Phase 1 Trial of LYL797, a ROR1-Targeted CAR T-Cell Therapy Enhanced With Genetic and Epigenetic Reprogramming, in Advanced Triple-Negative Breast Cancer (TNBC) and Non-Small Cell Lung Cancer (NSCLC)

Abstract 754

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Background

Targeting ROR1 in solid tumors

- Receptor tyrosine kinase-like orphan receptor (ROR1) is a cell surface antigen expressed during embryogenesis that is involved in cell migration, proliferation, and resistance to apoptosis[1]
- While not expressed in most postpartum tissues[1], ROR1 is highly expressed in multiple solid tumors, including approximately 60% of TNBC[2] and 40% of NSCLC[3] tumors (**Figure 1**) and is, therefore, an attractive target in patients with limited effective treatment options[4,5]
- High ROR1 expression has been associated with poor prognosis and metastasis in solid tumors[1]

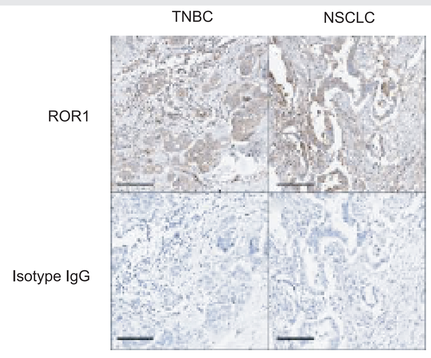
LYL797: A novel approach to CAR T-cell therapy

- CAR T-cell therapy has been successful for the treatment of hematologic malignancies but remains challenging for solid tumors due to T-cell exhaustion and lack of durable stemness, key barriers to effective T-cell therapy in solid tumors[5,6]
- LYL797 is an investigational, autologous ROR1-targeted CAR T-cell product enhanced with epigenetic (Epi-R) and genetic (c-Jun overexpression) reprogramming technologies designed to create more potent and durable T cells to overcome barriers to effective cell therapy in solid tumors (**Figures 2 – 4**)

Lyell's T-cell reprogramming technologies: Epi-R and c-Jun overexpression

- Epi-R manufacturing protocols are designed to generate populations of stem-like T cells with reduced exhaustion and improved proliferation and antitumor activity (**Figure 3**)
- Reprogramming T cells through c-Jun overexpression delays exhaustion and results in increased proliferation, sustained cytokine production, and durable antitumor activity in nonclinical models[6–8] (**Figure 4**)
- In nonclinical models, the combined use of Epi-R protocols and c-Jun overexpression further improved CAR T-cell expansion and cytotoxicity, as well as antitumor activity compared with conventional CAR T-cell preparations[6,8]

Figure 1: ROR1 expression in TNBC and NSCLC[6]



Representative images of IHC staining are shown for ROR1-positive TNBC (BR1301: US Biomax, Biomax, Inc.) and NSCLC (LC2801; US Biomax, Inc.). Scale bar: 100 µm.

