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

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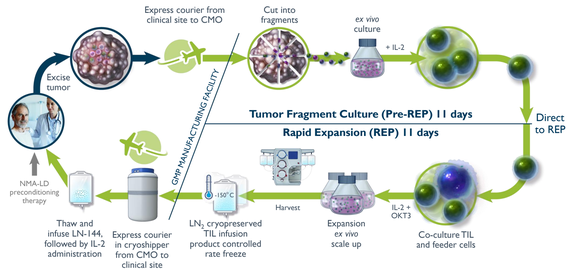
BACKGROUND

- There are an estimated 232,000 newly diagnosed cases of melanoma skin cancers occurring globally each year, making it the fifth most common malignancy in men and sixth most common malignancy in women.[1]
- With the approval of ipilimumab in 2011, followed by approvals for pembrolizumab and nivolumab in 2014, there has been rapid uptake of these immunotherapeutic agents without significant improvement in patient outcomes.[2]
- Following progression on anti-PD-1 therapy, additional checkpoint inhibitors are often selected with overall response rates of 16% and 21% for ipilimumab alone or ipilimumab plus nivolumab, respectively.[3]
- Adoptive cell therapy (ACT) utilizing tumor infiltrating lymphocytes (TIL) for patients with metastatic melanoma and other solid tumors, demonstrates durable and complete responses, even in heavily pretreated patients.[4]
- The C-144-01 study will enroll metastatic melanoma patients who have progressed following anti-PD-1 therapy, and BRAF inhibitor, if BRAF mutation positive.
- This phase 2 multicenter trial utilizes a central GMP facility for the manufacture of LN-144 in either a non-cryopreserved generation 1 (Gen 1), or cryopreserved generation 2 (Gen 2) investigational TIL infusion product.

Figure 1. Iovance cryopreserved LN-144 manufacturing process (22 days)



STUDY OVERVIEW

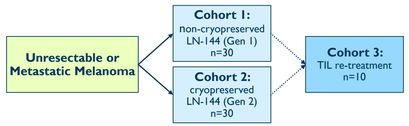
- Patients must have confirmed diagnosis of Stage IIIc or Stage IV Metastatic Melanoma with progression on/after prior immune checkpoint (anti-PD-1) therapy and, if BRAF mutant, after BRAF inhibitor systemic therapy
- Approximately 35 investigational centers in the US & Europe
- The study consists of three treatment cohorts:
  - Cohort 1: patients to receive Gen 1/non-cryopreserved LN-144
  - Cohort 2: patients to receive Gen 2/cryopreserved LN-144
  - Cohort 3: patients from Cohort1/Cohort 2 will be enrolled to receive a second treatment with LN-144 therapy

Note: Protocol amendment pending to update Sample Size

- Patients will receive a nonmyeloablative lymphodepletion (NMA-LD) preparative regimen (cyclophosphamide 60 mg/kg x 2 days followed by fludarabine 25 mg/m^2 x 5 days), preceding the autologous TIL infusion (LN-144), after which they receive up to six doses of intravenous IL-2 (600,000 IU/kg).
- Patients will be evaluated for tumor response approximately every 6 weeks following LN-144 for up to 6 months. After 6 months, patients will be assessed for tumor response at 9, 12, 18 and 24 months following LN-144 treatment.

Figure 2. Study Design

Now enrolling at sites in US and Europe



STUDY FLOWCHART, OBJECTIVES, MAJOR INCLUSION & EXCLUSION CRITERIA

Study Flowchart

Screening Period
≤ 28 days

Enrollment
Tumor harvest

Treatment Period
- NMA-LD (Day -7 to Day -1)
- TIL infusions (Day 0)
- IL-2 therapy (Day 0 to Day 4)

Response Assessment Period
- Every 6 weeks for the first 6 months
- Every 3 months thereafter

Overall Survival FU Period
Up to 3 years

Patients enrolled in Cohort 1 (Gen 1) or Cohort 2 (Gen 2)
Cohort 3: retreatment for patients who are eligible to receive 2nd treatment with TIL

Abbreviations: NMA-LD = nonmyeloablative lymphodepletion; TIL = tumor infiltrating lymphocytes; IL-2 = interleukin-2; OS = overall survival; FU = follow up; Gen 1 = generation 1; Gen 2 = generation 2.

Study Objectives

Primary:
- Evaluation of the efficacy of LN-144 in patients with metastatic melanoma using objective response rate (ORR).

Secondary:
- Additional efficacy parameters of complete response (CR) rate, duration of response (DOR), disease control rate (DCR), progression-free survival (PFS), and overall survival (OS).
- Characterize the safety profile of LN-144 in patients with metastatic melanoma.

Exploratory:
- Persistence of LN-144 and potential immune correlates of response, outcome, and toxicity of the treatment.
- Efficacy based on immune-related Response Evaluation Criteria in Solid Tumors (irRECIST).[5]
- Health-related quality of life (HRQoL).

Major Inclusion Criteria

- Metastatic melanoma (Stage IIIc or Stage IV) following progression of ≥1 prior line of systemic therapy, including immune checkpoint inhibitor (e.g., anti-PD-1), and if BRAF mutation-positive, after BRAF inhibitor systemic therapy;
- Must have at least 1 lesion resectable for TIL generation that yields at least 1.5 cm in diameter of tissue. If previously irradiated, the irradiation must have occurred at least 3 months prior to tumor resection;
- Patients must be ≥18 years and ≤70 years of age at the time of consent;
- ECOG performance status of 0 or 1, and estimated life expectancy of ≥3 months;
- Adequate bone marrow, liver, and renal function;
- Seronegative for the HIV antibody, hepatitis B antigen and hepatitis C antibody or antigen;
- Up to 1 year of birth control following completion of study treatment;
- Minimum 28 day washout from last dose of tumor-directed therapy prior to tumor resection;
- Patients must recover from prior immune-mediated Grade ≥ 2 diarrhea or colitis.

Major Exclusion Criteria

- Prior cell transfer therapy;
- Symptomatic and/or untreated brain metastases;
- Systemic steroid therapy greater than 10 mg daily equivalents of prednisone;
- Active systemic infections, coagulation disorders, or other active major medical illnesses of the cardiovascular, respiratory, or immune system that, in the opinion of the investigator, would increase the risk of participation;
- Primary or acquired immunodeficiency;
- Patients who have a history of severe immediate hypersensitivity reaction to cyclophosphamide, fludarabine, or IL-2;
- Patients with known allergic reaction to antibiotics of aminoglycoside group (i.e., streptomycin, gentamicin);
- No prior systemic therapy with a BRAF-directed kinase inhibitor if BRAF mutation positive (V600)
- Left ventricular ejection fraction < 45%;
- Forced expiratory volume in one second ≤ 60% predicted;
- Primary malignancy in the previous 3 years requiring treatment in the last year; and
- Pregnant or breastfeeding.

NCT02360579

SUMMARY

- Relapsed and refractory Metastatic Melanoma presents a high unmet medical need with low survival rates and with limited durable treatment options.
- TIL have demonstrated antitumor efficacy including durable long-term responses in heavily pretreated patients irrespective of prior therapy, including checkpoint inhibitors.
- An upcoming protocol amendment to this study will increase the number of patients to be enrolled.
- The Gen 2 manufacturing of LN-144 takes 22 days, significantly shortening the duration of time a patient has to wait to receive their TIL therapy.
- The cryopreservation of Gen 2 LN-144 offers flexibility in the timing of dosing patients, and leads to a reduction of cost of manufacturing.

Disclosure

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