IOVANCE BIOTHERAPEUTICS

ADVANCING IMMUNO-ONCOLOGY

CLINICAL PROTOCOL

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

PROTOCOL NUMBER:	C-144-01
SPONSOR:	Iovance Biotherapeutics Inc. 999 Skyway Rd, Suite 150 San Carlos, CA 94070 United States
PROTOCOL VERSION:	Version 9.0
PROTOCOL DATE:	22 Oct 2019
EudraCT NUMBER:	2017-000760-15
MEDICAL MONITOR	PPD PPD

SPONSOR PROTOCOL SIGNATURE PAGE

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

PPD

PPD

Date

INVESTIGATOR PROTOCOL SIGNATURE PAGE

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I agree to conduct the study as detailed in the protocol and in compliance with International Conference on Harmonisation (ICH) Guidelines for Good Clinical Practice (GCP). 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 receive the appropriate information throughout the study.

_____
Investigator Printed Name

_____ _____
Investigator Signature Date

SPONSOR MEDICAL MONITOR/EMERGENCY CONTACT INFORMATION

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RATIONALE FOR PROTOCOL AMENDMENT

The purpose of this amendment of Protocol C-144-01 from Version 8.0 to 9.0 is to incorporate nonsubstantial changes communicated via Version 8.0, Addendum 1 and other changes as specified below. In addition, the amendment incorporates administrative changes, including correction of inconsistent language and typographical errors.

Main changes include:

- Incorporation of the product release specification for total viable cells and clarification that patients will receive the full dose of product manufactured and released (Protocol Version 8.0, Addendum 1)
- Addition of the Independent Data Monitoring Committee (IDMC) (Protocol Version 8.0, Addendum 1)
- Clarification of the Data Safety Monitoring Board (DSMB) responsibility for Cohort 3 (Protocol Version 8.0, Addendum 1)
- Clarification on the interim analysis (Protocol Version 8.0, Addendum 1)
- Changes/clarification of study procedures, including hospitalization requirement, acceptable laboratory tests for viral infection and coagulation, and dosing calculation of chemotherapy using body weight
- Change of baseline brain MRI window from 3 weeks to 4 weeks prior to Day 0, to minimize unnecessary scan if not clinically indicated

See below for a comprehensive list of all changes with rationale.

Changes	Rationale
Change in the primary Medical Monitor	Administrative change
Section 2.1 (and others) Description of the Study Change Blinded Independent Review Committee (BIRC) to Independent Review Committee (IRC)	Administrative change to the committee name to reflect the open-label nature of the study; the composition and the responsibilities of the committee are unchanged.
Section 4.1 Inclusion Criteria k. Patients with immunotherapy-related endocrinopathies stable for at least 6 weeks (eg, hypothyroidism, ~~adrenal insufficiency, and hypophysitis stable on hormonal substitution~~), and controlled with hormonal replacement (non-**cortico**steroids), are allowed	To maintain consistency with exclusion criteria ‘f’ and Section 6.2.1. Prohibited Treatment (and others). No systemic corticosteroids are allowed even for hormonal replacement at physiological dose levels from 21 days prior to lymphodepletion to 60 days post-TIL infusion.

Changes	Rationale
Section 4.2 (and others) Exclusion Criteria Addition of anti-HBc antibody as part of the serology test to exclude HBV infection.	Add anti-HBc to the serology panel as part of the US and EU regulatory requirements for autologous donor sample handling
Section 4.2 (and others) Exclusion Criteria Exclude acute infection per protocol for CMV, EBV, and HSV Clarify that IgM tests required for determining presence/absence of active infection and PCR is an acceptable method if IgM is tested positive or when IgM tests are not available at the site	To specify that IgM will be required serology test to exclude acute viral infection and to allow PCR assay as part of evaluation for any acute/active viral infections, per institutional standards
Section 5.1 (and others) Screening Evaluation and measurement of skin and palpable lesions may be performed (if applicable). ~~but will not be sent for central review~~	Administrative change to maintain consistency across protocol
Section 5.1 (and others) Screening Remove reticulocyte count from the test panel.	This test does not provide information that adds to results from the tests already included in the CBC panel.
Section 5.1 Screening and Appendix 3 Assessments Coagulation tests clarified that either aPTT + INR **or** PT + INR	Clarification of the requirement of a coagulation panel
Section 5.1 Screening and Appendix 3 ~~Creatinine~~ Creatine kinase	Correct spelling
Section 5.1 (and others) Screening ~~Magnetic resonance imaging (MRI) or positron emission tomography (PET) scans will be allowed in lieu of CT scans for patients who have an intolerability to contrast media; the same imaging modality must be used throughout the duration of the study.~~ High-resolution CT with PO/IV contrast or contrast-enhanced MRI is the preferred imaging modality for assessing radiographic tumor response. If a patient has a known allergy to CT contrast material, please use the alternate modality. In cases where contrast is strictly contraindicated, a non-contrast scan is acceptable. The same imaging modality must be used throughout the duration of the study.	PET is not an allowable modality for RECIST assessment. PET alone is not sufficient for tumor assessment.
Section 5.2.1 Tumor Harvest and Processing Procedures Tumor specimens must undergo intraoperative frozen section (or FNA) **or touch prep cytology** examination by a pathologist to ensure that viable tumor is present.	To add additional text to verify presence of tumor during harvest. Adding additional text to ensure that tumor should still be shipped for manufacturing despite a

Changes	Rationale
Intraoperative frozen section (or FNA) or touch prep cytology examination is not a gold standard. If any of the above-mentioned methods is found to contain no viable tumor, the expert opinion of the pathologist and surgeon at the time of surgery will supersede, and if they believe there is viable tumor, the resected sample should still be sent for manufacturing.	negative finding of viable tumor cells.
Section 5.3 (and others) Baseline (Day -21 to Day -10) Procedures If a brain MRI was performed within ~~3~~ **4** weeks prior to Day 0 and considered normal or stable, and the patient is not showing any clinical symptoms of progression in the brain, then a brain MRI does not need to be repeated.	Expand the window for the baseline brain MRI listed in protocol Version 8 to reduce the unnecessary scan if not clinically indicated
Section 5.4 Patients Who Do Not Receive an LN-144 Infusion Procedure Added language: Patients who meet inclusion and exclusion criteria and do not receive LN-144 (eg, due to a manufacturing failure) may be rescreened after consultation with the Medical Monitor.	To allow for rescreening the case of a manufacturing failure
Section 5.5.1 (and others) Day -7 Procedures Cyclophosphamide and mesna dosing clarified to be consistent with prior protocol versions.	To provide additional details and clarifications of mesna dosing
Section 5.5.1 (and others) Day -7 Procedures Allow the use of body weight within 7 days of the start of chemotherapy to calculate the doses, per institutional standards.	To allow sites to follow institutional standards for body weight measurement
Section 5.5.3 Day -5 to Day -1 Procedures Fludarabine (25 mg/m^2) to be given IV over approximately 30 minutes, once daily. ~~each day. and may be stopped after two doses if absolute lymphocyte count (ALC) < 100/mm^3~~	This is to clarify that the full course of fludarabine (5 doses) should be given to ensure a thorough lymphodepletion. Dose hold or discontinuation will only be allowed in the case of toxicity described in the package insert or per institutional guidance
Section 5.5.4.2 (and others) LN-144 Infusion Add the product release specification of total number of viable cells between 1 x 10^9 and 150 x 10^9 per lot of LN-144 product and clarify that patients will receive the full dose of product manufactured and released.	Incorporate the changes listed in protocol Version 8.0, Addendum 1 to this protocol amendment
Section 5.5.4.2.1 (and others) IL-2 Dosing and Dose Adjustments Allow the use of body weight within 7 days of the start of IL-2 to calculate the dose, per institutional standards	To allow sites to follow institutional standards for body weight measurement

Changes	Rationale
Section 5.5.5 Day 1, Day 2, Day 3, and Day 4 Procedures Filgrastim (5 µg/kg/day) or biosimilar will be administered beginning on Day 1 by subcutaneous injection and continue each day until the ANC reaches > 1000/mm^3 for three consecutive days, discontinue if ANC rises to > 10,000/mm^3, or follow institutional standards.	To provide additional clarification on stopping rule per package insert and institutional standard.
Section 5.8 (and others) Hospitalization Protocol-mandated hospitalization was clarified.	Iovance does not require hospitalization during NMA-LD and defers to institutional guidelines.
Section 7.4.3 Fungal Prophylaxis (Fluconazole) Patients will start fluconazole 400 mg PO or IV daily on Day 1 and continue until the ~~ALC~~ ANC is > 1000/mm^3, or as per institutional standards. If ~~ALC~~ ANC count remains < 1000/mm^3 at 6 months post-chemotherapy, prophylaxis will continue until the CD4 count is > 200/mm^3 for at least 6 months, or as per institutional standards.	To correct a typographical error
Section 10.1 Tumor Response Assessments Added language: Photographic documentation and caliper measurement will be performed for superficial dermal and subcutaneous lesions that cannot be assessed by radiographic scan.	To clarify documentation and measurement of tumors.
Section 10.1 Tumor Response Assessments High-resolution CT with PO/IV contrast or contrast-enhanced MRI is the preferred imaging modality for assessing radiographic tumor response. If a patient has a known allergy to CT contrast material, please use the alternate modality. In cases where contrast is strictly contraindicated, a non-contrast scan will suffice.	To update the preferred imaging modality to comply with RECIST and to consider contraindication contrast scans.
Section 11.3.1 Primary Endpoint Patients without any baseline or post-baseline tumor measurements are considered non-evaluable.	To clarify the analysis population
Section 11.3.2 Secondary Endpoints For patients who received new anticancer therapies, the DOR will be censored at the date of last tumor response assessment prior to the start of new anticancer therapies.	For clinical information and clarification on DOR calculation.
Section 11.5 ~~Interim~~ **Final** Analysis All references to an interim analysis of data for Cohort 4 were deleted.	Incorporate the changes listed in protocol Version 8.0, Addendum 1 to this protocol amendment

Changes	Rationale
Section 12.3 Data Safety Monitoring Board Clarify DSMB responsibility to only review data for Cohort 3 (Re-treatment Cohort) when 3 patients have been enrolled into Cohort 3, have received their second LN-144 infusion, and 28 days have elapsed (end-of-treatment visit and safety assessments).	Incorporate the changes listed in protocol Version 8.0, Addendum 1 to this protocol amendment
Section 13 Independent Data Monitoring Committee Add the IDMC to the protocol to ensure highest quality, scientific, and ethical standards, and consistency of study conduct as well as data collection and analysis across international study sites.	Incorporate the changes listed in protocol Version 8.0, Addendum 1 to this protocol amendment
Section 14.1 Institutional Review Board/Independent Ethics Committee (IRB/IEC) The Sponsor's Statement of Investigator Commitments was added to the forms that could be signed to assure that all aspects of institutional review will be conducted in accordance with applicable regulations.	Form 1572 (FDA Statement of Investigator) is not completed by all sites but an equivalent form is completed.
Section 15.7 Publications The Sponsor will be responsible for determining when the study results should be published **after discussion with the Steering Committee.**	The Sponsor will discuss with the Steering Committee to determine when study results will be published.
Appendix 1 Schedule of Assessments (SOA) Changes made throughout the protocol were carried through to the SOA.	To align the body of the protocol with the SOA
Appendix 3 Assessments Allow the sites to calculate BSA and BMI using formulas per site standard practice.	To allow sites to follow institutional standards for body weight measurement

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:	Patients with unresectable or metastatic melanoma who have previously been treated with at least one systemic therapy including a PD-1 blocking antibody and if BRAF V600 mutation positive, a BRAF inhibitor or BRAF inhibitor with MEK inhibitor.
Investigational Agent:	LN-144: Autologous tumor infiltrating lymphocytes (TIL) derived from the patient's tumor.
Study Objectives:	**Primary Objective** • Evaluate the efficacy of LN-144 in patients with unresectable or metastatic melanoma using the objective response rate (ORR), as assessed by the Independent Review Committee (IRC) per Response Evaluation Criteria in Solid Tumors (RECIST) version 1.1 **Secondary Objectives** • Evaluate the efficacy endpoints of duration of response (DOR), disease control rate (DCR), and progression-free survival (PFS), as assessed by the IRC per RECIST v1.1 • Further evaluate efficacy of LN-144 in patients with unresectable or metastatic melanoma by assessing ORR, DOR, DCR, and PFS, as assessed by the Investigator per RECIST v1.1 • Evaluate overall survival (OS) • Characterize the safety profile of LN-144 in patients with unresectable or metastatic melanoma **Exploratory Objectives** • Explore the persistence of LN-144 and potential immune correlates of response, outcome, and toxicity of the treatment • Explore efficacy based on immune-related RECIST (irRECIST) criteria, as assessed by the Investigator • Assess health-related quality of life (HRQoL)
Study Design:	Prospective, interventional multicenter study evaluating adoptive cell therapy (ACT) via infusion of LN-144 (autologous TIL) followed by interleukin-2 (IL-2) after a nonmyeloablative lymphodepletion (NMA-LD) preconditioning regimen.
Dose and Treatment Schedule:	The cell transfer therapy used in this study involves patients receiving an NMA-LD preconditioning regimen, consisting of daily intravenous (IV) cyclophosphamide (60 mg/kg; IV × 2 doses) followed by daily fludarabine (25 mg/m^2; IV × 5 doses). Infusion of LN-144 is given on Day 0 and is followed by administration of IL-2 at 600,000 international units (IU)/kg approximately every 8–12 hours for up to a maximum of six doses, starting approximately 3–24 hours after completion of LN-144 infusion.
Duration of Study Participation and Study Periods:	Overall duration of the study will be approximately 5 years comprising the following periods: **Screening:** Up to 28 days from signing of the informed consent form (ICF).

	Enrollment: Upon tumor resection for TIL generation. **Treatment Period**: NMA-LD preconditioning regimen (up to 7 days), LN-144 infusion (1 day), IL-2 administration (up to 4 days), continuing to Day 28. Patients will need to return for safety assessment visits on Day 14 and Day 28 (Day 28 corresponds with the End of Treatment [EOT] visit). **Assessment Period:** Following the EOT visit, efficacy (eg, tumor response) assessments will be performed at Week 6 (Day 42) post-LN-144 infusion and then occur every 6 weeks until Month 6 (Week 24). Patients will continue to be evaluated for response every 3 months (12 weeks) for up to 5 years from Day 0 (LN-144 infusion) or until: • Disease progression • Start of a new anticancer therapy At that time, the End of Assessment (EOA) visit will be completed. **Overall Survival Follow-up Period:** Begins after completion of the last study assessment (eg, EOA) and will continue for up to 5 years from Enrollment (tumor resection) or until discontinuation from the study; with telephone contact every 3 months to obtain survival status and subsequent anticancer therapy information. Patients who had tumor resection but did not receive LN-144 for any reason will perform an EOA visit and transition directly into the OS Follow-up Period.
Number of Study Centers:	Approximately 60 enrolling clinical sites in North America and Europe.
Number of Planned Patients:	The total number of planned patients to be infused in this study will be approximately 164. Cohort 1: Infused 23 patients and is now closed. Cohort 2: Will infuse approximately 66 patients and is now closed to Screening. Cohort 3: Will include approximately 10 patients who have been previously treated in Cohort 1, Cohort 2 or Cohort 4 of this study, for a second administration of the cryopreserved TIL product. Cohort 4: Approximately 75 patients are planned to be infused.
Study Population: Diagnosis and Main Criteria for Inclusion:	Patients must meet *all* of the following inclusion criteria to be eligible for participation in the study: a. Patients with unresectable or metastatic melanoma (Stage IIIc or Stage IV) b. Patients must have progressed following ≥ 1 prior systemic therapy including a programmed cell death protein-1 (PD-1) blocking antibody; and if proto-oncogene B-Raf (BRAF) V600 mutation-positive, a BRAF inhibitor or BRAF inhibitor in combination with mitogen-activated extracellular signal-regulated kinase (MEK) inhibitor c. Prior to study Enrollment, documentation of radiological disease progression after the most recent therapy d. At least one measurable target lesion, as defined by RECIST v1.1 • Lesions in previously irradiated areas (or other local therapy) should not be selected as target lesions, unless treatment was ≥ 3 months prior to Screening, and there has been demonstrated disease progression in that particular lesion • If a lesion is partially resected to generate TIL, and remains visible on the Baseline scan after surgery, then the partially

	resected lesion can be used for RECIST v1.1 response assessment, but only as a non-target lesion e. At least one resectable lesion (or aggregate of lesions resected) of a minimum 1.5 cm in diameter post-resection to generate TIL; surgical removal with minimal morbidity (defined as any procedure for which expected hospitalization is ≤ 3 days) f. Patients must be ≥ 18 years of age at the time of consent. Enrollment of patients > 70 years of age may be allowed after consultation with the Medical Monitor g. Patients must have an Eastern Cooperative Oncology Group (ECOG) performance status of 0 or 1 and an estimated life expectancy of ≥ 3 months h. In the opinion of the Investigator, patients must be able to complete all study-required procedures i. Patients must have the following hematologic parameters: • Absolute neutrophil count (ANC) ≥ 1000/mm^3 • Hemoglobin (Hb) ≥ 9.0 g/dL • Platelet ≥ 100,000/mm^3 Note: Transfusions or growth factors are not allowed 28 days prior to signing the ICF and continuing through the Screening Period j. Patients must have adequate organ function: • Serum alanine transaminase (ALT)/serum glutamic-pyruvic transaminase (SGPT) and aspartate transaminase (AST)/serum glutamic-oxaloacetic transaminase (SGOT) ≤ 3 times the upper limit of normal (ULN); patients with liver metastasis ≤ 5 times ULN • Estimated creatinine clearance (eCrCl) ≥ 40 mL/min using the Cockcroft-Gault formula • Total bilirubin ≤ 2 mg/dL o Patients with Gilbert's syndrome must have a total bilirubin ≤ 3 mg/dL k. Patients must have recovered from all prior therapy-related adverse events (AEs) to ≤ Grade 1 (per Common Terminology Criteria for Adverse Events [CTCAE] v4.03), except for alopecia or vitiligo, prior to Enrollment (tumor resection) • Patients with documented ≥ Grade 2 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 tumor resection • Patients with immunotherapy-related endocrinopathies stable for at least 6 weeks (eg, hypothyroidism), and controlled with hormonal replacement (non-corticosteroids), are allowed l. Patients must have a washout period ≥ 28 days from prior anticancer therapy(ies) to the start of the planned NMA-LD preconditioning regimen: • Targeted therapy: MEK/BRAF or other targeted agent • Chemotherapy

	• Immunotherapy: anti-cytotoxic T lymphocyte-associated antigen 4 (CTLA-4)/anti-PD-1, other monoclonal antibody (mAb), or vaccine • Palliative radiation therapy is permitted so long as it does not involve lesions being selected for TIL, or as target or non-target lesions. Washout is not required if all related toxicities have resolved to ≤ Grade 1 as per CTCAE v4.03 m. Patients of childbearing potential or their partners of childbearing potential must be willing to take the appropriate precaution to avoid pregnancy or fathering a child for the duration of the study and practice an approved, highly effective method of birth control during treatment and for 12 months after receiving the last protocol-related therapy • Approved methods of birth control are as follows: o Combined (estrogen and progesterone containing) hormonal birth control associated with inhibition of ovulation: oral, intravaginal, transdermal o Progesterone-only hormonal birth control associated with inhibition of ovulation: oral, injectable, implantable o Intrauterine device (IUD) o Intrauterine hormone-releasing system (IUS) o Bilateral tubal occlusion o Vasectomized partner o True sexual abstinence when this is in line with the preferred and usual lifestyle of the patient. Periodic abstinence (eg, calendar ovulation, symptothermal, post-ovulation methods) is not acceptable n. Patients (or legally authorized representative) must have the ability to understand the requirements of the study, have provided written informed consent as evidenced by signature on an 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, including the OS Follow-up Period o. Patients have provided written authorization for use and disclosure of protected health information
Main Criteria for Exclusion:	Patients who meet *any* of the following criteria are not eligible for participation in this study: a. Patients who have been shown to be BRAF mutation positive (V600), but have not received prior systemic therapy with a BRAF inhibitor alone or a BRAF inhibitor in combination with a MEK inhibitor b. Patients who have received an organ allograft or prior cell transfer therapy c. Patients with melanoma of uveal/ocular origin d. Patients who have a history of hypersensitivity to any component or excipient of LN-144 or other study drugs: • NMA-LD preconditioning regimen (cyclophosphamide, mesna, and fludarabine) • Antibiotics (ABX) of the aminoglycoside group (ie, streptomycin, gentamicin); except those who are skin-test negative for gentamicin hypersensitivity

