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:	Lion Biotechnologies, Inc. 999 Skyway Rd, Suite 150 San Carlos, CA 94070 United States
PROTOCOL VERSION:	Final Version 6.0 (Incorporating Amendments 1-5)
PROTOCOL DATE:	13 May 2017
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 Lion Biotechnologies 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

Date

PPD

LEAD INVESTIGATOR PROTOCOL SIGNATURE PAGE

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INVESTIGATOR PROTOCOL SIGNATURE PAGE

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

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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 own tumor
Study Objectives:	**Primary Objective** • To evaluate the efficacy of LN-144 in patients with metastatic melanoma using the objective response rate (ORR) **Secondary Objectives** • To further evaluate efficacy of LN-144 in patients with metastatic melanoma such as complete response (CR) rate, duration of response (DOR), disease control rate (DCR), progression-free survival (PFS), and overall survival (OS) • To characterize the safety profile of LN-144 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 irRECIST[1] criteria as assessed by independent review • To assess health-related quality of life (HRQoL)
Study Design:	Prospective, interventional study evaluating adoptive cell therapy (ACT) with autologous TIL infusion (LN-144) followed by adjuvant interleukin-2 (IL-2) after a nonmyeloablative chemotherapy preparative regimen.
Dose and Treatment Schedule:	The cell transfer therapy used in this study involves patients receiving a nonmyeloablative lymphodepletion (NMA-LD) preparative regimen, consisting of cyclophosphamide IV (60 mg/kg x 2 doses) with mesna 15 mg/kg and fludarabine IV (25 mg/m^2 x 5 doses), followed by infusion of tumor-derived autologous TIL (LN-144) and administration of adjuvant IL-2 at 600,000 IU/kg approximately every 8 hours for up to a maximum of 6 doses, starting as soon as 3 hours, but no later than 24 hours after completion of LN-144 infusion. Patients will receive 1 course of LN-144 treatment in Cohort 1 and Cohort 2. Patients may be entered into a retreatment cohort (Cohort 3) for a second treatment with TIL therapy.

Duration of Study Participation:	Screening and tumor resection/TIL harvest: up to 28 days Treatment Period: up to 12 days, including NMA-LD (7 days) and LN-144 infusion followed by adjuvant IL-2 (up to 5 days) Patients will be evaluated for response at 6 weeks (Day 42 ± 3 days) following the LN-144 infusion and every 6 weeks thereafter, for up to 6 months. After 6 months, patients will be evaluated as noted below: • At 9 months (± 1 week) following LN-144 treatment • At 12 months (± 1 week) following LN-144 treatment • At 18 months (± 3 weeks) following LN-144 treatment • At 24 months (± 3 weeks) following LN-144 treatment Overall Survival Follow-up to collect subsequent anti-cancer therapy and survival status for 3 years from last patient receiving last dose of adjuvant IL-2 or end of study (EOS) visit.
Number of Study Centers:	Approximately 35 clinical sites globally
Number of Planned Patients:	Approximately sixty (60) patients will complete treatment (approximately 30 patients in Cohort 1 and 30 patients in Cohort 2). Complete treatment is defined as having received any volume of LN-144 infusion followed by at least 1 dose of adjuvant IL-2. Patients who participate in initial TIL therapy in Cohort 1 or Cohort 2 may enter a third treatment cohort (Cohort 3) where 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 metastatic melanoma (Stage IIIc or Stage IV) who progressed following ≥1 line of prior systemic therapy, including immune checkpoint inhibitor (e.g., anti-PD-1), and if BRAF mutation-positive, after BRAF inhibitor systemic therapy • At least one measurable target lesion as defined by RECIST version 1.1.[2] Lesions in previously irradiated areas should not be selected as target lesion, unless treatment was ≥ 3 months prior, and there has been demonstrated progression in the lesion • At least one resectable lesion to generate TILs of a minimum 1.5 cm in diameter post-resection 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 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 4 months after receiving all protocol related therapy 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 ALT/SGPT and AST/SGOT < 3 times the upper limit of normal ULN), patients with liver metastasis < 5 times ULN • an estimated creatinine clearance (eC_{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 HIV antibody, hepatitis B antigen, and hepatitis C antibody or antigen i. Patients must have recovered from all prior therapy-related AEs to Grade 1 or less (per CTCAE v4.03), except for alopecia or vitiligo, prior to enrollment (tumor resection) • A minimal washout period of 4 weeks is required prior to enrollment (tumor resection) • Palliative radiation therapy is permitted between biopsy and nonmyeloablative lymphodepletion if it does not involve lesions being selected as target or non-target lesions • Patients may undergo pre-planned procedures if within 2-3 weeks prior to the start of nonmyeloablative lymphodepletion j. 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 and/or had a normal colonoscopy post immune checkpoint inhibitor treatment by visual assessment, prior to start of nonmyeloablative lymphodepletion 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 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, will be considered for enrollment after discussion with Medical Monitor, and must be stable for 2-4 weeks prior to the start of treatment (nonmyeloablative lymphodepletion) 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, such as systemic 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 and AIDS) h. Patients who have a history of severe immediate hypersensitivity reaction to cyclophosphamide, fludarabine, or IL-2 i. Patients who have a left ventricular ejection fraction (LVEF) < 45% at Screening j. Patients who have obstructive or restrictive pulmonary disease and have a documented FEV1 (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 with known allergic reaction to antibiotics of aminoglycoside group (i.e. streptomycin, gentamicin) m. Patients who have been shown to be BRAF mutation positive (V600), but have not received prior systemic therapy with a BRAF-directed kinase inhibitor
Treatment Cohorts:	LN-144 (autologous TIL) followed by IL-2 after a lymphocyte-depleting preparative regimen as an open-label treatment. Cohort 1: LN-144 process without cryopreservation of the final TIL product Cohort 2: LN-144 process with cryopreservation of the final TIL product Cohort 3: Retreatment cohort: 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 b). These patients will have a second tumor harvest and TIL (LN-144) therapy. Examples of patients who may be eligible for retreatment in Cohort 3 are prior responders to LN-144 who relapse, non-responders, and patients with manufacturing failures. The Medical Monitor will have authority to adjudicate enrollment into Cohort 3 (second TIL therapy). Prior to enrollment in Cohort 3, patients must undergo abbreviated screening procedures.
Early Discontinuation from Study or Treatment:	Criteria for early discontinuation from treatment: • Grade 3 or greater autoimmunity that involves vital organs (heart, kidneys, brain, eye, liver, colon, adrenal gland, lungs) with symptoms emerging prior to first IL-2 administration • Grade 3 or greater allergic reaction including bronchospasm or generalized urticaria that does not resolve after medical management in the opinion of the Investigator • Grade 3 or greater toxicity due to IL-2 that does not decrease to Grade 2 or less within 96 hours of management • Determination by the Investigator that continued treatment is not in the best interest of the patient

	• Withdrawal by patient. The patient may withdraw consent to treatment but continue consent for follow-up evaluations and/or survival status. • Pregnancy Criteria for early discontinuation from study: • Patient becomes ineligible for the study after tumor harvest or did not receive LN-144 infusion for any reason • Withdrawal of consent • Death • Lost to follow-up after 3 documented attempts to contact the patient
Efficacy Assessment:	The descriptive summary of the ORR, CR rate, DOR, DCR, and PFS per cohort will be used to determine the potential efficacy of LN-144, per RECIST 1.1 criteria by Investigator review. Estimation of OS will depend on the dates of death or the last known alive status.
Safety Assessment:	Treatment-emergent adverse events (TEAEs) and clinical laboratory data will be collected and evaluated to assess the safety of this treatment. Adverse events (AEs) will be collected from the time the patient signs the ICF up until 6 month from their last dose of IL-2 or until the first dose of anti-cancer therapy, whichever occurs first. All AEs attributed to protocol-required procedures or treatment will be collected from signing of the ICF through Month 24 study visit.
Overview of Statistical Plan:	The primary statistical plan of analysis is based on use of descriptive methods and 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[2] for a confirmed complete (CR) or partial (PR) response will be classified as responders in the analysis of the ORR. This rate will be summarized using both a point estimate and its 2-sided 90% 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 lymphodepletion. The assessment of safety data will be descriptive and based on the summarization of TEAEs, SAEs, AEs leading to discontinuation from treatment and the study, vital signs, physical examinations, and clinical laboratory tests.
Sample Size Consideration:	The planned number of all-treated patients (see Section 10.2) per Cohort 1 and Cohort 2 is approximately 30 (total 60, inclusive of Cohort 3 re-treated patients). The hypotheses test of primary endpoint analysis per cohort in this study assumes an underlying ORR of 15% over best monotherapy available, as the historical control, for the treatment of patients with metastatic melanoma after progression on anti-PD-1 therapy.[3] Assuming a true response rate of 30% for the LN-144 therapy, a sample size of 30 all-treated patients provides approximately 70% power to to reject the null hypothesis $H_0 \leq 15\%$ at 1-sided 5% significance level.

DSMB Safety Assessments:	A Data Safety Monitoring Board (DSMB) will evaluate cumulative safety data on the first 3 patients completing 12 weeks of assessment in Cohort 1 and in Cohort 2, respectively. Enrollment will continue while under DSMB review. Additional evaluations of safety data may be specified in the DSMB charter.

