UNITED STATES
SECURITIES AND EXCHANGE COMMISSION
WASHINGTON, D.C. 20549

FORM 8-K

CURRENT REPORT
Pursuant to Section 13 or 15(d)
of the Securities Exchange Act of 1934

Date of Report (Date of earliest event reported): June 26, 2024

Lyell Immunopharma, Inc.
(Exact name of Registrant as Specified in Its Charter)

Delaware	**001-40502**	**83-1300510**
(State or Other Jurisdiction of Incorporation)	**(Commission File Number)**	**(IRS Employer Identification No.)**

201 Haskins Way **South San Francisco, California** **(Address of Principal Executive Offices)**	**94080** **(Zip Code)**

Registrant's Telephone Number, Including Area Code: 650 695-0677

(Former Name or Former Address, if Changed Since Last Report)

Not Applicable

Check the appropriate box below if the Form 8-K filing is intended to simultaneously satisfy the filing obligation of the registrant under any of the following provisions:

☐ Written communications pursuant to Rule 425 under the Securities Act (17 CFR 230.425)

☐ Soliciting material pursuant to Rule 14a-12 under the Exchange Act (17 CFR 240.14a-12)

☐ Pre-commencement communications pursuant to Rule 14d-2(b) under the Exchange Act (17 CFR 240.14d-2(b))

☐ Pre-commencement communications pursuant to Rule 13e-4(c) under the Exchange Act (17 CFR 240.13e-4(c))

Securities registered pursuant to Section 12(b) of the Act:

Title of each class	Trading Symbol(s)	Name of each exchange on which registered
Common Stock, $0.0001 par value per share	LYEL	The Nasdaq Global Select Market

Indicate by check mark whether the registrant is an emerging growth company as defined in Rule 405 of the Securities Act of 1933 (§ 230.405 of this chapter) or Rule 12b-2 of the Securities Exchange Act of 1934 (§ 240.12b-2 of this chapter).

Emerging growth company ☐

If an emerging growth company, indicate by check mark if the registrant has elected not to use the extended transition period for complying with any new or revised financial accounting standards provided pursuant to Section 13(a) of the Exchange Act. ☐

Item 7.01. Regulation FD Disclosure.

On June 26, 2024, Lyell Immunopharma, Inc. issued a press release (the "LYL797 Phase 1 Press Release") to report initial clinical and translational data from its Phase 1 clinical trial of LYL797, its intravenously-administered chimeric antigen receptor ("CAR") T-cell product targeting the receptor tyrosine kinase-like orphan receptor 1 ("ROR1") protein. A copy of the LYL797 Phase 1 Press Release is furnished hereby as Exhibit 99.1 and is incorporated herein by reference.

Item 8.01. Other Events.

On June 26, 2024, Lyell announced initial clinical and translational data from its Phase 1 trial of LYL797, a ROR1 CAR T-cell product candidate enhanced with Lyell's proprietary anti-exhaustion technology, for the treatment of advanced solid tumors. These initial data from 20 treated patients included 16 patients with triple-negative breast cancer ("TNBC") and 4 patients with non-small cell lung cancer. All patients enrolled had relapsed/refractory metastatic disease and the mean lines of prior therapies for metastatic disease was six. Four dose levels, including two interim dose levels, have been explored to date: 50 x 10^6 cells, 100 x 10^6 cells, 150 x 10^6 cells and 300 x 10^6 cells. There were 16 efficacy evaluable patients, and 18 safety evaluable patients included in the initial data set. Patients with TNBC treated with LYL797 had an objective response rate ("ORR") of 40% and a clinical benefit rate ("CBR") of 60% at the 150 x 10^6 CAR T cell dose level, the highest dose level cleared to-date, with a CBR of 38% across all dose levels evaluable to date. The most frequently reported related adverse events of any grade included cytokine release syndrome (61%, Grade 1 and 2), pneumonitis (22%), headache (17%), and cytopenia from lymphodepletion. The most frequently reported Grade $\geq$ 3 related adverse events were pneumonitis (17%) and hypoxia (11%), as well as the expected cytopenia from lymphodepletion in 78% of patients. One patient had Grade 5 respiratory failure on Day 41. There were no reports of immune effector cell-associated neurotoxicity syndrome ("ICANS") attributed to LYL797. The instances of pneumonitis occurred in patients with lung metastases, and Lyell is continuing dose escalation separately and more gradually in those patients. No dose-limiting toxicities have been reported in patients without lung involvement. All patients are now receiving prophylactic steroids prior to LYL797 treatment. Translational data from a subset of patients demonstrated that CAR T cells enhanced with anti-exhaustion technology expanded, infiltrated and persisted into solid tumors, in some cases with associated evidence of tumor killing. LYL797 CAR T-cell expansion was observed in peripheral blood samples at Day 60 in all patients assessed to date (n = 11), with peak expansion occurring between Days 8 and 11. Median peak expansion was about three-fold higher in patients receiving 150 x 10^6 cells compared to those receiving 50 x 10^6 cells. The exhaustion marker, TIGIT, was found in a low proportion of LYL797 CAR T cells at Day 11 (n = 4), providing support for the role of c-Jun overexpression as an anti-exhaustion technology. A significant proportion of cells with stem-like and effector memory phenotypes were demonstrated at Days 11 and 22 following RNAseq transcriptomic analysis supporting the role of Epi-R to preserve a stem-like phenotype. LYL797 CAR T cells were present in all evaluable solid-tumor biopsies (n = 9). An additional sample collected confirmed CAR T cell persistence more than four months post treatment. Collectively, these initial data indicate that LYL797 CAR T cells enhanced with Lyell's anti-exhaustion technology were able to infiltrate and persist in the solid tumor microenvironment.

A copy of the presentation related to the LYL797 Phase 1 clinical trial is posted on the Company's website and is filed herewith as Exhibit 99.2 to this Current Report on Form 8-K and is incorporated by reference herein.

Item 9.01. Financial Statements and Exhibits.

(d) Exhibits.

Exhibit No	
99.1	Press Release, dated June 26, 2024, titled "Lyell Immunopharma Reports Dose-dependent Clinical Activity from Phase 1 Trial of LYL797, a ROR1-targeted CAR-T Cell Product Candidate Enhanced with its Proprietary Anti-exhaustion Technology."
99.2	Lyell Immunopharma, Inc. Presentation dated June 2024
104.1	Cover Page Interactive Data File, formatted in inline XBRL.

SIGNATURES

Pursuant to the requirements of the Securities Exchange Act of 1934, the registrant has duly caused this report to be signed on its behalf by the undersigned thereunto duly authorized.

Lyell Immunopharma, Inc.

Date: June 26, 2024

By: /s/ Matthew Lang
Matthew Lang
Chief Business Officer

Lyell Immunopharma Reports Dose-dependent Clinical Activity from Phase 1 Trial of LYL797, a ROR1-targeted CAR-T Cell Product Candidate Enhanced with its Proprietary Anti-exhaustion Technology

- Dose-dependent antitumor clinical activity in ROR1+ relapsed/refractory triple-negative breast cancer; 40% objective response rate and 60% clinical benefit rate at the highest dose cleared to date (150 x 10^6 CAR T cells)
- First demonstration that CAR T cells enhanced with anti-exhaustion technology can both expand and infiltrate into solid tumors
- No significant safety signal related to LYL797 observed in patients without lung involvement; treatable pneumonitis observed in patients with lung metastatic disease; dose escalation continues in separate cohorts
- Expanding development into new tumor types including ROR1+ relapsed/refractory platinum-resistant ovarian cancer, endometrial cancer, multiple myeloma and chronic lymphocytic leukemia
- IND submission completed for LYL119, Lyell's next generation ROR1-targeted CAR T cell product candidate
- Investor Webcast with David R. Spigel, MD, Chief Scientific Officer at the Sarah Cannon Research Institute and a lead investigator in the Phase 1 clinical trial, scheduled for 8:30 am ET today

SOUTH SAN FRANCISCO, Calif., June 26, 2024 — Lyell Immunopharma, Inc. (Nasdaq: LYEL), a clinical-stage T-cell reprogramming company advancing a diverse pipeline of cell therapies for patients with solid tumors, today announced initial clinical and translational data from its Phase 1 trial of LYL797, its first-generation reprogrammed ROR1 CAR T-cell product candidate enhanced with proprietary anti-exhaustion technology. The initial dataset consists primarily of patients with triple-negative breast cancer (TNBC) and demonstrated dose-dependent antitumor clinical activity and the ability of LYL797 CAR T cells to proliferate, infiltrate tumors and kill cancer cells in patients with relapsed/refractory disease. Patients with TNBC treated with LYL797 had an objective response rate (ORR) of 40% and clinical benefit rate (CBR) of 60% at the 150 x 10^6 CAR T cell dose level, with a CBR of 38% across all dose levels evaluable to date. Common treatment-related adverse events in patients without lung metastases included Grade 1 and 2 cytokine release syndrome (CRS) and headache, and the expected cytopenia from lymphodepletion. There were no reports of immune effector cell-associated neurotoxicity syndrome (ICANS) attributed to LYL797. Pneumonitis occurred in patients with lung metastases and dose escalation is continuing separately and more gradually in those patients. No dose-limiting toxicities have been reported in patients without lung involvement. All patients are now receiving prophylactic steroids prior to LYL797 treatment.

“These are promising initial clinical findings demonstrating that LYL797 ROR-1-targeted CAR T cells had dose-dependent antitumor clinical activity and have the potential to deliver even more meaningful and durable benefit to patients as we continue to dose escalate,” said David R. Spigel, MD, Chief Scientific Officer at the Sarah Cannon Research Institute, medical oncologist and a lead investigator in the LYL797 study. “Pneumonitis is a known complication of radiotherapy and several approved cancer therapies, including immune checkpoint blockade and several antibody-drug conjugate therapies. We have implemented a protocol using steroids, the standard of care for treatment of patients with pneumonitis, that I believe will enable us to successfully monitor and manage these events.”

The LYL797 study includes a robust translational program from which Lyell reports the first demonstration that CAR T cells enhanced with anti-exhaustion technology expanded, persisted and infiltrated into solid tumors, in some cases with associated evidence of cancer cell killing. TIGIT, a marker of T cell exhaustion, was measured in samples collected on Day 11 post-infusion with only a low proportion of LYL797 CAR T cells demonstrated to be TIGIT-positive. RNAseq data also suggested a significant proportion maintained the targeted stem-like and effector memory cell phenotype.

