Phase 1 Trial of LYL845, an Autologous Tumor-Infiltrating Lymphocyte (TIL) Therapy Enhanced With Epigenetic Reprogramming for the Treatment of Advanced Solid Tumors

Abstract 747

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Background

Barriers to effective T-cell therapy in solid tumors

- Loss of tumor-reactive T-cell clonotypes during expansion and low numbers of stem-like T cells are barriers to effective TIL therapy in solid tumors[1,2]

Lyell's T-cell epigenetic reprogramming technology: Epi-R™

- Epi-R manufacturing protocols are designed to generate populations of stem-like T cells with reduced exhaustion and improved proliferation and antitumor activity
- Epi-R manufacturing protocols control T-cell activation and differentiation by optimizing cell culture media and other manufacturing steps (**Figure 1**), resulting in preservation of stem-like qualities[3-6] (**Figure 2**)
- T-cell products manufactured with Epi-R protocols have more durable antitumor activity relative to products generated with existing ex vivo expansion protocols[3,6]

LYL845: A novel TIL product candidate

- LYL845 is an investigational autologous TIL product enhanced with epigenetic reprogramming technology designed to preserve tumor-reactive T-cell clones with durable stemness to overcome barriers to effective TIL therapy in solid tumors
- LYL845 retains T-cell diversity, including >90% of tumor-reactive T-cell clonotypes when expanded from melanoma cells[5]
- LYL845 demonstrates enhanced T-cell function as indicated by increased activation and cytotoxicity[6]

Figure 1: Lyell's Epi-R protocol versus standard TIL expansion

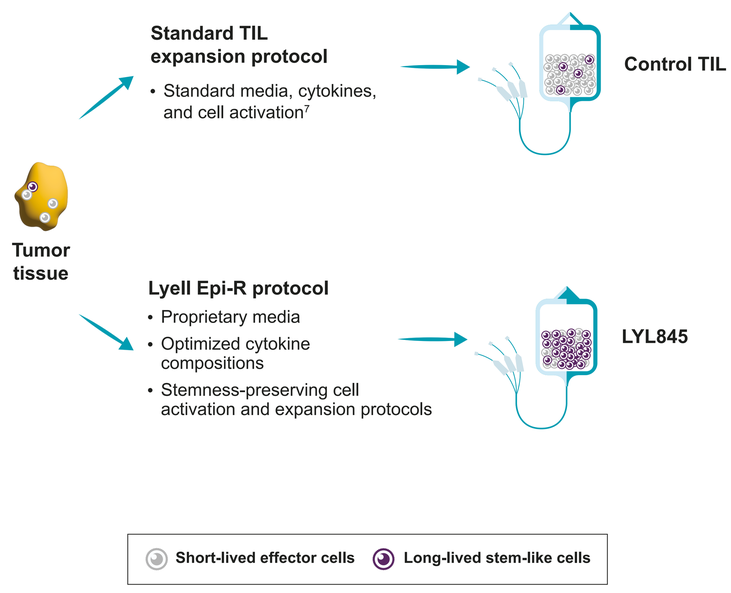
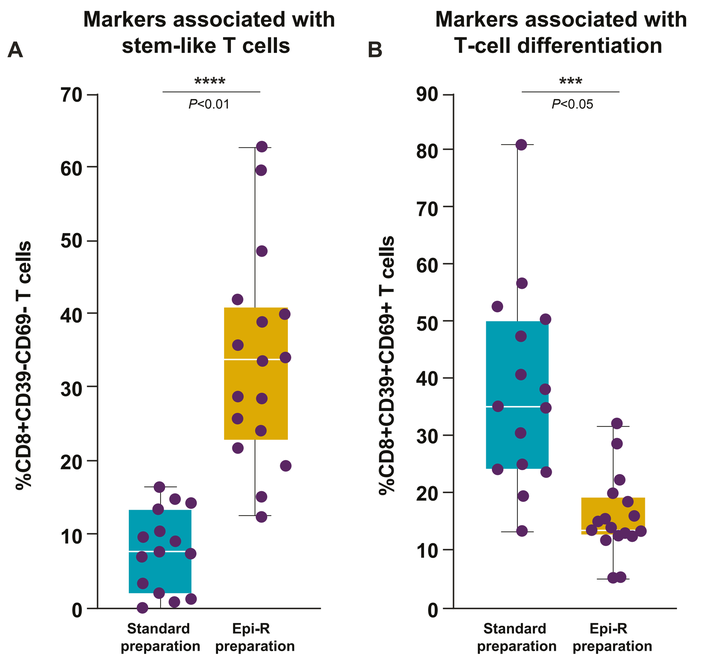