Figure 1 Cohort 1 or Cohort 2 Study Flowchart

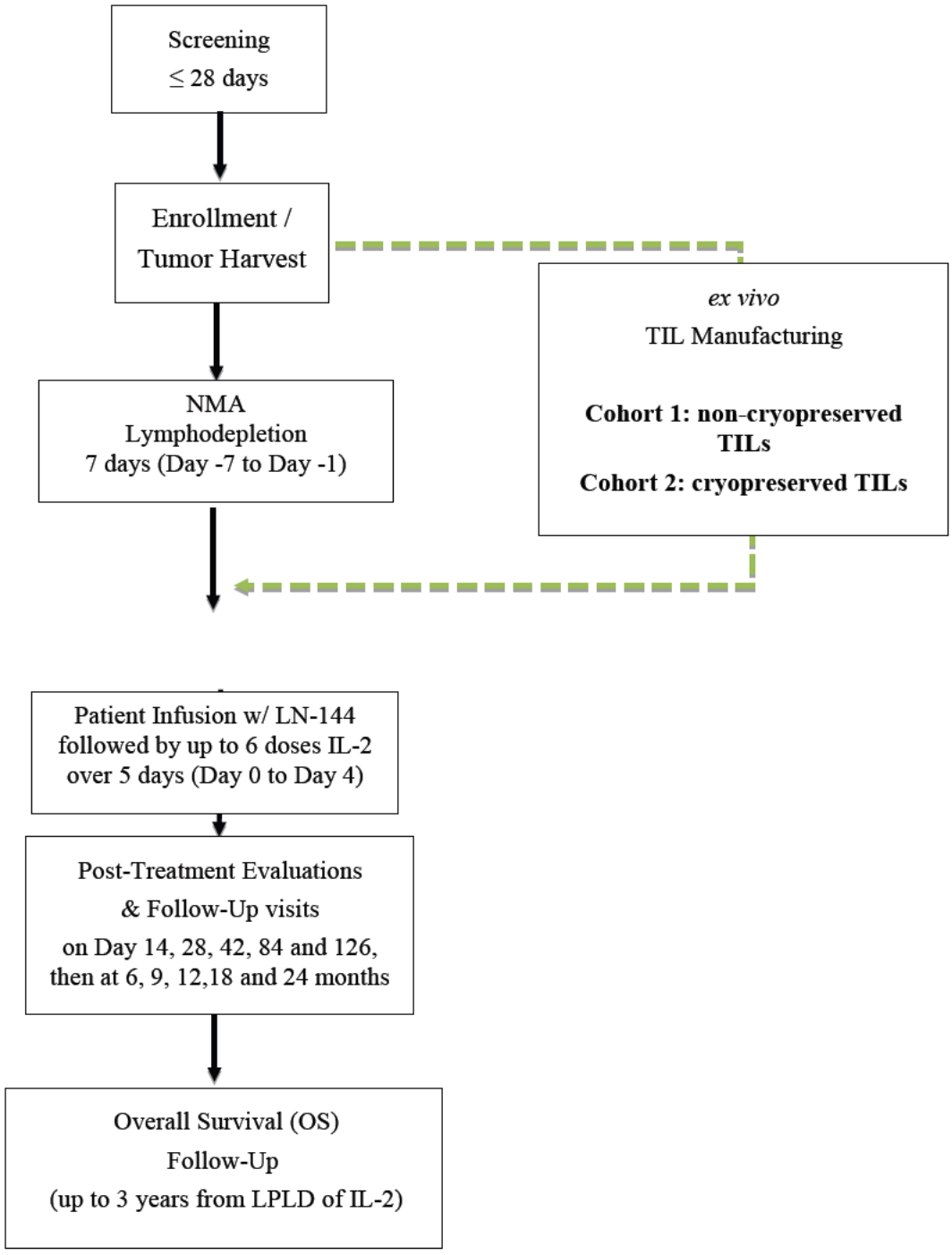


Figure 2 Cohort 3 Study Flowchart

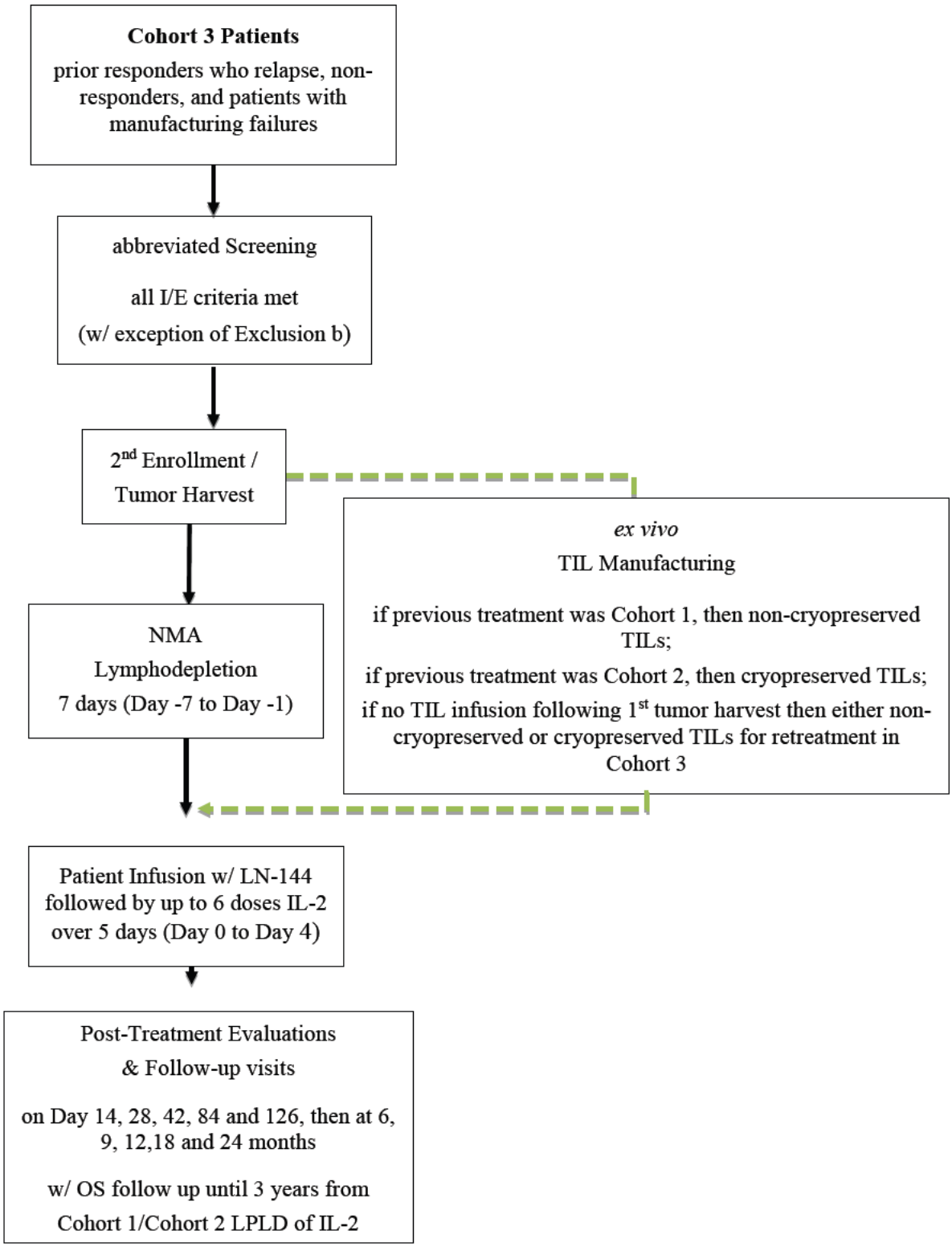


TABLE OF CONTENTS

LIST OF TABLES

LIST OF FIGURES

LIST OF ABBREVIATIONS

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
CBC	Complete blood count
CFR	Code of Federal Regulations
CMO	Contract Manufacturing Organization
CR	Complete response
CT	Computed tomography
CTL	Cytotoxic T lymphocyte
CTCAE v4.03	Common Terminology Criteria for Adverse Events Version 4.03
CY	Cyclophosphamide
DC	Dendritic cell
DCR	Disease control rate
DOR	Duration of response
DSMB	Data Safety Monitoring Board
EBV	Epstein-Barr virus
ECHO	Echocardiogram
eCRF	Electronic case report form
EDC	Electronic data capture
EEG	Electroencephalogram
EKG	Electrocardiogram
EOS	End of study
EORTC QLQ-C30	European Organisation for Research and Treatment of Cancer Quality-of-Life Questionnaire - Core 30 instrument
FDA	Food and Drug Administration
FEV1	Forced Expiratory Volume in 1 second
GCP	Good Clinical Practice
GDPR	General Data Protection Regulation
HIPAA	Health Insurance Portability and Accountability Act of 1996
HIV	Human immunodeficiency virus
HRQoL	Health related quality of life
HSA	Human serum albumin
ICF	Informed consent form
ICH	International Conference on Harmonization
ICU	Intensive Care Unit
IEC	Independent Ethics Committee
IL-2	Interleukin-2 (also known as “aldesleukin”)
IND	Investigational New Drug (Application)
IP	Investigational product
irRECIST	Immune-Related Response Evaluation Criteria in Solid Tumors
IRB	Institutional Review Board
IUD	Intrauterine device
IUS	Intrauterine hormone-releasing system

IV	Intravenous
LD	Lymphodepletion
LN-144	Autologous Tumor Infiltrating Lymphocytes
LPLD	Last patient last dose
LVEF	Left ventricular ejection fraction
MRI	Magnetic resonance imaging
MUGA	Multiple gated acquisition scan
NCCN	National Comprehensive Cancer Network
NCI	National Cancer Institute
NMA	Nonmyeloablative
Non-CR	Non-complete response
Non-PD	Non-progression
ORR	Objective response rate
OS	Overall survival
PBMC	Peripheral blood mononuclear cell
PD	Progressive disease
PE	Physical exam
PET	Positron emission tomography
PFS	Progression-free survival
PHI	Personal health information
PO	Per Os (by mouth)
PR	Partial response
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
SD	Stable disease
SGOT	Serum glutamic-oxaloacetic transaminase
SGPT	Serum glutamic-pyruvic transaminase
$T_{½}$	Half life
TEAE	Treatment-emergent adverse event
TH	Tumor Harvested patient population
TIL	Tumor infiltrating lymphocyte
TME	Tumor microenvironment
TSH	Thyroid stimulating hormone
ULN	Upper limit of normal
VDRL	Venereal disease research laboratory

1 INTRODUCTION

1.1 Background

There are an estimated 232,000 newly diagnosed cases of melanoma skin cancers occurring globally each year, making it the fifth most common malignancy in men and the sixth most common malignancy in women.[4] Unlike other malignancies, the incidence of melanoma is increasing by greater than 3.2% and 2.4% per year in males and females, respectively.[5] Globally, the incidence rate varies with 20-30 new melanoma cases per 100,000 inhabitants in the US, compared to <10-25 new melanoma cases per 100,000 inhabitants in EU, and with the highest incidence of 50-60 per 100,000 inhabitants in Australia.[6] One estimate predicted 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 UK.[7,8] Of interest, individuals under age 45 account for 25% of all new melanoma cases.[4]

The National Cancer Institute's Surveillance, Epidemiology, and End Results uptake (SEER) Program estimates that there will be 10,130 deaths due to melanoma in 2016 in the US, despite the approvals of ipilimumab in 2011, and pembrolizumab and nivolumab in 2014, and the rapid uptake of these immunotherapeutic agents.[5] Five-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.[7]

Current melanoma treatment guidelines are similar in Europe, the US, Canada, Australia and New Zealand.[9] Approved first line treatments for metastatic melanoma include immunotherapeutic strategies blocking PD-1 (pembrolizumab, nivolumab), or combining nivolumab with the anti-CTLA-4 blocker ipilimumab, or chemotherapy with agents targeting specific activating mutations in the BRAF pathway (e.g., vemurafenib, dabrafenib, trametinib). Following disease progression, patients can receive additional treatment with anti-PD-1 monotherapy; nivolumab/ipilimumab combination therapy; ipilimumab monotherapy; BRAF and/or MEK inhibitors, if BRAF mutant; high-dose aldesleukin (interleukin-2; IL-2); cytotoxic agents (e.g., dacarbazine, temozolomide, paclitaxel, cisplatin, carboplatin, vinblastine); or imatinib for KIT-mutant melanoma (NCCN Guidelines Version 2.2016).[10,11] 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.[12]

Until recently, high-dose aldesleukin was the only 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 tumor regressions (CRs) observed in up to 6% of treated patients [Proleukin® (aldesleukin) Label, FDA, July 2012; Alva 2016].[13,14] 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.[15,16] 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 administered in combination, although the CR rate remains low at 8.9% [Opdivo® (nivolumab) Label, FDA, October 2016].[17] Retreatment of patients who progressed post anti-PD-1 therapy with additional checkpoint inhibitors has been one method of therapy, however, overall response rates of 16% and 21% are the best noted in use of ipilimumab or ipilimumab plus nivolumab, respectively.[3]

Use of the immune checkpoint inhibitors is associated with a spectrum of immune-related adverse events, including pneumonitis, colitis, hepatitis, nephritis and renal dysfunction.[18,19] 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.[16,18]

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 100000 in 2011 and remained at this level in 2015.[20]

Cell transfer therapy with autologous 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.[21,22,23] At present, however, only a limited number of clinical centers in the US with access to suitable 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. Lion is utilizing the TIL manufacturing method developed by Dr. Steven A. Rosenberg's team at 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 anti-cancer therapeutic is based on observations that 1) The immune system is adept at producing antigen-specific anti-tumor cytotoxic T cell responses which have demonstrated anti-tumor reactivity both *in vitro* and *in vivo*, the latter having also demonstrated therapeutic efficacy. 2) such autologous cellular therapies represent the terminal engagement of Ag-specific effector mechanisms mediated by the pro-inflammatory immunologic cascade, which are subject to significantly fewer adverse autoimmune sequalae than more broad-spectrum, non-specific, 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,[24,25] and 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.[26,27,28] 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.[21]

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.[29,30,31] 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.[32] The latter are now thought to be the key type of antigen recognized by TIL mediating enhanced tumor eradication during TIL therapy.[33] 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.[34-38]