“We are encouraged to see clinical responses and a clear dose-dependent indication of antitumor clinical activity from treatment with LYL797 in patients with advanced triple-negative breast cancer,” said Lynn Seely, MD, President and Chief Executive Officer of Lyell. “Our translational data provide, to our knowledge, the first demonstration of persistent CAR T cell infiltration into solid tumors associated with evidence of cancer cell killing. This early validation of our anti-exhaustion technology gives us the conviction to expand our trial to include patients with ROR1+ ovarian or endometrial cancers, while continuing to enroll patients with triple-negative breast or non-small lung cancers, and also to initiate a new clinical trial for patients with multiple myeloma and chronic lymphocytic leukemia. This compelling early clinical data from LYL797 gives us a high degree of confidence to advance LYL119, our next generation ROR1-targeted product candidate with even more powerful anti-exhaustion technology. We have submitted an IND for LYL119 and expect to enter the clinic this year.”

Initial LYL797 Phase 1 Clinical Trial Results

This initial dataset of 20 treated patients includes 16 patients with TNBC and four patients with non-small cell lung cancer. All patients enrolled had relapsed/refractory metastatic disease and the mean lines of prior therapies for metastatic disease was six. Four dose levels, including two interim dose levels, have been explored to date: 50 x 10^6 cells, 100 x 10^6 cells, 150 x 10^6 cells and 300 x 10^6 cells. The efficacy evaluable subset includes 16 patients, and the safety evaluable subset includes 18 patients. The manufacturing success rate was 100%.

Of the five patients with TNBC treated with LYL797 at the 150 x 10^6 cell dose level, the highest dose level cleared to date, two patients had confirmed partial responses to Day 90, resulting in an ORR of 40%. The CBR, defined as a best response of stable disease, partial response or complete response, was dose-dependent with 60% at the 150 x 10^6 cell dose level and 38% across all four dose levels evaluated.

The most frequently reported related adverse events of any grade are CRS (61%), pneumonitis (22%) and headache (17%), as well as the expected cytopenia from lymphodepletion in all patients. The CRS was generally mild (Grade 1 or 2 only), characterized by fever, and treated with tocilizumab and steroids. There were no reports of immune effector cell-associated neurotoxicity syndrome (ICANS) attributed to LYL797. The most frequently reported Grade $\geq$ 3 related adverse events were pneumonitis (17%) and hypoxia (11%), as well as the expected cytopenia from lymphodepletion in 78% of patients. One patient had Grade 5 respiratory failure on Day 41. The adverse event of Grade $\geq$ 3 pneumonitis occurred only in patients with TNBC and lung metastases, resulting in the separation of dose escalation into two cohorts based upon lung involvement (lung primary, lung metastatic disease or pleural effusion). No dose-limiting toxicities occurred in patients without lung involvement. All patients are now receiving prophylactic therapy with dexamethasone to mitigate pneumonitis. Patients without lung involvement are currently under evaluation at the 300 x 10^6 cell dose level and patients with lung involvement are currently under evaluation at 75 x 10^6 cell dose level.

Translational data are described on a subset of patients and include CAR T cell expansion in peripheral blood, phenotypic analysis of T cell exhaustion and stem-like markers and on-study tumor biopsies to assess for CAR T cell tumor infiltration. LYL797 CAR T-cell expansion was observed in peripheral blood samples at Day 60 in all patients assessed to date (n = 11) with peak expansion occurring between Days 8 and 11. Peak expansion was on average three-fold higher in patients receiving 150 x 10^6 cells compared to those receiving 50 x 10^6 cells. The exhaustion marker, TIGIT, was found only in a low proportion of LYL797 CAR T cells at Day 11 (n = 4) providing support for the role of c-Jun overexpression as an anti-exhaustion technology. A significant proportion of cells with stem-like and effector memory phenotypes were demonstrated at Days 11 and 22 following RNAseq transcriptomic analysis supporting the role of Epi-R to preserve a stem-like phenotype. Nine evaluable on-treatment tumor biopsies collected between Days 21 and 30 after LYL797 infusion were assessed. LYL797 CAR T cells were present in all solid-tumor biopsies, indicating that LYL797 CAR T cells enhanced with Lyell's anti-exhaustion technology were able to infiltrate and persist in the solid tumor microenvironment. In addition, the tumor biopsies have features consistent with T cell-mediated tumor lysis, including T cell-rich inflammation with scattered tumor cells.

Conference Call and Webcast Details

Lyell's management, together with David R. Spigel, MD, Chief Scientific Officer at the Sarah Cannon Research Institute and a lead investigator in the Phase 1 clinical trial, will host an investor conference call and Webcast beginning at 8:30 am ET today, to discuss the initial data from the LYL797 Phase 1 clinical trial.

- The Webcast can be accessed here.
- To join the live conference call, please register here to receive a dial-in number and unique PIN to access the call.

It is recommended callers join ten minutes prior to the start of the event (although you may register and join at any time during the Webcast). A replay of the event and presentation materials will be archived on the Investor page of the Lyell Website following the end of the event.

LYL797 Phase 1 Clinical Trial Design (NCT05274451)

The Phase 1 clinical trial is designed as an open-label, dose-escalation and expansion trial in patients with relapsed/refractory TNBC who have failed at least two lines of therapy and NSCLC who have failed at least one line of therapy. The trial has been amended to also include patients with platinum-resistant ovarian cancer or endometrial cancer. All patients enrolled have tumor specimens positive for ROR1 protein expression by immunohistochemistry.

More information on the Phase 1 trial can be found on clinicaltrials.gov here.

About LYL797

LYL797 is a receptor tyrosine kinase-like orphan receptor 1 (ROR1) -targeted CAR T-cell product candidate enhanced with Lyell's anti-exhaustion genetic reprogramming technology (c-Jun) and epigenetic reprogramming technology (Epi-R). LYL797 overexpresses c-Jun to correct for an imbalance in the AP-1 family of transcription factors present in exhausted T cells. In preclinical studies, overexpression of c-Jun enables T cells to resist exhaustion, infiltrate solid tumors and maintain their functionality. LYL797 is manufactured utilizing Epi-R, Lyell's proprietary ex vivo manufacturing protocol that is designed to generate populations of stem-like T cells with reduced exhaustion and improved proliferation and antitumor activity.

ROR1 is a fetal protein expressed during embryogenesis and is believed to be important in cell migration, polarity and survival. Significant subsets of patients with common cancers express ROR1 and it is generally associated with a poor prognosis.

About Lyell Immunopharma, Inc.

Lyell is a clinical-stage T-cell reprogramming company advancing a diverse pipeline of cell therapies for patients with solid tumors. Lyell is currently enrolling a Phase 1 clinical trial evaluating a first-generation ROR1-targeted CAR T-cell therapy enhanced with anti-exhaustion technology in patients with relapsed/refractory triple-negative breast cancer, non-small cell lung cancer (NSCLC), ovarian cancer and endometrial cancer. A second Phase 1 clinical trial is ongoing to evaluate reprogrammed tumor infiltrating lymphocytes (TIL) in patients with advanced melanoma, NSCLC and colorectal cancer. An investigational new drug application has been submitted to the FDA for LYL119, a next-generation ROR1-targeted CAR T-cell product candidate with even more powerful anti-exhaustion technologies.

The technologies powering Lyell's product candidates are designed to address barriers that limit consistent and long-lasting responses to cell therapy for solid tumors: T-cell exhaustion and lack of durable stemness, which includes the ability to persist and self-renew to drive durable tumor cytotoxicity. Lyell is applying its proprietary ex vivo genetic and epigenetic reprogramming technologies to address these barriers to develop new medicines with improved durable clinical outcomes. Lyell is based in South San Francisco, California with facilities in Seattle and Bothell, Washington. To learn more, please visit www.lyell.com.

Forward Looking Statements

This press release contains forward-looking statements within the meaning of the Private Securities Litigation Reform Act of 1995. Forward-looking statements expressed or implied in this press release include, but are not limited to, statements regarding: the continued clinical progress of the LYL797 trials; the effectiveness of prophylactic steroids or other treatments to mitigate adverse events; the potential to deliver more meaningful and durable benefit to patients with dose escalation; Lyell's plans to enroll patients with platinum-resistant ovarian cancer and endometrial cancer in the LYL797 trial; Lyell's plans to submit an IND for LYL797 to initiate a new Phase 1 study evaluating LYL797 in patients with multiple myeloma or chronic lymphocytic leukemia and the timing thereof; Lyell's development plans for LYL119 and the effectiveness of any technologies incorporated into LYL119; the ability of Lyell's reprogramming technologies to infiltrate and persist in the solid tumor microenvironment; and other statements that are not historical fact. These statements are based on Lyell's current plans, objectives, estimates, expectations and intentions, are not guarantees of future performance and inherently involve significant risks and uncertainties. Actual results and the timing of events could differ materially from those anticipated in such forward-looking statements as a result of these risks and uncertainties, which include, but are not limited to, risks and uncertainties related to: macroeconomic conditions, including the effects of geopolitical instability and actual or perceived changes in interest rates and economic inflation; Lyell's ability to submit planned INDs, obtain approval of submitted INDs, or initiate or progress clinical trials on the anticipated timelines, if at all; the potential for results from clinical trials to differ from nonclinical, early clinical, preliminary or expected results; Lyell's limited experience as a company in enrolling and conducting clinical trials, and lack of experience in completing clinical trials; Lyell's ability to manufacture and supply its product candidates for its clinical trials; the nonclinical profiles of Lyell's product candidates or technology not translating in clinical trials; significant adverse events, toxicities or other undesirable side effects associated with Lyell's product candidates; the significant uncertainty associated with Lyell's product candidates ever receiving any regulatory approvals; Lyell's ability to obtain, maintain or protect intellectual property rights related to its product candidates; implementation of Lyell's strategic plans for its business and product candidates; the sufficiency of Lyell's capital resources and need for additional capital to achieve its goals; and other risks, including those described under the heading "Risk Factors" in Lyell's Annual Report on Form 10-K for the year ended December 31, 2023, filed with the Securities and Exchange Commission (SEC) on February 28, 2024, and the Quarterly Report on Form 10-Q for the quarter ended March 31, 2024, filed with the SEC on May 6, 2024. Forward-looking statements contained in this press release are made as of this date, and Lyell undertakes no duty to update such information except as required under applicable law**.**

