Phase 2 Study to Assess the Efficacy and Safety of Autologous Tumor Infiltrating Lymphocytes (LN-145) Alone and In Combination with Anti-PD-L1 Inhibitor Durvalumab (MEDI4736) in Patients with Locally Advanced or Metastatic Non-Small Cell Lung Cancer (NSCLC)

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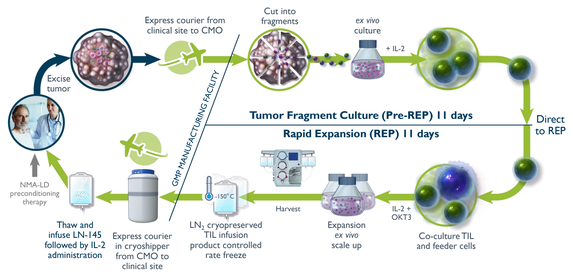
BACKGROUND

- Lung cancer is the leading cause of human cancer deaths worldwide, with approximately 1.7 million deaths reported in 2015, of which 80% to 85% were attributed to non-small cell lung cancer (NSCLC).[1]
- For patients with locally advanced or metastatic disease, the standard chemotherapy shows objective response rate (ORR) of 10% to 40%,[2,3] and a median survival of approximately 1 year.[4,5]
- Adoptive cell therapy (ACT) with tumor infiltrating lymphocytes (TIL) has demonstrated the potential for durable complete responses in immunogenic tumors with high mutational burden, such as melanoma, in studies conducted at National Cancer Institute (NCI).[6] A positive correlation has been demonstrated between the presence of TIL in NSCLC tumor specimens and patient outcome.[7,8]
- Recently, the anti-PD-L1 monoclonal antibody durvalumab (Imfinzi®) was approved for patients with locally advanced, unresectable Stage III NSCLC whose disease has not progressed following chemoradiotherapy.[9]
- Durvalumab dosing prior to harvest of tumor for LN-145 generation is expected to promote increased TIL trafficking into tumor lesions. In addition, anti-PD-L1 treatment prior to and immediately following TIL (LN-145) infusion may further dampen a suppressive tumor microenvironment, allowing improved engraftment and potency of the infused TIL (LN-145).[10,11]
- This study was designed to evaluate the efficacy and safety of LN-145 (an autologous investigational TIL therapy) given alone or in combination with durvalumab for the treatment of patients with Stage III or Stage IV NSCLC who are checkpoint therapy-naïve and who have received ≥ 1 line of prior systemic therapy in the locally advanced or metastatic setting.

Figure 1. Iovance cryopreserved LN-145 manufacturing process (22 days)



STUDY OVERVIEW

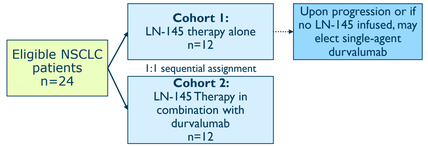
- Phase 2, multicenter, open-label, 2-cohort study evaluating ACT with autologous TIL therapy (LN-145) alone in Cohort 1, or in combination with durvalumab in Cohort 2.
- Approximately 10 investigational centers in the US
- The planned sample size is 24 treated patients; 12 patients in each cohort.
- The primary statistical analysis is based on the use of descriptive methods and estimation of efficacy and safety parameters performed by treatment cohort.

STUDY DESIGN

- LN-145 is prepared at a central GMP facility from TIL extracted from surgically-resected tumors. LN-145 infusion is preceded by a non-myeloablative lymphodepletion regimen of cyclophosphamide (60 mg/kg x 2 days) and fludarabine (25 mg/m^2 x 5 days), followed by up to 6 infusions of IV IL-2 (600,000 IU/kg).
- Cohort 1 patients receive LN-145 therapy alone. Patients in Cohort 1 who do not receive LN-145 or those who progress following LN-145 therapy may go on to receive durvalumab 1500 mg IV Q4W until disease progression or unacceptable toxicity.
- Cohort 2 patients receive 1500 mg IV durvalumab as follows: 2 weeks prior to and 2 weeks after tumor harvest; then 2 weeks following LN-145 infusion and continue 1500 mg IV durvalumab Q4W until disease progression or unacceptable toxicity.
- Patients in either cohort unable to receive LN-145 are allowed to go on to receive durvalumab alone.

