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Title: A Phase 2 Study of Autologous Tumor Infiltrating Lymphocytes (LN-145) in Patients with Pretreated Metastatic Triple Negative Breast Cancer

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CLINICAL PROTOCOL

A Phase 2 Study of Autologous Tumor Infiltrating Lymphocytes (LN-145) in Patients with Pretreated Metastatic Triple Negative Breast Cancer

PROTOCOL NUMBER:	2000025837
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SYNOPSIS

Protocol Title	A Phase 2 Study of Autologous Tumor Infiltrating Lymphocytes (LN-145) in Patients with Pretreated Metastatic Triple Negative Breast Cancer
Protocol Number	2000025837
Study Type	Phase 2
Investigational Agent	Tumor infiltrating lymphocytes (TIL) LN-145 as a single-therapy
Study Objectives	**Primary:** • To evaluate the efficacy of autologous LN-145 as a single therapy in Metastatic Triple Negative Breast Cancer (TNBC) patients by determining the objective response rate (ORR), using the Response Evaluation Criteria in Solid Tumors (RECIST) 1.1, as assessed by the Sponsor Investigator. • To characterize the safety profile of tumor infiltrating lymphocytes (TIL) as a single therapy in Metastatic Triple Negative Breast Cancer patients as measured by the incidence of Grade ≥ 3 treatment-emergent adverse events (TEAEs). **Secondary:** • To further evaluate the efficacy of autologous LN-145 as a single therapy in Metastatic Triple Negative Breast Cancer patients using complete response duration of response (DOR), disease control rate (DCR), andprogression-free survival (PFS), using RECIST 1.1, as assessed by the Sponsor Investigator, overall survival (OS) and (CR) rate. **Exploratory:** • To explore the persistence of LN-145 cells as a single therapy and its resultant immune correlates, which may affect response, outcome, and toxicity variables. • To explore efficacy parameters (excluding OS) using the immune-related Response Evaluation Criteria in Solid Tumors (irRECIST), as assessed by the Sponsor Investigator. • To explore the feasibility of generating TIL (LN-145) from patient-derived TNBC core biopsy tumor specimens using Iovance manufacturing process.

Study Design	A prospective, open-label, non-randomized, Phase 2 study to evaluate adoptive cell therapy (ACT) with LN-145 as a single therapy in patients with Metastatic Triple Negative Breast Cancer. • Patients must have had at least one and no more than three prior systemic anticancer therapies for metastatic disease. • All patients will receive autologous LN-145 therapy. The TIL autologous therapy with LN-145 is comprised of the following steps: 1. Tumor resection to provide the autologous tissue that serves as the source of the TIL cellular product; 2. LN-145 investigational product production at a central Good Manufacturing Practice (GMP) facility;

	3. A 7-day nonmyeloablative lymphodepletion (NMA-LD) preconditioning regimen (hospitalization per institution standards); 4. Infusion of the autologous LN-145 product on Day 0 (during inpatient hospitalization); 5. Intravenous (IV) interleukin-2 (IL-2) administrations for up to six doses maximum (during inpatient hospitalization). The following general study periods will take place unless specified otherwise: • Screening and Tumor Resection: Up to 4 weeks (28 days) from signing the informed consent form (ICF); • Enrollment: Upon tumor resection for TIL generation; • Manufacturing of the LN-145 Product: approximately 22 days from tumor resection; • Treatment Period: NMA-LD preconditioning regimen (up to 7 days), LN-145 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-145 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 3 years from Day 0 (LN-145 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 3 years from LN-145 infusion or until discontinuation from the study; with telephone contact every 3 months to obtain survival status and subsequent anticancer therapy information (Figure 1). Patients who had tumor resection but did not receive LN-145 for any reason will perform an EOA visit and transition directly into the OS Follow-up Period.

Doses and Treatment Schedule

TIL LN-145 Therapy:

The cell transfer therapy used in this study involves patients receiving an NMA-LD preconditioning regimen, consisting of daily IV cyclophosphamide (60 mg/kg; IV × 2 doses) followed by daily fludarabine (25 mg/m^2; IV × 5 doses). Infusion of LN-145 is given on Day 0 and is followed by administration of IL-2 at 600,000 international units (IU)/kg BID for up to a maximum of six doses, starting approximately 3–24 hours after completion of LN-145 infusion.

	Study Day											
Treatment Administration	**-7**	**-6**	**-5**	**-4**	**-3**	**-2**	**-1**	**0**	**1**	**2**	**3**	**4**
Cyclophosphamide 60 mg/kg	X	X										
Mesna 60 mg/kg	X	X										
Fludarabine 25 mg/m^2/day			X	X	X	X	X					
TIL LN-145 infusion								X				
IL-2 600,000 IU/kg									X	X	X	X

Duration of Participation	Overall, the study participation time will be up to 3 years: Screening (28 days), TIL manufacturing time (~22 days), preconditioning time prior to Day 0 TIL treatment (7 or 8 days), and 3 years (Month 36) follow-up from LN-145 infusion on Day 0.
Number of Study Sites	1
Number of Planned Patients	Ten (10) patients are planned to be evaluable for efficacy in this study. If an enrolled patient is unable to receive therapy for any reason, she will be replaced by a new patient until 10 patients will be evaluable for efficacy (infused and has received at least one dose of IL-2). All patients who complete the TIL LN-145 infusion on Day0 will be evaluable for safety. Patients who progressed or expired prior to reaching the first radiological assessment will also be included in efficacy analysis and categorized as progression.

Inclusion Criteria	1. Ability to understand the requirements of the study. Specifically, the patient has to provide written informed consent (as evidenced by signature on an IRB approved ICF. 2. All patients must have a triple negative metastatic breast cancer (TNBC) (Estrogen Receptor negative, Progesterone Receptor negative, human epidermal growth factor receptor 2 (HER2) negative) as defined by the 2018 ASCO CAP guidelines. Patients with low ER and/or low PR (defined as <10% expression by immunohistochemistry (IHC)) may be deemed eligible and considered as TNBC (following the ASCO CAP guidelines 2020 and ESO/ESMO 2020) 3. Patients must have a confirmed diagnosis of metastatic triple negative breast cancer (Stage IV) histologically confirmed as per American Joint Committee on Cancer [AJCC] staging system). 4. Patients must have had at least one and no more than three prior lines of systemic anticancer therapies for metastatic disease. 5. Patients must have disease progression from the last line of therapy. 6. Patients must have at least one resectable lesion of a minimum 1.5 cm in diameter (or aggregate of 1.5 cm if multiple lesions are sampled) post-resection for TIL investigational product production. It is encouraged that tumor tissue be obtained from multiple and diverse metastatic lesions, as long as the surgical resection does not pose additional risks to the patient. • If the lesion considered for resection for TIL generation is within a previously irradiated field, the lesion must have demonstrated radiographic progression post-radiotherapy (XRT) and prior to resection. • Patients must have an adequate histopathology specimen for protocol required testing. 7. Patients must have remaining measurable disease as defined by RECIST 1.1 following tumor resection for TIL manufacturing: • Lesions in previously irradiated areas should not be selected as target lesions unless there has been demonstrated progression in those lesions. • Lesions partially resected for TIL production may be chosen as non-target lesions but cannot be used as target lesions for RECIST assessment. 8. Patients must be ≥ 18 years of age at the time of consent. 9. Patients must have an Eastern Cooperative Oncology Group (ECOG) performance status of 0 or 1, and an estimated life expectancy of ≥ 3 months in the opinion of the Sponsor Investigator. 10. Patients of childbearing potential (or female partners of male participants) must be willing to use effective contraception during treatment and for 12 months after their last dose of IL-2.

	11. Patients must have the following hematologic parameters: • Absolute neutrophil count (ANC) ≥ 1000/mm^3; • Hemoglobin ≥ 9.0 g/dL; • Platelet count ≥ 100,000/mm^3 12. Patients must have adequate organ function: • Serum alanine aminotransferase (ALT) and aspartate aminotransferase (AST) ≤ 3 times the upper limit of normal (ULN), patients with liver metastasis ≤ 5 times ULN; • An estimated creatinine clearance ≥ 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 13. Patients must be seronegative for the human immunodeficiency virus (HIV1 and HIV2). Patients with positive serology for hepatitis B virus surface antigen (HBsAg), hepatitis B core antibody (anti-HBc), or hepatitis C virus (anti-HCV) indicating acute or chronic infection may be enrolled if the viral load by polymerase chain reaction (PCR) is undetectable with/without active treatment. 14. Patients must have a washout period of 21 days from last anticancer therapy prior to the first study treatment (ie, start of NMA LD) 15. Palliative radiation therapy: prior external beam radiation is allowed provided all radiation-related toxicities are resolved to Grade 1 or baseline; • The tumor lesion(s) being assessed as target for response via RECIST 1.1 must be outside of the radiation portal (however, if within the portal, they must have demonstrated progression); • Surgery/pre-planned procedure: previous surgical procedure(s) is permitted provided that wound healing has occurred, all complications have resolved, and at least 14 days have elapsed (for major operative procedures) prior to the tumor resection. 16. Patients must have recovered from all prior anticancer treatment-related adverse events (TRAEs) to Grade ≤ 1 (per Common Terminology Criteria for Adverse Events [CTCAE], version 5.0). Exceptions may be made, at the Sponsor Investigator's discretion, for persistent adverse events (AEs) that are corrected or do not pose a clinical risk, such as hypothyroidism, adrenal insufficiency, alopecia, and vitiligo: • Patients with Grade ≥ 2 neuropathy will be evaluated on a case-by-case basis; • Patients with irreversible toxicity not reasonably expected to be exacerbated by treatment may be included at the Sponsor Investigator's discretion; • Patients with Grade ≥ 2 toxicity from prior anticancer therapy may be considered on a case-by-case basis after consultation with the Sponsor Investigator. 17. Patients must have provided written authorization for use and disclosure of protected health information.

	18. Must be able and willing to comply with the study visit schedule and protocol requirements including long-term follow-up (LTFU).
Exclusion Criteria	1. Patients who have received an organ allograft or prior cell transfer therapy within the past 20 years that included a nonmyeloablative or myeloablative chemotherapy regimen. 2. Patients with symptomatic and/or untreated brain metastases: • Patients with definitively-treated brain metastases will be considered for enrollment if, prior to tumor resection for TIL, the patient is clinically stable for ≥ 2 weeks, there are no new brain lesions via magnetic resonance imaging (MRI) post-treatment, and the patient does not require ongoing corticosteroid treatment. 3. Patients who are on systemic steroid therapy except for those requiring steroid for management of adrenal insufficiency. Patients receiving steroids for management of adrenal insufficiency may receive no more than 10 mg prednisone or its equivalent daily. 4. Patients who are pregnant or breastfeeding. 5. Patients who have active medical illness(es) that would pose increased risk for study participation, including: active systemic infections requiring systemic antibiotics (ABX), coagulation disorders, or other active major medical illnesses of the cardiovascular, respiratory, or immune systems. 6. Patients who have received a live or attenuated vaccination within 28 days prior to the start of NMA-LD. 7. Patients who have any form of primary immunodeficiency (such as severe combined immunodeficiency disease [SCID] and acquired immune deficiency syndrome [AIDS]). 8. Patients with a history of hypersensitivity to any component of the study drugs. LN-145 should not be administered to patients with a known hypersensitivity to any component of TIL product formulation and TIL treatment regimen including, but not limited to: • NMA-LD (cyclophosphamide, mesna, and fludarabine); • Proleukin®, aldesleukin, IL-2; • ABX of the aminoglycoside group (ie, streptomycin, gentamicin); • Any component of the TIL product formulation including dimethyl sulfoxide [DMSO], human serum albumin [HSA], IL-2, and dextran-40. 9. Patients who have a left ventricular ejection fraction (LVEF) < 45% or who are New York Heart Association (NYHA) Class II or higher. A cardiac stress test demonstrating any irreversible wall movement abnormality in any patients ≥ 60 years of age or in patients who have a history of ischemic heart disease, chest pain, or clinically significant atrial and/or ventricular arrhythmias. 10. Patients who have obstructive or restrictive pulmonary disease and have a documented FEV1 (forced expiratory volume in 1 second) ≤ 60% of predicted normal: • If a patient is not able to perform reliable spirometry due to abnormal upper airway anatomy (ie, tracheostomy), a 6-minute walk test may be used to assess pulmonary function. Patients who are unable to walk a distance of at least 80% predicted for age and sex or demonstrates

	evidence of hypoxia at any point during the test (SpO2 < 90%) are excluded. 11. Patients who have had another primary malignancy within the previous 3 years (except for curatively treated localized malignancy that has not required treatment for greater than 1 year, and in the judgment of the Sponsor Investigator, does not pose a significant risk of recurrence including, but not limited to, nonmelanoma skin cancer or bladder cancer or cancers that do not require treatment in the judgement of the Sponsor Investigator). 12. Participation in another clinical study with an investigational product within 21 days of the initiation of NMA-LD treatment.
Early Discontinuation from Treatment	**From TIL Therapy:** • Withdrawal of consent to treatment: • Every effort should be made to continue OS Follow-up, when applicable • Grade 3 or greater immune TRAEs involving vital organs (heart, kidneys, brain, liver, colon, adrenal gland, lungs) with symptoms emerging following LN-145 infusion • Grade 3 or greater allergic reactions including bronchospasm or generalized urticaria that does not resolve after medical management in the opinion of the Sponsor Investigator • Meeting criteria for permanent discontinuation of IL-2 treatment. (must have received at least one dose of IL-2) • Administration of prohibited concomitant medication/start of new anti-cancer therapy • Determination by the Sponsor Investigator that continued treatment is not in the best interest of the patient • Death
End-of-Study Criteria	A patient may reach end-of-study (EOS) status for any of the following reasons: • Death • Lost to follow-up after 3 documented attempts to contact the patient/family/primary care physician • Withdrawal of consent • Study termination by Sponsor • 3 years (Month 36) of study participation after TIL infusion (Day 0)
Efficacy Assessment	The following efficacy parameters for LN-145 as a single-therapy for Metastatic Triple Negative Breast Cancer will be investigated: ORR, DOR, DCR, PFS, OS and CR Rate.

Safety Assessment	AEs will be collected and reported according to the following temporal intervals: • Signed ICF to tumor resection (serious adverse events [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/adverse events of special interest [AESI]); • Day 30 through 6 months post-LN-145 infusion, or the start of new anticancer therapy, whichever occurs first (Grade 3 and Grade 4 AEs; SAEs, AESIs if at least related to any study drug); • Post-Month 6, only SAEs/AESIs related to LN-145 will be collected and reported The LTFU period begins after the assessment period ends and continues until the EOS, where EOS = death, lost to follow-up, withdrawal of consent, study termination by sponsor Investigator, or 3 years (Month 36) of follow up after LN145 infusion, whichever occurs first. During the LTFU period, AEs will not be collected, and no visits are required; phone calls will determine survival status (dead or alive) and determine all currently-taken anti-cancer medications.
Statistical Considerations	Descriptive statistics will be used to summarize safety and efficacy parameters. The primary efficacy endpoint will be the ORR as assessed by Sponsor Investigator, and patients meeting RECIST 1.1 for a complete response (CR) or partial response (PR) will be classified as responders. The ORR, the incidence of Grade ≥ 3 TEAEs, CR rates, and the DCRs will be summarized using point-estimates and two-sided 90% confidence limits. Kaplan-Meier methods will be used to summarize time-to-event efficacy endpoints, such as DOR, PFS, and OS. DOR analyses will be performed for patients who achieve objective responses. For safety, the commonly observed TEAEs will be summarized descriptively in comparison to historical data of TIL LN-145. Other safety parameters will include TEAEs by grade, SAEs, AEs leading to discontinuations of study treatments, vital signs, physical examinations, and toxicity data from clinical laboratory results.
Sample Size Determination	Ten (10) patients are planned for this study. We assume that the ORR for any standard of care second line or greater line of chemotherapy is no more than 14%. The alternative hypothesis is that treatment with TIL will result in ORR > 35%. If ≥ 3 of 10 patients achieve response the efficacy null hypothesis is rejected. This design will give a 78% power to detect a difference using a one-sided alpha of 20%.
Data Safety Monitoring Committee (DSMC)	The Yale Cancer Center Data Safety Monitoring Committee (DSMC) will review cumulative safety data on the first five patients enrolled upon completion of 6 weeks (Day 42) of assessment post LN-145 infusion. Enrollment will continue while study data is under DSMC review. DSMC data review will follow Yale DSMC procedures.