	• Any component of the LN-144 infusion product formulation including dimethyl sulfoxide (DMSO), human serum albumin (HSA), IL-2, and dextran-40 e. Patients with symptomatic and/or untreated brain metastases (of any size and any number) • Patients with definitively treated brain metastases may be considered for Enrollment, and must be stable for ≥ 14 days prior to beginning the NMA-LD preconditioning regimen f. Patients who are on chronic systemic steroid therapy for any reason g. Patients who have active medical illness(es) that would pose increased risk for study participation, including: active systemic infections requiring systemic ABX, coagulation disorders, or other active major medical illnesses of the cardiovascular, respiratory, or immune system h. Patients who have ≥ Grade 2 hemorrhage within 14 days prior to Enrollment (tumor resection) i. Patients who are seropositive for any of the following: • Human immunodeficiency virus (HIV)-1 or HIV-2 antibodies • Hepatitis B antigen (HBsAg), hepatitis B core antibody (anti-HBc), or hepatitis C antibody (HCV Ab). Patients with acute or chronic hepatitis infections may be enrolled if the viral load by polymerase chain reaction (PCR) is undetectable with/without active treatment. • Syphilis (Rapid Plasma Reagin [RPR] test or venereal disease research laboratory [VDRL] test) • Cytomegalovirus (CMV) IgM antibody titer or PCR assay; and Epstein-Barr virus (EBV) IgM or PCR assay indicating active infection • Positive herpes simplex virus (HSV)-1 and HSV-2 IgM serology or PCR assay o Patients who are HSV immunoglobulin M (IgM) or PCR assay positive will need to receive appropriate treatment and become IgM or PCR assay negative prior to starting the NMA-LD preconditioning regimen j. Patients who have any form of primary immunodeficiency (such as severe combined immunodeficiency disease [SCID] and acquired immunodeficiency syndrome [AIDS]) k. Patients who have a left ventricular ejection fraction (LVEF) < 45% or New York Heart Association (NYHA) functional classification > Class 1 • Patients ≥ 60 years of age and who have a history of ischemic heart disease, chest pain, or clinically significant atrial and/or ventricular arrhythmias must have a cardiac stress test. Patients with any irreversible wall movement abnormalities are excluded l. Patients who have a documented forced expiratory volume in 1 second (FEV1) of ≤ 60% m. 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)

	n. Patients who have received a live or attenuated vaccine within 28 days of beginning the NMA-LD preconditioning regimen o. Patients who are pregnant or breastfeeding p. Patients whose cancer requires immediate attention or who would otherwise suffer a disadvantage by participating in this trial q. Patients protected by the following constraints: • Hospitalized persons without consent or persons deprived of liberty because of a judiciary or administrative decision • Adult persons with a legal protection measure or persons who cannot express their consent • Patients in emergency situations who cannot consent to participate in the trial
Treatment Cohorts:	LN-144 infusion is preceded by an NMA-LD preconditioning regimen of cyclophosphamide, and fludarabine, and followed by IL-2, as an open-label treatment **Cohort 1:** Patients received LN-144, non-cryopreserved TIL product • Note: Cohort 1 is closed to Enrollment **Cohort 2:** Patients to receive LN-144, cryopreserved TIL product • Note: Cohort 2 is closed to Screening **Cohort 3:** Patients from Cohort 1, Cohort 2, or Cohort 4, after having participated in the study and received LN-144, may rescreen for a second administration of LN-144, cryopreserved TIL product • Note: Patients in Cohort 3 must meet the inclusion and exclusion criteria (except exclusion criterion "b"). These patients may have a second tumor resection, if needed; especially when new lesions are available and feasible for resection. The decision for Enrollment into Cohort 3 will be based on discussion between the Investigator and the Medical Monitor **Cohort 4:** Patients to receive LN-144, cryopreserved TIL product • Note: Cohort 4 is open to enroll new patients
Criteria for Discontinuation from Treatment:	• Withdrawal of consent to treatment o Every effort should be made to continue OS Follow-up, when applicable • Grade ≥ 3 drug-related immune AEs that involve vital organs (heart, kidneys, brain, eye, liver, colon, adrenal gland, lungs) with symptoms emerging following LN-144 infusion • Grade ≥ 3 allergic reaction including bronchospasm or generalized urticaria that does not resolve after medical management in the opinion of the Investigator • Meeting criteria for permanent discontinuation of IL-2 treatment (must have received at least one dose of IL-2; Appendix 5) • Determination by the Investigator that continued treatment is not in the best interest of the patient • Administration of prohibited concomitant medications/start of new anti-cancer therapy • Death

Criteria for Discontinuation from the Study:	• Withdrawal of consent • Lost to follow-up • Death • Study terminated by the Sponsor
Efficacy Assessment:	Calculated from Day 0 (LN-144 infusion). The statistical analysis of the ORR, DOR, DCR, and PFS per cohort will be provided to determine the potential efficacy of LN-144, as assessed by the IRC per RECIST v1.1. Estimation of OS will depend on the date of death or the last known alive status.
Safety Assessment:	At each scheduled visit to the clinical site, AEs/serious adverse events (SAEs) will be collected and graded as per CTCAE v4.03, starting from signing the ICF until the end of the study. Analyses will include all study periods.
Overview of Statistical Plan	The statistical analysis is based on the estimation of efficacy and safety parameters and will be performed by cohort. There is no planned statistical comparison among cohorts. Patients who are retreated with LN-144 (Cohort 3) will have their safety and efficacy data tabulated separately. Patients meeting RECIST v1.1 criteria for a confirmed complete response (CR) or partial response (PR) as assessed by the IRC will be classified as responders in the analysis of the primary endpoint ORR. The ORR will be analyzed using a point estimate and its two-sided confidence limits based on the Clopper-Pearson exact method at an overall alpha level of 0.05. All other binary endpoints will be analyzed similarly as the primary endpoint. 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 received LN-144 infusion. The assessment of safety data will be descriptive and based on: 1) the summarization of treatment-emergent adverse events (TEAEs), SAEs, AEs leading to discontinuation from treatment; and 2) the study vital signs and clinical laboratory tests.
Sample Size Consideration:	**Cohort 1 (closed to Enrollment):** Infused 23 patients using the non-cryopreserved autologous TIL product manufacturing process. **Cohort 2 (closed to Screening):** The planned number of patients to be infused with cryopreserved LN-144 is approximately 66. Sixty patients will allow estimation of ORR using the maximum half width of the two-sided 95% confidence limit of less than 13.2% (Clopper-Pearson) when ORR is expected to range from 20–50%. **Cohort 4**: Approximately 75 patients are planned to be infused based on the null hypothesis of 10% ORR, which is based on historical control. This sample size will result in over 90% power to demonstrate superiority to this historical ORR using a conservative assumption for TIL therapy of 25% and two-sided overall significance level of 0.05.
Data Safety Monitoring Board Safety Assessments:	An independent Data Safety Monitoring Board (DSMB) has evaluated cumulative safety data as specified in the DSMB charter for Cohort 1 and Cohort 2. A DSMB meeting will also take place after 3 patients have been treated in Cohort 3 and 28 days have elapsed.

Independent Data Monitoring Committee:	An Independent Data Monitoring Committee (IDMC) will be responsible for oversight of the C-144-01 study to ensure the study is being conducted with the highest quality, scientific, and ethical standard and to ensure quality and consistency of study conduct as well as data collection and analysis across international study sites. The IDMC will review the study data when a total of 30 patients have completed 28 days of assessments post-LN-144 infusion for Cohort 4. Enrollment will continue while data is under review. The IDMC will also review the study data after up to a total of 75 patients for Cohort 4 have completed 28 days of assessments post-LN-144 infusion.

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LIST OF ABBREVIATIONS

Term	Definition
ABX	antibiotics
ACT	adoptive cell therapy
AE	adverse event
AIDS	acquired immune deficiency syndrome
ALC	absolute lymphocyte count
ALT	alanine transaminase
ANC	absolute neutrophil count
aPTT	activated partial thromboplastin time
AST	aspartate transaminase
BMI	body mass index
BRAF	proto-oncogene B-Raf
BSA	body surface area
BUN	blood urea nitrogen
CBC	complete blood count
CD4	cluster of differentiation 4
CFR	Code of Federal Regulations
CI	confidence interval
CK	creatine kinase
CLS	capillary leak syndrome
CMO	contract manufacturing organization
CMV	cytomegalovirus
CO_2	carbon dioxide
CR	complete response
CRO	contract research organization
CT	computed tomography
CTCAE	Common Terminology Criteria for Adverse Events
CTLA-4	cytotoxic T lymphocyte-associated antigen-4
D5W	5% dextrose in water
DCR	disease control rate
DMSO	dimethyl sulfoxide
DNA	deoxyribonucleic acid
DOR	duration of response
DSMB	Data Safety Monitoring Board
DTIC	dacarbazine
EBV	Epstein-Barr virus
ECG	electrocardiogram

Term	Definition
ECHO	echocardiogram
ECOG	Eastern Cooperative Oncology Group
eCrCl	estimated creatinine clearance
eCRF	electronic case report form
EDC	electronic data capture
EEG	electroencephalogram
EMA	European Medicines Agency
EOA	End of Assessment
EORTC QLQ-C30	European Organisation for Research and Treatment of Cancer Quality-of-Life Questionnaire - Core 30 instrument
EOT	End of Treatment
EU	European Union
FAS	Full Analysis Set
FDA	Food and Drug Administration
FDG-PET	fluorodeoxyglucose-positron emission tomography
FEV1	forced expiratory volume in 1 second
FNA	fine-needle aspiration
GCP	Good Clinical Practice
GDPR	General Data Protection Regulation
GMP	Good Manufacturing Practices
Hb	hemoglobin
HBc	hepatitis B core
HBsAg	hepatitis B surface antigen
β-HCG	β-human chorionic gonadotropin
Hct	hematocrit
HCV Ab	hepatitis C antibody
HIPAA	Health Insurance Portability and Accountability Act
HIT	heparin-induced thrombocytopenia
HIV	human immunodeficiency virus
HLA	human leukocyte antigen
HRQoL	health-related quality of life
HSA	human serum albumin
HSV	herpes simplex virus
ICF	informed consent form
ICH	International Conference on Harmonisation
ICU	intensive care unit
IDMC	Independent Data Monitoring Committee
IEC	Independent Ethics Committee

Term	Definition
IgM	immunoglobulin M
IL-2	interleukin-2 (also known as “aldesleukin”)
INR	International Normalized Ratio
IRB	Institutional Review Board
IRC	Independent Review Committee
irRECIST	immune-related Response Evaluation Criteria in Solid Tumors
IU	international unit
IUD	intrauterine device
IUS	intrauterine hormone-releasing system
IV	intravenous
LDH	lactate dehydrogenase
LN-144	autologous tumor infiltrating lymphocytes
LVEF	left ventricular ejection fraction
mAb	monoclonal antibody
MCH	mean corpuscular hemoglobin
MCV	mean corpuscular volume
MEK	mitogen-activated extracellular signal-regulated kinase
MRI	magnetic resonance imaging
MUGA	multiple gated acquisition scan
NaCl	sodium chloride
NCCN	National Comprehensive Cancer Network
NCI	National Cancer Institute
NMA-LD	nonmyeloablative lymphodepletion
NYHA	New York Heart Association
OKT3	muromonab CD3, murine monoclonal antibody to human CD3
OR	objective response
ORR	objective response rate
OS	overall survival
PBMC	peripheral blood mononuclear cell
PCR	polymerase chain reaction
PD	progressive disease
PD-1	programmed cell death protein-1
PD-L1	programmed death-ligand 1
PET	positron emission tomography
PFS	progression-free survival
PFT	pulmonary function test
PHI	personal health information

Term	Definition
PO	per os (by mouth)
PR	partial response
PRBC	packed red blood cells
PT	prothrombin time
RBC	red blood cells
RECIST v1.1	Response Evaluation Criteria in Solid Tumors version 1.1
REP	rapid expansion protocol
RNA	ribonucleic acid
RPR	Rapid Plasma Reagin
RSI	reference safety information
SAE	serious adverse event
SAP	Statistical Analysis Plan
SCID	severe combined immunodeficiency disease
SD	stable disease
SGOT	serum glutamic-oxaloacetic transaminase
SGPT	serum glutamic-pyruvic transaminase
SoD	sum of diameters
SOP	Standard Operating Procedure
SmPC	Summary of Product Characteristics
SUSAR	Suspected unexpected serious adverse reaction
TEAE	treatment-emergent adverse event
TH	tumor harvested
TIL	tumor infiltrating lymphocyte
TMP-SMX DS	trimethoprim-sulfamethoxazole double strength
TSH	thyroid-stimulating hormone
TVEC	talimogene laherparepvec
ULN	upper limit of normal
US	United States
USPI	United States package insert
UV	ultraviolet
VDRL	venereal disease research laboratory
WBC	white blood cells

1. INTRODUCTION

1.1. Disease Background

Melanoma is a potentially lethal cancer that is characterized by the uncontrolled growth of melanocytes, which are cells that protect against ultraviolet (UV) radiation through the production of the dark pigment melanin [Garbe 2016]. The incidence of melanoma, historically a rare cancer, has steadily increased in the last decade and is projected to continue increasing [Matthews 2017; Rutkowski 2017; Whiteman 2016]. The main known and modifiable risk factor for melanoma is cumulative UV radiation exposure, but despite local education campaigns regarding this risk, an estimated 91,270 Americans [Noone 2018] and more than 144,000 Europeans [Ferlay 2018] are diagnosed each year with melanoma; with about 10,000 and 20,000 dying each year, respectively. Melanoma is expected to be the fifth most frequently diagnosed cancer in the United States (US) in 2018, contributing 5.3% of all new cancers in 2018 [Noone 2018].

1.1.1. Main Features of the Disease

Approximately 90% of melanomas are diagnosed as primary tumors without any evidence of metastasis, and the 10-year survival rate for patients with such tumors is 75–85% [Garbe 2016]. While in situ and locally invasive melanomas are curable by surgery, metastatic disease is difficult to treat and remains a significant public health concern, as the cancer has already metastasized in approximately 4% of newly diagnosed cases of melanoma [Noone 2018]. Despite recent approvals of new medicines, the five-year survival rate for patients who cannot be cured with surgery remains unacceptably low. The five-year relative survival rate in the US for patients with metastatic melanoma is estimated to be 22.5% [Noone 2018]. A systematic literature review that included studies from several countries found that the reported five-year overall survival (OS) rate for metastatic (Stage IV) melanoma ranged from 9–28% [Svedman 2016]. Although immune checkpoint blockade and targeted therapies have become the standard of care for metastatic melanoma, 60–70% of patients either do not respond to, or relapse after, single-agent therapy, making this an unmet medical need. Furthermore, dual checkpoint inhibition with anti-cytotoxic T lymphocyte-associated antigen-4 (CTLA-4) and anti-programmed cell death protein-1 (PD-1) may be associated with prohibitive toxicity.

Ipilimumab was first approved in the US and European Union (EU) for the treatment of metastatic melanoma in 2011, and pembrolizumab and nivolumab were approved for the same indication in the US in 2014 and in the EU in 2015. Although there has been a broad and rapid uptake of these immunotherapeutic agents, metastatic melanoma remains a serious, life-threatening disease that is still inadequately addressed by available therapies, as indicated in the current five-year survival projections for patients with a diagnosis of metastatic melanoma.

1.1.2. Current Standard Therapy

Treatment planning for all unresectable, metastatic disease should be individualized to maximize therapeutic benefit while limiting toxicities [Kaufman 2018].

First-line therapy for metastatic disease includes anti-PD-1 monotherapy (nivolumab or pembrolizumab) or the combination of nivolumab (anti-PD-1) and ipilimumab (anti-CTLA-4), as well as therapies targeting driver mutations in the proto-oncogene B-Raf (BRAF) pathway for tumors with these mutations [Coit 2018; Dummer 2015]. In treatment-naïve melanoma (first-line use), the reported objective response rate (ORR) for single-agent pembrolizumab or nivolumab is about 34% with a complete response (CR) rate of 4–5%. Combination therapy with nivolumab and ipilimumab is associated with an ORR of 50% and CR rate of 8.9%. Thus, most melanoma patients either do not respond to, or progress while on the available first-line therapies.

Options for second-line therapy of metastatic melanoma, for the most part, duplicate the first-line therapies, along with the addition of cytotoxic chemotherapies and high-dose interleukin-2 (IL-2). However, response rates to pembrolizumab and nivolumab appear to be substantially reduced in patients whose disease has progressed following treatment with a PD-1 blocking antibody or BRAF inhibitor relative to responses achieved in treatment-naïve patients [Cowey 2018; Johnson 2017; Zimmer 2017]. In addition, use of checkpoint inhibitors is associated with a range of immune-related adverse events (AEs), including pneumonitis, colitis, hepatitis, nephritis, and renal dysfunction [Hofmann 2016]. In addition, treatment-related AEs leading to discontinuation of therapy occurred in 36.4%, 7.7%, and 14.8% of patients receiving ipilimumab/nivolumab combination therapy, nivolumab alone, or ipilimumab alone, respectively [Johnson 2016; Larkin 2015].

Moreover, agents used in second-line therapy should not be in the same class as those given in first-line therapy [Coit 2018]. Consequently, patients with disease progression after receiving an anti-PD-1 antibody and a targeted therapy, if indicated, have limited treatment options. These patients could receive high-dose IL-2 or cytotoxic agents as subsequent therapy, however the efficacy of these agents in such a late-line patient population is limited.

In summary, immune checkpoint blockade and targeted therapies constitute the standard of care for metastatic melanoma. However, following single-agent therapy, a majority of patients either do not respond to, or relapse with limited treatment options; highlighting these patients' unmet medical need. Furthermore, dual checkpoint inhibition with anti-PD-1 and anti-CTLA-4 can result in prohibitive toxicity, and no agents are approved for third line or greater use [Coit 2018; Dummer 2015]. Therefore, it is of major public health interest to develop additional therapeutic agents for patients with metastatic melanoma.

1.2. Clinical Experience with Autologous Tumor Infiltrating Lymphocyte Therapy of Melanoma

A substantial body of literature on tumor infiltrating lymphocytes (TIL) provides information that is relevant to the expected safety and efficacy profile of LN-144 in patients with metastatic melanoma. In particular, Professor Steven Rosenberg's research team at the US National Cancer Institute (NCI) National Institutes of Health has published extensively on preclinical and clinical research supporting the development of TIL-based therapies for cancer. Across clinical studies conducted by the NCI, immunotherapy with autologous TIL infusion in patients with advanced melanoma has induced objective responses (ORs) by Response Evaluation Criteria in Solid Tumors (RECIST) in 54% (54/101) of patients, including heavily pre-treated patients, with 24% (24/101) of patients achieving a CR. With a median follow-up of 40.9 months, only one of the 24 patients who achieved a CR had disease recurrence [Goff 2016; Rosenberg 2011].

Patients with metastatic melanoma have also been treated with autologous TIL therapy at the MD Anderson Cancer Center in Texas, US [Forget 2018; Radvanyi 2012]; the Moffitt Cancer Center in Florida, US [Pilon-Thomas 2012]; the Chaim Sheba Medical Center in Israel [Besser 2013]; and Herlev Hospital, in Copenhagen, Denmark [Andersen 2016]. Most protocols used a two-stage manufacturing process like that used in LN-144 production, and most trials also used a nonmyeloablative lymphodepletion (NMA-LD) preconditioning regimen prior to infusion of the *ex vivo* expanded TIL. Like the NCI, these institutions report objective tumor response rates averaging 40–50% in multiple phase 2 studies of TIL therapy in patients with treatment-refractory metastatic melanoma.

