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Phase 1 Study of LYL797, a ROR1-Targeted CAR T-Cell Therapy With Genetic and Epigenetic Reprogramming for the Treatment of Advanced Solid Tumors

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Background

LYL797: A novel approach to CAR T-cell therapy

- Chimeric antigen receptor (CAR) T-cell therapy has revolutionized the treatment of B-cell malignancies, but efficacy in solid tumors is lacking due to barriers such as T-cell exhaustion and lack of durable stemness[1,2]
- We have developed ex vivo genetic and epigenetic T-cell reprogramming technologies to address these barriers: Gen-R™ technology to overcome exhaustion and Epi-R™ technology to improve stemness
- LYL797 is an autologous ROR1-targeted CAR T-cell product incorporating Gen-R and Epi-R technologies in development to treat relapsed and/or refractory ROR1+ triple-negative breast cancer (TNBC) and non-small cell lung cancer (NSCLC)
- Preclinical studies in ROR1+ TNBC and NSCLC tumor models demonstrate improved functional activity compared to ROR1-targeted CAR T cells without Gen-R and Epi-R technologies[3-5]

Targeting ROR1 in solid tumors

- ROR1 is a cell-surface antigen expressed in several solid tumor types and is an attractive target for novel therapies, including adoptive cell therapy (ACT) (**Figure 1**)
  - Expressed in approximately 60% of TNBCs and 40% of lung adenocarcinomas[6]

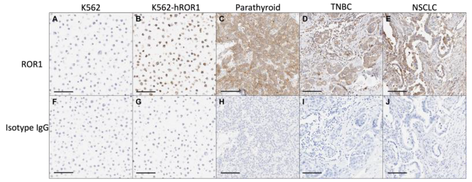
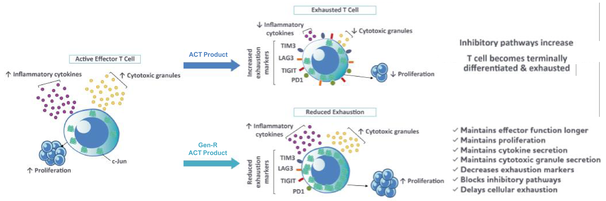


Figure 1: ROR1 cell-surface expression by immunohistochemistry in normal tissues and solid tumors. Anti-ROR1 IHC assay and ROR1 staining in TNBC and in NSCLC samples. Representative images of IHC staining are shown for K562 cells (ROR1-negative control) (A), K562 cells transduced to express human ROR1 (hROR1) (B), and normal parathyroid gland (C) that endogenously expresses ROR1, as assay controls. Representative images of ROR1-positive TNBC sample (D) (BR1301; U.S. Biomax. Inc.) and NSCLC sample (E) (LC2081; U.S. Biomax Inc.) are shown. (F–J): IHC staining with isotype-matched control. Scale bar: 100 µm.

Gen-R technology: Ex vivo genetic reprogramming to overcome exhaustion

- Exhausted T cells exhibit dysregulation of AP-1 complexes that can be countered by overexpression of the AP-1 family transcription factor c-Jun[2]
- Gen-R technology results in the overexpression of c-Jun in T cells and rebalances AP-1 complexes in favor of activation and away from exhaustion pathways
- This promotes maintenance of T-cell activation, proliferation, cytokine production, and cytotoxic activity in the exhausted T cell (**Figure 2**)

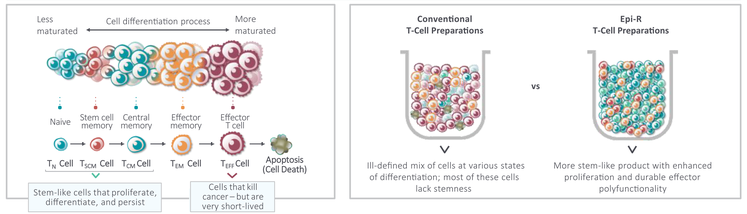
Figure 2: Effects of c-Jun overexpression via Gen-R technology on T-cell activity



Epi-R technology: Ex vivo epigenetic reprogramming to improve stemness

- Conventional ACTs consist of an ill-defined mix of cells at various states of differentiation; higher proportions of stem-like T cells are associated with improved anti-tumor efficacy[1]
- Epi-R technology is an optimized manufacturing process that is designed to reproducibly generate populations of T cells with properties of durable stemness that can proliferate, persist, and provide prolonged anti-tumor functionality (**Figure 3**)

Figure 3: Composition of conventional T-cell preparations vs Epi-R T-cell preparations



Objective

LYL797-101 is a Phase 1, first-in-human, multicenter, single-arm, open-label, dose-escalation and dose-expansion study designed to evaluate the safety, pharmacokinetics (PK), and anti-tumor activity of LYL797 in ROR1+ TNBC and NSCLC. The trial is currently open and recruiting.