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 two stages. Lion 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 3-week 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, two-agent nonmyeloablative (NMA) lymphodepletion (LD) preconditioning regimen, post-infusion IL-2 (up to a maximum of 6 doses), and the use of minimally cultured (so-called "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 RECIST criteria 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.[17,18]

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.[39] 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.[40–42] 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.[43, 44] 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 MART-1,

gp100, MAGE-1, tyrosinase, TRP-1, TRP-2 and NY-ESO-1.[44,45] 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 cells population *in vitro* has led to the development of adoptive cell transfer regimens for 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.[46, 47] 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 the re-infusion of these expanded cells as a potential therapeutic back into the patient. Some of the first clinical trials performed in individual centers in the USA and Europe, such as the National Cancer Institute (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.[48–51] 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 (e.g., Tessier et al.).[49]

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%-60%.[52–54] This prior CY pre-conditioning 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.[55, 56] Furthermore, this prior lymphodepletion preconditioning regimen with CY was also later found to remove suppressive $CD4^+$ T-regulatory cells ($CD4^+Foxp3^+$ 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 in cancer patients.[57–60] Alternatively, prior depletion of lymphocytes may create 'space' for the adoptively transferred cells within the lymphocyte compartment.[61] 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 such as IL-7, IL-15 and IL-21.[62]
The success of prior lymphodepletion in animal models and the use of single agent CY preconditioning in initial TIL therapy trials, led to testing of more intensive pre-conditioning 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.[63,64] 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 lymphodepletion 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.[63,64]

Because of the immunosuppression exhibited by fludarabine, 1 patient who had clonal repopulation from infused TIL and a complete objective tumor response to therapy, developed Epstein-Barr virus (EBV) - associated B cell lymphoma. This patient was EBV-naïve prior to treatment. The potential source of EBV was thought to be multiple blood products received after chemotherapy. The patient later died from complications of the treatment for the lymphoma. Another patient developed polyneuropathy consisting of vision loss and motor and sensory defects approximately 2 months after chemotherapy. The etiology of this complication is unknown, but was possibly related to fludarabine.[64]

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 objective response rates (ORR) by RECIST 1.0 criteria 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.[15,16]

Radvanyi et al.[65] reported the MD Anderson Cancer Center experience with ACT using selected TIL for treatment of metastatic melanoma with objective clinical response in 15/31 (48.4%) patients with 2 resulting in a complete response (6.5%). Progression-free survival of greater than 12 months duration was reported in 9/15 (60%) patients that responded to therapy. The H. Lee Moffitt Cancer Center also reported a 38% response rate in 13 treated patients with 2/13 (15%) achieving a complete response ongoing for more than 14 and 16 months at the time of publication, respectively.[66] Outside the U.S., Itzhaki et al[67] reported the experience from Sheba Medical Center in Israel using "young, unselected –TIL therapy." Of the 31 patients evaluated, 15 (48%) patients achieved a clinical response including 4 patients (12.9%) with complete responses. In addition, a group in Denmark[68] used decrescendo low-dose IL-2 as an adjuvant after cell infusion to reduce treatment related toxicity in a small study (6 patients). This study reported objective clinical responses in 2/6 patients (33%) with ongoing complete responses of more than 10 and 30 months (respectively), 2 patients (33%) with stable disease for 4 and 5 months (respectively) and 2 patients (33%) whose disease progressed shortly after treatment.

1.3 Production and Expansion of Tumor Infiltrating Lymphocytes

The LN-144 active biologic is composed of viable TILs 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 2-8°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-rapid expansion protocol (pre-REP) with human recombinant interleukin 2 (IL-2, Proleukin®) for 11 to 21 days to generate ≥1 x 10^8 total viable cells. The small-scale, pre-REP cells can then be cryopreserved allowing for flexibility in the subsequent scheduling of TIL therapy administration into the patient from which they were originally derived. The pre-REP cells are then further expanded in a rapid expansion protocol (REP), in which they are cultured for ~14 days 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 (TILs) are then harvested, washed, and formulated in a blood transport and infusion bag for shipment by courier to the clinical site. The dosage form of the investigational product is a live cell suspension of either non-cryopreserved or cryopreserved autologous TIL for intravenous infusion into the patient from which they were derived. Diagrams of the production processes for the non-cryopreserved and cryopreserved LN-144 investigational products are provided in Figure 3 and Figure 4, respectively.

Figure 3 LN-144 Manufacturing Process without Final Cryopreservation

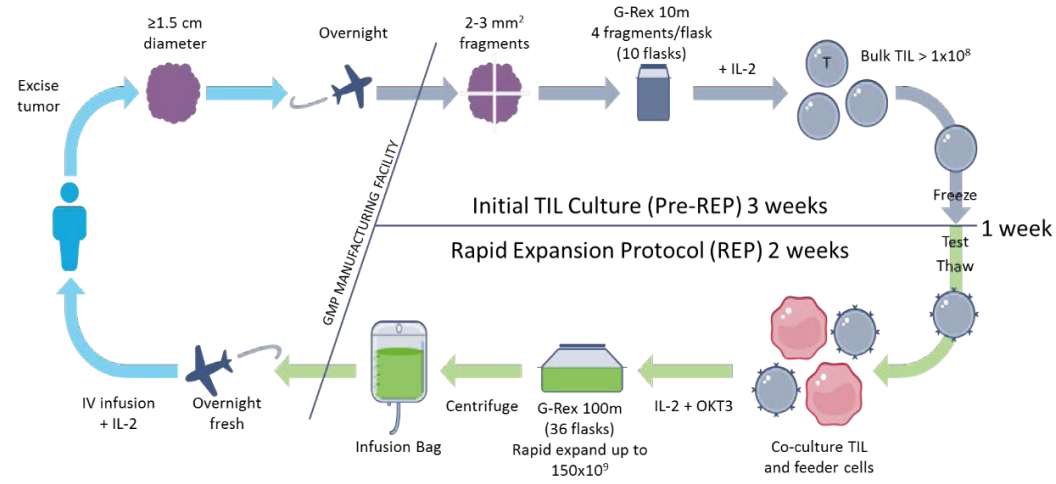
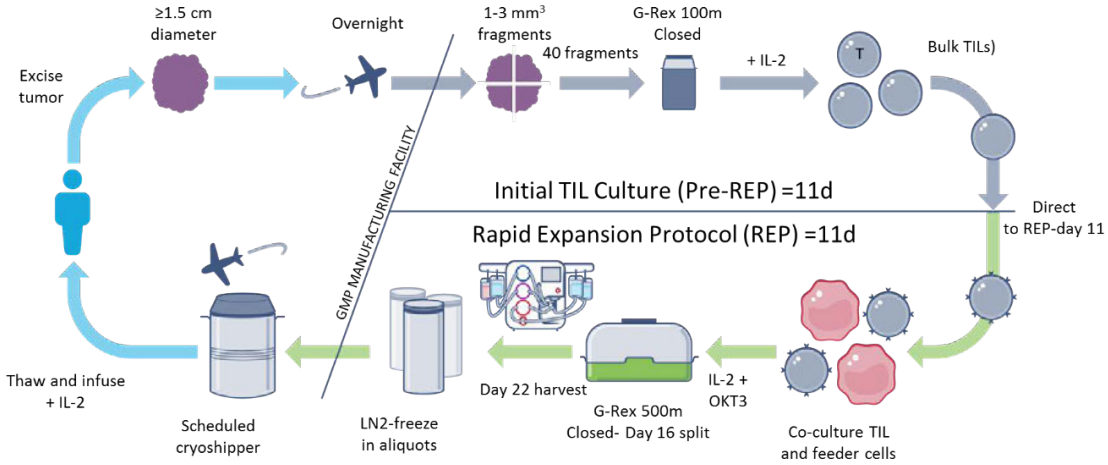


Figure 4 LN-144 Manufacturing Process with Final Cryopreservation



1.4 LN-144 TIL Therapy

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

Several pre-conditioning 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 lymphodepletion protocol 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) followed by adjuvant IL-2. Details for the tumor harvest and LN-144 administration as fresh or cryopreserved product are provided in the Pharmacy & Investigational Product Administration Manual.

The final investigational product will be available for administration in 1 of several volumes for infusion, as described in the Pharmacy & Investigatotional Product Administration Manual.

Cohort 1 (LN-144 manufacturing process **without** final cryopreservation). This final cellular investigational product 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 investigational product is formulated in 50% CryoStor10™ in Plasma-Lyte A™.

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

Cohort 3 patients will have their TILs 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 non-cryopreserved TIL or cryopreserved TIL), alternatively if no prior

LN-144 therapy/infusion was received, treatment in Cohort 3 will by which ever manufacturing process has the first availability.

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 adjuvant IL-2 at 600,000 IU/kg approximately every 8 hours starting as soon as 3 hours, but no later than 24 hours after the LN-144 infusion and continuing for up to 6 doses. Patients will be evaluated for objective response approximately 6 weeks following LN-144 infusion and then every 6 weeks up to 6 months.

After 6 months, patients will be evaluated for objective response at 9, 12, 18 and 24 months following LN-144 treatment. Formal response evaluations will follow RECIST 1.1 criteria.[2]

Overall Survival (OS) Follow-Up will continue until the last patient treated in the study has finished 3 years FU following their last dose of IL-2 or end of study (EOS) visit. It is the intent that all patients will be followed for OS for a minimum of 3 years.

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-lymphodepletion pretreatment regimen and then also just prior to the LN-144 infusion through the adjuvant IL-2 administration.

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 objective response rate (ORR)

3.1.2 Secondary Objectives

- To further evaluate efficacy of LN-144 in patients with metastatic melanoma by assessing complete response (CR) rate, duration of response (DOR), disease control rate (DCR), progression free survival (PFS) and overall survival (OS)
- To characterize the safety profile of LN-144 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 irRECIST criteria[1] as assessed by independent review
- To assess health-related quality of life (HRQoL)

3.2 Study Endpoints

3.2.1 Primary Endpoint

- Objective response rate (ORR)

3.2.2 Secondary Endpoints

- Complete response (CR) rate, duration of response (DOR), disease control rate (DCR), progression free survival (PFS) and overall survival (OS) per RECIST 1.1 criteria[2] by independent and Investigator review
- Incidence, severity, seriousness, relationship to study treatment, and characteristics of treatment-emergent AEs (TEAEs), including AEs leading to early discontinuation from treatment or withdrawal from the study, 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, utilizing peripheral blood mononuclear cells (PBMC), serum, plasma and tumor specimens to test for cellular and soluble factors via immunological assays and molecular assays related to exome sequencing
- ORR, CR rate, DCR, and PFS using irRECIST[1] as assessed by independent review
- Patient-reported outcomes based on the EORTC QLQ-C30 HRQoL questionnaire

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 (e.g., anti-PD-1), and if BRAF mutation-positive, after BRAF inhibitor systemic therapy

   - At least one measurable target lesion by RECIST version 1.1.[2] Lesions in previously irradiated areas should not be selected as target lesion, unless treatment was ≥ 3 months prior, and there has been demonstrated progression in the lesion
   - At least one resectable lesion to generate TILs of minimum 1.5 cm in diameter post-resection; surgical removal with minimal morbidity (defined as any procedure for which expected hospitalization is less than or equal to 3 days)

b. Patients must be ≥ 18 years and ≤ 70 years of age at the time of consent. Enrollment of patients > 65 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 4 months after receiving all protocol related therapy

   Approved methods of birth control are as follows:

   - combined (estrogen and progestogen containing) hormonal contraception associated with inhibition of ovulation: oral; intravaginal; transdermal
   - progestogen-only hormonal contraception associated with inhibition of ovulation: oral; injectable; implantable
   - intrauterine device (IUD)
   - intrauterine hormone-releasing system (IUS)