Recently, Forget et al. reported the results of a study investigating the impact of prior therapy with immune checkpoint inhibitors on the response to TIL therapy in patients with metastatic melanoma [Forget 2018]. The best ORR for the entire cohort was 42%; 47% in 43 checkpoint-blocker-naïve patients; 38% when patients were exposed to anti-CTLA-4 alone (21 patients); and 33% if also previously exposed to anti-PD-1 (nine patients) prior to TIL therapy. There were eight CRs in the study, three of which were in the 21 patients who received prior anti-CTLA-4 therapy, for an overall CR rate of 11% (8/74). Median OS was 17.3 months in this study [Forget 2018].

1.2.1. LN-144 TIL Therapy Regimen

The LN-144 treatment regimen involves a course of NMA-LD using cyclophosphamide and fludarabine for one week prior to TIL infusion, and a limited course of IL-2 administration (up to six doses) following the TIL infusion. The NMA-LD and IL-2 are included in the regimen to support the engraftment, expansion, and activation of the transferred TIL.

Several preconditioning regimens have been used in conjunction with TIL therapies. NMA-LD regimens have included cyclophosphamide/fludarabine, total body irradiation, or the combination of the two. The NMA-LD preconditioning regimen used in the current study is based on the method developed and tested by the NCI, which involves 2 days of cyclophosphamide followed by 5 days of fludarabine. Each patient will undergo an NMA-LD preconditioning regimen prior to infusion of LN-144.

1.2.2. Brief Description of the Product

LN-144 is a ready-to-infuse, autologous TIL therapy based on that developed by Dr. Rosenberg and colleagues at the NCI and further optimized by Iovance.

LN-144 is composed of autologous TIL, which are obtained from an individual patient's tumor and expanded *ex vivo* through cell culture in the presence of the cytokine IL-2 and muromonab CD3, a monoclonal antibody (mAb) to human CD3 (OKT3).

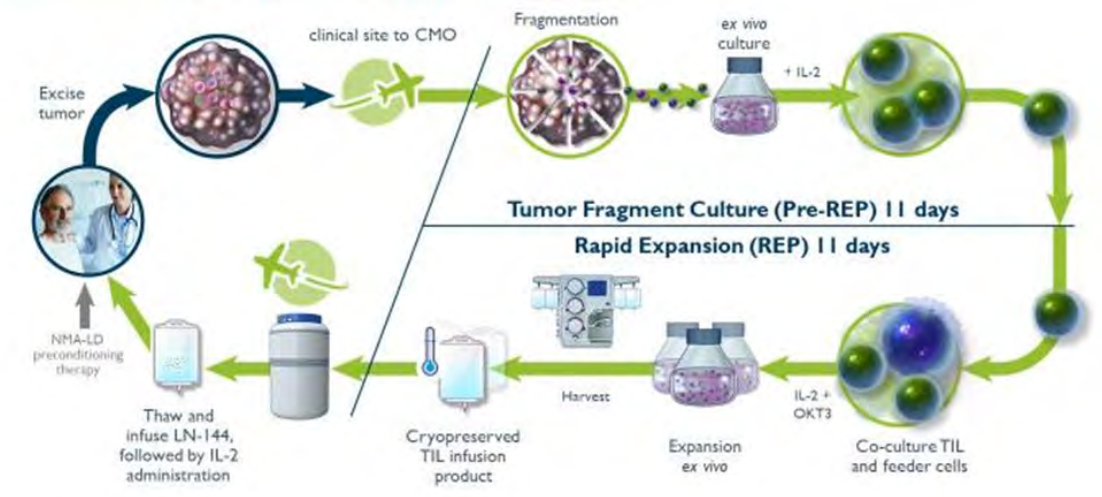
The final drug product is a cryopreserved live-cell suspension that is formulated for intravenous (IV) infusion. The *ex vivo* expanded autologous TIL are formulated in CryoStor® CS10 cryopreservation medium/Plasma Lyte (final dimethyl sulfoxide [DMSO] concentration: 5%), with 0.5% human serum albumin (HSA) and 300 international units (IU)/mL (12 ng/mL) of IL-2. The formulated product is frozen at a controlled rate to < -150°C in vapor phase liquid nitrogen, shipped in a cryoshipper to the appropriate clinical site, and thawed before use for infusion into the patient.

1.2.3. Production and Expansion of TIL

The manufacturing process begins at the clinical site with the surgical resection of a tumor lesion containing viable tumor material of ≥ 1.5 cm. An aggregate of multiple separate lesion biopsies may also be resected from the patient and is encouraged if patient safety allows. The tumor specimen is placed in transport media and shipped express at 2–8°C to the Good Manufacturing Practices (GMP) manufacturing facility. Upon arrival at the GMP manufacturing facility, the tumor specimen is dissected into fragments, which are then cultured in a pre-rapid expansion protocol (REP) stage with human recombinant IL-2 to generate the minimum number of viable cells required for the REP stage. The REP stage further expands the cells in the presence of IL-2, OKT3, and irradiated allogeneic peripheral blood mononuclear cell (PBMC). The REP-expanded cells are then harvested, washed, and formulated in a blood transport/infusion bag for shipment by courier to the clinical site.

A diagram of the manufacturing process for LN-144 is provided in Figure 1.

Figure 1 LN-144 GMP Manufacturing Process for Cryopreserved Product Supplied to Cohorts 2 and 4



Abbreviations: CMO=contract manufacturing organization; IL-2=interleukin-2; NMA-LD=nonmyeloablative lymphodepletion; REP=rapid expansion protocol; TIL=tumor infiltrating lymphocytes

Each cryopreservation bag of the LN-144 final product is labeled with a patient-specific label. LN-144 is shipped from the manufacturing facility to clinical sites for administration to patients as described in the Pharmacy & Administration Manual.

1.3. Benefit-Risk Assessment of LN-144

This protocol is enrolling patients with unresectable or metastatic melanoma who have previously been treated with at least one systemic therapy including a PD-1 blocking antibody and if BRAF V600 mutation positive, a BRAF inhibitor or BRAF inhibitor in combination with mitogen-activated extracellular signal-regulated kinase (MEK) inhibitor.

As discussed above, immune checkpoint blockade and targeted therapies constitute the current standard of care for metastatic melanoma; however, many patients either do not respond to, or relapse after available single-agent therapy, and the combination of two checkpoint inhibitors often have unacceptable toxicity. Once a patient progresses after receiving a checkpoint inhibitor, they have limited treatment options. These patients could receive high-dose IL-2 or cytotoxic agents as subsequent therapy, but the efficacy of these agents in such a late-line patient population has not been reported. A response

rate of 4–10% has been observed for Investigator's choice of chemotherapy (dacarbazine [DTIC], carboplatin plus paclitaxel, paclitaxel alone, or temozolomide) administered as second-line therapy in patients who had progressed after ipilimumab in phase 3 trials of nivolumab [Weber 2015] and pembrolizumab [Hamid 2017]. Similarly, a retrospective study of the response to chemotherapy in melanoma patients previously treated with anti-PD-1 therapy found an ORR of 11% to chemotherapy and a median progression-free survival (PFS) of only 2.5 months (2.1, 2.8) in these patients [Goldinger 2018].

The feasibility of cell therapy with autologous TIL has been demonstrated by durable tumor responses, including CRs, in patients with metastatic melanoma, irrespective of prior systemic treatment with immune checkpoint inhibitors (anti-PD-1 and/or anti-CTLA-4), BRAF-mutation targeted therapies, chemotherapies, IL-2, or interferon-alpha. Dramatic and durable reductions in tumor burden have been attained in even heavily pretreated metastatic melanoma patients [Forget 2018; Goff 2016; Rosenberg 2011; Tran 2016].

In addition, the mechanism of action of LN-144 affords at least three important advantages in the treatment of solid tumors over other forms of immunotherapy: 1) the substantial clinical experience with TIL therapy of metastatic melanoma shows an encouraging safety profile for TIL therapy; 2) TIL recognizes a diverse array of tumor antigens, especially mutated neoantigens in melanoma, many of which are undefined but are effective targets for TIL in achieving anti-tumor effects; 3) clinical studies have demonstrated that the effects of TIL therapy persist in patients for weeks to months, and even years, after infusion, thereby mediating highly durable tumor responses after only a single treatment regimen in even highly pre-treated patients.

The risks associated with TIL therapy include: a delay in treatment due to the need to harvest and grow the cells; a surgical procedure (possibly major) to obtain tumor for the cell product; the possibility that a cell product cannot be generated; and the toxicities known to be associated with the NMA-LD regimen and IL-2 administration. However, current methods for the expansion of autologous TIL from excised tumors are shorter than previously used for TIL at 22 days for manufacturing. These methods are well

established with over 90% success rates for manufacturing and are sufficiently robust to ensure a high degree of success in consistently generating adequate numbers of high-quality therapeutic cells from resected melanoma lesions. As such, the risk-benefit balance for Study C-144-01 should be viewed as favorable considering the following:

- Substantial clinical experience with TIL in the treatment of advanced melanoma and other solid tumors has demonstrated the capacity to induce clinically meaningful responses in patients with progressive disease (PD) following PD-1 blocking antibodies who had also received targeted therapy, if indicated
- Safety monitoring and risk mitigation strategies are incorporated into this C-144-01 study protocol

In summary, adoptive cell therapy (ACT) with TIL represents a one-time treatment, with the possibility of offering a durable treatment option for patients with cancer, especially those with advanced metastatic disease who have limited to no treatment options after the failure of available conventional therapies (eg, immune checkpoint inhibitors or targeted therapies).

2. STUDY DESIGN

2.1. Description of the Study

This is a prospective, interventional multicenter study evaluating patients who receive ACT via infusion of LN-144 (composed of autologous TIL). Patients will receive an NMA-LD preconditioning regimen, then a single infusion of LN-144, followed by the administration of a regimen of IL-2.

This clinical trial consists of four cohorts, which enrolled similar patient populations with unresectable or metastatic melanoma:

- Cohort 1 infused 23 patients with non-cryopreserved autologous TIL and is closed to Enrollment.
- Cohort 2 will infuse approximately 66 patients with the cryopreserved autologous TIL product and is closed to Screening.
- Cohort 3 is limited to infused patients from Cohort 1, Cohort 2, or Cohort 4, who may rescreen after having participated in the study for a second administration of LN-144, cryopreserved product, and will include approximately 10 patients.
- Cohort 4 will include approximately 75 patients who are planned to be infused with the cryopreserved autologous TIL product. Cohort 4 is open to enroll new patients.

Patients must be hospitalized prior to the planned LN-144 infusion for overnight hydration. Patients will remain hospitalized until completion of the IL-2 administration, or as per institutional standards.

All visits following LN-144 infusion, except OS Follow-up, are calculated from LN-144 infusion (Day 0). Patients will need to return for safety assessment visits on Day 14 and Day 28 (Day 28 corresponds with the End of Treatment [EOT] visit).

Patients will be evaluated for efficacy (eg, tumor response) following the EOT visit, and at Week 6 (Day 42), then every 6 weeks until Month 6 (Week 24). Response assessments will be conducted by the Investigator following both RECIST v1.1 and immune-related RECIST (irRECIST), and by the Independent Review Committee (IRC) following RECIST v1.1 (primary endpoint).

Patients will continue to be evaluated for response every 3 months (12 weeks) for up to 5 years from Day 0 or until: disease progression; or the start of a new anticancer therapy (Appendix 1).

OS Follow-up is calculated from Enrollment (tumor resection), will begin after completion of the End of Assessment (EOA) visit (eg, last study assessment), and will continue for up to 5 years or until discontinuation from the study.

Patients who had tumor resection but did not receive LN-144 for any reason will perform an EOA visit and transition directly into the OS Follow-up Period.

2.2. Re-treatment Cohort (Cohort 3)

Patients who initially received LN-144 in Cohort 1, Cohort 2, or Cohort 4 may receive a second administration of LN-144. Patients, who in the opinion of the Investigator and the Medical Monitor will benefit from a second LN-144 treatment regimen, will need to be rescreened and meet the inclusion and exclusion criteria (except exclusion criterion “b”) as described in Sections 4.1 and 4.2.

Patients may have a second tumor resection, if needed, especially when new lesions are available and feasible for resection.

3. STUDY OBJECTIVES AND ENDPOINTS

3.1. Study Objectives

3.1.1. Primary Objective

- Evaluate the efficacy of LN-144 in patients with unresectable or metastatic melanoma using the ORR, as assessed by the IRC per RECIST v1.1

3.1.2. Secondary Objectives

- Evaluate the efficacy endpoints of duration of response (DOR), disease control rate (DCR), and PFS, as assessed by the IRC per RECIST v1.1
- Further evaluate efficacy of LN-144 in patients with unresectable or metastatic melanoma by assessing ORR, DOR, DCR, and PFS, as assessed by the Investigator per RECIST v1.1
- Evaluate OS
- Characterize the safety profile of LN-144 in patients with unresectable or metastatic melanoma

3.1.3. Exploratory Objectives

- Explore the persistence of LN-144 and potential immune correlates of response, outcome, and toxicity of the treatment
- Explore efficacy based on irRECIST criteria [Bohnsack 2014], as assessed by the Investigator
- Assess health-related quality of life (HRQoL; Appendix 14)

3.2. Study Endpoints

3.2.1. Primary Endpoints

- ORR, as assessed by the IRC per RECIST v1.1

3.2.2. Secondary Endpoints

- DOR, DCR, and PFS per RECIST v1.1, as assessed by the IRC
- ORR, DOR, DCR, and PFS per RECIST v1.1, as assessed by the Investigator
- OS
- Incidence, severity, seriousness, relationship to study treatment, and characteristics of treatment-emergent adverse events (TEAEs), including AEs

leading to early discontinuation from treatment or withdrawal from the Assessment Period, and AEs resulting in deaths

3.2.3. Exploratory Endpoints

- TIL persistence in the peripheral blood and immune correlates with respect to response, outcome, and/or toxicity of the treatment will be determined by immunological and molecular assays
- ORR, DOR, DCR, and PFS using irRECIST, as assessed by the Investigator
- Patient-reported outcomes for HRQoL based on the European Organisation for Research and Treatment of Cancer Quality-of-Life Questionnaire – Core 30 Instrument (EORTC QLQ-C30; Appendix 14)

4. SELECTION OF PATIENT POPULATION

4.1. Inclusion Criteria

Patients must meet *all* of the following inclusion criteria to be eligible for participation in the study:

a. Patients with unresectable or metastatic melanoma (Stage IIIc or Stage IV)

b. Patients must have progressed following ≥ 1 prior systemic therapy including a PD-1 blocking antibody; and if BRAF V600 mutation-positive, a BRAF inhibitor or BRAF inhibitor in combination with MEK inhibitor

c. Prior to study Enrollment, documentation of radiological disease progression after the most recent therapy

d. At least one measurable target lesion, as defined by RECIST v1.1

- Lesions in previously irradiated areas (or other local therapy) should not be selected as target lesions, unless treatment was ≥ 3 months prior to Screening, and there has been demonstrated disease progression in that particular lesion
- If a lesion is partially resected to generate TIL, and remains visible on the Baseline scan after surgery, then the partially resected lesion can be used for RECIST v1.1 response assessment, but only as a non-target lesion

e. At least one resectable lesion (or aggregate of lesions resected) of a minimum 1.5 cm in diameter post-resection to generate TIL; surgical removal with minimal morbidity (defined as any procedure for which expected hospitalization is ≤ 3 days)

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

g. Patients must have an Eastern Cooperative Oncology Group (ECOG) performance status of 0 or 1 (Appendix 2) and an estimated life expectancy of ≥ 3 months

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

i. Patients must have the following hematologic parameters:

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

Note: Transfusions or growth factors are not allowed 28 days prior to signing the informed consent form (ICF) and continuing through the Screening Period

j. Patients must have adequate organ function:

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

k. Patients must have recovered from all prior therapy-related AEs to ≤ Grade 1 (per Common Terminology Criteria for Adverse Events [CTCAE] v4.03), except for alopecia or vitiligo, prior to Enrollment (tumor resection)

- Patients with documented ≥ Grade 2 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 tumor resection
- Patients with immunotherapy-related endocrinopathies stable for at least 6 weeks (eg, hypothyroidism), and controlled with hormonal replacement (non-corticosteroids), are allowed

l. Patients must have a washout period of ≥ 28 days from prior anticancer therapy(ies) to the start of the planned NMA-LD preconditioning regimen:

- Targeted therapy: MEK/BRAF or other targeted agents

- Chemotherapy
- Immunotherapy: anti-CTLA-4/anti-PD-1, other mAb, or vaccine
- Palliative radiation therapy is permitted so long as it does not involve lesions being selected for TIL, or as target or non-target lesions. Washout is not required if all related toxicities have resolved to ≤ Grade 1 as per CTCAE v4.03

m. Patients of childbearing potential or their partners of childbearing potential must be willing to take the appropriate precaution to avoid pregnancy or fathering a child for the duration of the study and practice an approved, highly effective method of birth control during treatment and for 12 months after receiving the last protocol-related therapy

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

n. Patients (or legally authorized representative) must have the ability to understand the requirements of the study, have provided written informed consent as evidenced by signature on an 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, including the OS Follow-up Period

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

4.2. Exclusion Criteria

Patients who meet *any* of the following criteria are not eligible for participation in this study:

a. Patients who have been shown to be BRAF mutation positive (V600), but have not received prior systemic therapy with a BRAF inhibitor alone or a BRAF inhibitor in combination with a MEK inhibitor

b. Patients who have received an organ allograft or prior cell transfer therapy

c. Patients with melanoma of uveal/ocular origin

d. Patients who have a history of hypersensitivity to any component or excipient of LN-144 or other study drugs:

- NMA-LD preconditioning regimen (cyclophosphamide, mesna, and fludarabine)
- Antibiotics (ABX) of the aminoglycoside group (ie, streptomycin, gentamicin); except those who are skin-test negative for gentamicin hypersensitivity
- Any component of the LN-144 infusion product formulation including DMSO, HSA, IL-2, and dextran-40

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

- Patients with definitively treated brain metastases may be considered for Enrollment, and must be stable for ≥ 14 days prior to beginning the NMA-LD preconditioning regimen

f. Patients who are on chronic systemic steroid therapy for any reason

g. Patients who have active medical illness(es) that would pose increased risk for study participation, including: active systemic infections requiring systemic ABX, coagulation disorders, or other active major medical illnesses of the cardiovascular, respiratory, or immune system

h. Patients who have ≥ Grade 2 hemorrhage within 14 days prior to Enrollment (tumor resection)

i. Patients who are seropositive for any of the following:

- Human immunodeficiency virus (HIV)-1 or HIV-2 antibodies
- Hepatitis B antigen (HBsAg), hepatitis B core antibody (anti-HBc), or hepatitis C antibody (HCV Ab); patients with acute or chronic hepatitis infections may be enrolled if the viral load by polymerase chain reaction (PCR) is undetectable with/without active treatment.
- Syphilis (rapid plasma reagin [RPR] test or venereal disease research laboratory [VDRL] test)
- Cytomegalovirus (CMV) IgM antibody titer or PCR assay and Epstein-Barr virus (EBV) IgM or PCR assay indicating active infection
- Positive herpes simplex virus (HSV)-1 and HSV-2 IgM serology or PCR assay
    - Patients who are HSV immunoglobulin M (IgM) or PCR assay positive will need to receive appropriate treatment and become IgM or PCR assay negative prior to starting the NMA-LD preconditioning regimen

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

k. Patients who have a left ventricular ejection fraction (LVEF) < 45% or New York Heart Association (NYHA) functional classification Class > 1

- Patients ≥ 60 years of age and who have a history of ischemic heart disease, chest pain, or clinically significant atrial and/or ventricular arrhythmias must have a cardiac stress test. Patients with any irreversible wall movement abnormalities are excluded

l. Patients who have a documented forced expiratory volume in 1 second (FEV1) of ≤ 60%

m. 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)

n. Patients who have received a live or attenuated vaccine within 28 days of beginning the NMA-LD preconditioning regimen

o. Patients who are pregnant or breastfeeding

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

q. Patients protected by the following constraints:

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

4.3. Definition of Screening and Patient Enrollment

Patients have 28 days from signing the ICF to complete the study assessments required to meet all inclusion and no exclusion criteria. Patients will then be approved to proceed to Enrollment in the study.

