A Phase 2 Multicenter Study of Autologous Tumor Infiltrating Lymphocytes (LN -145) in Patients with Metastatic Non-Small-Cell Lung Cancer

Published: 05-01-2021
Last updated: 24-12-2024

This study has been transitioned to CTIS with ID 2024-510778-26-00 check the CTIS register for the current data. Primary Objective:To evaluate the efficacy of LN-145 measured by objective response rate (ORR) usingResponse Evaluation Criteria in...

Ethical review	Approved WMO
Status	Completed
Health condition type	Miscellaneous and site unspecified neoplasms benign
Study type	Interventional

Summary

ID

NL-OMON52190

Source
ToetsingOnline

Brief title
IOV-LUN-202

Condition

- Miscellaneous and site unspecified neoplasms benign

Synonym
Lung Cancer, Non-Small-Cell Lung Cancer

Research involving
Human

Sponsors and support

Primary sponsor: Iovance Biotherapeutics, Inc.

Source(s) of monetary or material Support: farmaceutische industrie

Intervention

Keyword: Cell Therapy, Metastatic Non-Small-Cell Lung Cancer, Tumor Infiltrating Lymphocytes

Outcome measures

Primary outcome

ORR is defined as the proportion of patients who have a confirmed CR or PR as assessed per RECIST v1.1 by the IRC (Cohorts 1 and 2) or by the Investigator (Cohort 3, 4 and Retreatment Cohort) from the date of LN-145infusion until disease progression or start of a new anticancer therapy.

Secondary outcome

Secondary Endpoints:

• ORR is defined as the proportion of patients who have a confirmed CR or PR as assessed per RECIST v1.1 by the Investigator (Cohort 1 and 2) from the date of LN-145 infusion until disease progression or start of a new anticancer therapy.

•CR rate is defined as the proportion of patients who have a confirmed CR per RECIST v1.1 as assessed by the IRC (Cohort 1 and 2) or by the Investigator (all cohorts) from the date of LN-145 infusion until disease progression or start of a new anticancer therapy.

•DOR is measured from the time that criteria are met for CR or PR per RECIST v1.1 as assessed by IRC (Cohorts 1 and 2) or by the Investigator (all cohorts) until disease progression or death due to any cause.

•DCR is measured by the percentage of patients with a best overall confirmed response of CR or PR at any time plus stable disease (SD) >= 6 weeks per RECIST

v1.1 as assessed by IRC (Cohorts 1 and 2) or by the Investigator (all cohorts) from the date of LN-145 infusion until disease progression or the start of a new anticancer therapy.

•PFS is defined as the time from the date of LN-145 infusion until disease progression, per RECIST v1.1 as assessed by IRC (Cohorts 1 and 2) or by the Investigator (all cohorts) or death due to any cause.

•OS is the time from the date of LN-145 infusion to death due to any cause.

•Incidence of Grade >=3 TEAEs and SAEs per CTCAE v5.0 in all patients•Percentage of successful LN-145 product generated from core biopsies in Cohort 3

Exploratory Endpoints:

• In vivo persistence of the T cells comprising the TIL product to be assessed by monitoring the presence of TIL product-specific T-cell receptor-beta complementarity determining region 3 (CDR3) sequences in each patient's blood over time; CDR3 sequences present in the product and peripheral blood samples to be identified using deep sequencing

• Exploratory endpoints aiming at identifying predictive and pharmacodynamic clinical biomarkers of the activity of LN-145:

o Phenotypic and functional characteristics of LN 145

o Immune profile of the tumor tissues

o Gene expression profiles of the TIL product, tumor tissues, and/or PBMCs

o Mutational landscape of the tumors

o Circulating immune factors

o Immune composition of PBMCs

• HRQoL as assessed per the European Organization for Research and Treatment of

Cancer (EORTC) quality of life questionnaire (QLQ) C30 and QLQ LC13

Study description

Background summary

Lung cancer is the leading cause of cancer deaths worldwide, with approximately 1.7 million deaths reported in 2015. Of the lung cancer deaths, >80% were attributed to non-small-cell lung cancer (NSCLC). In 2020, there will be an estimated 228,820 new cases and 135,720 deaths attributed to lung and bronchus cancer in the United States. Thus, despite the approval of checkpoint inhibitors (CPIs), which revolutionized NSCLC treatment and outcomes, there remains a significant unmet medical need in NSCLC for patients who progress on CPIs.