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Term	Definition
ABX	antibiotics
ACT	adoptive cell therapy
ADP	adenosine diphosphate
AE	adverse event
AESI	adverse events of special interest
AIDS	acquired immune deficiency syndrome
AJCC	American Joint Committee on Cancer
ALC	absolute lymphocyte count
ALT	alanine aminotransferase
ANC	absolute neutrophil count
anti-HBc	hepatitis B core antibody
anti-HCV	hepatitis C virus antibody
aPTT	activated partial thromboplastin time
AST	aspartate aminotransferase
ß-HCG	beta human chorionic gonadotropin
BMI	body mass index
BRAF	human proto-oncogene that encodes the B-Raf protein
BSA	body surface area
CBC	complete blood count
CD3+	T-cells positive for cluster of differentiation 3 surface molecule
CD4+	T-cells positive for cluster of differentiation 4 surface molecule
CD8+	T-cells positive for cluster of differentiation 8 surface molecule
CFR	Code of Federal Regulations
CI	confidence interval
CMO	contract manufacturing organization
CMV	cytomegalovirus
CR	complete response
CRO	contract research organization

CT	computed tomography

CTCAE v4.03	Common Terminology Criteria for Adverse Events, version 4.03
CTLA-4	cytotoxic T lymphocyte-associated antigen-4
Cy	cyclophosphamide
D5W	dextrose 5% in water
DCR	disease control rate
DFS	disease-free survival
DMSO	dimethyl sulfoxide
DNA	deoxyribonucleic acid

Term	**Definition**
DOR	duration of response
DS	double strength
DSMC	Data Safety Monitoring Committee
EBV	Epstein-Barr virus
ECG	electrocardiogram
ECHO	echocardiogram
ECOG	Eastern Cooperative Oncology Group
EGFR	epidermal growth factor receptor
EORTC	European Organization for Research and Treatment of Cancer
EOA	end-of-assessment
EOS	end-of-study
EOT	end-of-treatment
eCRF	electronic case report form
EGFR	epidermal growth factor receptor
EMA	European Medicines Agency
EU	European Union
FDA	Food and Drug Administration
FEV1	forced expiratory volume in 1 second
FFPE	formalin-fixed, paraffin-embedded

Flu	fludarabine
FPI	full prescribing information
GCP	Good Clinical Practice
GDPR	General Data Protection Regulation
GMP	Good Manufacturing Practice
HBc	hepatitis B core antigen
HBsAg	hepatitis B virus surface antigen
HCV	hepatitis C virus
HER2	human epidermal growth factor receptor 2
HIC	Human Investigation Committee
HIPAA	Health Insurance Portability and Accountability Act
HIV	human immunodeficiency virus
HLA	human leukocyte antigen
HNSCC	head and neck squamous cell carcinoma
HPV	human papilloma virus
HRCT	high-resolution computed tomography
HSA	human serum albumin
HSV	herpes simplex virus
IB	Investigator's Brochure

Term	**Definition**
ICF	informed consent form
ICH	International Council for Harmonization
IEC	Independent Ethics Committee
IgG	immunoglobulin G
IgM	immunoglobulin M
IHC	immunohistochemistry
IL-2	interleukin-2 (aldesleukin, Proleukin®)
IND	investigational new drug

IRB	Institutional Review Board
irRECIST	immune-related Response Evaluation Criteria in Solid Tumors
IU	international units
IV	intravenous
LN-145	autologous tumor infiltrating lymphocytes derived from the patient's tumor
LTFU	long-term follow-up
LVEF	left ventricular ejection fraction
mAb	monoclonal antibody
MEK	mitogen-activated protein kinase
MRI	magnetic resonance imaging
MUGA	multi-gated acquisition
NCI	National Cancer Institute
NCI-CTCAE	National Cancer Institute-Common Terminology Criteria for Adverse Events
NE	not evaluable
NEJM	New England Journal of Medicine
NIH	National Institutes of Health
NMA-LD	nonmyeloablative lymphodepletion
ORR	objective response rate
OS	overall survival
PARPi	poly adenosine diphosphate ribose polymerase inhibitors
PBMC	peripheral blood mononuclear cells
PD	progressive disease
PD-1	programmed cell death-1
PD-L1	programmed cell death-ligand 1
PET	positron emission tomography
PFS	progression-free survival
PFT	pulmonary function test
PI	prescribing information / package insert
PJP	pneumocystis jirovecii pneumonia

PR	partial response
Term	**Definition**
Q3W	every 3 weeks
QLQ	quality-of-life questionnaire
RECIST 1.1	Response Evaluation Criteria in Solid Tumors, version 1.1
REP	rapid expansion protocol
RNA	ribonucleic acid
RPR	rapid plasma reagin
SAE	serious adverse event
SAP	statistical analysis plan
SCID	Severe Combined Immune Deficiency
SD	stable disease
SEER	National Cancer Institute's Surveillance, Epidemiology, and End Results Program
SGOT	serum glutamic-oxaloacetic aminotransferase
SGPT	serum glutamic-pyruvic aminotransferase
SmPC	summary of product characteristics
SMX	sulfamethoxazole
SMX-TMP DS	sulfamethoxazole-trimethoprim double strength
SpO2	saturation of peripheral oxygen
SUSAR	suspected unexpected serious adverse reaction
TCR	T-cell receptor
TEAE	treatment-emergent adverse event
TH	tumor harvested
TIL	tumor infiltrating lymphocytes
TMP	trimethoprim
TNBC	triple negative breast cancer
TRAE	treatment-related adverse event
Treg	regulatory T cell
TSH	thyroid-stimulating hormone

ULN	upper limit of normal
US	United States
VDRL	venereal disease research laboratory
XRT	radiation therapy or radiotherapy
YCC	Yale Cancer Center

1. INTRODUCTION

1.1. Triple Negative Breast Cancer

In the United States (US), breast cancer is the most common cancer in women with an estimated 234,190 new diagnoses and 40,920 breast cancer related deaths in 2018 [1]. Breast cancers are characterized by whether they express three receptors: The Estrogen Receptor (ER), Progesterone Receptor (PR), and human epidermal growth factor receptor 2 (HER2). Expression of these receptors confers prognostic significance with important therapeutic implications. Tumors that do not express any of these receptors are called triple negative breast cancer (TNBC) and account for 10–15% of diagnosed breast cancer [2]. TNBC is associated with a shorter time to first recurrence of 25 months vs 67 months in ER+/PR+/HER2- [3]. In addition, TNBC recurs more frequently in visceral organs including brain, lung and liver compared with hormone receptor positive breast cancer [4]. In a review of the SEER database between 2010 and 2012 median overall survival (OS) for metastatic TNBC was 12 months vs 35 months in nonTNBC with a hazard ratio of 2.51 [5].

The management of TNBC with curative intent consists of a multidisciplinary approach including medical oncology, radiation oncology and surgery. The role of surgery alone is limited to T1aN0M0 TNBC, whereas disease > T1a or node positive disease requires multimodality therapy including chemotherapy. In general, chemotherapy can be used either in the neoadjuvant or adjuvant setting. Upfront surgery followed by adjuvant chemotherapy allows for correct pathologic staging. Whereas neoadjuvant chemotherapy provides an opportunity to assess for response to treatment at the time of surgery. Multiple studies have demonstrated that patients with TNBC that do not attain pathologic complete response (CR) following neoadjuvant chemotherapy have worse survival compared with patients with hormone receptor (HR) positive disease and that only a small population of these patients are disease-free at 5 years [4, 6]. Preferred regimens in the adjuvant or neoadjuvant setting include dose dense doxorubicin/cyclophosphamide (ddAC) followed by paclitaxel every 2 weeks, ddAC followed by weekly paclitaxel, and docetaxel and cyclophosphamide [7−9]. Despite this, many patients will develop recurrent or metastatic disease.

In patients with residual disease after neoadjuvant chemotherapy, or with recurrent or metastatic disease effective treatment options become limited. A study by Masuda et al. randomized HER2(-) residual invasive breast cancer following neoadjuvant chemotherapy to receive standard post-surgical treatment vs capecitabine with improvement of the 5-year overall survival to 89.2%

compared with 83.6% [10]. In the metastatic setting, single agent taxanes or anthracyclines are recommended in the first line setting. Chemotherapy combinations can be used in select circumstances with rapidly progressing disease, high tumor burden or visceral crisis [11]. Despite this, outcomes remain poor with OS of 14.5 months as demonstrated in a multicenter French observational cohort including 2317 patients with TNBC [12]. Recent data published in the New England Journal of Medicine (NEJM) by Schmid et al. investigated the use of atezolizumab plus nab-paclitaxel in the phase III setting compared with nab-paclitaxel and placebo. Median OS in the atezolizumab plus nab-paclitaxel was 21.3 vs 17.6 months. Among patients with programmed cell death-ligand 1 (PD-L1) positive tumors (defined at ≥ 1% of tumor infiltrating immune cells) median OS was 25.0 vs 15.5 months [13]. Based on this study, atezolizumab plus nab-paclitaxel has become a Food and Drug Administration (FDA) approved therapy for patients with metastatic disease or recurrent disease after treatment with curative intent. In patients with germline BRCA1/2 mutations, poly adenosine diphosphate (ADP) ribose polymerase inhibitors (PARPi) including olaparib and talazoparib are approved [14, 15]. Despite the improvement in OS, many patients will still succumb to this disease and novel therapies are needed.

1.2. Adoptive Cell Transfer of Tumor-Infiltrating Lymphocytes as Cancer Immunotherapy

Adoptive cell transfer of tumor-infiltrating lymphocytes (TIL) represents a potentially effective treatment for patients with a variety of solid tumors. The method involves the recovery and ex vivo expansion of autologous antitumor lymphocytes that have infiltrated a patient's tumor. The basic concept of using lymphoid cells for the immunotherapy of cancer arose from animal experiments that demonstrated, by histologic analysis, the presence of T-lymphocytes within the microenvironment of most solid tumors and their metastases [16−18].

Recent findings have clearly shown a predictive relationship between the frequency and phenotype of TIL in solid tumors (especially CD8+ T cells) and an increased OS and progression-free survival (PFS) in patients with melanoma [19−22], lung cancer [23−26], ovarian cancer [27−29], squamous cell carcinomas [56 , 30], triple negative breast cancer, HER2-positive breast cancer [31], basal-like breast cancer [32−39], and colorectal cancer [40−43]. One study found that an increased Foxp3+ regulatory T cell (Treg)/CD8+ ratio and the presence of intra-tumoral high Foxp3+ Treg predicted worse outcomes [44]. In addition, gene expression studies using deoxyribonucleic acid (DNA) microarrays have indirectly correlated "immune signature" genes and T-cell associated gene expression (eg, CD3, CD8, CD4, inducible costimulator, granzyme B, dendritic cell-lysosome-associated membrane glycoprotein, and chemokine and chemokine receptors) with improved OS and PFS in both primary and metastatic tumor settings [22, 40, 41, 45−47]. These findings support the development of therapies based on the isolation and expansion of autologous TIL cells as a therapeutic agent against solid tumors.

Adoptive cell therapy (ACT) with TIL has several theoretical and practical advantages over other immunotherapeutic approaches. First, the isolation of T cells directly from the tumor tissue ensures the recovery of tumor-specific TIL without prior knowledge of their antigens. Second,

the ex vivo culture steps involved in TIL manufacturing favor both the expansion of T cells over other cell types and the reinvigoration of these T cells through the elimination of immune suppressive factors (eg, Treg which are present in the tumor microenvironment) and the exposure to activating factors [48−50]. The result is a polyclonal TIL product mostly comprised of effector T cells that recognize a potentially wide array of tumor antigens [51−54]. Finally, preparation of the patient with lymphodepletion immediately prior to TIL infusion eliminates in vivo suppressive influences (eg, Treg and cytokine sinks) to provide an optimal milieu for the activity of the transferred T cells [70].

The feasibility of TIL preparation was demonstrated in early preclinical studies. Metastatic melanoma (MM) tumors were excised and placed in tissue culture conditions under which tumor cells do not survive, but under which TIL contained within the excised tumor tissue can survive and proliferate to very large numbers ($\geq 1 \times 10^8$ cells) [16, 18, 53, 54]. Expanded TIL were shown to be effective at killing tumor cells in vitro and promoting durable antitumor effects in vivo when infused back into the original donor [16, 18, 53, 54]. Further preclinical studies established that the efficacy of TIL infusions is enhanced by pretreatment with cyclophosphamide (ie, to induce a transient drop in endogenous lymphocytes in the host) and by post-dose interleukin-2 (IL-2) administration [16].These findings set the stage for the National Cancer Institute (NCI) initiating clinical trials using TIL to treat MM patients; whereby, a nonmyeloablative preconditioning regimen consisting of fludarabine and cyclophosphamide was combined with post-doses of IL-2. These studies have consistently demonstrated high objective response rates (ORRs), from 49% to 72%, with long-term, durable, and potentially curative CR rates of ≤ 25% [55, 71]. As a result, Iovance uses this core TIL regimen in its current clinical studies, while working in collaboration with the NCI to continually refine original treatment protocol.

Iovance Biotherapeutics has been able to successfully culture TILs from a variety of tumors including Triple Negative Breast Cancer (TNBC) [72]. The average yield of TILs from pre-REP of 13 TNBC tumors was 429 x 10^6. Phenotypic characterization of TILs from TNBC were >80% CD4+ T-cells. Further characterization of CD4+ and CD8+ TILs demonstrated effector memory phenotypic cells that were also CD27+ and CD28+. The success in growth of TIL from TNBC allows for the application of Iovance's Gen 2 manufacturing process for an autologous cellular infusion product to treat TNBC patients.

1.3. Rationale for Tumor-Infiltrating Lymphocytes for Selected Indication

Immunotherapy is an area of active investigation in the treatment of patients with breast cancer. Of breast subtypes, TNBC tumors are found to have the greatest immune infiltrate in the range of 40–60%, followed by HER2+ with 16% and ER+ subtypes with the least immune infiltrates [56]. High numbers of tumor infiltrating lymphocytes (TILs) correlate with pCR to neoadjuvant chemotherapy in patients with TNBC [57−60]. Studies have shown that the presence of TIL in treatment-naïve TNBC is an independent prognostic factor for disease-free survival (DFS) and OS [61, 62]. Specifically, TIL counts correlate with DFS, and for every 10% increase in TIL there is an 18% reduction in distant metastases [63, 64].

ACT with TIL has been successful in treating a proportion of patients with metastatic melanoma and cervical cancer. It is currently being investigated in other tumor types including breast, ovarian, endometrial, urothelial, and digestive tract in a phase II study at the National Institutes of Health (NIH) (NCT01174121). Recently, Lee et al. have demonstrated consistency in the ability to expand TIL from primary breast tumors with a success rate of 70%. These TIL were able to recognize autologous tumor cells and to induce tumor regression in a xenograft tumor mouse model [65]. Zacharakis et al. reported the successful treatment of a patient with hormone receptor positive metastatic breast cancer that was treated with TIL reactive against mutant versions of four proteins, SLC3A2, KIAA0368, CADPS2, and CTSB in NCT01174121 [66]. The 40-year-old female patient was treated with a lymphodepleting chemotherapy regimen of cyclophosphamide 60 mg/kg and fludarabine 25 mg/m^2 followed by a single infusion of 82 x 109 TIL containing tumor antigen-reactive T cells and pembrolizumab 2 mg/kg every 3 weeks for 7 doses. At 6 weeks the target tumor burden had decreased by 51%, and at > 22 months all lesions had radiographically resolved. Although the patient was treated with pembrolizumab, there are no data to support the efficacy of pembrolizumab in hormone receptor positive breast cancer and thus this response was attributed to ACT with TIL. The difference in the prior study and our proposed study is that we are using manufactured TIL LN-145 in patients with TNBC rather than using TIL selected for tumor antigen reactivity in a patient with hormone receptor positive breast cancer. Hormone receptor positive disease (which this patient had) is typically associated with less immunogenicity than TNBC. Additionally, TIL selection does not insure antitumor activity of the final product as demonstrated in several studies, including the one mentioned above. In this study, as well as another TIL trial conducted in cervical cancer, at least a fraction of the TIL involved in the antitumor response were not specific for the selected antigens [66, 67]. Earlier work also showed that selecting TIL for tumor reactivity did not provide any benefit in terms of clinical response relative to non-selected TIL [68]. Thus, we might expect that patients with TNBC treated with LN-145 could be responsive as well.

This study will investigate the safety and efficacy of TIL therapy in female patients with metastatic TNBC who have progressed on at least one and no more than three prior systemic anticancer therapies.

1.4. Safety of the TIL LN-144/LN-145 Cellular Therapy

LN-144 and LN-145 are TIL expansion products that are differentiated only by their indication: LN-144 is the product for melanoma and LN-145 is used in all other solid tumor indications. As both products share the same manufacturing process and infusion regimen (nonmyeloablative lymphodepletion [NMA-LD] preconditioning and then IL-2 post TIL infusion), safety data is pooled. Overall, toxicities and adverse events (AEs) observed during the TIL LN-144/LN-145 cellular therapy have been associated primarily with either the lymphodepletion preconditioning regimen or the IL-2 administration given after TIL infusion. Few infusion-related AEs have been documented following the TIL infusion itself, with Grade ≥ 3 events rarely observed [34].

The TIL LN-144/LN-145 product contains: TIL; medium, human serum albumin (HSA); human recombinant IL-2; and small amounts of gentamicin and streptomycin, aminoglycoside ABX. The cryopreserved TIL cellular product contains the cryopreservation medium CryoStor® CS10,

which consists of the cryoprotectants dimethyl sulfoxide (DMSO) and dextran-40, among other substances.

Hypersensitivity events, including severe allergic reactions or anaphylaxis, have occurred during infusion with LN-144 (melanoma-specific TIL) and LN-145; this may be anticipated because hypersensitivity reactions have been associated with at least one of the aforementioned formulation components. Patients who have a known history of hypersensitivity to any component or excipient of the TIL treatment regimen and the other study drugs will be excluded from this study. Pre-medication and supportive therapy instructions can be found in Section 8.2.

Details concerning specific risks for patients participating in this clinical study may be found in the accompanying TIL LN-144/LN-145 Investigator's Brochure (IB), informed consent documents, and each of the following prescribing information/package insert (PI) documents for these components: cyclophosphamide, mesna, fludarabine, and IL-2 (Proleukin®).

2. STUDY DESIGN

2.1. Overview

This is a prospective, open-label, non-randomized, Phase 2 study evaluating ACT with LN-145 as a single therapy.

The following indication will be investigated:

- LN-145 monotherapy in patients with Metastatic Triple Negative Breast Cancer who must have had at least one and no more than three prior lines of systemic anticancer therapies for metastatic breast cancer.
- All patients will receive autologous cryopreserved TIL LN-145 therapy, preceded by NMA-LD preconditioning regimen consisting of cyclophosphamide and fludarabine. Following LN-145 infusion, up to six IV IL-2 doses will be administered.

The following general study periods will take place, unless specified otherwise:

- Screening and Tumor Resection: Up to 4 weeks (28 days) from signing the informed consent form (ICF);
- Enrollment: Upon tumor resection for TIL generation;
- Manufacturing of the TIL LN-145 Product: approximately 22 days from tumor resection;
- Treatment Period: NMA-LD preconditioning regimen (up to 7 days), LN-145 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); At the discretion of the Investigator, and if deemed in the patient's best interest, the D28 visit can be conducted as a telehealth visit. Results of tests performed outside investigator's office within the positive window period of assessment may accept to enter in the eCRF as appreciate.
- Assessment Period: Following the EOT visit, efficacy (eg, tumor response) assessments will be performed at Week 6 (Day 42) post-LN-145 infusion and then occur every 6 weeks until Month 6 (Week 24). Patients will continue to be evaluated for response every

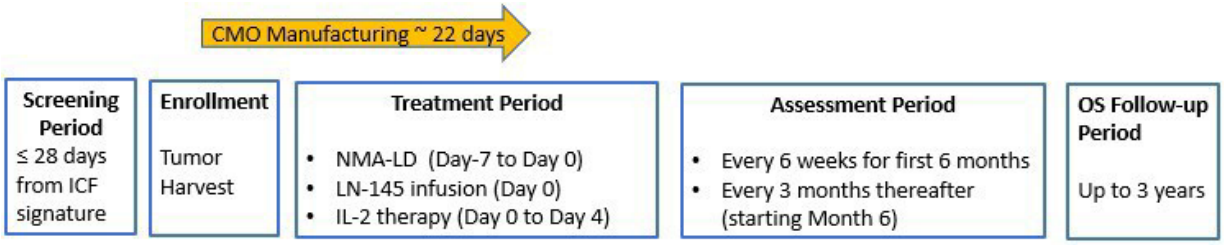
3 months (12 weeks) for up to 3 years from Day 0 (LN-145 infusion) or until:

- Disease progression
- Start of a new anticancer therapy
- At that time, the End of Assessment (EOA) visit will be completed. At the discretion of the Investigator, and if deemed in the patient's best interest, a visit can be conducted as a telehealth visit if patient is unable to return to the study site. Results of tests performed outside investigator's office within the positive window period of assessment timepoints may accept to enter in the eCRF as appreciate.
- Overall Survival Follow-up Period: Begins after completion of the last study assessment (eg, EOA) and will continue for up to 3 years from LN-145 infusion or until discontinuation from the study; with telephone contact every 3 months to obtain survival status and subsequent anticancer therapy information (Figure 1). Patients who had tumor resection but did not receive LN-145 for any reason will perform an EOA visit and transition directly into the OS Follow-up.

