



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

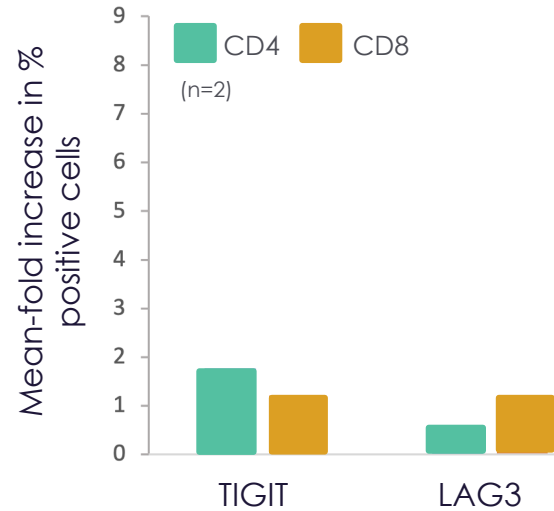
Expanding into Additional ROR1-expressing Tumor Types Given Clinical Activity

- **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

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

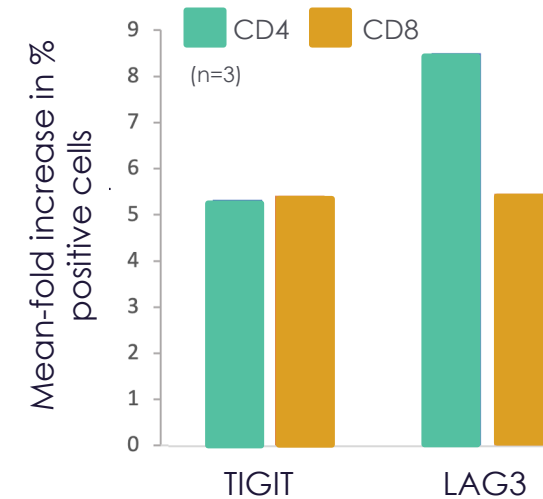


No elevation of exhaustion markers