- If a patient does not meet the inclusion and exclusion criteria, then they will be defined as a screen failure

- The case for a patient who meets the inclusion and exclusion criteria, but does not have tumor resection within 28 days of signing the ICF, must be discussed with the Medical Monitor
- Assessments that become 'out of window' (eg, more than 28 days from Enrollment [tumor resection]) will need to be repeated
- Patients who meet inclusion and exclusion criteria and do not receive LN-144 (eg, due to a manufacturing failure) may be re-screened after consultation with the Medical Monitor

Enrollment will occur upon tumor resection.

4.3.1. Screen Failure

Patients who do not meet eligibility criteria will need to have the reason for the screen failure documented. Any serious adverse events (SAEs) occurring in such patients after signing the ICF until study discontinuation (the day of screen failure) will also be documented/reported in the Electronic Data Capture (EDC) system.

5. STUDY PROCEDURES

5.1. Screening (up to 28 days from signing the ICF)

After signing the ICF, the following procedures should be performed in all patients (exceptions for Cohort 3 are noted; Appendix 1):

- Review of inclusion and exclusion criteria
- Demographic data (date of birth, age, sex, and race/ethnic origin)
- Medical history (does not need to be repeated for Cohort 3 patients)
- Melanoma medical history, including BRAF mutational status as well as programmed death-ligand 1 (PD-L1) expression when available (does not need to be repeated for Cohort 3 patients)
    - All cancer-related therapies including surgeries, radiotherapy, neoadjuvant or adjuvant systemic therapies, other local therapies and all palliative therapies should be recorded. Best response to each therapy should be recorded
    - Documentation of most recent prior therapy: documentation of best response to such therapy and radiological disease progression
- ECOG performance status evaluation
- Physical examination will be performed as clinically indicated, unless otherwise specified, and findings will be source documented: (Appendix 3)
    - Clinically relevant changes will be recorded on the electronic case report form (eCRF) AE page
    - The examination will be symptom-driven, including, as applicable: weight, gastrointestinal (abdomen, liver), cardiovascular, extremities, head, eyes, ears, nose, throat, respiratory system, dermatological, musculoskeletal, neurological, and psychiatric (mental status)
        - Body weight will include calculated body surface area (BSA), and body mass index (BMI) as described in Appendix 3; all patients must be dosed using actual body weight
        - Height to be measured at Screening only; does not need to be repeated for Cohort 3 patients
- Vital signs (Appendix 3)
    - Pulse rate, respiratory rate, blood pressure, and temperature

- All AEs/SAEs occurring after the patient has signed the ICF will be collected
- List all concomitant medications taken within 28 days prior to signing the ICF
- Blood and urine tests
    - Hematology: (Appendix 3)
        - Complete blood count (CBC) with differentials, when available; transfusions or growth factors are not allowed 28 days prior to signing ICF and continuing through the Screening Period
        - White blood cell (WBC) count with differentials (neutrophils, lymphocytes, monocytes, eosinophils, and basophils), red blood cell (RBC) count, Hb, hematocrit (Hct), mean corpuscular volume (MCV), mean corpuscular hemoglobin (MCH), platelet count
    - Coagulation: (Appendix 3)
        - International Normalized Ratio (INR) and prothrombin time (PT) or INR and activated partial thromboplastin time (aPTT)
    - Chemistry: (Appendix 3)
        - Sodium, potassium, chloride, total carbon dioxide (CO_2) or bicarbonate, creatinine, glucose, blood urea nitrogen (BUN), albumin, calcium total, magnesium total, phosphorus, alkaline phosphatase, ALT/SGPT, AST/SGOT, total bilirubin, direct bilirubin, lactate dehydrogenase (LDH), total protein, total creatine kinase (CK), uric acid
    - Thyroid panel to include thyroid stimulating hormone (TSH) and free T4
    - Serology testing: HIV-1 and HIV-2 antibody titer, HBsAg, anti-HBc, HCV Ab, syphilis (eg, RPR test or VDRL test), HSV-1 serology, HSV-2 serology, anti-CMV titer, EBV panel (Appendix 3)
        - In patients who are seropositive for HSV IgM or PCR assay: valacyclovir (500 mg per os [by mouth; PO] daily), or acyclovir (250 mg/m^2 IV every 12 hours) if the patient is unable to take medication by mouth, or as per institutional standards. Treatment should be administered as soon as infection is diagnosed and must be completed prior to the start of NMA-LD preconditioning regimen to ensure patient is seronegative for HSV (IgM) or PCR assay
    - Serum pregnancy test (β-human chorionic gonadotropin [β-HCG]) for women of childbearing potential

  - Dipstick urinalysis (with complete urinalysis and culture, if applicable; Appendix 3)
  - Human leukocyte antigen (HLA) typing (to be shipped to the Central Laboratory); does not need to be repeated for Cohort 3 patients
- Evaluation and measurement of all skin and palpable lesions (if applicable)
  - Evaluation and measurement of skin and palpable lesions may be performed (if applicable)
- Skin test for gentamicin hypersensitivity, as needed
- Slit-lamp eye examination in patients with history of uveitis. Previous evaluation within 28 days prior to signing the ICF is allowed
- Electrocardiogram (ECG); if an ECG was performed within 60 days prior to signing the ICF, and considered normal, it does not have to be repeated
- Echocardiogram (ECHO) or multiple gated acquisition scan (MUGA) for all patients
  - Patients ≥ 60 years of age and who have a history of ischemic heart disease, chest pain, or clinically significant atrial and/or ventricular arrhythmias must have a cardiac stress test
- Pulmonary function tests (PFTs)
- Colonoscopy on patients with documented ≥ Grade 2 diarrhea or colitis as a result of previous treatment with immune checkpoint inhibitor(s) who have not been asymptomatic for at least 6 months
- Imaging assessments (Appendix 3)
  - Computed tomography (CT) of chest, abdomen, pelvis, and additional anatomic regions (eg, extremities, neck) per disease history and clinical symptoms
    - High-resolution CT with PO/IV contrast or contrast-enhanced MRI is the preferred imaging modality for assessing radiographic tumor response. If a patient has a known allergy to CT contrast material, please use the alternate modality. In cases where contrast is strictly contraindicated, a non-contrast scan is acceptable. The same imaging modality must be used throughout the duration of the study.
    - Previous CT/MRI/PET scans performed within 28 days prior to signing the ICF can be used for Screening

  - MRI of the brain
    - MRI scans performed within 28 days prior to signing the ICF with normal results do not have to be repeated
  - All imaging assessments, including scheduled and unscheduled scans, should be recorded in the eCRF and will be assessed by the IRC
- Tumor assessment (per RECIST v1.1)

5.2. Enrollment and Tumor Resection

The patient is enrolled into the study upon tumor resection.

Use of systemic corticosteroids is not allowed starting 21 days prior to beginning the NMA-LD preconditioning regimen, through treatment, and up to 60 days post-LN-144 infusion. Prophylactic use of systemic corticosteroids is not allowed under any circumstances. Such medications should only be used to treat immediate life-threatening conditions.

The following procedures should be completed during this visit: (Appendix 1)

- Physical examination (Appendix 3)
- Assessment of AEs/SAEs (Section 12.2.1)
- List all concomitant medications
  - Concomitant medications include those that are administered as part of the tumor resection procedure
- Repeat serology testing only for tumor samples acquired in the EU (HIV-1, HIV-2, HBsAg, anti-HBc, HCV Ab, and syphilis). These are to be done on the day of the tumor resection or within 7 days after the resection (Appendix 3)
- Blood for immune monitoring (± 3-day window); refer to Laboratory Manual
- Tumor resection
- Intraoperative frozen section (or fine-needle aspiration [FNA]) or touch prep cytology
- The following medications should be administered as follows or as per institutional standards:
  - Herpetic treatment as per Screening (Section 5.1)

5.2.1. Tumor Harvest and Processing Procedure

If the patient has only one identified target lesion at Screening, then another lesion needs to be identified and used for TIL generation.

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

Tumor specimens must undergo intraoperative frozen section (or FNA) or touch prep cytology examination by a pathologist to ensure that viable tumor is present. In addition, at the time of tumor resection, the surgeon and/or pathologist must use their best judgement to evaluate the results of the frozen section (or FNA) or touch prep cytology, incorporating visual inspection of the specimen. This is done to ensure that viable tumor specimens are being shipped for TIL generation. The pathologist and surgeon must perform these assessments in parallel prior to shipping the tumor specimen for TIL generation to the contract manufacturing organization (CMO).

Intraoperative frozen section (or FNA) or touch prep cytology examination is not a gold standard. If any of the above-mentioned methods is found to contain no viable tumor, the expert opinion of the pathologist and surgeon at the time of surgery will supersede, and if they believe there is viable tumor, the resected sample should still be sent for manufacturing.

If a portion of the viable tumor tissue is still available after completion of preparation of tumor tissue for LN-144 manufacturing, then the excess tumor tissue will be utilized for exploratory biomarker analysis. If no excess tumor tissue is available, then a single 2-mm punch biopsy from the center of the resected tumor can be collected. Ensure that this biopsy does not bring final tumor tissue for TIL generation to < 1.5 cm. If excess viable

tumor tissue and punch biopsy are not available, then excess viable tumor tissue can be resected from an additional lesion (if available). Note that this excess tumor tissue cannot originate from a target lesion. Please refer to the Laboratory Manual for details on utilization, processing, and shipping of excess viable tumor tissue/punch biopsy.

5.3. Baseline (Day -21 to Day -10) Procedures

To ensure the patient still meets the inclusion and exclusion criteria, the following procedures should be completed during this visit. If the Day 0 visit is re-scheduled to a later date and assessments, which have already been performed, become out of window, then they will need to be repeated within 4 weeks prior to the new Day 0.

- Review of inclusion and exclusion criteria
    - Reconfirmation of eligibility requires review and approval by the Medical Monitor or designee
- ECOG performance status evaluation
- Physical examination (Appendix 3)
- Vital signs (Appendix 3)
- Assessment of AEs/SAEs (Section 12.2.1)
- List all concomitant medications
- Blood and urine tests
    - Hematology (Appendix 3)
    - Chemistry (Appendix 3)
    - Serum pregnancy test for women of childbearing potential
    - Dipstick urinalysis (Appendix 3)
- Evaluation and measurement of all skin and palpable lesions (if applicable)
- ECG
- Complete imaging assessments (Appendix 3)
    - MRI of the brain:
        - If a brain MRI was performed within 4 weeks prior to Day 0 and considered normal or stable, and the patient is not showing any

clinical symptoms of progression in the brain, then a brain MRI does not need to be repeated

- Tumor assessment (per RECIST v1.1)
    - Baseline target lesions should also have been measured at Screening (Section 10.1.1.1)
- HRQoL questionnaire EORTC QLQ-C30 (Appendix 14)
- The following medications should be administered as follows or as per institutional standards:
    - Herpetic treatment as per Screening (Section 5.1)

5.4. Patients Who Do Not Receive an LN-144 Infusion Procedure

Some patients may undergo tumor resection but will not receive infusion of LN-144 (eg, discontinue treatment; Section 8.2). Such patients who do not begin the NMA-LD preconditioning regimen and/or do not receive LN-144 infusion for any reason, will perform an EOA visit and transition directly into the OS Follow-up Period (Section 5.7).

Patients who meet inclusion and exclusion criteria and do not receive LN-144 (eg, due to a manufacturing failure) may be rescreened after consultation with the Medical Monitor.

5.5. Treatment Period

The Treatment Period will begin on Day -7 (start of NMA-LD preconditioning regimen) and continue to Day 28 (EOT visit; Appendix 1).

Use of systemic corticosteroids is not allowed starting 21 days prior to beginning the NMA-LD preconditioning regimen, through treatment, and up to 60 days post-LN-144 infusion. Prophylactic use of systemic corticosteroids is not allowed under any circumstances. Such medications should only be used to treat immediate life-threatening conditions.

5.5.1. Day -7 Procedures

Verification of sufficient LN-144 viable cell expansion will be confirmed by the Sponsor and site will receive the authorization to begin the NMA-LD preconditioning regimen.

Furthermore, prior to beginning the NMA-LD preconditioning regimen, patients must be seronegative for HSV IgM or PCR assay.

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

- ECOG performance status evaluation
- Physical examination (Appendix 3)
- Vital signs (Appendix 3)
- Assessment of AEs/SAEs (Section 12.2.1)
- List all concomitant medications
- Blood and urine tests (to be drawn prior to cyclophosphamide administration)
    - Hematology (Appendix 3)
    - Chemistry (Appendix 3)
    - Serum pregnancy test for women of childbearing potential
    - Dipstick urinalysis (Appendix 3)
    - Blood for immune monitoring (prior to starting NMA-LD)
- Authorization for lymphodepletion
    - Authorization to Receive Lymphodepletion must be received by the site from the Sponsor or designee prior to beginning the NMA-LD preconditioning regimen (with a planned start on Day -7)
- The following medications must be dosed using actual body weight (as recorded at Day -7 or within 7 days of the start of the chemotherapy per institutional standards) and administered as follows or as per institutional standards:
    - Cyclophosphamide (60 mg/kg) with mesna (15 mg/kg) will be infused over approximately 2 hours. Cyclophosphamide may be prepared in 250 mL or 500 mL (eg, 5% dextrose in water [D5W] or 0.9% sodium chloride [NaCl]). Refer to the current package insert or Summary of Product Characteristics (SmPC) for cyclophosphamide full prescribing information (Appendix 7)
    - Mesna will continue to be infused at a rate of 3 mg/kg/hour in a suitable diluent over 22 hours after each cyclophosphamide dose. Higher or continued doses of mesna can be administered for prevention of hemorrhagic cystitis. Refer to the current package insert or SmPC for mesna full prescribing information (Appendix 8)

- Ondansetron (0.15 mg/kg/dose [rounded to the nearest even mg dose between 8 mg and 16 mg] IV every 8 hours × 3 days), or as per institutional standards, will be given for nausea. Refer to the current package insert or SmPC for ondansetron full prescribing information (Appendix 9)
- Broad-spectrum ABX will be initiated if fever (defined as 38.3°C, one or two temperatures of 38.0°C or above at least 1 hour apart), AND an ANC ≤ 500/mm^3 (Section 7.4.4), or per institutional standard

5.5.2. Day -6 Procedures

The following procedures should be performed:

- Physical examination (Appendix 3)
- Vital signs (Appendix 3)
- Assessment of AEs/SAEs (Section 12.2.1)
- List all concomitant medications
- Blood tests (to be drawn prior to cyclophosphamide administration)
  - Hematology (Appendix 3)
  - Chemistry (Appendix 3)
- The following medications should be administered as follows or as per institutional standards:
  - Cyclophosphamide as per Day -7 (Section 5.5.1)
  - Mesna as per Day -7 (Section 5.5.1)
  - Ondansetron as per Day -7 (Section 5.5.1)
  - Broad Spectrum ABX as per Day -7 (Section 5.5.1)

5.5.3. Day -5 to Day -1 Procedures

The following procedures should be performed:

- Physical examination (Appendix 3)
- Vital signs (Appendix 3)
- Assessment of AEs/SAEs (Section 12.2.1)
- List all concomitant medications
- Blood and urine tests (to be drawn prior to fludarabine administration)

- Hematology (Appendix 3)
- Chemistry (Appendix 3)
- Dipstick urinalysis (Appendix 3)
  - Day -4 and Day -1 only

- The following medication must be dosed using actual body weight (as recorded at Day -7 or within 7 days of the start of the chemotherapy per institutional standards) and administered as follows or as per institutional standards:
  - Fludarabine (25 mg/m^2) to be given IV over approximately 30 minutes, once daily
    - Fludarabine dose will be adjusted according to eCrCl as follows:

      eCrCl 50–79 mL/min: reduce dose to 20 mg/m^2

      eCrCl 40–49 mL/min: reduce dose to 15 mg/m^2
    - Dose hold or discontinuation of fludarabine will only be allowed in the case of toxicity described in the package insert. Refer to the current package insert or SmPC for fludarabine full prescribing information (Appendix 12) or per institutional standard.
  - Broad Spectrum ABX as per Day -7 (Section 5.5.1)

5.5.4. Day 0 (Infusion Day) Procedures

Patients must be hospitalized prior to the planned LN-144 infusion for overnight hydration and will remain hospitalized until completion of the IL-2 administration, or as per institutional standards.

Day 0 is the day of LN-144 infusion.

5.5.4.1. Pre-LN-144 Infusion

On Day 0, just prior to LN-144 infusion, the following procedures should be performed:

- Physical examination (Appendix 3)
- Vital signs (Appendix 3)
  - Vital signs will be monitored every 30 minutes during infusion then hourly (± 15 minutes) for 4 hours, and then routinely (every 4–6 hours), unless otherwise clinically indicated, for up to approximately 24 hours post-LN-144 infusion

- Assessment of AEs/SAEs (Section 12.2.1)
- List all concomitant medications
- Blood and urine tests
    - Hematology (Appendix 3)
    - Chemistry (Appendix 3)
    - Serum pregnancy test for women of childbearing potential
    - Dipstick urinalysis (Appendix 3)
    - Blood for immune monitoring must be collected:
        - Day 0 OR Day 1 (after LN-144 AND prior to first IL-2 dose)
- The following medications will be administered to the patient prior to LN-144 infusion as follows or as per institutional standards:
    - Within 24 hours, hydration
    - Within 30–60 minutes, premedicate the patient with acetaminophen (650 mg) or equivalent and diphenhydramine (25–50 mg IV), or another H1-histamine antagonist
        - Prophylactic use of systemic corticosteroids is not allowed; such medications should only be used to treat immediate life-threatening conditions
- During infusion of LN-144, appropriate emergency medications (eg, epinephrine and diphenhydramine) should be available at bedside, and institutional emergency guidelines should be followed as needed. Additional supportive therapy may include:
    - Continued acetaminophen (650 mg q4h) or equivalent
    - Indomethacin (50–75 mg q6h)
    - Ranitidine (150 mg q12h)
    - Meperidine (25–50 mg)
    - Other medications as per institutional standards

5.5.4.2. LN-144 Infusion

Each lot of LN-144 product contains between 1 x 10^9 and 150 x 10^9 viable cells per the product specification. Patients will receive the full dose of product that is manufactured and released.

LN-144 should be infused as soon as practically possible, after approximately 24 hours following the last dose of fludarabine. If ≥ 4 days have elapsed between the last fludarabine dose and LN-144 infusion, the ALC should be measured and there should be a discussion with the Medical Monitor.

Each cryobag of LN-144 will be thawed at 37°C using a water bath or other thawing device, one at a time, for sequential infusion.

LN-144 will be administered IV and infused by gravity beginning at a rate of 1 mL/min for the first 5 minutes. If no adverse reaction is observed, the infusion rate can then increase to between 5 and 10 mL/minute for the completion of the infusion. During periods of infusion interruption, any remaining cryobags of LN-144 should be kept in the cryoshipper. Any thawed LN-144 should be infused within 3 hours of being thawed. Refer to the LN-144 Pharmacy and Administration Manual for details on the thawing and administration procedure.

Blood for immune monitoring must be collected after LN-144 infusion and prior to the first dose of IL-2 (Day 0 or Day 1).

All visits following LN-144 infusion are calculated from Day 0 forward.