Primary objectives

- Evaluate safety and tolerability
- Determine the recommended Phase 2 dose (RP2D)

Secondary objectives

- Evaluate anti-tumor activity
- Evaluate PK

Exploratory objectives

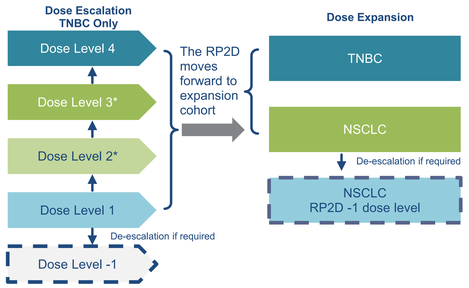
- Evaluate effects of Gen-R and Epi-R technologies on T-cell phenotype and activity
- Evaluate relationship between ROR1 expression and LYL797 activity

Study Design

Overview

- Up to 54 patients with locally advanced or metastatic, unresectable ROR1+ TNBC or NSCLC will be enrolled in dose-escalation or dose-expansion cohorts (**Figure 4**)
- The dose-escalation phase has 4 planned dose levels and will enroll TNBC patients using an mTPI-2 design with a 28-day dose-limiting toxicity (DLT) monitoring period
- Dose escalation will continue until an RP2D is determined
- Dose expansion is designed to enroll 15 patients with TNBC and 15 patients with NSCLC at the RP2D
- The study schema shown here is current as of September 1, 2022. Please use the QR code at the top of the poster to visit https://clinicaltrials.gov/ct2/show/NCT05274451 to access the most up-to-date trial information

Figure 4: Dose-escalation and dose-expansion study design

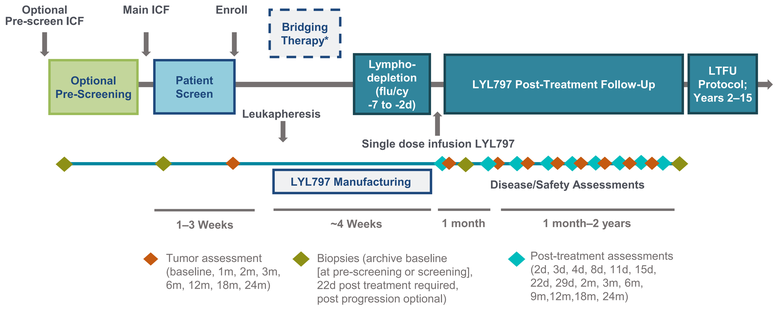


*Intermediate doses will be tested if safety data suggest the higher dose level is not safe or if the Safety Monitoring Committee and/or Sponsor recommend evaluating intermediate dose prior to further escalation.

Screening and assessments

- After leukapheresis and manufacturing, patients receive lymphodepleting chemotherapy (fludarabine and cyclophosphamide) followed by LYL797 infusion at the protocol-assigned dose level. An overview of screening and assessments is shown in **Figure 5**

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



*Bridging therapy for disease control is permitted at the discretion of the treating physician.

Patients

- Key inclusion and exclusion criteria as of September 1, 2022, are listed in **Table 1**
- Please use the QR code above to visit https://clinicaltrials.gov/ct2/show/NCT05274451 to access the most up-to-date trial information

