancer requires immediate attention or who would otherwise suffer a disadvantage by participating in this trial

o. Patients protected by the following constraints:

- Hospitalized persons without consent or persons deprived of liberty because of a judiciary or administrative decision
- Adult persons with a legal protection measure or persons who cannot express their consent
- Patients in emergency situations who cannot consent to participate in the trial

4.3 Number of Patients

Patients who meet all inclusion criteria and do not meet any exclusion criteria will be enrolled in the study.

Patients will be enrolled until approximately 60 patients in the Efficacy Analysis set received either US or EU GMP manufactured Gen 2 cryopreserved LN-144 infusion product and complete treatment. Treatment completion is defined as having received LN-144 infusion followed by at least 1 dose of IL-2. Approximately 10 patients may enter the third cohort (Cohort 3) in which they will be retreated with a second administration of TIL therapy.

Patients who sign an ICF and fail to meet the inclusion and/or exclusion criteria will be defined as a Screen Failure. However, patients who do not have tumor resection within 4 weeks (28 days) of signing the ICF may be reconsented after a discussion with the Medical Monitor, if there is delay in scheduling the tumor resection.

The Investigator is to maintain a master screening log of all consented patients that documents all screen failures and the reason(s) for screen failure. A copy of the log should be retained in the Investigator's study files.

As of December 2017, enrollment in Cohort 1 had been terminated with patients being enrolled in Cohort 2 only.

Patients from Cohort 1 and Cohort 2 may screen for retreatment in Cohort 3 as long as this study is open. Prior to enrollment in Cohort 3, patients must undergo abbreviated screening evaluation and procedures (see Appendix 2**).**

4.3.1 Rescreening Patients

Patients who fail the initial screening process will be deemed a Screen Failure but may be reconsented and rescreened at a later date. Patients who exceed the 4 weeks (28 days) in Screening without tumor resection (Enrollment) may re-sign the ICF and be reassessed for eligibility following a discussion between the Investigator and Medical Monitor to agree on which screening procedures need to be redone.

4.3.2 Patient Cohorts

Patients are no longer being enrolled into Cohort 1. Patients will be assigned Cohort 2 based on IRB/IEC approval of appropriate protocol/ICF. If Cohort 2 approaches or passes the desired 60-patient enrollment, assignment will be adjusted to minimize over-enrollment.

The primary efficacy and safety analyses will take place after the last patient in Cohort 2 has an opportunity to be followed at least for 6 months tumor assessment, and the final analysis will take place at the end of the 2-year (24-month) Treatment Response Period.

Cohort 3 will consist of patients who had received initial TIL regimen as part of Cohort 1 or Cohort 2 treatment. These patients may have a second tumor resection, especially when new lesions are available and feasible for resection. Patients who in the opinion of the Principal Investigator will benefit from a second TIL regimen treatment will need to be rescreened and meet eligibility criteria as described in the Sections 4.1 and 4.2.
The decision for enrollment in Cohort 3 will be based on discussion between the Principal Investigator and the Medical Monitor. The Medical Monitor will have authority to adjudicate enrollment into Cohort 3 (second TIL therapy). Patients who are enrolled in

Cohort 3 will receive treatment with Gen 2 cryopreserved LN-144 infusion product. Patients in Cohorts 1 and 2 who did not receive an LN-144 infusion will remain in the assigned cohort and, based on the Medical Monitor's discretion, be readmitted to the tumor resection and TIL generation and infusion procedure.

5 PRIOR TREATMENTS, CONCOMITANT MEDICATIONS AND NONDRUG THERAPIES

5.1 Prior Treatment and Concomitant Medications

Use of all medications taken by the patient 30 days prior to consent will be recorded in the site's source documentation and the patient's eCRF. All medications taken by the patient, or any changes in medications, will also be recorded throughout the course of the study until completion of the Response Assessment Period follow-up phase, including those that are part of the tumor resection procedure. The OS follow-up period will start after completion of the Response Assessment Period following the LN-144 infusion, and will continue for up to 5 years for each patient from the last study treatment.

Verification of all ongoing concomitant medications will be conducted as part of data monitoring.

5.2 Prohibited and Permitted Medications During Study Treatment

5.2.1 Prohibited Treatment

The following guidelines should be used regarding concomitant medications/concomitant therapies:

- Systemic therapies intended to treat melanoma are not permitted
- Patients should not receive live or attenuated vaccine within 4 weeks (28 days) prior to the start of NMA-LD, and should not receive a live or attenuated vaccine within 3 months after the last dose of IL-2 (Day 84) and until ANC is $\geq 1000/mm^3$
- Use of investigational drugs (other than the LN-144 investigational therapy), is not permitted

- Palliative radiation therapy is permitted between biopsy and NMA-LD as long as it does not involve selected target or nontarget lesions
- Patients may undergo preplanned procedures if ≥ 2 weeks prior to the start of NMA-LD

5.2.1.1 Permitted Medications – Use with Caution

Concurrent medications for conditions other than their metastatic melanoma are permitted, with the exception of any medications that may have an antitumor effect. Although prohibited at study entry, at > 10 mg/day prednisone or equivalent may be initiated in cases of exacerbation of known disease or for treatment of new symptoms on study per Investigator discretion.

6 STUDY PROCEDURES

6.1 Screening (up to 28 days from signing the ICF)

The following procedures should be performed in all patients in Cohorts 1, 2, and 3 (exceptions for Cohort 3 are noted) after signing the ICF:

- Review of inclusion and exclusion criteria
- Medical history (repeat medical history not needed for Cohort 3 patients)
- Melanoma medical history, including prior therapies, response to prior therapies, and BRAF mutational status
- Concurrent medications within 30 days prior to signing the ICF
- Physical exam, including height and weight
- Vital signs: pulse rate, respiratory rate, blood pressure, and temperature
- Evaluation and measurement of all skin and palpable lesions
- Slit lamp eye examination. Previous evaluation within 30 days prior to signing the ICF is allowed
- Electrocardiogram (EKG). Prior evaluation within 60 days prior to signing the ICF is allowed

- Cardiac evaluation for all patients should consist of echocardiogram (ECHO) or multiple gated acquisition scan (MUGA) at Screening. For patients ≥ 60 years or patients who have a history of ischemic heart disease, chest pain, or clinically significant atrial and/or ventricular arrhythmias, a cardiac stress tests must be performed showing normal LVEF, NYHA functional classification < class 1 and if any wall movement abnormalities, they must be reversible
- Pulmonary function tests (PFTs).
- Computed tomography (CT), of anatomic regions per disease history and clinical symptoms, including:
  - Chest (include neck if there is prior or suspected neck disease)
  - Abdomen
  - Pelvis
- Magnetic resonance imaging (MRI) of brain
  - Previous CT/MRI scans performed within 30 days of ICF signing can be used for Screening visit
- Blood and Urine Tests
  - Hematology – complete blood count (CBC) with differential
  - Chemistry - Sodium, potassium, chloride, total carbon dioxide (CO_2) or bicarbonate, creatinine, glucose, blood urea nitrogen (BUN), albumin, calcium, magnesium, phosphorus, alkaline phosphatase, ALT/SGPT, AST/SGOT, total bilirubin, direct bilirubin, lactate dehydrogenase (LDH), total protein, total creatinine (CK), uric acid, and thyroid panel (to include thyroid-stimulating hormone (TSH) and free T_4)
  - Serum pregnancy test (β-human chorionic gonadotropin [β-HCF]) for women of childbearing potential
  - Cytomegalovirus (CMV) serology (IgG and IgM, as per local standard)
  - Urinalysis (complete urine culture if indicated)

- Syphilis screening (as per local standard; eg, Rapid Plasma Reagin [RPR] venereal disease research laboratory [VDRL] or other) at Screening, and thereafter as clinically indicated
- HIV antibody titer, hepatitis B surface antigen (HBsAg) and hepatitis B core antigen (HBcAg) determinations, HCV Ab, herpes simplex virus (HSV) serology ([HSV-1] IgG and [HSV-2] IgG), and EBV serology (viral capsid antigen [VCA]-IgM, VCA-IgG, EA-D IgG, EBNA, IgG). Serology for infection must be repeated for Cohort 3 patients if there is > 30 days from the last tests results.
- HLA typing (to be shipped to the central laboratory); repeat HLA typing not needed for Cohort 3 patients. Refer to the Laboratory Manual for details.
- Calculate estimated creatinine clearance (eCl_{Cr}) using Cockcroft-Gault formula

Males: • Creatinine Clearance = Weight (kg) x (140 – Age) • (mL/min) 72 x serum creatinine (mg/dL)
Females: • Creatinine Clearance = Weight (kg) x (140 – Age) x 0.85 • (mL/min) 72 x serum creatinine (mg/dL)

- ECOG performance status evaluation
- Patients with documented Grade 2 or greater diarrhea or colitis as a result of previous treatment with immune checkpoint inhibitor(s) must have been asymptomatic for at least 6 months or had a normal colonoscopy post immune checkpoint inhibitor treatment, with uninflamed mucosa by visual assessment, prior to the start of NMA-LD
- Assessment of AEs / serious AEs (SAEs). All AEs occurring after the patient has consented, but before enrollment (prior to tumor resection), will be collected on the medical history eCRF unless the event is new and attributed to protocol-required procedures or assessments

6.2 Enrollment and Tumor Resection

Following confirmation of patient eligibility, the Medical Monitor, or designee, will either approve or decline patient for enrollment into the clinical study.

When the Medical Monitor has approved the patient to be enrolled into the study, tumor resection will take place. The patient is enrolled into the study when resection has started. The following procedures should be completed during this visit.

- List all medications including those that are part of the tumor resection procedure
- Obtain blood for immune monitoring/phenotyping (refer to Laboratory Manual)
- Serology testing (HIV, HBsAg, HBcAg, HCV Ab, and syphilis) is to be done on the day of the tumor resection or within 7 days after the resection (required only for tumor samples entering the EU for manufacture of the TIL product in the EU).
- Tumor resection (see Section 6.2.1)
- Assessment of AE/SAEs. All AEs occurring after the patient has consented, but before enrollment (prior to tumor resection), will be collected on the medical history eCRF unless the event is new and attributed to protocol-required procedures or assessments
- Dates of hospitalization of the patient need to be recorded in the eCRF.

6.2.1 Tumor Harvest and Processing Procedure

The detailed Tumor Procurement & Shipping Manual will be provided to each clinical site and training will be conducted on the procedures for collecting and shipping of the tumor to the LN-144 manufacturing facility. Ideally, the resected tumor specimen for TIL manufacturing should be ≥ 1.5 cm, but no more than 4.0 cm in diameter, of viable solid tumor tissue. Viable solid tumor tissue is tissue that has necrotic, hemorrhagic and fatty tissue removed. Tumor tissue is to be sent to the manufacturing facility. Biopsy from multiple lesions is encouraged.

If after completion of preparation of tumor tissue for TIL manufacturing, a portion of the viable tumor tissue is still available, up to 5 mm × 5 mm × 5 mm is to be placed in a formalin-fixed, paraffin-embedded (FFPE) block and sent to the central laboratory (refer to the Laboratory Manual for details). Provision of adequate amount of tumor tissue for TIL manufacturing is priority over tumor tissue to be sent to the central laboratory. When tumor tissue is limiting, a single 2-mm punch biopsy from the center of the resected tumor will be placed into an FFPE block and sent to the central laboratory (refer to the Laboratory Manual for details). Every effort should be made to obtain adequate tumor tissue for both TIL manufacturing and to be sent to the central laboratory.

Tumor tissue sent to the central laboratory will be used as follows:

- For immunohistochemistry (IHC) to identify different immune cell populations, and
- For isolation of deoxyribonucleic acid (DNA), which will be used for "exome" (not whole genome) sequencing as a part of neoepitopes interrogation.

The patient will be requested to sign the optional consent (eg, Genetic Research ICF) for exome sequencing.

Tumors will be resected at the investigational sites participating in the trial according to their respective institutional protocols for sterile resection for TIL preparation.

LN-144 is an autologous IP that is procured and delivered by means that have more in common with autologous blood product delivery than those of traditional drug production.

It is imperative that only the patient's own (autologous) study treatment (LN-144) be administered to that same individual patient. For these reasons, the patient specimen must be procured and handled per a strict protocol to ensure optimal quality of the specimen and minimum transport time to and from the processing Contract Manufacturing Organization (CMO) facility, as well as to ensure the unique identification of the specimen at all time including infusion back into the patient.

6.2.1.1 Additional Tumor Tissue from Resected Tumor

If there is an excess of tumor tissue after resection for TIL manufacturing, to process this additional tumor tissue please follow the procedures outline in Section 6.2.1.

6.2.2 Immune Monitoring and Phenotyping (Sequencing of Tumor and PBMC/Cell-Free DNA)

Peripheral blood will be collected from the patient utilizing vacutainer blood collection vials for immune monitoring (biomarker analysis) and sequencing (exome and high-throughput T-cell antigen receptor [TCR] sequencing) of lymphocyte DNA. Refer to the Laboratory Manual for the complete procedure details. In addition, exome sequencing of DNA collected from the tumor will be performed.

6.3 Baseline (Day -21 to Day -14)

The following procedures should be completed during this visit:

- Physical examination, including weight. Baseline (Day -21 to Day -14) weight can be used for calculation of dosing of cyclophosphamide, fludarabine, and IL-2.
- Vital signs – pulse rate, respiratory rate, blood pressure, and temperature
- Evaluation and measurement of all skin and palpable lesions
- Verification of all concomitant medications
- EKG (If the EKG was done within 2 weeks prior to Screening, it does not have to be repeated.)
- CT Exam, include anatomic regions per disease history and clinical symptoms, (the same CT series as completed at Baseline [Day -21 to Day -14] is to be repeated at all Response Assessment Period disease assessments, [scheduled and unscheduled])
  - Chest (include neck there is prior or suspected neck disease)
  - Abdomen
  - Pelvis

- MRI of the brain in patients who had brain abnormalities at Screening.
  For those patients who had negative brain scans at Screening, the Baseline (Day -21 to Day -14) assessment should be done only if clinically indicated. These Baseline scans can be done as early as Day -21 (the same MRI series to be repeated at all Response Assessment Period disease assessments [scheduled and unscheduled]).

- Blood and urine tests
  - Hematology: CBC with differential
  - Chemistry: sodium, potassium, chloride, total carbon dioxide (CO_2) or bicarbonate, creatinine, glucose, blood urea nitrogen (BUN), albumin, calcium, magnesium, phosphorus, alkaline phosphatase, ALT/SGPT, AST/SGOT, total bilirubin, direct bilirubin, lactate dehydrogenase (LDH), total protein, total creatinine (CK), uric acid, and thyroid panel (to include thyroid-stimulating hormone [TSH] and free T_4, only if clinically indicated)
  - Serum pregnancy test for women of childbearing potential
  - Urinalysis (complete urine culture if indicated)

- ECOG performance status evaluation

- Assessment of AE/SAEs. All AEs occurring after the patient has consented, but before enrollment (prior to tumor resection), will be collected on the medical history eCRF unless the event is new and attributed to protocol-required procedures or assessments

- EORTC QLQ-C30 HRQoL questionnaire

- Recheck of abbreviated Inclusion/Exclusion Criteria to ensure that patient performance status and main eligibility criteria have not changed from time of Screening, a reconfirmation is to be perform and approved by Sponsor or designee

6.4 Patients Who Do Not Receive a LN-144 Infusion

Some patients may undergo tumor resection and LN-144 manufacture but will not receive the infusion of IP. Patients who discontinue the study (prior to NMA-LD) are to complete the Early Termination Visit (ETV). The ETV is not required if the same procedures are performed within 2 weeks from the previous visit. However, a follow-up visit for safety should be performed 30 days following tumor resection, or until all surgery-related AEs have resolved or are without clinical sequalae.

