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

Amid Samadi1, Brendan Curtis2, Dwiskar Dawar2, Omid Hamid3, Joe Latchy3, Melissa Wilson4, Harriet Kluger5, Jason Chessney5, Kevin Kim6, Giao Phan7, Sajee Thomas8, Igor Garbosiachvily2, Benta Larsen8, Sam Suki8, Nancy Samberg9, Maria Fardis10, John M. Kirkwood11

1City of Hope Cancer Center, Duarte, CA; 2The University of Texas MD Anderson Cancer Center, Houston, TX; 3Mount Sinai Comprehensive Cancer Center, New York, NY; 4University of Pennsylvania School of Medicine, Philadelphia, PA; 5University of Connecticut, Farmington, CT; 6University of California, San Francisco, CA; 7University of Michigan Comprehensive Cancer Center, Ann Arbor, MI; 8University of California, Los Angeles, CA; 9Memorial Sloan Kettering Cancer Center, New York, NY; 10Hospital for Special Surgery, New York, NY; 11Mount Sinai Comprehensive Cancer Center, New York, NY; 12MedStar Georgetown University Hospital, Washington, DC;

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
• Adaptive cell therapy (ACT) utilizing tumor infiltrating lymphocytes (TIL) for patients with metastatic melanoma and other solid tumors, demonstrates durable complete responses, even in heavily pretreated patients.4
• The Phase 1-01 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.

STUDY OVERVIEW
• Patients must have confirmed diagnosis of Stage IIIc or Stage IV Metastatic Melanoma with progression after prior immune checkpoint (anti-PD-1) therapy and, if BRAF mutant, after BRAF inhibitor systemic therapy.
• Approximately 33 investigational centers in the US & Europe.
• The study consists of three treatment cohorts: Cohort 1: patients to receive Gen 1 cryopreserved LN-144; Cohort 2: patients to receive Gen 2 cryopreserved LN-144; Cohort 3: patients from Cohorts 1/2 will be enrolled to receive a second treatment with LN-144 therapy.
• Normal renal function prior to enrollment. If previously treated with chemotherapy, patients may have non-critical renal toxicity.
• The cryopreservation of Gen 2 TIL (Gen 1), or cryopreserved generation 2 (Gen 2) investigational TIL infusion product. (See Figure 1).

STUDY FLOWCHART, OBJECTIVES, MAJOR INCLUSION & EXCLUSION CRITERIA

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

Major Inclusion Criteria
• Metastatic melanoma (Stage IIIc or Stage IV) following progression of 2 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 be at least 1 lesion measurable 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 ≥ 21 years and ≤ 57 years of age at the time of consent.
• ECOG performance status 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 2-3 dermals or colitis.

Major Exclusion Criteria
• Prior cell transfer therapy.
• Symptomatic and/or untreated brain metastases.
• Symptomatic dermatologic disease.
• Primary or acquired immunodeficiency.
• Patients with a history of severe immediate or delayed hypersensitivity reaction to cyclophosphamide, fludarabine, or IL-2.
• Patients with known allergic reaction to antibiotics of ampicillin 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.
• Major primary malignancy in the previous 3 years requiring treatment in the last year.
• Pregnancy or breastfeeding.

References
3. European Academy of Dermatology and Venereology. EADV Program Book 2017