5.5.4.2.1. IL-2 Dosing and Dose Adjustments

The following medications will be administered as follows or as per institutional standards:

- IL-2: the first IL-2 administration will begin approximately 3–24 hours after the completion of LN-144 infusion at a dose of approximately 600,000 IU/kg (based on actual body weight recorded at Day 0 [Section 5.5.4.1] or within 7 days of the start of IL-2, per institutional standards). IL-2 is administered by IV at a frequency of approximately every 8–12 hours. Continue for up to a maximum of six doses
    - 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 1–6 doses based on tolerance

- IL-2 dosing is allowed for up to 4 days post-LN-144 infusion to allow for proper management of any IL-2 toxicities
- If toxicities can be easily reversed within 24 hours by supportive measures, then the additional doses of IL-2 (up to the protocol-defined maximum of six doses) may be given
- IL-2 dosing may be held or stopped at the discretion of the Investigator
- Skipping IL-2 doses is allowed if patient experiences a Grade 3 or Grade 4 toxicity (Appendix 4 and Appendix 5). If > 2 doses of IL-2 are skipped, then IL-2 administration will be discontinued
- IL-2 AEs are described in Appendix 4 and toxicities/management are described in Section 7.3 and Appendix 5

- Broad Spectrum ABX as per Day -7 (Section 5.5.1)

5.5.5. Day 1, Day 2, Day 3, and Day 4 Procedures

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

- Physical examination (Appendix 3)
- Vital signs, including pulse oximetry (Appendix 3)
- Assessment of AEs/SAEs (Section 12.2.1)
- List all concomitant medications
- Blood and urine tests (must be drawn each day prior to the first IL-2 administration)
  - Hematology (Appendix 3)
  - Chemistry (Appendix 3)
  - Dipstick urinalysis on days that IL-2 is administered, and subsequently, if clinically indicated (Appendix 3)
  - Blood for immune monitoring must be collected:
    - Day 0 OR Day 1 (after LN-144 AND prior to first IL-2 dose)
    - After last dose of IL-2, but no earlier than Day 3
- IL-2 treatment per Day 0 (Section 5.5.4.2.1)
- Filgrastim (5 µg/kg/day) or biosimilar will be administered beginning on Day 1 by subcutaneous injection and continue each day until the ANC reaches > 1000/mm^3 for three consecutive days, discontinue if ANC rises to > 10,000/mm^3,

or follow institutional standards. Refer to the current package insert or SmPC for filgrastim full prescribing information (Appendix 10)

- Fluconazole (400 mg PO or IV daily) will be administered beginning on Day 1 and continue daily until the ANC reaches > 1000/mm^3. Refer to the current package insert or SmPC for fluconazole full prescribing information (Appendix 11)
- Broad Spectrum ABX as per Day -7 (Section 5.5.1)

5.5.6. Procedures on Day 14 (± 3 Days) and Day 28 (EOT Visit; ± 3 Days)

The following procedures will be performed:

- ECOG performance status evaluation (Day 14 only)
- Physical examination (Appendix 3)
- Assessment of AEs/SAEs (Section 12.2.1)
- List all concomitant medications
- Blood tests:
  - Hematology (Appendix 3)
  - Chemistry
  - Thyroid panel to include TSH and free T4 on Day 14 only (Appendix 3)
  - Serum pregnancy test for women of childbearing potential (Day 28 [EOT visit] only)
  - Blood for immune monitoring (Day 14 only)
- If required, the following medications will be administered as follows or per institutional standards:
  - Filgrastim or biosimilar is administered as per Day 1 (Section 5.5.5)
  - Fluconazole is administered as per Day 1 (Section 5.5.5)
  - Trimethoprim-sulfamethoxazole double strength (TMP-SMX DS; 160mg/800 mg) to be administered daily beginning on Day 14 and continue until ALC reaches > 1000/mm^3 for three consecutive days; if at 6 months, ALC < 1000/mm^3, continue treatment until CD4 count is > 200/mm^3 for at least 6 months. Refer to the current package insert or SmPC for TMP-SMX full prescribing information
  - Viral prophylaxis: valacyclovir (500 mg PO daily), or acyclovir (250 mg/m^2 IV every 12 hours) if the patient is unable to take medication

by mouth. Valacyclovir PO or acyclovir IV should begin on Day 14, or as the Investigator deems appropriate, and continue until ALC > 1000/mm^3; if at 6 months, ALC < 1000/mm^3, continue until CD4 > 200/mm^3 for at least 6 months

- Broad Spectrum ABX as per Day -7 (Section 5.5.1)

5.6. Assessment Period

Following the EOT visit, efficacy/imaging (eg, tumor response) assessments will be performed at Week 6 (Day 42) with a + 7-day window. Subsequent assessments will occur every 6 weeks (± 3-days) until Month 6 (Week 24), and then every 3 months (12 weeks) with a ± 7-day window for up to 5 years from Day 0; or until disease progression or start of new anticancer therapy. Subsequently, patients will perform the EOA visit and begin the OS Follow-up Period (Section 5.7).

5.6.1. Procedures Every 6 Weeks (Week 6 [Day 42 {+ 7 Days}]; Week 12 [Day 84 {± 3 Days}], and Week 18 [Day 126 {± 3 Days}])

The following procedures will be performed:

- ECOG performance status evaluation
- Physical examination (Appendix 3)
- Vital signs (Appendix 3)
- Assessment of AEs/SAEs (Section 12.2.1)
- List all concomitant medications
- Blood tests
  - Hematology (Appendix 3)
  - Chemistry (Appendix 3)
  - Serum pregnancy test for women of childbearing potential
  - Blood for immune monitoring (Day 42 and Day 84 only)
- Evaluation and measurement of all skin and palpable lesions (if applicable)
- Slit-lamp eye examination in patients with history of uveitis, if clinically indicated (Day 84 only)
- Imaging assessments (Appendix 3)

  - Brain MRI following the Baseline visit should only be performed if clinically indicated or if positive at Baseline

- Tumor response assessment (per RECIST v1.1 and irRECIST)
- HRQoL questionnaire EORTC QLQ-C30 (Day 84 only; Appendix 14)
- If required, the following medications will continue to be administered as follows, or as per institutional standards:
  - Filgrastim or biosimilar is administered as per Day 1 (Section 5.5.5)
  - Fluconazole is administered as per Day 1 (Section 5.5.5)
  - TMP-SMX DS as per Day 14 (Section 5.5.6)
  - Herpetic treatment as per Day 14 (Section 5.5.6)
- On-study, post-treatment (post-LN-144 infusion) core biopsy at Week 6 (Day 42) following the first post-Baseline tumor response assessment scans
  - Mandatory when available and if patient consent is provided, two to six post-treatment core biopsies should be collected from a lesion distinct from those used as target or non-target for tumor response assessment
  - Refer to the Laboratory Manual for details on collection, processing, and shipment to the Central Laboratory

5.6.2. Procedures Every 3 Months (± 1 Week) Starting at Month 6 Until the End of Assessment (EOA)

The following procedures will be performed during these visits:

- ECOG performance status evaluation
- Physical examination (Appendix 3)
- Vital signs (Appendix 3)
- Assessment of AEs/SAEs (Section 12.2.1)
- List all concomitant medications
- Blood tests:
  - Hematology (Appendix 3)
  - Chemistry (Appendix 3)
  - Serum pregnancy test for women of childbearing potential (every 3 months until Month 12 or the EOA visit, whichever occurs first)
  - Blood for immune monitoring (Month 6, Month 9, and Month 12 only)

- Evaluation and measurement of all skin and palpable lesions (if applicable)
- Imaging assessments (Appendix 3)
- Tumor response assessment (per RECIST v1.1 and irRECIST)
- If required, the following medications will continue to be administered as follows or as per institutional standards:
    - Filgrastim (5 µg/kg/day) or biosimilar is administered by as per Day 1 (Section 5.5.5)
    - Fluconazole is administered as per Day 1 (Section 5.5.5)
    - TMP-SMX DS as per Day 14 (Section 5.5.6)
    - Herpetic treatment as per Day 14 (Section 5.5.6)
- HRQoL questionnaire EORTC QLQ-C30 (Month 6, Month 12, and Month 24; Appendix 14)

5.6.3. End of Assessment (EOA) Visit Procedures

The EOA visit will be completed at any time, post-Enrollment if: a patient withdraws from treatment, at the time of disease progression, or the start of a new anticancer therapy. Assessments performed within 14 days prior to the EOA visit do not need to be repeated.

The following procedures should be performed:

- Documentation of the cause leading to EOA
- ECOG performance status evaluation
- Physical examination (Appendix 3)
- Vital signs (Appendix 3)
- Assessment of AEs/SAEs (Section 12.2.1)
- List all concomitant medications
- Blood tests:
    - Hematology (Appendix 3)
    - Chemistry
    - Thyroid panel (Appendix 3)
    - Serum pregnancy test for women of childbearing potential

- Evaluation and measurement of all skin and palpable lesions (if applicable)
- Imaging assessments (Appendix 3)
- Tumor response assessment (per RECIST v1.1 and irRECIST)
- HRQoL questionnaire EORTC QLQ-C30 (Appendix 14)

Imaging assessment will be performed at least 28 days from the last date of progression to confirm disease progression per irRECIST, as applicable, as assessed by the Investigator.

5.7. Overall Survival Follow-up Period

The OS Follow-up Period will begin when a patient completes the EOA visit (last efficacy assessment) and will continue for up to 5 years from Enrollment or until discontinuation from the study (eg, withdrawal of consent to the study, lost to follow up, death, or study terminated by the Sponsor).

Patients who had tumor resection but did not receive LN-144 for any reason will perform an EOA visit and transition directly into OS Follow-up Period.

OS Follow-up will consist of telephone calls (or other means of contact) with the patient or designee every 3 months for survival and subsequent anticancer therapy.

5.8. Hospitalization

Patients will require hospitalization as per protocol preconditioning regimen, and for hydration prior to the LN-144 infusion through completion of IL-2 administration or per institutional standards.

Patients may also require hospitalization as per institutional guidelines (for tumor resection; fludarabine preconditioning regimen; and treatment recovery). However, if the institutional guidelines mandate a required hospitalization longer than the protocol, this pre-planned hospitalization event will not be considered as an AE.

All dates of hospitalization, regardless if required per protocol, including intensive care unit (ICU) stays, must be recorded in the Hospitalization eCRF.

6. CONCOMITANT MEDICATIONS AND NON-DRUG THERAPIES

6.1. Concomitant Medications

Use of all medications taken by the patient 28 days prior to signing the ICF will be recorded in the eCRF. All medications taken by the patient, or any changes in medications will also be recorded throughout the duration of the study, including those taken as part of the tumor-resection procedure.

6.2. Prohibited and Permitted Medications During Study Treatment

6.2.1. Prohibited Treatment

- Systemic therapies intended to treat melanoma or any medications that may have an antitumor effect
- Use of systemic corticosteroids are not allowed starting 21 days prior to beginning the NMA-LD preconditioning regimen, through treatment, and up to 60 days post-LN-144 infusion. Prophylactic use of systemic corticosteroids is not allowed under any circumstances. Such medications should only be used to treat immediate life-threatening conditions.
- Palliative radiation therapy that involves lesions selected as target or non-target
- Investigational drugs (other than LN-144)
- Live or attenuated vaccine within 28 days prior to beginning the NMA-LD preconditioning regimen or within 3 months after the last dose of IL-2 (Day 84) until ANC is $\geq 1000/mm^3$

6.2.2. Permitted Medications

Concurrent medications for conditions other than patients' unresectable or metastatic melanoma are permitted.

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

7. EXPECTED TOXICITIES AND TREATMENT GUIDELINES

The following sections present information for common adverse effects. For more details on side effects, refer to the Investigator's Brochure and relevant prescribing information.

An overdose is not applicable for LN-144. In the event of cyclophosphamide, fludarabine, or IL-2 overdose, refer to the package insert for details on management (Section 12.1.1.1).

7.1. Cyclophosphamide and Fludarabine Toxicities

Expected toxicities with cyclophosphamide and fludarabine administration, as well as supportive care and management of toxicities are listed in the package inserts (Appendix 7 and Appendix 12, respectively). Treatment will be given as per institutional standards.

In general, the use of the NMA-LD preconditioning regimen (cyclophosphamide and fludarabine) prior to LN-144 administration can to lead to myelosuppression. Therefore, a high index of suspicion for occult bacteremia should be maintained until marrow recovery.

Additional guidelines for toxicity management are outlined below.

7.1.1. Hemorrhagic Cystitis Prophylaxis

To reduce the risk of cyclophosphamide-associated hemorrhagic cystitis, patients will receive continuous infusion of mesna in addition to IV fluids. Higher doses of mesna are allowed if the institutional standards recommend. Refer to treatment guidelines for recommended mesna dosing (Appendix 8).

7.1.2. Fludarabine Hypersensitivity

Fludarabine has been reported to cause skin toxicity consisting primarily of skin rashes. If this or other fludarabine-related toxicity events occur, consultation with the Medical Monitor is recommended prior to administration of LN-144.

7.1.3. Blood Product Support

Using daily CBCs as a guide, the patient may receive platelets and packed red blood cells (PRBCs) as needed or as per institutional standards. Attempts will be made to keep Hb > 7.5 g/dL, and platelets > 10,000/mm^3. All blood products must 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.

7.2. LN-144 Toxicity

Toxicities related to the infusion of LN-144 (those which may be seen immediately following LN-144 infusion and prior to IL-2 administration), are generally mild and include fevers, chills, headache, and malaise. Dysgeusia may occur and should be limited to the duration of infusion. It also is possible that patients may experience severe allergic reaction including anaphylaxis that can be life threatening during infusion of LN-144 product.

7.2.1. Expected Toxicities with LN-144

Allergic reactions to components of the cryopreserved LN-144 product (Section 9.2) may present with symptoms such as rash, low blood pressure, shortness of breath, swelling of the face or throat, cough, chest tightness, and/or wheezing. These symptoms can usually be reversed promptly using an inhaled bronchodilator. Hypersensitivity events, including severe allergic reactions or anaphylaxis have occurred during infusion with LN-144 because hypersensitivity has been associated with at least one of the above-mentioned formulation components. Rarely have severe allergic reactions, such as anaphylaxis, developed. If anaphylaxis does occur, it will be treated immediately with an injection of epinephrine, steroids, and inhaled bronchodilators.

Patients who have known allergies to ABX of the aminoglycoside group are excluded from studies of LN-144 (except those who are skin-test negative for gentamicin). Premedication and supportive therapy instructions are provided in Section 7.2.2.

Details on the specific toxicities and risks may be found in the Investigator's Brochure.

7.2.2. LN-144 Toxicity Prevention and Management

During infusion of LN-144, appropriate emergency medications (eg, epinephrine and diphenhydramine) should be available at bedside, and institutional emergency guidelines should be followed as needed.

The following medications will be administered to the patient prior to LN-144 infusion as follows or as per institutional standards:

- Within 24 hours, hydration
- Within 30–60 minutes, premedicate the patient with acetaminophen (650 mg) or equivalent, and diphenhydramine (25–50 mg IV), or another H1-histamine antagonist
    - Prophylactic use of systemic corticosteroids is not allowed under any circumstances; such medications should only be used to treat immediate life-threatening conditions

Additional supportive therapy may include:

- Continued acetaminophen (650 mg q4h) or equivalent
- Indomethacin (50–75 mg q6h)
- Ranitidine (150 mg q12h)
- Meperidine (25–50 mg)
- Other medications as per institutional standards

7.3. IL-2 Toxicity

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 patients require significant supportive measures during this period, almost all toxicities are reversible, and most patients have experienced no long-term sequelae following this treatment regimen. However, fatal complications are possible. Subcutaneous administration of IL-2 is not permitted.

Refer to the prescribing information for IL-2 in Appendix 13.

7.3.1. Expected Toxicities with IL-2

7.3.1.1. Decreased Mental Status with IL-2

IL-2 can result in decreased mental status, which can range from somnolence to obtundation; continued administration may result in coma. Agitation may also be observed due to mild hallucinations. Administration of IL-2 should be withheld or permanently discontinued in patients with decreased mental status. See Appendix 4 and Appendix 5 for IL-2 AEs and toxicity management guidelines.

7.3.1.2. Pulmonary Risk

LN-144 can remain in the pulmonary circulation for 24–48 hours following infusion and may cause transient shortness of breath. In addition, pulmonary edema is commonly observed with IL-2 treatment. Supplemental oxygen should be administered as needed. Subsequent IL-2 dosing should be delayed until supplemental oxygen has been weaned or is minimal (< 2 L/min per nasal cannula). If hypoxia persists or is significant, then IL-2 should be withheld or stopped. Refer to Appendix 4 and Appendix 5 for IL-2 AEs and toxicity management guidelines.

7.3.1.3. Cardiac Arrhythmias and Myocarditis

All new cardiac arrhythmias should be promptly evaluated and continuously monitored with intensive management. Upon patient recovery from the cardiac event, continuation of IL-2 administration is per the Investigator's discretion.

7.3.1.4. Capillary Leak Syndrome

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

Resultant intravascular volume depletion should be managed with IV fluids. Diuresis should be initiated as tolerated following completion of IL-2 treatment. Hypotension not responsive to IV fluids should raise suspicion for occult bacteremia and associated sepsis.

7.3.1.5. Heparin-Induced Thrombocytopenia

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

7.3.2. Renal Toxicity

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

7.4. Infection Prophylaxis

Treatment with IL-2 is associated with impaired neutrophil function (reduced chemotaxis) and with an increased risk of disseminated infection, including sepsis and bacterial endocarditis. Preexisting bacterial infections should be adequately treated prior to start of IL-2 administration. 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.

Other anti-infective agents may be substituted at the discretion of the Investigator as per institutional standards.

7.4.1. *Pneumocystis jiroveci* Pneumonia

Pneumonia prophylaxis should begin on Day 14 and continue until ALC is > 1000/mm^3 or for at least 6 months post-chemotherapy at the discretion of the Investigator as per institutional standards. All patients will receive the fixed combination of TMP-SMX DS (160 mg/800 mg; PO) daily, three times a week on non-consecutive days, or as per institutional standards.

Pentamidine or alternative as per institutional standards may be substituted for TMP-SMX DS in patients with sulfa allergies. It will be administered aerosolized at 300 mg per nebulizer within 1 week prior to receiving study treatment and continued monthly until ALC is > 1000/mm^3.

If the ALC remains < 1000/mm^3 at 6 months post-chemotherapy, prophylaxis will continue until the CD4 count is > 200/mm^3 for at least 6 months, or as per institutional standards.

7.4.2. Herpes Virus Prophylaxis

Patients with positive HSV IgM or PCR assay will be given valacyclovir orally at a dose of 500 mg daily, or acyclovir 250 mg/m^2 IV every 12 hours if the patient is not able to take medication by mouth. IgM or PCR assay must be tested negative prior to initiation of NMA-LD.

Herpes prophylaxis should begin for all patients on Day 14 and will continue for at least 6 months, or until ALC count > 1000/mm^3. If ALC count remains < 1000/mm^3 at 6 months post-chemotherapy, prophylaxis will continue until the CD4 count is > 200/mm^3, or as per institutional standards.

Reversible renal insufficiency has been reported with IV, but not oral acyclovir. Neurologic toxicity including delirium, tremors, coma, acute psychiatric disturbances, and abnormal electroencephalogram (EEG) has been reported with higher doses of acyclovir. If this occurs, then the acyclovir dose should be adjusted or discontinued. Acyclovir cannot be used concomitantly with other nucleoside analogs, which interfere with deoxyribonucleic acid (DNA) synthesis (eg, ganciclovir). In renal disease, the dose is adjusted as per product labeling.

7.4.3. Fungal Prophylaxis (Fluconazole)

Patients will start fluconazole 400 mg PO or IV daily on Day 1 and continue until the ANC is > 1000/mm^3, or as per institutional standards. If ANC count remains < 1000/mm^3

at 6 months post-chemotherapy, prophylaxis will continue until the CD4 count is > 200/mm^3 for at least 6 months, or as per institutional standards.

7.4.4. Empiric Antibiotics

Patients will start on broad-spectrum ABX, either a third or fourth generation cephalosporin or a quinolone, for: fever (defined as 38.3°C, one or two temperatures of 38.0°C or above at least 1 hour apart); AND 1) ANC ≤ 500/mm^3; or 2) receiving IL-2 administration, or follow institutional standards.

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 institutional standards.

7.4.5. Sepsis

Sepsis can mimic IL-2 side effects. Fever may be masked during IL-2 administration due to scheduled indomethacin and acetaminophen or equivalent. Neutropenic patients exhibiting hypotension or oliguria unresponsive to IV fluids should be tested for infection, and broad-spectrum ABX should be initiated.