In a situation in which due to a medical event (AE), a patient did not complete NMA-LD and/or did not receive any LN-144 infusions, a potential for continuing therapy is available to the patient after the patient recovers and becomes fit to complete NMA-LD and/or LN-144 infusion. The REP cells (for Cohort 2 patients) may remain frozen for a period of time, and upon agreement between the Investigator and the Medical Monitor, treatment may continue after the patient meets criteria to receive LN-144 infusion. If a decision is made that the patient will not receive their TIL, then the patient should remain on study, but the data collection will be reduced to survival status and start of any new anticancer therapy.

6.5 Day -7

Prior to beginning the LD for all cohorts, the Investigator should assess whether the patient has had any clinical deterioration, which would put them at increased risk when subsequently receiving the IL-2. Specifically, the Investigator should consider whether a worsening of ECOG status and/or a deterioration of laboratory values is such that the patient no longer meets the requirements of the inclusion and exclusion criteria. If this deterioration is believed to be reversible, the LN-144 IP may remain frozen at the appropriate stage and the schedule adjusted to allow recovery and subsequent LN-144 administration. If the deterioration is believed irreversible and of sufficient magnitude to increase the risk of IL-2 administration, the patient should not proceed to LD and subsequent therapy and be followed as per Section 6.4.

Prior to the start of NMA-LD, verification of sufficient TIL (LN-144) cell expansion ($\geq 250 \times 10^6$ cells) will be confirmed by the Sponsor and authorization to initiate LD will be sent to the site.

The following procedures/assessments should be completed during this visit:

- Physical exam including weight, calculated body surface area (BSA), and body mass index (BMI)
- Verification of all concomitant medications
- ECOG performance status evaluation
- Vital signs – pulse rate, respiratory rate, blood pressure and temperature
- Blood and urine tests (to be drawn prior to cyclophosphamide administration)
  - Hematology: CBC with differential
  - Chemistry: Sodium, potassium, chloride, total carbon dioxide (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
  - Urinalysis (complete Urine culture if indicated)
  - CMV serology (IgG and IgM, as per local standard), only if clinically indicated
  - Serum pregnancy test for women of childbearing potential
  - Obtain blood for immune monitoring (refer to the Laboratory Manual)
- Authorization for Lymphodepletion
  Note: The 'Authorization to Receive Lymphodepletion' form is to be completed by the Investigator between Day -10 to Day -8 and sent to the Sponsor or designee and then will be returned to the site prior to the initiation of the NMA-LD preconditioning regimen.

- Cyclophosphamide, 60 mg/kg IV with mesna 15 mg/kg, are infused over approximately 2 hours. Cyclophosphamide may be prepared in 250 or 500 mL per institutional standard of practice (D5W or 0.9% NaCl can per used as per institutional standard of practice). If the patient is obese (BMI > 35 kg/m^2) drug dosage will be calculated using practical weight as described in Appendix 4. Refer to the current package insert or SmPC for cyclophosphamide for full prescribing information (Appendix 8).
- Mesna infusion will continue to be infused at a rate of 3 mg/kg/hour in a suitable diluent over 22 hours after each cyclophosphamide dose or per site institutional standard. Patient may be discharged following completion of the mesna administration. Dates of hospitalization of the patient need to be recorded in the eCRF. Higher or continued doses of mesna can be administered as per standard of care at the treating institution for prevention of hemorrhagic cystitis. Local standards of care for mesna use can be used. Refer to the current package insert or SmPC for mesna for full prescribing information (Appendix 9).
- Ondansetron (0.15 mg/kg/dose [rounded to the nearest even mg dose between 8 mg and 16 mg based on patient weight] IV every 8 hours × 3 days) will be given for nausea, or as per standard of care at the treating institution. If the patient is obese (BMI > 35 kg/m^2), drug dosage will be calculated using practical weight as described in Appendix 4. Refer to the current package insert or SmPC for ondansetron for full prescribing information (Appendix 10).
- Prophylactic antibiotics such as TMP/SMX DS 160 mg/800 mg may be given as clinically indicated, per standard of care. Refer to the current package insert or SmPC for the specific antibiotic presribed for full prescribing information.
- Assessment of AE/SAEs. All AEs occurring after the patient has consented, but before enrollment (prior to tumor resection), will be collected on the medical history eCRF unless the event is new and attributed to protocol-required procedures or assessments

6.6 Day -6

The following procedures should be performed:

- Verification of all concomitant medications
- Vital signs – pulse rate, respiratory rate, blood pressure and temperature
- Blood and urine tests (to be drawn prior to cyclophosphamide administration)
  - Hematology: CBC with differential
  - 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
  - CMV serology (IgG and IgM, as per local standard), only if clinically indicated
  - Urinalysis (complete urine culture if indicated)
- Administration of the following medications
- Cyclophosphamide, 60 mg/kg IV with mesna 15 mg/kg, are infused over approximately 2 hours. Cyclophosphamide may be prepared in 250 or 500 mL per institutional standard of practice (D5W or 0.9% NaCl can per used as per institutional standard of practice). If the patient is obese (BMI > 35 kg/m^2) drug dosage will be calculated using practical weight as described in Appendix 4. Refer to the current package insert or SmPC for cyclophosphamide for full prescribing information (Appendix 8).
- Mesna infusion will continue to be infused at a rate of 3 mg/kg/hour in a suitable diluent over 22 hours after each cyclophosphamide dose or per site institutional standard. Patient may be discharged following completion of the mesna administration. Dates of hospitalization of the patient need to be recorded in the eCRF. Higher or continued doses of mesna can be administered as per standard of care at the treating institution for prevention of hemorrhagic cystitis. Local

standards of care for mesna use can be used. Refer to the current package insert or SmPC for mesna for full prescribing information (Appendix 9).

- Ondansetron (0.15 mg/kg/dose [rounded to the nearest even mg dose between 8 mg and 16 mg based on patient weight] IV every 8 hours × 3 days) will be given for nausea, or as per standard of care at the treating institution. If the patient is obese (BMI > 35 kg/m^2), drug dosage will be calculated using practical weight as described in Appendix 4. Refer to the current package insert or SmPC for ondansetron for full prescribing information (Appendix 10).
- Prophylactic antibiotics such as TMP/SMX DS 160 mg/800 mg may be given as clinically indicated, per standard of care. Refer to the current package insert or SmPC for the specific antibiotic presribed for full prescribing information.
- Assessment of AE/SAEs. All AEs occurring after the patient has consented, but before enrollment (prior to tumor resection), will be collected on the medical history eCRF unless the event is new and attributed to protocol-required procedures or assessments

6.7 Day -5 to Day -1

The following procedures should be performed:

- Physical examination including weight (Day -1 only)
- Verification of all concomitant medications
- Vital signs: pulse rate, respiratory rate, blood pressure, and temperature
- Blood and urine tests (to be drawn prior to fludarabine administration)
  - Hematology: CBC with Differential
  - 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

- CMV serology (IgG and IgM, as per local standard), only if clinically indicated. Note: CMV serology (as per local standard) at Screening, within 3 days of LN-144 infusion and thereafter as clinically indicated.
- Urinalysis (complete urine culture if indicated)

- The following medication should be administered:
  - Fludarabine, 25 mg/m^2 to be given IV over approximately 30 minutes once daily each day.
  - Note: Fludarabine dose will be adjusted according to estimated creatinine clearance (CrCl) as follows:
    - CrCl 50-79 mL/min: reduce dose to 20 mg/m^2
    - CrCl 40-49 mL/min: reduce dose to 15 mg/m^2
  - Note: If the patient is obese (BMI > 35.0 kg/m^2), fludarabine dosage will be calculated using practical weight as described in Appendix 4. Refer to the current package insert or SmPC for fludarabine for full prescribing information (Appendix 13).
- Prophylactic antibiotics such as TMP/SMX DS 160 mg/800 mg may be given as clinically indicated, per standard of care. Refer to the current package insert or SmPC for the specific antibiotic prescribed for full prescribing information.
- Assessment of AE/SAEs. All AEs occurring after the patient has consented, but before enrollment (prior to tumor resection), will be collected on the medical history eCRF unless the event is new and attributed to protocol-required procedures or assessments

6.8 Day 0 (Infusion Day)

Day 0 is the day of LN-144 infusion.

If not already hospitalized, the patient will be admitted the day prior to the planned LN-144 infusion. Patients will remain hospitalized until completion of the IL-2 administration, as per institutional standards. Dates of hospitalization of the patient need to be recorded in the eCRF. The following procedures should be performed:

- Physical examination, including weight

- Verification of all concomitant medications
- Vital signs: pulse rate, respiratory rate, blood pressure, and temperature
- Vital signs will be monitored every 30 minutes during infusion then hourly (± 15 minutes) for 4 hours and then routinely (every 4 to 6 hours), unless otherwise clinically indicated, for up to approximately 24 hours post LN-144 infusion
- Blood and urine tests
    - Urine tests (to be drawn prior to LN-144 infusion)
    - Hematology: CBC with differential
    - 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, and thyroid panel (to include TSH and free T4, only if clinically indicated)
    - Urinalysis (complete urine culture if indicated)
    - Serum pregnancy test for women of childbearing potential

The following medications will be administered:

- Prophylactic antibiotics such as TMP/SMX DS 160 mg/800 mg will be given as per standard of care. Refer to the current package insert or SmPC for the specific antibiotic prescribed for full prescribing information

The patient will be admitted prior to planned LN-144 administration and prepared with overnight intravenous hydration prior to the IP administration. Patients will remain hospitalized until the completion of the IL-2 therapy, as per institutional standards.

Concomitant medications will be given to the patient starting within 24 hours prior to LN-144 infusion. This therapy will include the following:

- Hydration per institutional standards

- Within 30 to 60 minutes prior to infusion of LN-144, premedicate the patient with acetaminophen (650 mg) and diphenhydramine (25 to 50 mg IV), or another H1-histamine antagonist. Avoid prophylactic use of systemic corticosteroids, which may interfere with the activity of LN-144. Corticosteroids should only be used to treat life-threatening conditions.

For details, please, refer to Section 8.6.

- Assessment of AE/SAEs. All AEs occurring after the patient has consented, but before enrollment (prior to tumor resection), will be collected on the medical history eCRF unless the event is new and attributed to protocol-required procedures or assessments

6.8.1 Investigational Product

Upon completion of the manufacturing process, the IP, LN-144, will be labeled with a patient specific label. The IP will then be shipped overnight from the manufacturing facility by courier to the clinical site pharmacy in a shipping container validated to maintain the appropriate IP temperature. All visit dates following the LN-144 infusion (Day 0) are calculated from Day 0 forward.

The IP will be received by the appropriate clinical pharmacy or designee for subsequent administration into the specific patient from whom the TIL were derived. See the LN-144 Pharmacy & Administration Manual for precise details for handling of LN-144 for Cohort 1 (noncryopreserved cells) or Cohort 2 (cryopreserved cells).

Receipt is defined as the moment the LN-144 package is signed for by site personnel and released from courier's custody. After receiving, verifying, and labelling with the clinical site's specific labels at the pharmacy, the IP, LN-144, will be transferred to the patient's bedside in the shipping container. Release for infusion status will be made available and must be confirmed as received at the clinical site prior to LN-144 infusion.

At the time of release of LN-144 product for infusion, the results of the in-process sterility test are available, as are the results for the Gram stain test on the final product.

With this supportive information, it is felt that the benefit of administering the product to patients who urgently require therapy outweighs the potential risk of administering a product prior to the final sterility test results.

In the case of a positive sterility test for an administered LN-144 product, the site will be immediately notified of the results of the test. Appropriate and prompt evaluation of the patient will be required and immediate initiation of appropriate anti-infective management per local standard of care must be instituted based on the results of the sterility tests.

6.8.1.1 LN-144 Infusion

Autologous TIL (LN-144) will be administered intravenously. The fresh LN-144 IP (for Cohort 1 patients) will be administered (by gravity) at an infusion rate of 5 to 10 mL/minute. If interruption of infusion is required for medical reasons, the infusion should be restarted when appropriate and completed within 3 hours of the initial start of the infusion. During periods of infusion interruption, the remaining LN-144 fresh (Cohort 1) IP should be refrigerated.

The frozen LN-144 IP (for Cohort 2 patients) will be thawed in a 37^{o}C water bath and each infusion bag will be administered sequentially. The cryopreserved LN-144 IP (for Cohort 2 and Cohort 3 patients) will be administered (by gravity) at an infusion rate of 5 to 10 mL/minute. During periods of infusion interruption, the remaining cryobags of frozen TIL (Cohort 2) should be kept in the cryoshipper.

- Further details of the administration procedure are provided in the LN-144 Pharmacy and Administration Manual
- Assessment of AE/SAEs. All AEs occurring after the patient has consented, but before enrollment (prior to tumor resection), will be collected on the medical history eCRF unless the event is new and attributed to protocol-required procedures or assessments

Autologous TIL (LN-144) infusion is Day 0 of the Treatment Period (Section 6.9 below).

6.9 Treatment Period

6.9.1 Day 1, Day 2, Day 3, and Day 4

While the patient remains hospitalized (hospitalization days should be recorded in the eCRF), the following procedures should be performed:

- Physical examination including weight
- List all concomitant medications
- Vital signs: pulse rate, respiratory rate, blood pressure, and temperature; pulse oximetry is to be conducted during IL-2 administration
- Blood and urine tests (must be drawn prior to the first IL-2 administration of each calendar day)
  - Hematology: CBC with differential
  - 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
  - CMV serology (IgG and IgM, as per local standard) only if clinically indicated
  - Urinalysis (complete urine culture if indicated)
  - Obtain blood for immune monitoring samples. Sample must be collected before first IL-2 dose and on Day 4 only (Refer to Laboratory Manual).
    Note: The first sample for immune monitoring panel should be drawn prior to IL-2 dosing.
- Assessment of AE/SAEs. All AEs occurring after the patient has consented, but before enrollment (prior to tumor resection), will be collected on the medical history eCRF unless the event is new and attributed to protocol-required procedures or assessments

The following medications will be administered:

- IL-2: the first IL-2 administration can begin approximately 3 hours to 24 hours after the conclusion of the LN-144 infusion. IL-2 will be administered at a dose of approximately 600,000 IU/kg (based on total body weight). Note: If the patient is obese (BMI > 35.0 kg/m^2), the IL-2 dosage will be calculated using practical weight as described in Appendix 4. IL-2 is to be administered by intravenous infusion at a frequency of every 8 to 12 hours, as per institutional standard of care, up to the protocol-defined maximum of 6 doses. Continue for up to a maximum of 6 doses. IL-2 doses will be skipped if patient experiences a Grade 3 or Grade 4 toxicity due to IL-2 except: 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 as detailed in Appendix 5. Toxicities will be managed as outlined in Appendix 6. If these toxicities can be easily reversed within 24 hours by supportive measures, then the additional doses of IL-2 up to the protocol-defined maximum of 6 doses may be given. If greater than 2 doses of IL-2 are skipped, IL-2 administration will be discontinued. In addition, IL-2 dosing may be held or stopped at the discretion of the treating Investigator. Refer to Appendix 6 for guidance about the management of IL-2 toxicities.
- Filgrastim, 5 µg/kg/day administered by subcutaneous injection, or as per standard of care at the treating institution. This will be administered each day until the absolute neutrophil count reaches >1000/mm^3 for 3 consecutive days or as per standard of care at the treating institution. Refer to the current package insert or SmPC for filgrastim for full prescribing information (Appendix 11).
- Fluconazole, 400 mg PO daily, or as per standard of care at the treating institution. This should be administered each day until the absolute neutrophil count reaches > 1000/mm^3 or as per standard of care at the treating institution. Refer to the current package insert or SmPC for fluconazole for full prescribing information (Appendix 12).