The TIL autologous therapy with LN-145 is comprised of the following steps:

1. Tumor resection to provide the autologous tissue that serves as the source of the TIL cellular product;
2. LN-145 investigational product production at a central Good Manufacturing Practice (GMP) facility;
3. A 7-day NMA-LD preconditioning regimen (hospitalization will be per institution standards);
4. Infusion of the autologous TIL LN-145 product on Day 0 (during inpatient hospitalization);
5. IV IL-2 administrations for up to six doses maximum (during inpatient hospitalization)

Figure 1: Study Flowchart



Abbreviations: CMO=contract manufacturing organization; ICF=informed consent form; IL-2=interleukin-2; NMALD=nonmyeloablative lymphodepletion; OS=overall survival.

3. STUDY OBJECTIVES AND ENDPOINTS

3.1. Objectives

Primary:

- To evaluate the efficacy of autologous TIL LN-145 as a single therapy in Metastatic Triple Negative Breast Cancer patients by determining the ORR, by Response Evaluation Criteria in Solid Tumors (RECIST) 1.1, as assessed by the Sponsor Investigator.
- To characterize the safety profile of TIL LN-145 as a single-therapy in Metastatic Triple Negative Breast Cancer patients as measured by the incidence of Grade ≥ 3 treatment-emergent adverse events (TEAEs).

Secondary:

- To further evaluate the efficacy of autologous TIL LN-145 as a single therapy in Metastatic Triple Negative Breast Cancer patients using duration of response (DOR), disease control rate (DCR), PFS, using RECIST 1.1, as assessed by the Sponsor Investigator, OS and CR Rate.

Exploratory:

- To explore the persistence of TIL LN-145 cells as a single therapy and its resultant immune correlates which may affect response, outcome, and toxicity variables.
- To explore efficacy parameters (excluding OS) using the immune-related Response Evaluation Criteria in Solid Tumors (irRECIST), as assessed by the Sponsor Investigator.
- To explore the feasibility of generating TIL (LN-145) from patient derived TNBC core biopsy tumor specimens using Iovance manufacturing process.

3.2. Endpoints

Primary:

- ORR
- Incidence of Grade ≥ 3
- TEAEs **Secondary:**
- DOR
- DCR
- PFS
- OS
- CR Rate

Exploratory:

- Immune correlations with respect to response, percent reduction in target lesion sum of

diameters, toxicity of the LN-145 therapy as a single-therapy

- ORR, DOR, DCR, and PFS as assessed by Sponsor Investigators per irRECIST

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:

1. Ability to understand the requirements of the study. Specifically, the patient has to provide written informed consent (as evidenced by signature on an ICF approved by the IRB of Record).
2. All patients must have a triple negative metastatic breast cancer (Estrogen Receptor negative, Progesterone Receptor negative, HER2 negative) as defined by 2018 ASCO CAP guidelines. Patients with low ER and/or low PR (defined as <10% expression by IHC) may be deemed eligible and considered as TNBC (following the ASCO CAP guidelines 2020 and ESO/ESMO 2020)
3. Patients must have a confirmed diagnosis of metastatic triple negative breast cancer (Stage IV) histologically confirmed as per American Joint Committee on Cancer [AJCC] staging system).
4. Patients must have had at least one and no more than three prior lines of systemic anticancer therapies for metastatic disease.
5. Patients must have disease progression from the last line of therapy.
6. Patients must have at least one resectable lesion of a minimum 1.5 cm in diameter (or aggregate of 1.5 cm if multiple lesions are sampled) post-resection for TIL investigational product production. It is encouraged that tumor tissue be obtained from multiple and diverse metastatic lesions, as long as the surgical resection it does not pose additional risks to the patient.
    - If the lesion considered for resection for TIL generation is within a previously irradiated field, the lesion must have demonstrated radiographic progression postradiotherapy (XRT) and prior to resection.
    - Patients must have an adequate histopathology specimen for protocol-required testing.
7. Patients must have a remaining measurable disease as defined by RECIST 1.1 following tumor resection for TIL manufacturing:
    - Lesions in previously irradiated areas should not be selected as target lesions unless there has been demonstrated progression in those lesions.
    - Lesions partially resected for TIL production may be chosen as non-target lesions but cannot be used as target lesions for RECIST assessment.
8. Patients must be ≥ 18 years of age at the time of consent.
9. Patients must have an Eastern Cooperative Oncology Group (ECOG) performance status

of 0 or 1, and an estimated life expectancy of ≥ 3 months in the opinion of the Investigator.

10. Female patients of childbearing potential or female partners of childbearing potential of male participants, must be willing to practice an approved method of birth control during treatment and for 12 months after receiving all protocol-related therapy.

    Approved methods of birth control are as follows:

    - Combined (estrogen and progestogen containing) hormonal birth control associated with inhibition of ovulation: oral; intravaginal; transdermal
    - Progestogen-only hormonal birth control associated with inhibition of ovulation: oral; injectable; implantable
    - Intrauterine device (IUD)
    - Intrauterine hormone-releasing system (IUS)
    - Bilateral tubal occlusion
    - Vasectomized partner (female participant)/ Vasectomized male participant
    - 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.

11. Patients must have the following hematologic parameters:
    - Absolute neutrophil count (ANC) ≥ 1000/mm^3;
    - Hemoglobin ≥ 9.0 g/dL;
    - Platelet count ≥ 100,000/mm^3

12. Patients must have adequate organ function:
    - Serum alanine aminotransferase (ALT) and aspartate aminotransferase (AST) ≤ 3 times the upper limit of normal (ULN), patients with liver metastasis ≤ 5 times ULN;
    - An estimated creatinine clearance ≥ 40 mL/min using the Cockcroft Gault formula at Screening;
    - Total bilirubin ≤ 2 mg/dL: ○ Patients with Gilbert's Syndrome must have a total bilirubin ≤ 3 mg/dL

13. Patients must be seronegative for the human immunodeficiency virus (HIV1 and HIV2). Patients with positive serology for hepatitis B virus surface antigen (HBsAg), hepatitis B core antibody (anti-HBc), or hepatitis C virus (anti-HCV) indicating acute or chronic infection may be enrolled if the viral load by polymerase chain reaction (PCR) is undetectable with/without active treatment.
14. Patients must have a washout period of 21 days from prior anti-cancer therapy prior to the first study treatment (i.e start of NMA LD)
15. Palliative radiation therapy: prior external beam radiation is allowed provided all radiation- related toxicities are resolved to Grade 1 or baseline;

- The tumor lesion(s) being assessed as target for response via RECIST 1.1 must be outside of the radiation portal (however, if within the portal, they must have demonstrated progression);
- Surgery/pre-planned procedure: previous surgical procedure(s) is permitted provided that wound healing has occurred, all complications have resolved, and at least 14 days have elapsed (for major operative procedures) prior to the tumor resection.

16. Patients must have recovered from all prior anticancer treatment-related adverse events (TRAEs) to Grade ≤ 1 (per Common Terminology Criteria for Adverse Events [CTCAE], version 5.0). Exceptions may be made, at the Investigator's discretion, for persistent AEs that are corrected or do not pose a clinical risk, such as hypothyroidism, adrenal insufficiency, alopecia, and vitiligo:
    - Patients with Grade ≥ 2 neuropathy will be evaluated on a case-by-case basis;
    - Patients with irreversible toxicity not reasonably expected to be exacerbated by treatment may be included at the Investigator's discretion;
    - Patients with Grade ≥ 2 toxicity from prior anticancer therapy may be considered on a case-by-case basis after consultation with the Investigator.
17. Patients must have provided written authorization for use and disclosure of protected health information.
18. Must be able and willing to comply with the study visit schedule and protocol requirements including long-term follow-up (LTFU).

4.2. Exclusion Criteria

1. Patients who have received an organ allograft or prior cell transfer therapy within the past 20 years that included a nonmyeloablative or myeloablative chemotherapy regimen.
2. Patients with symptomatic and/or untreated brain metastases:
    - Patients with definitively-treated brain metastases will be considered for enrollment if, prior to tumor resection for TIL, the patient is clinically stable for ≥ 2 weeks, there are no new brain lesions via magnetic resonance imaging (MRI) post-treatment, and the patient does not require corticosteroid treatment.
3. Patients who are on systemic steroid therapy except for those requiring steroid for management of adrenal insufficiency. Patients receiving steroids for management of adrenal insufficiency may receive no more than 10 mg prednisone or its equivalent daily.
4. Patients who are pregnant or breastfeeding.
5. Patients who have active medical illness(es)that would pose increased risk for study participation, including: active systemic infections requiring systemic antibiotics (ABX), coagulation disorders, or other active major medical illnesses of the cardiovascular, respiratory, or immune systems.
6. Patients who have received a live or attenuated vaccination within 28 days prior to the start of NMA-LD.

7. Patients who have any form of primary immunodeficiency (such as severe combined immunodeficiency disease [SCID] and acquired immune deficiency syndrome [AIDS]).
8. Patients with a history of hypersensitivity to any component of the study drugs. LN-145 should not be administered to patients with a known hypersensitivity to any component of TIL product formulation including, but not limited to:
   - NMA-LD (cyclophosphamide, mesna, and fludarabine);
   - Proleukin®, aldesleukin, IL-2;
   - ABX of the aminoglycoside group (ie, streptomycin, gentamicin);
   - Any component of the TIL product formulation including dimethyl sulfoxide [DMSO], HSA, IL-2, and dextran-40.
9. Patients who have a left ventricular ejection fraction (LVEF) < 45% or who are New York Heart Association (NYHA) Class II or higher. A cardiac stress test demonstrating any irreversible wall movement abnormality in any patients ≥ 60 years of age or in patients who have a history of ischemic heart disease, chest pain, or clinically significant atrial and/or ventricular arrhythmias.
10. Patients who have obstructive or restrictive pulmonary disease and have a documented FEV1 (forced expiratory volume in 1 second) ≤ 60% of predicted normal:
    - If a patient is not able to perform reliable spirometry due to abnormal upper airway anatomy (ie, tracheostomy), a 6-minute walk test may be used to assess pulmonary function. Patients who are unable to walk a distance of at least 80% predicted for age and sex or demonstrates evidence of hypoxia at any point during the test (SpO2 < 90%) are excluded.
11. Patients who have had another primary malignancy within the previous 3 years (except for curatively treated localized malignancy that has not required treatment for greater than 1 year, and in the judgment of the Investigator, does not pose a significant risk of recurrence including, but not limited to, non-melanoma skin cancer or bladder cancer or cancers that do not require treatment in the judgement of the Investigator).
12. Participation in another clinical study with an investigational product within 21 days of the initiation of NMA-LD treatment.

5. TREATMENT

Comprehensive treatment plan can be found in the Schedule of Assessments (Appendix 14.1).

5.1. Investigational Products

The investigational products used in this study are listed in Table 1.

Table 1: List of Investigational Products

Therapy Type	Investigational Product	Dosage Form and Strength
	Cyclophosphamide	Section 5.3.1

LN-145 regimen consisting of NMA-LD, LN-145, and IL-2	Mesna	Section 5.3.2
	Fludarabine	Section 5.3.4
	LN-145	1.0×10^9 to 150×10^9 total viable lymphocytes
	IL-2	Section 5.5

5.2. Treatment Overview

The cell transfer therapy used in this study involves patients receiving an NMA-LD preparative chemotherapy regimen, consisting of cyclophosphamide IV (60 mg/kg x 2 doses) with mesna (60 mg/kg x 2 doses with cyclophosphamide) and fludarabine IV (25 mg/m^2 x 5 doses). Patients will receive on Day 0 infusion of tumor-derived LN-145 (1–150 x 109 cells) and administration of multiple doses of adjuvant IL-2 at 600,000 international units (IU)/kg.

5.3. Nonmyeloablative Lymphodepletion Regimen

The NMA-LD regimen is scheduled to start on Day -7 for patients, after notification from Iovance that TIL production is expected to be successful for the patient. Patients may receive lymphodepletion chemotherapy as inpatient or outpatient at the discretion of the Investigator or per institutional standards. Modification of the lymphodepletion regimen is allowed as clinically indicated and should be guided by daily hematological parameters as described below for fludarabine in heavily pre-treated patients or patients with a history of prolonged myeloid recovery. Patients may remain hospitalized until the completion of the lymphodepletion regimen for close monitoring of toxicity and hematologic parameters. If indicated by daily hematological parameters, any modification of the lymphodepletion regimen is at the discretion of the Investigator.

The NMA-LD regimen is comprised of single daily doses of cyclophosphamide on Day -7 and Day -6 for a total of two doses followed by single daily doses of fludarabine on Day -5 through Day -1 for a total of five doses (until the absolute lymphocyte count [ALC] is < 100 cells/mm^3) and should be administered as per institutional protocol/standards for nonmyeloablative chemotherapy. Guidelines for preparation and administration are described below. For consistency in dosing, all patients should be dosed using actual body weight, as described in Appendix 14.2.

Drugs required for lymphodepletion including cyclophosphamide and fludarabine will be procured and supplied by Iovance. Antimicrobials will be obtained through the participating site's clinical pharmacy. For formulation and packaging of the lymphodepletion regimen please refer to respective package inserts for cyclophosphamide, fludarabine, and mesna. Variations from the lymphodepletion (eg, infusion times, schedule of treatments, etc.) prior to Day -1 will be documented in the medical record but will not be considered protocol violations/deviations. Lymphodepletion, LN-145 infusion, and IL-2 administration will all be performed per the Pharmacy & Investigational Product Administration Manual by faculty and staff who are experienced in these therapies.

5.3.1. Cyclophosphamide Preparation

The dose of cyclophosphamide is 60 mg/kg. Cyclophosphamide is to be reconstituted and given per institutional standards.

5.3.2. Mesna Preparation

Mesna is administered to prevent the occurrence of hemorrhagic cystitis related to cyclophosphamide. Mesna will be prepared and administered per institutional standards.

5.3.3. Infusion of Cyclophosphamide and Mesna

Cyclophosphamide (60 mg/kg) plus mesna are to be infused together on Day -7 and Day -6. Hydration with intravenous fluids will be given as per the guideline below or per investigator discretion. Hydration is to begin 4 hours prior to the first Cyclophosphamide dose. This infusion will continue until 6 hours after the last Cyclophosphamide dose. If the urine output is less then 150 ml/hr, increase hydration rate to 200 ml/h. Hold fluid infusion during the Cyclophosphamide infusion.

- Mesna 60 mg/kg IV is given once on Day -7 to infuse over 24 hours. The infusion is to begin 15 minutes prior to Cyclophosphamide infusion and continue 24 hours after the first dose of Cyclophosphamide. Modifications can occur at the Investigator discretion as per Clinical Practice Guidelines.
- Mesna 60 mg/kg IV is given once on Day -6 to infuse over 9 hours. The infusion is to begin 15 minutes prior to Cyclophosphamide infusion and continue 6 hours after the second dose of Cyclophosphamide. Modifications can occur at the Investigator discretion as per Clinical Practice Guidelines.
- Refer to the current PI/summary of product characteristics (SmPC) for cyclophosphamide, as applicable.

5.3.4. Infusion of Fludarabine

The fludarabine dose of 25 mg/m^2 is administered IV over approximately 30 minutes once daily for five consecutive days from Day -5 through Day -1.

- NS 1000ml IV is to be infused over 2 hours prior to the Day -5 Fludarabine dose or per investigator discretion The final dose of fludarabine should be administered on Day -1 (at least 24 hours prior to the LN-145 infusion).

Hematological parameters (complete blood count [CBC] and differential) are to be reviewed daily during lymphodepletion. If after three or four doses of fludarabine, the ALC falls below 100 cells/mm^3, the remaining dose(s) of fludarabine may be omitted at the discretion of the Investigator.

The fludarabine dose will be adjusted according to measured/estimated creatinine clearance (CrCl) as follows:

- CrCl 50-79 mL/min: Reduce dose to 20 mg/m^2
- CrCl 40-49 mL/min: Reduce dose to 15 mg/m^2

Note: 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 Sponsor Investigator is recommended.