Clinical Outcome: Response in 2/2 patients

- 1 partial response
- 1 complete response

Solid Tumors: Cells Exhaust

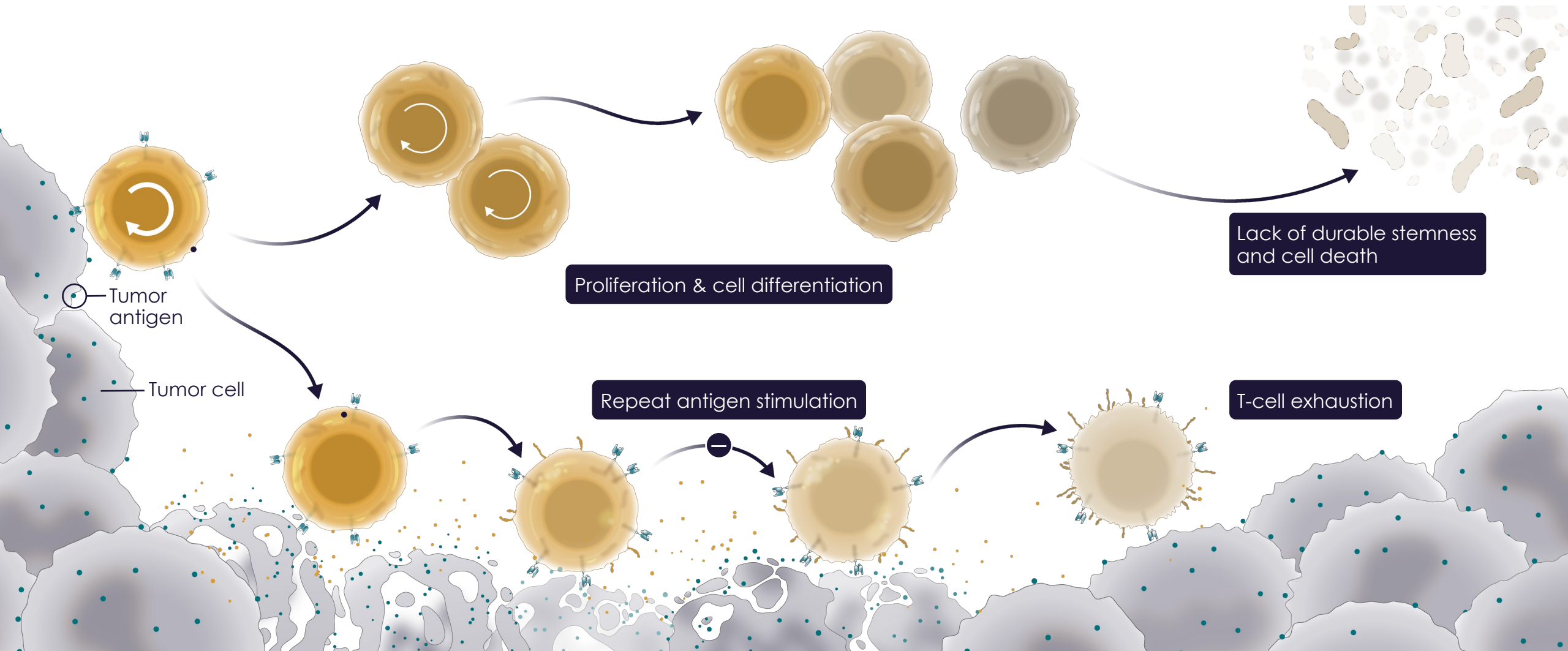


Elevation of exhaustion markers

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

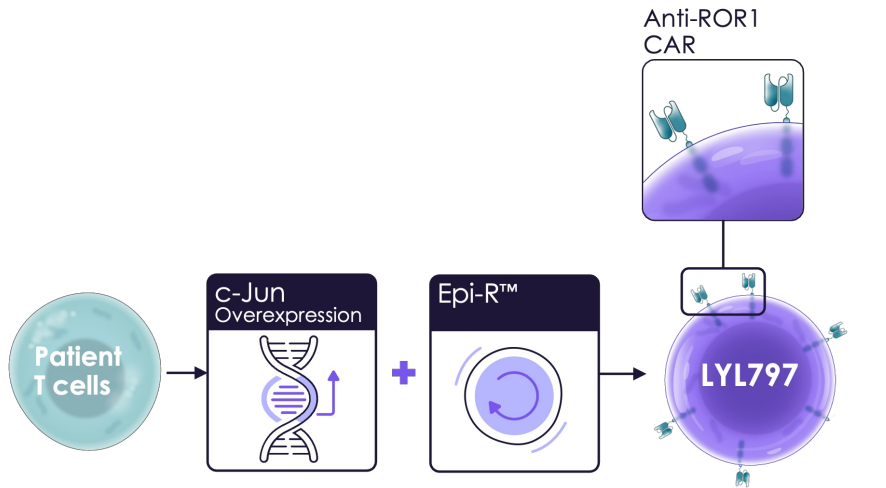
- 1 partial response after re-treatment

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