- Prophylactic antibiotics, such as TMP/SMX DS 160 mg/800 mg, may be given as clinically indicated, per standard of care. Refer to the current package insert or SmPC for the specific antibiotic prescribed for full prescribing information.
- Herpetic treatment will be initiated in patients positive for HSV as per standard of care at the treating institution. Valacyclovir PO or acyclovir IV will be administered daily, and continued until absolute lymphocyte count (ALC) > 1000/mm^3 or as per standard of care at the treating institution
- Assessment of AE/SAEs

6.10 Visits Prior to Start of Response Assessment Period

6.10.1 Day 14 and Day 28 (Both Visits ± 3 Days [(Calculated from Day 0, TIL Infusion)

The following procedures will be performed on Days 14 and 28 calculated from Day 0 (tumor resection):

- Physical examination including weight
- List of all concomitant medications
- ECOG performance status evaluation (Day 14 only)
- Blood tests
  - Hematology: CBC with differential
  - 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, and thyroid panel (to include TSH and free T_4). Thyroid panel only to be done at Day 14.
  - Serum pregnancy test for women of childbearing potential (Day 28 only, or when clinically indicated)
  - Obtain blood for immune monitoring (Day 14 only) (Refer to the Laboratory Manual)

- If required, the following medications will continue to be administered
  - Filgrastim, 5 µg/kg/day administered by subcutaneous injection, or as per standard of care at the treating institution. This will be administered each day until the absolute neutrophil count reaches > 1000/mm^3 for 3 consecutive days, or as per standard of care at the treating institution. Refer to the current package insert or SmPC for filgrastim for full prescribing information (Appendix 11).
  - Fluconazole 400 mg PO daily, or as per standard of care at the treating institution. This should be administered each day until the absolute neutrophil count reaches > 1000/mm^3 or as per standard of care at the treating institution. Refer to the current package insert or SmPC for fluconazole for full prescribing information (Appendix 12).
  - Prophylactic antibiotics such as TMP/SMX DS 160 mg/800 mg may be given as clinically indicated, per standard of care. Refer to the current package insert or SmPC for the specific antibiotic prescribed for full prescribing information.
  - Herpetic treatment will be initiated in patients positive for HSV as per standard of care at the treating institution. Valacyclovir PO or acyclovir IV will be administered daily, and continued until ALC > 1000/mm^3 or as per standard of care at the treating institution

- Assessment of AE/SAEs. All AEs occurring after the patient has consented, but before enrollment (prior to tumor resection), will be collected on the medical history eCRF unless the event is new and attributed to protocol-required procedures or assessments

6.11 Response Assessment Period

The Response Assessment Period includes all assessments every 6 weeks until 6 months after Day 0 and then every 3 months until the end of the study for each patient (End of Study: death, lost to follow-up, or withdrawal of consent, or Month 60 from last study treatment).

6.11.1 Every 6 Weeks (Week 6 [Day 42]; Week 12 [Day 84]Week 18 [Day 126], and Month 6 [Week 24, Day 168] [All Visits ± 3 Days Calculated from Day 0, TIL Infusion])

The following procedures will be performed during this post treatment evaluation visit:

- Physical examination including weight
- List of all concomitant medications
- ECOG performance status evaluation
- Evaluation and measurement of all skin and palpable lesions
- Vital signs - pulse rate, respiratory rate, blood pressure and temperature
- Assessment of AE/SAEs. All AEs occurring after the patient has consented, but before enrollment (prior to tumor resection), will be collected on the medical history eCRF unless the event is new and attributed to protocol-required procedures or assessments
- Slit lamp eye exam, if clinically indicated
- Blood tests
  - Hematology: CBC with Differential
  - 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, and thyroid panel (to include TSH and free T_4, only if clinically indicated)
  - CMV serology (IgG and IgM, as per local standard), only if clinically indicated
  - Serum pregnancy test for women of childbearing potential
- Obtain blood for immune monitoring (Refer to the Laboratory Manual)
- Calculate creatinine clearance using Cockcroft-Gault formula

- CT Examination (repeat the same CT series for Response Assessment Period tumor assessment [scheduled and unscheduled] as completed at Baseline [Day -21 to Day -14])
  - Chest (include neck if there is prior or suspected neck disease)
  - Abdomen
  - Pelvis
- MRI of brain if positive for CNS involvement at Screening or Baseline, or as clinically indicated (repeat the same MRI series for Response Assessment Period tumor assessment [scheduled and unscheduled] as completed at Baseline [Day -21 to Day -14])
- EORTC QLQ-C30 HRQoL questionnaire
- If required, the following medications will continue to be administered
  - Filgrastim, 5 µg/kg/day administered by subcutaneous injection, or as per standard of care at the treating institution. This will be administered each day until the absolute neutrophil count reaches > 1000/mm^3 for 3 consecutive days, or as per standard of care at the treating institution. Refer to the current package insert or SmPC for filgrastim for full prescribing information (Appendix 11).
  - Fluconazole, 400 mg PO daily, or as per standard of care at the treating institution. This should be administered each day until the absolute neutrophil count reaches > 1000/mm^3, or as per standard of care at the treating institution. Refer to the current package insert or SmPC for fluconazole for full prescribing information (Appendix 12).
  - Prophylactic antibiotics, such as TMP/SMX DS 160 mg/800 mg, may be given as clinically indicated, per standard of care. Refer to the current package insert or SmPC for the specific antibiotic prescribed for full prescribing information.
  - Herpetic treatment will be initiated in patients positive for HSV as per standard of care at the treating institution. Valacyclovir PO or acyclovir IV

will be administered daily, and continued until ALC > 1000/mm^3, or as per standard of care at the treating institution

6.11.2 Every 3 Months After Month 6 Until End of Study Visit (All Visits ± 1 Week, Calculated from Day 0, TIL Infusion) or End of Study (EOS) Visit

The following procedures will be performed during these visits:

- Physical exam including weight
- ECOG performance status evaluation
- Verification of all concomitant medications
- Vital signs: pulse rate, respiratory rate, blood pressure and temperature
- Evaluation and measurement of all skin and palpable lesions
- Blood tests
  - Hematology - CBC with Differential
  - Chemistry - Sodium, 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, and thyroid panel (to include TSH and free T4 at Month 24 or if clinically indicated at other timepoints)
  - CMV serology (IgG and IgM, as per local standard), only if clinically indicated
  - Serum pregnancy test for women of childbearing potential (every 3 months until Month 12 or EOS Visit, whichever occurs first)
  - Obtain blood for immune monitoring (Refer to the Laboratory Manual) (Months 6, 9, and 12 only)
- CT Examination (repeat the same CT series for Response Assessment Period tumor assessment [scheduled and unscheduled] as completed at Baseline [Day -21 to Day -14])
  - Chest (include neck if there is prior or suspected neck disease)

- Abdomen
- Pelvis

- MRI of brain if positive for CNS involvement at Screening or Baseline (Day -21 to Day -14) or as clinically indicated (repeat the same MRI series for Response Assessment Period tumor assessment [scheduled and unscheduled] as completed at Baseline [Day -21 to Day -14])

- If required, the following medications will continue to be administered (Month 6)
  - Filgrastim, 5 µg/kg/day administered by subcutaneous injection, or as per standard of care at the treating institution. This will be administered each day until the absolute neutrophil count reaches > 1000/mm^3 for 3 consecutive days, or as per standard of care at the treating institution. Refer to the current package insert or SmPC for filgrastim for full prescribing information (Appendix 11).
  - Fluconazole, 400 mg PO daily, or as per standard of care at the treating institution. This should be administered each day until the absolute neutrophil count reaches > 1000/mm^3, or as per standard of care at the treating institution. Refer to the current package insert or SmPC for fluconazole for full prescribing information (Appendix 12).
  - Prophylactic antibiotics, such as TMP/SMX DS 160 mg/800 mg, may be given as clinically indicated, per standard of care. Refer to the current package insert or SmPC for the specific antibiotic prescribed for full prescribing information.
  - Herpetic treatment will be initiated in patients positive for HSV as per standard of care at the treating institution. Valacyclovir PO or acyclovir IV will be administered daily, and continued until ALC > 1000/mm^3, or as per standard of care at the treating institution

- Assessment of AEs/SAEs (see Section 12.2 for guidance on AE/SAE reporting requirements during the follow-up period). All AEs occurring after the patient has consented, but before enrollment (prior to tumor resection), will be collected on

the medical history eCRF unless the event is new and attributed to protocol-required procedures or assessments

- EORTC QLQ-C30 HRQoL questionnaire (Every visit until End of Study Visit)

6.12 Overall Survival Follow-Up Period

Patients are to be followed in Overall Survival (OS) Follow-Up (FU) to collect subsequent anticancer therapy and survival status. Overall Survival FU Period will start when a patient completes the Response Assessment Period and continues up to 5 years from the last study treatment until death, lost to follow-up, or withdrawal of consent.

Patients who receive no study drug, including LN-144 infusion will be followed for OS follow-up for a minimum of 3 years from the tumor resection, in addition, information about new anticancer therapy will be collected during this period.

6.13 Treatment Discontinuation (Following LN-144 Infusion)

A patient who is discontinued from treatment or the Response Assessment Period follow-up, after receiving LN-144 should remain on the study and continue with all scheduled study visit assessments.

However, if a patient must initiate a new anticancer therapy or exhibits disease progression after LN-144 infusion, they will remain in the study, but the data collection will be reduced to survival status and other anticancer therapy

6.14 Expected Toxicities and Treatment Guidelines

6.14.1 LN-144

Early toxicities related specifically to the infusion of the cells (those which are seen immediately following the cell infusion and prior to IL-2 administration) are generally mild and include fevers, chills, headache, and malaise. Toxicities that occur following administration of IL-2, but are thought to be related to the cells include immune mediated events such as vitiligo, transient uveitis, hearing loss and vestibular dysfunction. (IL-2 specific toxicity is discussed in Section 6.14.2).

6.14.2 IL-2 Administration

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

Decreased mental status may occur and can range from somnolence to obtundation. IL-2 should be discontinued for any significance status changes or hallucinations. Agitation may be observed due to mild hallucinations. Treatment with IL-2 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. Administration of IL-2 should be withheld in patients developing moderate to severe lethargy or somnolence; continued administration may result in coma.

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

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

The standard approach to the administration of IL-2 is to continue dosing until Grade 3 or 4 events occur but this study calls for 1 to 6 doses based on tolerance. 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, almost all toxicities are reversible, and most patients have experienced no long-term sequelae following this treatment regimen. However, fatal complications are possible. Subcutaneous administration of IL-2 is not permitted.

The full prescribing information for IL-2 is presented in Appendix 14.

6.15 Treatment Guidelines for Toxicity Management

Concomitant medications must be given to the patient starting within 24 hours prior to LN-144 infusion. Premedication instructions are provided in Section 8.6.

Additional supportive therapy may include:

- Acetaminophen (650 mg q4h), indomethacin (50 to 75 mg q6h), and ranitidine (150 mg q12h)
- Meperidine (25 to 50 mg), or other medication per institutional standards may be given IV if severe chills develop

Other supportive therapy shall be given as required.

The Investigator should use supportive therapies as per institutional standard of care. Additional antiemetic therapy will be administered for breakthrough nausea and vomiting. Patients shall receive supportive care as indicated for IL-2 toxicities as listed in Appendix 6.

6.15.1 Expected Toxicities with LN-144

The cryopreserved TIL product formulations contain 0.5% human serum albumin (HSA), 300 IU/mL of interleukin-2 (IL-2), and potentially low residual amounts of gentamycin and streptomycin, which belong to the aminoglycoside group of antibiotics. Cryopreserved TIL product formulations include the cryopreservation medium

CryoStor® CS10, which contains the cryoprotectants dimethyl sulfoxide (DMSO) and dextran-40.

Hypersensitivity events, including severe allergic reactions or anaphylaxis have occurred during infusion with LN-144 because hypersensitivity has been associated with at least one of the above-mentioned formulation components. Patients who have known allergies to antibiotics of the aminoglycoside group are excluded from the studies of LN-144. Premedication and supportive therapy instructions are provided in Section 8.6.

Allergic reaction may present with symptoms such as rash, low blood pressure, shortness of breath, swelling of the face or throat, cough, chest tightness, and/or wheezing. These symptoms can usually be reversed promptly using an inhaled bronchodilator. During infusion of LN-144 product, appropriate emergency medications (eg, epinephrine and diphenhydramine) should be available at bedside during administration and institutional guidelines should be followed for the treatment of anaphylaxis. A more severe reaction is less likely but may occur and may require treatment with an injection of epinephrine, steroids, and inhaled bronchodilators.

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

Details concerning specific risks for patients participating in this clinical study may be found in the accompanying LN-144 Investigator's Brochure.

6.15.2 Expected Toxicities with Cyclophosphamide and Fludarabine

Expected toxicities with cyclophosphamide and fludarabine administration are listed in the package inserts (see Appendix 8 and Appendix 13, respectively). Also included in the package inserts is information on supportive care and management of toxicities. Treatment will be given as per Investigator discretion and can be given as per institutional standard of care. Additional guidelines for toxicity management are as below.

6.15.2.1 Hemorrhagic Cystitis Prophylaxis

To reduce the risk of cyclophosphamide-associated hemorrhagic cystitis, patients will receive mesna in addition to intravenous fluids. Please refer to treatment guidelines for recommended mesna dosing. Alternative dosing regimens of mesna are allowed if the dose is greater than what is suggested in this protocol per institutional standards and Investigator discretion.

6.15.3 Nonmyeloablative Lymphodepletion Regimen Toxicity Management

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

Refer to cyclophosphamide and fludarabine current package inserts for additional information. Expected toxicities with cyclophosphamide and fludarabine administration are listed in the package inserts (see Appendix 8 and Appendix 13). Also included in the package inserts is information on supportive care and management of toxicities. Treatment will be given as per Investigator discretion and can be given as per institutional standard of care. Additional guidelines for toxicity management are as below.

6.15.4 Expected Toxicities with IL-2

6.15.4.1 Decreased Mental Status with IL-2

Decreased mental status may occur and can range from somnolence to obtundation. IL-2 should be discontinued for any significant mental status changes or hallucinations. Agitation may be observed due to mild hallucinations. See Appendix 5 and Appendix 6 for guidelines for IL-2 toxicity management.

6.15.4.2 Pulmonary Risk

Tumor infiltrating lymphocytes can remain in the pulmonary circulation for 24 to 48 hours following infusion and may cause transient shortness of breath. In addition, pulmonary edema is commonly observed with IL-2 dosing. Supplemental oxygen may be

administered as needed. Subsequent IL-2 dosing should be delayed until supplemental oxygen has been weaned or is minimal (< 2 L/min per nasal cannula). If hypoxia persists or is significant, IL-2 should be discontinued. Pulse oximetry is to be conducted during IL-2 administration. Refer to Appendix 5 for IL-2 AEs.

6.15.4.3 Cardiac Arrhythmias and Myocarditis

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

6.15.4.4 Capillary Leak Syndrome

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

6.15.5 Blood Product Support

Using daily CBCs as a guide, the patient will receive platelets and packed red blood cells (PRBCs) as needed as per standard of care at the treating institution. 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.

6.15.5.1 Heparin-Induced Thrombocytopenia

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

6.15.6 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.

6.16 Infection Prophylaxis

Other anti-infective agents may be substituted at the discretion of the Investigator as per standard of care at the treating institution.

6.16.1 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 3 times a week on non-consecutive days, beginning on the first Monday, Wednesday, or Friday on or after the first dose of chemotherapy or as per standard of care at the treating institution.

Pentamidine or alternative as per standard of care at the treating institution may be substituted for TMP/SMX DS in patients with sulfa allergies. It will be administered aerosolized at 300 mg per nebulizer within 1 week prior to receiving study treatment and continued monthly until ALC is above 1000/mm^3 and for at least 6 months post chemotherapy, or as Investigator deems appropriate as per standard of care at the treating institution.