Once a patient has disease progression on CPI + chemotherapy, treatment options are limited and suffer from low efficacy (ORR ~ 10% and short duration of response [DOR] and high toxicity). The most commonly used agent is docetaxol, although other single-agent cytotoxic drugs or cytotoxic drugs combined with vascular endothelial growth factor (VEGF) inhibitors are sometimes employed, but all have similarly poor outcomes. Thus, there is an urgent need for better therapeutic options for patients with NSCLC in second-line treatment following CPI + chemotherapy.

From a safety perspective, TIL therapy was found to have a manageable toxicity profile comprised of expected adverse events (AEs), which included cytopenia, hypophosphatemia, hypoalbuminemia, and nausea. The AEs occurred early, within the first 14 days of the lymphodepleting regimen, and had largely resolved within 2 weeks of onset. No unexpected serious adverse reactions were reported. TIL clonotypes persisted through Day 100 and correlated with clinical benefit, and CCR7+ CD95+ CD45RA+ memory cells were increased at post infusion time points. The frequency of T cells with specificity for tumor antigens was assessed to be 10% to 15%. Of the 2 patients with CRs, it was found that both had T cells that recognized multiple antigens.

Preliminary data demonstrates that TIL therapy elicits clinically meaningful responses in NSCLC patients who had disease progression on prior lines of therapy, including CPIs. That TIL treatment generated objective tumor response, including CR and/or decrease in tumor size after failure to respond to a CPI, which suggests that TIL therapy in metastatic NSCLC following CPI could be an important addition to the treatment options. Due to the high unmet medical need and clinical evidence of benefit of TIL in the study by Creelan et al. (2020),

continued evaluation of TIL in NSCLC is warranted.

Study objective

This study has been transitioned to CTIS with ID 2024-510778-26-00 check the CTIS register for the current data.

Primary Objective:

To evaluate the efficacy of LN-145 measured by objective response rate (ORR) usingResponse Evaluation Criteria in Solid Tumors (RECIST) v1.1 assessed by theIndependent Review Committee (IRC) for Cohorts 1 and 2 and by the Investigator for Cohorts 3 and 4 and the Retreatment Cohort

Secondary Objectives:
• To evaluate the efficacy of LN-145 measured by ORR using RECIST v1.1assessed by the Investigator for Cohorts 1 and 2
• To further evaluate the efficacy of LN-145 measured by complete response(CR) rate, duration of response (DOR), disease control rate (DCR), andprogression-free survival (PFS) using RECIST v1.1 assessed by the IRC(Cohorts 1 and 2) and the Investigator (all cohorts); and overall survival(OS)
• To characterize the safety profile of LN-145 in patients with non-small-cell lung cancer (NSCLC) measured by the incidence of Grade >=3 treatment emergent adverse events (TEAEs)
• Cohort 3 only: To determine the feasibility of LN-145 production using tumor tissue obtained via image-guided core biopsy of tumor

Study design

A prospective, open-label, multi-cohort, non-randomized, multicenter phase 2 study evaluating adoptive cell therapy (ACT) with LN-145.

All patients will receive autologous TIL regimen, consisting of the following steps, regardless of tumor harvest timing (pre-progression or post-progression):
1. Tumor harvest by surgical resection or image-guided core biopsy to obtain the autologous tissue that is the source of the TIL cellular product.
2. TIL production at a Good Manufacturing Practice (GMP) facility
3. Optional continuation of previously ongoing clinical management (no new therapy) in the interval from tumor harvest to the start of nonmyeloablative lymphodepletion (NMA-LD).
4. Baseline assessments including imaging within 28 days prior to NMA-LD to confirm the patient's health status is acceptable to receive autologous TIL therapy.
5. A 5-day NMA-LD preconditioning regimen
4. TIL infusion (Day 0)