Contact:

Ellen Rose
Senior Vice President, Communications and Investor Relations
erose@lyell.com

Exhibit 99.2

Initial Clinical and Translational Data from Phase 1 Trial of LYL797, an Enhanced ROR1-targeted CAR-T Cell Product Candidate

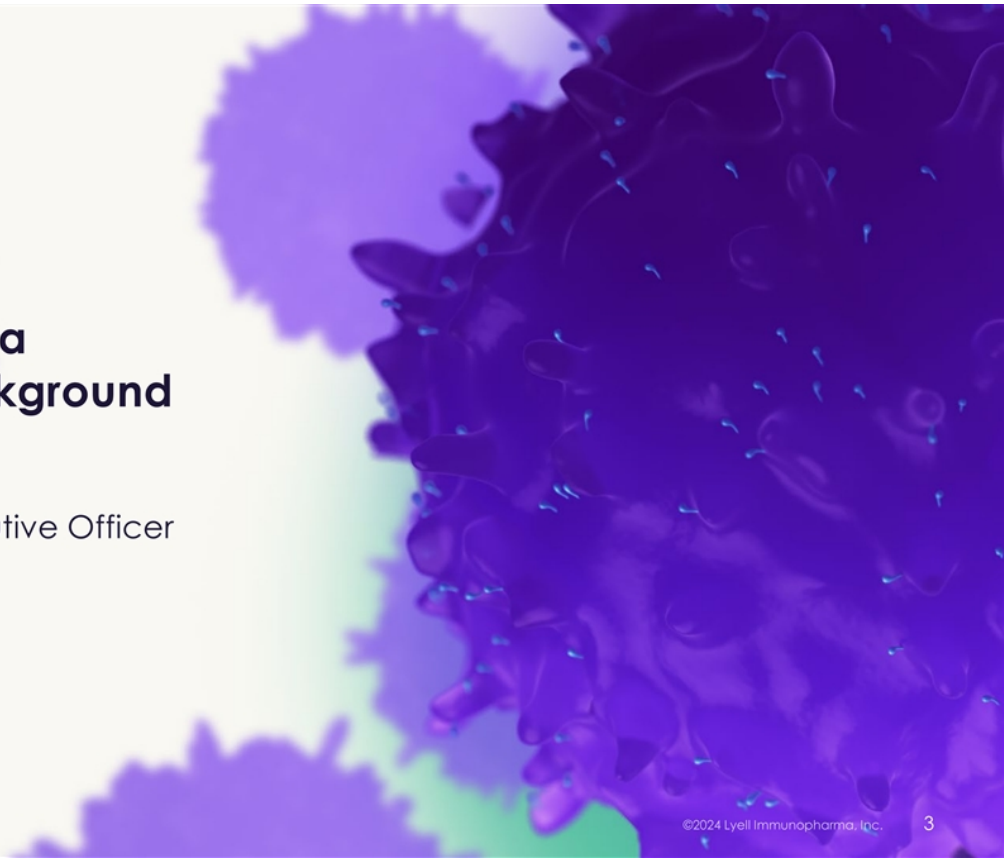
June 26, 2024

Forward Looking Statements

Certain matters discussed in this presentation are "forward-looking statements" of Lyell Immunopharma, Inc. (hereinafter referred to as the "Company," "we," "us," or "our") within the meaning of the Private Securities Litigation Reform Act of 1995 (the "PSLRA"). All such written or oral statements made in this presentation are forward-looking statements, including expansion of clinical trials in other indications, plans for dose escalation, Lyell's plans to submit an IND for LYL797 and the timing thereof, the ability of Lyell's reprogramming technologies to infiltrate and persist in the solid tumor microenvironments, indicative milestones and other statements that are not statements of historical fact, and are intended to be covered by the safe harbor for forward-looking statements provided by the PSLRA. Without limiting the foregoing, we may, in some cases, use terms such as "predicts," "believes," "potential," "continue," "estimates," "anticipates," "expects," plans"," "intends," "forecast," "guidance," "outlook," "may," "could," "might," "will," "should" or other words that convey uncertainty of future events or outcomes and are intended to identify forward-looking statements. Forward-looking statements are based on assumptions and assessments made in light of management's experience and perception of historical trends, current conditions, expected future developments and other factors believed to be appropriate. Forward looking statements in this presentation are made as of the date of this presentation, and we undertake no duty to update or revise any such statements, whether as a result of new information, future events or otherwise. Forward-looking statements are not guarantees of future performance and are subject to risks, uncertainties and other factors, many of which are outside of our control, that may cause actual results, levels of activity, performance, achievements, timelines and developments to be materially different from those expressed in or implied by these forward-looking statements. Important factors that could cause actual results, developments and business decisions to differ materially from forward-looking statements are described in the sections titled "Risk Factors" in our filings with the Securities and Exchange Commission (the "SEC"), and include, but are not limited to, the following substantial known and unknown risks and uncertainties inherent in our business related to: the effects of geopolitical instability; macroeconomic conditions, including the effects of geopolitical instability and actual or perceived changes in interest rates and economic inflation; our ability to initiate or progress our current and planned clinical trials or to submit planned INDs on the anticipated timelines, if at all; the potential for results from clinical trials to differ from nonclinical, early clinical, preliminary or expected results; our limited experience as a company in enrolling, conducting or completing clinical trials; our ability to manufacture and supply our product candidates for our clinical trials; significant adverse events, toxicities or other undesirable side effects associated with our product candidates; the significant uncertainty associated with our product candidates ever receiving any regulatory approvals; our ability to obtain, maintain, or protect intellectual property rights related to our product candidates; implementation of our strategic plans for our business and product candidates; the sufficiency of our capital resources and the need for additional capital to achieve our goals; other risks, including general economic conditions and regulatory developments, not within our control; and those risks described under the heading "Risk Factors" in our SEC filings, including our Quarterly Report on Form 10-Q for the quarter ended March 31, 2024 and subsequent filings with the SEC. This presentation concerns product candidates and technologies that are under clinical investigation, and which have not yet been approved for marketing by the U.S. Food and Drug Administration. These are currently limited by federal law to investigational use, and no representation is made as to their safety or effectiveness for the purposes for which they are being investigated.

LYL797 Clinical Data Summary and Background

Lynn Seely, MD
President and Chief Executive Officer



LYL797 Initial Clinical Data and Progress Update

Dose-Dependent Clinical Activity Observed

- **40% Objective Response Rate, including 2 confirmed partial responses,** at 150M CAR T cell dose (n=5), the highest dose level cleared to date
  - **Clinical Benefit Rate of 60%** at 150M CAR T cell dose and 38% across all dose levels
- **LYL797 CAR T cells successfully expanded, infiltrated solid tumors and killed cancer cells**
  - First clinical demonstration of robust CAR T cell solid tumor infiltration

Dose Escalation Ongoing Separately in Patients With or Without Lung Involvement

- **No DLTs in patients without lung involvement;** 300M cell dose under evaluation
- **Pneumonitis observed in patients with lung involvement;** dose escalation continuing with dexamethasone prophylaxis; treatable with steroids; 75M cell dose under evaluation

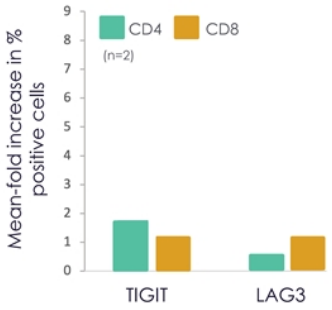
Expanding into Additional ROR1-expressing Tumor Types Given Clinical Activity

- **Expanding into ovarian and endometrial cancers**
- Initiating a new clinical trial of **LYL797 in multiple myeloma and chronic lymphocytic leukemia**
- **IND submitted for LYL119,** a next-generation ROR1-targeted product candidate

Data cutoff of 29 May 2024; CAR, chimeric antigen receptor; DLTs, dose-limiting toxicities; ROR1, receptor tyrosine kinase-like orphan receptor

Fred Hutch Cancer Center Study: ROR1 CAR T Cells in Peripheral Blood Samples Demonstrated Increased Markers of Exhaustion in Patients with Solid Tumors Compared to Those with Chronic Lymphocytic Leukemia (CLL)