Pneumonia prophylaxis will continue for 6 months post chemotherapy. If the ALC is less than 1000/mm^3 at 6 months post chemotherapy, or as Investigator deems appropriate as per standard of care at the treating institution, prophylaxis will continue until the CD4 count is greater than 200/mm^3.

6.16.2 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/m^2 IV every 12 hours if the patient is not able to take medication by mouth as per standard of care at the treating institution. Oral acyclovir is also an acceptable treatment regimen. Reversible renal insufficiency has been reported with IV but not oral acyclovir. Neurologic toxicity including delirium, tremors, coma, acute psychiatric disturbances, and abnormal electroencephalogram (EEG) has been reported with higher doses of acyclovir. 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, eg, ganciclovir. In renal disease, the dose is adjusted as per product labeling.

Herpes prophylaxis will continue for 6 months post-chemotherapy, or as long as Investigator deems necessary. If the ALC count is less than 1000/mm^3 at 6 months post chemotherapy, prophylaxis will continue until the ALC count is greater than 1000/mm^3, or as per standard of care of the treating institution.

6.16.3 Fungal Prophylaxis (Fluconazole)

Patients will start fluconazole 400 mg (PO) the day after chemotherapy concludes and continue until the ALC is greater than 1000/mm^3, or as per standard of care of the treating institution. 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 as per standard of care at the treating institution.

6.16.4 Empiric Antibiotics

Patients will start on broad-spectrum antibiotics, either a third or fourth generation cephalosporin or a quinolone for fever – defined as 38.3°C, 1 or 2 temperatures of 38.0°C or above at least 1 hour apart, AND an ANC $\leq$ 500/mm^3 or receiving IL-2 administration. Aminoglycosides should be avoided unless there is clear evidence of sepsis. Infectious disease consultation will be obtained for all patients with unexplained fever or any infectious complications as per standard of care at the treating institution.

6.16.5 Sepsis

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

7 COMPLETION / DISCONTINUATION AND WITHDRAWAL OF PATIENTS

7.1 Treatment Completion

Completion of treatment is defined as having received any volume of LN-144 infusion followed by at least 1 dose of IL-2.

7.2 Criteria for Early Discontinuation from Treatment

Criteria for early discontinuation from treatment:

- Grade 3 or greater drug-related immune AEs that involve vital organs (heart, kidneys, brain, eye, liver, colon, adrenal gland, lungs) with symptoms emerging following LN-144 infusion
- Grade 3 or greater allergic reaction including bronchospasm or generalized urticaria that does not resolve after medical management in the opinion of the Investigator
- Meeting criteria for permanent discontinuation of IL-2 treatment
- Determination by the Investigator that continued treatment is not in the best interest of the patient
- Administration of prohibited concomitant medications

Criteria for early discontinuation from study:

- Full withdrawal of consent by patient
  - Every effort should be made to continue overall survival follow-up
- Administration of any other anticancer therapy(ies)
  - Every effort should be made to continue overall survival follow-up
- Lost to follow-up after 3 documented attempts to contact the patient
- Death
- Study terminated by the Sponsor

8 STUDY DRUG INFORMATION

8.1 Investigational Product

Investigational Product Name: LN-144

Active Investigational Product Components: Autologous, viable, tumor infiltrating lymphocytes (TIL)

Dosage Form: Live cell suspension either noncryopreserved (Cohort 1) or cryopreserved (Cohort 2)

8.2 Qualitative Composition of LN-144

LN-144 is a cellular IP of autologous tumor-infiltrating lymphocytes (TIL) derived from the patient's own tumor. LN-144 is an autologous cell therapy for the treatment of patients with advanced melanoma. LN-144 is a live cell suspension that is either formulated in either HypoThermosol™ transport medium (noncryopreserved product) or CryoStor® medium (cryopreserved product) with Plasma-Lyte® A as diluent, with 0.5% HSA (human serum albumin) and 300 IU/mL of IL-2. The suspension volume will be between 250 to 500 mL. Only a single LN-144 intravenous infusion is given following the NMA-LD preconditioning regimen. After the LN-144 infusion is completed, the IL-2 administration starts as soon as 3 hours, but not later than 24 hours, and continues for up to 6 doses of intravenous IL-2. The total volume of LN-144 to be infused will be approximately 250 mL (300-mL transfer bag for Cohort 1) for cell concentrations $\leq 75 \times 10^9$ LN-144 or 500 mL (up to 600-mL transfer bag for Cohort 1) for cell concentrations $\leq 150 \times 10^9$ LN-144. Patients on Cohort 2 will have up to 4 bags containing up to approximately 100 to 150 mL of thawed cells.

8.3 Manufacturing Process

The overall process of tumor shipping, LN-144 manufacturing, and LN-144 IP shipping, and infusion is shown in Figure 2 (Cohorts 1 and 2). The LN-144 IP is manufactured ex vivo using autologous tumor as starting material. The key manufacturing steps include:

- Surgical resection of autologous metastatic tumor and shipment to manufacturing facility
- Culture of small 2-mm to 3-mm (length × width × height) fragments of autologous tumor in IL-2 to expand TIL
- A rapid expansion protocol (REP) in the presence of IL-2, OKT3, and irradiated allogeneic MNC feeder cells
- Harvesting and formulation of REP expanded IP in transport medium or cryopreserved and overnight shipment to clinical site for infusion

8.4 Final Investigational Product Container

The live suspension of LN-144 for Cohort 1 is stored in a 300-mL blood transfer pack (Baxter) for cell concentrations ≤ 75×10^9 LN-144 or 600-mL blood transfer pack (Baxter) for cell concentrations ≤ 150×10^9 LN-144. Alternatively, in Cohort 2, TIL will be received cryopreserved in up to 4 bags containing up to approximately 100 to 125 mL of thawed cells.

8.5 Transport

Each dose of the live suspension LN-144 will be shipped/sent by courier to the clinical site from the LN-144 manufacturing facility by a method that is intended to support 24-hour delivery. The live suspension IP will be packaged in a protective bag containing absorbent padding then placed into an insulated container (Therapak NanoCool™ shipper), designed to maintain transit temperature between 2°C to 8°C (Cohort 1).
For Cohort 2, a dry cryoshipper will be utilized. A temperature monitoring device will be included to monitor the temperature inside the container during shipping.

8.6 Receipt at Clinical Site and Administration

The dose of LN-144 IP will be received at the clinical site on or prior to Day 0.

Receipt is defined as the moment the LN-144 package is signed for by site personnel and released from courier's custody. After receiving, verifying, and labeling with the clinical sites' specific labels at the pharmacy, the IP, LN-144, will be transferred to the patient bedside in the cryoshipper. The clinical site is instructed to administer the autologous LN-144 IP immediately after thawing each cryopreserved infusion bag, sequentially. Additional details are specified in the Pharmacy & Administration Manual.

The LN-144 IP is infused by gravity within approximately 15 minutes for each sequentially thawed and infused bag. If interruption of infusion is required for medical reasons, the LN-144 infusion bags not yet thawed should be kept in the cryoshipper and any thawed LN-144 product should be infused within 3 hours of being thawed.
The Pharmacy & Administration Manual should be consulted. Continuous supervision of the patient by site medical staff is required until completion of infusion of the first bag of TIL, to monitor for potential signs and symptoms (eg, of a severe hypersensitivity reaction such as anaphylaxis that may require immediate medical attention and treatment).

The cryopreserved TIL product formulations contain 0.5% human serum albumin (HSA), 300 IU/mL of interleukin-2 (IL-2), and potentially low residual amounts of gentamycin and streptomycin, which belong to the aminoglycoside group of antibiotics. Cryopreserved TIL product formulations include the cryopreservation medium CryoStor® CS10, which contains the cryoprotectants dimethyl sulfoxide (DMSO) and dextran-40. Hypersensitivity events, including severe allergic reaction and anaphylaxis, have occurred during infusion with LN-144/LN-145 product, as hypersensitivity has been associated with at least one of the above-mentioned formulation components.

If not already hospitalized, the patient will be admitted prior to planned LN-144 administration and prepared with overnight intravenous hydration prior to the IP administration. Patients will remain hospitalized until the completion of the IL-2 therapy, as per institutional standards.

Concomitant medications must be given to the patient starting within 24 hours prior to LN-144 infusion. This therapy will include the following:

- Hydration per institutional standards
- Within 30 to 60 minutes prior to infusion of LN-144, premedicate the patient with acetaminophen (650 mg) and diphenhydramine (25 to 50 mg IV), or another H1-histamine antagonist. Avoid prophylactic use of systemic corticosteroids, as it may interfere with the activity of LN-144. Corticosteroids should only be used to treat life-threatening conditions.

Additional supportive therapy may include:

- Acetaminophen (650 mg q4h), indomethacin (50 to 75 mg q6h), and ranitidine (150 mg q12h)
- Meperidine (25 to 50 mg), or other medication per institutional standards may be given IV if severe chills develop

Patients may experience severe allergic reaction including anaphylaxis that can be life threatening during infusion of LN-144 product. During infusion of LN-144 product, appropriate emergency medications (eg, epinephrine and diphenhydramine) should be available at bedside during administration and institutional guidelines should be followed for the treatment of anaphylaxis.

Earlier versions of the protocol required that Cohort 3 patients received their TIL manufactured per the same process for the second LN-144 infusion as used for the original TIL manufacturing if the first LN-144 infusion was completed (either noncryopreserved TIL or cryopreserved TIL), alternatively if no prior LN-144 infusion was received, treatment in Cohort 3 would be by whichever manufacturing process has the first availability. As of December 2017, all patients receiving retreatment in Cohort 3 will receive the Gen 2 LN-144 infusion product.

8.7 Retreatment with LN-144

Retreatment with LN-144 will be permitted for patients who received TIL therapy. Patients from Cohort 1 or Cohort 2 may rescreen for a second tumor resection and LN-144 treatment, if they meet all Inclusion and Exclusion Criteria (except exclusion criterion b). These patients may have a second tumor resection, especially when new lesions are available and feasible for resection.

The decision for enrollment in Cohort 3 will be based on discussion between the Principal Investigator and the Medical Monitor. The Medical Monitor will have authority to adjudicate enrollment into Cohort 3 (second TIL therapy). All procedures and assessments assigned to receiving LN-144 therapy are the same as described in Sections 6.2, 6.2.2, and 6.8.

9 STUDY ASSESSMENTS

9.1 Tumor Assessments

Tumor assessment (scheduled or unscheduled) will be performed by clinical exam (skin lesions) and by conventional or spiral CT scans of the chest, abdomen, pelvis and MRI of brain conducted at Screening, Baseline (Day -21 to Day -14), and
(Week 6 [Day 42 ± 3 days]) following the LN-144 infusion and every
Week 6 (Day 42± 3 days) thereafter, up to 6 months post-LN-144 infusion (Response Assessment Period), at which time the tumor assessments (scheduled and unscheduled) will occur every 3 months until the following criteria are met:

- Disease progression
- Start of a new anticancer therapy
- Withdrawal of consent
- Lost to Follow-Up
- Death

Overall survival follow-up will start after completion of the Response Assessment Period and will continue for up to 5 years for each patient from the last study treatment.

CT scans of additional anatomical locations will be conducted at the above referenced visits if prior or suspected disease is clinically indicated (the same CT series and brain MRI as completed at Baseline [Day -21 to Day -14] is to be repeated at all Response Assessment Period disease assessments, [scheduled and unscheduled]). Assessments should be made and recorded by the Investigator or an individual authorized by the Investigator.

Magnetic resonance imaging or positron emission tomography (PET; specifically, fluorodeoxyglucose-PET [FDG-PET]) scans may be used in lieu of CT scans for patients who have an intolerability to contrast media. The imaging modality used must be uniform for the duration of the study.

Note: The use of the same imaging location/equipment and settings should be kept constant for each individual patient during their participation in the study.

The same method of assessment (CT or MRI) and the same technique for acquisition of data should be used to characterize each identified and reported lesion at Baseline (Day -21 to Day -14) and at all post-treatment tumor assessments (scheduled and unscheduled). At the Investigator's discretion, the Baseline brain MRI and CT scans may be performed as early as Day -21. Patients will be evaluated for response at 6, 12, 18, and 24 weeks after the last dose of IL-2; then every 3 months until disease progression, initiation of a new anticancer therapy, or patient withdrawal from the study. Additional radiological assessments may be performed per Investigator's discretion.

All patients should have radiographic tumor measurements performed at the participating study center or an acceptable alternate imaging facility using an identical imaging protocol. The same imaging equipment and parameters should be used for all scans throughout the study.

9.1.1 Response Criteria

Tumor response will be determined using RECIST version 1.1 [61] with a modification to require confirmation of PD. Refer to Table 1 and Table 2 for RECIST 1.1 response criteria definitions. Images (CT scans and/or MRI) obtained at Baseline Visit (Day -21 to Day -14) are to be utilized for RECIST 1.1 response assessments throughout the study.

Local tumor assessments (scheduled or unscheduled) should be used for clinical treatment decisions, and may include photographic/caliper measurement of superficial dermal and subcutaneous lesion.

All locally-obtained images will be forwarded to a central imaging facility for IRC assessment of tumor responses.

9.1.1.1 Evaluation of Target Lesions[1]

- Complete Response (CR): Disappearance of all target lesions. Any pathological lymph nodes (whether target or nontarget) must have a reduction in short axis to <10 mm).
- Partial Response (PR): At least a 30% decrease in the sum of the diameter of target lesions taking as reference the Baseline (Day -21 to Day -14) 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 (Day -21 to Day -14) sum if that is the smallest on study). In addition to the relative increase of 20%, the sum must also demonstrate an absolute increase of at least 5 mm. (Note: the appearance of 1 or more new lesions is also considered progression).

[1] All measurable lesions up to a maximum of 2 lesions per organ and 5 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.

- 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.

9.1.1.2 Evaluation of Nontarget Lesions[2]

- Complete Response (CR): Disappearance of all nontarget 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 1 or more nontarget lesion(s) and/or maintenance of tumor marker level above normal limits.
- Progressive Disease (PD): Unequivocal progression of existing nontarget lesions. (Note: the appearance of 1 or more new lesions is also considered progression).

9.1.1.3 Evaluation of Best Overall Response

The best overall response is determined once all the data for the patient is known. The best overall response is the best response recorded until disease progression/recurrence, the initiation of new anticancer therapy, death or 24 months whichever comes first.
The patient's best response assignment will depend on target lesion SoD, nontarget lesion status, absence of a new lesion, and the confirmation criteria.

Table 1 Time Point Response: Patients with Target (± Nontarget) Disease

Target Lesions	Nontarget Lesions	New Lesions	Response
CR	CR	No	CR
CR	Non-CR/Non-PD	No	PR
CR	Not evaluated	No	PR
PR	Non-PD or not all evaluated	No	PR
SD	Non-PD or not all evaluated	No	SD
Not all evaluated	Non-PD	No	NE
PD	Any	Yes or No	PD
Any	PD	Yes or No	PD
Any	Any	Yes	PD

[2] All other lesions (or sites of disease) should be identified as nontarget lesions and should also be recorded at Baseline.

Table 2 Time Point Response: Patients with Nontarget Disease Only

Nontarget Lesions	New Lesions	Response
CR	No	CR
Non-CR/Non-PD	No	Non-CR/Non-PD
Not all evaluated	No	NE
Unequivocal PD	Yes or No	PD
Any	Yes	PD

9.1.1.4 Confirmatory Measurement/Duration of Response

9.1.1.4.1 Confirmation

A response of PR or CR must be confirmed by a subsequent assessment of response, which should be performed at least 4 weeks after the criteria for response are first met.