- bilateral tubal occlusion
- vasectomized partner
- sexual abstinence

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:

- ALT/SGPT and AST/SGOT < 3 times the upper limit of normal (ULN); patients with liver metastasis < 5 times ULN
- an estimated creatinine clearance (eC_{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 HIV antibody, hepatitis B antigen, and hepatitis C antibody or antigen

i. Patients must have recovered from all prior therapy-related AEs to Grade 1 or less (per CTCAE v4.03), except for alopecia or vitiligo prior to enrollment (tumor resection)

- A minimal washout period of 4 weeks is required prior to enrollment (tumor resection)
- Palliative radiation therapy is permitted between biopsy and nonmyeloablative lymphodepletion for LN-144 infusion if it does not involve lesions selected as target or non-target lesions
- Patients may undergo pre-planned procedures if 2-3 weeks prior to the start of nonmyeloablative lymphodepletion

j. 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 and/or had a normal colonoscopy postimmune checkpoint inhibitor treatment, by visual assessment, prior to the start of nonmyeloablative lymphodepletion

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 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, who can be considered for enrollment after discussion with Medical Monitor, must be stable for 2-4 weeks prior to the start of treatment (nonmyeloablative lymphodepletion)

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

- Short course of higher dose steroid therapy is allowed in case of exacerbation of known disease or for treatment 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, such as systemic 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 and AIDS)

h. Patients who have a history of severe immediate hypersensitivity reaction to cyclophosphamide, fludarabine, or IL-2

i. Patients who have a left ventricular ejection fraction (LVEF) < 45%

j. Patients who have obstructive or restrictive pulmonary disease and a documented FEV1 (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 with known allergic reaction to antibiotics of aminoglycoside group (i.e. streptomycin, gentamicin)

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

4.3 Number of Patients

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

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. Minimum data for screen failures will be captured in the electronic data capture (EDC) database as defined in the electronic case report form (eCRF) completion manual.

Patients will be enrolled until approximately 60 patients across both Cohort 1 and Cohort 2 have received any volume of LN-144 infusion followed by at least 1 dose of adjuvant IL-2, and approximately 10 patients may enter the third cohort (Cohort 3) where they will be retreated with a second administration of LN-144 (second TIL therapy). Screening may halt once it becomes likely that the full enrollment goals for Cohort 1 and Cohort 2 will be met. Patients from Cohorts 1 and 2 may screen for the retreatment Cohort 3 as long as this study is open. Prior to enrollment in Cohort 3, patients must undergo abbreviated screening evaluation and procedures.

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 resign the informed consent form and be reassessed for eligibility following a discussion between the Investigator and Medical Monitor to agree on which screening procedures need to be redone.

Patients from Cohort 1 or Cohort 2 may also be rescreened, have a second tumor resected, and be retreated in Cohort 3 with a second LN-144 infusion if they meet all inclusion and exclusion criteria (except exclusion b). Cohort 3 patients will have a second tumor harvest for TIL manufacturing by the same process (either Cohort 1 [fresh TILs] or Cohort [cryopreserved TILs]) as their prior cohort assignment, unless they did not receive an LN-144 infusion from the initial tumor resected, in which case the most immediately available manufacturing slot will be assigned. Examples of patients who may be eligible for retreatment in Cohort 3 are prior responders to LN-144 who relapse, non-responders, and patients with manufacturing failures. The Medical Monitor will have authority to adjudicate enrollment into Cohort 3 (second TIL therapy).

4.3.2 Patient Cohorts

All patients who receive any volume of LN-144 infusion followed by at least 1 dose of adjuvant IL-2 are defined as the ‘all-treated population’, and all patients resected for harvest will be defined as the Tumor Harvested (TH) population.

Patients will be assigned to Cohort 1 or Cohort 2 based on IRB/IEC approval of appropriate protocol/ICF versions at the site and the most immediately available manufacturing slot. If either Cohort 1 or Cohort 2 approaches or passes the desired 30-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 reach the 6-month tumor assessment, and the final analysis will take place at the end of the 2-year (24 month) post-treatment follow-up.

Cohort 3 will consist of patients who wish to rescreen for a second tumor harvest of tumor for TIL manufacture and LN-144 treatment as per their prior cohort assignment. Examples of patients who may be eligible for retreatment in Cohort 3 are prior responders to LN-144 who relapse, non-responders, and patients with manufacturing failures. The Medical Monitor will have authority to adjudicate enrollment into Cohort 3 (second TIL therapy). These Cohort 3 patients will need to be rescreened and meet all eligibility criteria (except exclusion criteria b). Of the approximate 60 enrolled patients enrolled across Cohort 1 and Cohort 2, and approximately 10 patients may rescreen for a second tumor harvest for LN-144 treatment in Cohort 3.

5 PRIOR TREATMENTS, CONCOMITANT MEDICATIONS AND NON-DRUG 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 electronic case report form (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 post-treatment follow-up phase.

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 who complete the NMA-LD should not receive a live or attenuated vaccine 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 lymphodepletion as long as it does not involve selected target or non-target lesions

- Patients may undergo pre-planned procedures if 2-3 weeks prior to the start of lymphodepletion

5.2.2 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 anti-tumor 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 of informed consent form)

The following procedures should be performed after signing of informed consent form (ICF):

- Review of inclusion and exclusion criteria
- Medical history
- Melanoma medical history, including prior therapies, response to prior therapies and BRAF mutational status
- Concurrent medications within 30 days prior to signing of 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 exam. Prior evaluation within 30 days prior to signing of ICF is allowed
- Electrocardiogram (EKG). Prior evaluation within 60 days prior to signing of ICF is allowed
- Cardiac evaluation (stress thallium) for all patients. Echocardiogram or multiple gated acquisition scan (MUGA) for patients ≥60 years or patients who have a history of ischemic heart disease, chest pain, or clinically significant atrial and/or ventricular arrhythmias. Stress thallium must show normal LVEF and unimpaired wall movement. Prior evaluations within 6 months of signing of ICF is allowed.

- Pulmonary function tests. Prior evaluations within 6 months prior to signing ICF is allowed.
- 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
- Blood and Urine Tests
    - Hematology – complete blood count (CBC) with differential
    - Chemistry - Sodium, Potassium, Chloride, Total CO2 or Bicarbonate, Creatinine, Glucose, BUN, Albumin, Calcium, Magnesium, Phosphorus, Alkaline Phosphatase, ALT/SGPT, AST/SGOT, Total Bilirubin, Direct Bilirubin, LDH, Total protein, Total CK, Uric Acid, and thyroid panel (to include TSH and free T4)
- Serum pregnancy test for all women of childbearing potential
- CMV serology (IgG and IgM, as per local standard)
- Syphilis screening (as per local standard; e.g., Rapid Plasma Reagin [RPR] venereal disease research laboratory [VDRL] or other) at Screening, and thereafter as clinically indicated
- HIV antibody titer, HbsAG determination (HSV-1 IgG and HSV-2 IgG), Anti HCV, HSV serology and EBV serology (VCA-IgM, VCA-IgG, EA-D IgG, EBNA, IgG) (may be within previous 3 months as of enrollment)
- HLA typing (to be shipped to central laboratory). Refer to central Laboratory Manual for details.
- Urinalysis (complete urine culture if indicated)

- Calculate estimated creatinine clearance (eC_{Cr}) using Cockcroft-Gault formula

• Males: • Creatinine CL (mL/min)	=	Weight (kg) x (140 – Age) 72 x serum creatinine (mg/dL)
• Females: • Creatinine CL (mL/min)	=	Weight (kg) x (140 – Age) x 0.85 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 nonmyeloablative lymphodepletion
- Assessment of adverse events (AEs) / serious AEs (SAEs)

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.

- Verification of all ongoing concomitant medications (list only medications that are NOT part of the tumor harvest procedure)
- Obtain blood for immune monitoring/phenotyping (refer to Laboratory Manual)
- Tumor Harvest (see Section 6.2.1)
- Assessment of AE/SAEs

6.2.1 Tumor Harvest and Processing Procedure

Detailed Tumor Procurement & Shipping Manuals will be provided to each clinical site and training will be performed 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.

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 x 5 mm x 5 mm is to be placed in formalin and sent to the Central Lab (refer to central 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 Lab. When tumor tissue is limiting, a single 2 mm punch biopsy from the center of the resected tumor will be placed into formalin and sent to the Central Lab (refer to central 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 Lab.

Tumor tissue sent to the Central Lab will be used as follows 1) for immunohistochemistry to identify different immune cell populations 2) for isolation of 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 (e.g. Genetic Research ICF) for exome sequencing.

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

LN-144 is an autologous investigational product which 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.

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

Peripheral blood will be collected from the patient for immune monitoring (biomarker analysis) and sequencing (exome and TCR sequencing) of lymphocyte DNA utilizing vacutainer blood collection vials. Refer to the study 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 exam including weight
- 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
- 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 post-treatment disease assessments, [scheduled and unscheduled])
    - Chest (include neck there is prior or suspected neck disease)
    - Abdomen
    - Pelvis
- MRI – Brain in patients who had brain abnormalities at Screening. For those patients who had negative brain scans at Screening, the Baseline 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 post-treatment disease assessments [scheduled and unscheduled]).
- Blood and urine tests
    - Hematology - CBC with differential
    - Chemistry - Sodium, Potassium, Chloride, Total CO2 or Bicarbonate, Creatinine, Glucose, BUN, Albumin, Calcium, Magnesium, Phosphorus, Alkaline Phosphatase, ALT/SGPT, AST/SGOT, Total Bilirubin, Direct

Bilirubin, LDH, Total protein, Total CK, Uric Acid, and thyroid panel (to include TSH and free T4, only if clinically indicated)

- Serum pregnancy test for all women of childbearing potential
- Urinalysis (complete urine culture if indicated)

- ECOG performance status evaluation
- Assessment of AE/SAEs
- EORTC QLQ-C30 HRQoL questionnaire
- Re-check of abbreviated Inclusion/Exclusion Criteria in order to ensure that patient performance status and main eligibility criteria have not changed from time of Screening, a re-confirmation 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 harvest and LN-144 manufacture but will not receive the infusion of investigational product. Early Treatment Discontinuation (prior to NMA-LD).

6.5 Early Treatment Discontinuation (prior to NMA-LD)

If the patient does not receive any volume of LN-144 infusion and this is prior to NMA-LD, due to a potentially treatable medical event, the pre-REP cells (for Cohort 1 patients) or the REP cells (for Cohort 2 patients) may remain frozen for a period of time agreed upon between the Investigator and Medical Monitor, to see if the patient recovers and meets criteria to receive LN-144 infusion. If a decision is take that the patient will not receive their TILs, then the patient should remain on study, but the data collection will be reduced to survival status and start of any new anticancer therapy.

6.6 Day -7

Prior to the start of lymphodepletion, verification of sufficient LN-144 expansion at this time point will be confirmed by the Sponsor with the manufacturing facility. In Cohort 2, the REP may be extended an additional 7 days if growth is inadequate in which case, the Day -7 and subsequent visits will be delayed by 1 week.

Prior to beginning the lymphodepletion 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 adjuvant 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 investigational product 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 adjuvant IL-2 administration, the patient should not proceed to lymphodepletion and subsequent therapy and be followed as per Section 1.1.