Figure 2: Epi-R produces products with a greater proportion of stem-like cells and a lower proportion of differentiated cells



Objectives

- **LYL845-101** is an open-label, multi-center, dose-escalation study with expansion cohorts designed to evaluate the safety and antitumor activity of LYL845 in participants with R/R metastatic, locally advanced or unresectable melanoma, NSCLC, or CRC (**Figure 3**)

Primary objectives

- Evaluate safety and tolerability
- Determine the RP2DR

Secondary objectives

- Evaluate antitumor activity

Exploratory objectives

- Measurement of tumor mutational burden, clonal diversity of the TIL drug product, and T-cell clonal expansion and persistence in the periphery
- Measurement of the presence of TIL drug product-derived T-cell clones in the tumor post-infusion

LYL845-101 Design: NCT05573035

- Part A (dose escalation) will evaluate two planned dose level ranges of LYL845 using the modified toxicity probability interval-2, with a 28-day dose-limiting toxicity period. Part B (dose expansion) will treat 15 – 30 patients in each disease cohort at the RP2DR determined in Part A (**Figure 3**)
- After TIL tissue collection and LYL845 manufacturing, enrolled patients receive lymphodepleting chemotherapy followed by LYL845 infusion at the assigned dose level. High-dose IV IL-2 is then administered every 8 hours for up to 6 doses as tolerated (**Figure 4**)

Figure 3: Dose-escalation and dose-expansion study design

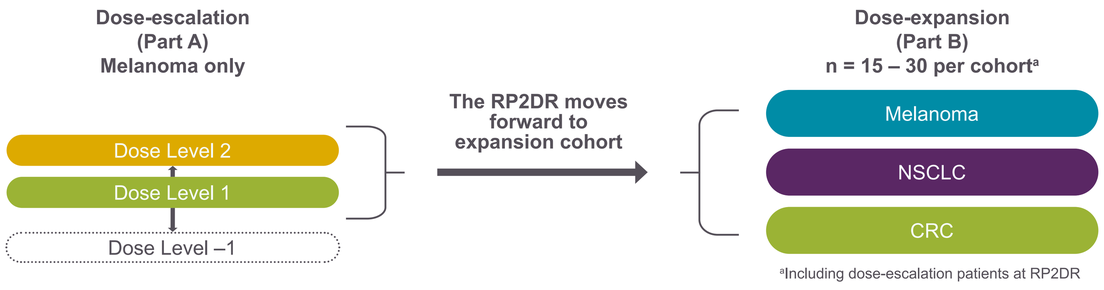
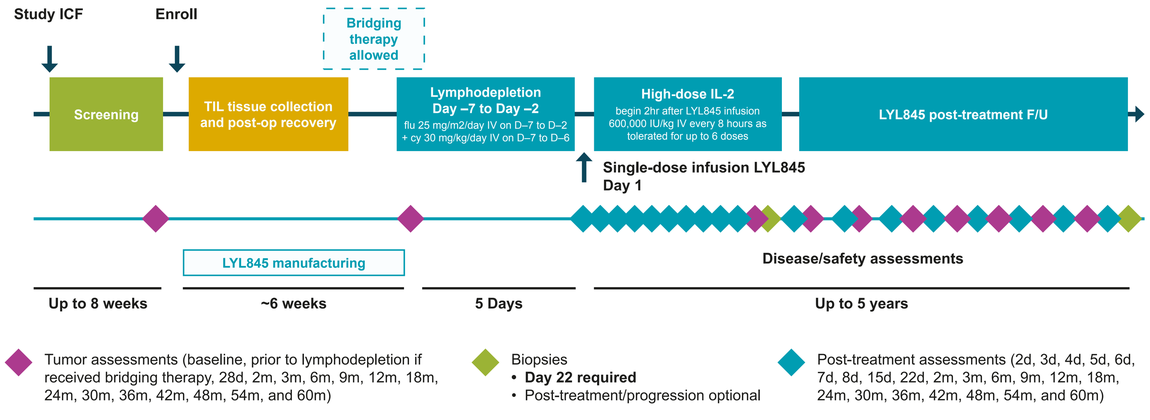


