A Phase 2, Multicenter Study of Autologous Tumor Infiltrating Lymphocytes (LN-144/LN-145/LN-145-S1) in Patients with Solid Tumors

Objectives

Primary:
To evaluate the efficacy of autologous TIL LN-144 in combination with pembrolizumab in MM, HNSCC, or NSCLC patients and TIL LN-145-S1 in patients with MM who have previously progressed on or after treatment with CPIs, as determined by ORR, using the Response Evaluation Criteria in Solid Tumors (RECIST 1.1), as assessed by Investigator.
To characterize the safety profile of TIL LN-144 in combination with pembrolizumab in MM, HNSCC, and NSCLC patients and TIL LN-145-S1 in MM patients as measured by the incidence of Grade >= 3 treatment-emergent adverse events (TEAEs).

Secondary:
To further evaluate the efficacy of autologous TIL LN-144 in combination with pembrolizumab in MM, HNSCC, and NSCLC patients and TIL LN-145-S1 in MM patients using CR rate, duration of response (DOR), disease control rate (DCR), PFS using RECIST 1.1 as assessed by Investigator, and OSExploratory:
To explore the in vivo persistence of TIL LN-144 in combination with pembrolizumab and that of TIL LN-145-S1 as a single agent.
To identify predictive and pharmacodynamic biomarkers of clinical responses to the TIL products.
To explore efficacy parameters (excluding OS) using the immune-related Response Evaluation Criteria in Solid Tumors (irRECIST), as assessed by Investigator.
To assess respective, indication-specific, health-related quality of life (HRQoL) parameters.

Inclusion Criteria

All patients must have a histologically or pathologically confirmed diagnosis of malignancy of their respective histologies:
Unresectable or metastatic melanoma Stage IIIC or Stage IV (Cohorts 1A and 1B)
For definitions of Cohorts 1A, 2A, and 3A and required prior lines of therapy, see Section 4.1 in the full protocol.
Patients must have radiologically documented disease progression while receiving, or after the completion of, the most recent prior treatment. For definitions of Cohorts 1B and 3B and required prior lines of therapy, see Section 4.1 in the study protocol.
Patients must have radiologically documented disease progression while receiving, or after the completion of, the most recent prior treatment. Patients must have at least 1 resectable lesion (or aggregate lesions) of a minimum 1.5 cm.
in diameter 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 prior to resection and irradiation has not occurred within the past 3 months. Patients must have an adequate histopathology specimen for protocol-required testing (see Section 5.18). 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 of disease in those lesions and irradiation has not occurred within the past 3 months. Lesions that are partially resected for TIL generation that are still measurable per RECIST may be selected as non-target lesions but cannot serve as a target lesion for response assessment. Patients must be >= 18 years at the time of consent for Cohorts 1A, 2A, 3A, and 3B. Patients must be >= 12 years at the time of consent for Cohort 1B (University of Utah will not enroll patients under 18). Enrollment of patients > 70 years of age may be allowed after consultation with the Medical Monitor. Patients must have an Eastern Cooperative Oncology Group (ECOG) performance status of 0 or 1, and an estimated life expectancy of >=6 months in the opinion of the Investigator. 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 (Note: Females of reproductive potential are to use effective contraception during treatment and for 12 months after their last dose of IL-2, or 4 months after their last dose of pembrolizumab, whichever occurs later). Males may not donate sperm during the study or for 12 months after treatment discontinuation, whichever occurs later. 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
* Male condom plus spermicide
* True absolute 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. Patients must have the following hematologic parameters independent of transfusion and/or blood product support for at least 5 days prior to laboratory testing: (as defined in the protocol) Patients must have adequate organ function: (as defined in the protocol) 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. Additional serology testing may be required depending on local prevalence of certain viral exposures. Patients must have a washout period from prior anticancer therapy(ies) of a minimum duration, as detailed below prior to the first study treatment (ie, start of NMA-LD or pembrolizumab):

- Targeted therapy: prior targeted therapy with an epidermal growth factor receptor (EGFR), MEK, BRAF, ALK, ROS1 or other-targeted agents (eg, erlotinib, afatinib, dacomitinib, osimertinib, crizotinib, ceritinib, lorlatinib) is allowed provided the washout is a minimum of 14 days prior to the start of treatment;
- Chemotherapy: adjuvant, neoadjuvant or definitive chemotherapy/chemoradiation is allowed provided the washout is a minimum of 14 days prior to the start of treatment;
- Immunotherapy for Cohorts 1B and 3B only: checkpoint-targeted therapy with an anti-PD-1/anti-PD-L1, other mAbs, or vaccines are allowed with a washout period of \( \geq 21 \) days before the start of NMA-LD.
- Palliative radiation therapy: prior external beam radiation is allowed provided all radiation-related toxicities are resolved to Grade 1 or baseline, excluding alopecia, skin pigmentation change, or other clinically insignificant events, eg, small area radiation dermatitis or rectal or urinary urgency.