Figure 2. Study Design

Now enrolling at sites in US



STUDY OBJECTIVES

Primary:

- To evaluate the efficacy of LN-145 therapy alone or in combination with durvalumab in patients with locally advanced or metastatic NSCLC using the objective response rate (ORR).
- To evaluate the safety of LN-145 therapy alone or in combination with durvalumab in patients with locally advanced or metastatic NSCLC as measured by any ≥ Grade 3 adverse event (AE) rate.

Secondary:

- To further evaluate the efficacy of LN-145 therapy alone or in combination with durvalumab in the study population by assessing duration of response (DOR), progression-free survival (PFS), and overall survival (OS).

Exploratory:

- Evaluate the efficacy of LN-145 therapy alone or in combination with durvalumab in the study population by assessing complete response (CR) rate and disease control rate (DCR).
- To explore the persistence of LN-145 and immune correlates of response, survival, and toxicity of the treatment.
- To explore efficacy based on immune-related Response Evaluation Criteria in Solid Tumors (irRECIST).[12]
- To assess health-related quality of life (HRQoL) per the EORTC QLQ-C30 and QLQ-LC13.

NCT03419559

MAJOR INCLUSION & EXCLUSION CRITERIA

Major Inclusion Criteria

- Histologically/cytologically confirmed diagnosis of Stage III or Stage IV NSCLC (squamous, nonsquamous, adenocarcinoma, large cell carcinoma), and have received ≥ 1 line of prior systemic therapy in the locally advanced or metastatic setting;
- Must have at least 1 lesion resectable for TIL generation;
- Must have a different lesion measurable by RECIST 1.1 for response assessment;
- Male or female, 18 years of age or older;
- Minimum of 21 days or 5 half-lives washout from last dose of tumor-directed therapy to the first study treatment;
- ECOG performance status of 0 or 1;
- Adequate bone marrow, liver, and renal function at Screening;
- Agreement to use up to 6 months of approved methods of birth control after receiving last protocol-related therapy.

Major Exclusion Criteria

- History of other malignancies, except for curatively treated with no evidence of disease for ≥ 3 years;
- Prior cell transfer therapy;
- Prior anti-PD-1 or anti-PD-L1 inhibitors (including durvalumab). Other prior immunotherapy(ies) allowed;
- Active or prior documented autoimmune or inflammatory disorders or active infections;
- History of primary immunodeficiency, history of allogeneic organ transplant that requires therapeutic immunosuppression;
- Received live or attenuated vaccination within 28 days prior;
- History of hypersensitivity to any of components of the protocol-required therapies, including known allergic reaction to antibiotics of the aminoglycoside group (ie, streptomycin, gentamicin);
- Left ventricular ejection fraction (LVEF) < 45%;
- Forced expiratory volume (FEV) in one second ≤ 60% predicted;
- Active central nervous system metastases and/or leptomeningeal disease;
- Pregnant or breastfeeding.

SUMMARY

- Locally advanced or metastatic NSCLC presents a high unmet medical need with low survival rates and with limited effective treatment options.
- The presence of TIL in tumor lesions has been correlated with improved outcomes in a number of solid tumors, including NSCLC.
- Our hypothesis is that the combination of the anti-PD-L1 checkpoint inhibitor, durvalumab and LN-145 therapy may further enhance the efficacy and persistence of TIL.
- This study aims to assess the potential of TIL therapy with LN-145 either alone or in combination with durvalumab for the treatment of patients with locally advanced or metastatic NSCLC.

Disclosure

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