5. Iinterleukin-2 (IL-2) administration (up to 6 doses)

The following general sequential periods will occur in all cohorts, unless otherwise specified:
1. Screening Period: Up to 28 days after the patient signs the informed consent form (ICF) and prior to tumor harvest (i.e., enrollment)
2. Pre-treatment Period: From enrollment (i.e., tumor harvest) to initiation of preconditioning NMA-LD regimen.
3. Treatment Period: From initiation of preconditioning NMA-LD (Day -5) to End-of-Treatment (EOT) Visit.
• NMA-LD: Days -5 to -1
• TIL infusion: Day 0
• IL-2: Days 0 to 3 (may be Days 1 to 4)
• EOT visit: Day 30 ±3 days
4. Post-treatment Period
• Assessment Period: From completion of the EOT visit (Day 30 ±3 days) to the End of Assessment (EOA) visit
• EOA visit: Occurs after complete or partial withdrawal of consent, at disease progression, prior to initiation of a new anticancer therapy (if possible), after failure to receive TIL infusion for any reason, or at 5 years (Month 60/Day 1680) from Day 0, whichever occurs first.
• Long-term Follow-up (LTFU) Period: From EOA visit to End-of-Study (EOS)
• EOS: Occurs due to death, patient lost to follow-up, withdrawal of consent, study termination by Sponsor, or 4 years (Month 60/Day 1680) after Day 0, whichever occurs first.

Intervention

Patients will undergo a 5-day preconditioning NMA-LD regimen that will be initiated prior to the planned LN-145 infusion on Day 0 (i.e., Days -5 through 1. The NMA-LD regimen consists of 2 days of intravenous (IV) cyclophosphamide (60 mg/kg) with mesna (per site standard of care or USPI/SmPC) on Days -5 and 4, and 5 days of fludarabine IV (25 mg/m2, Days -5 through 1).

IL-2 IV administrations at a dose of 600,000 IU/kg may begin as soon as 3 hours after, but no later than 24 hours after, completion of the LN-145 infusion on Day 0. Additional IL-2 doses will be given approximately every 8 to 12 hours for up to 6 total doses.

Study burden and risks

Burden:
- Up to 28 visits to the investigator + a hospitalization of 12 days
- Physical examination (at most visits)
- Blood draws (at every visit)
- Collection of urine samples (2x or at the indication of the investigator)

- ECHO or MUGA scan (1x)
- Cardiac stress test & Lung function tests (1x)
- Skin test (1x)
- CT / MRI scans (19x)
- Assessment of daily activities (during screening, baseline and daily during the treatment period)
- Questionnaires, including questions about quality of life (15x)
- Surgery and collection of tumor sample (1x and 2 possible optional biopsies).
- Long-term follow up with contact every 3 months by phone or other means (e.g. e-mail) for up to 5 years to confirm the status of the disease and whether another anti-cancer treatment is started.

Risks of LN-145:
LN-145 is a new investigational product that we know has potentially serious or life-threatening side effects. Subjects are asked to inform their research doctor and / or study staff immediately if they experience problems with:
- Fever, chills, cough
- Rash
- Increased heart rate
- Low blood pressure which can make you feel dizzy or faint
- Chest tightness and / or wheezing, shortness of breath
- Swelling of the face or throat swelling

The risks associated with TIL therapy include a delay in treatment due to the need to harvest and grow the cells (this manufacturing process takes approximately 16 to 22 days); an interventional harvesting procedure to obtain tumor tissue for the cell product; the possibility that a cell product cannot be generated; and the toxicities known to be associated with the NMA-LD preparatory regimen and IL-2 administration.

Risks associated with the approved agents IL-2, cyclophosphamide, fludarabine and mesna are detailed in the subject information, section 6 and the provided SPC's.

Contacts

Public
Iovance Biotherapeutics, Inc.