8. COMPLETION / DISCONTINUATION AND WITHDRAWAL OF PATIENTS

8.1. Treatment Completion

The Treatment Period is from Day -7 (start of NMA-LD preconditioning regimen) to Day 28 (EOT visit).

Treatment completion is defined as having received LN-144 infusion.

8.2. Criteria for Early Discontinuation from Treatment

Some patients may undergo tumor resection but will not receive infusion of LN-144. Such patients will perform an EOA visit and transition directly into the OS Follow-up Period of the study.

Patients may discontinue any component of the study regimen. Criteria for discontinuation from treatment:

- Withdrawal of consent to treatment (every effort should be made to continue OS Follow-up, when applicable)
- Grade ≥ 3 drug-related immune AEs that involve vital organs (heart, kidneys, brain, eye, liver, colon, adrenal gland, lungs) with symptoms emerging following LN-144 infusion
- Grade ≥ 3 allergic reaction including bronchospasm or generalized urticaria that does not resolve after medical management in the opinion of the Investigator
- Meeting criteria for permanent discontinuation of IL-2 treatment (must have received at least one dose of IL-2; Appendix 5)
- Determination by the Investigator that continued treatment is not in the best interest of the patient
- Administration of prohibited concomitant medications/start of new anti-cancer therapy
- Death

8.3. Assessment Completion / End of Assessment (EOA)

All patients will be assessed for up to 5 years from Day 0 or until disease progression or the start of new anticancer therapy.

8.4. Discontinuation from the Study

Patients will be discontinued from the study after 5 years from Enrollment (tumor resection), withdrawal of consent to the study, lost to follow-up, death, or if the study is terminated by the Sponsor.

8.5. Study Completion

The study is expected to be completed approximately 5 years (60 months) from Enrollment (tumor resection) of the last patient. This is the time point when all patients have exited the study for any reason, or study is terminated by the Sponsor, whichever occurs first.

9. STUDY DRUG INFORMATION

9.1. Investigational Product Overview

Investigational Product Name

- LN-144

Active Investigational Product Components

- Autologous TIL

Dosage Form

- Live cell suspension either noncryopreserved (Cohort 1) or cryopreserved (Cohort 2, Cohort 3, and Cohort 4)

9.2. Qualitative Composition of LN-144

The product is composed of autologous TIL obtained from an individual patient through surgical resection of tumor and expanded *ex vivo* through cell culture in the presence of IL-2 and a mAb to CD3. The cryopreserved final drug product is a cell suspension that is formulated in CryoStor® CS10 cryopreservation medium/Plasma-Lyte (final DMSO concentration: 5%) containing 0.5% HSA, and 300 IU/mL of IL-2. The non-cryopreserved final drug product, used to treat patients from Cohort 1, is formulated in HypoThermosol™ transport medium.

9.3. Manufacturing Process

An overview of the manufacturing process for cryopreserved product from tumor resection through to infusion of LN-144 product is provided in Figure 2.

LN-144 is manufactured *ex vivo* using autologous tumor as starting material. The key steps to manufacturing drug substance and drug product are:

Drug Substance

- Surgical removal of tumor tissue from a single patient and shipment of the material to the GMP manufacturing facility
- *Ex vivo* expansion of the TIL present in the tumor sample through placement of fragments of the tumor into medium containing the cytokine IL-2, and subsequent

expansion of the TIL through culture in medium with IL-2 and OKT3 mAb, and irradiated PBMC "feeder" cells

- Harvesting and washing of the cultured TIL

Drug Product

- Suspension of the culture-derived TIL in medium suitable for cryopreservation and patient infusion
- The product release specification requires that each LN-144 product lot contain between 1 x 10^9 and 150 x 10^9 viable cells. Patients will receive the full dose of product that is manufactured and released.

9.4. Final Investigational Product Container

Cryopreserved LN-144 is packaged in up to four cryopreservation bags containing 300–500 mL of viable cells. Each bag of product is labeled with patient-specific information.

9.5. Shipping/Transport of Investigational Product

LN-144 is shipped by express courier to the clinical site in a shipping container qualified to maintain a temperature of < -150°C for cryopreserved product.

9.6. Receipt of Investigational Product at Clinical Site

LN-144 will be received by the clinical site's pharmacy or designee prior to, or on, the day of infusion (Day 0). The date and time that possession of the product transfers from the courier to the clinical site will be documented on, and determined by, the courier's shipping paperwork.

10. RESPONSE ASSESSMENTS

10.1. Tumor Response Assessments

Tumor response assessments will be performed by clinical examination (skin lesions) and by conventional or spiral CT scans of the chest, abdomen, pelvis, and MRI of the brain. Photographic documentation and caliper measurement will be performed for superficial dermal and subcutaneous lesions that cannot be assessed by radiographic scan. Tumor assessments are planned for: Screening and Baseline (Day -21 to Day -10). Tumor response assessments are planned for: Week 6 (Day 42), then every 6 weeks until Month 6 (Week 24), and every 3 months (12 weeks) for up to 5 years from Day 0 or until the EOA visit has been completed.

CT scans of additional anatomical locations will be conducted at the above referenced visits if prior or suspected disease is clinically indicated. Additional radiological assessments may be performed per Investigator's discretion. All imaging assessments, including scheduled and unscheduled scans, must be recorded in the eCRF by the Investigator or designee, and will be assessed by the IRC.

High-resolution CT with PO/IV contrast or contrast-enhanced MRI is the preferred imaging modality for assessing radiographic tumor response. If a patient has a known allergy to CT contrast material, please use the alternate modality. In cases where contrast is strictly contraindicated, a non-contrast scan will suffice. The same image modality must be used throughout the study.

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

10.1.1. Response Criteria

Tumor response will be determined using RECIST v1.1 with a modification to require confirmation of PD per irRECIST performed at least 28 days from the last date of progression, as applicable, as assessed by the Investigator. Refer to Table 1 for RECIST v1.1 definitions. Images (CT scans and/or MRI scan) obtained at Baseline visit (Day -21

to Day -10) are to be utilized for RECIST v1.1 response assessments throughout the study.

Tumor response assessments performed at the site should be used for clinical treatment decisions and may include photographic and caliper measurement of superficial dermal and subcutaneous lesion.

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

10.1.1.1. Definition of Target and Non-Target Lesions

Patients should have at least one measurable target lesion as defined by RECIST v1.1. If the patient has only one identified target lesion at Screening, then another lesion needs to be identified and harvested for TIL generation. If a lesion was partially resected to generate TIL, and remains visible on the Baseline scan after surgery, then the partially resected lesion can be used for RECIST v1.1 response assessment, but only as a non-target lesion.

Ideally, Baseline target lesions should have also been measured at Screening so as to understand the tumor dynamics and potentially identify hyperprogressors.

Lesions in previously irradiated areas (or other local therapy [eg, talimogene laherparepvec {TVEC}]) should not be selected as target lesions unless treatment was ≥ 3 months prior to Screening and there has been demonstrated disease progression of the lesion.

The on-study, post-treatment (post-LN-144 infusion) core biopsy at Week 6 is mandatory, when available and if patient consent is provided, and should be done in a lesion not being followed for response assessment (either as a target or as a non-target lesion; Section 5.6.1).

10.1.1.2. Evaluation of Best Overall Response

The best overall response is the best response recorded from the first post-Baseline tumor assessment at Week 6 (Day 42) until disease progression or the start of a new anticancer

therapy. The patient's best response assignment will depend on target lesion sum of diameters (SoD), non-target lesion status, absence of a new lesion, and the confirmation criteria. The best overall response is determined once all the data for the patient is known.

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

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

Abbreviations: CR=complete response; PD=progressive disease; PR=partial response; SD=stable disease

10.2. Biomarkers

Immune monitoring samples and tumor specimens will be collected to identify biomarkers of LN-144. Refer to the Laboratory Manual for additional details.

11. STATISTICAL AND ANALYTICAL PLANS

11.1. Introduction

The statistical analysis will be performed by cohort. Patients who receive a second TIL regimen therapy (Cohort 3) will have their safety and efficacy data tabulated separately. Rescreened patients, who received LN-144 for the first time due to a previous manufacturing failure or other reasons, will be included in the analysis sets of the original cohort. There is no planned statistical comparison among cohorts.

11.2. Study Analysis Sets

Two analysis sets are defined for the analysis and presentation of the data. The Full Analysis Set (FAS) will be the primary set for the analysis of safety and efficacy data. Additional analysis for the primary efficacy endpoint, AEs, and SAEs will be conducted using the Tumor Harvested (TH) Set.

11.2.1. Tumor Harvested Set (also termed Enrolled Set)

The TH Set is defined as all tumor-resected patients for production of LN-144, regardless of whether they have received treatment or not.

11.2.2. Full Analysis Set

The FAS is defined as patients who have received LN-144 infusion.

11.3. Endpoints

11.3.1. Primary Endpoint

The primary endpoint is the ORR using RECIST v1.1 criteria as assessed by the IRC. Patients without any baseline or any post-baseline tumor measurements are considered non-evaluable.

11.3.2. Secondary Endpoints

The secondary endpoints will include DOR, DCR, and PFS per RECIST v1.1 criteria as assessed by the IRC. In addition, the secondary endpoints will include the ORR, DOR,

DCR, and PFS per RECIST v1.1 criteria as assessed by the Investigator. OS will be assessed as a secondary endpoint.

The DOR is measured from the time point at which the initial measurement criteria are met for a CR or PR, whichever response is observed first, until the first date that PD or death occurs. Patients not experiencing PD or death prior to the time of data cut or database lock will have their event times censored on the last complete tumor response assessment date. For patients who received new anticancer therapies, the DOR will be censored at the date of last tumor response assessment prior to the start of new anticancer therapies. DCR is the sum of confirmed CR/PR and stable disease tumor responses divided by the number of patients in the analysis set. PFS is defined as the time (in months) from the start date of LN-144 infusion to PD or death due to any cause, whichever occurs earlier. Patients not experiencing PD or death at the time of data cut or database lock will have their event times censored on the last tumor response assessment date. For patients who received new anticancer therapies, the PFS is measured from the date of LN-144 infusion to the date of last tumor response assessment prior to the start of new anticancer therapies.

The OS is defined as the time (in months) from the start date of LN-144 infusion to death due to any cause. Patients not having expired at the time of data cut 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 AEs, clinical laboratory tests, and vital signs.

11.3.3. Exploratory Endpoints

The exploratory endpoints include measures of LN-144 persistence in the peripheral blood as well as immune response with the objective to evaluate their correlation with response, outcome, and toxicity of the treatment. Tumor responses (ORR, DOR, DCR, and PFS) per irRECIST will be assessed by the Investigator. HRQoL will be assessed using the EORTC QLQ-C30 instrument (Appendix 14) and scored/evaluated as described in the Statistical Analysis Plan (SAP).

11.4. Sample Size Consideration

Cohort 1: Infused 23 patients using the non-cryopreserved autologous TIL product manufacturing process. Enrollment into this cohort was stopped to focus on the cryopreserved autologous TIL product manufacturing process.

Cohort 2: Approximately 66 patients are planned to be infused and receive cryopreserved LN-144. Sixty patients will allow estimation of ORR using the maximum half width of the two-sided 95% confidence limit of less than 13.2% (Clopper-Pearson) when ORR is expected to range from 20–50%.

Cohort 3: This cohort will infuse approximately 10 patients from Cohort 1, Cohort 2, or Cohort 4 who have elected to undergo a second retreatment.

Cohort 4: Approximately 75 patients are planned to be infused and receive cryopreserved LN-144. It will test the prospectively defined hypothesis for the primary endpoint of ORR as assessed by the IRC based on the null hypothesis of ORR ≤ 10% and alternative hypothesis of ORR > 10%. A sample size of 75 patients in the FAS will provide more than 90% power to demonstrate statistical significance at a two-sided overall significance level of 0.05 using the exact test. It is assumed the true response rate for TIL therapy in this population is 25%.

Justification of the null hypothesis of ORR ≤ 10% for Cohort 4 based on historical control estimate:

As cited in the National Comprehensive Cancer Network (NCCN) guideline for metastatic melanoma and/or frequently observed as prior therapies in Cohorts 1 and 2, only DTIC is an approved therapy for the metastatic melanoma patient population. Other agents such as carboplatin, paclitaxel, docetaxel, nab-paclitaxel and temozolomide are not approved by the US Food and Drug Administration (FDA) and therefore they are not appropriate comparators for Cohort 4 of LN-144.

Table 2 below is a summary of historical studies that included a DTIC monotherapy arm. The first half of the table summarizes those trials conducted in the post-checkpoint era,

therefore more closely matching the patient population planned to be enrolled in this study. Of note, Cohort 2 enrolled patients who received a mean of 3.3 prior lines including a checkpoint inhibitor, which presents a population with an overall worse prognosis.

Table 2 Historical Studies with DTIC Monotherapy in Advanced or Metastatic Melanoma

Population	Study arms	ORR from DTIC arm	Publication
Checkpoint Inhibitor Era			
Post-anti-PD-1 (no prior BRAF/MEK), metastatic melanoma	various chemotherapies	10%	[Goldinger 2018]
Post-ipilimumab (+/- BRAF inhibitor), advanced melanoma	nivolumab vs ICC	10.6%	[Weber 2015]
Treatment-naïve, unresectable stage IIIc or IV, melanoma	tremelimumab vs chemotherapy	9.8%	[Ribas 2013]
Chemo-naïve, metastatic melanoma (65% stage M1c), 9% received a prior therapy for metastatic disease in DTIC arm	Nab-paclitaxel vs DTIC	11%	[Hersh 2015]
Prior to Checkpoint Inhibitor Approval			
Chemo-naïve, advanced melanoma		7.5%	[Bedikian 2006]
Treatment-naïve metastatic melanoma		10.3%	[Robert 2011]
Advanced melanoma trials up to 2010 (multiple studies)		5–12%	[Livingstone 2012]
Treatment-naïve for metastatic melanoma		7.2%	[Avril 2004]
30-year overview of metastatic melanoma		5–20% *	[Serrone 2000]
Overview of 24 metastatic melanoma clinical trials		15.3% (average) *	[Lui 2007]

Abbreviations: BRAF=proto-oncogene B-Raf; DTIC=dacarbazine; ICC=Investigators' choice of chemotherapy; MEK=mitogen-activated extracellular signal-regulated kinase; ORR=objective response rate
* No specific information was available on the study design and its patient population in some studies reached ORR > 15%. All patients were naïve to anti-PD-1 and exposure to a prior BRAF inhibitor if mutated was unknown.

The patient population that most closely matches C-144-01 Cohort 4 is represented in the first referenced publication [Goldinger 2018]. The patient populations from all other studies listed in Table 2 are earlier lines without prior anti-PD-1 and not pertinent comparators for the C-144-01 study population. The 10 % ORR observed in this study is supported by consistently low ORRs seen in other recent studies, which enrolled treatment-refractory and treatment-naïve patients. These data support a null hypothesis of 10%, which will be used to determine the sample size and in the demonstration of efficacy in this cohort.

Furthermore, response rates to chemotherapy, including DTIC, in multiple recent phase 3 melanoma trials ranged from 4–10% (studies comparing DTIC with trametinib or vemurafenib in patients with BRAF V600 mutant tumors; or pembrolizumab and nivolumab in patients who are refractory to ipilimumab) [Hamid 2017; Weber 2015].

The historical control ORR of 10% for advanced melanoma was also used for the single arm study Keynote-001 [Kang 2017], which enrolled ipilimumab-naïve patients, and for the randomized study Checkmate-037 after it discontinued the control arm (ie, Investigators' choice) due to a high dropout rate.

11.5. Final Analysis

An interim analysis of patients within Cohort 4 will not be conducted for this study. The primary analysis will be conducted after all Cohort 4 patients have been infused.

The primary statistical analysis will utilize a two-sided significance level of 0.05. The lower bound of the two-sided 95% Clopper-Pearson exact CI for ORR would need to be > 10% to reject the null hypothesis. The details will be described in the SAP.

11.6. Statistical Analyses

11.6.1. Patient Disposition

Patient disposition (analysis population allocation, entered, completed, discontinued, along with primary reason for discontinuation) will be summarized using frequency and percentage. A summary of patients enrolled by site will be provided.

11.6.2. Baseline Demographics and Clinical Characteristics

Baseline (Day -21 to Day -10) demographic and clinical (disease) characteristics will be summarized descriptively for the FAS.

11.6.3. Analysis of the Primary Efficacy Endpoint

The ORR as assessed by the IRC is expressed as binomial proportions and will be summarized for the best overall response using a point estimate and its two-sided

confidence limits based on the Clopper-Pearson exact method, at an overall alpha level of 0.05.

11.6.4. Analysis of the Secondary Efficacy Endpoints

The DCR is expressed as binomial proportions and will be summarized using both a point estimate and its two-sided 95% confidence limits based on the Clopper-Pearson exact method.

The PFS, OS, and DOR are time-to-event variables subjected to right censoring. Kaplan-Meier probabilities and related summary statistics will be provided for the entire time-to-event curve as well as for the following landmark event-free rates: 6 months, 12 months, 18 months, and 24 months from the date on which patients received LN-144 infusion (Day 0), depending on the maturity of the study data at the time of analysis.

11.6.5. Safety Analysis

The assessment of safety data will be descriptive and based on the summarization of TEAEs, SAEs, and AEs leading to discontinuation from the study, vital signs, and clinical laboratory tests. Treatment emergent is considered to start at the time of the LN-144 infusion through 30 days post-infusion for the FAS. AE summaries will be based on patient incidence counts and their related percentages. In addition to an overall summary of AEs, 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 v4.03 for each measure under consideration (eg, ANCs for neutropenia; platelets for thrombocytopenia; Appendix 6).

11.6.6. Other Planned Analyses

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

12. SAFETY MONITORING AND REPORTING

12.1. Adverse Events

Safety events will be recorded as AEs and SAEs in the patient's source documents and on the AE eCRF, and must be graded using the NCI's CTCAE v4.03 dated 14 June 2010 (Appendix 6).

12.1.1. Definitions

12.1.1.1. Adverse Event

An AE as defined by the International Conference on Harmonisation (ICH) Guidelines for Good Clinical Practice (GCP) as any untoward medical occurrence in a patient or clinical trial patient starting from signing the ICF, which does not necessarily have a causal relationship with LN-144 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 LN-144.

Events meeting the definition of an AE include:

- AE temporally associated with the use of any of the study drugs, including LN-144 treatment, whether or not considered related to the use of any of the study drugs or LN-144 treatment
- Abnormal laboratory test values or results (eg, hematology, clinical chemistry, urinalysis) or other safety assessments (eg, ECGs, radiological scans, vital sign measurements, significant physical examination changes) or events related to protocol mandated procedures (eg, incidental patient injury during a procedure), will be reported as AEs only if they are deemed by the Investigator as being clinically significant, led to hospitalization or prolongation of hospitalization, required a change in dosing or treatment of study therapies, or required initiation of concomitant therapy for laboratory abnormalities
- Exacerbation of a chronic or intermittent pre-existing condition including either an increase in frequency and/or intensity of the condition
- New conditions detected or diagnosed after LN-144 administration
- Signs, symptoms, or the clinical sequelae of a suspected interaction with LN-144

- Signs, symptoms, or the clinical sequelae of special situations (eg, suspected overdose of either cyclophosphamide, fludarabine, IL-2, or a concomitant medication; medication error; product complaint; or occupational/accidental exposure)

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

- Any clinically significant abnormal laboratory finding or other abnormal safety assessments that is associated with the underlying disease, unless judged by the Investigator to be more severe than expected for the patient's condition
- Medical or surgical procedure (eg, endoscopy, appendectomy). The condition that leads to the procedure is an AE
- Situations where an untoward medical occurrence did not occur (social and/or convenience admission to a hospital)
- Special situations, as described above (eg, overdose from a study medication or concomitant medication; medication error; product complaint; or occupational/accidental exposure) without clinical sequelae (Section 12.2.1)
- Anticipated day-to-day fluctuations of pre-existing disease(s) or condition(s) present (eg, AE grade change from 1 to 2 is an anticipated fluctuation) 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.