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

- Physical exam including weight, calculated BSA and 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 CO2 or Bicarbonate, Creatinine, Glucose, BUN, Albumin, Calcium, Magnesium, Phosphorus, Alkaline Phosphatase, ALT/SGPT, AST/SGOT, Total Bilirubin, Direct Bilirubin, LDH, Total protein, Total CK
    - Urinalysis (complete Urine culture if indicated)
    - CMV serology (IgG and IgM, as per local standard), only if clinically indicated
- Obtain blood for immune monitoring (refer to Laboratory Manual)

6.6.1 Initiation of administration of the NMA-LD preconditioning medications

- Cyclophosphamide 60 mg/kg intravenously (IV) in 250 mL D5W with mesna 15 mg/kg are infused over approximately 2 hours. If the patient is obese (BMI >35) drug dosage will be calculated using practical weight as described in Appendix 4
- 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. Patient may be hospitalized overnight during the mesna administration.

- 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 X 3 days) will be given for nausea, or as per standard of care at the treating institution. (If the patient is obese (BMI >35) drug dosage will be calculated using practical weight as described in Appendix 4)
- Prophylactic antibiotics such as TMP/SMX DS 160 mg/800 mg may be given as clinically indicated, per standard of care
- Assessment of AE/SAEs

6.7 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 CO2 or Bicarbonate, Creatinine, Glucose, BUN, Albumin, Calcium, Magnesium, Phosphorus, Alkaline Phosphatase, ALT/SGPT, AST/SGOT, Total Bilirubin, Direct Bilirubin, LDH, Total protein, Total CK
    - 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 in 250 mL D5W with mesna15 mg/kg are infused over approximately 2 hours. If the patient is obese (BMI >35) drug dosage will be calculated using practical weight as described in Appendix 4
    - 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. Patient may be discharged following completion of the mesna administration.

- 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 X 3 days) will be given for nausea, or as per standard of care at the treating institution. If the patient is obese (BMI >35) drug dosage will be calculated using practical weight as described in Appendix 4
- Prophylactic antibiotics such as TMP/SMX DS 160 mg/800 mg may be given as clinically indicated, per standard of care

- Assessment of AE/SAEs

6.8 Day -5 to Day -1

The following procedures should be performed:

- Physical exam 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 CO2 or Bicarbonate, Creatinine, Glucose, BUN, Albumin, Calcium, Magnesium, Phosphorus, Alkaline Phosphatase, ALT/SGPT, AST/SGOT, Total Bilirubin, Direct Bilirubin, LDH, Total protein, Total CK
  - CMV serology (IgG and IgM, as per local standard), only if 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
  - Prophylactic antibiotics such as TMP/SMX DS 160 mg/800 mg may be given as clinically indicated, per standard of care
- Assessment of AE/SAEs

6.9 Day 0 (Infusion day)

Day 0 is the day of LN-144 infusion.

Upon completion of the manufacturing process, the investigational product, LN-144, will be labeled with a patient specific label. The investigational product will then be shipped from the manufacturing facility to the respective clinical site for infusion, as described in the Pharmacy & Investigational Product Administration manual. All visits following LN-144 infusion (Day 0) are calculated from that date forward.

6.9.1 Investigational Product

The investigational product, LN-144, will be shipped overnight by courier to the clinical site pharmacy in a shipping container validated to maintain the appropriate investigational product temperature.

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

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 adjuvant IL-2 administration, as per institutional standards. The following procedures should be performed:

- Physical exam 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 (to be drawn prior to LN-144 infusion)
    - Hematology – CBC with differential
    - Chemistry - Sodium, Potassium, Chloride, Total CO2 or Bicarbonate, Creatinine, Glucose, BUN, Albumin, Calcium, Magnesium, Phosphorus,

Alkaline Phosphatase, ALT/SGPT, AST/SGOT, Total Bilirubin, Direct Bilirubin, LDH, Total protein, Total CK, Uric Acid, and thyroid panel (to include TSH and free T4, only if clinically indicated)

- Urinalysis (complete urine culture if indicated)

- 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

6.9.1.1 LN-144 Infusion

- Autologous TIL (LN-144) will be administered intravenously. The fresh LN-144 investigational product for Cohort 1 patients) will be administered (by gravity) within approximately 45 minutes. 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) investigational product should be refrigerated.
- The frozen LN-144 investigational product (for Cohort 2 patients) will be thawed in a 37^{o}C water bath and each infusion bag will be administered sequentially. During periods of infusion interruption, the remaining cryobags of frozen TILs (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

6.10 Day 1, Day 2, Day 3 and Day 4

While the patient remains hospitalized, the following procedures should be performed:

- Physical exam including weight (physical exam Day 1 and Day 4 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 the first IL-2 administration of each calendar day)

  - Hematology - CBC with differential
  - Chemistry - Sodium, Potassium, Chloride, Total CO2 or Bicarbonate, Creatinine, Glucose, BUN, Albumin, Calcium, Magnesium, Phosphorus, Alkaline Phosphatase, ALT/SGPT, AST/SGOT, Total Bilirubin, Direct Bilirubin, LDH, Total protein, Total CK
  - CMV serology (IgG and IgM, as per local standard) - required only once from Day 1 through Day 3
  - Urinalysis (complete urine culture if indicated)

- Obtain blood for immune monitoring on Day 1 and Day 4 only (Refer to Laboratory Manual)
- Assessment of AE/SAEs
- The following medications will be administered:
  - Adjuvant IL-2 – the first adjuvant IL-2 administration can begin as soon as 3 hours, but no later than 24 hours after conclusion of the LN-144 infusion. IL-2 will be administered at a dose of 600,000 IU/kg (based on total body weight). Adjuvant IL-2 is to be administered by intravenous infusion at a frequency not greater than every 8 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 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 adjuvant 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, adjuvant IL-2 dosing may be held or stopped at the discretion of the treating Investigator. Refer to Appendix 6 for guidance
  - Filgrastim 5 mcg/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

- 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
- Prophylactic antibiotics such as TMP/SMX DS 160 mg/800 mg may be given as clinically indicated, per standard of care
- 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

6.11 Day 14 and 28 (both visits +/- 3 days)

The following procedures will be performed:

- Physical exam including weight
- ECOG performance status evaluation (Day 14 only)
- Blood tests
  - Hematology - CBC with differential
  - Chemistry - Sodium, Potassium, Chloride, Total CO2 or Bicarbonate, Creatinine, Glucose, BUN, Albumin, Calcium, Magnesium, Phosphorus, Alkaline Phosphatase, ALT/SGPT, AST/SGOT, Total Bilirubin, Direct Bilirubin, LDH, Total protein, Total CK, Uric Acid, and thyroid panel (to include TSH and free T4). Thyroid panel only to be done at Day 14
- Obtain blood for immune monitoring (Refer to Laboratory Manual) (Day 14 only)
- If required, the following medications will continue to be administered
  - Filgrastim 5 mcg/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

  - 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
  - Prophylactic antibiotics such as TMP/SMX DS 160 mg/800 mg may be given as clinically indicated, per standard of care
  - 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

6.12 Day 42 (Week 6) (+/- 3 days)

The following procedures will be performed:

- Physical exam including weight
- Evaluation and measurement of all skin and palpable lesions
- Verification of all concomitant medications
- Vital signs- pulse rate, respiratory rate, blood pressure and temperature
- Assessment of AE/SAEs
- Blood tests
  - Hematology - CBC with differential
  - Chemistry - Sodium, Potassium, Chloride, Total CO2 or Bicarbonate, Creatinine, Glucose, BUN, Albumin, Calcium, Magnesium, Phosphorus, Alkaline Phosphatase, ALT/SGPT, AST/SGOT, Total Bilirubin, Direct Bilirubin, LDH, Total protein, Total CK, Uric Acid, and thyroid panel (to include TSH and free T4, only if clinically indicated)
  - CMV serology (IgG and IgM, as per local standard), only if clinically indicated
- Obtain blood for immune monitoring (Refer to Laboratory Manual)

- CT Exam (repeat the same CT series for post-treatment 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 CNS involvement at Screening or Baseline, or as clinically indicated (repeat the same MRI series for post-treatment tumor assessment [scheduled and unscheduled] as completed at Baseline [Day -21 to Day -14])
- If required, the following medications will continue to be administered
    - Filgrastim 5 mcg/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
    - 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
    - Prophylactic antibiotics such as TMP/SMX DS 160 mg/800 mg may be given as clinically indicated, per standard of care
    - 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

6.13 Day 84 (Week 12) and Day 126 (Week 18) (both visits +/- 3 days)

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

- Physical exam including weight
- ECOG performance status evaluation
- Evaluation and measurement of all skin and palpable lesions
- Verification of all concomitant medications

- Vital signs - pulse rate, respiratory rate, blood pressure and temperature
- Assessment of AE/SAEs
- Slit lamp eye exam (Day 84 only)
- Blood tests
    - Hematology - CBC with Differential
    - Chemistry - Sodium, Potassium, Chloride, Total CO2 or Bicarbonate, Creatinine, Glucose, BUN, Albumin, Calcium, Magnesium, Phosphorus, Alkaline Phosphatase, ALT/SGPT, AST/SGOT, Total Bilirubin, Direct Bilirubin, LDH, Total protein, Total CK, Uric Acid, and thyroid panel (to include TSH and free T4, only if clinically indicated)
    - CMV serology (IgG and IgM, as per local standard), only if clinically indicated
- Calculate Creatinine Clearance using Cockcroft-Gault formula (Day 84 only)
- Obtain blood for immune monitoring (Refer to Laboratory Manual) (Day 84 only)
- CT Exam (repeat the same CT series for post-treatment 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 post-treatment tumor assessment [scheduled and unscheduled] as completed at Baseline [Day -21 to Day -14])
- EORTC QLQ-C30 HRQoL questionnaire (Day 84 only)
- If required, the following medications will continue to be administered
    - Filgrastim 5 mcg/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

- 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
- Prophylactic antibiotics such as TMP/SMX DS 160 mg/800 mg may be given as clinically indicated, per standard of care
- 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

6.14 Month 6, Month 9, Month 12, Month 18, and Month 24 (all visits +/- 1 week)

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, Potassium, Chloride, Total CO2 or Bicarbonate, Creatinine, Glucose, BUN, Albumin, Calcium, Magnesium, Phosphorus, Alkaline Phosphatase, ALT/SGPT, AST/SGOT, Total Bilirubin, Direct Bilirubin, LDH, Total protein, Total CK, Uric Acid, 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
- Obtain blood for immune monitoring (Refer to Laboratory Manual) (Months 6, 9 and 12 only)

- CT Exam (repeat the same CT series for post-treatment 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 post-treatment 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 mcg/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
    - 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
    - Prophylactic antibiotics such as TMP/SMX DS 160 mg/800 mg may be given as clinically indicated, per standard of care
    - 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 for future guidance on AE/SAE reporting requirements during the follow-up period)
- EORTC QLQ-C30 HRQoL questionnaire (Months 6, 12, and 24 only)

6.15 Overall Survival Follow-Up

Patients are to be followed in Overall Survival (OS) Follow-up to collect subsequent anti-cancer therapy and survival status for 3 years from last patient receiving last dose of adjuvant

IL-2 or end of study (EOS) visit. It is the intent that all patients will be followed for OS for a minimum of 3 years.

6.16 Late Treatment Discontinuation (following LN-144 infusion)

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

- However, if a patient must initiate anti-cancer 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 anti-cancer therapy

6.17 Expected Toxicities and Treatment Guidelines

6.17.1 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 6.17.2)

6.17.2 IL-2

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

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

administration should be withheld in patients developing moderate to severe lethargy or somnolence; continued administration may result in coma.

The standard approach to the administration of 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 the overwhelming majority of patients have suffered no long-term sequelae following this treatment regimen. However, fatal complications are possible.

Treatment Guidelines for Toxicity Management

Concomitant medications to control side effects of therapy will be given. Meperidine (25-50 mg), or other medication per site standard of care may be given intravenously if severe chills develop. Other supportive therapy shall be given as required. Supportive therapy includes acetaminophen (650 mg q4h), indomethacin (50-75 mg q6h) and ranitidine (150 mg q12h). 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.