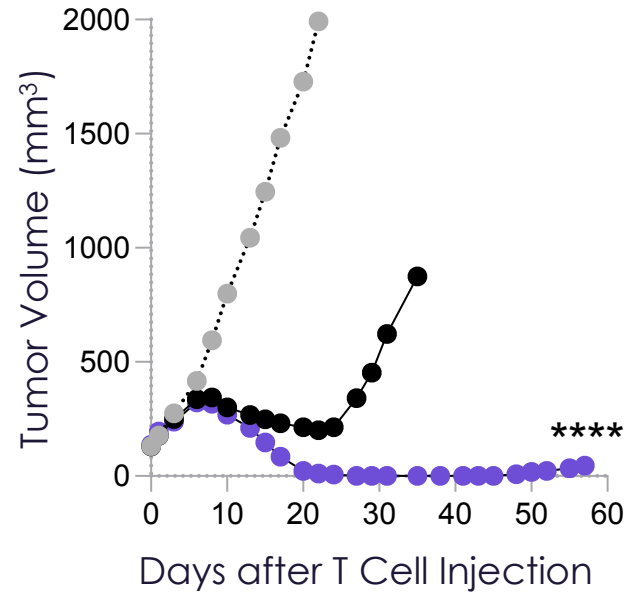
Epigenetic Reprogramming

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

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

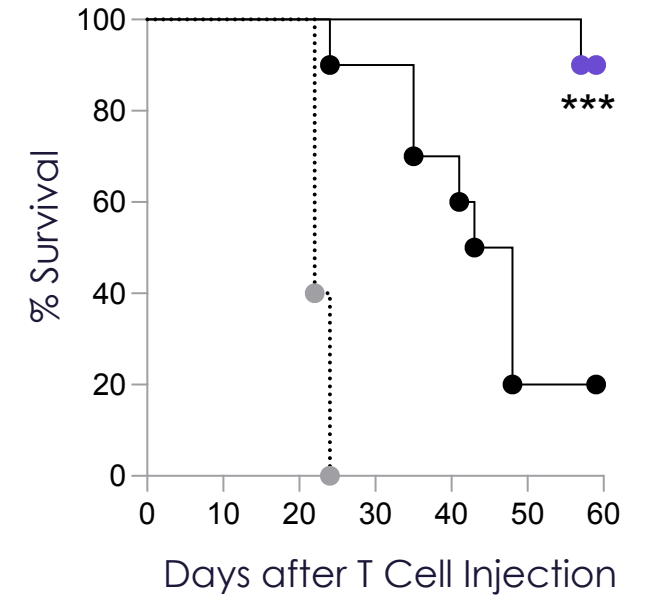
LYL797 Reduced Tumor Burden

5 x 10⁶ CAR T cells



LYL797 Prolonged Survival

5 x 10⁶ CAR T cells



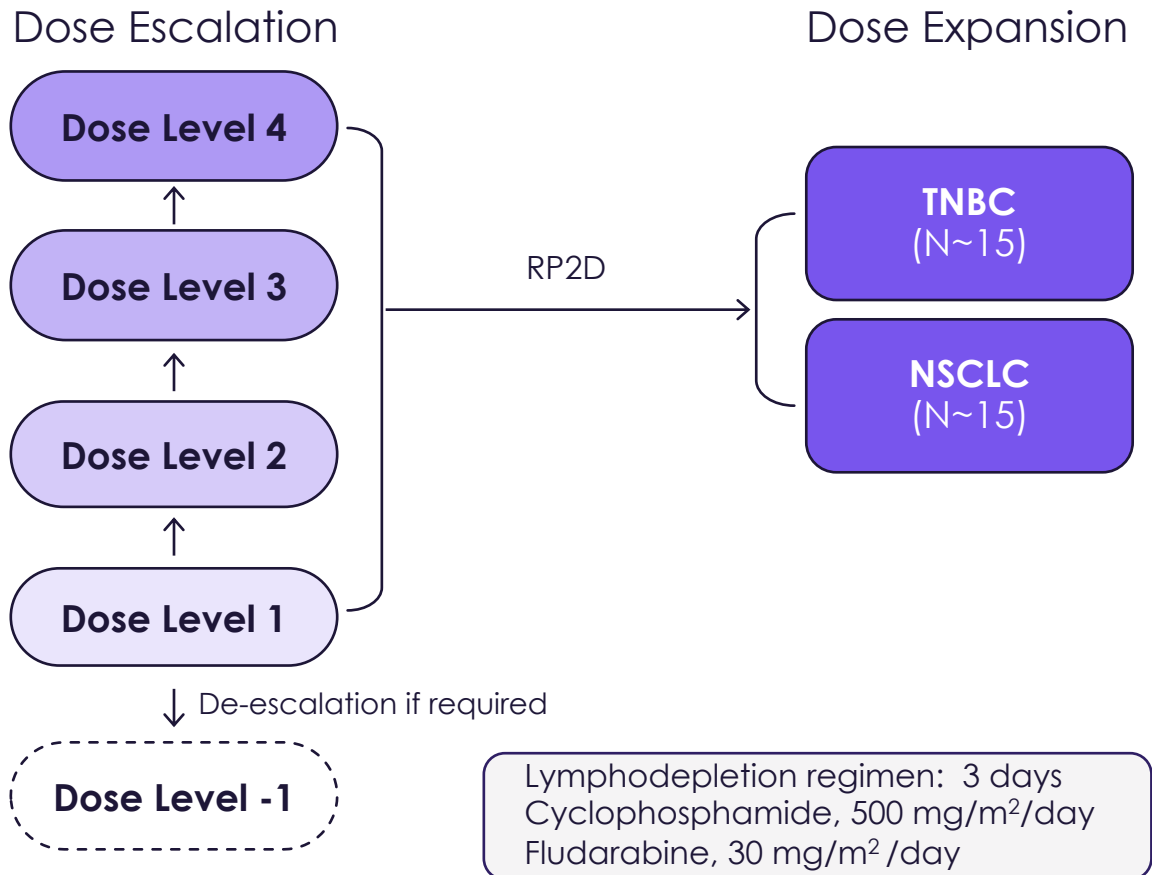
● Mock ● Control ROR1 CART ● LYL797