12.1.1.2. Serious Adverse Event

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

- Death
- A life-threatening situation
- Requires 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
- An important medical event or a medically significant event that may not result in death, be immediately life-threatening, or require hospitalization but may be

considered serious when, based on appropriate medical judgment, the event may jeopardize the subject or may require medical or surgical intervention to prevent one of the outcomes listed above

Note: Hospitalization including admission to a telemetry unit or ICU specifically when pre-planned for administration of study treatment is not considered an SAE.

12.1.1.3. 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, too late, or study drug not taken), or there is known causal relationship between the AE/SAE and another drug, concurrent disease, or other circumstance

12.1.1.4. 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 v4.03 (Appendix 6). If the CTCAE v4.03 does not apply, the severity descriptions below will be used:

Mild: Asymptomatic, clinical or diagnostic observations only; intervention not indicated

Moderate: Minimal, local, or noninvasive intervention indicated; limiting age-appropriate activities of daily life

Severe: Medically significant but not immediately life-threatening; hospitalization or prolongation of hospitalization may be required; disabling; limiting activities of daily life

Life-threatening: Urgent intervention is required

12.2. Reporting Procedures for Adverse Events

12.2.1. All Adverse Events

All AEs/SAEs occurring after the patient has signed the ICF will be collected and recorded in the eCRFs and graded as per CTCAE v4.03. Disease progression is not considered an AE for the purposes of this study.

AEs will be collected and reported according to the following temporal intervals:

- Signed ICF to tumor resection (SAEs only, if patient did not have tumor resected)
- Tumor resection to start of NMA-LD preconditioning regimen (AEs and SAEs)
- NMA-LD preconditioning regimen to Day 0 (AEs and SAEs)
- Day 0 to Day 30 (TEAEs and treatment-emergent SAEs)
- Day 30 through 6 months post-LN-144 infusion, or the start of new anti-cancer therapy, whichever occurs first (Grade 3 and Grade 4 AEs; SAEs, if at least related to any study drug)
- Post-Month 6, only SAEs related to LN-144 will be collected and reported

Medically significant AEs considered related to LN-144 by either the Investigator or the Sponsor will be reported and followed until resolved or resolved with sequelae.

If a patient dies while on the study, the Investigator will inform the Sponsor within 24 hours and report the cause of death as an SAE. The clinical event leading to 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. On the SAE Report Form, the cause of death should be recorded as follows:

- If due to an AE, it should be specified from which AE
    - Disease progression is not considered an AE
- If due to sequelae of disease under study, the specific reason should be identified (eg, clinical deterioration, respiratory insufficiency, liver failure, etc.)
- If due to "other" causes, the specific cause should be identified
- For patients who expired during OS Follow-up and medical records were unavailable, the cause of death should be marked as "unknown"

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 if 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 LN-144 due to an SAE, this information must be included in either the initial or follow-up SAE Report Form and in the eCRF.

12.2.1.1. Investigator Reporting to Sponsor

All SAEs of any attribution will be collected from the time the patient signs the ICF through Day 30. In patients who fail the initial Screening process, any SAEs occurring after signing ICF until study discontinuation (ie, the day of screen failure) will be collected.

Only Grade 3 and Grade 4 AEs and SAEs possibly attributed to any study drug should be reported from Day 30 through 6 months post-LN-144 infusion, or the start of a new anti-cancer therapy, whichever occurs first. After 6 months, only SAEs related to LN-144 will be collected and reported.

If the Investigator learns of any SAEs that occur after the OS 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 contract research organization (CRO).

All SAEs that occur during the study must be reported by the Investigator to the Sponsor or designee within 24 hours of learning of the event. The initial notification should be as complete as possible with the information available and include the Investigator's assessment of study drug relationship, as defined in Section 12.1.1.3. All AEs, regardless of their severity, will be captured in the eCRF within the timelines outlined in the eCRF completion guidelines.

SAE terminology and severity grading will be based on the NCI's CTCAE v4.03 guidelines (Appendix 6).

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

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

12.2.1.2. Special Situation Reporting

Definition of Special Situations

Special situation reports include: reports of medication error; overdose; AEs associated with product complaints; occupational exposure; and pregnancy reports regardless of an associated AE. Medication error is considered any unintentional error in the prescribing,

dispensing, or administration of 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 that is above the maximum recommended dose as per protocol or in the product label.

Product complaints are 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 product as a result of one's professional or nonprofessional occupation.

Special situation reports must be reported to the Safety CRO using the SAE Report Form within 24 hours of becoming aware of the situation.

12.2.1.3. Pregnancy Reporting

Any pregnancy that occurs while on the study through 12 months from the last study treatment or until the first dose of the next anticancer therapy, whichever occurs first, must be reported using the Pregnancy Report Form within 24 hours of becoming aware of the pregnancy. The pregnancy itself is not considered an AE, nor is an induced abortion to terminate a pregnancy without medical reasons. Any premature termination of pregnancy (eg, a spontaneous abortion, an induced therapeutic abortion due to complications, or other medical reasons), must be reported within 24 hours as an AE or SAE. The underlying medical reason for this procedure should be recorded as the AE or SAE term. A spontaneous abortion is always considered to be an SAE and will be reported as described in Section 12.2.1.2.

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 Assessment Period follow-up visits, must be promptly reported to the Sponsor or their representative.

The pregnancy must be followed up until discharge following delivery or premature termination to determine outcome and status of mother and child. Pregnancy complications and elective terminations for medical reasons must be reported as an AE or SAE. Spontaneous abortions must be reported as an SAE. Any SAE occurring in association with a pregnancy, brought to the Investigator's attention after the patient has completed the study, and considered by the Investigator as possibly related to LN-144, 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.

12.2.1.4. Regulatory Reporting Requirements

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

Assessment of expectedness for SAEs will be determined by Iovance Biotherapeutics Inc. using reference safety information (RSI) in the Investigator's Brochure and relevant prescribing information for TIL, as well as the RSI for cyclophosphamide, fludarabine and IL-2. Assessment of expectedness based on local label (US package insert [USPI]) for cyclophosphamide, fludarabine, and IL-2 will apply for reports to the FDA.

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 (CFR) 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 that occur during the trial including the post-study treatment follow-up phase.

12.2.1.5. Product Complaints

The Sponsor collects product complaints arising from potential deviations in the manufacture, packaging, or distribution of LN-144 in order to ensure the safety of study participants, monitor quality, and facilitate process and product improvements.

All product complaints associated with material packaged, labeled, and released by the Sponsor or its designee will be reported to the Sponsor. All product complaints associated with other study material will be reported directly to the respective manufacturer.

The Investigator or his/her designee is responsible for reporting a complete description of the product complaint via email or other written communication to the Sponsor contact or respective manufacturer as noted in the packaging information. Any AE associated with a product complaint should be reported as described in Section 12.2.

If the Investigator is asked to return the product for investigation, he/she will return a copy of the product complaint communication with the product. Any AE associated with a product complaint should be reported as described in Section 12.2.1.2.

12.3. Data Safety Monitoring Board

A Data Safety Monitoring Board (DSMB) has evaluated cumulative safety data as specified in the DSMB charter for Cohort 1 and Cohort 2. A meeting will also take place after 3 patients have been treated in Cohort 3 (initially infused patients who have been re-treated with a second course of LN-144) and 28 days have elapsed (end of treatment visit and safety assessments). Enrollment in Cohort 4 will continue while the DSMB reviews the patient data.

13. INDEPENDENT DATA MONITORING COMMITTEE

An Independent Data Monitoring Committee (IDMC) composed of a group of clinicians appointed by Iovance will provide oversight of this clinical trial to ensure the study is being conducted with the highest quality, scientific, and ethical standards and to ensure quality and consistency of study conduct as well as data collection and analysis across international study sites. The IDMC will review the study data when up to a total of 30 patients have completed 28 days of assessments post-LN-144 infusion for Cohort 4. Enrollment will continue while data is under review. IDMC will also review the study data after up to a total of 75 patients in Cohort 4 have completed 28 days of assessments post-LN-144 infusion.

14. ADMINISTRATIVE REQUIREMENTS

14.1. Good Clinical Practice

The procedures set out in this study protocol pertaining to the conduct, evaluation, and documentation of this study are designed to ensure that the Sponsor, its authorized representative, and Investigator abide by GCP, as described in ICH Guideline (ICH E6) and in accordance with the general ethical principles outlined in the Declaration of Helsinki. The study will receive approval from an IRB/IEC prior to commencement. The Investigator will conduct all aspects of this study in accordance with applicable national, state, and local laws of the pertinent regulatory authorities.

The specific contact details of the Iovance Biotherapeutics Inc. 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.

14.2. Adherence to the Protocol

The Investigator is responsible for ensuring the study is conducted in accordance with the procedures and evaluations described in the protocol. The Investigator will not deviate from this protocol without obtaining the concurrence of the Sponsor, specifically without discussion with the Medical Monitor. All protocol amendments must be issued by the Sponsor, signed and dated by the Investigator, and should not be implemented without prior IRB/IEC approval, except where necessary to eliminate immediate hazards to the patients or when the change(s) involves only logistical or administrative aspects of the trial (eg, change in Medical 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.

14.3. 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 LN-144. These documents will be retained for a longer period if required by the applicable regulatory requirements or by an agreement with the Sponsor. It is the responsibility of the Sponsor to inform the Investigator/Institution as to when these documents no longer need to be retained. If the responsible Investigator retires, relocates, or for other reasons withdraws from the responsibility of keeping the study records, custody must be transferred to a person who will accept the responsibility. The Sponsor must be notified in writing of the name and address of the new custodian.

14.4. 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).

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; and periodic monitoring visits by the Sponsor/designee. The eCRFs 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.

14.5. Data Handling and Recordkeeping

14.5.1. Regulatory Approval and Documentation

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

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

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

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

14.5.2. Electronic Data

When using electronic data processing, the Sponsor or their designee ensures 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 Standard Operating Procedures (SOPs) for that particular task.

14.5.3. Data Handling and Recordkeeping

14.5.3.1. Electronic Case Report Form (eCRF) Completion

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.

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.

14.6. Study Completion/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

Upon completion of the study, the Investigator will ensure that the complete set of source data has been entered into the eCRFs.

14.7. 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 AEs, administration of concomitant medications, 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.

15. INVESTIGATOR REGULATORY OBLIGATIONS

15.1. Institutional Review Board/Independent Ethics Committee (IRB/IEC)

Before Enrollment of patients into the study, as required by federal regulations (21 CFR 56), international regulations, and ICH-GCP Guidelines, the protocol and ICF(s) must be reviewed and approved by an appropriate IRB/IEC. By signing the FDA Statement of Investigator Form 1572 or the Sponsor's Statement of Investigator Commitments, the Investigator assures that all aspects of the institutional review will be conducted in accordance with current applicable regulations. A letter documenting the IRB/IEC approval with the names and titles of the IRB/IEC members must be received by the Sponsor before the initiation of the trial. Amendments to the protocol will be subject to the same requirements as the original protocol. In other countries, the protocol and any amendments must be approved by the concerned IECs as per the applicable laws and requirements on the national and EU level.

15.2. Informed Consent

Each patient (or a legally authorized representative) must give written consent (and sign other locally required documents) according to local requirements after the nature of the study has been fully explained. The consent form must be signed prior to performance of any study-related activity. The consent form that is used must be approved both by the Sponsor and by the reviewing IRB/IEC. The informed consent should be in accordance with the current revision of the Declaration of Helsinki, current ICH and GCP guidelines, Directive 2001/20/EC (and when in force EU Regulation 536/2014), and General Data Protection Regulation 2016/679 (GDPR), as interpreted by the national laws and regulatory bodies, and the Sponsor's policies.

The Investigator must explain to potential patients or their legal representatives the purpose, methods, reasonably anticipated benefits and potential hazards of the study, its duration, and any discomfort it may entail. Patients will be informed in their native language, comprehensive, concise, clear, relevant, and understandable to a layperson, that their participation is voluntary and that they are free not to participate in the study and 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 patient or his/her legally designated representative to consider his/her decision to participate in the study.

In accordance with the Health Insurance Portability and Accountability Act (HIPAA), the written ICF must include a patient authorization to release medical information to the Sponsor or their representative and/or allow the Sponsor or their representative, a regulatory authority, or IRB/IEC access to patient's medical information that includes all hospital records relevant to the study, including a patient's medical history and other data that may identify him/her, including the purpose of this access and data processing connected with it.

15.3. Patient Data Protection

The Investigator at each site and designees, employees, and agents involved with the study will comply with relevant state, federal national, and regional 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 Investigator or their employees or agents during the course of the study to the Sponsor, the Sponsor's collaborators, IRB/IEC, FDA, European Medicines Agency (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.

Patients will not be individually identified but will be referred to in records by the study-assigned number and patient initials (if allowed by law).

15.4. Adverse Event Reporting

The Investigator agrees to report all AEs/SAEs to the Sponsor as described in Section 12. Furthermore, the Investigator is responsible for ensuring that any co-Investigator or sub-Investigator promptly bring AEs to the attention of the Principal Investigator. The Investigator shall promptly notify the IRB/IEC of any SAEs, or any other information that may affect the safe use of LN-144 during the course of the trial as applicable per the local IRB/IEC requirements.

15.5. Investigator

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

15.6. Confidentiality

Unless otherwise specified in the clinical study agreement, the following process shall occur: the Investigator must assure that patients' anonymity will be maintained and that their identities are protected from unauthorized parties. In the eCRFs or other documents submitted to the Sponsor, patients should not be identified by their names, but by an identification code. The Investigator should keep a site-enrollment log showing codes,

names, and addresses. Documents not for submission to the Sponsor (eg, patients' written ICFs) 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.

15.7. Publications

The Sponsor will be responsible for determining when the study results should be published after discussion with the Steering Committee. The Sponsor will work jointly with the Investigators to publish information on study results. An Investigator shall not submit a publication or abstract to journals or scientific meetings without the prior written approval of the Sponsor, except as permitted by the agreed terms of the clinical trial agreement, including after the reporting of the results of this multi-center study by the Sponsor and other institutions.

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APPENDICES

Appendix 1 SCHEDULE OF ASSESSMENTS

Assessments	Screening, Enrollment, & Baseline Period			Treatment Period (All visit dates are calculated from LN-144 infusion [Day 0])														Assessment Period (All visit dates are calculated from LN-144 infusion [Day 0])			Overall Survival Follow-up Period [a]
	Screening (≤ 28 days from ICF signature)	Enrollment/Tumor Resection	Baseline (Day -21 to Day -10)	Day -7	Day -6	Day -5	Day -4	Day -3	Day -2	Day -1	Day 0	Day 1	Day 2	Day 3	Day 4	Day 14 (± 3 days)	End of Treatment Visit Day 28 (± 3 days)	Every 6 Weeks (Week 6 [+ 7 days], Week 12 [± 3 days], and Week 18 [± 3 days])	Every 3 Months (± 1 Week) (Starting at Month 6)	EOA Visit [b]	Every 3 Months (± 3 Weeks)
SCREENING																					
Informed consent	X																				
Inclusion/Exclusion	X		X [c]																		
Demographics	X																				
Medical history [d]	X																				
Melanoma medical history	X																				
ECOG performance status	X		X	X												X		X	X	X	
Physical examination [e]	X [e]	X	X	X [e]	X	X	X	X	X	X	X [e]	X	X	X	X	X	X	X	X	X	
Vital signs	X		X	X	X	X	X	X	X	X	X [f]	X [f]	X [f]	X [f]	X [f]			X	X	X	
Skin test for hypersensitivity [g]	X																				
GENERAL PROCEDURES																					
Eye examination (slit lamp) [h]	X																	X			
ECG	X [i]		X																		
ECHO or MUGA (and stress test) [j]	X																				
PFT	X																				
Colonoscopy [k]	X																				
GENERAL ASSESSMENTS																					
Assessment of AEs/SAEs	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X [l]	X	X

Assessments	Screening, Enrollment, & Baseline Period			Treatment Period (All visit dates are calculated from LN-144 infusion [Day 0])														Assessment Period (All visit dates are calculated from LN-144 infusion [Day 0])			Overall Survival Follow-up Period [a]
	Screening (≤ 28 days from ICF signature)	Enrollment/Tumor Resection	Baseline (Day -21 to Day -10)	Day -7	Day -6	Day -5	Day -4	Day -3	Day -2	Day -1	Day 0	Day 1	Day 2	Day 3	Day 4	Day 14 (± 3 days)	End of Treatment Visit Day 28 (± 3 days)	Every 6 Weeks (Week 6 [+ 7 days], Week 12 [± 3 days], and Week 18 [± 3 days])	Every 3 Months (± 1 Week) (Starting at Month 6)	EOA Visit [b]	Every 3 Months (± 3 Weeks)
Concomitant medications [m]	X [m]	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	
Hospitalization(s) [n]										X	X	X	X	X	X						
Survival status/anti-cancer therapy [a]																					X
IMAGING & TUMOR RESPONSE ASSESSMENT																					
Evaluation and measurement of skin and palpable lesions [o]	X		X															X	X	X	
Tumor assessment [p]	X [p]		X [p]															X	X	X	
CT – chest, abdomen, pelvis [q]	X		X															X	X	X [r]	
MRI – brain [s]	X		X															X	X	X [r]	
LABORATORY EVALUATIONS																					
Hematology	X		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	
Coagulation	X																				
Chemistry	X		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	
Thyroid panel	X															X				X	
ß-HCG pregnancy test [t]	X		X	X							X						X	X	X [t]	X [t]	
Dipstick urinalysis [u]	X		X	X			X			X	X	X	X	X	X						
SEROLOGY TESTING																					
HIV Ab	X	X [v]																			
HBsAg, anti-HBc	X	X [v]																			
HCV Ab	X	X [v]																			
Syphilis testing	X	X [v]																			
HSV	X [w]																				

Assessments	Screening, Enrollment, & Baseline Period			Treatment Period (All visit dates are calculated from LN-144 infusion [Day 0])														Assessment Period (All visit dates are calculated from LN-144 infusion [Day 0])			Overall Survival Follow-up Period [a]
	Screening (≤ 28 days from ICF signature)	Enrollment/Tumor Resection	Baseline (Day -21 to Day -10)	Day -7	Day -6	Day -5	Day -4	Day -3	Day -2	Day -1	Day 0	Day 1	Day 2	Day 3	Day 4	Day 14 (± 3 days)	End of Treatment Visit Day 28 (± 3 days)	Every 6 Weeks (Week 6 [+ 7 days], Week 12 [± 3 days], and Week 18 [± 3 days])	Every 3 Months (± 1 Week) (Starting at Month 6)	EOA Visit [b]	Every 3 Months (± 3 Weeks)
CMV	X																				
EBV	X																				
TUMOR RESECTION																					
Tumor resection		X																			
Intraoperative frozen section (or FNA) or touch prep cytology		X																			
Post-treatment (LN-144) biopsy																		X [x]			
TREATMENT																					
Authorization to Receive Lymphodepletion [y]				X																	
Cyclophosphamide (with mesna)				X	X																
Fludarabine						X	X	X	X	X											
LN-144 infusion [z]											X										
IL-2 [aa]											X	X	X	X	X						
PROPHYLACTIC MEDICATIONS																					
Ondansetron				X	X																
Filgrastim [bb]												X	X	X	X	X	X	X	X		
Fluconazole [cc]												X	X	X	X	X	X	X	X		
TMP-SMX DS, or appropriate ABX [dd]																X	X	X	X		
Broad spectrum ABX				X	X	X	X	X	X	X	X	X	X	X	X	X	X				
Valacyclovir/acyclovir [w]	X [w]	X [w]	X [w]													X	X	X	X		
EXPLORATORY																					