Table 1. Key inclusion and exclusion criteria

Disease	*Prior treatment*	*Age and health status*
Inclusion criteria • Locally advanced or metastatic, unresectable, histologically confirmed TNBC (escalation, expansion) or NSCLC (expansion only) • ROR1+ per central laboratory IHC* • Measurable disease that includes a target lesion plus 1 additional lesion for biopsy (unless target lesion ≥30 mm) not exposed to prior local RT	**Inclusion criteria** • Relapsed/refractory TNBC after receiving ≥2 prior lines of therapy (including prior taxane and prior anti–PD-1, if applicable) • Relapsed/refractory NSCLC after receiving ≥2 prior systemic therapies (including checkpoint inhibitors and FDA-approved targeted therapy for molecular aberrations, if applicable)	**Inclusion criteria** • ≥18 years of age at time of informed consent† • ECOG PS 0–1 with life expectancy of >3 months • Adequate organ and marrow function per protocol
Exclusion criteria • Active CNS or leptomeningeal disease (previously treated brain metastases, if stable, are allowed)	**Exclusion criteria** • No prior solid organ transplant, adoptive T cell, or anti-ROR1 therapy	**Exclusion criteria** • Untreated or active infections at time of screening or leukapheresis • Uncontrolled pleural or pericardial effusion, or ascites • HIV, HTLV-1, active acute/chronic HBV or HCV, active TB • Other malignancy within 3 years prior, unless treated with expected curative outcome • Significant cardiovascular disease • Required chronic anticoagulation • Pregnant or lactating individuals • Inability to provide a 24-hour caregiver during the infusion and for the 4-week post-treatment monitoring phase • Inability to stay within a 2-hour driving radius of the treating facility for at least 4 weeks following treatment for timely and appropriate management of any AEs, should they occur

*ROR1 expression will be confirmed via IHC performed by central study lab on an archival tumor biopsy sample collected within 3 years of screening.
†Individuals of childbearing potential or partners of individuals of childbearing potential must agree to effective methods of contraception from screening through 12 months post treatment.

Endpoints

Primary endpoints

- Incidence of DLTs
- Incidence and severity of TEAEs

Secondary endpoints

- ORR and CR rates by RECIST v1.1
- DOR, PFS, and OS
- LYL797 PK parameters (C_{max}, T_{max}, AUC, and T_{last} of LYL797 in the PB)

Exploratory endpoints

- Memory, activation, and exhaustion status of LYL797 CAR T cells in the blood and in the infusion product based on phenotypic and gene expression analyses
- Ex vivo functional activity of LYL797 CAR T cells before and after LYL797 infusion
- Correlation of tumor-specific ROR1 expression with clinical activity
- Tumor infiltration of LYL797 based on in situ hybridization
- Tumor-specific expression of ROR1 and markers associated with immune activation and/or resistance before and after treatment with LYL797

Abbreviations

ACT, adoptive cell therapy; AE, adverse event; AP-1, activator protein 1; AUC, area under the concentration-time curve; CAR, chimeric antigen receptor; C_{max}, maximum concentration; CNS, central nervous system; CR, complete response; d, days; DLT, dose-limiting toxicity; DOR, duration of response; ECOG PS, Eastern Cooperative Oncology Group performance status; flu/cy, fludarabine and cyclophosphamide; HBV, hepatitis B virus; HCV, hepatitis C virus; HIV, human immunodeficiency virus; HTLV-1, human T-lymphotropic virus 1; ICF, informed consent form; IgG, immunoglobulin G; IHC, immunohistochemistry; LAG3, lymphocyte activation gene 3; LTFU, long-term follow-up; m, months; mTPI-2, modified toxicity probability interval 2; NSCLC, non-small cell lung cancer; ORR, overall response rate; OS, overall survival; PB, peripheral blood; PD-1, programmed cell death protein 1; PFS, progression-free survival; PK, pharmacokinetics; RECIST v1.1, Response Evaluation Criteria in Solid Tumors, version 1.1; ROR1, receptor tyrosine kinase-like orphan receptor-1; RP2D, recommended phase 2 dose; RT, radiation therapy; TB, tuberculosis; TEAE, treatment-emergent adverse event; TIGIT, T-cell immunoreceptor with immunoglobulin and ITIM domains; TIM3, T-cell immunoglobulin and mucin domain-containing protein 3; T_{last}, time to last detectable; T_{max}, time to C_{max}, TNBC, triple-negative breast cancer.

References

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Disclosures

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Supplementary Materials

Please scan the Quick Response (QR) code at the top of the poster to access the latest trial information at ClinicalTrials.gov (https://clinicaltrials.gov/ct2/show/NCT05274451).

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