Figure 2: LYL797, ROR1-targeted CAR T Cell

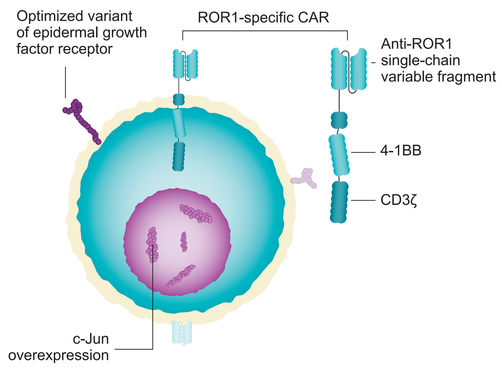


Figure 3: Lyell's Epi-R protocol versus standard expansion

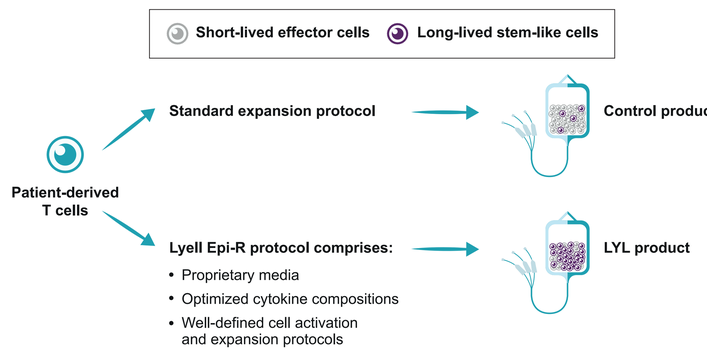
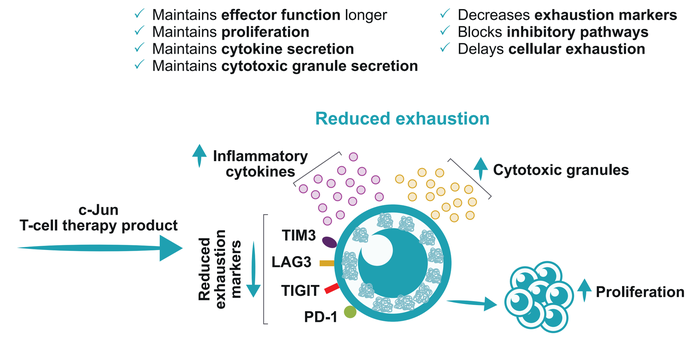


Figure 4: Effects of c-Jun overexpression on T-cell activity



Objectives

- **LYL797-101** is a phase 1, single-arm, open-label, multi-center, dose-escalation and -expansion study that will evaluate the safety and efficacy of LYL797 in adults with relapsed and/or refractory ROR1-positive TNBC or NSCLC

Primary objectives

- Evaluate safety and tolerability
- Determine the RP2D

Secondary objectives

- Evaluate anti-tumor activity
- Evaluate pharmacokinetics

Exploratory objectives

- Evaluate the effects of c-Jun overexpression and Epi-R protocols on T-cell phenotype and activity
- Evaluate the relationship between ROR1 expression and LYL797 activity

Key Eligibility Criteria

- Locally advanced or metastatic ROR1-positive (centrally determined) TNBC or NSCLC
- Measurable disease by RECIST v1.1, including a target lesion and an additional lesion for biopsy
- Prior therapies:
  - TNBC: at least two prior lines of systemic therapy; participants with PD-L1-positive disease must have progressed on an anti-PD-1 antibody therapy
  - NSCLC: at least one prior line of systemic therapy, including a checkpoint inhibitor and targeted therapy if applicable
- ECOG PS of 0 or 1
- Life expectancy of 3 months or greater
- Participants with active, untreated brain metastases or leptomeningeal disease are excluded; however, participants with successfully treated brain metastases are allowed if stable after completion of therapy for at least 3 months
- No prior ROR1-targeted therapies

LYL797-101 Design: NCT05274451

- The dose-escalation phase includes participants with TNBC and NSCLC and will investigate four dose levels to determine the RP2D using a modified toxicity probability interval 2 design with a 28-day dose-limiting toxicity period. In the dose-expansion phase, 15 – 30 participants will be enrolled in each of the TNBC and NSCLC cohorts at the RP2D (**Figure 5**)
- Enrolled participants will undergo leukapheresis for LYL797 manufacturing, during which bridging anti-cancer therapy is allowed for disease control. Participants will then receive lymphodepleting chemotherapy followed by LYL797 infusion at the assigned dose level (**Figure 6**)