9.2 Biomarkers

Biomarkers, or immune monitoring, include peripheral blood mononuclear cells (PBMCs), serum, plasma and tumor specimens that will be collected to test for cellular and soluble factors, via immunological assays and molecular assays related to exome sequencing, TCR sequencing, mRNA analysis, and immunohistochemistry staining.

9.3 Data Safety Monitoring Board

An independent Data Safety Monitoring Board (DSMB) will evaluate cumulative safety data on the first 3 patients completing 12 weeks of assessment in Cohort 1 and Cohort 2, respectively. As of November 2017, the DSMB had reviewed the data from Cohort 1 and Cohort 2 and recommended to continue enrollment without any changes to the clinical study protocol. Additional evaluations of safety data may be conducted as specified in the DSMB charter.

10 STATISTICAL AND ANALYTICAL PLANS

10.1 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. Point estimates of treatment effect will be derived from maximum likelihood methods. Estimation of confidence limits will use 2-sided, 95% criteria and implement the Wilson score method. Missing data will not be imputed unless defined in the statistical analysis plan (SAP). If inferential statistics are calculated (eg, p-values), they will be used in a descriptive manner).

A more detailed description of the analyses and reporting plan of the study data will be provided in the SAP.

10.2 Study Analysis Sets

The Tumor Harvested (TH) set is defined as all tumor-resected patients for production of LN-144. The TH set is further divided into the efficacy and safety sets for analyses. There is no planned statistical or descriptive comparison among cohorts.

10.2.1 Safety Analysis Set

The Safety Analysis set consists of patients who have received TIL LN-144 infusion.

10.2.2 Efficacy Analysis Set

The Efficacy Analysis set consists of subjects in the Safety Analysis set with a Baseline (Day -21 to Day -14) and at least one post-Baseline radiological assessments. Patients who progressed or expired prior to reaching the first radiological assessment will be included.

10.2.3 Cohort 3

Patients who are retreated with LN-144 therapy (Cohort 3) will have their safety and efficacy data tabulated separately. Patients who received LN-144 for the first time in Cohort 3 due to a previous manufacturing failure or other reasons, will be included in the Efficacy and Safety Analysis sets of the original cohort. There will be no formal comparisons among cohorts.

10.3 Endpoints

10.3.1 Primary Endpoint

The primary endpoint is the ORR using RECIST 1.1 criteria [61] as assessed by the Investigator. The ORR is derived as the sum of the number of patients with a best response of complete response (CR) or partial response (PR) divided by the number of patients in the Efficacy Analysis set × 100%.

10.3.2 Secondary Endpoints

The secondary endpoint will include DOR, DCR, and PFS per RECIST 1.1 criteria as assessed by the Investigator. In addition, the secondary endpoints will include the ORR, DOR, DCR, and PFS per RECIST 1.1 criteria as assessed by the IRC. Overall survival will be assessed as a secondary endpoint.

The DOR is measured from the time point at which the initial measurement criteria are met for a CR or PR, whichever response is observed first, until the first date that progressive disease (PD) or death occurs. Patients not experiencing PD or death prior to the time of data cut or end of study will have their event times censored on the last complete tumor assessment date.

The DCR is derived as the sum of the number of patients who achieved PR/CR or SD per the RECIST v1.1 divided by the number of patients in the Efficacy Analysis set multiplied by 100%.

The PFS is defined as the time (in months) from the start date of lymphodepletion to PD or death due to any cause, whichever event is earlier. Patients not experiencing PD or death at the time of data cut or end of study (ie, database lock) will have their event times censored on the last complete tumor assessment date.

The OS is defined as the time (in months) from the start date of the LD to death due to any cause. Patients not having expired at the time of data cut or end of study will have their event times censored on the last date of their known survival status.

Safety and toxicity will be based on the assessment of multiple clinical evaluations and will mainly include adverse events, clinical laboratory tests, vital signs, and physical examinations.

10.3.3 Exploratory Endpoints

The exploratory endpoints include measures of LN-144 persistence in the peripheral blood as well as immune response with the objective to evaluate their correlation with response, outcome, and toxicity of the treatment. Tumor responses via ir-RECIST [61] will also be assessed. -HRQoL will be assessed using the EORTC QLQC30 instrument (see Appendix 15) and scored/evaluated as described in the Statistical Analysis Plan.

10.4 Sample Size Consideration

The planned number of patients is approximately 60 in the Efficacy Analysis set who received either US or European manufactured LN-144 infusion product in Cohort 2. The total number of patients to be enrolled across all cohorts will be approximately 85.

The lower 95% confidence limit for ORR is estimated per the Wilson Score method. The maximum half width of the 2-sided confidence limit is less than 12.3% when ORR is expected to range from 20% to 50%.

The primary analysis will occur when more than 60 patients have been followed for a minimum of 6 months. This allows sufficient time for disease-controlled patients (SD or better) to demonstrate emergence and durability of response.

10.5 Analysis Methods

10.5.1 Baseline Demographics and Clinical Characteristics

Baseline (-21 to Day -14) demographic and clinical (disease) characterized will be summarized descriptively for the Safety and Efficacy Analysis sets if they are not identical. Age will be derived as a function of the date of informed consent.

10.5.2 Primary Endpoint

The ORR is expressed as binomial proportions and will be summarized for the best overall response using a point estimate and its 2-sided 95% confidence limits based on the Wilson's score method.

10.5.3 Secondary Endpoints

The DCR is also expressed as binomial proportions and will be summarized using both a point estimate and its 2-sided 95% confidence limits based on the Wilson's score method.

The PFS, OS, and DOR are time-to-event variables subjected to right censoring. Kaplan-Meier probabilities and related summary statistics will be provided for the entire time-to-event curve as well as for the following landmark event-free rates: 6 months, 12 months, 18, months, and 24 months depending on the maturity of the study data at the time of analysis.

The primary safety variable is a binomial proportion of a safety event and will be summarized using both a point estimate and its 2-sided 95% confidence limits.

10.5.4 Safety Analysis

The assessment of safety data will be descriptive and based on the summarization of treatment-emergent adverse events, serious adverse events, adverse events leading to discontinuation from the study, vital signs, physical examinations, and clinical laboratory tests. Treatment emergent is considered to start at the time of the LN-144 infusion for the Safety Analysis set. Adverse event summaries will be based on patient incidence counts and their related percentages. In addition to an overall summary of adverse events,

separate displays will be made by severity and relationship. Certain safety data will be amenable to summary by use of toxicity grades, and all such analyses will evaluate the worst grade observed per patient during the treatment-emergent period. These toxicity grade summaries will be derived separately based on the current version of CTCAE for each measure under consideration (eg, ANCs for neutropenia; platelets for thrombocytopenia).

10.5.5 Other Planned Analyses

Should additional analyses other than those described in this study protocol, but described in the SAP or the DSMB charter be performed, their details will be described in the Clinical Study Report.

11 CONTRAINDICATIONS, PRECAUTIONS AND WARNINGS

11.1 Medications Administered during the Study

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

11.2 LN-144 Treatment

Early toxicities related specifically to the infusion of the cells (those seen immediately following cell infusion and prior to IL-2 administration) are generally mild and include fevers, chills, headache, and malaise. Toxicities that occur following administration of IL-2 but thought to be related to the cells include immune mediated events such as vitiligo, transient uveitis, hearing loss and vestibular dysfunction. (IL-2 specific toxicity is discussed in Section 6.14.2). The use of the nonmyeloablative regimen prior to cell administration increases the toxicity of this treatment as profound myelosuppression occurs in all patients.

12 ADVERSE EVENTS

Toxicities will be recorded as AEs and SAEs in the patient's source documents and on the Adverse Event eCRF and must be graded using the NCI's CTCAE v4.03 dated 14 June 2010.

12.1 Definitions

12.1.1 Adverse Event

An adverse event (AE) as defined by ICH-Good Clinical Practice (GCP) is any untoward medical occurrence in a patient or clinical trial patient administered a medicinal/IP and which does not necessarily have a causal relationship with this treatment. An AE can therefore be any unfavorable and unintended sign (including an abnormal laboratory finding), symptom or disease temporally associated with the use of a medicinal product, whether or not considered related to the medicinal/IP.

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
- Abnormal laboratory test results (eg, hematology, clinical chemistry, or urinalysis) or other safety assessments (eg, EKGs, radiological scans, vital signs measurements), will be reported as AEs only if they are clinically significant; led to hospitalization or prolongation of hospitalization, required change in dosing or treatment of study therapies, required initiation of concomitant therapy for laboratory abnormalities.
- Exacerbation of a chronic or intermittent pre-existing condition including either an increase in frequency and/or intensity of the condition
- New conditions detected or diagnosed after IP administration
- Signs, symptoms, or the clinical sequelae of a suspected interaction with IP

- Signs, symptoms, or the clinical sequelae of a suspected overdose of either IP or a concomitant medication

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

- Any clinically significant abnormal laboratory finding or other abnormal safety assessments that is associated with the underlying disease, unless judged by the Investigator to be more severe than expected for the patient's condition
- Medical or surgical procedure (eg, endoscopy, appendectomy); the condition that leads to the procedure is an AE
- Situations where an untoward medical occurrence did not occur (social and/or convenience admission to a hospital)
- Overdose without clinical sequelae (see Section 12.2.1)
- 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

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

12.1.2 Serious Adverse Event

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

- Death
- Is Life Threatening
- Inpatient hospitalization or prolongation of an existing hospitalization
- A persistent or significant incapacity or substantial disruption of the ability to conduct normal life functions
- A congenital anomaly/birth defect

Important medical events that may not directly result in death, be life-threatening, or require hospitalization may be considered serious when, based on Investigator decision, they may jeopardize the patient and may require intervention to prevent 1 of the above outcomes as listed in this definition.

Hospitalization including admission to a telemetry unit or intensive care unit (ICU) specifically for administration of study treatment is not considered a serious adverse event.

12.1.3 Relationship to Study Drug

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

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

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

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

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

Not related: There is not a temporal relationship to study drug administration (too early, 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.

12.1.4 Severity

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

AE grading will be defined by the CTCAE v 4.03. In the event that 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

12.2 Reporting Procedures for Adverse Events

12.2.1 All Adverse Events

Adverse Events occurring after signature of informed consent and either observed by the Investigator or reported by the patient must be entered into the eCRFs. All AEs occurring after the patient has consented, but before enrollment (prior to tumor resection), will be collected on the medical history eCRF unless the event is new and attributed to protocol-required procedures or assessments.

Monitoring and reporting of AEs, regardless of cause or relationship will be collected until completion of response assessment period. All AEs attributed to treatment will be collected from signing of the informed consent form until lost to follow-up, withdrawal of consent or the start of a new anti-cancer therapy, whichever occurs first.

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

If any patient should die while on the study, the Investigator will inform the Sponsor within 24 hours and report the cause of death as an SAE. The cause of death should be recorded in detail on the SAE Report Form. Disease progression itself is not an AE, but the clinical signs or symptoms leading to death should be reported as an SAE with an outcome of death.

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

It will be left to the Investigator's clinical judgment 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 the patient was permanently removed from the study or IP due to an SAE, this information must be included in either the initial or follow-up SAE Report Form and in the eCRF.

12.2.1.1 Serious Adverse Events

12.2.1.1.1 Investigator Reporting to Sponsor

All SAEs of any attribution will be collected from the time the patient signs the ICF up until completion of the Response Assessment Period and/or from the start of a new anticancer therapy.

All AEs/SAEs attributed to treatment will be collected from signing of the ICF until the end of the Response Assessment Period, lost to follow-up, withdrawal of consent, or the start of a new anti-cancer therapy, whichever occurs first.

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

All SAEs that occur during the study must be reported by the Investigator to the Sponsor or designee within 24 hours of learning of the event. The initial notification should be as complete as is possible with the information available and include the Investigator's assessment of study drug relationship, as defined in Section 12.1.3. All AEs, regardless of their severity, will be captured in the eCRF within the timelines outlined in the eCRF completion guidelines.

SAE terminology and severity grading will be based on the NCI's CTCAE v 4.03 guidelines.

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

Safety CRO	Contact Information for Submission of SAE Report Form
Synteract	PPD PPD

12.2.1.1.2 Special Situation Reporting

Definition of Special Situations

Special situation reports include reports of medication error, overdose, adverse events associated with product complaints, occupational exposure, and pregnancy reports regardless of an associated AE.

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

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

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

Occupational exposure is defined as the exposure to a medicinal/IP as a result of one's professional or non-professional occupation.

12.2.1.1.3 Pregnancy Reporting

Any pregnancy that occurs while on the study through 12 months from the last study treatment or until the first dose of the next anticancer therapy, whichever occurs first, must be reported using the Pregnancy Report form within 24 hours of becoming aware of the pregnancy. The pregnancy itself is not considered an AE nor is an induced abortion to terminate a pregnancy without medical reasons. Any premature termination of pregnancy (eg, a spontaneous abortion, an induced therapeutic abortion due to complications or other medical reasons) must be reported within 24 hours as an AE or SAE. The underlying medical reason for this procedure should be recorded as the AE or SAE term. A spontaneous abortion is always considered to be an SAE and will be reported as described in Section 12.2.1.1.4.

The patient should receive appropriate monitoring and care until the conclusion of the pregnancy to determine the outcome and status of the patient and child. The outcome should be reported to the safety CRO using the Pregnancy Outcome form. Any SAE occurring in association with a pregnancy, brought to the Investigator's attention after the patient has completed the study treatment and Response Assessment Period follow-up visits, must be promptly reported to the Sponsor or their representative.

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

Pregnancies of female partners of male study participants exposed to study treatment must also be reported and relevant information should be submitted to the safety CRO using the Pregnancy and Pregnancy Outcome forms within 24 hours. Monitoring of the female partners should continue until the conclusion of the pregnancy.

12.2.1.1.4 Other Special Situations Reporting

All other special situation reports involving the study treatment must be reported on to the Safety CRO using the SAE Report Form within 24 hours of becoming aware of the situation. Special situations involving concomitant medications do not need to be reported; however, any AE resulting from a special situation should be reported on the AE eCRF page.

12.2.1.1.5 Regulatory Reporting Requirements

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

Assessment of expectedness for SAEs will be determined by Iovance Biotherapeutics, Inc. using reference safety information in the Investigator's Brochure and relevant prescribing information, as applicable.

In addition, the Sponsor must submit expedited reports of potential serious risks from clinical trials or any other source based on relevant local legislation or regulations, including the applicable US FDA Code of Federal Regulations and the EU Clinical Trial

Directive (2001/20/EC) and relevant updates. The Sponsor will notify participating sites of relevant SUSAR reports and other applicable serious safety findings, which occur during the trial including the post study treatment follow-up phase.

13 ADMINISTRATIVE REQUIREMENTS

13.1 Adherence to the Protocol

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

13.2 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 IP. 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.

13.3 Data Quality Assurance

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

Steps to be taken to assure the accuracy and reliability of data include; the selection of qualified Investigators and appropriate study centers, review of protocol procedures with the Investigator and associated personnel prior to the study, periodic monitoring visits by the Sponsor/designee. 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.

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

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

13.4 Data Handling and Recordkeeping

13.4.1 Regulatory Approval and Documentation

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

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

- Up-to-date curriculum vitae for each Investigator
- Signed and dated Investigator Agreement
- Applicable local regulatory documentation (eg, FDA 1572 Form)
- A copy of the formal written notification to the Investigator regarding approval of the protocol by an IRB/IEC that is in compliance with regulatory guidelines. The written notification is to be signed by the chairman or authorized designee and must identify the specific protocol. In cases where an IRB/IEC member has a known conflict of interest, abstention of that individual from voting should be documented; an Investigator may be a member of the IRB/IEC, but may not vote on any research in which he or she is involved.
- Name and address of the IRB/IEC with a statement that it is organized and operates according to GCP and the applicable laws and regulations, and a current list of the IRB/IEC members. If accompanied by a letter of explanation from the IRB/IEC, a general statement may be substituted for this list.
- A copy of the IRB/IEC approved informed consent and other adjunctive materials (eg, advertising) to be used in the study, including written documentation of IRB/IEC approval of these items
- Name and address of any local laboratory conducting tests for the study, a dated copy of the laboratory reference values for tests to be performed during the study and a copy of the certification or other documentation establishing adequacy of the facility

- Required financial agreement
- In addition to the documents required prior to the study, other documentation may be required during the course of the study.