825 Industrial Road Suite 400
San Carlos, California 94070
US
Scientific
Iovance Biotherapeutics, Inc.

825 Industrial Road Suite 400
San Carlos, California 94070
US

Trial sites

Listed location countries

Netherlands

Eligibility criteria

Age
Adults (18-64 years)
Elderly (65 years and older)

Inclusion criteria

1. Provide written informed consent and written authorization for use and disclosure of protected health information.
2. Be 18 to 70 years of age at the time of signing of informed consent form. Patients who are >70 years of age may be allowed to enroll after consultation with the Medical Monitor.
3. Have histologically or pathologically confirmed diagnosis of metastatic Stage IV NSCLC (squamous, nonsquamous, adenocarcinoma, large cell, or mixed histologies) without EGFR, ALK, or ROS genomic alterations.
4. Meet prior therapy criteria:
-post-progression tumor harvest: Patient must have documented radiographic disease progression on or after the first-line therapy, inclusive of prior ICI and platinum-based chemotherapy ± bevacizumab or targeted therapy.
-pre-progression tumor harvest and TIL production: Patient must have residual resectable disease after completion of the platinum-based chemotherapy component of either concurrent or sequential ICI and platinum-based chemotherapy, meet all eligibility criteria except documented disease progression, and intend to receive TIL therapy after disease progression on current therapy.
5. Have an Eastern Cooperative Oncology Group (ECOG) performance status of 0 or 1 and an estimated life expectancy of >6 months, in the Investigator*s opinion.
6. Cohorts 1, 2 and 4: Have at least 1 resectable lesion (or aggregate lesions) with an expected minimum 1.5 cm diameter for TIL production. Cohort 3: Have a single, measurable lesion (RECIST v1.1) and/or are unable to undergo a surgical

tumor resection, but able to undergo tumor harvest for TIL generation via image-guided core biopsy. Retreatment Cohort: Meet any tumor requirement listed above. All Cohorts: If the lesion considered for harvest is within a previously irradiated field, the lesion must have demonstrated radiographic progression prior to harvest, and the irradiation must have been completed at least 3 months prior to enrollment. Patients must have an adequate histopathology specimen for protocol-required testing
7. Have at least 1 remaining measurable lesion as defined by RECIST v1.1 following tumor harvest for TIL manufacturing that is documented at Screening for post disease progression tumor harvest and at Baseline forpre- and post-progression tumor harvest
8.Required hematologic parameters:
•Absolute neutrophil count >=1000/mm3.
•Hemoglobin >=8.0 g/dL.
•Platelet count >=100,000/mm3
9. Have adequate organ function with the following laboratory test values:
•ALT and AST <=3times the upper limit of normal (<=3 × ULN); for patients with liver metastases <=5 × ULN.
•Total bilirubin <=2 mg/dL; patients with Gilbert*s Syndrome <=3mg/dL.
•Estimated creatinine clearance >=40 mL/min using the Cockcroft-Gault formula at Screening
10. Have a left ventricular ejection fraction (LVEF) >45% and be New York Heart Association (NYHA) Class 1. A cardiac stress test is required for patients over >=60 years of age or who have a history of ischemic heart disease, cardiac chest pain, or clinically significant atrial and/or ventricular arrhythmias; the cardiac stress test must demonstrate no irreversible wall movement abnormality. Patients with an abnormal cardiac stress test may be enrolled if they have adequate ejection fraction and cardiology clearance after discussion with the Medical Monitor.
11. Have adequate pulmonary function.
If a patient is unable to perform reliable spirometry due to abnormal upper airway anatomy, a 6-minute walk test may be used to assess pulmonary function. Patients must be able to walk a distance at least 80% of predicted for age and sex with no evidence of hypoxia at any point during the test (i.e., saturation of peripheral oxygen [SpO2] must remain >=90%).
12. Have completed/discontinued chemotherapy >=21 days prior to tumor harvest.
13. Must have recovered from all prior anticancer treatment-related adverse events to Grade<=1 (per CTCAE v5.0). Patients with irreversible toxicity (eg, alopecia, vitiligo) after prior anticancer therapies that are not considered by the Investigator to be a likely safety risk may qualify for the study after discussion with the Medical Monitor.
14. Patients of childbearing potential or those with partners of childbearing potential must be willing to practice an approved method of highly effective birth control during treatment and for 12 months after receiving all protocol-related therapy. Approved methods of birth control:
•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
•Intrauterine hormone-releasing system
•Bilateral tubal occlusion
•Vasectomy
•Absolute sexual abstinence if in line with the preferred/usual lifestyle of the patient. Periodic abstinence (eg, calendar ovulation) is unacceptable.