Figure 5: Dose-escalation and dose-expansion study design

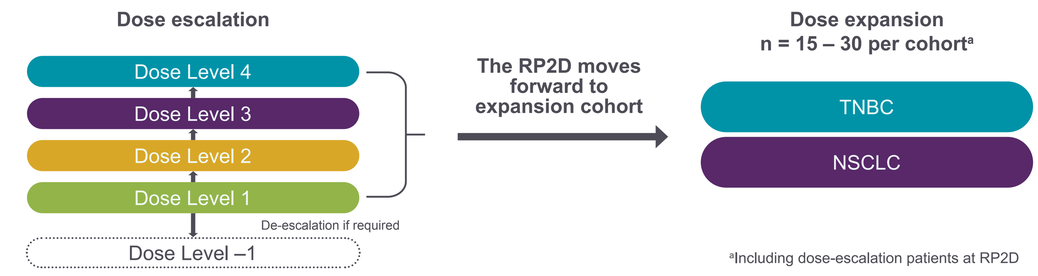
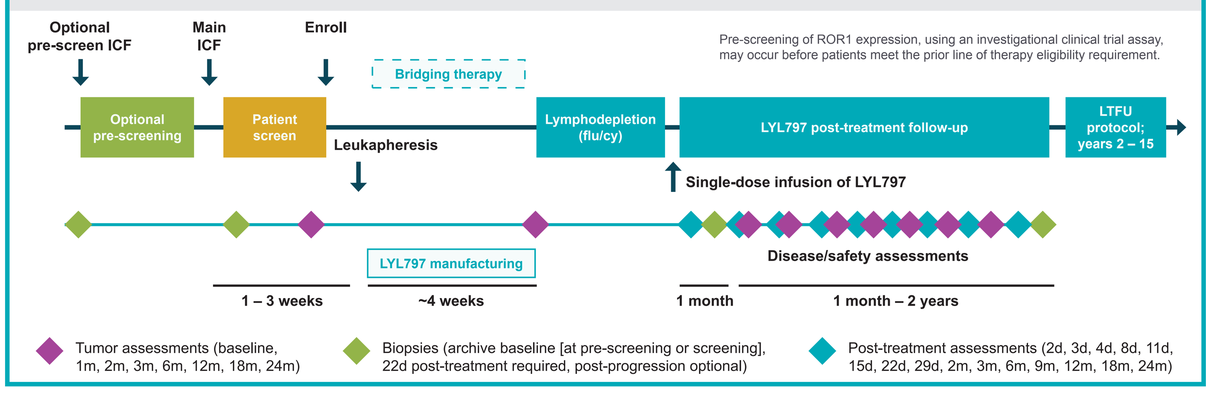


Figure 6: Timeline of screening, treatment, and disease/safety assessments



Participating Sites

Participating study locations

- Mayo Clinic, Phoenix, AZ
- University of California, Los Angeles, Los Angeles, CA
- Yale New Haven Hospital, New Haven, CT
- Georgetown University, Washington, DC
- Mayo Clinic, Jacksonville, FL
- University of Miami, Coral Gables, FL
- Karmanos Cancer Institute, Detroit, MI
- Mayo Clinic, Rochester, MN
- Memorial Sloan Kettering Cancer Center, New York, NY
- Montefiore Medical Center, Bronx, NY
- Oregon Health and Science University Hospital, Portland, OR
- Thomas Jefferson University Hospital, Philadelphia, PA
- Sarah Cannon Research Institute and Tennessee Oncology, Nashville, TN
- MD Anderson Cancer Center, Houston, TX
- Fred Hutchinson Cancer Research Center, Seattle, WA
- Medical College of Wisconsin, Milwaukee, WI

Abbreviations

CAR, chimeric antigen receptor; CD, cluster of differentiation; d, days; ECOG PS, Eastern Cooperative Oncology Group performance status; flu/cy, fludarabine/cyclophosphamide; ICF, informed consent form; IgG, immunoglobulin G; IHC, immunohistochemistry; LAG3, lymphocyte activation gene-3; LTFU, long-term follow up; m, months; n, number of patients; NSCLC, non-small cell lung cancer; PD-1, programmed cell death 1; PD-L1, programmed cell death ligand 1; RECIST, Response Evaluation Criteria In Solid Tumors; ROR1, receptor tyrosine kinase-like orphan receptor; RP2D, recommended phase 2 dose; TIGIT, T cell immunoreceptor with immunoglobulin and ITIM domain; TIM3, T-cell immunoglobulin and mucin domain 3; TNBC, triple-negative breast cancer.

References

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