13.4.2 Electronic Data

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

13.4.3 Data Handling and Recordkeeping

13.4.3.1 Electronic Case Report Form (eCRF) Completion

Electronic data capture (EDC) will be used for the study. The site will be suitably trained on the use of the eCRF and appropriate site personnel will be provided electronic signatures. Data must be entered into the eCRF 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 study.

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

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

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

13.5 Study Completion/Termination

13.5.1 Study Completion

Upon completion of the study, the Investigator will ensure that the complete set of source data has been entered into the eCRFs and sign-off on the final eCRF.

13.5.2 Study Termination

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

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

13.6 Monitoring

On-site monitoring visits will be performed by the Sponsor as frequently as necessary. At these visits the monitor will compare the data entered into the eCRFs with the hospital or clinic records (source documents). At a minimum, source documentation must be available to substantiate proper informed consent procedures, adherence to protocol procedures, adequate reporting and follow-up of 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 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 Board/Independent Ethics Committee (IRB/IEC)

Before enrollment of patients into the study, as required by Federal regulations (21 CFR 56) and international regulations (ICH GCP Guidelines), the protocol and

informed consent form(s) must be reviewed and approved by an appropriate IRB/IEC. By signing the FDA Statement of Investigator Form 1572, the Investigator assures that all aspects of the institutional review will be conducted in accordance with current federal regulations. A letter documenting the IRB/IEC approval with the names and titles of the IRB/IEC members must be received by the Sponsor before the initiation of the trial. Amendments to the protocol will be subject to the same requirements as the original protocol. In other countries, the protocol and any amendments must be approved by the concerned Ethics Committees as per the applicable laws and requirements on the national and EU level.

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/IEC. 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, Directive 2001/20/EC (and when in force EU Regulation 536/2014), and Regulation 2016/679 (GDPR), as interpreted by the national laws and regulatory bodies, and the Sponsor's policies.

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

will be treated as strictly confidential and will not be publicly available. Patients must be given the opportunity to ask questions. After this explanation and before entry into the study, consent should be appropriately recorded by means of the patient's or his/her legal representative's dated signature. If a patient and his/her legal representative are unable to read, an impartial witness must be present during the entire informed consent discussion. The signature of the impartial witness will certify the patient's consent. The patient and their legally designated representative must receive a signed and dated copy of the informed consent. The informed consent process should be documented in the patient's medical record. Adequate time shall be given for the subject or his or her legally designated representative to consider his or her decision to participate in the study.

In accordance with the Health Insurance Portability and Accountability Act (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/IEC access to patient's medical information that includes all hospital records relevant to the study, including a patient's medical history and other data that may identify him/her, including of the purpose of this access and data processing connected with it.

14.3 Patient Data Protection

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

14.4 Adverse Event Reporting

The Investigator agrees to report all AEs/SAEs to the Sponsor as described in Section 12, Adverse Events. Furthermore, the Investigator is responsible for ensuring that any Investigator or sub-Investigator promptly bring AEs to the attention of the Investigator. The PI shall promptly notify the IRB/IEC of any SAEs, or any other information that may affect the safe use of the IP during the course of the trial as applicable per the local IRB/IEC requirements.

14.5 Investigator

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

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

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

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 (eg, patients' written consent forms) should be maintained by the Investigator in strict confidence, in

accordance with all applicable local and national regulations. All information provided to the Investigator prior to the study, as well as all data developed during the study, is confidential and remains the property of the Sponsor. The Investigator agrees that no information based on the conduct of this study (including the protocol, the data resulting from the study, or the fact that the study is/was conducted) will be released without prior written consent of the Sponsor unless this requirement is superseded by local or national regulations.

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 or abstract to journals or professional societies without the prior written approval of the Sponsor, except as permitted by the agreed terms of the clinical trial agreement, including after the reporting of the results of this multi-center study by the Sponsor and other institutions.

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APPENDICES

Appendix 1 SCHEDULE OF EVENTS – FOR COHORT 1 AND COHORT 2 PATIENTS

Assessments[b]	Screening & Enrollment Period			Treatment Period[a] (All visits following LN-144 infusion [Day 0] calculated from Day 0 forward)												Visits Prior to Response Assessment Period[a]		Response Assessment Period[a] (All visits following LN-144 infusion [Day 0] calculated from Day 0 forward.)		End of Study (EOS) or Early Termination Visit[a]	Overall Survival Follow-Up Period
	Screening (up to 28 days)	Enrollment/ Tumor Resection	Day -21 to Day -14 (Baseline)	Day -7	Day -6	Day -5	Day -4	Day -3	Day -2	Day -1	Day 0	Day 1	Day 2	Day 3	Day 4	Day 14 (+/- 3 days)	Day 28 (+/- 3 days)	Visit Every 6 Weeks (±3 days) (Weeks 6, 12, and 18)	Visit Every 3 Months (±1 Week) (Starting at Month 6)	End of Study (EOS) or Early Termination Visit (Month 24 or upon Early Termination)	Visit Every 3 Months / Month 27 to Month 60 (+/- 3 weeks)
Informed consent	X																				
Inclusion/Exclusion	X		X[c]																		
Physical examination[d]	X		X	X						X	X	X	X	X	X	X	X	X	X	X	
Evaluation and measurement of skin and palpable lesions	X		X															X	X	X	
Eye examination (slit lamp)[e]	X[e]																	X[e]			
Medical history[f]	X																				
Concomitant medications[g]	X	X[g]	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	
Height	X																				
Weight[h]	X		X	X[h]						X	X[h]	X	X	X	X	X	X	X	X	X	
Vital signs[i]	X		X	X	X	X	X	X	X	X	X	X[i]	X	X	X			X	X	X	
Pulse oximetry[j]												X	X	X	X						
CMV serology[k]	X							X[k]	X[k]	X[k]											
Syphilis testing[l]	X	X[l]																			
EKG	X		X																		
Cardiac function tests with ECHO or	X																				

Assessments[b]	Screening & Enrollment Period			Treatment Period[a] (All visits following LN-144 infusion [Day 0] calculated from Day 0 forward)												Visits Prior to Response Assessment Period[a]		Response Assessment Period[a] (All visits following LN-144 infusion [Day 0] calculated from Day 0 forward.)		End of Study (EOS) or Early Termination Visit[a]	Overall Survival Follow-Up Period
	Screening (up to 28 days)	Enrollment/ Tumor Resection	Day -21 to Day -14 (Baseline)	Day -7	Day -6	Day -5	Day -4	Day -3	Day -2	Day -1	Day 0	Day 1	Day 2	Day 3	Day 4	Day 14 (+/- 3 days)	Day 28 (+/- 3 days)	Visit Every 6 Weeks (±3 days) (Weeks 6, 12, and 18)	Visit Every 3 Months (±1 Week) (Starting at Month 6)	End of Study (EOS) or Early Termination Visit (Month 24 or upon Early Termination)	Visit Every 3 Months / Month 27 to Month 60 (+/- 3 weeks)
MUGA. cardiac stress test[m]																					
CT chest, abdomen, pelvis[n]	X		X															X	X	X	
MRI – brain[n]	X		X															X	X	X	
Serum chemistry[o]	X		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	
Thyroid panel[p]	X															X				X	
Hematology[q]	X		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	
Urinalysis[r]	X		X	X	X	X	X	X	X	X	X	X	X	X	X						
Calculated creatinine clearance[s]	X																	X			
ß-HCG pregnancy test[t]	X		X	X							X						X	X	X	X	
ECOG performance status	X		X	X												X		X	X	X	
HIV titer[u]	X	X[u]																			
HBcAg[v]	X	X[v]																			
HBsAg[v]	X	X[v]																			
HCV Ab[w]	X	X[w]																			
HLA typing[x]	X																				
HSV serology	X	X																			
EBV serology	X	X																			

Assessments[b]	Screening & Enrollment Period			Treatment Period[a] (All visits following LN-144 infusion [Day 0] calculated from Day 0 forward)												Visits Prior to Response Assessment Period[a]		Response Assessment Period[a] (All visits following LN-144 infusion [Day 0] calculated from Day 0 forward.)		End of Study (EOS) or Early Termination Visit[a]	Overall Survival Follow-Up Period
	Screening (up to 28 days)	Enrollment/ Tumor Resection	Day -21 to Day -14 (Baseline)	Day -7	Day -6	Day -5	Day -4	Day -3	Day -2	Day -1	Day 0	Day 1	Day 2	Day 3	Day 4	Day 14 (+/- 3 days)	Day 28 (+/- 3 days)	Visit Every 6 Weeks (±3 days) (Weeks 6, 12, and 18)	Visit Every 3 Months (±1 Week) (Starting at Month 6)	End of Study (EOS) or Early Termination Visit (Month 24 or upon Early Termination)	Visit Every 3 Months / Month 27 to Month 60 (+/- 3 weeks)
Pulmonary function testing[y]	X																				
Colonoscopy[z]	X[z]																				
Tumor resection[aa]		X																			
Ondansetron				X	X																
Authorization to Receive Lymphodepletion[bb]				X																	
Cyclophosphamide 60 mg/kg				X	X																
Mesna				X	X																
Fludarabine 25 mg/m^2/day						X	X	X	X	X											
LN-144 infusion[cc]											X										
IL-2 600,000 IU/kg[dd]												X	X	X	X						
Filgrastim[ee]												X	X	X	X	X	X	X	X		
TMP/SMX DS, or appropriate Abx[ff]				X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X		
Fluconazole[gg]												X	X	X	X	X	X	X	X		
Valacyclovir/ acyclovir[hh]												X	X	X	X	X	X	X	X		
Immune monitoring[ii]		X		X								X			X	X		X	X		
Tumor assessment (local)[jj]	X		X															X	X	X	

Assessments[b]	Screening & Enrollment Period			Treatment Period[a] (All visits following LN-144 infusion [Day 0] calculated from Day 0 forward)											Visits Prior to Response Assessment Period[a]		Response Assessment Period[a] (All visits following LN-144 infusion [Day 0] calculated from Day 0 forward.)		End of Study (EOS) or Early Termination Visit[a]	Overall Survival Follow-Up Period
	Screening (up to 28 days)	Enrollment/ Tumor Resection	Day -21 to Day -14 (Baseline)	Day -7	Day -6	Day -5	Day -4	Day -3	Day -2	Day -1	Day 0	Day 1	Day 2	Day 3	Day 4	Day 14 (+/- 3 days)	Day 28 (+/- 3 days)	Visit Every 6 Weeks (±3 days) (Weeks 6, 12, and 18)	Visit Every 3 Months (±1 Week) (Starting at Month 6)	End of Study (EOS) or Early Termination Visit (Month 24 or upon Early Termination)	Visit Every 3 Months / Month 27 to Month 60 (+/- 3 weeks)
Assessment of AEs/SAEs[kk]	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	
Hospitalization(s)[ll]	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	
EORTC QLQ-C30 HRQoL[mm]			X															X	X	X	
Overall survival (OS) follow-up telephone contac[nn]																					X

Abbreviations: Ab=antibody; ABX=antibiotics; AE=adverse events; Ag=antigen; ALC=absolute lymphocyte count; ALT=alanine transaminase; ANC=absolute neutrophil count; AST=aspartate transaminase; BUN=blood urea nitrogen; CK=creatine kinase; CMV=cytomegalovirus; CT=computed tomography; EBV=Epstein-Barr virus; ECHO=echocardiogram; ECOG=Eastern Cooperative Oncology Group; EKG=electrocardiogram; EORTC=European Organization for Research and Treatment of Cancer; EOS=end of study; HBcAg=hepatitis B virus core antigen; HBsAg=hepatitis B virus surface antigen; βHCG=beta human chorionic gonadotropin; HCV=hepatitis C virus; HIV=human immunodeficiency virus; HLA=human leukocyte antigen; HRQoL=health-related quality of life; HSV=herpes simplex virus; IL-2 interleukin-2; LD=lymphodepletion; LDH=lactate dehydrogenase; LPLD=last patient last dose; LVEF=left ventricular ejection fraction; MRI=magnetic resonance imaging; MUGA=multiple gated acquisition; NMA-LD=nonmyeloablative-lymphodepletion; OS=overall survival; PE=physical examination; PET=positron emission tomography; PFT=pulmonary function test; QD=once daily; RECIST=Response Evaluation Criteria in Solid Tumors; RPR=rapid plasma reagin; SAE=serious adverse event; SGOT=serum glutamic-oxaloacetic transaminase; SGPT=serum glutamic pyruvic transaminase; TIL=tumor-infiltrating lymphocytes; TMP-SMX DS=trimethoprim-sulfamethoxazole double strength; TSH=thyroid-stimulating hormone; VDRL=venereal disease research laboratory.

a. All visits preceding LN-144 infusion (Day 0) are calculated going backwards (eg, Day -1, Day -2, Day -3, …Day -7, etc.), and all visits following LN 144 infusion (Day 0) are calculated going forward from Day 0 (eg, Day 1, Day 2, Day 3…Day 28, etc).

b. Unscheduled visit(s) for any assessment may be conducted per the medical judgement of Investigator.

c. Re-check of Inclusion/Exclusion Criteria at Baseline (Day -21 to Day -7) to ensure that patient performance status and eligibility has not changed from time of Screening; this re-confirmation of eligibility is to be reviewed and approved by Sponsor or designee.