Expected toxicities with cyclophosphamide and fludarabine administration are listed in the package inserts (see Appendix 8 and 9, 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.

6.17.3 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.

6.17.4 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.

6.18 Infection Prophylaxis

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

6.18.1 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 will 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.

6.18.2 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. Reversible renal insufficiency has been reported with IV but not oral acyclovir. Neurologic toxicity including delirium, tremors, coma, acute psychiatric disturbances, and abnormal EEGs has been reported with higher doses of acyclovir. Should this occur, a dosage adjustment will be made or the drug will be discontinued. Acyclovir will not be used

concomitantly with other nucleoside analogs, which interfere with DNA synthesis, e.g. ganciclovir. In renal disease, the dose is adjusted as per product labeling.

Herpes prophylaxis will continue for 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.

6.18.3 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.

6.18.4 Empiric Antibiotics

Patients will start on broad-spectrum antibiotics, either a 3rd or 4th generation cephalosporin or a quinolone for fever – defined as 38.3°C, 1 or 2 temperatures of 38.0°C or above at least 1 hour apart, AND an ANC <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.

6.18.5 Blood Product Support

Using 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.

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 adjuvant IL-2.

7.2 Criteria for Early Discontinuation from Treatment

Criteria for early discontinuation from treatment:

- Grade 3 or greater autoimmunity that involves vital organs (heart, kidneys, brain, eye, liver, colon, adrenal gland, lungs) with symptoms emerging 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
- Grade 3 or greater toxicity due to IL-2 that does not decrease to Grade 2 or less within 96 hours of management
- Determination by the Investigator that continued treatment is not in the best interest of the patient
- Withdrawal by patient. The patient may withdraw consent to treatment but continue consent for follow-up evaluations and/or survival status
- Pregnancy
- Criteria for early discontinuation from study
- Patient has become ineligible for study after tumor harvest and prior to LN-144 or IL-2 administration
- Withdrawal of consent
- Death
- Lost to follow-up after 3 documented attempts to contact the patient

7.3 Criteria for Early Discontinuation from Study

- Withdrawal by patient. The patient may withdraw consent. All efforts should be made to continue consent for survival status follow-up
- Patient has become ineligible for study after tumor harvest
- Death
- Lost to follow-up after 3 documented attempts to contact the patient

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 non-cryopreserved (Cohort 1) or cryopreserved (Cohort 2)

8.2 Qualitative Composition of LN-144

LN-144 is a cellular investigational product 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 (non-cryopreserved 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 one LN-144 dose is given intravenously a NMA-LD lymphodepletion preconditioning regimen followed by adjuvant IL-2 therapy starting as soon as 3 hours, but not later than 24 hours after completion of LN-144 infusion. 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 5 bags containing up to approximately 100 mL of thawed cells.

8.3 Manufacturing Process

The overall process of tumor shipping, LN-144 manufacturing, and LN-144 investigational product shipping, and infusion is shown in Figure 3 (Cohort 1) and Figure 4 (Cohort 2).
The LN-144 investigational product 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 2-3 mm (length x width x 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 investigational product 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 $\leq 75 \times 10^9$ LN-144 or 600 mL blood transfer pack (Baxter) for cell concentrations $\leq 150 \times 10^9$ LN-144. Alternatively, in Cohort 2, TILs will be received cryopreserved in up to 5 bags containing up to approximately 100 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 investigational product 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 2-8^{o}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 investigational product will be received at the clinical site on or prior to Day 0. Refer to the LN-144 Pharmacy and Administration Manual for additional details.

9 STUDY ASSESSMENTS

9.1 Tumor Assessments

Tumor assessment 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, Day -14 and Day 42 (6 weeks, ± 3 days) following the LN-144 infusion and every 6 weeks thereafter, up to 6 months post-LN-144 infusion, at which time the tumor assessments will follow the schedule below:

- At 9 months (± 1 week) following LN-144 treatment
- At 12 months (± 1 week) following LN-144 treatment
- At 18 months (± 3 weeks) following LN-144 treatment
- At 24 months (± 3 weeks) following LN-144 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 post-treatment disease assessments, [scheduled and unscheduled]). Assessments should be made and recorded by the Investigator or an individual authorized by the Investigator.

MRI or positron emission tomography (PET) scans in lieu of CT scans will be allowed for patients who have an intolerability to contrast media. The imaging modality used must be uniform for the duration of the study.

9.1.1 Response Criteria

Tumor response will be determined using RECIST version 1.1[2] with a modification to require confirmation of PD. Refer to Table 1 and Table 2 for RECIST 1.1 response criteria[2] 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 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 independent 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 non-target) must have a reduction in short axis to <10 mm).

[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.

- Partial Response (PR): At least a 30% decrease in the sum of the diameter of target lesions taking as reference the baseline sum diameters.
- Progressive Disease (PD): At least a 20% increase in the sum of diameters of target lesions taking as reference the smallest sum on study (this includes the baseline sum if that is the smallest on study). In addition to the relative increase of 20%, the sum must also demonstrate an absolute increase of at least 5 mm. (Note: the appearance of 1 or more new lesions is also considered progression).
- Stable Disease (SD): Neither sufficient shrinkage to qualify for PR nor sufficient increase to qualify for PD taking as references the smallest sum diameters while on study.

9.1.1.2 Evaluation of Non-target Lesions[2]

- Complete Response (CR): Disappearance of all non-target lesions and normalization of tumor marker level. All lymph nodes must be non-pathological in size (<10 mm short axis).
- Non-Complete Response: Persistence of 1 or more non-target lesion(s) and/or maintenance of tumor marker level above normal limits.
- Progressive Disease (PD): Unequivocal progression of existing non-target lesions. (Note: the appearance of 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 from Day -21 to Day -14 (Baseline) until disease progression/recurrence, the initiation of new anti-cancer therapy, death or 24 months whichever comes first. The patient's best response assignment will depend on the achievement of both measurement and confirmation criteria.

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

Table 1. Time Point Response: Patients with Target (± Non-target) Disease

Target Lesions	Non-Target Lesions	New Lesions	Overall 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

Table 2. Time Point Response: Patients with Non-Target Disease Only

Non-Target Lesions	New Lesions	Overall 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

Peripheral blood mononuclear cells (PBMC), serum, plasma and tumor specimens 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

A 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.

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, 90% 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 (e.g., p-values), they will be used in a descriptive manner.

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

10.2 Study and Analysis Populations

The 2 study cohorts (Cohort 1 and Cohort 2) comprise the Tumor Harvested (TH) population defined as all resected patients. The TH population is further divided into the following analysis populations:

10.2.1 Efficacy Population

Primary: the All-Treated population that consists of patients in the safety population who have been successfully treated with nonmyeloablative chemotherapy, LN-144 followed by IL-2 (at least 1 dose), based on Investigators' assessment

10.2.2 Safety Population

Primary: all patients in the TH population who received at least one component of the study treatment; cyclophosphamide, fludarabine, LN-144 or IL-2.

Secondary: all patients in the TH population. Non-treated patients who are not a part of the primary safety population will be summarized separately

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 original cohort for efficacy and safety analyses. There will be no formal comparisons among cohorts.

10.3 Endpoints

10.3.1 Primary

The primary endpoint is the ORR using RECIST 1.1 criteria[2]. The ORR is derived as the sum of the number of patients with a CR or partial response (PR) divided by the number of patients in the All-Treated population x 100%.

10.3.2 Secondary

CR rate is derived as the sum of the number of patients with a confirmed CR divided by the number of patients in the All-Treated population x 100%.

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 (i.e., database lock) will have their event times censored on the last adequate tumor assessment date.

DOR is measured from the first time 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 adequate tumor assessment date.

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 All-Treated population x 100%.

OS is defined as the time (in months) from the start date of the lymphodepletion 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

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[1] will also be assessed. HRQoL will be assessed using the EORTC QLQ-C30 instrument (see Appendix 10) and scored/evaluated as described in the Statistical Analysis Plan.

10.4 Sample Size Consideration

The planned number of all-treated patients per Cohort 1 and Cohort 2 is approximately 30 (total 60, inclusive of Cohort 3 retreated patients). The hypotheses test of primary endpoint analysis per cohort in this study assumes an underlying ORR of 15% over best monotherapy available, as the historical control, for the treatment of patients with metastatic melanoma after progression on anti-PD-1 therapy.[3] Assuming a true response rate of 30% for the LN-144 therapy, a sample size of 30 all-treated patients provides approximately 70% power to reject the null hypothesis $H_0 \leq 15\%$ at 1-sided 5% significance level.

10.4.1 Baseline Demographics and Clinical Characteristics

Baseline demographic and clinical (disease) characterized will be summarized descriptively for the Safety and the All-Treated patient populations if they are not identical. Age will be derived as a function of the date of informed consent.

10.4.2 Primary Endpoint

ORR is expressed as binomial proportions and will be summarized using both a point estimate and its 2-sided 90% confidence limits based on the Wilson's score method.

10.4.3 Secondary Endpoints

CR rate and DCR are also expressed as binomial proportions and will be summarized using both a point estimate and its 2-sided 90% confidence limits based on the Wilson's score method.

PFS, OS, durations of overall 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. The landmark analyses will be applied to the PFS and OS data.

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 90% confidence limits.

10.4.4 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 the time of lymphodepletion for the Safety and All-Treated populations. Adverse event summaries will be based on patient incidence counts and their related percentages; the number of events will be displayed as appropriate. 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 (e.g., ANCs for neutropenia; platelets for thrombocytopenia).

10.4.5 Other Planned Analyses

Should exploratory 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 6.17.2). The use of the nonmyeloablative regimen prior to cell administration increases the toxicity of this treatment as profound myelosuppression occurs in all patients.

11.3 IL-2 Administration

See Section 6.17.2 for IL-2 toxicity considerations. The standard approach to the administration of adjuvant IL-2 in all studies is to continue dosing without putting the patient at risk for severe or irreversible toxicities. The most commonly seen Grade 4 events are pulmonary and renal impairment, and mental status changes. It is important to note that although these patients require significant supportive measures during this period, most toxicities are reversible and the overwhelming majority of patients have suffered no long-term sequelae following this treatment regimen. However, fatal complications are possible and it is therefore only appropriate to carry out this experimental treatment in the context of life threatening metastatic cancer.

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-GCP is any untoward medical occurrence in a patient or clinical trial patient administered a medicinal/investigational product and which does

not necessarily have a causal relationship with this treatment. An AE can therefore be any unfavorable and unintended sign (including an abnormal laboratory finding), symptom or disease temporally associated with the use of a medicinal product, whether or not considered related to the medicinal/investigational product.

Events meeting the definition of an AE include:

- Adverse event temporally associated with the use of any of the study drugs or TIL treatment whether or not considered related to the use of any of the study drugs or TIL treatment
- Any abnormal laboratory test results (e.g., hematology, clinical chemistry, or urinalysis) or other safety assessments (e.g., EKGs, radiological scans, vital signs measurements), that worsen from baseline, and are felt to be clinically significant in the medical and scientific judgment of the Investigator
- Exacerbation of a chronic or intermittent pre-existing condition including either an increase in frequency and/or intensity of the condition
- New conditions detected or diagnosed after investigational product administration
- Signs, symptoms, or the clinical sequelae of a suspected interaction with investigational product
- Signs, symptoms, or the clinical sequelae of a suspected overdose of either investigational product or a concomitant medication

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

- Any clinically significant abnormal laboratory finding or other abnormal safety assessments that is associated with the underlying disease, unless judged by the Investigator to be more severe than expected for the patient's condition
- Medical or surgical procedure (e.g., endoscopy, appendectomy); the condition that leads to the procedure is an AE
- Situations where an untoward medical occurrence did not occur (social and/or convenience admission to a hospital)
- Overdose without clinical sequelae (see 12.2.1.2.2.1)
- 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 one 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 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 Relationship to Study Drug

12.2.1.1 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 harvested), 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 through 6 months from the last dose date of IL-2 or until the first dose of anti-cancer therapy, whichever occurs first. All AEs attributed to protocol-required procedures or treatment will be collected from signing of the informed consent form through Month 24 study visit.