CLL: Cells Did Not Exhaust

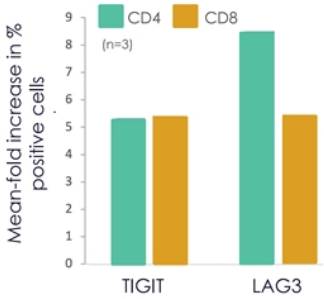


No elevation of exhaustion markers

Clinical Outcome: Response in 2/2 patients

- 1 partial response
- 1 complete response

Solid Tumors: Cells Exhaust



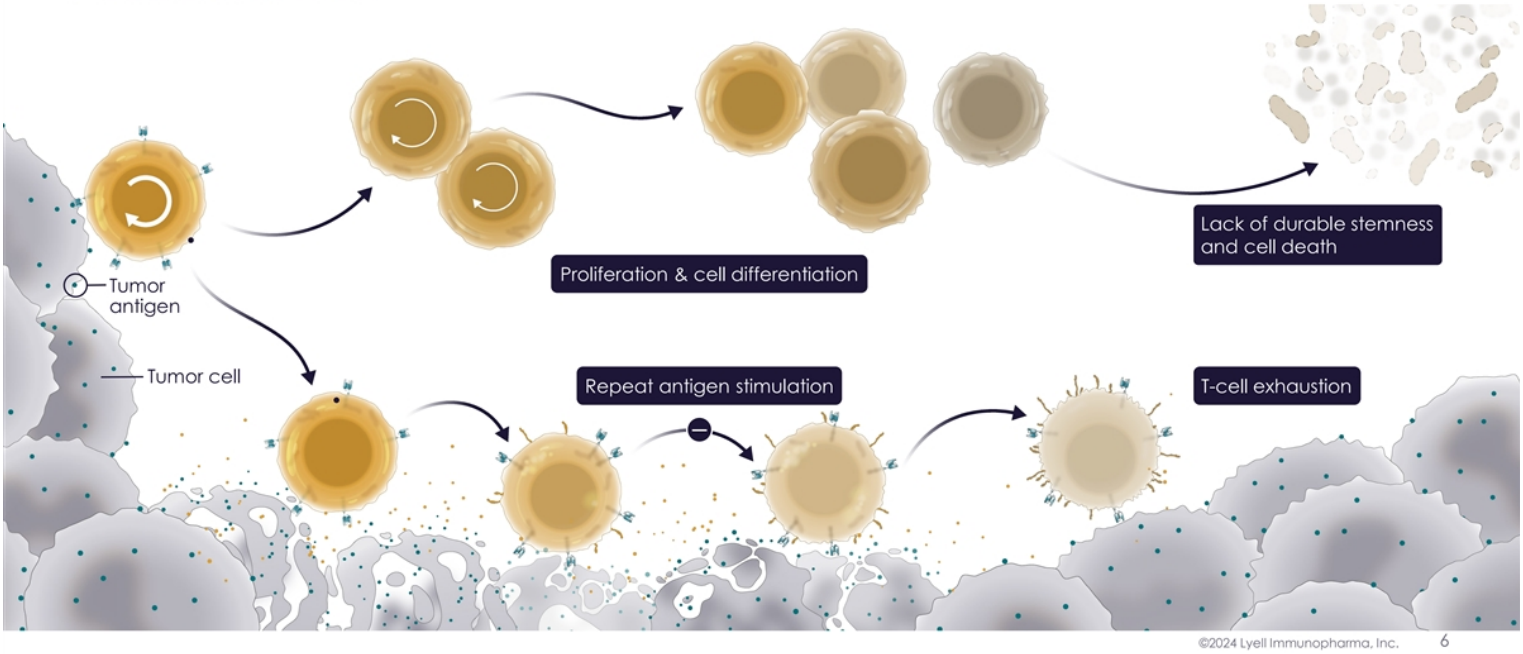
Elevation of exhaustion markers

Clinical Outcome: Response in 0/14 patients with single dose

- 1 partial response after re-treatment

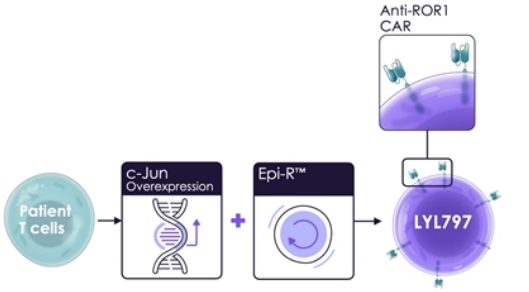
Riddell et al, Keystone, 2020
CAR, chimeric antigen receptor; ROR1, receptor tyrosine kinase-like orphan receptor 1

LYL797 was Designed to Overcome Two Key Barriers to Cell Therapy in Solid Tumors: Lack of T-cell Expansion and Rapid T-cell Exhaustion



LYL797: Improved Tumor Control and Prolonged Survival In Vivo

NSCLC (H1975) Xenograft Model



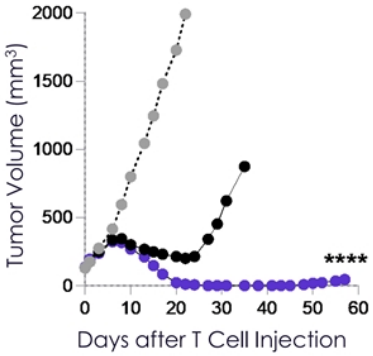
Genetic Reprogramming

c-Jun regulates the AP-1 transcription factor pathway, which plays a key role in T-cell effector function and resistance to T-cell exhaustion

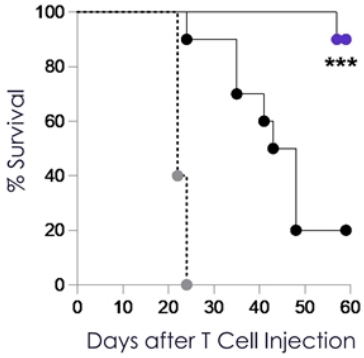
Epigenetic Reprogramming

Manufacturing protocol that is designed to generate more stem-like cells that self renew and persist despite repeat antigen stimulation

LYL797 Reduced Tumor Burden
5 x 10^6 CAR T cells



LYL797 Prolonged Survival
5 x 10^6 CAR T cells

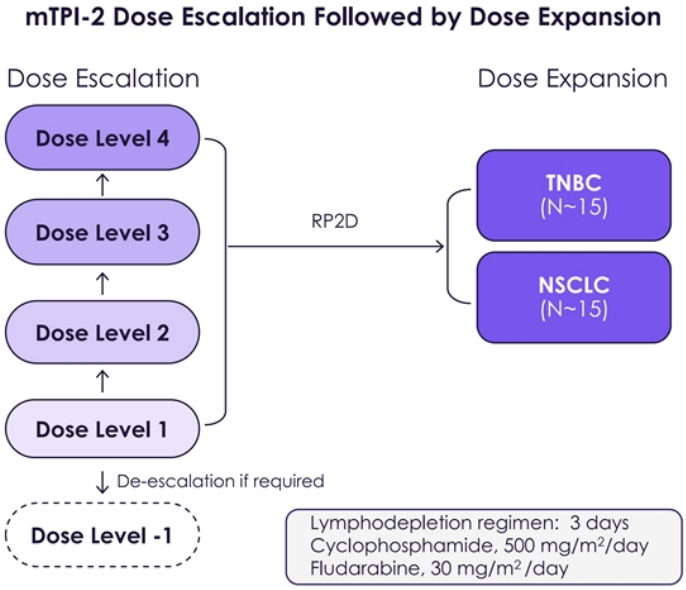


Mock ● Control ROR1 CAR T ● LYL797

AP-1, Activator Protein-1; CAR, chimeric antigen receptor; NSCLC, non-small cell lung cancer; ROR1, receptor tyrosine kinase-like orphan receptor 1

Park et al., ASGCT, 2022
*P<0.05, ***P<0.001, ****P<0.0001

LYL797: Phase 1 Trial Design



Patient Population

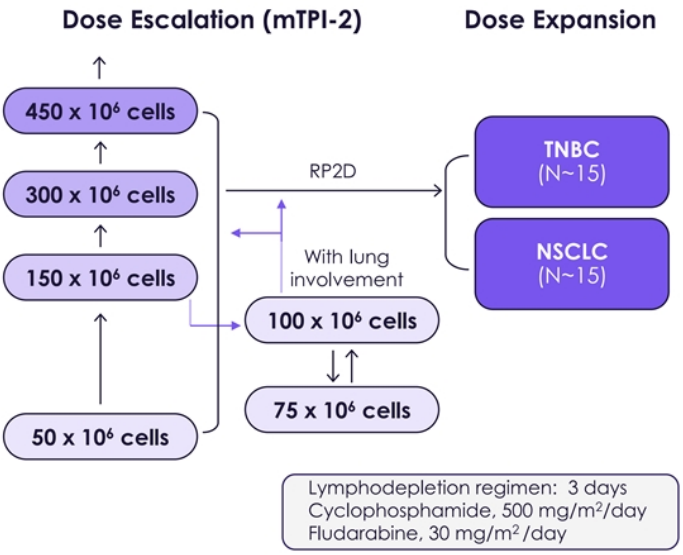
- Patients with relapsed/refractory TNBC after failure of at least two lines of therapy
- Patients with relapsed/refractory NSCLC after failure of at least one line of therapy
- ROR1 positive tumors

Study Objectives

- Safety and tolerability
- Objective response rate and durability
- Recommended Phase 2 dose
- CAR T-cell pharmacokinetics
- Assessment of T-cell phenotype and infiltration

NCT05274451; CAR, chimeric antigen receptor; m-TPI-2, Modified Toxicity Probability Interval; NSCLC, non-small cell lung cancer; ROR1, receptor tyrosine kinase-like orphan receptor 1; RP2D, recommended phase 2 dose; TNBC, triple-negative breast cancer

LYL797: Updated Dose Escalation Design



- No dose-limiting toxicities in patients without lung metastases
- Pneumonitis observed in some patients with lung metastases
  - Separately escalating cohorts of patients based on lung involvement
  - Dexamethasone prophylaxis for all patients
- Dexamethasone prophylaxis regimen intended to enable dose expansion regardless of lung involvement

Data cutoff of 29 May 2024; NCT05274451
m-TPI-2, Modified Toxicity Probability Interval; NSCLC, non-small cell lung cancer; RP2D, recommended phase 2 dose; TNBC, triple-negative breast cancer

LYL797 Clinical Data Update

David R. Spigel, MD
Chief Scientific Officer
Sarah Cannon Research Institute
Nashville, TN

Patient Characteristics
Predominantly TNBC with Multiple Lines of Prior Therapy

	50 x 10^6 cells n = 8	75 x 10^6 cells n = 2	100 x 10^6 cells n = 4	150 x 10^6 cells n = 5	300 x 10^6 cells n = 1	Total N = 20
Age, mean	54	59	48	48	58	52
Indication, n (%)						
TNBC	6 (75%)	1 (50%)	3 (75%)	5 (100%)	1 (100%)	16 (80%)
NSCLC	2 (25%)	1 (50%)	1 (25%)	0	0	4 (20%)
Prior lines of treatment*, mean (range)	5 (3 – 9)	8 (4 – 12)	5 (4 – 7)	5 (2 – 8)	8	6 (2 – 12)
ECOG at Screening, n (%)						
0	3 (38%)	1 (50%)	2 (50%)	3 (60%)	1 (100%)	10 (50%)
1	5 (62%)	1 (50%)	2 (50%)	2 (40%)	0	10 (50%)