d. Physical examination (PE) to include gastrointestinal (abdomen, liver), cardiovascular, extremities, head, eyes, ears, nose, and throat, respiratory system, skin, psychiatric (mental status), and general nutrition.
e. Eye examination (slit lamp) required at Screening and Week 12 (Day 84 ± 3 days) visits, and when clinically indicated.
f. Medical history, including melanoma disease history, prior radiotherapy, prior cancer-related surgery, and prior systemic therapy (with start/stop dates). In addition, date of most recent disease progression, if applicable should be documented.
g. List all medications, including those that are administered as part of the tumor resection procedure.
h. Weight at Day -7 to be used for dose calculations for cyclophosphamide and fludarabine; whereas weight at Day 0 to be used for dose calculation for IL-2.
i. Vital signs will include pulse rate, respiratory rate, blood pressure, and temperature. On Day 0 (LN-144 infusion), vital signs will be monitored every 30 minutes during infusion then hourly (± 15 minutes) for 4 hours and then routinely (every 4 to 6 hours), unless otherwise clinically indicated, for up to approximately 24 hours post LN-144 infusion.
j. Pulse oximetry to be conducted during IL-2 administration
k. CMV serology (as per local standard) at Screening, within 3 days of LN-144 infusion, and thereafter as clinically indicated.
l. Syphilis testing (as per local standard; eg, Rapid Plasma Reagin [RPR] venereal disease research laboratory [VDRL], or other) at Screening, at Enrollment (within 7 days of tumor resection [required only for tumor samples entering the EU for manufacture of the TIL product in the EU]), and thereafter as clinically indicated.
m. Cardiac evaluation (stress test) for all patients (per current package insert for IL-2). All patients must have echocardiogram (ECHO) or multiple gated acquisition scan (MUGA) at Screening. For patients ≥ 60 years or patients who have a history of ischemic heart disease, chest pain, or clinically significant atrial and/or ventricular arrhythmias, a cardiac stress tests must be performed showing LVEF ≥45%, and if any wall movement abnormalities, they must be reversible.
n. Required radiographic imaging at Screening, and at Baseline (Day -21 to Day -14). Anatomic regions included in CT scans or MRIs per disease history and clinical symptoms, (repeat the same CT and MRI series for all post-treatment tumor assessment [scheduled and unscheduled] as completed at Baseline [Day -21 to Day -14]). At Investigator discretion, the Baseline brain MRI and CT scans may be done as early as Day -21. Include neck if there is prior or suspected neck disease. MRI or PET scans will be allowed in lieu of CT for patients who have an intolerability to contrast media. The imaging modality and anatomic regions assessed used must be uniform for the duration of the study.
o. Chem 20: [sodium (Na), potassium (K), chloride (Cl), total CO_2 (bicarbonate), creatinine, glucose, urea nitrogen (BUN), albumin, calcium total, magnesium total (Mg), phosphorus, alkaline phosphatase, ALT/SGPT, AST/SGOT, total bilirubin, direct bilirubin, LDH, total protein, total CK, uric acid]. Uric acid not collected on Day -7 through Day -1 and Day +1 through Day +4.
p. Thyroid panel must include TSH and Free T_4. Obtain only at Screening, Day 14, and End of Study (EOS) Visit, also at any visit as clinically indicated.
q. Hematology panel must include complete blood count with differential
r. Dipstick urinalysis with culture, if indicated
s. Calculate creatinine clearance using Cockcroft-Gault calculation
t. Serum pregnancy test for women of childbearing potential only. Serum pregnancy testing to continue to Week 52 (Month 12) or EOS visit, whichever occurs first.
u. At Screening, at Enrollment (on the day of tumor resection or within 7 days of tumor resection [required only for tumor samples entering the EU for manufacture of the TIL product in the EU]), and when clinically indicated
v. At Screening, at Enrollment (on the day of tumor resection or within 7 days of tumor resection [required only for tumor samples entering the EU for manufacture of the TIL product in the EU]), and when clinically indicated
w. At Screening, at Enrollment (on the day of tumor resection or within 7 days of tumor resection [required only for tumor samples entering the EU for manufacture of the TIL product in the EU]), and when clinically indicated
x. Sample for HLA tissue typing to be sent to the central laboratory
y. Pulmonary function testing (PFT) required for all patients at Screening

z. Colonoscopy only for patients with documented Grade 2 or greater diarrhea or colitis as a result of previous treatment with immune checkpoint inhibitors who have not been asymptomatic for at least 6 months. To meet eligibility, patients must have been asymptomatic for at least 6 months or had a normal colonoscopy post treatment, with uninflamed mucosa by visual assessment, prior to the start of NMA-LD.

aa. For detailed instructions on processing and shipment of resected tumor tissue to the manufacturing facility and central laboratory refer to protocol Section 6.2.1: Tumor Harvest and Processing Procedures, and the separate Tumor Procurement & Shipping Manual.
NOTE: All serology testing is to be done on the day of the tumor resection or within 7 days after the resection (required only for tumor samples entering the EU for manufacture of the TIL product in the EU).

bb. The 'Authorization to Receive Lymphodepletion' form is to be completed by the Investigator prior to Day -7 (eg, between Day -10 to Day -8) and sent to the Sponsor or designee, if acceptable, will be signed and returned to the site prior to the initiation of the NMA-LD preconditioning regimen start on planned Day -7.

cc. LN-144 infusion to be given 1 to 2 days after the last dose of the preparative NMA-LD preconditioning regimen. All visits following LN-144 infusion (Day 0) are calculated from that date.

dd. The first IL-2 dose should be administered within 3 hours to 24 hours after completion of the LN-144 infusion, and continue every 8 hours for up to protocol-defined maximum of 6 doses of IL-2. IL-2 dosing is allowed for up to 4 days post LN-144 infusion to allow for proper management of IL-2 toxicity, if necessary (see Section 6.14.2 and Appendix 6).

ee. Continue filgrastim until ANC >1000/mm^3 × 3 consecutive days or per standard of care at the institution.

ff. The TMP/SMX DS schedule should be adjusted to once-daily (QD) 3 times per week (Monday, Wednesday, Friday) and continue for at least 6 months and until ANC >1000/mm^3 or per standard of care at the institution

gg. Continue fluconazole until ANC >1000/mm^3 or per standard of care at the institution

hh. In patients positive for HSV, continue until ALC >1000/mm^3 or per standard of care at the institution

ii. Blood for immune monitoring to be drawn at Enrollment (tumor resection), Day -7, Day 1, Day 4, Day 14, Day 42, Day 84, Month 6, Month 9 and Month 12. Refer to the Laboratory Manual, for vacutainer tubes for peripheral blood draws to be sent to the central laboratory. There is a ± 2-day window for the Immune Monitoring samples. If the scheduled visit is on a Friday, the Immune Monitoring sample should be collected on the prior Thursday. If the scheduled visit is on a Saturday or Sunday, the Immune Monitoring sample should be collected on the following Monday. On Day 1 immune monitoring samples should be drawn prior to IL-2 dosing.

jj. Local tumor assessment (per RECIST 1.1) (scheduled or unscheduled) should be used for clinical treatment decisions, and may include photographic/caliper measurement of superficial dermal and subcutaneous lesion. For Independent Review Committee (IRC) tumor assessment, adhere to the IRC Manual for submission of radiographic images.

kk. All adverse events (AEs) occurring after the patient has signed the informed consent form (ICF), but prior to enrollment (prior to tumor resection), will be collected on the medical history eCRF, unless the event is new and attributed to protocol-required procedures or assessments.

ll. Dates of any hospitalization from signing of ICF through the LN-144 Therapy Treatment Period are to be collected in the eCRFs.

mm. The health-related quality of life (HRQoL) questionnaire EORTC QLQ-C30 is to be completed at Baseline (Day -21 to Day -7), Day 84, and Month 6, Month 12 and Month 24 (or EOS/ET) visits.

nn. Overall Survival (OS) Follow-Up Period will commence when each patient has their last response assessment visit, and will consist of telephone contact made quarterly with the patient or designee up until 5 years after the last study treatment. Collect information about subsequent anticancer therapy.

Appendix 2 SCHEDULE OF EVENTS – FOR COHORT 3 PATIENTS

Assessments[b]	Screening & Enrollment Procedures			Treatment Period[a] (All visit dates following LN-144 infusion (Day 0) calculated from Day 0 forward)												Visits Prior to Response Assessment Period[a]		Response Assessment Period[a] (All visit dates following LN-144 infusion (Day 0) calculated from Day 0 forward)		End of Study (EOS) or Early Termination Visit[a]	Overall Survival Follow-Up Period
	Screening (up to 28 days)	Enrollment/ Tumor Resection	Day -21 to Day -14 (Baseline)	Day -7	Day -6	Day -5	Day -4	Day -3	Day -2	Day -1	Day 0	Day 1	Day 2	Day 3	Day 4	Day 14 (+/- 3 days)	Day 28 (+/- 3 days)	Visit Every 6 Weeks (±3 days) (Weeks 6, 12, and 18)	Visit Every 3 Months (± 1 Week) (Starting at Month 6)	Early Termination Visit (Mont 24 [Week 104 ± 3 Weeks] or upon Early Termination)	Visit Every 3 Months / Month 27 to Month 60 (+/- 3 Weeks)
Informed consent	X																				
Inclusion/ Exclusion	X		X[c]																		
Physical Examination[d]	X		X	X						X	X	X	X	X	X	X	X	X	X	X	
Evaluation and measurement of skin and palpable lesions	X		X															X	X	X	
Eye examination (slit lamp)	X[e]																	X[e]			
Concomitant medications[f]	X	X[f]	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	
Weight[g]	X		X	X						X	X	X	X	X	X	X	X	X	X	X	
Vital signs[h]	X		X	X	X	X	X	X	X	X	X[i]	X	X	X	X			X	X	X	
Pulse oximetry[i]												X	X	X	X						
CMV serolog[j]	X							X[j]	X[j]	X[j]											
Syphilis testing[k]	X	X[k]										X									
EKG	X		X																		
Cardiac function tests with ECHO or	X																				

Assessments[b]	Screening & Enrollment Procedures			Treatment Period[a] (All visit dates following LN-144 infusion (Day 0) calculated from Day 0 forward)												Visits Prior to Response Assessment Period[a]		Response Assessment Period[a] (All visit dates following LN-144 infusion (Day 0) calculated from Day 0 forward)		End of Study (EOS) or Early Termination Visit[a]	Overall Survival Follow-Up Period
	Screening (up to 28 days)	Enrollment/ Tumor Resection	Day -21 to Day -14 (Baseline)	Day -7	Day -6	Day -5	Day -4	Day -3	Day -2	Day -1	Day 0	Day 1	Day 2	Day 3	Day 4	Day 14 (+/- 3 days)	Day 28 (+/- 3 days)	Visit Every 6 Weeks (±3 days) (Weeks 6, 12, and 18)	Visit Every 3 Months (± 1 Week) (Starting at Month 6)	Early Termination Visit (Mont 24 [Week 104 ± 3 Weeks] or upon Early Termination)	Visit Every 3 Months / Month 27 to Month 60 (+/- 3 Weeks)
MUGA. cardiac stress test[l]																					
CT chest, abdomen, pelvis[m]	X		X															X	X	X	
MRI – brain[m]	X		X															X	X	X	
Serum chemistry[n]	X		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	
Thyroid pane[lo]	X															X				X	
Hematology[p]	X		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	
Urinalysis[q]	X		X	X	X	X	X	X	X	X	X	X	X	X	X						
Calculated creatinine clearance[r]	X																	X			
ß-HCG pregnancy test[s]	X		X	X							X						X	X	X	X	
ECOG performance status	X		X	X												X		X	X	X	
HIV titre[t]	X	X[t]																			
HBcAg[u]	X	X[u]																			
HBsAg[u]	X	X[u]																			
HCV Ab[v]	X	X																			
HSV serology[v]	X	X																			
EBV serology[v]	X	X																			
Pulmonary fuction testing[w]	X																				

Assessments[b]	Screening & Enrollment Procedures			Treatment Period[a] (All visit dates following LN-144 infusion (Day 0) calculated from Day 0 forward)												Visits Prior to Response Assessment Period[a]		Response Assessment Period[a] (All visit dates following LN-144 infusion (Day 0) calculated from Day 0 forward)		End of Study (EOS) or Early Termination Visit[a]	Overall Survival Follow-Up Period
	Screening (up to 28 days)	Enrollment/ Tumor Resection	Day -21 to Day -14 (Baseline)	Day -7	Day -6	Day -5	Day -4	Day -3	Day -2	Day -1	Day 0	Day 1	Day 2	Day 3	Day 4	Day 14 (+/- 3 days)	Day 28 (+/- 3 days)	Visit Every 6 Weeks (±3 days) (Weeks 6, 12, and 18)	Visit Every 3 Months (± 1 Week) (Starting at Month 6)	Early Termination Visit (Mont 24 [Week 104 ± 3 Weeks] or upon Early Termination)	Visit Every 3 Months / Month 27 to Month 60 (+/- 3 Weeks)
Colonoscopy[x]	x[x]																				
Tumor resection[y]		X																			
Ondansetron				X	X																
Authorization to Receive Lymphodepletion[z]				X																	
Cyclophosphamide 60 mg/kg				X	X																
Mesna				X	X																
Fludarabine 25 mg/m^2/day						X	X	X	X	X											
LN-144 infusion[aa]											X										
IL-2 600,000 IU/kg[bb]												X	X	X	X						
Filgrastim[cc]												X	X	X	X	X	X	X	X		
TMP/SMX DS, or appropriate Abx[dd]				X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X		
Fluconazole[ee]												X	X	X	X	X	X	X	X		
Valacyclovir/ acyclovir[ff]												X	X	X	X	X	X	X	X		
Immune monitoring[gg]		X		X								X			X	X		X	X		

Assessments[b]	Screening & Enrollment Procedures			Treatment Period[a] (All visit dates following LN-144 infusion (Day 0) calculated from Day 0 forward)												Visits Prior to Response Assessment Period[a]		Response Assessment Period[a] (All visit dates following LN-144 infusion (Day 0) calculated from Day 0 forward)		End of Study (EOS) or Early Termination Visit[a]	Overall Survival Follow-Up Period
	Screening (up to 28 days)	Enrollment/ Tumor Resection	Day -21 to Day -14 (Baseline)	Day -7	Day -6	Day -5	Day -4	Day -3	Day -2	Day -1	Day 0	Day 1	Day 2	Day 3	Day 4	Day 14 (+/- 3 days)	Day 28 (+/- 3 days)	Visit Every 6 Weeks (±3 days) (Weeks 6, 12, and 18)	Visit Every 3 Months (± 1 Week) (Starting at Month 6)	Early Termination Visit (Mont 24 [Week 104 ± 3 Weeks] or upon Early Termination)	Visit Every 3 Months / Month 27 to Month 60 (+/- 3 Weeks)
Tumor assessment (local)[hh]	X		X															X	X	X	
Assessment of AEs/SAEs[ii]	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	
Hospitalization(s)[ij]	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	
EORTC QLQ-C30 HRQoL[kk]			X															X	X	X	
Overall survival (OS) follow-up telephone contact[ll]																					X

Abbreviations: Ab=antibody; ABX=antibiotics; AE=adverse events; Ag=antigen; ALC=absolute lymphocyte count; ALT=alanine transaminase; ANC=absolute neutrophil count; AST=aspartate transaminase; BUN=blood urea nitrogen; CK=creatine kinase; CMV=cytomegalovirus; CT=computed tomography; EBV=Epstein-Barr virus; ECHO=echocardiogram; ECOG=Eastern Cooperative Oncology Group; EKG=electrocardiogram; EORTC=European Organization for Research and Treatment of Cancer; EOS=end of study; HBcAg=hepatitis B virus core antigen; HBsAg=hepatitis B virus surface antigen; β-HCG=β-human chorionic gonadotropin; HCV=hepatitis C virus; HIV=human immunodeficiency virus; HLA=human leukocyte antigen; HRQoL=health-related quality of life; HSV=herpes simplex virus; IL-2 interleukin-2; LD=lymphodepletion; LDH=lactate dehydrogenase; LPLD=last patient last dose; LVEF=left ventricular ejection fraction; MRI=magnetic resonance imaging; MUGA=multiple gated acquisition; NMA-LD=nonmyeloablative-lymphodepletion; OS=overall survival; PE=physical examination; PET=positron emission tomography; PFT=pulmonary function test; QD=once daily; RECIST=Response Evaluation Criteria in Solid Tumors; RPR=rapid plasma reagin; SAE=serious adverse event; SGOT=serum glutamic-oxaloacetic transaminase; SGPT=serum glutamic pyruvic transaminase; TIL=tumor-infiltrating lymphocytes; TMP-SMX DS=trimethoprim-sulfamethoxazole double strength; TSH=thyroid-stimulating hormone; VDRL=venereal disease research laboratory.

a. All visits preceding LN-144 infusion (Day 0) are calculated going backwards (eg, Day -1, Day -2, Day -3, …Day -7, etc), and all visits following LN 144 infusion (Day 0) are calculated going forward from Day 0 (eg, Day 1, Day 2, Day 3…Day 28, etc.).