5.4. LN-145

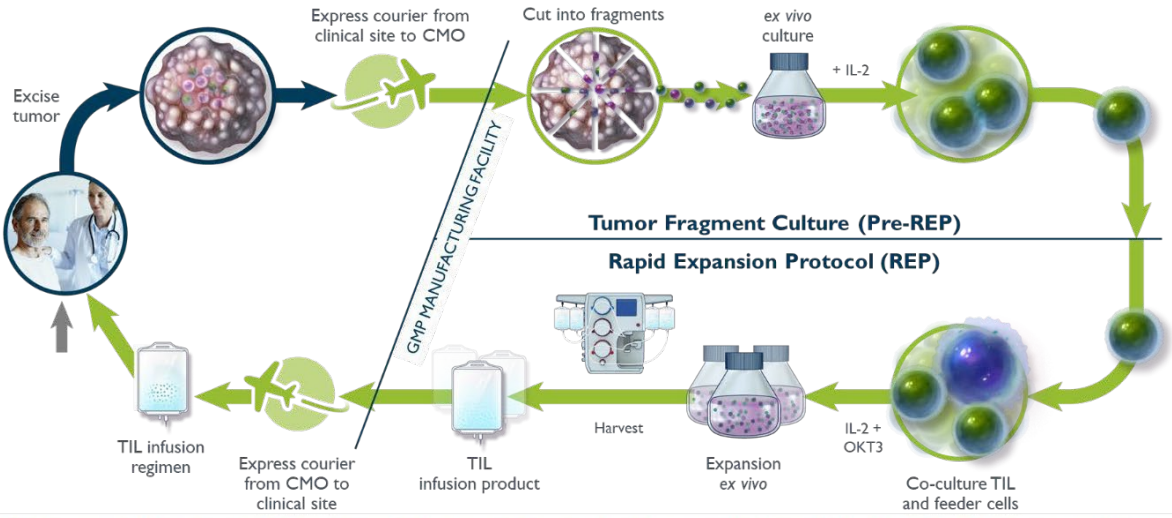
5.4.1. LN-145 Description

LN-145 is a cellular investigational product comprising a live cell suspension of autologous TIL derived from the patient's own tumor that is shipped as cryopreserved product. A summary of the LN-145 manufacturing process is described in Figure 2. For details about tumor handling, see Section 6.20 as well as the Tumor Procurement and Shipping Manual.

Each dose of LN-145 contains from 1.0×10^9 to 150×10^9 total viable lymphocytes. The total volume to be infused will be dependent on total cell dose.

At the time of completion of TIL manufacturing, the appropriate number of cells will be harvested and provided in the final investigational product.

Figure 2: LN-145 Manufacturing Process



CMO, Contract Manufacturing Organization; TIL, tumor infiltrating lymphocytes; IL-2, interleukin-2; NMA-LD, nonmyeloablative-lymphodepletion; OKT3, muromonab-CD3; REP, Rapid Expansion Protocol.

5.4.2. LN-145 Composition

Cryopreserved formulations of LN-145 have been developed for use in clinical studies. The cryopreserved investigational TIL product is a sterile product formulated in CryoStor® CS10 cryopreservation media (a cryopreservation medium containing DMSO and other cryoprotectants diluted with Plasma-Lyte A, containing 0.5% HSA and 300 IU/mL (12 ng/mL) of IL-2. The cryopreserved product is provided in one or more 750-mL cryopreservation bags, each containing approximately 100 mL of cells suspended at 100 to 300 x 10^6 cells/mL.

5.4.3. LN-145 Transport

Each dose of the live suspension LN-145 product will be shipped/sent by courier from the contract manufacturing organization (CMO) to the clinical site at least the day before planned administration using a method that is intended to support 24-hour delivery and expected to arrive on the morning of scheduled infusion (Day 0) or can be held for a later infusion, per the flexibility the cryopreserved LN-145 product allows.

Additional details are specified in the Pharmacy & Investigational Product Administration Manual.

5.4.4. LN-145 Receipt

LN-145 will be received at the clinical site prior to administration (Day 0). Receipt is defined as the moment the LN-145 shipper is signed for by site personnel and released from the courier's custody.

After receiving, inspecting, verifying, and re-labeling with the clinical site's specific labels, the investigational product, LN-145, will be transferred to the patient's bedside, preferably in its original shipping container (vapor phase liquid nitrogen container for the cryopreserved product) for administration. The clinical site is instructed to administer the LN-145 investigational product immediately after thawing each cryopreserved infusion bag, sequentially.

Additional details are specified in the Pharmacy & Investigational Product Administration Manual.

5.4.5. Administration of LN-145

At least 24 hours must have elapsed from the last dose of fludarabine and the administration of LN-145. If fludarabine is discontinued due to a low ALC, then LN-145 may be administered 24 hours after the last dose of fludarabine given. If fludarabine is discontinued due to an AE, LN-145 may be given after resolution of that AE or with approval of the Investigator. Approval of the Investigator is required prior to administration of LN-145 if more than 4 days has elapsed from the last dose of fludarabine.

Within 24 hours prior to administering LN-145, the patient must be hospitalized and prepared with IV hydration, as needed, to ensure good hydration status. Patients must be premedicated with acetaminophen/paracetamol 650 mg PO and diphenhydramine 25 to 50 mg IV (or other histamine H1 antagonist) between 30 and 60 minutes prior to administration of LN-145. In addition, emergency anaphylaxis medications must be available at bedside (epinephrine, and diphenhydramine, and corticosteroids). Prophylactic use of systemic corticosteroids should be avoided, as it may interfere with the activity of LN-145. Corticosteroids should only be given in a life-threatening situation. Patients will remain hospitalized until the completion of IL-2 administration or until deemed necessary per treating ŧInvestigator, as per institutional standards. Prolongation of admission post IL-2 will not be considered an SAE.

Additional supportive medications may include the following:

- Acetaminophen (650 mg q4h)
- Indomethacin (50 to 75 mg q6h)
- Ranitidine (150 mg q12h)
- Meperidine (25 to 50 mg) IV or other medications per institutional standards may be given for severe rigors/chills

The LN-145 is to be infused by gravity beginning at a rate of 1 mL/min for the first 5 minutes. If no adverse reaction is observed, the rate can then increase to between 5 and 10 mL/min for the completion of the infusion. Multiple cryopreserved bags are thawed individually and administered sequentially. If interruption of infusion is required for medical reasons, the LN-145 infusion bags not yet thawed should be kept in the cryoshipper and any thawed LN-145 product should be infused within 3 hours of being thawed. The Pharmacy & Investigational Product Administration Manual should be consulted.

Continuous supervision of the patient by site medical staff is required until completion of infusion of the first bag of LN-145 to monitor for potential signs and symptoms (eg, of a severe hypersensitivity reaction, such as anaphylaxis) that may require immediate medical attention and treatment. For details on LN-145 toxicities, see Section 8.7.

5.5. Interleukin-2

The IL-2 infusion will begin no sooner than 3 and no later than 24 hours after completion of the LN-145 infusion. IL-2 will be administered at a dose of 600,000 IU/kg (based on total body weight) and will be administered by IV infusion BID.As per institutional standard of care, and continued for up to a maximum of six doses. Pulse oximetry is to be conducted during IL-2 administration.

Days 0-4

- Zofran is to be given 16 mg PO q12h

IL-2 doses will be skipped if patient experiences a Grade 3 or 4 toxicity due to IL-2, except for reversible Grade 3 toxicities common to IL-2 (such as diarrhea, nausea, vomiting, hypotension, skin changes, anorexia, mucositis, dysphagia, constitutional symptoms, or laboratory changes). Management of IL-2 toxicity is detailed in Appendix 14.4. If these toxicities can be easily reversed within 24 hours by supportive measures, then additional doses may be given. If greater than two doses of IL-2 are skipped, IL-2 administration will be stopped. In addition, dosing may be held or stopped at the discretion of the treating Investigator.

When a patient experiences any AE Grade ≥ 3 after infusion of LN-145, which in opinion of the Sponsor Investigator could be exacerbated by the IL-2 infusion or cause delay of IL-2 infusion for ≥ 48 hours, IL-2 infusion can be skipped.

All patients will remain hospitalized until the completion of IL-2 administration, as per institutional standards.

For details on IL-2 toxicities, please refer to Appendix 14.4.

Refer to the IL-2/aldesleukin (Proleukin®) (80) current PI/SmPC for additional information.

5.6. Permitted and Prohibited Medications

5.6.1. Permitted Medications

The following treatments are permitted during the study:

- Palliative radiation therapy is permitted between tumor resection and lymphodepletion if it does not affect target and nontarget lesions.

Any changes in concomitant medications also will be recorded in the source documentation and the patient's electronic case report form (eCRF) throughout the study.

5.6.2. Prohibited Medications and Prior Treatment Washout

5.6.2.1. Prohibited Medications

The following treatments are prohibited during the study:

- Systemic therapies and radiation intended to treat TNBC are not permitted while the patient is on study. Palliative radiation may be allowed if it is not directed at any target or nontarget lesions.
- Systemic use of corticosteroids is not allowed starting 21 days prior to beginning the NMA-LD preconditioning regimen, through treatment, and up to 60 days post-LN-145 infusion. Such medications should only be used to treat immediate life-threatening conditions. Prophylactic use of steroids is absolutely contraindicated. The one exception is for those requiring steroid for management of adrenal insufficiency. Patients receiving steroids for management of adrenal insufficiency may receive no more than 10 mg prednisone or its equivalent daily.
- Other investigational drugs
- Live attenuated vaccines (should not be given during the study and through 30 days after the last dose of study treatment)
- Monoclonal Abs against CTLA-4, PD-1, or PD-L1

5.6.2.2. Prior Treatment Washout

A washout period from prior anticancer therapy(ies) of a minimum duration as detailed below is required prior to start of NMA-LD:

- Cellular therapy: patients may not have received prior cell therapy
- A washout period of 21 days from last anticancer therapy to the start of NMA LD

- Surgery: previous surgical procedure(s) is permitted provided that wound healing has occurred and at least 28 days have elapsed (for major operative procedures) prior to start of treatment

5.7. Pregnancy

Patients of childbearing potential must be willing to take the appropriate precaution to avoid pregnancy for the duration of the study and practice an approved, highly effective method of birth control during treatment and for 12 months after LN-145 therapy from the last dose of IL-2.

- 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 (female participant), vasectomized (male participant) ○ 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

Highly effective methods of contraception, defined as one that results in a low failure rate (< 1% per year), when used consistently and correctly, are described in Table 2. **Table 2: Highly Effective Methods of Contraception (< 1% Failure Rate)**

Barrier/Intrauterine methods	**Hormonal Methods**	
Copper T intrauterine device Levonorgestrel-releasing intrauterine system (eg, Mirena®)*	Implants:	Etonogestrel-releasing implants: eg, Implanon® or Norplant®
	Intravaginal:	Ethinylestradiol/etonogestrel-releasing intravaginal devices: eg, NuvaRing®
	Injection:	Medroxyprogesterone injection: eg, Depo-Provera®
	Combined Pill:	Normal and low dose combined oral contraceptive pill
	Patch:	Norelgestromin/ethinylestradiol-releasing transdermal system: eg, Ortho Evra®
	Minipill:	Progesterone based oral contraceptive pill using desogestrel: Cerazette® is currently the only highly effective progesterone-based

* This is also considered a hormonal method.

6. STUDY ASSESSMENTS/PROCEDURES

The study assessments and procedures described below will be performed at the time points specified in Appendix 14.1.

6.1. Informed Consent

An ICF must be signed before any study-related assessments are performed.

6.2. Inclusion/Exclusion Criteria

Patients must meet all inclusion criteria (Section 4.1) and must not meet any of the exclusion criteria (Section 4.2). Patients must continue to meet eligibility criteria at Baseline (Day -21 to Day -9).

6.3. Demographic Data

The demographic data will include date of birth, age, sex, and race/ethnic origin.

6.4. Medical History

Relevant and significant medical/surgical history and concurrent illnesses will be collected for all patients at Screening.

6.5. Confirmation of Diagnosis

Patients must have a confirmed diagnosis of metastatic triple negative breast cancer and have received at least one prior systemic anticancer therapy. Histologic confirmation is required for all patients via pathology report.

6.6. Physical Examinations

Physical examinations will be conducted at the time points specified in Appendix 14.1. Physical examinations will include gastrointestinal (abdomen, liver), cardiovascular, extremities, head, eyes, ears, nose, and throat, respiratory system, skin, and psychiatric (mental status).

Height will be measured at Screening only. Body surface area (BSA) and body mass index (BMI) will be calculated at Day -7 only.

Physical examinations conducted after Day 14 will be symptom-directed only. Clinically significant changes should be recorded as AEs.

6.7. Vital Signs

Vital signs will include: weight, pulse rate, respiratory rate, blood pressure, and temperature. Vital signs will be measured at the time points specified in Appendix 14.1. On Day 0 (LN-145 infusion), vital signs will be taken pre-infusion, every 15 minutes during infusion and then every 30 minutes for 2 hours post infusion or until stable.

6.8. Concomitant Medications

All medications and therapies (prescription, and nonprescription, including herbal supplements) taken by the patient up to 28 days prior to screening will be collected and recorded in the database (including the stop dates for medications prohibited in the study) at the time of consent. All medications and therapies being taken by the patients, or changes thereof, at any time during the study, must also be recorded. Concomitant medications, therapies, or interventions will be collected at each visit until completion of the assessment period. The assessment period begins after LN-145 infusion on Day 0 and ends at disease progression, the start of a new anticancer therapy, or 3 years (Month 36), whichever occurs first.

6.9. Eastern Cooperative Oncology Group Performance Status

The patient's ECOG performance status will be assessed at the time points specified in Appendix 14.1.

6.10. Blood and Urine Tests

The following safety blood and urine tests will be collected at the time points specified in Appendix 14.1:

- Serum chemistry: sodium, potassium, chloride, total CO_2 (bicarbonate), serum creatinine, glucose, blood urea nitrogen, albumin, calcium, magnesium, phosphorus, alkaline phosphatase, lactate dehydrogenase, total protein, total creatine kinase, uric acid, amylase, and lipase;
- Liver function tests: ALT, AST, total bilirubin, direct bilirubin;
- Thyroid panel: thyroid-stimulating hormone (TSH) and free T_4;
- Hematology: CBC with differential;
- Coagulation panel: prothrombin time, activated partial thromboplastin time (aPTT), and international normalized ratio;
- Urinalysis dipstick (a complete urine culture will be performed if clinically indicated).

6.11. Human Leukocyte Antigen Typing

High resolution human leukocyte antigen (HLA) Class I typing samples will be collected and analyzed locally at the Screening Visit.

6.12. Estimated Creatinine Clearance

Creatinine clearance will be calculated by the site using the Cockcroft-Gault formula at Screening and Day 84 (Week 12).

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

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

6.13. ß-HCG Serum Pregnancy Test

Serum ß-HCG pregnancy tests will be performed for all women of childbearing potential at the timepoints indicated in the schedule of assessments (Appendix 14.1) and as clinically indicated.

If pregnancy is discovered at any point in time during the study, it should be reported immediately to the Sponsor Investigator.

6.14. Infection Testing

Blood samples will be collected and tested for the following viral infections at Screening and thereafter as clinically indicated (as per local standard):

- Cytomegalovirus (CMV) serology (CMV immunoglobulin G [IgG] and CMV immunoglobulin M [IgM]);
- Syphilis assay (as per local standard; eg, rapid plasma reagin [RPR], venereal disease research laboratory [VDRL], or other);
- HIV1 and HIV2 antibody titer;
- HBsAg and anti-HBc;
- Anti-HCV;
- Herpes simplex virus (HSV) serology determination (HSV-1 IgG and HSV-2 IgG);
- Epstein-Barr virus (EBV) Panel (VCA-IgG, and/or Epstein-Barr nuclear antigen IgG [or tests conducted as per local standard to confirm absence of acute or active EBV infection] (may have been done within 3 months prior to tumor resection).

Infection testing must be repeated if > 28 days occurs from the last tests results.

6.15. PD-L1 Status

A sample of tumor resected for TIL generation will be analyzed locally for PD-L1 status by immunohistochemistry (IHC). See Section 6.22.

6.16. Cardiac Evaluations

All cardiac evaluations (NYHA, echocardiogram [ECHO], electrocardiogram [ECG], cardiac stress test) will be performed during screening, and ECG will be performed at screening and baseline. Cardiac stress test will only be performed if clinically indicated. If an ECG was performed within 2 weeks prior to screening, then it does not need to be repeated. Other evaluations completed within 3 months prior to screening will be accepted.

6.16.1. Electrocardiograms

At Screening and Baseline, a 12-lead ECG will be performed after the patient has been supine for at least 3 minutes. If an ECG has been performed within 2 weeks prior to Screening, an ECG does not need to be repeated.

6.16.2. Echocardiograms or Multigated Acquisition Scans

During screening, an ECHO or multigated acquisition scan (MUGA) will be performed to assess ventricular function for all patients.

6.17. Pulmonary Function Tests

Prior evaluations completed within 6 months prior to Screening will be accepted, apart from patients with known pulmonary metastases or clinically significant pulmonary disease. Pulmonary function tests using spirometry will be completed during screening, as clinically indicated. Patients who are unable to conduct reliable pulmonary function test measurements due to abnormal anatomy may undergo a 6-minute walk test to evaluate pulmonary function [69]. These patients must walk a distance of at least 80% predicted for age and sex as well as maintain oxygen saturation > 90% throughout.

6.18. Radiographic Assessments

Computed tomography (CT) scans which have been performed within 4 weeks prior to enrollment can be utilized for Screening. Radiographic assessments by CT scans with contrast of the chest, abdomen, and pelvis are required for all patients for tumor assessments. CT scans are performed throughout the study as outlined in the Schedule of Assessment (Appendix 14.1) until disease progression as measured by RECIST 1.1 is noted (or if the patient withdraws full consent). Radiographic assessments of additional anatomical locations will be conducted at the referenced visits (see Appendix 14.1 for specific timepoints) if clinically indicated per disease history and clinical symptoms. Magnetic resonance imaging (MRI) or positron emission tomography (PET) scans of the chest, abdomen, and pelvis in lieu of CT scans may be allowed for patients are intolerant to contrast media. The same method of assessment (CT or MRI) and the same technique for acquisition of data should be used consistently throughout the study to characterize each identified and reported lesion at Baseline (Day -21 to Day -9). At the Investigator's discretion, the baseline brain MRI and CT scans may be performed as early as Day -21. The baseline Brain MRI may not be repeated if negative at screening.

Patients will be evaluated for response at Weeks 6, 12, 18, 24; and then every 3 months thereafter until disease progression, initiation of a new anticancer therapy, or patient withdrawal from the study. Tumor assessments are to be performed within the positive window period only, for the timepoints mentioned above. The same imaging parameters should be utilized for all scans throughout the study. Response assessments should be evaluated and documented by a qualified Investigator participating in the study.

6.19. Tumor Resection / Harvest

Preferably, the targeted tumor will not have been previously irradiated. Prior irradiation of the resected tumor is allowed if at least 3 months have elapsed between irradiation and resection and the tumor has demonstrated growth during that interim. Whenever possible, resection from multiple tumors for TIL generation should be obtained if it would not significantly increase the potential morbidity of the surgical procedure. If there is only one lesion, then it may be used for both TIL generation and as a target lesion, provided the appropriate criteria are met. Tumor resection is expected to occur approximately 23 days prior to the LN-145 infusion on Day 0 and is dependent on the rate of TIL cell growth at the CMO.