The tumor lesion(s) being assessed as target for response via RECIST 1.1 must be outside of the radiation portal or they must have demonstrated radiologic progression (see Inclusion Criterion 5).

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. Patients must have recovered from all prior anticancer treatment-related adverse events (TRAEs) to Grade \( \leq 1 \) (per Common Terminology Criteria for Adverse Events [CTCAE],...
version 4.03 [v4.03]), except for alopecia or vitiligo. Patients with stable Grade >=2 toxicity from prior anticancer therapy may be considered on a case-by-case basis after consultation with the Medical Monitor. Cohorts 1A, 2A, and 3A patients with irreversible toxicity not reasonably expected to be exacerbated by treatment with pembrolizumab may be included only after consultation with the Medical Monitor. For patients in Cohorts 1B and 3B only: patients with documented Grade >=2 or higher diarrhea or colitis as a result of a previous treatment with CPI(s) must have been asymptomatic for at least 6 months or had a normal by visual assessment colonoscopy post-treatment prior to tumor resection. Patients must have provided written authorization for use and disclosure of protected health information. In the opinion of the Investigator, the patient must be able to complete all study required procedures and have the ability to understand the requirements of the study and freely give consent to participate. In the case of legal minors, parental or legal guardian consent is required. Specifically, the patient has to provide written informed consent (as evidenced by signature on an ICF approved by an Institutional Review Board/Independent Ethics Committee [IRB/IEC]) and has to agree to abide by the study restrictions and return to the site for required assessments.

**Exclusion Criteria**

Patients with melanoma of uveal/ocular origin Patients who have received an organ allograft or prior cell transfer therapy that included a nonmyeloablative or myeloablative chemotherapy regimen within the past 20 years. Note: This criterion is applicable for patients undergoing retreatment with TIL LN-144/LN-145-S1, with the exception that they will have had a prior NMA-LD regimen with their prior TIL treatment. Patients with symptomatic and/or untreated brain metastases Patients with definitively treated brain metastases will be considered for enrollment after discussion with Medical Monitor; if, prior to enrollment 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. Patients who are on systemic steroid therapy > 10 mg/day of prednisone or other steroid equivalent. Patients receiving steroids as replacement therapy for adrenocortical insufficiency at <= 10 mg/day of prednisone or other steroid equivalent may be eligible. Patients who are pregnant or breastfeeding Patients who have an active medical illness(es), which in the opinion of the Investigator, would pose increased risks for study participation; such as systemic infections (eg, syphilis or any other infection requiring antibiotics), coagulation disorders, or other
active major medical illnesses of the cardiovascular, respiratory, or immune systems. Patients may not have active or prior documented autoimmune or inflammatory disorders (including pneumonitis, inflammatory bowel disease [eg, colitis or Crohn's disease], diverticulitis [with the exception of diverticulosis], systemic lupus erythematosus, sarcoidosis syndrome, or Wegener syndrome [granulomatosis with polyangiitis, Graves' disease, rheumatoid arthritis, hypophysitis, uveitis, etc.]). The following are exceptions to this criterion: * Patients with vitiligo or alopecia
* Any chronic skin condition that does not require systemic therapy
* Patients with celiac disease controlled by diet alone
* Patients with hypothyroidism (eg, following Hashimoto syndrome) stable on hormone replacement
* Any chronic skin condition that does not require systemic therapy

Patients who have received a live or attenuated vaccination within 28 days prior to the start of treatment. Patients who have any form of primary immunodeficiency (such as severe combined immunodeficiency disease [SCID] and acquired immune deficiency syndrome [AIDS]). Patients with a history of hypersensitivity to any component of the study drugs. LN-144/LN-145/LN-145-S1 should not be administered to patients with a known hypersensitivity to any component of 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 (ie, streptomycin, gentamicin [excluding those who are skin-test negative for gentamicin hypersensitivity])
* Any component of the TIL product formulation including dimethyl sulfoxide [DMSO], HSA, IL-2, and dextran-40
* Pembrolizumab Patients who have a left ventricular ejection fraction (LVEF) = 60 years of age or in patients who have a history of ischemic heart disease, or clinically significant atrial and/or ventricular arrhythmias. Patients with an abnormal cardiac stress test may be enrolled if they have adequate ejection fraction and cardiology clearance with approval of the Sponsor's Medical Monitor. Inadequate Pulmonary Function as defined in the protocol. Patients who have had another primary malignancy within the previous 3 years (except for those which do not require treatment or have been curatively treated greater than 1 year ago, and in the judgment of the Investigator, do not pose a significant risk of recurrence including, but not limited to, non-melanoma skin cancer, DCIS, LCIS, or prostate cancer Gleason score <=6). Participation in another interventional clinical study within 21 days of the initiation of treatment.
This posting is a summary of the basic requirements for participation in this study, and it is not intended to provide all the information needed to decide whether or not to participate.

For additional information on all aspects of cancer, please contact the Huntsman Cancer Institute Information Service at the phone numbers listed below.

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