b. Unscheduled visit(s) for any assessment may be conducted per the medical judgement of Investigator. List all medications even those that are part of the tumor resection procedure.
c. Re-check of Inclusion/Exclusion Criteria at Baseline (Day -21 to Day -7) to ensure that patient performance status and eligibility has not changed from time of Screening; this re-confirmation of eligibility is to be reviewed and approved by Sponsor or designee.
d. Physical examination (PE) to include gastrointestinal (abdomen, liver), cardiovascular, extremities, head, eyes, ears, nose, and throat, respiratory system, skin, psychiatric (mental status), and general nutrition.
e. Eye examination (slit lamp) required at Screening and Week 12 (Day 84 ± 3 days) visits, and when clinically indicated.
f. List all medications, including those that are administered as part of the tumor resection procedure.
g. Weight at Day -7 to be used for dose calculations for cyclophosphamide and fludarabine; whereas weight at Day 0 to be used for dose calculation for IL-2.
h. Vital signs will include pulse rate, respiratory rate, blood pressure, and temperature. On Day 0 (LN-144 infusion), vital signs will be monitored every 30 minutes during infusion then hourly (± 15 minutes) for 4 hours and then routinely (every 4 to 6 hours), unless otherwise clinically indicated, for up to approximately 24 hours post LN-144 infusion.
i. Pulse oximetry to be conducted during IL-2 administration
j. CMV serology (as per local standard) at Screening, within 3 days of LN-144 infusion and thereafter as clinically indicated.
k. Syphilis testing (as per local standard; eg, Rapid Plasma Reagin [RPR] venereal disease research laboratory [VDRL], or other) at Screening, at Enrollment (within 7 days of tumor resection [required only for tumor samples entering the EU for manufacture of the TIL product in the EU]), and thereafter as clinically indicated.
l. Cardiac evaluation (stress test) for all patients (per current package insert for IL-2). All patients must have echocardiogram (ECHO) or multiple gated acquisition scan (MUGA) at Screening. For patients ≥ 60 years or patients who have a history of ischemic heart disease, chest pain, or clinically significant atrial and/or ventricular arrhythmias, a cardiac stress tests must be performed showing LVEF ≥45%, and if any wall movement abnormalities, they must be reversible.
m. Required radiographic imaging at Screening, and at Baseline (Day -21 to Day -14). Anatomic regions included in CT scans or MRIs per disease history and clinical symptoms, (repeat the same CT and MRI series for all post-treatment tumor assessment [scheduled and unscheduled] as completed at Baseline [Day -21 to Day -14]). At Investigator discretion, the Baseline brain MRI and CT scans may be done as early as Day -21. Include neck if there is prior or suspected neck disease. MRI or PET scans will be allowed in lieu of CT for patients who have an intolerability to contrast media. The imaging modality and anatomic regions assessed used must be uniform for the duration of the study.
n. Chem 20: [sodium (Na), potassium (K), chloride (Cl), total CO_2 (bicarbonate), creatinine, glucose, urea nitrogen (BUN), albumin, calcium total, magnesium total (Mg), phosphorus, alkaline phosphatase, ALT/SGPT, AST/SGOT, total bilirubin, direct bilirubin, LDH, total protein, total CK, uric acid]. Uric acid not collected on Day -7 through Day -1 and Day +1 through Day +4.
o. Thyroid panel must include TSH and Free T_4. Obtain only at Screening, Day 14, and End of Study (EOS) Visit, also at any visit as clinically indicated.
p. Hematology panel must include complete blood count with differential
q. Dipstick urinalysis with culture, if indicated
r. Calculate creatinine clearance using Cockcroft-Gault calculation
s. Serum pregnancy test for women of childbearing potential only. Serum pregnancy testing to continue to Week 52 (Month 12) or EOS visit, whichever occurs first.
t. At Screening, at Enrollment (on the day of tumor resection or within 7 days of tumor resection [required only for tumor samples entering the EU for manufacture of the TIL product in the EU]), and when clinically indicated. Serology for infection must be repeated for Cohort 3 patients if there is >30 days from the last test results.
u. At Screening, at Enrollment (on the day of tumor resection or within 7 days of tumor resection [required only for tumor samples entering the EU for manufacture of the TIL product in the EU]), and when clinically indicated. Serology for infection must be repeated for Cohort 3 patients if there is >30 days from the last test results.
v. At Screening, at Enrollment (on the day of tumor resection or within 7 days of tumor resection [required only for tumor samples entering the EU for manufacture of the TIL product in the EU]), and when clinically indicated. Serology for infection must be repeated for Cohort 3 patients if there is >30 days from the last test results.

w. Pulmonary function testing (PFT) required for all patients at Screening
x. Colonoscopy only for patients with documented Grade 2 or greater diarrhea or colitis as a result of previous treatment with immune checkpoint inhibitors who have not been asymptomatic for at least 6 months. To meet eligibility, patients must have been asymptomatic for at least 6 months or had a normal colonoscopy post treatment, with uninflamed mucosa by visual assessment, prior to the start of NMA-LD.
y. For detailed instructions on processing and shipment of resected tumor tissue to the manufacturing facility and central laboratory refer to protocol Section 6.2.1: Tumor Harvest and Processing Procedures, and the separate Tumor Procurement & Shipping Manual.
NOTE: All serology testing is to be done on the day of the tumor resection or within 7 days after the resection (required only for tumor samples entering the EU for manufacture of the TIL product in the EU).
z. The 'Authorization to Receive Lymphodepletion' form is to be completed by the Investigator prior to Day -7 (eg, between Day -10 to Day -8) and sent to the Sponsor or designee, if acceptable, will be signed and returned to the site prior to the initiation of the NMA-LD preconditioning regimen start on planned Day -7.
aa. LN-144 infusion to be given 1 to 2 days after the last dose of the preparative NMA-LD preconditioning regimen. All visits following LN-144 infusion (Day 0) are calculated from that date.
bb. The first IL-2 dose should be administered within 3 hours to 24 hours after completion of the LN-144 infusion, and continue every 8 hours for up to protocol-defined maximum of 6 doses of IL-2. IL-2 dosing is allowed for up to 4 days post LN-144 infusion to allow for proper management of IL-2 toxicity, if necessary (see Section 6.14.2 and Appendix 6**)**.
cc. Continue filgrastim until ANC >1000/mm^3 × 3 consecutive days or per standard of care at the institution.
dd. The TMP/SMX DS schedule should be adjusted to once-daily (QD) 3 times per week (Monday, Wednesday, Friday) and continue for at least 6 months and until ANC >1000/mm^3 or per standard of care at the institution
ee. Continue fluconazole until ANC >1000/mm^3 or per standard of care at the institution
ff. In patients positive for HSV, continue until ALC >1000/mm^3 or per standard of care at the institution
gg. Blood for immune monitoring to be drawn at Enrollment (tumor resection), Day -7, Day 1, Day 4, Day 14, Day 42, Day 84, Month 6, Month 9 and Month 12. Refer to the Laboratory Manual, for vacutainer tubes for peripheral blood draws to be sent to the central laboratory. There is a ± 2-day window for the Immune Monitoring samples. If the scheduled visit is on a Friday, the Immune Monitoring sample should be collected on the prior Thursday. If the scheduled visit is on a Saturday or Sunday, the Immune Monitoring sample should be collected on the following Monday. On Day 1 immune monitoring samples should be drawn prior to IL-2 dosing.
hh. Local tumor assessment (per RECIST 1.1) (scheduled or unscheduled) should be used for clinical treatment decisions, and may include photographic/caliper measurement of superficial dermal and subcutaneous lesion. For Independent Review Committee (IRC) tumor assessment, adhere to the IRC Manual for submission of radiographic images.
ii. All adverse events (AEs) occurring after the patient has signed the informed consent form (ICF), prior before enrollment (prior to tumor resection), will be collected on the medical history eCRF, unless the event is new and attributed to protocol-required procedures or assessments.
jj. Dates of any hospitalization from signing of ICF through the LN-144 Therapy Treatment Period are to be collected in the eCRFs.
kk. The health-related quality of life (HRQoL) questionnaire EORTC QLQ-C30 is to be completed at Baseline (Day -21 to Day -7), Day 84, and Month 6, Month 12 and Month 24 (or EOS/ET) visits.
ll. Overall Survival (OS) Follow-Up Period will commence when each patient has their last response assessment visit, and will consist of telephone contact made quarterly with the patient or designee up until 5 years after the last study treatment. Collect information about subsequent anticancer therapy.

Appendix 3 ECOG SCALE

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

Adapted from Oken MM et al, 1982 [63]

Appendix 4 PRACTICAL WEIGHT

Modification of Dose Calculations* in Patients whose BMI is > 35 mg/m^2

Unless otherwise specified in this protocol, actual body weight is used for dose calculations of treatment agents. In patients who are determined to be obese (BMI > 35), the **practical weight** (see #3 below) will be used.

1. BMI Determination:

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

2. Calculation of ideal body weight

   Male = 50 kg + 2.3 (number of inches over 60 inches)

   Example: ideal body weight of 5'10'' male

   50 + 2.3 (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 (3) = 57 kg

3. Calculation of "practical weight"

Calculate the average of the actual and the ideal body weights. This is the practical weight to be used in calculating the doses of chemotherapy and associated agents designated in the protocol.

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

Appendix 5 IL-2 ADVERSE EVENTS

Adverse Events occurrence in ≥ 10% of patients treated with IL-2 (n=525)			
Body System/Events	% patients	Body System/Events	% patients
Body as a whole		*Metabolic and Nutritional Disorders*	
Chills	52	Bilirubinemia	40
Fever	29	Creatinine Increase	33
Malaise	27	Peripheral Edema	28
Asthenia	23	SGOT increase	23
Infection	13	Weight gain	16
Pain	12	Edema	15
Abdominal pain	11	Acidosis	12
Enlarged Abdomen	10	Hypomagnesemia	12
Cardiovascular System		Hypocalcemia	11
Hypotension	71	Alkaline Phosphatase Increase	10
Tachycardia	23	*Nervous System*	
Vasodilation	13	Confusion	34
Supraventricular Tachycardia	12	Somnolence	22
Cardiovascular disorder[a]	11	Anxiety	12
Arrhythmia	10	Dizziness	11
Digestive System		*Respiratory System*	
Diarrhea	67	Dyspnea	43
Vomiting	50	Lung disorder[b]	24
Nausea	35	Respiratory disorder[c]	11
Stomatitis	22	Cough increase	11
Anorexia	20	Rhinitis	10
Nausea and Vomiting	19	*Skin and Appendages*	
Hematologic and Lymphatic		Rash	42
Thrombocytopenia	37	Pruritus	24
Anemia	29	Exfoliative dermatitis	18
Leukopenia	16	*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 [9]

Appendix 6 EXPECTED IL-2 TOXICITIES AND THEIR MANAGEMENT[1]

Expected toxicity	Expected grade	Supportive Measures suggested	Stop Cycle*	Stop Treatment **
Chills	3	IV Meperidine 25 to 50 mg, IV q1h, prn,	No	No
Fever	3	Acetaminophen 650 mg, po, q4h; Indomethacin 50 to 75 mg, po, q8h	No	No
Pruritus	3	Hydroxyzine HCl 10 to 20 mg po q6h, prn; Diphenhydramine HCl 25 to 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 to 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 to 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

Expected toxicity	Expected grade	Supportive Measures suggested	Stop Cycle*	Stop Treatment **
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
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 (Day -21 to Day -14) levels by next dose
Myocardial Infarction	3	Supportive care	Yes	Yes
Elevated transaminases	3 or 4	Observation	For Grade 4 without liver metastases	If changes have not improved to Baseline (Day -21 to Day -14) levels 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.
Proleukin® Prescribing Information – January 2012 [9]

Appendix 7 COMMON TERMINOLOGY CRITERIA FOR ADVERSE EVENTS

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

Appendix 8 CYCLOPHOSPHAMIDE PACKAGE INSERT

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

Appendix 9 MESNA (MEXNEX®) PACKAGE INSERT

Mesna (Mesnex®), Full Prescribing Information, Sargeant Pharmaceutials, July 2015
http://www.sagentpharma.com/wp-content/uploads/2016/01/Mesna_PI.pdf

Appendix 10 ONDANSETRON PACKAGE INSERT

Ondansetron hydrochloride (Zofran®), Full Prescribing Information, Novartis, October 2017
https://www.pharma.us.novartis.com/sites/www.pharma.us.novartis.com/files/zofran.pdf

Appendix 11 FILGRASTIM PACKAGE INSERT

Filgrastim (Neupogen®), Full Prescribing Information, Amgen, 2016. https://pi.amgen.com/~/media/amgen/repositorysites/pi-amgen-com/neupogen/neupogen_pi_hcp_english.pdf

Appendix 12 FLUCONAZOLE PACKAGE INSERT

Fluconazole (Diflucan®), Full Prescribing Information Pfizer, 2016.
http://labeling.pfizer.com/ShowLabeling.aspx?id=575

Appendix 13 FLUDARABINE PACKAGE INSERT

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

Appendix 14 IL-2 (ALDESLEUKIN) PACKAGE INSERT

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

Appendix 15 EORTC QLQ-C30

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EORTC QLQ-C30 (version 3)

We are interested in some things about you and your health. Please answer all of the questions yourself by circling the number that best applies to you. There are no "right" or "wrong" answers. The information that you provide will remain strictly confidential.

Please fill in your initials: ____

Your birthdate (Day, Month, Year): ____

Today's date (Day, Month, Year): 31 ____

	Not at All	A Little	Quite a Bit	Very Much
1. Do you have any trouble doing strenuous activities, like carrying a heavy shopping bag or a suitcase?	1	2	3	4
2. Do you have any trouble taking a long walk?	1	2	3	4
3. Do you have any trouble taking a short walk outside of the house?	1	2	3	4
4. Do you need to stay in bed or a chair during the day?	1	2	3	4
5. Do you need help with eating, dressing, washing yourself or using the toilet?	1	2	3	4

During the past week:	Not at All	A Little	Quite a Bit	Very Much
6. Were you limited in doing either your work or other daily activities?	1	2	3	4
7. Were you limited in pursuing your hobbies or other leisure time activities?	1	2	3	4
8. Were you short of breath?	1	2	3	4
9. Have you had pain?	1	2	3	4
10. Did you need to rest?	1	2	3	4
11. Have you had trouble sleeping?	1	2	3	4
12. Have you felt weak?	1	2	3	4
13. Have you lacked appetite?	1	2	3	4
14. Have you felt nauseated?	1	2	3	4
15. Have you vomited?	1	2	3	4
16. Have you been constipated?	1	2	3	4

Please go on to the next page

During the past week:	Not at All	A Little	Quite a Bit	Very Much
17. Have you had diarrhea?	1	2	3	4
18. Were you tired?	1	2	3	4
19. Did pain interfere with your daily activities?	1	2	3	4
20. Have you had difficulty in concentrating on things, like reading a newspaper or watching television?	1	2	3	4
21. Did you feel tense?	1	2	3	4
22. Did you worry?	1	2	3	4
23. Did you feel irritable?	1	2	3	4
24. Did you feel depressed?	1	2	3	4
25. Have you had difficulty remembering things?	1	2	3	4
26. Has your physical condition or medical treatment interfered with your family life?	1	2	3	4
27. Has your physical condition or medical treatment interfered with your social activities?	1	2	3	4
28. Has your physical condition or medical treatment caused you financial difficulties?	1	2	3	4

For the following questions please circle the number between 1 and 7 that best applies to you

29. How would you rate your overall health during the past week?

1	2	3	4	5	6	7
Very poor						Excellent

30. How would you rate your overall quality of life during the past week?

1	2	3	4	5	6	7
Very poor						Excellent

Appendix 16 SUMMARY OF CHANGES (MAJOR/MINOR) IN PROTOCOL C-144-01 VERSION 7.0 (DATED, 23 March 2018)

The major changes and purposes for revising the C-144-01 protocol are to:

- Update of Primary and Secondary Objectives and Endpoints
- Clarification of Exploratory Objectives and Endpoints
- Adjustment of Eligibility Criteria for definition of Patient Population
- Adjustment of Sample Size and rationale for determination
- Clarification around requirements for Cohort 3 patients
- Clarification around assessment and procedure timing
- Numerous clarifications to Safety and Statistical sections

The minor changes and purposes for revising the C-144-01 protocol are to:

- Numerous typographical changes were made for clarity and consistency
- Minor administrative changes addressing clarification of operational issues

A separate Summary of Changes document outlines noteworthy changes from Version 6.0 to Version 7.0, and includes rationale for the changes.