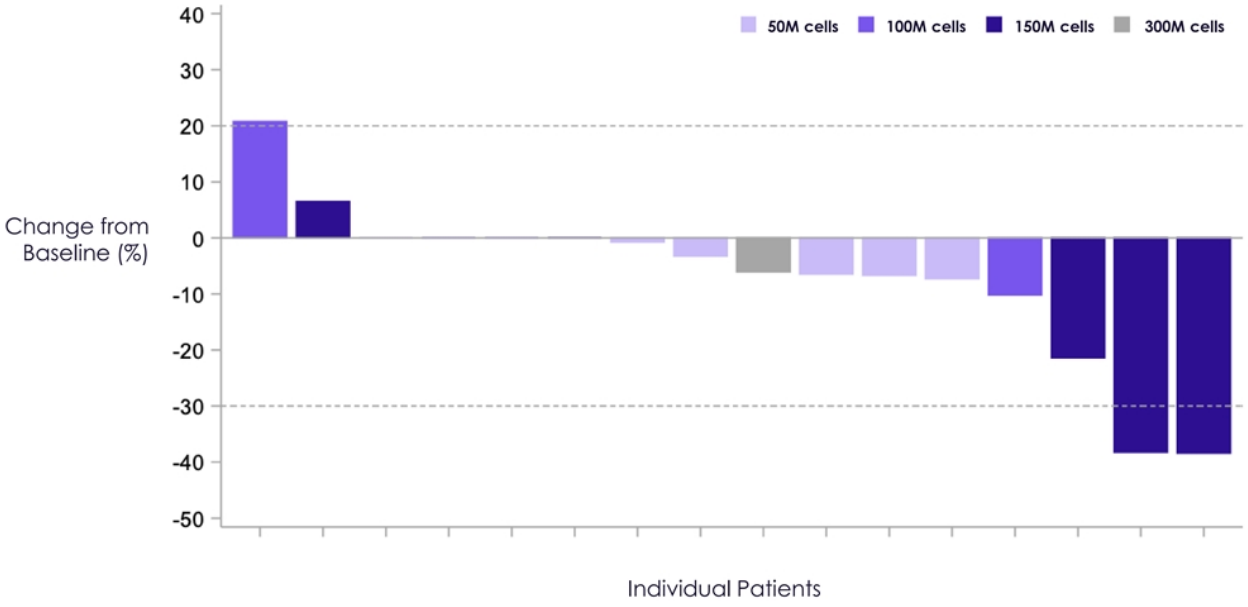
*In the metastatic setting; Data Cutoff of 14 June 2024
ECOG, Eastern Cooperative Oncology Group; NSCLC, non-small cell lung cancer, TNBC, triple-negative breast cancer

Dose-Dependent Clinical Activity with 40% Objective Response Rate at Highest Completed Dose Level

Efficacy evaluable patients, n	50 x 10^6 cells n = 6	100 x 10^6 cells n = 4	150 x 10^6 cells n = 5*	300 x 10^6 cells n = 1	Total N = 16
Patients with CR/PR, n	0	0	2	0	2
Patients with SD, n	1	1	1	1	4
ORR %	0%	0%	**40%**	0%	13%
Duration of Response			2 cPRs to Day 90		
Clinical Benefit Rate	17%	25%	**60%**	100%	**38%**

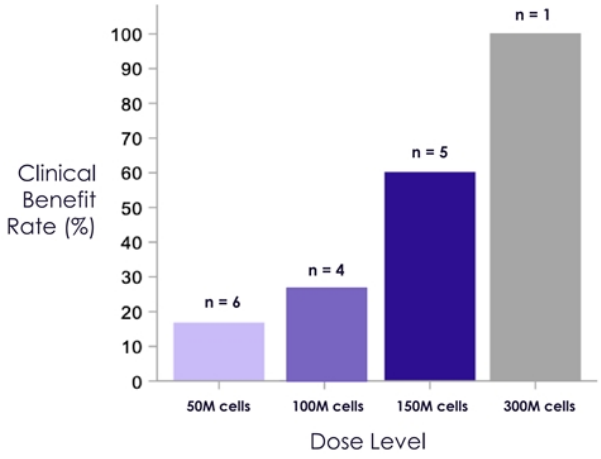
* 5 patients with TNBC; Data cutoff of 29 May 2024
cPR, confirmed partial response; CR, complete response; ORR, objective response rate; PR, partial response; SD, stable disease

Best Response for Target Lesions Demonstrating Clinical Activity



Data cutoff of 29 May 2024

Clinical Benefit Rate was Dose Dependent



- Clinical benefit rate is defined as SD, PR or CR as best response
- Several patients had additional observations of clinical benefit including weight gain, decreased pain and improved liver function tests

Data cutoff of 29 May 2024
CR, complete response, DL, dose level; PR, partial response, SD, stable disease

Treatment Related Adverse Events:

All Dose-Limiting Toxicities in Patients with Lung Involvement and Prior to Implementing Dexamethasone Prophylaxis

Safety Evaluable Patients With:	50 x 10^6 cells n = 7	75 x 10^6 cells n = 1	100 x 10^6 cells n = 4	150 x 10^6 cells n = 5	300 x 10^6 cells n = 1
TRAEs Grade ≥ 3	2	0	2	3	0
DLTs (pneumonitis, hypoxia)	0	0	2	2	0
CRS	4 (G1, 2)	0	3 (G1, 2)	3 (G1, 2)	1 (G1)
ICANS	0	0	0	0	0

- The most frequently reported related adverse events of any grade were CRS, pneumonitis and headache, and the expected cytopenia from lymphodepletion
- CRS was generally mild (Grade 1 or 2), characterized by fever, and treated with tocilizumab and steroids
- The most frequently reported Grade ≥ 3 related adverse events were pneumonitis and hypoxia, and the expected cytopenia from lymphodepletion; the first patient with pneumonitis had acute Grade 5 respiratory failure on Day 41. Subsequently, all patients were treated early for any sign of pneumonitis

Data cutoff of 29 May 2024; CRS, cytokine release syndrome; DLT, dose-limiting toxicity; ICANS, immune-effector cell-associated neurotoxicity syndrome; TRAE, treatment-related adverse event

Pneumonitis has a Predictable Onset and is Treatable

- Pneumonitis does not appear to be related to on-target, off-tumor toxicity; we believe it is related to local cytokine production due to underlying lung disease
- The onset is predictable(generally 4 – 10 days after treatment)
- It has been effectively treated with early high-dose steroids
- All patients now treated prophylactically with dexamethasone
  - Dexamethasone use has resulted in decreased CRS without diminished efficacy in hematological malignancies and CD19 CAR therapy*
- Dose escalation is moving forward separately in patients with or without NSCLC or lung metastatic disease
  - Dosing at 300 x 10^6 cells for patients without lung involvement
  - Dosing at 75 x 10^6 cells for patients with lung involvement

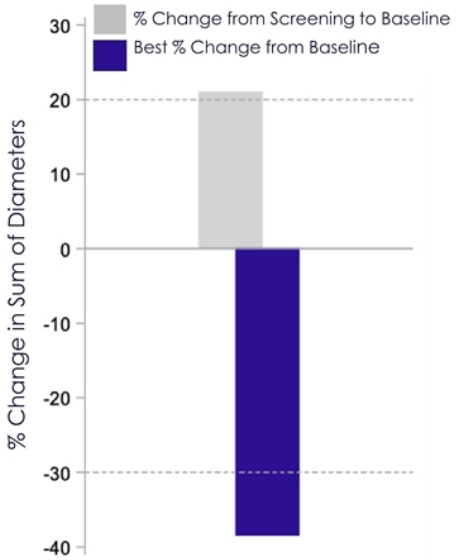
Data cutoff of 29 May 2024
CAR, chimeric antigen receptor; CRS, cytokine release syndrome; NSCLC, non-small cell lung cancer
*Oluwole, OO, et al, *Bone Marrow Transplant*, 59, 2024

Case Report of LYL797 Clinical Activity

Patient with metastatic triple-negative breast cancer with confirmed partial response following LYL797 after having failed 3 prior lines of treatment

51-year-old female previously treated with (1) doxorubicin, cyclophosphamide, pembrolizumab, paclitaxel and carboplatin, (2) capecitabine and (3) doxorubicin before enrolling in LYL797 trial with enlarging pelvic mass. Treated with 150 x 10^6 LYL797 CAR T cells.

Pelvic mass decreased in size from 17.6 cm at baseline to 11.4 cm at Day 60.



Data cutoff of 29 May 2024, Patient 5
CAR, chimeric antigen receptor; CT, computed tomography

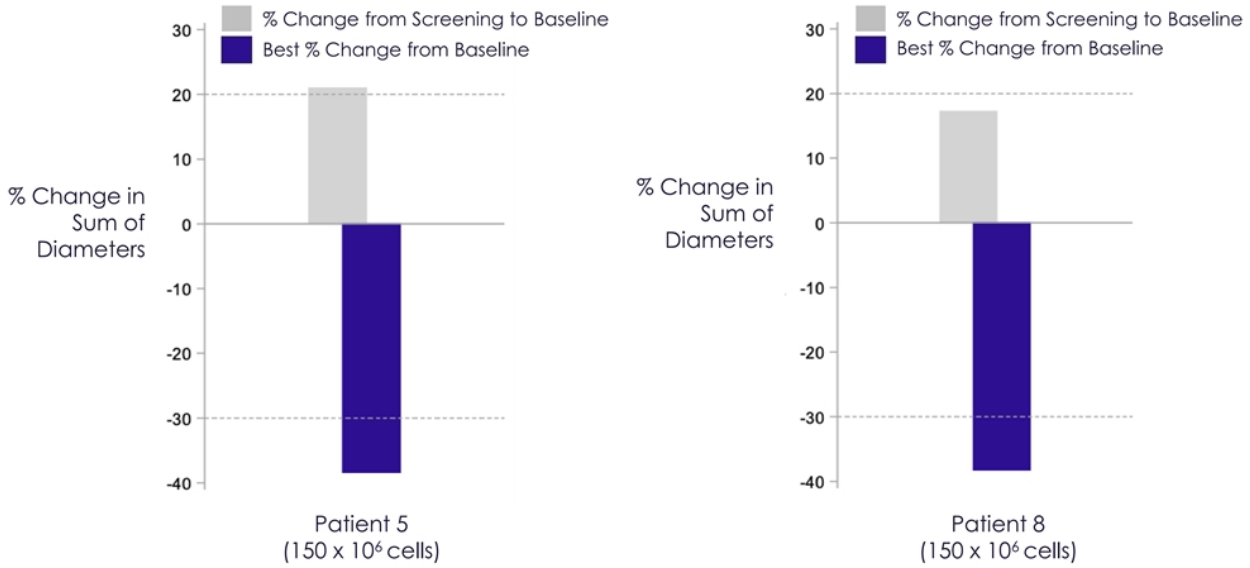
Case Report of LYL797 Clinical Activity

Patient with metastatic non-small cell lung cancer with stable disease for 4 months following LYL797 at a dose of 50 x 10^6 cells

- 49-year-old male diagnosed with metastatic NSCLC and treated with XRT then (1) carbo/pemetrexed and pembrolizumab, (2) a novel IL-2, additional XRT for rib metastasis and 2 RUL lesions, (3) taxotere/ramucirumab prior to LYL797
- No CRS after LYL797 infusion; no ≥ G3 events other than cytopenia
- Patient's rapidly growing right upper lobe lesion had doubled in the 3 months prior to treatment, growing from 1.4 to 3.1 cm in longest diameter, then remained stable until progression four months after treatment
- During that time patient experienced weight gain, improved sleep and quality of life