Exclusion criteria

1. Have a history of allogeneic organ transplant or any form of cell therapy involving a prior nonmyeloablative or myeloablative chemotherapy regimen within the past 20 years. Patients being retreated with LN-145 are not excluded due to prior NMA-LD during this study.
2. Have known actionable EGFR, ALK, or ROS driver mutations.
3. Have symptomatic untreated brain metastasis. Patients with brain metastases may be enrolled with the following considerations and only after discussion with the Medical Monitor:
a.Patients with asymptomatic brain metastases who do not clinically require treatment may be enrolled.
b.Patients with historically treated brain metastases (i.e., treatment of brain metastases was completed >28 days prior to date of informed consent) will be considered for enrollment if the patient is clinically stable for >=2 weeks, there are no new or worsening brain lesions via screening magnetic resonance imaging (MRI), and the patient does not require ongoing corticosteroid treatment (>10 mg/day prednisone or equivalent).
c.Patients with recently treated brain metastases (i.e., treatment of brain metastases was completed <=28 days prior to date of informed consent) may be considered for enrollment if the patient is asymptomatic, clinically stable for >=2 weeks, and does not require corticosteroids (>10 mg/day prednisone or equivalent)
d.Patients with progressive or new brain metastases on screening magnetic resonance imaging (MRI) should suspend screening procedures and receive appropriate treatment of brain metastases. Screening can resume after completion of brain metastases treatment, when the patient is asymptomatic, clinically stable for >=2 weeks, and does not require corticosteroids (>10 mg/day prednisone or equivalent) at the start of NMA-LD (Day -5). Note: Patients who develop symptomatic brain metastases at any time after signing the ICF until starting NMA-LD should receive appropriate treatment of brain metastases prior to NMA-LD. Such patients must be asymptomatic, clinically stable for >=2 weeks, and not require corticosteroids (>10 mg/day prednisone or equivalent) at the start of NMA-LD (Day -5)
4. Require systemic steroid therapy >10 mg/day prednisone or equivalent. Patients receiving steroids as replacement therapy for adrenocortical

insufficiency at <=10 mg/day prednisone or equivalent are not excluded.
5. Have evidence of any active viral, bacterial, or fungal infection requiring ongoing systemic treatment or as per required screening tests.
6. Are pregnant or breastfeeding. Female patients of childbearing potential must have a negative beta-human chorionic gonadotropin (β-HCG) test with minimum sensitivity of 25 IU/L β-HCG (or equivalent) at Screening.
7. Have an active medical illness(es) that in the opinion of the Investigator would pose increased risks for study participation, such as systemic infections, coagulation disorders, or other active major medical illnesses of the cardiovascular, respiratory, or immune systems.
8. Have received a live or attenuated vaccination within 28 days prior to the start of NMA-LD.
9. Have any form of primary immunodeficiency (eg, severe combined immunodeficiency disease [SCID] or acquired immune deficiency syndrome [AIDS]).
10. Have 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 the autologous TIL product formulation, including, but not limited to, any of the following:
•NMA-LD (cyclophosphamide, mesna, and fludarabine)
•Proleukin®, aldesleukin, IL-2
•Antibiotics of the aminoglycoside group (i.e., streptomycin, gentamicin). These patients may be eligible if current hypersensitivity has been excluded.
•Any component of the TIL product formulation, including dimethyl sulfoxide (DMSO), human serum albumin (HSA), IL-2, or dextran-40
11. Have had another primary malignancy within the previous 3 years (except for malignancies that do not require treatment or have been curatively treated >1 year ago, and in the judgment of the Investigator do not pose a significant risk of recurrence including, but not limited to: in situ carcinoma of the cervix; early stage skin cancer, including non-melanoma skin cancer; ductal carcinoma in situ (DCIS) or lobular carcinoma in situ (LCIS) of the breast; prostate cancer with Gleason score <=6; or superficial bladder cancer).
12. Participated in another clinical study with an investigational product within 21 days prior to enrollment with the exception of investigational programmed cell death-1 (PD-1)/PD-L1 inhibitors or tyrosine kinase inhibitors (TKIs), which may be continued until 7 days prior to initiation of NMA-LD
13. Have any condition or characteristic (e.g., known psychiatric diagnosis/symptoms, alcohol abuse, or substance abuse) that, in the opinion of the Investigator, could interfere with the evaluation or interpretation of study treatment, patient safety, or study results