Figure 4: Timeline of screening, treatment, and disease/safety assessments



Key Eligibility Criteria

Key Inclusion Criteria

Disease

- Confirmed diagnosis of R/R metastatic or locally advanced or unresectable melanoma, NSCLC, or CRC
- Measurable disease that includes a target lesion (≥10 mm) or lymph node (≥15 mm), plus one additional lesion ~1.5 x 1.5 cm that is safely resectable
  - Two lesions may be combined to achieve this volume

Subject Health

- ≥18 years of age at time of informed consent
- ECOG PS of 0 – 1
- Adequate organ and marrow function per protocol

Key Exclusion Criteria

Disease

- Active CNS or leptomeningeal disease

Prior Treatment

- No prior solid organ transplant or adoptive cell therapy

Subject Health

- Untreated or active infections at time of screening or TIL tissue collection surgery
- Uncontrolled pleural or pericardial effusion or ascites
- HIV or active acute or chronic HBV or HCV
- Other malignancy within 3 years prior unless treated with expected curative outcome
- Significant cardiovascular disease
- Required chronic anticoagulation (stable regimen may be allowed)
- Pregnant or lactating women

Participating Sites

Participating study locations

- UCLA Medical Center, Los Angeles, CA
- Yale School of Medicine, Smilow Cancer Hospital, New Haven, CT
- Georgetown University, Washington, DC
- Massachusetts General Hospital, Boston, MA
- Rutgers Cancer Institute of New Jersey, New Brunswick, NJ
- Hackensack Meridian Health, Inc., Hackensack, NJ
- Duke University Medical Center, Durham, NC
- The Ohio State University Medical Center, Columbus, OH
- Oregon Health Sciences University, Portland, OR
- Allegheny General Hospital, Pittsburgh, PA
- Huntsman Cancer Institute, Salt Lake City, UT
- Fred Hutchinson Cancer Center, Seattle, WA

Abbreviations

CD, cluster of differentiation; CNS, central nervous system; CRC, colorectal cancer; cy, cyclophosphamide; d, days; ECOG PS, Eastern Cooperative Oncology Group performance status; F/U, follow up; flu, fludarabine; HBV, hepatitis B virus; HCV, hepatitis C virus; HIV, human immunodeficiency virus; ICF, informed consent form; IL-2, interleukin-2; IV, intravenous; m, months; n, number of patients; NSCLC, non-small cell lung cancer; RP2DR, recommended phase 2 dose range; R/R, relapsed/refractory; TIL, tumor-infiltrating lymphocyte.

References

1. Krishna S, et al. *Science.* 2020;370(6522):1328–1334. **2.** Rosenberg SA, et al. *Clin Cancer Res.* 2011;17(13):4550–4557. **3.** Patel Y, et al. Poster presented at the 37th SITC Annual Meeting 2022, November 8–12, 2022. Abstract 370. **4.** Park S, et al. Poster presented at the AACR Annual Meeting 2022, April 8–13, 2022. Abstract 2754. **5.** Harris BD, et al. Poster presented at the 37th SITC Annual Meeting 2022, November 8–12, 2022. Abstract 340. **6.** Patel Y, et al. Poster presented at the AACR Special Conference: Tumor Immunology and Immunotherapy 2022, October 21–24, 2022. Abstract A54. **7.** Dudley ME, et al. *J Immunother.* 2003;26(4):332–342.

Acknowledgments

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