Data cutoff of 29 May 2024 , Patient 17
CRS, cytokine release syndrome; NSCLC, non-small cell lung cancer; XRT, radiation therapy

Confirmed Partial Responses in Patients Who had Progression in their Target Lesions Between Screening and Baseline



Data cutoff of 29 May 2024

LYL797 Translational Science

Gary Lee, PhD
Chief Scientific Officer

LYL797 Translational Data: Key Findings

Expansion

- LYL797 **CAR T-cell expansion observed in the peripheral blood** from all patients (n=11)

CAR T Cell Phenotype

- LYL797 cells had **low exhaustion markers** and a significant proportion of cells with the **desired stem-like and effector-memory phenotype** (n=6)

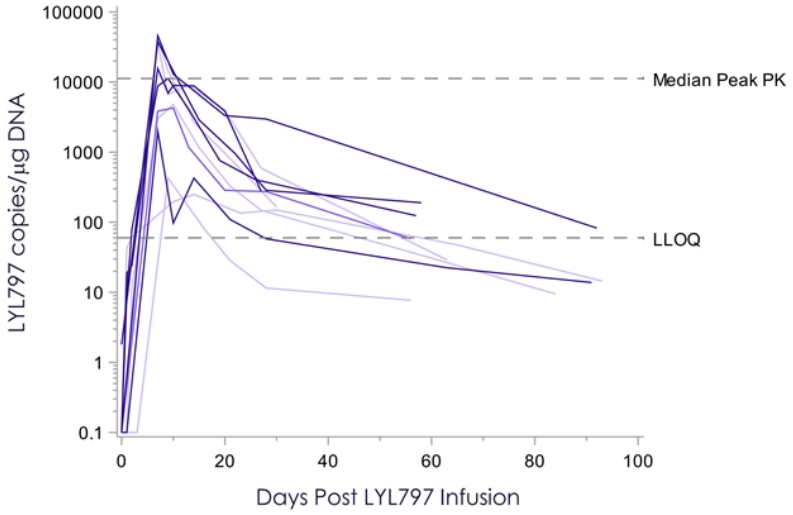
Infiltration and Tumor Lysis

- Persistent **LYL797 CAR T cell infiltration present in all evaluable on-study tumor biopsies** (n=9) with histologic evidence of tumor lysis in some samples

Data cutoff of 29 May 2024
CAR, chimeric antigen receptor

LYL797 CAR T-cell Expansion Observed in Peripheral Blood Samples from All Treated Patients

Peak Expansion Between Days 8 and 11



- 50 x 10^6 cells (n = 5)
- 100 x 10^6 cells (n = 1)
- 150 x 10^6 cells (n = 5)

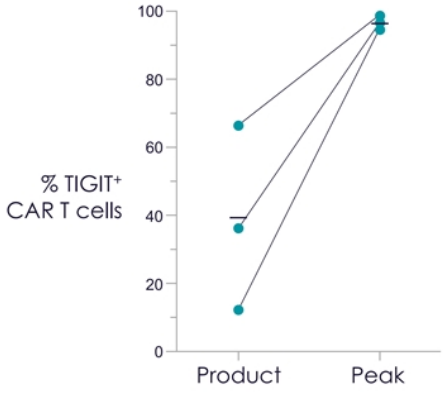
Median peak PK = 11,251 copies/µg DNA

- 50 x 10^6: 4,783 copies/µg DNA
- 150 x 10^6: 15,598 copies/µg DNA

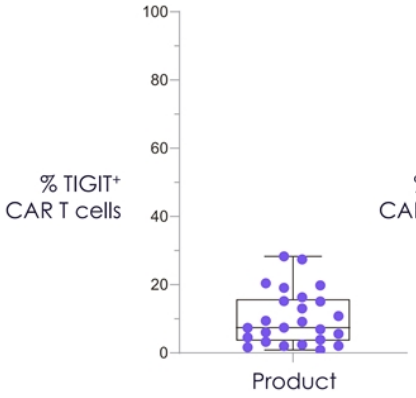
Data cutoff of 29 May 2024; CAR, chimeric antigen receptor; cPR, confirmed partial response; PK, pharmacokinetics; DNA, deoxyribonucleic acid

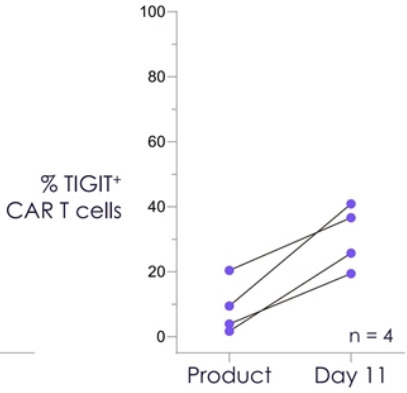
Infusion Products and LYL797 in Day 11 Peripheral Blood Samples Had Significantly Lower Percent TIGIT+ Cells (Exhaustion Marker)

Fred Hutch Cancer Center: Solid Tumor Patients



LYL797 CAR T Cell Data

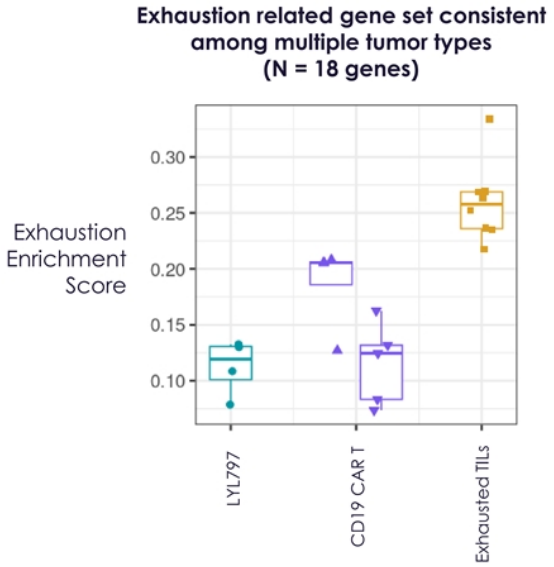




Data cutoff of 29 May 2024; CAR, chimeric antigen receptor; TIGIT, T cell immunoreceptor with immunoglobulin and ITIM domain
Specht J. Jan 31 2020, EHA
*LYL797 defined by CD8+ EGFR+

LYL797 Cells Had an Exhaustion Profile More Comparable to Published Data from CD19 CAR PBMC Samples than Exhausted TNBC TIL Samples

mRNA by RNAseq/ transcriptomic analyses



Study

- LYL797
- PublicStudy1
- PublicStudy2
- Exhausted TILs

LYL797: EGFR+CD8+ cells from Day11 PBMC

PublicStudy1: CD8 CAR-T cells from PBMC at expansion peak of CD19 CAR-T in Sheih, A. *et al., Nat Commun* 2020

PublicStudy2: CD8 CAR-T cells from PBMC at expansion peak of CD19 CAR-T in Mercedes Guerrero-Murillo, et al., bioRxiv, 2024

Exhausted TILs: refer to the t_CD8_CXCL13 cluster from TNBC samples *in Zhang, et al., Cancer Cell.* 2021. Only patients with at least 300 cells in the t_CD8_CXCL13 cluster were included in the comparison

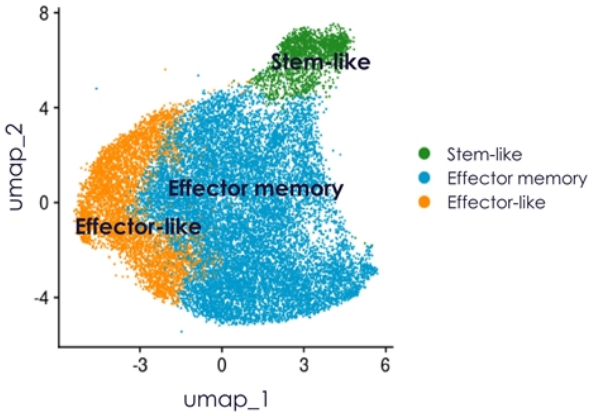
Exhaustion enrichment score is average of enrichment score calculated by UCell across all cells

Data cutoff of 29 May 2024; Zhang et al., *Nature* 2018
CAR, chimeric antigen receptor; mRNA, messenger RNAseq, RNA sequencing; PBMC, peripheral blood mononuclear cells; TIL, tumor infiltrating lymphocytes

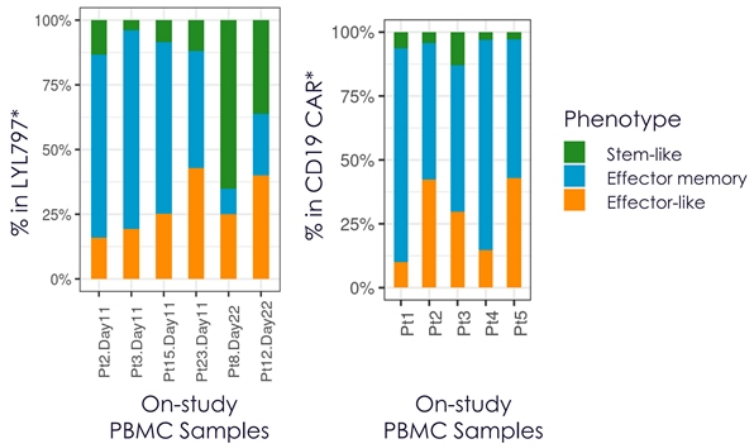
LYL797 Cells from Day 11 and Day 22 PBMC Samples Had a Significant Proportion of Cells with Stem-like and Effector-memory Phenotype