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

Refer to the Tumor Procurement and Shipping Manual for details.

6.20. Optional Sub Study − TIL Growth from Core Biopsies

If available and if patient consent to the substudy is provided, additional core biopsies from primary and/or metastatic tumor will be collected during tumor harvest. Core biopsies should be from an area of the tumor lesion that will be different from that prepared for TIL manufacturing. Ideally, 10 or more cores (14G) of 20 mm will be collected and sent to Iovance per the Tumor Procurement and Shipping Manual (for Research Specimens to Iovance Tampa). The core biopsies will be used to determine the feasibility of generating TIL using the Iovance LN-145 manufacturing process, from patient derived TNBC specimens that are much smaller than the current specimens and obtainable through non-invasive procedures.

If exploratory TIL growth from core biopsy tissue collected during this sub study is found to be successful, the protocol may be amended in the future to allow tissue collected via core biopsy to be used for LN-145 generation.

6.21. Additional Resected Tumor Tissue for Molecular Analyses

If there is an excess of tumor tissue available after resection for TIL manufacturing, it will be utilized for exploratory biomarker analysis.

If no excess tumor tissue is available, a single 2 mm punch biopsy from the center of the resected tumor can be collected. If excess viable tumor tissue and punch biopsy are not available, excess viable tumor tissue can be resected from additional (non-target) lesion (if feasible). Depending on the size of excess viable tumor tissue collected, tissue will be divided into approximately three 0.5 cm diameter portions in the following order of priority:

(1) 0.5 cm tissue prepared as formalin-fixed, paraffin-embedded (FFPE) block (sent to local laboratory)

(2) 0.5 cm tissue can be placed in hypothermosol (send to Iovance Tampa)

(3) 0.5 cm tissue placed in ribonucleic acid (RNA) later (send to local laboratory)

(4) Any remaining tissue will be sent fresh to Dr Tristen Park, Yale Cancer Center laboratory

Any additional available tissue can be further prepared in the following order:

FFPE -> Hypothermosol -> RNA later -> fresh applications

Tumor tissue sent to the Yale Cancer Center laboratory and Iovance laboratory may be used as follows:

(1) For IHC to identify different immune cell populations and PD-L1 status; and for isolation of DNA, which will be used for sequencing of common oncogenic mutations, tumor-associated gene and/or T cell receptors and for whole exome sequencing and tumor mutation analyses (subject to patient consent)

(2) For tumor-reactivity assays

(3) For gene expression analyses; and

(4) For the production of Research TIL, the generation of patient-derived xenografts into immunocompromised mice, and the establishment of primary breast tumor lines

Provision of adequate amount of tumor tissue for TIL manufacturing sent to the CMO is priority over the collection of additional tumor tissue that is sent for exploratory purposes. Every effort should be made to obtain adequate tumor tissue for both TIL manufacturing and additional analysis.

Refer to the Tumor Procurement and Shipping Manual for Research Specimens for sending fresh tissue to Iovance Tampa.

6.22. Optional Post-TIL Treatment Biopsy

If available and if patient consent is provided, on-study post-treatment (post LN-145 infusion) biopsy will be collected at Week 6 (Day 42) following the first post-baseline tumor response assessment scans; Core biopsies (1-6 cores) from lesions not being assessed by RECIST will be collected. FFPE blocks need to be prepared from first core and second core and can be placed in RNA later solution. If more than two core biopsies are available, they should be utilized in the following order:

FFPE -> RNA later -> FFPE -> RNA later

The Week 6 (Day 42) core biopsies may be used to ascertain molecular and immunological changes in the tumor following treatment as described below:

- FFPE block sent to Yale Cancer Center laboratory may be used for IHC including PD-L1 staining and DNA sequencing; and

- Sample in RNA later (sent to Yale Cancer Center) may be used for gene expression analyses

6.23. Biological and Immune Monitoring

In addition to tumor tissue samples, samples of the TIL product as well as blood samples collected at different time points before and after TIL infusion will be studied to identify biomarkers of TIL antitumor activity.

TIL from the infusion product will be stored for research. The samples used in these research studies will be used to gain further information about the disease and the characteristics of the TIL before and after infusion (TIL phenotype, TIL function, TIL reactivity, and TIL diversity). Lab experiments will include flow cytometry analyses, cell-based assays, gene expression analyses, and T-cell receptor (TCR) sequencing.

Mandatory peripheral blood will be collected at the timepoints of surgery/tumor resection and day 1 for immune monitoring by testing for an array of cellular and soluble factors that may include:

- The detection of circulating immune molecules, such as cytokines;
- The monitoring of immune cell numbers;
- The identification, characterization, and functional assessment of circulating TIL; and
- The identification of circulating tumor DNA

Blood for immune monitoring will be collected at the following timepoints: Week 6 (Day 42), Week 12 (Day 84), Month 6, and Month 12 if patient is able to return to the study site . See Appendix 14.1.

Refer to Blood Immuno-Monitoring Shipping Manual for more details.

6.24. Adverse Events

All AEs for all patients will be assessed as per NCI CTCAE Version 5.0 during all visits after the ICF is signed. Additional safety reporting requirements are described in Section 10.5.

6.25. End of Assessment Visit

Once a patient has reached disease progression or started a new anticancer therapy, an EOA visit should take place according the schedule of assessments in Appendix 14.1. If the patient has performed the required assessments during a visit within the previous 6 weeks, and results are either normal, or abnormal but expected, the assessments do not need to be repeated for the EOA visit.

6.26. Long-term Safety Follow-up Period

Long-term follow-up for OS will commence when a patient completes the EOA visit and will consist of telephone contact (or other means of communication) made every 3 months with the patient (or designee) to collect subsequent anticancer therapy and survival status. Patients are to be followed for OS for at least 3 years from the end of LN-145 infusion (Day 0).

During the LTFU for OS period, AEs will not be collected, and no visits are required, with only phone calls determining the survival status and any current anticancer therapy the patient is taking.

7. WITHDRAWAL OF PATIENTS

7.1. Treatment Completion

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

7.2. Study Completion

The study is expected to be completed: at approximately 3 years after LN-145 infusion; at the time point when all patients have exited the study for any reason; or at the Sponsor PI's/ Regulatory Agency/Iovance's discretion, whichever occurs first. The intent is that all patients will be followed post-treatment (LN-145) for a minimum of 3 years.

7.3. Criteria for Discontinuation Prior to or During Study Treatment

Patients who have tumor harvested, but do not receive any of the study treatment (NMA-LD, LN-145, and/or IL-2) will perform an EOA visit and transition directly into the LTFU for OS period, if study if consent remains in place. Patients who discontinue from the study for any reasons are to complete the EOA visit. An EOA visit is not required if the same procedures are done within 2 weeks from the previous visit (see Appendix 14.1). End-of-study (EOS) occurs when the patient has completed study participation (eg, death or lost to follow-up). Appropriate reasons for the discontinuation must be documented in the patient's source documentation and eCRF page.

Criteria for discontinuation from the study are as follows:

- Withdrawal of consent from further participation in the study
- Sponsor Investigators' decision
- Death
- Lost to follow-up after 3 documented attempts to contact the patient
- Study terminated by Sponsor Investigator

Criteria for treatment discontinuation from NMA-LD, LN-145, and/or IL-2 administration are as follows:

- Grade 3 or greater immune TRAEs that involves vital organs (heart, kidneys, brain, liver, colon, adrenal gland, lungs) with symptoms emerging following LN-145 infusion
- Grade 3 or greater allergic reaction including bronchospasm or generalized urticaria that does not resolve after medical management in the opinion of the Sponsor Investigator
- Grade 3 or greater toxicity due to NMA-LD that does not decrease to Grade 2 or less within 96 hours of management
- Determination by the Sponsor Investigator that continued treatment is not in the best

interest of the patient

- Withdrawal of consent from further study treatment. The patient is, at any time, free to discontinue treatment, without prejudice to further treatment. A patient who discontinues treatment is normally expected to continue to participate in the study unless they specifically withdraw their consent to further participation in any study procedures and assessments
- Pregnancy
- Patient becomes ineligible for study after tumor harvest and prior to LN-145 or IL-2 administration
- Administration of prohibited concomitant medication
- Patient meets any of the criteria for early discontinuation from study

In the event of a patient's full withdrawal of consent from post-treatment follow-up, the Sponsor Investigator will make every effort to complete the EOA visit as appropriate. All AEs attributable to the investigational product may be followed until resolution or permanent sequelae. The final outcome of unrelated AEs ongoing at the time of the EOA visit will be captured as "Not Recovered/Not Resolved."

7.4. Overall Survival Follow-up

Approximately every 3 months following the EOA visit, patients will be contacted (eg, via telephone contact, or other means) to assess survival status, receipt, and ongoing status of subsequent anticancer therapies. Quarterly follow-up will continue until death, full withdrawal of consent by patient, lost to follow-up, or study terminated by Sponsor PI's/ Regulatory Agency/Iovance. Patients are to be followed for 3 years from the end of LN-145 infusion (Day 0).

Every effort must be made to locate any patient who is lost to follow-up. Patients can only be considered as lost to follow-up after 3 documented attempts to contact the patient, with no response.

7.5. Early Termination of Study

The study may be terminated at any time by Sponsor PI's/ Regulatory Agency/Iovance.

8. EXPECTED TOXICITIES AND MANAGEMENT GUIDELINES

Expected toxicities due to the chemotherapy preparative regimen, cytokines or support medication administration (as listed in the protocol or in the package inserts for commercial agents) will not result in discontinuing therapy (please refer to Sections 8.1 and 8.3).

8.1. Nonmyeloablative Lymphodepletion Regimen Toxicity Management

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

Refer to cyclophosphamide and fludarabine current PI/SmPC for additional information.

Expected toxicities with cyclophosphamide and fludarabine administration are listed in the PI/SmPC. Also included in the package inserts is information on supportive care and management of toxicities. Treatment will be given as per Investigator discretion and per institutional standard of care.

8.2. Infection Prophylaxis

8.2.1. Pneumocystis Jiroveci Pneumonia

All patients should receive appropriate *Pneumocystis jiroveci* pneumonia (PJP) prophylaxis per institutional standards for patients undergoing chemotherapy-induced immunosuppression. This may include any of the following and should begin on or after their first dose of chemotherapy (Day -7), or as the Investigator deems appropriate, and continue until the ALC is > 1000 cells/mm^3 (typically for at least 6 months) or as per institutional standard of care.

- Trimethoprim (TMP) and sulfamethoxazole (SMX) as double strength (DS) tab (DS tabs = TMP 160 mg/tab, and SMX 800 mg/tab) by mouth two times daily, three times a week on nonconsecutive days, beginning on the first Monday, Wednesday, or Friday on or after the first dose of chemotherapy.
- Pentamidine or alternative as per standard of care at the treating institution may be substituted for TMP/SMX DS in patients with sulfa allergies and may be administered either IV or aerosolized monthly using standard doses indicated for PJP prophylaxis.

Note: Other appropriate PJP prophylactic agents may be substituted at the discretion of the treating Investigator.

8.2.2. Herpes Virus Prophylaxis

Patients with positive HSV serology should receive appropriate re-activation prophylaxis with either valacyclovir or acyclovir.

Herpes prophylaxis should begin on Day7 or as theInvestigator deems appropriate and continue until the absolute lymphocyte count is > 1000/mm^3 (typically for at least 6 months) or as per standard institutional guidelines.

Note: Other appropriate viral prophylactic agents may be substituted at the discretion of the treating Investigator.

8.2.3. Fungal Prophylaxis (Fluconazole)

Patients will start fluconazole 400 mg (by mouth) from Day 1, or when patient becomes neutropenic and continue until ANC > 1000/mm^3, or another suitable fungal prophylaxis regimen as per standard of care at the treating institution.

8.3. Hemorrhagic Cystitis Prophylaxis

Patients will receive mesna to reduce the risk of cyclophosphamide-associated hemorrhagic cystitis in addition to IV fluids. Please refer to treatment guidelines for recommended mesna dosing. Alternative dosing regimens of mesna are allowed per institutional standards and Investigator discretion.

8.4. Febrile Neutropenia

Patients are expected to become neutropenic following the lymphodepletion regimen. Furthermore, IL-2 causes neutrophil migration dysfunction putting patients at risk for pseudomonas infection as well as severe occult bacteremia. Therefore, for first fever > 38.3°C (or 38.0°C or above at least 1 hour apart) at any point following lymphodepletion (from Day 0 onward), patients will be started on empiric broad-spectrum ABX with adequate *Pseudomonas* coverage (as per local institutional antibiogram) regardless of neutrophil count.

Empiric ABX should continue until the neutrophil count is > 500 cells/mm^3, even if no bloodstream infectious agent is identified. If a bloodstream agent is identified, broad-spectrum ABX may be tailored to treat the infection as per institutional standard of care. Infectious disease consultation will be obtained for all patients with unexplained fever, any infectious complications, or as per standard of care at the treating institution.

8.5. Filgrastim

Patients will receive filgrastim 5 µg/kg/day (recommended maximum dose of 300 µg/day or higher as per institutional standard) subcutaneously starting from Day 1 until ANC is > 1000/mm^3 for 3 consecutive days, or as per standard of care at the treating institution.

8.6. Blood Product Support

Using daily CBCs as a guide, the patient will receive platelets and packed red blood cells as clinically indicated. As a general guideline, patients may be transfused to maintain:

- Hemoglobin ≥ 7.5 g/dL
- Platelets ≥ 10,000/mm^3

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

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

8.7. LN-145 Toxicity Management

8.7.1. Hypersensitivity Reactions, Including Severe Allergic Reactions and Anaphylaxis

The TIL product formulations contain 0.5% HSA, 300 IU/mL of IL-2, and potentially low residual amounts of gentamycin and streptomycin, which belong to the aminoglycoside group of ABX. The cryopreserved TIL product formulation includes the cryopreservation medium CryoStor® CS10, which contains the cryoprotectants DMSO and dextran-40.

Hypersensitivity reactions, including severe allergic reactions and life-threatening anaphylaxis, have occurred during infusion with the LN-145 investigational product. Within 24 hours prior to administering LN-145, the patient must be hospitalized and prepared with IV hydration, as needed, to ensure good hydration status. The following must be administered as premedication prior to the LN-145 infusion:

- Within 30 to 60 minutes prior to the LN-145 infusion, premedicate the patient with acetaminophen (650 mg) and diphenhydramine (25 to 50 mg IV), or another H1 histamine antagonist.
    - Avoid prophylactic use of systemic corticosteroids, as it may interfere with the activity of LN-145. Corticosteroids should only be used to treat life-threatening conditions.

In addition, emergency anaphylaxis medications must be available at bedside (epinephrine and diphenhydramine; corticosteroids should only be given in a life-threatening situation).

Additional supportive medications may include the following:

- Indomethacin (50 to 75 mg q6h);
- Ranitidine (150 mg q12h);
- Meperidine (25 to 50 mg), or other medication per institutional standards may be given IV if severe chills/rigors develop.

The initial infusion rate should not exceed 1 mL/min for the first 5 minutes. The rate of infusion may be increased thereafter to 5–10 mL/min as tolerated. Continuous supervision of the patient by site medical staff is required until completion of infusion of the first bag of TIL, to monitor for potential signs and symptoms (eg, of a severe hypersensitivity reaction such as anaphylaxis) that may require immediate medical attention and treatment. For additional information, please refer to the study-specific Pharmacy & Investigational Product Administration Manual.

Hypersensitivity events 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. More severe reactions, including anaphylaxis, have occurred and require immediate treatment with emergency medications. During infusion of the LN-145 product, appropriate emergency medications (eg, epinephrine, diphenhydramine, and corticosteroids) should be available at bedside during administration and institutional guidelines should be followed for the treatment of anaphylaxis. Corticosteroids should only be used in life-threatening conditions.

Infusion of LN-145 must occur before the expiration time (usually within 24 hours of manufacture). Please refer to the Pharmacy & Investigational Product Administration Manual for specific LN-145 infusion instructions. Historically, toxicities or AEs during TIL infusion have almost entirely been associated with either the NMA-LD regimen or the IL-2 therapy given after TIL infusion [61]. The following AEs have been observed in published studies that treated patients with TIL products prepared by a process like that being used to prepare LN-145:

- Short-term, transient/reversible effects of TIL infusion include fever, chills, shortness of breath, increased heart rate, hypotension (prolonged hypotension necessitating pressor treatment has been reported) [61] following TIL infusion
- Lung congestion, which could be mild (shortness of breath) to severe (difficulty breathing – possibly needing a breathing tube and breathing machine for a few days)
- Autoimmune reaction such as loss of skin pigment (known as vitiligo) or inflammation of the eye (uveitis, refer to 8.7.2), which may require the use of steroid eye drops

8.7.2 Uveitis and Vitiligo

Uveitis and vitiligo have been observed in studies of patients with melanoma who received treatment with a TIL product. Melanocytes, melanin, and pigment in the human uvea tissues share many surface proteins with skin melanocytes. Hence, it is possible that a therapy targeting melanocytes involved in melanoma may trigger autoantibodies against normal melanocytes in uveal tissue or skin melanocytes, leading to uveitis or vitiligo.

- Uveitis may present with mild to moderate in intensity, associated with symptoms such as blurred vision, dull, aching, eye pain, nyctalopia, photopsia, retinal hemorrhage, and/or vitreous floaters, and often improved with corticosteroid therapy. Uveitis may be caused by a number of different etiologies; therefore, diagnosis and treatment of the underlying disease are imperative not only to treat the disease but also to preserve vision and potentially uncover underlying systemic diseases. If untreated or not appropriately treated, acute inflammation can develop into chronic, sight-threatening inflammation. Thus, when a patient presents with clinical signs and symptoms that may be associated with uveitis, the Investigator should complete a thorough examination to determine an appropriate etiology for the diagnosis. The examination should include an evaluation of location (anterior vs intermediate vs posterior), duration (acute vs chronic), pathology (granulomatous vs non-granulomatous), and laterality (unilateral vs bilateral). Once an etiology has been established, appropriate treatment should be commenced and customized to each participant as suboptimal treatment may lead to complications and loss of vision.
- Vitiligo may present in these patients with mild to moderate in intensity. For patients who develop vitiligo, a thorough history should be taken including the site and type of vitiligo (segmental, nonsegmental), disease extent (affected body surface area), disease stability, and speed of onset. Topical corticosteroids (medium or high potency) are recommended for localized vitiligo (<10% of body surface area) and may be used at Investigator discretion. Specialized dermatology consultation is recommended for appropriate management in all cases unless vitiligo is self-limited, localized, and non-progressive.