Medically significant AEs considered related to the investigational product 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 hour 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 investigational product due to an SAE, this information must be included in either the initial or follow-up SAE Report Form and in the eCRF.

12.2.1.2 Serious Adverse Events

12.2.1.2.1 Investigator Reporting to Sponsor

All SAEs, regardless of relationship to study treatment, must be collected while on the study (from patient signing of informed consent through 6 months from the last dose of IL-2 or until the first dose of the next anti-cancer therapy, whichever occurs first). All AEs/SAEs attributed to protocol-required procedures or treatment will be collected through Month 24 of the study. If the Investigator learns of any SAEs that occur after the follow-up period and there is a reasonable possibility that the event may have been caused by the study treatment, then the SAE should be promptly reported to the Sponsor or designated Safety CRO.

All SAEs that occur during the study must be reported by the Investigator to the Sponsor or designee within 24 hours of learning of the event. The initial notification should be as

complete as is possible with the information available and include the Investigator's assessment of study drug relationship, as defined in Section 12.2.1. 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**
SynteractHCR	**E-mail:** PPD **Fax:** PPD

12.2.1.2.2 Special Situation Reporting

12.2.1.2.2.1 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/investigational product while in the control of the health care provider, patient, or consumer.

An overdose is defined as an accidental or intentional administration of a quantity of a medicinal/investigational product 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/investigational product.

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

12.2.1.2.3 Pregnancy Reporting

Any pregnancy that occurs while on the study through 12 months from the last dose of IL-2 or until the first dose of the next anti-cancer 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 (e.g., 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 12.2.1.2.4.

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 post-treatment 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 investigational product, 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.

12.2.1.2.4 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.

12.2.1.2.5 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 Lion 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 (e.g., change in monitor[s], change of telephone number[s]). Responsibilities for reporting protocol amendments to any Regulatory Authority (if applicable) and/or IRB/IEC are further described per Sponsor or designee operating procedures and delegation of regulatory obligations.

13.2 Regulatory Approval and Documentation

Lion Biotechnologies, Inc. (Sponsor) will determine the appropriate local, national and or regional regulatory approvals that need to be obtained in order 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 (e.g., 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 (e.g., 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.

13.3 Record Retention

In compliance with the ICH/GCP guidelines the Investigator/Institution will be responsible for all information in the eCRF and will maintain the source documents that support the data collected from each patient, and all trial documents as specified in Essential Documents for the Conduct of a Clinical Trial and as specified by the applicable regulatory requirement(s).

The Investigator/Institution will take measures to prevent accidental or premature destruction of these documents. Essential documents must be retained until at least 2 years after the last approval of a marketing application in an ICH region or at least 2 years have elapsed since the formal discontinuation of clinical development of the investigational product. These documents will be retained for a longer period if required by the applicable regulatory requirements or by an agreement with the Sponsor. It is the responsibility of the Sponsor to inform the Investigator/institution as to when these documents no longer need to be retained. If the responsible Investigator retires, relocates, or for other reasons withdraws from the responsibility of keeping the study records, custody must be transferred to a person who will accept the responsibility. The Sponsor must be notified in writing of the name and address of the new custodian.

13.4 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.

13.5 Data Handling and Recordkeeping

13.5.1 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.

13.5.2 Data Handling and Recordkeeping

13.5.2.1 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.

13.6 Study Completion/Termination

13.6.1 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. Continuation of the study beyond this time must be agreed upon by both the Investigator and Sponsor and may be implemented without amendment to the protocol.

13.6.2 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

13.7 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.

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, it's 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 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 co-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 investigational product 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 (e.g., patients' written consent forms) should be maintained by the Investigator in strict confidence, in accordance with all applicable local and national regulations. All information provided to the Investigator prior to the study, as well as all data developed during the study, is confidential and remains the property of the Sponsor. The Investigator agrees that no information based on the conduct of this study (including the protocol, the data resulting from 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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APPENDIX 1: SCHEDULE OF EVENTS – FOR COHORT 1 AND COHORT 2 PATIENTS

Assessment	Screening & Enrollment Procedures			Treatment												Follow-up										OS follow-up
	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 d)	Day 28 (+/- 3 d)	Day 42 (+/-3d)	Day-84 (+/- 3d) / Week 12	Day 126 (+/- 3d) / Week 18	Month 6 (+/- 1 wk)	Month 9 (+/- 1 wk)	Month 12 (+/- 1 wk)	Month 18 (+/- 3 wks)	Month 24 (+/- 3 wks / or End of Study (EOS)	Every 3 months / Month 27 to Month 60 (+/- 3 wks)
Informed Consent	X																									
Inclusion/Exclusion	X		X[1]																							
Physical Exam[2]	X		X	X						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	X	X	X	X	X	
Eye Exam	X																		X							
Medical History[3]	X																									
Concomitant Meds	X	X[4]	X	X	X	X	X	X	X	X	X	X	X	X	X			X	X	X	X	X	X	X	X	X	
Height	X																									
Weight	X		X	X						X	X	X			X	X	X	X	X	X	X	X	X	X	X	
Vital Signs[5]	X		X	X	X	X	X	X	X	X	X	X	X	X	X			X	X	X	X	X	X	X	X	X	
CMV Serology[6]	X											X[6]														
Syphilis Screening[7]	X																									
EKG	X		X																							
Stress Thallium[8]	X																									
CT Chest, Abdomen, Pelvis[9]	X		X															X	X	X	X	X	X	X	X	
MRI – Brain[9]	X		X															X	X	X	X	X	X	X	X	
Serum Chemistry[10]	X		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	
Thyroid Panel[11]	X															X									X	
Hematology[12]	X		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	
Urinalysis[13]	X		X	X	X	X	X	X	X	X	X	X	X	X	X											

Assessment	Screening & Enrollment Procedures			Treatment											Follow-up										OS follow-up
	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 d)	Day 28 (+/- 3 d)	Day 42 (+/-3d)	Day-84 (+/- 3d) / Week 12	Day 126 (+/- 3d) / Week 18	Month 6 (+/- 1 wk)	Month 9 (+/- 1 wk)	Month 12 (+/- 1 wk)	Month 18 (+/- 3 wks)	Month 24 (+/- 3 wks / or End of Study (EOS)	Every 3 months / Month 27 to Month 60 (+/- 3 wks)
Calculated Creatinine Clearance[14]	X																		X							
ß-HCG Pregnancy Test[15]	X		X																							
ECOG performance status	X		X	X												X			X	X	X	X	X	X	X	
HIV Titer	X																									
Hb_sAG	X																									
Anti-HCV	X																									
HLA Typing[16]	X																									
HSV serology	X																									
EBV serology	X																									
PFT[17]	X																									
Colonoscopy[18]	X																									
Tumor Harvest[19]		X																								
Ondansetron				X	X																					
Authorization to Initiate Lymphodepletion[20]				X																						
Cyclophosphamide 60 mg/kg				X	X																					
Mesna				X	X																					
Fludarabine 25 mg/m^2/day						X	X	X	X	X																
LN-144 Infusion[21]											X															
IL-2 600,000 IU/kg[22]												X	X	X	X											
Filgrastim[23]												X	X	X	X	X	X	X	X	X	X					
TMP/SMX DS, or				X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X					

Assessment	Screening & Enrollment Procedures			Treatment												Follow-up										OS follow-up
	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 d)	Day 28 (+/- 3 d)	Day 42 (+/-3d)	Day-84 (+/- 3d) / Week 12	Day 126 (+/- 3d) / Week 18	Month 6 (+/- 1 wk)	Month 9 (+/- 1 wk)	Month 12 (+/- 1 wk)	Month 18 (+/- 3 wks)	Month 24 (+/- 3 wks / or End of Study (EOS)	Every 3 months / Month 27 to Month 60 (+/- 3 wks)
appropriate Abx[24]																										
Fluconazole[25]												X	X	X	X	X	X	X	X	X	X					
Valacyclovir/Acyclovir[26]												X	X	X	X	X	X	X	X	X	X					
Immune Monitoring[27]		X		X								X			X	X		X	X		X	X	X			
Tumor Assessment (Local)[28]	X		X															X	X	X	X	X	X	X	X	
Assessment of AE/SAEs	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	
EORTC QLQ-C30 HRQoL			X																X		X		X		X	
Overall Survival (OS) Follow-up Telephone contact[29] (q 3-months ± 3 weeks)																										X

1. Re-check of Inclusion/Exclusion Criteria in order to ensure that patient performance status and main eligibility criteria have not changed from time of Screening, a re-confirmation is to be perform and approved by Sponsor or designee.
2. Physical examination (PE) will include gastrointestinal (abdomen, liver), cardiovascular, extremities, head, eyes, ears, nose, and throat, respiratory system, skin, psychiatric (mental status), general nutrition.
3. 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.
4. List only medications that are NOT part of the tumor harvest procedure.
5. 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.
6. CMV serology (as per local standard) at Screening, within 3 days of LN-144 infusion and thereafter as clinically indicated.
7. Syphilis screening (as per local standard; e.g., Rapid Plasma Reagin [RPR] venereal disease research laboratory [VDRL] or other) at Screening, and thereafter as clinically indicated.
8. Cardiac evaluation (stress thallium) for all patients (per current package insert for IL2). ECHO or MUGA for patients ≥ 60 years or patients who have a history of ischemic heart disease, chest pain, or clinical significant atrial and/or ventricular arrhythmias. Stress thallium must show normal LVEF and unimpaired wall movement.
9. Required for Screening, and at Baseline (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 -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.
10. Chem 20: [Sodium (Na), Potassium (K), Chloride (Cl), Total CO2 (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 Days -7 through Day -1 and Day +1 through Day +4.
11. Thyroid panel: TSH and Free T4. Obtain only at Screening, Day 14 and Month 24/End of Study (EOS) Visit, also at any visit as clinically indicated.
12. Complete blood count with differential
13. Dipstick urinalysis with culture, if indicated
14. Calculate creatinine clearance using Cockcroft-Gault calculation
15. Serum pregnancy test for women of childbearing potential
16. HLA typing to be sent to central laboratory
17. Pulmonary evaluation for all patients
18. Patients with documented Grades 2 or greater diarrhea or colitis as a result of previous treatment with immune checkpoint inhibitor antibodies 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 nonmyeloablative lymphodepletion.

19. For detailed instructions on processing and shipment of tumor tissue to the Manufacturing Facility and Central Lab refer to protocol Section 6.2.1: Tumor Harvest and Processing Procedures, and the separate Tumor Procurement & Shipping Manuals.
20. The 'Authorization to Initiate 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 ot the site prior to the initiation of the lymphodepletion preconditioning regimen.
21. 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.
22. Initiate adjuvant IL-2 dosing no sooner than 3 hours, but no later than 24 hours after completion of the LN-144infusion and continue every 8 hours for up to protocol-defined maximum of 6 doses of adjuvant 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.
23. Continue until ANC >1000/mm^3 X 3 consecutive days or per standard of care at the institution.
24. The TMP/SMX DS schedule should be adjusted to 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
25. Continue until ANC >1000/mm^3 or per standard of care at the institution
26. In patients positive for HSV continue until ALC >1000/mm^3 or per standard of care at the institution
27. Refer to the Laboratory Manual, for vacutainer tubes for peripheral blood drawnsto be sent to central laboratory. There is a ± 2-days 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.
28. Local tumor assessment (per RECIST 1.1)[2] should be used for clinical treatment decisions, and may include photographic/caliper measurement of superficial dermal and subcutaneous lesion.
29. Overall Survival (OS) Follow-Up will commence when each patient has their Month 24 or EOS visit and will consist of telephone contact made quarterly with the patient or designee up until 3 years following when Last Patient Last Dose (LPLD) of IL-2 is met.