Study design

Design

Study phase:	2
Study type:	Interventional
Masking:	Open (masking not used)
Control:	Uncontrolled
Primary purpose:	Treatment

Recruitment

NL

Recruitment status:	Completed
Start date (anticipated):	01-02-2022
Enrollment:	30
Type:	Actual

Medical products/devices used

Product type:	Medicine
Generic name:	Somatic cells autologous
Product type:	Medicine
Brand name:	Cyclofosfamide Injection
Generic name:	Cyclofosfamide
Registration:	Yes - NL outside intended use
Product type:	Medicine
Brand name:	Fludarabine Fosfaat
Generic name:	Fludarabine
Registration:	Yes - NL outside intended use
Product type:	Medicine
Brand name:	LN-145
Generic name:	-
Product type:	Medicine
Brand name:	Proleukin®
Generic name:	Aldesleukin
Registration:	Yes - NL outside intended use
Product type:	Medicine
Brand name:	Uromitexan

Generic name:	Mesna
Registration:	Yes - NL intended use

Ethics review

Approved WMO Date:	05-01-2021
Application type:	First submission
Review commission:	CCMO: Centrale Commissie Mensgebonden Onderzoek (Den Haag)
Approved WMO Date:	05-05-2021
Application type:	First submission
Review commission:	CCMO: Centrale Commissie Mensgebonden Onderzoek (Den Haag)
Approved WMO Date:	03-02-2022
Application type:	Amendment
Review commission:	CCMO: Centrale Commissie Mensgebonden Onderzoek (Den Haag)
Approved WMO Date:	25-03-2022
Application type:	Amendment
Review commission:	CCMO: Centrale Commissie Mensgebonden Onderzoek (Den Haag)
Approved WMO Date:	13-05-2022
Application type:	Amendment
Review commission:	CCMO: Centrale Commissie Mensgebonden Onderzoek (Den Haag)
Approved WMO Date:	12-07-2022
Application type:	Amendment
Review commission:	CCMO: Centrale Commissie Mensgebonden Onderzoek (Den Haag)
Approved WMO Date:	09-11-2022

Application type:	Amendment
Review commission:	CCMO: Centrale Commissie Mensgebonden Onderzoek (Den Haag)
Approved WMO Date:	12-12-2022
Application type:	Amendment
Review commission:	CCMO: Centrale Commissie Mensgebonden Onderzoek (Den Haag)
Approved WMO Date:	23-12-2022
Application type:	Amendment
Review commission:	CCMO: Centrale Commissie Mensgebonden Onderzoek (Den Haag)
Approved WMO Date:	31-01-2023
Application type:	Amendment
Review commission:	CCMO: Centrale Commissie Mensgebonden Onderzoek (Den Haag)
Approved WMO Date:	27-11-2023
Application type:	Amendment
Review commission:	CCMO: Centrale Commissie Mensgebonden Onderzoek (Den Haag)
Approved WMO Date:	10-01-2024
Application type:	Amendment
Review commission:	CCMO: Centrale Commissie Mensgebonden Onderzoek (Den Haag)
Approved WMO Date:	15-02-2024
Application type:	Amendment
Review commission:	CCMO: Centrale Commissie Mensgebonden Onderzoek (Den Haag)

Study registrations

Followed up by the following (possibly more current) registration

No registrations found.

Other (possibly less up-to-date) registrations in this register

No registrations found.

In other registers

Register	ID
EU-CTR	CTIS2024-510778-26-00
EudraCT	EUCTR2020-003629-45-NL
ClinicalTrials.gov	NCT04614103
CCMO	NL76099.000.20