Patients may experience severe allergic reaction (anaphylaxis) due to DMSO contained in LN-145. Thus, appropriate emergency medications (eg, epinephrine and diphenhydramine) should be

available at bedside during time of administration and institutional guidelines should be followed for administering supportive care for anaphylaxis.

Details concerning specific risks for patients participating in this clinical study may be found in the accompanying LN-145 IB.

8.8. Interleukin-2 Toxicity Management

IL-2 (Proleukin, aldesleukin) can affect nearly every organ system, but essentially every abnormality will most often normalize following discontinuation of IL-2 dosing. Below is a list of the commonly seen toxicities. Appendix 14.4 has further details for suggested management as well as decision for holding (skipping a dose) and discontinuing IL-2 therapy.

8.8.1. Rigors

IL-2 associated rigors can routinely be treated with meperidine/pethidine. An initial dose of 25 mg can be initiated and followed with an additional 25 mg 15 minutes later if rigors persist or as per local standard institutional guidelines. Prophylactic use of meperidine is discouraged.

8.8.2. Diarrhea

IL-2 associated diarrhea may be observed. Anti-motility agents, such as loperamide and Lomotil, may be used as per local standard institutional guidelines (after testing for infectious etiologies such as *Clostridium difficile*, if present).

8.8.3. Neurologic Toxicity

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

8.8.4. Renal Toxicity

Renal toxicity defined by rapid rise in serum/plasma creatinine levels or clinical symptoms is a risk that is commonly observed (creatinine 1.5 to 2.0 x ULN for mild elevation, or greater than 3.0 x ULN for marked elevation). If patients exhibit signs or symptoms of renal toxicity, manage as per institutional standard of care (and may include low-dose dopamine to improve perfusion or continuous veno-venous hemofiltration). Hemodialysis should be reserved for life-threatening renal failure such as prolonged anuria, hyperkalemia, and profound uremia.

8.8.5. Capillary Leak Syndrome and Weight Gain

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

8.8.6. Cardiac Arrhythmias and Myocarditis

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

8.8.7. Pulmonary

LN-145 can remain in the pulmonary circulation for 24 to 48 hours following infusion and may cause transient shortness of breath. In addition, pulmonary edema is commonly observed with IL-2 dosing. Supplemental oxygen may be administered as needed. Subsequent IL-2 dosing should be delayed until supplemental oxygen has been weaned or is minimal (< 2 L/min per nasal cannula). If hypoxia persists or is significant, IL-2 should be discontinued.

8.8.8. Sepsis/Febrile Neutropenia During IL-2

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

8.8.9. Heparin-Induced Thrombocytopenia

Heparin-induced thrombocytopenia has been observed with IL-2 administration. To minimize this risk, heparin flushes should be avoided or minimized, if possible during IL-2 dosing.

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

8.9. Other Concomitant Medications to Control Side Effects

8.9.1. Nausea/Vomiting

Nausea and vomiting should be controlled with ondansetron or similar medication. Other second- and third-line medications (eg, prochlorperazine, promethazine, lorazepam, scopolamine, and aprepitant) can be used per local standard institutional guidelines. Steroids, such as dexamethasone may be used as an antiemetic only during cyclophosphamide administration but should be avoided and only used with intractable nausea and vomiting. Steroids must be discontinued a minimum of 3 days prior to administration of LN145.

8.9.2. Fever

Premedication for fever should be initiated as per standard institutional guidelines and may begin the night prior to LN-145 administration (Day -1) and continue throughout IL-2 treatment. Medications may include indomethacin 50 mg every 8 hours and/or acetaminophen every 4 to 6 hours. Indomethacin 75 mg may be used for persistently febrile patients.

9. TUMOR RESPONSE ASSESSMENTS

9.1. Response Criteria

Response assessment will be evaluated using RECIST 1.1 with a modification to require confirmation of progressive disease. Refer to Table 3 and Table 4 for RECIST 1.1 response criteria definitions [1].

9.2. Baseline Documentation of "Target" and "Nontarget" Lesions

Baseline documentation of all lesions will occur on Day -21 to Day -9. Measurable disease is defined as the presence of at least one measurable lesion of ≥ 10 mm in diameter by CT scan. When > 1 measurable lesion is present at Baseline, all lesions up to a maximum of five lesions total (and a maximum of two lesions per organ system) should be identified as target lesions and will be recorded and measured at Baseline. Target lesions should be selected based on their size (lesions with the longest diameter) and should be representative of all involved organs.

Pathological lymph nodes which are defined as measurable and may be identified as target lesions must meet the criterion of a short axis of ≥ 15 mm by CT scan. Only the short axis of these nodes will contribute to the baseline sum. All other pathological nodes (those with short axis ≥ 10 mm but < 15 mm) should be considered nontarget lesions. Nodes that have a short axis < 10 mm are considered nonpathological and should not be recorded or followed.

A sum of diameters (longest for non-nodal lesions, short axis for nodal lesions) for all target lesions will be calculated and reported as the Baseline sum diameters. If lymph nodes are to be included in the sum, then as noted above, only the short axis is to be added into the sum. The baseline sum diameters will be used as reference to further characterize any objective tumor regression in the measurable dimension of the disease.

All other lesions (or sites of disease) including pathological lymph nodes should be identified as nontarget lesions and should also be recorded at Baseline. Measurements are not required, and these lesions should be followed as "present," "absent," or in rare cases "unequivocal progression."

9.3. Evaluation of Target Lesions

This section provides the definition of the criteria used to determine objective tumor response for target lesions.

Table 3: Definition of Objective Tumor Response

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

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

9.4. Evaluation of Nontarget Lesions

This section provides the definitions of the criteria used to determine the tumor response for the group of nontarget lesions. While some nontarget lesions may be measurable, they need not be measured and instead should be assessed only qualitatively at the time points of radiographic assessments.

Table 4: Definition of Nontarget Lesions Response

Response	**Criteria**
Complete Response (CR)	Disappearance of all nontarget lesions. All lymph nodes must be nonpathological in size (< 10 mm short axis).
Non-complete Response / Non-Progressive Disease	Persistence of 1 or more nontarget lesion(s).
Progressive Disease (PD)	Unequivocal progression of existing non-target lesions. (Note: the appearance of one or more new lesions is also considered progression).

9.5. Evaluation of New Lesions

New measurable lesions may be identified if the new lesions meet criteria as defined for Baseline target lesion selection and meet the same minimum RECIST 1.1 size requirements of 10 mm in long diameter for non-nodal lesions and a minimum of 15 mm in short axis for nodal lesions.

New measurable lesions shall be prioritized according to size with the largest lesions selected as new measured lesions.

All new lesions not selected as new measurable lesions are considered new non-measurable lesions and are followed qualitatively. Only unequivocal progression of new non-measurable lesions leads to an overall assessment of PD for the time point.

The finding of a new lesion should be unequivocal, ie, not attributable to differences in scanning technique, change in imaging modality or findings thought to represent something other than tumor (for example, some ‘new’ bone lesions may be simply healing or flare of pre-existing lesions). This is particularly important when the patient’s Baseline lesions show PR or CR.

For example, necrosis of a liver lesion may be reported on a CT scan report as a ‘new’ cystic lesion, which it is not.

If a new lesion is equivocal, for example because of its small size, continued therapy and follow-up evaluation will clarify if it represents truly new disease. If repeat scans confirm a definite new lesion, then progression should be declared using the date of the initial scan.

9.6. Evaluation of Overall Response

The best overall response for each patient is the best response recorded from the start of treatment until disease progression/recurrence, the initiation of subsequent anticancer therapy, death, or 36 months after therapy with LN-145 whichever occurs first (taking reference for PD the smallest measurements recorded since the treatment started). The patient's best response assignment will depend on the achievement of both measurement and confirmation criteria (see Section 9.2). The assignment of response for an individual patient, based on both target and nontarget lesions, at each assessment time point is shown in Table 5. The best overall response for each patient is determined as shown in Table 6.

Table 5: Response at Each Assessment Timepoint for Patients

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

CR = complete response; NE = not evaluable; PD = progressive disease; PR = partial response; SD = stable disease *If the Investigator's response assessment is difficult to determine due to presence of confounding factors (ie, tumor flare), then overall response should be SD until proven otherwise.

Table 6: Examples of Best Overall Response for Each Patient Across All Assessments

Overall Response at Timepoint 1	Overall Response at Timepoint 2	Overall Response at Timepoint 3	Best Overall Response Across Assessment Timepoints
CR	CR	CR	CR
PR	PR	CR	PR
SD	SD	PR	SD
SD	PR	SD	SD

SD	SD	PD	SD
CR = complete response; NE = not evaluable; PD = progressive disease; PR = partial response; SD = stable disease			

9.7. Confirmation of Tumor Assessments

9.7.1. Confirmation of Response (PR or CR)

Confirmation of response (either PR or CR) is required. Changes in tumor measurements must be confirmed by repeat assessments that should be performed ≥ 4 weeks apart after the criteria for response are first met. If the confounding factor/tumor flare is considered at subsequent assessment points, as the previous assessment was SD or PR, then the response should be SD or PR, until proven otherwise. The response assessment should be updated, if needed, based on the consecutive observation. 'Not Evaluable (NE)' should only be selected if the response was truly not evaluable (eg, scan was not done).

9.7.2. Confirmation of Progressive Disease

If PD is assessed, then this must be confirmed by objective measures or symptomatic deterioration that was based on other clinical data suggesting clear evidence of disease progression.

For patients with a minimum increase of over 20% in the sum of diameters of target lesions taking as reference the smallest sum on study or for nontarget or new non-measurable lesions, a confirmation scan is required at least 4 weeks after the first PD assessment.

10. ADVERSE EVENTS

Toxicities will be recorded as AEs, AESIand serious adverse events (SAEs) in the patient's source documents and on the AEs eCRF and must be graded using the CTEP Version 5.0 of the NCI Common Terminology Criteria for Adverse Events (CTCAE).

http://ctep.cancer.gov/protocolDevelopment/electronic_applications/ctc.htm.

10.1. Adverse Event

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

Events meeting the definition of an AE include:

- AEs temporally associated with the use of any of the investigational products or TIL treatment whether or not considered related to the use of any of the investigational products or TIL treatment

- Any abnormal laboratory test results (eg, hematology, clinical chemistry, or urinalysis) or other assessments (eg, ECGs, radiological scans, vital signs measurements) that are abnormal and are considered clinically significant (eg, led to hospitalization or prolongation of hospitalization, required change in study treatment, required initiation of concomitant therapy or intervention)
- Exacerbation of a chronic or intermittent pre-existing condition including either an increase in frequency and/or intensity of the condition
- New conditions detected or diagnosed after investigational product administration
- Signs, symptoms, or the clinical sequelae of a suspected interaction with investigational product
- Signs, symptoms, or the clinical sequelae of a suspected overdose of either investigational product or a concomitant medication

- *Events that do not meet the definition of an AE include:*
- Any clinically significant abnormal laboratory finding or other abnormal safety assessments that is associated with the underlying disease, unless judged by the Investigator to be more severe than expected for the patient's condition
- Any laboratory abnormal value that has not clinical significance and does not require treatment
- Medical or surgical procedure (eg, endoscopy, appendectomy); the condition that leads to the procedure is an AE. Planned elective procedures are not AEs
- Overdose without clinical sequelae (see Section 10.9)
- Situations where an untoward medical occurrence did not occur (social and/or convenience admission to a hospital)
- Anticipated day-to-day fluctuations of pre-existing disease(s) or condition(s) present or detected at the start of the study that do not worsen

10.2. Serious Adverse Event

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

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

Important medical events: such events may not directly result in death, be life-threatening, or require hospitalization but may be considered serious when, based on Sponsor Investigator

decision, they may jeopardize the patient and may require intervention to prevent one of the above outcomes as listed in this definition.

Hospitalization including admission to a telemetry unit or intensive care unit specifically for administration of study treatment is not considered an SAE.
Prolongation of admission post IL-2 is not considered an SAE.

10.3. Relationship to the Investigational Product

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

- **Definite**: There is a known causal relationship between the investigational product and the AE/SAE. The event responds to withdrawal of study treatment (dechallenge) and recurs with rechallenge when clinically feasible.
- **Probable**: There is reasonable causal relationship between the investigational product and the AE/SAE. The event responds to dechallenge.
- **Possible**: There is reasonable causal relationship between the investigational product and the AE/ SAE. Dechallenge information is lacking or unclear.
- **Not likely**: There is temporal relationship to the investigational product administration, but there is not a reasonable causal relationship between the study drug and the AE/SAE.
- **Not related**: There is not a temporal relationship to investigational product administration (too early, or late, or investigational product not administered), or there is known causal relationship between the AE/SAE and another drug, concurrent disease, or other circumstance.

10.4. Severity

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

AE grading will be defined by the CTCAE v 5.0. In the event the CTCAE v 5.0 does not apply, the severity descriptions below will be used.

- **Mild**: Asymptomatic; clinical or diagnostic observations only; intervention not indicated.
- **Moderate**: Minimal, local, or noninvasive intervention indicated; limiting age appropriate activities of daily life.
- **Severe**: Medically significant but not immediately life-threatening; hospitalization or prolongation of hospitalization may be required; disabling; limiting activities of daily life.
- **Life-threatening**: Urgent intervention is required.
- **Death**: When death is the outcome of the AE.

10.5. Reporting Procedures for 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 v5.0. 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)
- 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-145 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)
- After this period, only SAEs related to LN-145 will be collected and reported

Medically significant AEs considered related to LN-145 by either the Investigator will be reported and followed until resolved or resolved with sequelae.

If a patient dies while on the study, the Sponsor Investigator will report to Iovance and the Data Safety Monitoring Committee (DSMC) 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"

The investigator will be responsible for reporting SAEs to the IRB of record. It will be left to the Sponsor 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-145 due to an SAE, this information must be included in the initial or follow-up SAE Report Form and in the eCRF.

10.6. Reporting Procedures for Serious Adverse Events

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 study treatment should be reported from Day 30 through 6 months post-LN-145 infusion, or the start of a new anticancer

therapy, whichever occurs first. After 6 months, only SAEs related to LN-145 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 DSMC and Iovance/designee.

The Sponsor Investigator will report to Iovance and the FDA as applicable, any SAE that occurs during the study. The initial notification should be as complete as possible with the information available and include the Investigator's assessment of study drug relationship.
Iovance shall have the opportunity to review and comment on the Investigator's determination as to causality and Severity for each AE and shall have the opportunity to submit comments for consideration by Investigator in accordance with the contractual agreement between Yale Cancer Center and Iovance Biotherapeutics. All AEs, regardless of their severity, will be captured in the eCRF.

SAE terminology and severity grading will be based on the NCI's CTCAE v5.00 guidelines.

10.7. Investigator Communications with Iovance Biotherapeutics

The Sponsor Investigator, or designee, will report to Iovance in accordance with the contractual agreement between Yale Cancer Center and Iovance Biotherapeutics. Reports will be sent to Iovance Biotherapeutics' designated mailboxes:

iovancesafety@iovance.com and safetyfax@synteract.com

10.8. Special Situations Reporting

10.8.1. Definitions of Special Situations

Special situation reports include reports of medication error, overdose, AEs associated with product complaints, occupational exposure, and pregnancy reports regardless of an associated AE. The special situation reports will be reported as an SAE but not considered an AE/SAE unless associated with an AE/SAE.

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

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

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

Occupational exposure is defined as the exposure to a medicinal product as a result of one's professional or nonprofessional occupation.

Special situation reports must be reported to Iovance Biotherapeutics' designated mailboxes

using the SAE Report Form within 24 hours of becoming aware of the situation to:

iovancesafety@iovance.com and safetyfax@synteract.com

10.8.2. Procedures for Special Situations

10.8.2.1. Pregnancy Reporting

Any pregnancy that occurs while on the study through 12 months from the last dose of IL-2 or until the first dose of the next anti-cancer therapy, whichever occurs first, must be reported using the Pregnancy Report form within 24 hours of becoming aware of the pregnancy. The pregnancy itself is not considered an AE nor is an induced abortion to terminate a pregnancy without medical reasons. Any premature termination of pregnancy (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 10.7.

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 to Iovance Biotherapeutics' designated mailboxes using the Pregnancy Outcome form. Any SAE occurring in association with a pregnancy, brought to the Sponsor Investigator's attention after the patient has completed the study treatment and post-treatment follow-up visits, must be promptly reported to Iovance 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 Sponsor Investigator's attention after the patient has completed the study and considered by the Sponsor Investigator as possibly related to the investigational product, must be promptly reported to Iovance 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 using the Pregnancy and Pregnancy Outcome forms within 24 hours. Monitoring of the female partners should continue until the conclusion of the pregnancy.

10.8.2.2 Adverse Events of Uveitis Special Interest Reporting

AEs of uveitis is considered as AESI, must be recorded in the eCRFs and reported to the sponsor or designee within 24 hours of the study personnel's discovery of the event, even if they are considered nonserious according to the usual regulatory criteria. The investigator must follow any patient experiencing uveitis until resolution or stabilization of the event, an alternative explanation other than study intervention is provided for the event, or the patient is lost to follow-up. The Sponsor investigator should submit any further details obtained from follow-up to the sponsor within 24 hours of it becoming available.

10.9. Study Halting Rules

The study may be stopped following review of the safety data by the Yale Cancer Center DSMC according to their normal procedures.

10.10. Regulatory Reporting Requirements

AEs classified as "serious" and "unexpected" that are possibly, probably, or definitely attributed to drug administration (suspected unexpected serious adverse reaction [SUSAR]), or SAEs whose frequency exceeds expectations, require expeditious handling and reporting.

Within 24 hours of awareness of an AE deemed serious, unexpected and related to LN-145, the Sponsor Investigator will promptly investigate all safety information related to the adverse event and will promptly discuss the event details with Iovance Biotherapeutics for comments. The Sponsor Investigator will review Iovance' s comments and shall provide such comments to the IRB of record. Any updated information shall be submitted by the Sponsor Investigator as a follow-up SAE report.

The Sponsor Investigator is the Sponsor of this study and is responsible for expedited reporting to regulatory agencies.