APPENDIX 2: SCHEDULE OF EVENTS – FOR COHORT 3 PATIENTS

Assessment	Screening & Enrollment Procedures			Treatment												Follow-up										OS follo w-up
	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 d)	Day 28 (+/- 3 d)	Day 42 (+/-3d)	Day 84 (+/- 3d) / Week 12	Day 126 (+/- 3d) / Week 18	Month 6 (+/- 1 wk)	Month 9 (+/- 1 wk)	Month 12 (+/- 1 wk)	Month 18 (+/- 3 wks)	Month 24 (+/- 3 wks / or End of Study (EOS)	Every 3 months / Month 27 to Month 60 (+/- 3 wks)
Inclusion/Exclusion	X		X[1]																							
Physical Exam[2]	X		X	X						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	X	X	X	X	X	
Concomitant Meds	X	X[3]	X	X	X	X	X	X	X	X	X	X	X	X	X			X	X	X	X	X	X	X	X	
Weight	X		X	X						X	X	X			X	X	X	X	X	X	X	X	X	X	X	
Vital Signs[4]	X		X	X	X	X	X	X	X	X	X	X	X	X	X			X	X	X	X	X	X	X	X	
CMV Serology[5]	X											X[5]														
Syphilis Screening[6]	X											X[6]														
EKG[7]	X		X																							
CT Chest, Abdomen, Pelvis[8]	X		X															X	X	X	X	X	X	X	X	
MRI – Brain[8]	X		X															X	X	X	X	X	X	X	X	
Serum Chemistry[9]	X		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	
Thyroid Panel[10]	X															X									X	
Hematology[11]	X		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	
Urinalysis[12]	X		X	X	X	X	X	X	X	X	X	X	X	X	X											
Calculated Creatinine Clearance[13]	X																		X							
ß-HCG Pregnancy Test[14]	X		X																							

Assessment	Screening & Enrollment Procedures			Treatment												Follow-up										OS follow-up
	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 d)	Day 28 (+/- 3 d)	Day 42 (+/-3d)	Day 84 (+/- 3d) / Week 12	Day 126 (+/- 3d) / Week 18	Month 6 (+/- 1 wk)	Month 9 (+/- 1 wk)	Month 12 (+/- 1 wk)	Month 18 (+/- 3 wks)	Month 24 (+/- 3 wks / or End of Study (EOS)	Every 3 months / Month 27 to Month 60 (+/- 3 wks)
ECOG performance status	X		X	X												X			X	X	X	X	X	X	X	
Anti-HCV	X																									
HSV serology	X																									
EBV serology	X																									
Tumor Harvest		X																								
Ondansetron				X	X																					
Authorization to Initiate Lymphodepletion[15]				X																						
Cyclophosphamide 60 mg/kg				X	X																					
Mesna				X	X																					
Fludarabine 25 mg/m^2/day						X	X	X	X	X																
LN-144 Infusion[16]											X															
IL-2 600,000 IU/kg[17]												X	X	X	X											
Filgrastim[18]												X	X	X	X	X	X	X	X	X	X					
TMP/SMX DS, or appropriate Abx[19]				X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X					
Fluconazole[20]												X	X	X	X	X	X	X	X	X	X					
Valacyclovir/Acyclovir[21]												X	X	X	X	X	X	X	X	X	X					
Immune Monitoring[22]		X		X								X			X	X		X	X		X	X	X			

Assessment	Screening & Enrollment Procedures			Treatment											Follow-up										OS follow-up
	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 d)	Day 28 (+/-3 d)	Day 42 (+/-3d)	Day 84 (+/- 3d) / Week 12	Day 126 (+/- 3d) / Week 18	Month 6 (+/- 1 wk)	Month 9 (+/- 1 wk)	Month 12 (+/- 1 wk)	Month 18 (+/- 3 wks)	Month 24 (+/- 3 wks / or End of Study (EOS)	Every 3 months / Month 27 to Month 60 (+/- 3 wks)
Tumor Assessment (Local)[23]	X		X															X	X	X	X	X	X	X	X	
Assessment of AE/SAEs	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	
EORTC QLQ-C30 HRQoL			X																X		X		X		X	
Overall Survival (OS) Follow-up Telephone contact[24] (q 3-months ± 3 weeks)																										X

1. Re-check of Inclusion/Exclusion Criteria in order to ensure that patient performance status and main eligibility criteria have not changed from time of Screening, a re-confirmation is to be perform and approved by Sponsor or designee.
2. Physical examination (PE) will include gastrointestinal (abdomen, liver), cardiovascular, extremities, head, eyes, ears, nose, and throat, respiratory system, skin, psychiatric (mental status), general nutrition.
3. List only medications that are NOT part of the tumor harvest procedure.
4. 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.
5. CMV serology (as per local standard) at Screening, within 3 days of LN-144 infusion and thereafter as clinically indicated.
6. Syphilis screening (as per local standard; e.g., Rapid Plasma Reagin [RPR] venereal disease research laboratory [VDRL] or other) at Screening, and thereafter as clinically indicated.
7. If the test was done within 2 weeks prior to screening, there is no need to repeat it.
8. All appropriate scans should be repeted before enrollment in Cohort 3 if the latest scans are done ≥ 4 weeks prior to enrollment. If scans the latest scans were done within 4 weeks prior to enrollment they can be utilized for screening purpose. Required for Screening, and at Baseline (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 -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.
9. Chem 20: [Sodium (Na), Potassium (K), Chloride (Cl), Total CO2 (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 Days -7 through Day -1 and Day +1 through Day +4
10. Thyroid panel: TSH and Free T4. Obtain only at Screening, Day 14 and Month 24/End of Study (EOS) Visit, also at any visit as clinically indicated.
11. Complete blood count with differential
12. Dipstick urinalysis with culture, if indicated
13. Calculate creatinine clearance using Cockcroft-Gault calculation
14. Serum pregnancy test for women of childbearing potential
15. The ‘Authorization to Initiate 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 ot the site prior to the initiation of the lymphodepletion preconditioning regimen.
16. 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.
17. Initiate adjuvant IL-2 dosing no sooner than 3 hours, but no later than 24 hours after completion of the LN-144infusion and continue every 8 hours for up to protocol-defined maximum of 6 doses of adjuvant 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.
18. Continue until ANC >1000/mm^3 X 3 consecutive days or per standard of care at the institution.

19. The TMP/SMX DS schedule should be adjusted to 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
20. Continue until ANC >1000/mm^3 or per standard of care at the institution
21. In patients positive for HSV continue until ALC >1000/mm^3 or per standard of care at the institution
22. Refer to the Laboratory Manual, for vacutainer tubes for peripheral blood drawnsto be sent to central laboratory. There is a ± 2-days 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.
23. Local tumor assessment (per RECIST 1.1)[2] should be used for clinical treatment decisions, and may include photographic/caliper measurement of superficial dermal and subcutaneous lesion.
24. Overall Survival (OS) Follow-Up will commence when each patient has their Month 24 or EOS visit and will consist of telephone contact made quarterly with the patient or designee up until 3 years following when Last Patient Last Dose (LPLD) of IL-2 is met.

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 (e.g., light housework, office work).
2	In bed <50% of the time. Ambulatory and capable of all self-care, but unable to carry out any work activities. Up and about more than 50% of waking hours.
3	In bed >50% of the time. Capable of only limited self-care, confined to bed or chair more than 50% of waking hours.
4	100% bedridden. Completely disabled. Cannot carry on any self-care. Totally confined to bed or chair.
5	Dead.

Adapted from Oken MM, Creech RH, Tormey DC, et al. Toxicity and Response Criteria Of The Eastern Cooperative Oncology Group. Am J Clin Oncol. 1982;5:649-655.

APPENDIX 4: PRACTICAL WEIGHT

Modification of Dose Calculations* in Patients whose BMI is > 35

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 TOXICITIES

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 – June 2007

APPENDIX 6: EXPECTED IL-2 TOXICITIES AND THEIR MANAGEMENT

Expected toxicity	Expected grade	Supportive Measures suggested	Stop Cycle*	Stop Treatment **
Chills	3	IV Meperidine 25-50 mg, IV q1h, prn,	No	No
Fever	3	Acetaminophen 650 mg, po, q4h; Indomethacin 50-75 mg, po, q8h	No	No
Pruritus	3	Hydroxyzine HCl 10-20 mg po q6h, prn; Diphenhydramine HCl 25-50 mg, po, q4h, prn	No	No
Nausea/ Vomiting/ Anorexia	3	Ondansetron 10 mg, IV, q8h, prn; Granisetron 0.01 mg/kg IV daily prn; Droperidol 1 mg, IV q4-6h, prn; Prochlorperazine 25 mg q4h p.r., prn or 10 mg IV q6h prn	No	No
Diarrhea	3	Loperamide 2mg, po, q3h, prn; Diphenoxylate HCl 2.5 mg and atropine sulfate 25 µg, po, q3h, prn; codeine sulfate 30-60 mg, po, q4h, prn	If uncontrolled after 24 hours despite all supportive measures	No
Malaise	3 or 4	Bedrest interspersed with activity	If other toxicities occur simultaneously	No
Hyperbilirubinemia	3 or 4	Observation	If other toxicities occur simultaneously	No
Anemia	3 or 4	Transfusion with PRBCs	If uncontrolled despite all supportive measures	No
Thrombocytopenia	3 or 4	Transfusion with platelets	If uncontrolled despite all supportive measures	No

Expected toxicity	Expected grade	Supportive Measures suggested	Stop Cycle*	Stop Treatment **
Edema/Weight gain	3	Diuretics prn	No	No
Hypotension	3	Fluid resuscitation Vasopressor support	If uncontrolled despite all supportive measures	No
Dyspnea	3 or 4	Oxygen or ventilatory support	If requires ventilatory support	No
Oliguria	3 or 4	Fluid boluses or dopamine at renal doses	If uncontrolled despite all supportive measures	No
Increased creatinine	3 or 4	Observation	Yes (Grade 4)	No
Renal failure	3 or 4	Dialysis	Yes	Yes
Pleural effusion	3	Thoracentesis	If uncontrolled despite all supportive measures	No
Bowel perforation	3	Surgical intervention	Yes	Yes
Confusion	3	Observation	Yes	No
Somnolence	3 or 4	Intubation for airway protection	Yes	Yes
Arrhythmia	3	Correction of fluid and electrolyte imbalances; chemical conversion or electrical conversion therapy	If uncontrolled despite all supportive measures	No
Elevated Troponin levels	3 or 4	Observation	Yes	If changes in LV function have not improved to baseline by next dose
Myocardial Infarction	4	Supportive care	Yes	Yes

Expected toxicity	**Expected grade**	**Supportive Measures suggested**	**Stop Cycle***	**Stop Treatment ****
Elevated transaminases	3 or 4	Observation	For Grade 4 without liver metastases	If changes have not improved to baseline by next dose
Electrolyte imbalances	3 or 4	Electrolyte replacement	If uncontrolled despite all supportive measures	No
Neutropenia	4	Observation	No	No

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

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

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

APPENDIX 9: FLUDARABINE PACKAGE INSERT

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

APPENDIX 10: IL-2 (ALDESLEUKIN) PACKAGE INSERT

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

APPENDIX 11: 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 12: SUMMARY OF CHANGES (MAJOR/MINOR) IN PROTOCOL C-144-01 VERSION 6.0 (DATED, 13 MAY 2017)

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
- Updating of key Sponsor and designee contact information

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 5.0 to Version 6.0, and includes rationale for the changes.