Assessments	Screening, Enrollment, & Baseline Period			Treatment Period (All visit dates are calculated from LN-144 infusion [Day 0])														Assessment Period (All visit dates are calculated from LN-144 infusion [Day 0])			Overall Survival Follow-up Period [a]
	Screening (≤ 28 days from ICF signature)	Enrollment/Tumor Resection	Baseline (Day -21 to Day -10)	Day -7	Day -6	Day -5	Day -4	Day -3	Day -2	Day -1	Day 0	Day 1	Day 2	Day 3	Day 4	Day 14 (± 3 days)	End of Treatment Visit Day 28 (± 3 days)	Every 6 Weeks (Week 6 [± 7 days], Week 12 [± 3 days], and Week 18 [± 3 days])	Every 3 Months (± 1 Week) (Starting at Month 6)	EOA Visit [b]	Every 3 Months (± 3 Weeks)
HLA typing [ee]	X																				
Immune monitoring [ff]		X		X							X				X	X		X	X		
HRQoL			X															X [gg]	X [gg]	X	

Table and footnote abbreviations: ABX=antibiotics; AE=adverse events; ALC=absolute lymphocyte count; ANC=absolute neutrophil count; CD4=cluster of differentiation 4; CMV=cytomegalovirus; CT=computed tomography; EBV=Epstein-Barr virus; ECG=electrocardiogram; ECHO=echocardiogram; ECOG=Eastern Cooperative Oncology Group; eCRF=electronic case report form; EOA=end of assessment; EU=European Union; FNA=fine-needle aspiration; HBsAg=hepatitis B virus surface antigen; anti-HBc=hepatitis B virus core antibody; β-HCG=beta human chorionic gonadotropin; HCV=hepatitis C virus; HIV=human immunodeficiency virus; HLA=human leukocyte antigen; HRQoL=health-related quality of life; HSV=herpes simplex virus; ICF=informed consent form; ICU=intensive care unit; IgM=immunoglobulin M; IL-2=interleukin-2; irRECIST=immune related Response Evaluation Criteria in Solid Tumors; MRI=magnetic resonance imaging; MUGA=multiple gated acquisition scan; NMA-LD=nonmyeloablative lymphodepletion; OS=overall survival; PFT=pulmonary function test; RECIST v1.1=Response Evaluation Criteria in Solid Tumors version 1.1; SAE=serious adverse event; TMP-SMX DS=trimethoprim-sulfamethoxazole double strength.

a. OS Follow-up will begin when a patient completes the EOA visit (last efficacy assessment) and will continue for up to 5 years from Enrollment/tumor resection or until discontinuation from study. Patients who had tumor resection but did not receive LN-144 for any reason will perform an EOA visit and transition directly into the OS Follow-up Period. Patients or designees will be contacted every 3 months by telephone to obtain survival status and subsequent anti-cancer therapy information.

b. Assessments for the EOA visit do not need to be repeated if the same assessments were performed within 14 days prior to the EOA visit.

c. Medical Monitor or designee will review and reconfirm if patient meets inclusion/exclusion criteria.

d. Medical history does not need to be repeated for Cohort 3 patients.

e. Physical examination (Appendix 3) will be source documented and symptom-driven; clinically relevant findings will be recorded on the eCRF AE page. Height to be measured at Screening only and does not need to be repeated for Cohort 3. Weight at Day -7 or within 7 days of the start of the chemotherapy per institutional standards should be used for dose calculations for cyclophosphamide and fludarabine. Weight at Day 0 or within 7 days of the start of IL-2 to be used for IL-2 (Appendix 3).

f. 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 4–6 hours) for up to approximately 24 hours post-LN-144 infusion. Pulse oximetry to be assessed during IL-2 administration.

g. Skin test is performed, as needed, for patients who have history of hypersensitivity to any drugs of the aminoglycoside group.

h. Slit-lamp eye examination in patients with history of uveitis. Day 84 is required if clinically indicated. Eye examination performed within 28 days prior to signing the ICF is allowed.

i. ECG evaluations performed within 60 days prior to signing the ICF, and considered normal, do not have to be repeated.

j. ECHO or MUGA at Screening required for all patients. Patients ≥ 60 years of age and who have a history of ischemic heart disease, chest pain, or clinically significant atrial and/or ventricular arrhythmias, must have a cardiac stress test.

k. Colonoscopy on patients with documented ≥ Grade 2 diarrhea or colitis as a result of previous treatment with immune checkpoint inhibitors who have not been asymptomatic for at least 6 months.

l. Post-Month 6, only SAEs related to LN-144 will be collected and reported.

m. All concomitant medications taken within 28 days prior to signing the ICF are to be collected, and subsequently throughout the duration of study.

n. Dates of all hospitalizations, including ICU stays, are collected and recorded in the Hospitalization eCRF. Patients may require hospitalization at the Investigator's discretion or as per institutional guidelines (for tumor resection; NMA-LD [cyclophosphamide, fludarabine] preconditioning regimen; and treatment recovery). If the institutional guidelines mandate a required hospitalization longer than the protocol required hospitalization, this pre-planned hospitalization event will not be considered an AE.

o. Evaluation and measurement of skin and palpable lesions may be performed (if applicable).

p. Screening and Baseline tumor assessments are per RECIST v1.1 only. Tumor response assessment performed per RECIST v1.1 and irRECIST.

q. CT of chest, abdomen, pelvis, and additional anatomic regions (eg, extremities, neck) per disease history and clinical symptoms. The same imaging modality must be used throughout the duration of the study. Radiographic imaging performed within 28 days prior to signing the ICF do not have to be repeated (Appendix 3).

r. Patients will have disease progression confirmed at least 28 days from the last date of progression per irRECIST, as applicable, assessed by the Investigator.

s. MRI scans performed within 28 days prior to signing the ICF do not have to be repeated at Screening if normal. If a brain MRI was performed within 4 weeks prior to Day 0 and considered normal or stable, and the patient is not showing any clinical symptoms of progression in the brain, then a brain MRI does not need to be repeated at Baseline. Brain MRI following the Baseline visit should only be performed if clinically indicated or if positive at Baseline.

t. Serum pregnancy test for women of childbearing potential only. Serum pregnancy testing to continue to Month 12 (Week 52) or EOA, whichever occurs first.

u. On the days of IL-2 administration, dipstick urinalysis (with complete urinalysis and culture, if applicable) will be collected on the same days. Subsequently collections are done only if clinically indicated (Appendix 3).

v. Serology for HIV-1, HIV-2, HBsAg, anti-HBc, HCV Ab, and syphilis are required at tumor resection or within 7 days after tumor resection, for tumor samples acquired in the EU. (Appendix 3).

w. In patients who are seropositive for HSV IgM or PCR assay at Screening, herpetic treatment will be initiated and must be completed prior to starting NMA-LD to ensure patient is seronegative for HSV (IgM). Patients who are not HSV IgM positive at Screening will begin herpetic prophylaxis on Day 14 (or as the Investigator deems appropriate) and continue until ALC > 1000/mm^3.

x. The post-treatment core biopsy at Week 6 is mandatory (when available and patient consent is provided) and should be done in a lesion not being followed for response assessment (either as a target or non-target lesion).

y. Site must receive Authorization to Receive Lymphodepletion from the Sponsor or designee prior to beginning the NMA-LD preconditioning regimen.

z. Refer to Section 5.5.4.1 for a list of pre-medications to be administered to the patient prior to LN-144 infusion.

aa. The first IL-2 dose should be administered approximately 3–24 hours after completion of the LN-144 infusion and continue approximately every 8–12 hours for up to protocol-defined maximum of six doses. Broad-spectrum ABX will be initiated if fever (defined as 38.3°C, one or two temperatures of 38.0°C or above at least one hour apart), AND an ANC ≤ 500/mm^3, or per institutional standards.

bb. Filgrastim or biosimilar may be administered beginning on Day 1 and continued each day until ANC > 1000/mm3 × three consecutive days, discontinue if ANC rises to > 10,000/mm^3, or follow institutional standards.

cc. Fluconazole should be administered beginning on Day 1 and continue each day until ANC > 1000/mm^3. If ANC count remains < 1000/mm^3 at 6 months post-chemotherapy, prophylaxis will continue until the CD4 count is > 200/mm^3 for at least 6 months, or as per institutional standards.

dd. TMP-SMX DS should be administered once daily, beginning on Day 14 and continue until the ALC reaches > 1000/mm^3 for three consecutive days; if at 6 months ALC < 1000/mm^3, continue until CD4 count is > 200/mm^3 for at least 6 months.

ee. HLA typing does not need to be repeated for Cohort 3 patients.

ff. Immune monitoring will be collected at the following timepoints: Enrollment/tumor resection (+ 3 days), Day -7 (prior to NMA-LD), Day 0 or Day 1 (after LN-144 infusion and before first IL-2 dose), Day 4 (after last dose of IL-2, but not earlier than Day 3), Day 42, Day 84, Month 6, Month 9, and Month 12.

gg. HRQoL is performed at Baseline, Day 84, Month 6, Month 12, Month 24, and the EOA visit.

Appendix 2 ECOG SCALE

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

Adapted from Oken MM et al, 1982 [Oken 1982]

Appendix 3 ASSESSMENTS

Assessment	Notes	Tests included
Physical Examination	The examination will be symptom-driven, and source documented only. Clinically relevant findings should be recorded on the eCRF AE page. Physical examinations will consist of the following assessments, as clinically indicated, unless otherwise specified:	Height (only at Screening), weight, gastrointestinal (abdomen, liver), cardiovascular, extremities, head, eyes, ears, nose, and throat, respiratory system, dermatological, musculoskeletal, neurological, and psychiatric (mental status)
BMI and BSA Calculations	Actual body weight should be used for dose calculations of treatment agents.	**BMI** Determination: BMI = weight (kg) / [height (m)]^2 **BSA** Determination: BSA = 0.007184 x height (cm)$^{0.725}$ x weight (kg)$^{0.425}$ or per institutional standards
Vital Signs	The following assessments will be performed, unless otherwise noted:	Pulse rate, respiratory rate, blood pressure, and temperature; pulse oximetry is to be conducted during IL-2 administration
Hematology	Transfusions or growth factors are not allowed within 28 days prior to signing the ICF and continuing through the Screening Period	Complete blood count (CBC) with differentials, when available: White blood cell (WBC) count with differentials (neutrophils, lymphocytes, monocytes, eosinophils, and basophils) Red blood cell (RBC) count, hemoglobin (Hb), hematocrit (Hct), mean corpuscular volume (MCV), mean corpuscular hemoglobin (MCH). Platelet count
Coagulation	The following assessments will be performed, unless otherwise noted:	International Normalized Ratio (INR) and prothrombin time (PT) or INR and activated partial thromboplastin time (aPTT)
Chemistry Assessments	The following assessments will be performed, unless otherwise noted:	Sodium, potassium, chloride, total carbon dioxide (CO_2) or bicarbonate, creatinine, glucose, blood urea nitrogen (BUN), albumin, calcium total, magnesium total, phosphorus, alkaline phosphatase, ALT/SGPT, AST/SGOT, total bilirubin, direct bilirubin, lactate dehydrogenase (LDH), total protein, total creatine kinase (CK), and uric acid
Thyroid panel	The following assessments will be performed, unless otherwise noted:	To include thyroid-stimulating hormone (TSH) and free T_4
Urinalysis	Urinalysis must be collected per protocol and if clinically indicated	Dipstick urinalysis (with complete urinalysis and culture, if applicable)
Viral Serology	The following assessments will be performed unless otherwise noted:	– Human immunodeficiency virus (HIV-1 and HIV-2) antibody titer – Hepatitis B virus surface antigen (HBsAg), hepatitis B core antibody (anti-HBc), hepatitis C virus (HCV-Ab)

Assessment	Notes	Tests included
		– Syphilis (Rapid Plasma Reagin [RPR] test or venereal disease research laboratory [VDRL] test) – Herpes simplex virus (HSV)-1, and HSV-2 IgM serology or PCR assay – Cytomegalovirus (CMV) antibody titer, including IgM or PCR assay – Epstein-Barr virus (EBV) panel, including IgM or PCR assay
Imaging Assessments	The same imaging modality must be used throughout the duration of the study Imaging assessments can be done at any time if clinically indicated. All imaging assessments, including scheduled and unscheduled scans, should be recorded in the eCRF and will be assessed by the IRC.	Computed tomography (CT) examination of chest, abdomen, pelvis, and additional anatomic regions (eg, extremities, neck) per disease history and clinical symptoms Magnetic resonance imaging (MRI) of the brain if positive for central nervous system involvement at Screening or Baseline, or as clinically indicated High-resolution CT with PO/IV contrast or contrast-enhanced MRI is the preferred imaging modality for assessing radiographic tumor response. If a patient has a known allergy to CT contrast material, please use the alternate modality. In cases where contrast is strictly contraindicated, a non-contrast scan will suffice. Photographic documentation and caliper measurement will be performed for superficial dermal and subcutaneous lesions which cannot be assessed by radiographic scan.

Appendix 4 IL-2 ADVERSE EVENTS

Adverse Events occurrence in > 10% of patients treated with IL-2 (n=525)			
Body System/Events	% patients	Body System/Events	% patients
Body as a whole		*Metabolic and Nutritional Disorders*	
Chills	52	Bilirubinemia	40
Fever	29	Creatinine Increase	33
Malaise	27	Peripheral Edema	28
Asthenia	23	SGOT increase	23
Infection	13	Weight gain	16
Pain	12	Edema	15
Abdominal pain	11	Acidosis	12
Enlarged Abdomen	10	Hypomagnesemia	12
Cardiovascular System		Hypocalcemia	11
Hypotension	71	Alkaline Phosphatase Increase	10
Tachycardia	23	*Nervous System*	
Vasodilation	13	Confusion	34
Supraventricular Tachycardia	12	Somnolence	22
Cardiovascular disorder [a]	11	Anxiety	12
Arrhythmia	10	Dizziness	11
Digestive System		*Respiratory System*	
Diarrhea	67	Dyspnea	43
Vomiting	50	Lung disorder [b]	24
Nausea	35	Respiratory disorder [c]	11
Stomatitis	22	Cough increase	11
Anorexia	20	Rhinitis	10
Nausea and Vomiting	19	*Skin and Appendages*	
Hematologic and Lymphatic		Rash	42
Thrombocytopenia	37	Pruritus	24
Anemia	29	Exfoliative dermatitis	18
Leukopenia	16	*Urogenital System*	
		Oliguria	63

[a] Cardiovascular disorder: fluctuations in blood pressure, asymptomatic ECG changes, congestive heart failure (CHF).
[b] Lung disorder: physical findings associated with pulmonary congestion, rales, rhonchi.
[c] Respiratory disorder: Acute respiratory distress syndrome (ARDS), Chest X-Ray (CXR) infiltrates, unspecified pulmonary changes.
Source: Proleukin® Prescribing Information – January 2015 [Novartis 2015]

Appendix 5 EXPECTED IL-2 TOXICITIES AND THEIR MANAGEMENT

Expected Toxicity	Expected Grade	Supportive Measures	Skip Dose/Stop Treatment*
Anemia	3 or 4	Transfusion with pRBCs	Yes, if active bleeding or hemolysis, despite supportive measures
Arrythmia	3	Correction of fluid and electrolyte imbalances; chemical conversion or electrical conversion therapy	Yes, if uncontrolled despite all supportive measures
Bowel Perforation	3	Surgical intervention	Yes
Chills/Rigors	3	Meperidine (Pethidine) 25-50 mg, IV q1h, prn	No
Confusion, Delirium	3	Look for and treat other contributors	Yes
Creatinine Increase	3 or 4	Medical management of hemodynamic needs	Yes (if Grade 4)
Diarrhea	3	Loperamide 2 mg, po, q3h, prn; Diphenoxylate HCl 2.5 mg and Atropine sulfate 25 mcg, po, q3h, prn; Codeine sulfate 30-60 mg, po, q4h, prn	Yes, if uncontrolled after 24 hours despite all supportive measures
Dyspnea	3 or 4	Oxygen or ventilatory	Yes, if requires ventilatory support
Edema/Weight Gain	3	Diuretics prn, after initial volume resuscitation and falling pressor requirement	No
Electrolyte Imbalance	3 or 4	Electrolyte replacement	Yes, if uncontrolled despite all supportive measures
Fever	3	Acetaminophen 650 mg, po, q4h; Indomethacin 50-75 mg, po, q8h	No
Hyperbilirubinemia	3 or 4	Observation - r/o other causes	Yes, if other toxicities occur simultaneously
Hypotension	3	Fluid resuscitation; Vasopressor support	Yes, if uncontrolled despite all supportive measures. NOTE: Hypotension is the most common reason for permanent discontinuation of IL-2 dosing. In most situations there is a constellation of life-threatening toxicities, including hypotension, rather than a single DLT that results in permanent discontinuation of IL-2 dosing.
Malaise	3 or 4	Bedrest interspersed with activity	Yes, if other toxicities occur simultaneously
Myocardial Infarction	3 or 4	Standard management, thrombolytic therapy only if considered safe	Yes

Expected Toxicity	Expected Grade	Supportive Measures	Skip Dose/Stop Treatment*
Nausea/Vomiting/Anorexia	3	Ondansetron 8 mg, IV, q8h, prn; Granisetron 0.01 mg/kg IV daily prn; Droperidol 1 mg, IV q4-6h, prn; Lorazepam 0.5–1 mg po q8h, as needed (w/ attention to somnolence, altered mental status, etc.); Prochlorperazine 25 mg q4h or prn or 10 mg IV q6h prn (maximum dose: 40 mg/day)	No
Neutropenia	4	Observation	Yes, if contributing to sepsis
Oliguria	3 or 4	Fluid resuscitation and maintenance; consider dopamine at "renal" doses	Yes, if uncontrolled despite all supportive measures
Pleural Effusion	3	Thoracentesis	Yes, if uncontrolled despite all supportive measures
Pruritis	3	Hydroxyzine HCL 10-20 mg po q6h, prn; Diphenhydramine HCL 25-50 mg, po, q4h, prn	No
Renal Failure	3 or 4	Dialysis	Yes
Somnolence	3 or 4	Intubation for airway protection	Yes
Thrombocytopenia	3 or 4	Transfusion with platelets	Yes, if not recovering despite supportive measures
Transaminase Elevation	3 or 4	Observation - r/o other causes	Yes, for Grade 4 (> 20 times ULN) either without or without liver metastases
Troponin Elevation	3 or 4	Look for causes of ischemia and correct; routine management of ischemia	Yes

*Unless the toxicity is not reversed to ≤ Grade 2 by next retreatment. If two consecutive doses are missed, then treatment is permanently discontinued.

Proleukin® Prescribing Information – January 2012 [Novartis 2015]

Appendix 6 COMMON TERMINOLOGY CRITERIA FOR ADVERSE EVENTS

https://www.eortc.be/services/doc/ctc/CTCAE_4.03_2010-06-14_QuickReference_5x7.pdf

Appendix 7 CYCLOPHOSPHAMIDE PACKAGE INSERT

Cyclophosphamide, Full Prescribing Information, 2013

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

Cyclophosphamide, Summary of Product Characteristics, 2017

https://www.medicines.org.uk/emc/product/3526/smpc

Appendix 8 MESNA (MEXNEX®) PACKAGE INSERT

Mesna (Mesnex®), Full Prescribing Information, Sargent Pharmaceuticals, July 2015

http://www.sagentpharma.com/wp-content/uploads/2016/01/Mesna_PI.pdf

Appendix 9 ONDANSETRON PACKAGE INSERT

Ondansetron hydrochloride (Zofran®), Full Prescribing Information, Novartis,

October 2017

https://www.pharma.us.novartis.com/sites/www.pharma.us.novartis.com/files/zofran.pdf

Appendix 10 FILGRASTIM PACKAGE INSERT

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

Appendix 11 FLUCONAZOLE PACKAGE INSERT

Fluconazole (Diflucan®), Full Prescribing Information Pfizer, 2016.

http://labeling.pfizer.com/ShowLabeling.aspx?id=575

Appendix 12 FLUDARABINE PACKAGE INSERT

Fludarabine, Full Prescribing Information, 2008

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

Fludarabine, Summary of Product Characteristics, 2018

https://www.medicines.org.uk/emc/product/1274/smpc

Appendix 13 IL-2 (ALDESLEUKIN) PACKAGE INSERT

Proleukin (aldesleukin), Full Prescribing Information, 2008

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

Proleukin, Summary of Product Characteristics, 2017
https://www.medicines.org.uk/emc/product/291/smpc

Appendix 14 EORTC QLQ-C30 QUESTIONNAIRE

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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