If the results of the Sponsor Investigator's investigation show an adverse drug experience not initially determined to be reportable (based on whether the event is serious, unexpected, and associated with drug administration) is so reportable, the Sponsor Investigator will report such experience. Follow-up information to a safety report shall be submitted as soon as the relevant information is available.

Final assessment of expectedness for SAEs will be determined by the Sponsor Investigator using reference safety information in the IB, comments from Iovance and relevant prescribing information, as applicable.

There are two types of expedited safety reports to the FDA:

1. 7-Calendar-Day FDA Telephone or Fax Report: The Sponsor Investigator will directly notify the FDA, within 7 calendar days after his initial receipt of the information, of any adverse event that is ALL of the following:

Death or immediately life-threatening
Unexpected
Associated with the use of study drug

Notification to the FDA will be made directly to the new drug review division in the Center for Drug Evaluation and Research or in the product review division for the Center for Biologics Evaluation and Research, whichever was responsible for the review of the investigational new drug (IND) application. [21CFR312.32(c)] A written report of the event is to follow within 15 calendar days.

2. 15-Calendar-Day FDA Written Report: The Sponsor investigator will directly notify the FDA within 15 calendar days of any adverse event that is ALL of the following:

Serious (due to non-fatal and non-life-threatening criteria
Unexpected
Associated with the use of study drug

Note: SAEs which do not meet the criteria for expedited reporting will be reported to the FDA in the IND Annual Report.

In addition, the Sponsor investigator must submit expedited reports of potential serious risks from clinical studies or any other source based on relevant local legislation or regulations, including the applicable US FDA Code of Federal Regulations and relevant updates. The Sponsor investigator should notify the IRB of record of SUSAR reports as soon as is practical where required by local regulatory agencies and in accordance with the local institutional policy.

10.11. Safety Review and Data Safety Monitoring Committee (DSMC)

The safety parameters will be reviewed on an on-going basis including Grades 3 and 4 AEs, SAEs, deaths, TRAEs, AEs that lead to reduced or missed doses of lymphodepletion or IL-2, clinical laboratory tests, vital signs, and physical examinations. The expected toxicities of the NMA-LD regimen and IL-2 regimens will be closely monitored.

Safety data in this study will be reviewed by the Yale University DSMC on an ongoing basis to identify any potential new safety risks. The DSMC will have authority to suspend the trial.

The Sponsor Investigator and the Yale University DSMC will review cumulative safety data on the first five patients enrolled upon completion of 6 weeks (Day 42) of assessment post- LN-145 infusion.

Enrollment will continue while study data are under DSMC review.

10.12 Data and Safety Monitoring Committee

The Yale Cancer Center (YCC) Data and Safety Monitoring Committee (DSMC) will provide the primary oversight of data and safety monitoring. The Yale DSMC will review and monitor compliance, toxicity and deviations from this study. The committee is composed of clinical specialists with experience in oncology and who have no direct relationship with the study. Information that raises any questions about participant safety will be addressed with the Sponsor Investigator.

The DSMC will review this protocol bi-annually, at a minimum. Information to be provided to the committee includes: a study narrative by the PI, a summary DSMC report produced by OnCore (which includes participant accrual, response, trial status history, SAEs, adverse events, deviations and survival); audit results, and monitoring reports, as applicable. Other

information (e.g., scans, laboratory values, etc.) will be provided upon request. Upon completing the review, the DSMC will approve whether the study should continue as planned, require modification/ amendment, or be placed on administrative hold with accrual temporarily suspended.

Trials being monitored by the YCC DSMC will remain under the YCC DSMC purview until a DSMC review has occurred that includes the research activity of the last subject who completed the intervention, or until the DSMC feels there are no patient safety concerns that require further monitoring. The DSMC will determine the length of continued DSMC review.

The DSMC has authority to intervene in the conduct of these studies as necessary to ensure the safety of the participants and to maintain the highest quality in the clinical research performed at YCC. The DSMC has the authority to require additional monitoring and/ or more frequent reporting on study progress and serious adverse events.

11. STATISTICAL CONSIDERATIONS

11.1. Introduction

The statistical analysis will be based on the use of descriptive methods unless mentioned otherwise. Continuous data will be summarized as the number of patients with non-missing data (n), mean, standard deviation, median, minimum, and maximum values. Categorical data will be summarized as counts and their related percentages, where applicable. Estimation of confidence limits will use two-sided, 90% criteria. Missing data will not be imputed unless mentioned otherwise.

All laboratory results will be summarized using descriptive statistics. SAEs will also be summarized. A separate safety summary will be provided for patients in the tumor harvested (TH) population starting from the tumor resection for 30 days (TH non-treated population) and until date of first dose of the study treatment (safety population).

11.2. Study Analysis Sets

The TH Set is defined as all tumor-resected patients for production of LN-145. The TH population is further divided into the efficacy and safety sets for analyses.

11.2.1. Safety Analysis Set

The Safety Analysis Set consists of patients who received LN-145 infusion.

11.2.2. Efficacy Analysis Set

The Efficacy Analysis Set consists of patients in the Safety Analysis set with Baseline assessments (Day -21 or Day -9) and at least one post-Baseline radiological assessments. Patients who progressed or expired prior to reaching the first radiological assessment will be included and considered as non-responders.

11.3. Sample Size Justification

The planned sample size consists of 10 patients in the efficacy evaluable set. The null hypothesis

for this trial is 14% based on the ORR rates for standard of care second line chemotherapy in metastatic triple negative breast. A sample size of 10 patients yields over 78% power to test the alternative hypothesis of an ORR rate of 35% at one-tailed alpha level of 20%. The sample size is based on the number of patients in the efficacy analysis set, consisting of patients who have received LN-145 infusion and had at least one post-Baseline radiological assessment. Patients who progressed or died prior to reaching the first radiological assessment will be included and considered as non-responders. The planned analysis will be conducted when the 10th patient has had the opportunity to be followed for a minimum of 3 months. This will allow sufficient time for disease-controlled patients (SD or better) to demonstrate extended durability. If the number of responding patients is three or greater (out of 10) the lower bound of an 80% one-sided confidence interval will exclude the null ORR rate of 14%.

11.4. Baseline Demographic and Clinical Characteristics

Baseline demographic and clinical (disease) characteristics will be summarized descriptively for the treated and untreated populations. Age will be derived as a function of the date of informed consent. Patients among the resected, untreated population will be summarized by the primary reason of not receiving the treatment together with the safety events.

11.5. Study Endpoints and Planned Analyses

11.5.1. Primary Endpoints

The ORR is defined as the proportion of patients who achieve either a confirmed PR or CR as best response as assessed by Investigators per RECIST 1.1 among the Efficacy Analysis Set.

Objective response will be evaluated per each disease assessment and the ORR will be calculated with the corresponding 90% two-sided confidence interval.

The primary safety analysis will be descriptive and based on the summarization of TEAEs, including SAEs, AEs leading to discontinuation from the study treatment and efficacy follow-up. The treatment-emergent period is defined from LN-145 infusion until 30 days thereafter. AE summaries will be based on patient incidence counts and percentages per the Safety Analysis Set. In addition to the overall summary of AEs, breakdown summaries will be made by NCI CTCAE grade of severity, and relationship to the study treatment

11.5.2. Secondary Endpoints

Additional Measures of Efficacy:

The secondary efficacy endpoints are defined as follows:

- DOR is measured from the first-time response (PR/CR) criteria are met until the first date that recurrent or progressive disease is objectively documented, or receipt of subsequent anticancer therapy or the patient expires (whichever is first recorded). Patients not experiencing PD or who have not died prior to the time of data cut or the final database lock will have their event times censored on the last date that an adequate assessment of tumor status is made
- DCR is derived as the sum of the number of patients who achieved confirmed PR/CR or

sustained SD (at least 6 weeks) divided by the number of patients in the All Treated population x 100%

- PFS is defined as the time (in months) from the time of lymphodepletion to PD, or death due to any cause, whichever event is earlier. Patients not experiencing PD or not having died at the time of the data cut or the final database lock will have their event times censored on the last date that an adequate assessment of tumor status is made
- OS is defined as the time (in months) from the time of lymphodepletion to death due to any cause. Patients not having died by the time of data cut or the final database lock will have their event times censored on the last date of their known survival status
- CR rate is based on responders who achieved confirmed CR as assessed by the Investigators. The CR rate will be summarized using a point estimate and its two-sided 90% confidence interval (CI)
- DOR, DCR, PFS, and OS will be subjected to right censoring. Kaplan-Meier methods will apply

11.5.3. Exploratory Endpoints

- Correlations of immune factors with efficacy and safety will be explored. The results will be reported in a separate document
- Details of exploratory tissue biomarkers analyses will be provided in a separate report
- Feasibility of generating TIL (LN-145) from patient derived TNBC core biopsy tumor specimens using Iovance manufacturing process. analyses will be provided in a separate report

12. ADMINISTRATIVE PROCEDURES AND STUDY MANAGEMENT

12.1. Good Clinical Practice

It is the responsibility of the Sponsor Investigator to oversee the safety of the patients in the study. The Sponsor Investigator will ensure that this study is conducted in full compliance with the principles of the "Declaration of Helsinki" (as amended in Tokyo, Venice, Hong Kong, and South Africa), ICH guidelines, or with the laws and regulations of the country in which the research is conducted. The Sponsor Investigator will conduct all aspects of the study in accordance with applicable country, national, state and local laws of the pertinent regulatory authority. All Investigators will ensure adherence to ICH guidelines for GCP and Clinical Safety Data Management.

By signing the US FDA Form 1572, "Statement of Investigator," the Investigator commits to adhere to applicable sections of the US Code of Federal Regulations (CFR) parts 50 "Protection of Human Patients," 54 "Financial Disclosure by Clinical Investigators," 56 "Institutional Review Boards," and 312 subpart D "Responsibilities of Sponsors and Investigators."

12.2. Institutional Review Board (IRB) Approval

The Investigator shall assure that the IRB of record provides initial and continuing review of the study according to local policy. Prior to screening and enrollment of study patients, documented

IRB approval of the protocol, ICF and any patient materials, must be obtained.

12.3. Protocol Modifications

Protocol amendments should not be implemented without prior regulatory submission and IRB approval, except where necessary to eliminate immediate hazards to the patients or when the change(s) involves only logistical or administrative aspects of the study (eg, change in monitor[s], change of telephone number[s]).

12.4. Record Retention

In compliance with the ICH/GCP guidelines, the Sponsor Investigator 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 study documents as specified in Essential Documents for the Conduct of a Clinical Trial and as specified by the applicable regulatory requirement(s). The Sponsor Investigator will take measures to prevent accidental or premature destruction of these documents. Essential documents must be retained until at least 2 years after the last approval of a marketing application in an ICH region or at least 2 years have elapsed since the formal discontinuation of clinical development of the investigational product. These documents will be retained for a longer period if required by the applicable regulatory requirements or by an agreement with Iovance. It is the responsibility of Iovance to inform the Sponsor Investigator/institution as to when these documents no longer need to be retained. If the Sponsor 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. Iovance must be notified in writing of the name and address of the new custodian.

12.5. Data Quality Assurance

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

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

. On-site audit representatives of Iovance 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 eCRF. Patient privacy must, however, be respected. Prior notice will be provided to allow the Sponsor Investigator to prepare properly for the audit.

12.6. Data Processing and Recordkeeping

12.6.1. Electronic Data

When using electronic data processing, the Sponsor Investigator will ensure that systems comply with 21 CFR Part 11, CTR EU No. 536/2014 and General Data Protection Regulation (GDPR) EU 2016/679 requirements, as applicable. Documentation regarding the electronic data systems used in this protocol is described in the relevant study-specific plans or standard operating procedures.

12.6.2. Electronic Case Report Form Completion

Electronic data capture 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 in the eCRFs in English. The eCRFs are to be completed at the time of the patient's visit. Tests performed outside the Sponsor Investigator's office may be used, provided that the tests are done within the window dictated by the protocol.

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

12.7. Study Monitoring

In accordance with 21 CFR Part 312.56, a clinical monitor will periodically inspect eCRF, study documents, research facilities, and clinical laboratory facilities associated with this study at mutually convenient times during and after completion of the study. As required by 21 CFR Part 312, Subpart D: Responsibilities of Sponsors and Investigators, the monitoring visits provide the Principal Investigator with the opportunity to evaluate the progress of the study; verify the accuracy and completeness of eCRF against source documentation; ensure that all protocol requirements, applicable to FDA regulations, and Investigator's obligations are being fulfilled; and resolve any inconsistencies in the study records. This includes inspection of all documents and records related to the study that are required to be maintained by the Investigator, including but not limited to medical records (office, clinic, or hospital) and investigational pharmacy records for the patients participating in this study. The names and identities of all research patients will be kept in strict confidence and will not appear on eCRF or other records provided to or retained by the Sponsor-Investigator. Regulations also require the Investigator to allow authorized representatives of Yale Cancer Center, Iovance, the FDA or Regulatory Authorities to inspect and make copies of the same records. The Investigator should immediately notify the Principal Investigator and Iovance if they have been contacted by a regulatory agency concerning an upcoming inspection.

12.8. Institutional Review Board/Independent Ethics Committee (HIC)

Before enrollment of patients into the study, as required by Federal regulations (21 CFR 56) and international regulations (ie, ICH/GCP Guidelines), the protocol and ICF must be reviewed and approved by the IRB of Record. By signing the FDA Statement of Investigator Form 1572, the Sponsor Investigator assures that all aspects of the institutional review will be conducted in accordance with current federal regulations. A letter documenting IRB approval must be received by Iovance before the initiation of the study. Amendments to the protocol will be subject to the same requirements as the original protocol.

Reports on, and reviews of, the study and its progress will be submitted to the IRB by the

Sponsor Investigator at intervals stipulated in their local policies and guidelines.

12.9. Informed Consent

Each patient (or a legally authorized representative) preferably gives 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 reviewing IRB of Record. 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 Regulation 2016/679 (GDPR), as interpreted by the national laws and regulatory bodies.

At the discretion of the Investigator, and if deemed in the patient's best interest and approved by the IRB of record, the consent form can be sent to the patient by facsimile or email. The consent discussions with the study participant or study participant's legally authorized representative may be conducted by telephone or via teleconference systems. After the consent discussion, the patient or the study participant's legally authorized representative will sign and date the consent form and provide a copy of the document to the study staff by facsimile, scanning the consent form and returning a copy through a secure e-mail account, or by mail. An original signed consent document must be provided to the study staff at a subsequent study visit or via mail.

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 that they may withdraw consent to participate at any time. They will be told which alternative treatments are available if they refuse to take part and that such refusal will not prejudice future treatment. Finally, they will be told that their records may be examined by competent authorities and authorized persons but their personal data will be treated as strictly confidential and will not be publicly available. Patients must be given the opportunity to ask questions. After this explanation and before entry into the 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 or her legally designated representative to consider his or her decision to participate in the study.

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

12.10. Patient Data Protection

The Sponsor Investigator and designees, employees, and agents involved with the study will comply with relevant state, federal national and regional regulations relating to the confidentiality, privacy, and security of patient's personal health information. 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 study to Iovance, the IRB of Record, FDA, European Medicines Agency (EMA), Regulatory Agencies, or other authorized recipients as appropriate for the execution, analysis, review, and reporting of this study. Such information shall not be used for any other purposes and will remain confidential. Patient will not be individually identified but will be referred to in records by the study-assigned number and patient initials (if applicable by local regulations).

12.11. Adverse Event Reporting

The Sponsor Investigator agrees to report all AEs/AESI//SAEs to Iovance per the Study Order. Furthermore, the Investigator is responsible for ensuring that any sub-investigator promptly bring AEs/AESI to the attention of the PI. The Sponsor Investigator shall promptly notify Iovance of any SAEs or any other information that may affect the safe use of the investigational product during the study. The Investigator shall promptly notify the IRB of Record of any SAEs, or any other information that may affect the safe use of the investigational product during the study as applicable.

12.12. Investigator

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

All required data will be recorded in the eCRF in a timely manner. All eCRF data and periodic reports must be submitted to Iovance per the Study Order.

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

12.13. 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 eCRF or other documents submitted to Iovance, 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 Iovance (eg, patients' written consent forms) should be maintained by the Investigator in strict confidence, in accordance with all applicable local and national regulations. All information provided to the Investigator prior to the study, as well as all data developed during the study, is confidential and remains the property of Iovance. The Investigator agrees that no information based on the conduct of this study (including the protocol, the data resulting from this study, or the fact that this study is/was conducted) will be released without prior written consent of Iovance unless this requirement is superseded by local or national regulations.

12.14. Publications

The Sponsor Investigator and Iovance will be responsible for determining when the study results should be published. The Investigator shall not submit a publication or abstract to journals or professional societies without the prior written approval of Iovance (and vice versa), except as permitted by the agreed terms of the Study Order agreement, including after the reporting of the results of this study by Iovance.

12.15. Data Sharing

In accordance with the study order, Iovance, its project monitor(s) and others designated by Iovance, at mutually agreeable times during the study or as applicable after completion or early termination of the study shall be entitled to (in each case subject to study sites's generally applicable measures for confidentiality, security, and generally applicable premises rules): examine and inspect, at regular business hours, study sites facilities being used, or otherwise required, for performance of the Study; subject to applicable patient confidentiality considerations, inspect, audit, and copy or have copied, all records, data and work product relating to the Study conducted under the Study Order; and inspect and make copies of all data necessary to confirm that the Study is being or was conducted in conformance with the Study Order.

Yale Cancer Center, through the Sponsor Investigator, shall provide to Iovance interim written reports regarding the research, no less than once per calendar quarter, and a draft final written study report per the Study Order. Further subsequent development of the final written study report will follow the terms specified in Study Order or Strategic Alliance Agreement.

12.16. Use of Stored Specimens

Research material from patients enrolled on this study will be kept at Yale Cancer Center, Iovance or Iovance designated laboratory. De-identified patient material will be shared with Iovance for testing during the study. Residual material will be sent to Iovance at the completion of the study.