mRNA by RNAseq/ transcriptomic analyses

LYL797* from Day 11 PBMC Samples



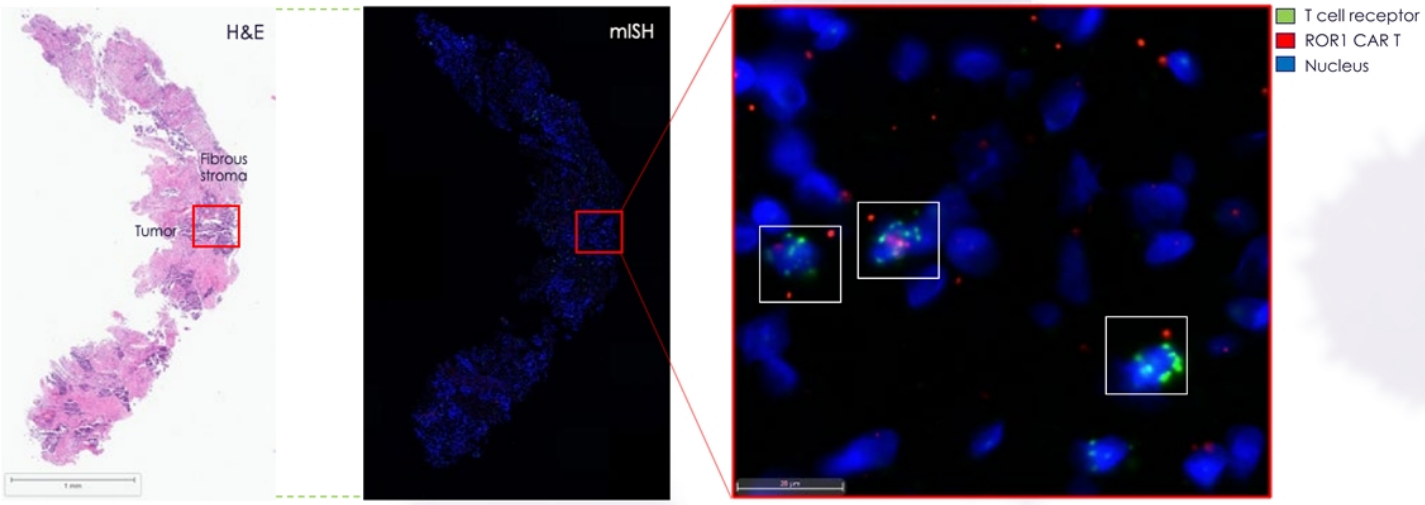
LYL797* Compared to CD19 CAR



Data cutoff of 29 May 2024; *LYL797 defined by CD8+ EGFR+
PBMC, peripheral blood mononuclear cells; mRNA, messenger RNAseq, RNA sequencing; CAR, chimeric antigen receptor

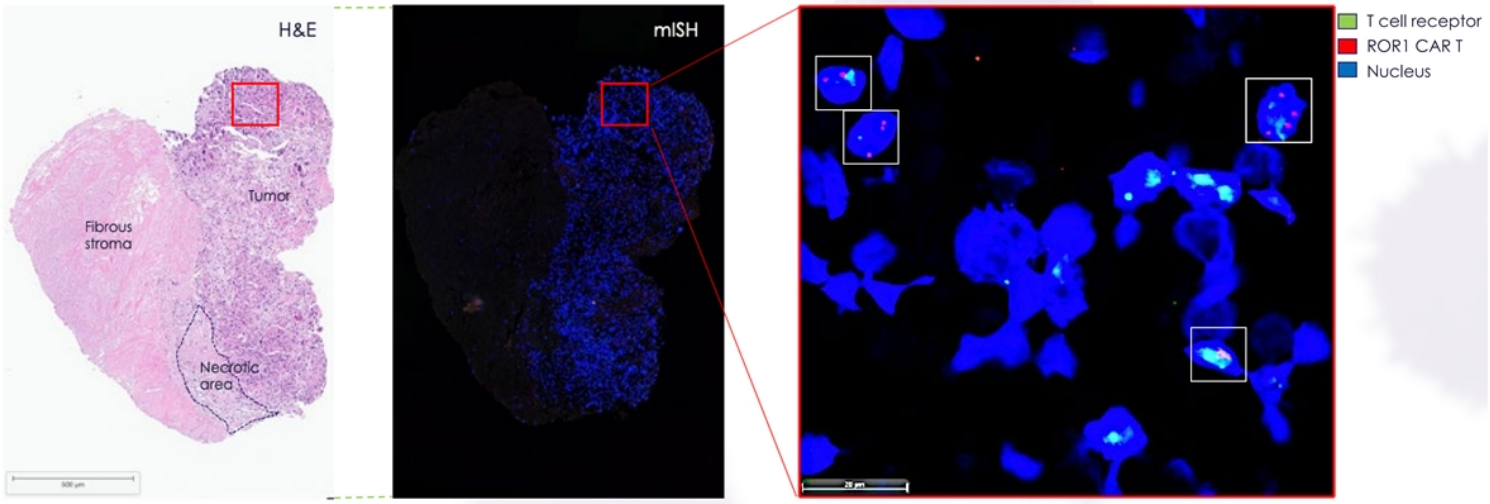
Detection of LYL797 CAR T Cell Infiltration in All Evaluable (N=9) On-study Tumor Biopsies (Days 21-30)

In situ detection of CAR-specific T cells using anti-ROR1 scFv mRNA in situ hybridization (ISH) assay



Data cutoff of 29 May 2024; Patient 18; TNBC; 100 x 10^6 cells; Day 29 tumor biopsy of abdominal mass
CAR, chimeric antigen receptor; H&E: Hematoxylin & Eosin; mISH: multiplex fluorescent in situ hybridization; mRNA, messenger RNA; ROR1, receptor tyrosine kinase-like orphan receptor 1

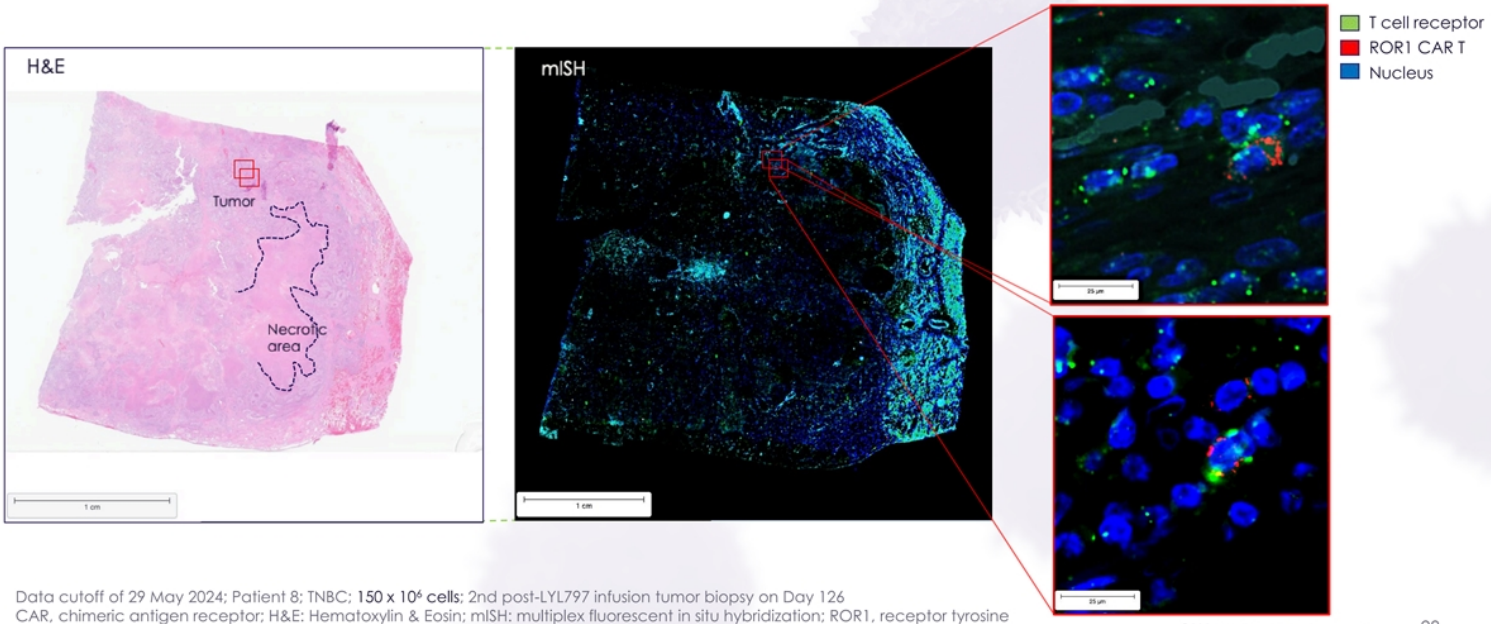
LYL797 CAR T Cell Infiltration in Patient with Confirmed Partial Response (Patient 8)



Data cutoff of 29 May 2024; Patient 8; TNBC; 150 x 10^6 cells; Day 28 tumor biopsy of lung
CAR, chimeric antigen receptor; H&E: Hematoxylin & Eosin; mISH: multiplex fluorescent in situ hybridization; ROR1, receptor tyrosine kinase-like orphan receptor 1

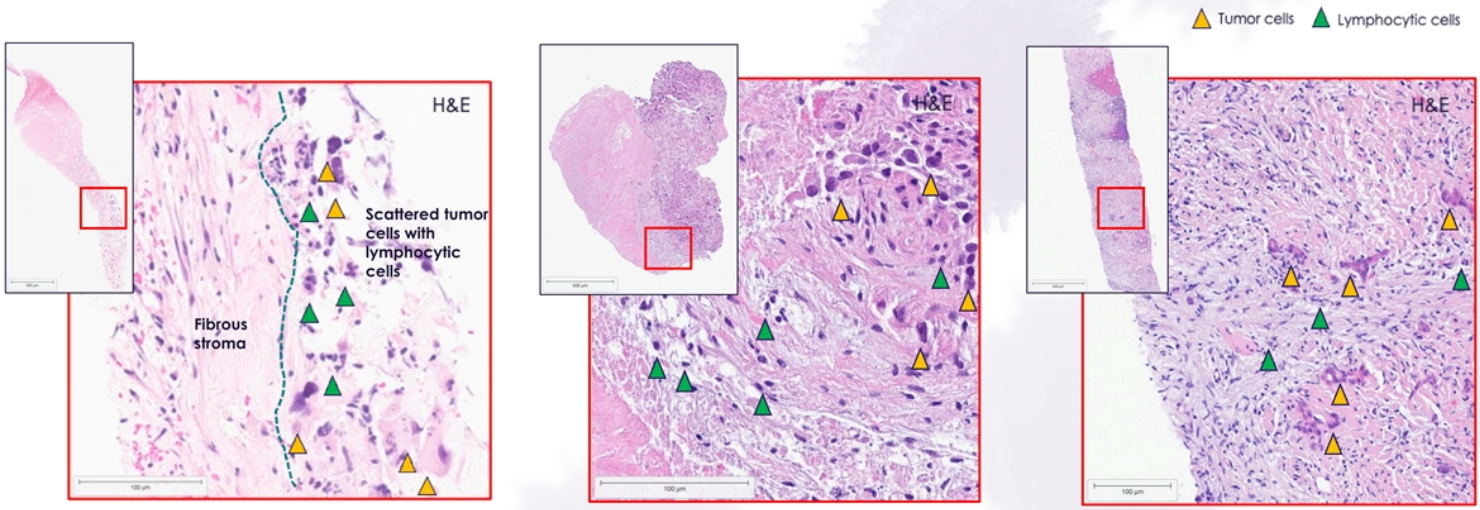
Persistent LYL797 CAR T Cell Infiltration Observed in Tumor Sample >4 months Post-infusion (Patient 8)

