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

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.4
- While not expressed in most postpartum tissues, ROR1 is highly expressed in multiple solid tumors, including approximately 65% of TNBC and 46% of NSCLC5 (Figure 1), and is, therefore, an attractive target in patients with limited effective treatment options.6
- High ROR1 expression has been associated with poor prognosis and metastasis in solid tumors.7

LYL797: A novel approach to CAR T-cell therapy

- In the dose-escalation phase, participants with TNBC and NSCLC will investigate four dose levels to determine the RP2D (Figure 3).
- De-escalation if required

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 (TPI) design with a 28-day dose-limiting toxic period. In the dose-escalation phases, 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)
- Pre-screening of ROR1 expression, using an investigational clinical trial assay, is a requirement to enroll participants in the dose-escalation study.
- 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

Objectives

- LY797-101 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

Explanatory 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

Participating Sites

- Mayo Clinic, Phoenix, AZ
- University of California, Los Angeles, CA
- Yake New Haven Hospital, New Haven, CT
- Georgetown University, Washington, DC
- Mayo Clinic, Jacksonville, FL
- University of Miami, Coral Gables, FL
- Kermans 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
- University of Miami, Coral Gables, FL
- Thomas Jefferson University Hospital, Philadelphia, PA
- MD Anderson Cancer Center, Houston, TX
- Disneyland Cancer Research Center, Seattle, WA
- Saint Francis Medical Center, Milwaukee, WI
- Medical College of Wisconsin, Milwaukee, WI

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

References


Acknowledgments

We would like to thank the patients, their families, and their caregivers for participation in this study as well as the study site staff for their contributions. Medical writing and editorial support were funded by Lyell Immunopharma and provided by Madison Fagan, PhD of BOLDSCIENCE, Inc.

Presented at SITC Annual Meeting 2023; Nov 1 – 5; San Diego, CA, USA

LYL797 manufacturing

Patient receives lymphodepleting chemotherapy

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

Pre-screening

Figure 5: Timeline of screening, treatment, and disease/safety assessments

Figure 3: LYL797’s anti-tumor activity

Figure 2: LYL797, ROR1-targeted CAR T Cell

Figure 1: ROR1 expression in TNBC and NSCLC

Dose expansion

Long-lived stem-like cells

Disease/safety assessments

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