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14. APPENDICES

14.1. Schedule of Assessments

				Treatment Period[a] (Day-7 to Last Dose of IL-2 [ie, not specifically to Day 4])							Assessment Period[a] After TIL Infusion on Day 0 to EOA											EOA[a]	LTFU[a]
Assessment [b]	**Screening & Enrollment Period [a]**																						
	Screening (≤28 days from ICF)	**Enrollment/Tumor Resection**	**Baseline (Day -21 to Day -9)-**	**Day -7**	**Day -6**	**Day -5**	**Day -4**	**Day -3**	**Day -2**	**Day -1**	**Day 0 LN-145**	**Day 1**	**Day 2**	**Day 3**	**Day 4**	**Day 14 (± 3 days)**	**Day 28 (± 7 days) / Week 4**	**Day 42 (± 7 days) / Week 6**	**Day 84 (± 7 days) / Week 12**	**Day 126 (± 7 days) / Week 18**	**Month 6/Week 24 (± 1 Week) and Every 3 Months**	**Thereafter until EOA Disease Progression or New Therapy**	
Informed consent	X																						
Confirmation of diagnosis	X																						
Inclusion/Exclusion[b]	X		X																				
Demographics	X																						
Medical history	X																						
Physical examination[c]	X		X	X		X					X	X		X		X	X	X	X	X	X	X	
Concomitant medications[d]	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	
Vital signs, weight[e]	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	
ECOG performance status	X	X	X	X												X	X	X	X	X	X	X	
Serum chemistry and LFTs[f]	X		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	
HLA Typing	X																						
Thyroid panel[g]	X															X						X	
Hematology[h]	X		X	X	X	if clinically indicated					X	X	X	X	X	X	X	X	X	X	X	X	

Coagulation panel [i]	X																						

Urinalysis [j]	X		X	X	X	if clinically indicated					X	X	X	X	X	X	X	X	X	X	X	X	
Calculated creatinine clearance [k]	X																		X				

				Treatment Period [a] (Day-7 to Last Dose of IL-2 [ie, not specifically to Day 4])																			

Assessment [b]	**Screening & Enrollment Period [a]**										**Assessment Period [a] After TIL Infusion on Day 0 to EOA**											**EOA[a]**	**LTFU[a]**
	Screening (≤28 days from ICF)	**Enrollment/Tumor Resection**	**Baseline (Day -21 to Day -9)-**	**Day -7**	**Day -6**	**Day -5**	**Day**	**Day**	**Day -2**	**Day**						**Day 14 (± 3 days)**	**Day 28 (± 7 days) / Week 4 (EOT)**	**Day 42 (± 7 days) / Week 6**	**Day 84 (± 7 days) / Week 12**	**Day 126 (± 7 days) / Week 18**	**Month 6/Week 24 (± 1 Week) and Every 3 Months**	**Thereafter until EOA**	
ß-HCG pregnancy test [l]	X		X	X							X						X	X	X	X	X	X	
CMV, EBV, HIV, HBsAg, anti-HBc, anti-HCV, Syphilis, HSV[m]	X																						
PD-L1 status [n]		X																					
ECG [o]	X		X																				
ECHO or MUGA stress test [p]	X																						
Pulmonary function tests [q]	X																						
Radiographic imaging CT – chest, abdomen, pelvis; MRI – brain [r]	X		X															X	X	X	X	X	
Tumor harvest [s]		X																					

Biopsy tissue sample (biomarkers) [t]		X																						
Optional TIL growth from Core Biopsy Sub Study		X																						
Optional post-treatment (Post TIL LN-145) biopsy [u]																		X						
Authorization for NMA-LD[v]				X																				
Hospitalization		X		X	X						X													
Cyclophosphamide 60 mg/kg				X	X																			
Mesna 60 mg/kg				X	X																			
Fludarabine 25 mg/m^2/day						X	X	X	X	X														
LN-145 infusion [w]											X													

Treatment Period [a]
(Day-7 to Last Dose of IL-2 [ie, not specifically to Day 4])

Assessment [b]	**Screening & Enrollment Period [a]**										**Assessment Period [a] After TIL Infusion on Day 0 to EOA**											**EOA [a]**	**LTFU[a]**
	Screening (≤28 days from ICF)	**Enrollment/Tumor Resection**	**Baseline (Day -21 to Day -9)-**	**Day -7**	**Day -6**	**Day -5**	**Day -4**	**Day -3**	**Day -2**	**Day -1**	**Day 0 LN-145**	**Day 1**	**Day 2**	**Day 3**	**Day 4**	**Day 14 (± 3 days)**	**Day 28 (± 7 days) / Week 4**	**Day 42 (± 7 days) / Week 6**	**Day 84 (± 7 days) / Week 12**	**Day 126 (± 7 days) / Week 18 24**	**Month 6/Week 24 (± 1 Week) and Every 3 Months Thereafter until EOA**		
IL-2 600,000 IU/kg [x]												X	X	X	X								

Pulse Oximetry[y]												X	X	X	X								
Filgrastim [z]												X	X	X									

SMX-TMP DS, or appropriate ABX [aa]				X																			
Fluconazole [bb]												X											
Valacyclovir/acyclovir [cc]																X							
Immune Monitoring (blood sample collection) [dd]		X										X						X	X		X		
Assessment of AE/SAEs [ee]	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	
Response assessment																		X	X	X	X	X	
Telephone contact [ff]																							X

ABX = antibiotic; AE = adverse event; ALC = absolute lymphocyte count; ANC = absolute neutrophil count; ß-HCG = beta human chorionic gonadotropin; 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; EOS = end of study; FFPE = formalin-fixed paraffin-embedded; HBc = hepatitis B core antigen; HBsAg = hepatitis B virus surface antigen; HCV = hepatitis C virus; HIV = human immunodeficiency virus;; HPV = human papilloma virus;; HSV = herpes simplex virus; ICF = informed consent form; IHC = immunohistochemistry; IL-2 = interleukin-2; LFTs = liver function tests; LTFU = long-term follow-up; LVEF = left ventricular ejection fraction; MRI = magnetic resonance imaging; MUGA = multi- gated acquisition; NCI-CTCAE = National Cancer Institute-Common Terminology Criteria for Adverse Events; NMA-LD = nonmyeloablative-lymphodepletion; ; OS = overall survival; PD = progressive disease; PD1 = programmed cell death; PET = positron emission tomography; PJP = *Pneumocystis jiroveci* pneumonia; Q3W = every 3 weeks; ; RECIST = Response Evaluation Criteria in Solid Tumors; RPR = rapid plasma reagin; SAE = serious adverse event; SMX-TMP DS = sulfamethoxazole and trimethoprim double strength; TIL = tumor infiltrating lymphocytes; TSH = thyroid-stimulating hormone;

a. All visits preceding LN-145 infusion (Day 0) are calculated going backwards (eg, Day -1, Day -2, Day -3, …Day -7, etc.), and all visits following LN-145 infusion (Day 0) are calculated going forward from Day 0 (eg, Day 1, Day 2, Day 3…Day 28, etc.). The treatment period lasts from Day -7 to the last dose of IL-2. D4 assessments may not be performed if the last day of IL-2 is on D3The maximum duration for IL-2 is six doses from Days 0 to 4. The assessment period begins after TIL infusion on Day 0 and ends at disease progression, the start of a new anticancer therapy, or Month 36, whichever occurs first – this is EOT The LTFU period begins after the assessment period ends and stops at the EOS, where EOS = death, lost to follow-up, withdrawal of consent, study termination by Sponsor/Investigator, or Month 36, whichever occurs first.
b. A re-check of inclusion/exclusion criteria at Baseline (Day -21 to Day -9) must be performed to ensure that patient performance status and eligibility criteria have not changed after Screening.
c. Physical examination (PE) to include gastrointestinal (abdomen, liver), cardiovascular, extremities, head, eyes, ears, nose, and throat, respiratory system, skin, and psychiatric (mental status). Height will be recorded at Screening only. Body surface area (BSA) and body mass index (BMI) will be calculated at Day -7 only. Physical examinations conducted after Day 14 will be symptom-directed. Clinically significant changes should be recorded as AEs.
d. All medications, therapies, or interventions, including those that are part of the tumor resection procedure received by the patient at any time during the study must be recorded and entered into the eCRF.
e. Vital signs will include: weight, pulse rate, respiratory rate, blood pressure, and temperature. On Day 0 (LN-145 infusion), vital signs will be taken pre-infusion, every 15

minutes during infusion and then every 30 minutes for 2 hours post infusion or until stable. Serum chemistry and liver function tests will be performed for the following parameters: sodium, potassium, chloride, total CO2 (bicarbonate), creatinine, glucose, blood urea nitrogen, albumin, calcium, magnesium, phosphorus, alkaline phosphatase, alanine aminotransferase, aspartate aminotransferase, total bilirubin, direct bilirubin, lactate dehydrogenase, total protein, total creatine kinase, uric acid, amylase, and reflex lipase.

f. Thyroid panel will include TSH and free T4. Obtain only at Screening, Day 14, and EOA visit, also at any visit as clinically indicated. h. Complete blood count with differential is to be performed.

i. Coagulation panel including prothrombin time, activated partial thromboplastin time, and international normalized ratio is to be performed at Screening, and as clinically indicated.

j. Dipstick urinalysis with culture to be performed, if indicated.

k. Calculate estimated creatinine clearance using Cockcroft-Gault calculation.

l. Serum ß-HCG pregnancy tests will be performed for women of childbearing potential at Screening, Day -7, Day 0, Day 28, Day 42, Day 84, Day 126 and then at visits every 3 months to Week 52 (Month 12) or EOA visit, whichever occurs first, as well as anytime and as clinically indicated. (NOTE: If pregnancy is discovered at any point in time during the study, it should be reported immediately).

m. Infectious disease testing to be performed at Screening and when clinically indicated.

n. A sample of tumor resected for TIL generation will be analyzed locally for PD-L1 status by IHC

o. At Screening and Baseline, ECG (12-lead) to be performed after patient has been supine for at least 3 minutes. If an ECG has been performed within 2 weeks prior to Screening, no need to repeat.

p. All patients must have an ECHO or a MUGA at Screening. For patients ≥ 60 years or patients who have a history of ischemic heart disease, chest pain, or clinically significant atrial and/or ventricular arrhythmias, a cardiac stress tests must be performed showing LVEF ≥ 45%; and if any wall movement abnormalities are present, they must be reversible.

q. Pulmonary evaluation using spirometry will be completed for all patients. Patients who are unable to conduct reliable pulmonary function test measurements due to abnormal anatomy may undergo a 6-minute walk test to evaluate pulmonary function.

r. CT scans are required at Screening and Baseline (Day -21 to Day -9). MRI or PET scans will be allowed in lieu of CT scans for patients who have an intolerability to contrast media. If scans have been performed within 4 weeks prior to enrollment, these scans can be utilized for Screening. Anatomic regions included in the CT or MRI scans (for patients with intolerance to contrast media) should be per disease history and clinical symptoms (repeat the same CT and MRI series for all post-treatment tumor assessments [scheduled and unscheduled] as completed at Baseline [Day -21 to Day -9]). Include a neck scan if there is prior or suspected neck disease. The imaging modality and anatomic regions assessed must be kept the same for all assessments while on study. At the Investigator's discretion, the Baseline MRI and CT scans may be performed as early as Day -21. Brain MRI should not be repeated at baseline if negative at screening.

s. At least one resectable target lesion to generate TIL of a minimum 1.5 cm in diameter (or aggregate of 1.5 cm if multiple lesions are sampled) post-resection. Biopsies from multiple lesions are recommended.

t. Refer to Section 6.21.

u. An optional "post-LN-145 infusion" biopsy will be collected at Week 6 (Day 42), if feasible and if patient consent is provided. See Section 6.22.

v. 'Authorization to Receive Lymphodepletion' form is to be completed by the Investigator between Day -10 to Day -7 and submitted to Iovance for approval prior to the initiation of the NMA-LD preconditioning regimen

w. TIL LN-145 infusion will be administered no sooner than 24 hours following the last dose of the preparative NMA-LD preconditioning regimen. All visits following TIL infusion (Day 0) are calculated from that date.

x. Initiate IL-2 dosing no sooner than 3 hours, but no later than 24 hours after completion of the LN-145 infusion and continue BID for up to the protocol defined maximum of six doses of IL-2. IL-2 dosing is allowed for up to 4 days following LN-145 infusion to allow for proper management of IL-2 toxicity, if necessary. y. Pulse oximetry is to be conducted during IL-2 administration.

z. Patients will receive filgrastim 5 µg/kg/day (recommended maximum dose of 300 µg/day) subcutaneously daily starting from Day 1 until the ANC is > 1000/mm^3 for 3 consecutive days, or as per standard of care at the treating institution.

aa. All patients should receive appropriate PJP prophylaxis per institutional standard of care for patients undergoing chemotherapy-induced immunosuppression. Such prophylaxis may include any of the following (below) and should begin on or after their first day of chemotherapy, or as the Investigator deems appropriate, and continue until the ALC is > 1000 cells/mm^3 (approximately 3–6 months), or as per institutional standard of care. One acceptable regimen includes trimethoprim (TMP) and sulfamethoxazole (SMX) as double strength (DS) tab (DS tabs = TMP 160 mg/tab, and SMX 800 mg/tab) (PO) twice daily three times a week on non-consecutive days, beginning on the first Monday, Wednesday, or Friday. Pentamidine may be substituted for TMP/SMX DS in patients with sulfa allergies and may be administered either

IV or aerosolized monthly using standard doses indicated for PJP prophylaxis. Other appropriate PJP prophylactic agents may be substituted at the discretion of the treating Investigator.

bb. Patients will start fluconazole 400 mg (PO) from Day 1, or when patients become neutropenic, and continue until the ANC is > 1000/mm^3. Another suitable fungal prophylaxis regimen as per standard of care at the treating institution may also be used for the duration of Grade 3 neutropenia. In patients, positive for HSV, herpes prophylaxis should begin by Day 7, or as the Investigator deems appropriate and continue until the ALC is > 1000/mm^3 (typically for at least 6 months).

cc. Patients with positive HSV serology should begin herpes reactivation prophylaxis (typically valacyclovir or acyclovir) by Day 14, or as the Investigator deems appropriate, and continue until the ALC is > 1000/mm^3 (approximately 3-6 months), or as per institutional standard of care. Other appropriate viral prophylactic agents may be substituted at the discretion of the treating Investigator.

dd. Mandatory peripheral blood will be collected at timepoints of Surgery/Tumor resection, Day 1 for immune monitoring (biomarker analysis). Collection timepoints: Week 6 (Day 42), Week 12 (Day 84), Month 6 and Month 12 if patient is able to return to the study site. See Section 6.23

ee. All AEs for all patients will be assessed as per NCI-CTCAE Version 5.00 during all visits after the ICF is signed. Any events occurring after Screening, but prior to the tumor resection will be recorded as medical history in the eCRF, unless the events are related to protocol-mandated procedures and assessments. Any events occurring after the tumor resection should be captured as AEs in the eCRF.

ff. The LTFU period begins after the assessment period ends and stops at the EOS, where EOS = death, lost to follow-up, withdrawal of consent, study termination by Sponsor -Investigator, or Month 36, whichever occurs first. Patients will be called every 3 Months (± 3 weeks) after the assessment period until they reach an EOS designation.

14.2. ECOG Performance Status Scale

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

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

14.3. Calculation of BMI, BSA, Practical Weight, and Ideal Body Weight

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

BMI

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

BSA

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

Practical Weight

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

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

Ideal Body Weight

Female = 45.5 kg + 2.3 (number of inches over 60 inches)

Example: ideal body weight of 5’3’’female 45.5 + 2.3 x (3) = 57 kg

14.4. Expected Aldesleukin Toxicities and Their Management

Expected Toxicity	Expected Grade	Supportive Measures	Stop Treatment[a]
Chills	3	IV Meperidine 25-50 mg, IV q1h, prn	No
Fever	3	Acetaminophen 650 mg, po, q4h; Indomethacin 50-75 mg, po, q8h	No
Pruritus	3	Hydroxyzine HCL 10-20 mg po q6h, prn; Diphenhydramine HCL25-50 mg, po, q4h, prn	No
Nausea/ Vomiting/ Anorexia	3	Ondansetron 8 mg, IV, q8h, prn nausea/vomiting If Zofran is ineffective: add prochlorperazine 10 mg IV q6h prn nausea/vomiting. If above is ineffective add Lorazepam 0.5 mg PO q6h PRN anticipatory nausea or Lorazepam 0.5 mg IV q6h PRN for anticipatory nausea and unable to take PO.	No
Diarrhea	3	Loperamide 2 mg, po, q3h, prn; Diphenoxylate HCl 2.5 mg and atropine sulfate 25 mcg, po, q3h, prn; codeine sulfate 30 mg, po, q4h, prn If above regimen of Loperamide and Diphenoxylate/Atropine is ineffective: - Add loperamide 2mg PO QID PRN - Add Diphenoxylate 2.5 mg and Atropine 25 mcg QID PRN	If uncontrolled after 24 hours despite all supportive measures
Malaise	3 or 4	Bedrest interspersed with activity	If other toxicities occur simultaneously
Hyperbilirubinemia	3 or 4	Observation	If other toxicities occur simultaneously
Anemia	3 or 4	Transfusion with PRBCs	If uncontrolled despite all supportive measures
Thrombocytopenia	3 or 4	Transfusion with platelets	If uncontrolled despite all supportive measures
Neutropenia	4	Observation	No
Edema/Weight gain	3	Diuretics prn	No

Hypotension	3	Fluid resuscitation; Vasopressor support	If uncontrolled despite all supportive measures
Dyspnea	3 or 4	Oxygen or ventilatory support	If requires ventilatory support
Oliguria	3 or 4	Fluid boluses or dopamine at renal doses	If uncontrolled despite all supportive measures
Increased creatinine	3 or 4	Observation	Yes (grade 4)
Renal failure	3 or 4	Dialysis	Yes
Pleural effusion	3	Thoracentesis	If uncontrolled despite all supportive measures
Bowel perforation	3	Surgical intervention	Yes
Confusion	3	Observation	Yes
Somnolence	3 or 4	Intubation for airway protection	Yes
Arrhythmia	3	Correction of fluid and electrolyte imbalances; chemical conversion or electrical conversion therapy	If uncontrolled despite all supportive measures
Elevated troponin levels	3 or 4	Observation	Yes
Expected Toxicity	**Expected Grade**	**Supportive Measures**	**Stop Treatment[a]**
Myocardial Infarction	3 or 4	Supportive care	Yes
Elevated transaminases	3 or 4	Observation	For Grade 4 without liver metastases
Electrolyte imbalances	3 or 4	Electrolyte replacement	If uncontrolled despite all supportive measures