Lymph node resected at time of surgery with no evidence of disease



Data cutoff of 29 May 2024; Patient 8; TNBC; 150 x 10^6 cells; 2nd post-LYL797 infusion tumor biopsy on Day 126
CAR, chimeric antigen receptor; H&E: Hematoxylin & Eosin; mISH: multiplex fluorescent in situ hybridization; ROR1, receptor tyrosine kinase-like orphan receptor 1

Multiple Tumor Biopsies Had Features Consistent with T Cell-mediated Tumor Lysis Including T Cell-rich Inflammation with Scattered Tumor Cells



Patient 3, TNBC
50 x 10^6 cells, Day 26 liver biopsy

Patient 5, TNBC
150 x 10^6 cells, Day 23 liver biopsy

Patient 8, TNBC
150 x 10^6 cells, Day 28 lung biopsy

Data cutoff of 29 May 2024
H&E: Hematoxylin & Eosin; TNBC, triple-negative breast cancer

LYL797 Data Summary

LYL797 CAR T cells had dose-dependent clinical activity and expanded, infiltrated, persisted and killed tumor cells in patients with TNBC

- ✓ 40% ORR and 60% CBR at 150M cells; dose escalation continuing
- ✓ No significant safety signal related to LYL797 observed in patients without lung involvement; steroid prophylaxis to mitigate pneumonitis in patients with lung involvement
- ✓ Persistent LYL797 CAR T cell infiltration (up to 4 months) present in all evaluable on-study tumor biopsies with histologic evidence of tumor lysis in some samples
- ✓ CAR T cell expansion observed in the peripheral blood, with low inhibitory markers of exhaustion and a significant proportion of cells with the desired stem-like and effector-memory phenotype
- ✓ Clinical data validate preclinical models that demonstrate benefit of LYL797 over ROR1 CAR T cells without c-Jun and Epi-R
- ✓ Translational and early clinical data validate hypothesis that c-Jun overexpression and Epi-R technologies can improve clinical benefit of LYL797 ROR1 CAR T cell activity
- ✓ 100% manufacturing success rate to date

Data cutoff of 29 May 2024; CAR, chimeric antigen receptor; CBR, clinical benefit rate; ORR, objective response rate; ROR1, receptor tyrosine kinase-like orphan receptor 1; TNBC, triple-negative breast cancer

Next Steps for ROR1 CAR T Cell Program

Demonstrated clinical activity supports expanded development of LYL797 and LYL119

LYL797

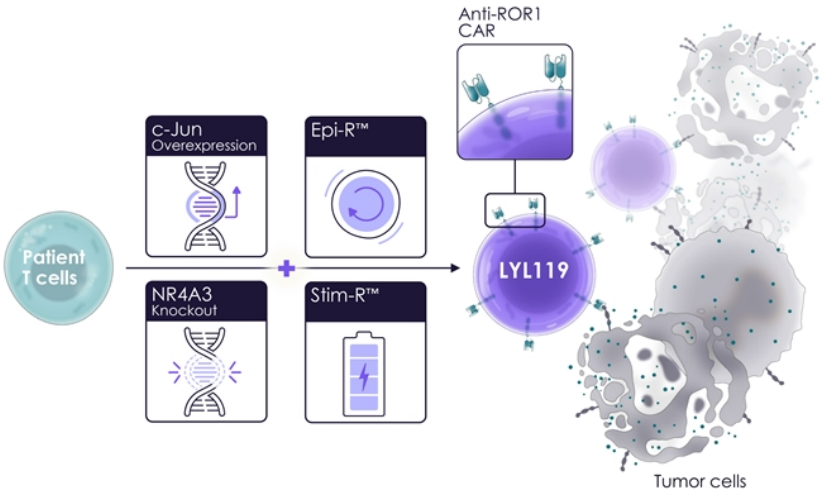
- Select Recommended Phase 2 Dose for LYL797 expansion cohort(s)
- Generate data at higher dose levels expected to achieve more durable responses
- Dose escalate with steroid prophylaxis in patients with lung involvement
- Enroll patients with platinum-resistant ovarian and endometrial cancers in addition to TNBC and NSCLC
- Initiate a study in hematologic malignancies including multiple myeloma and CLL

LYL119

- IND submitted and awaiting clearance
- Protocol includes enrollment of patients with platinum-resistant ovarian, endometrial, NSCLC, TNBC and colorectal cancers

CAR, chimeric antigen receptor; CLL, chronic lymphocytic leukemia; IND, investigational new drug application; NSCLC, non-small cell lung cancer; TNBC, triple-negative breast cancer

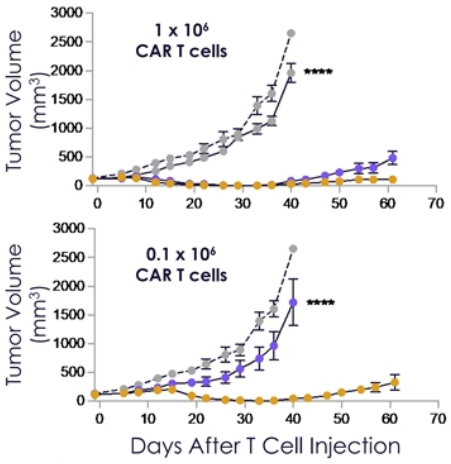
LYL119: Incorporates Novel Stackable Technologies Designed to Improve Potency



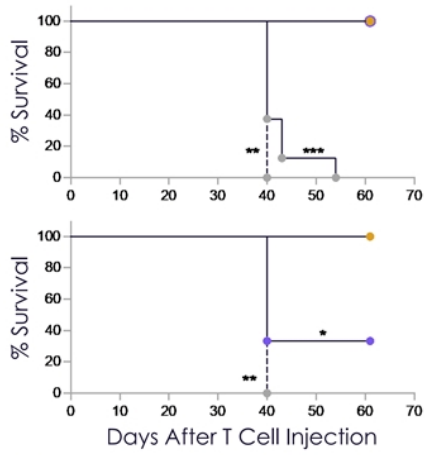
CAR, chimeric antigen receptor; NR4A3, The nuclear receptor 4A3; ROR1, receptor tyrosine kinase-like orphan receptor 1
NR4A3 knockout with CRISPR/Cas9

LYL119, Next-generation ROR1-targeted CAR T, Demonstrated More Potent Anti-tumor Activity In Vivo

Significantly Improved Elimination of Xenograft Tumors at the Lower 0.1 x 10^6 CAR T-cell Dose



Significantly Improved Animal Survival at the Lower 0.1 x 10^6 CAR T-cell Dose



PBS · Mock non-transduced (Epi-R + Stim-R) 1.42 x 10^6 cells · LYL797 (non-edited + c-Jun + Epi-R) · LYL119 (NR4A3 KO + c-Jun + Epi-R + Stim-R)

*P<0.05, **P<0.01, ***P<0.001, ****P<0.0001
PBS, phosphate buffered saline; CAR, chimeric antigen receptor; ROR1, receptor tyrosine kinase-like orphan receptor 1

ROR1 is Highly Expressed in Many Malignancies

Expression associated with a poor prognosis in solid tumors

Solid Tumor Indications in Development				
	TNBC	NSCLC	Endometrial	Ovarian
ROR1 Expression	**51%***	**35%***	**~50%**	**~50%**
US Incidences	~40K new cases ~10K deaths	~200K new cases ~110K deaths	~68K new cases ~13K deaths	~20K new cases ~13K deaths

Hematologic Indications in Development		
	Multiple Myeloma	CLL
ROR1 Expression	**~60%**	**~95%**
US Incidences	~36K new cases ~13K deaths	~ 21K new cases ~ 4.4K deaths

*Data from Lyell's LYL797 clinical trial (TNBC N=259, NSCLC, N=104)
CLL, chronic lymphocytic leukemia; NSCLC, non-small cell lung cancer; TNBC, triple-negative breast cancer
American Cancer Society (cancer.org); Balakrishnan et al., *Clin Cancer Res* 2017; Liu et al., Sci Reports, 2020; Mosaad et al., *Asian Pac J Cancer Prev*, 2023; Zhang et al., *Am J Pathol*, 2012.; Daneshmanesh, et al., *Leuk Lymphoma*, 2013

Upcoming Potential Milestones

Balance sheet of $526M* provides cash runway into 2027, through multiple clinical milestones

LYL797	**ROR1 CAR T cell + c-Jun + Epi-R**
2H24	❑ Begin enrolling patients with ovarian or endometrial cancers
	❑ Submit IND for trial in patients with multiple myeloma or CLL
	❑ Clinical data update including initiation of dose expansion (late-2024/early-2025)
1H25	❑ Present updated Phase 1 data at a major medical conference
LYL119	**ROR1 CAR T cell + c-Jun + NR4A3 CRISPR Knockout + Epi-R + Stim-R**
2H24	❑ IND clearance
1H25	❑ Progress update on Phase 1 trial
2H25	❑ Initial clinical data
LYL845	**TIL + Epi-R**
2H24	❑ Initial clinical data in patients with advanced melanoma

*Cash, cash equivalents and marketable securities as of 3/31/2024
CAR, chimeric antigen receptor; CLL, chronic lymphocytic leukemia; IND, investigational new drug application; NR4A3, nuclear receptor 4A; ROR1, receptor tyrosine kinase-like orphan receptor 1; TIL, tumor-infiltrating lymphocytes

With Thanks

Our gratitude to patients, caregivers, investigators, clinical site teams and Lyell employees for their contributions to advance innovative cell therapies to people with cancer

Q&A