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

LYL797: Phase 1 Trial Design



mTPI-2 Dose Escalation Followed by Dose Expansion



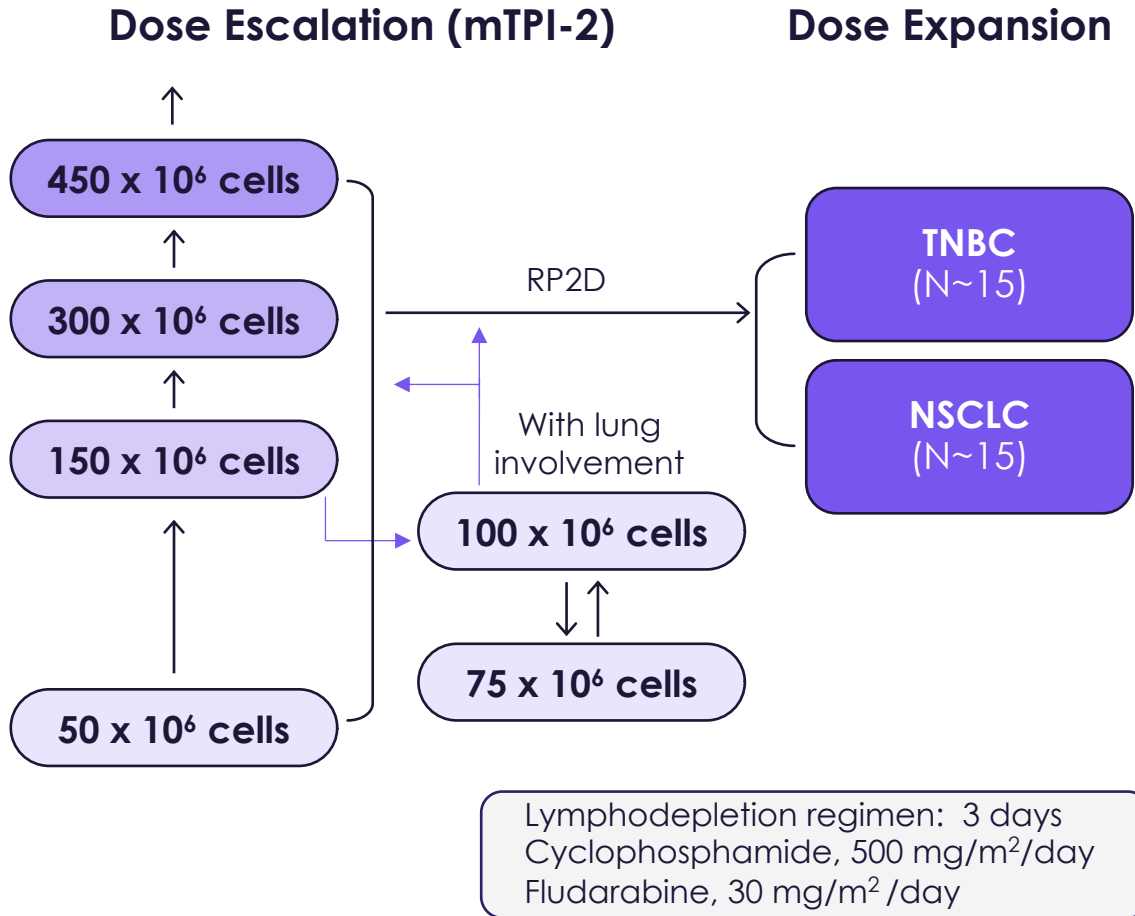
Patient Population

- 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

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



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

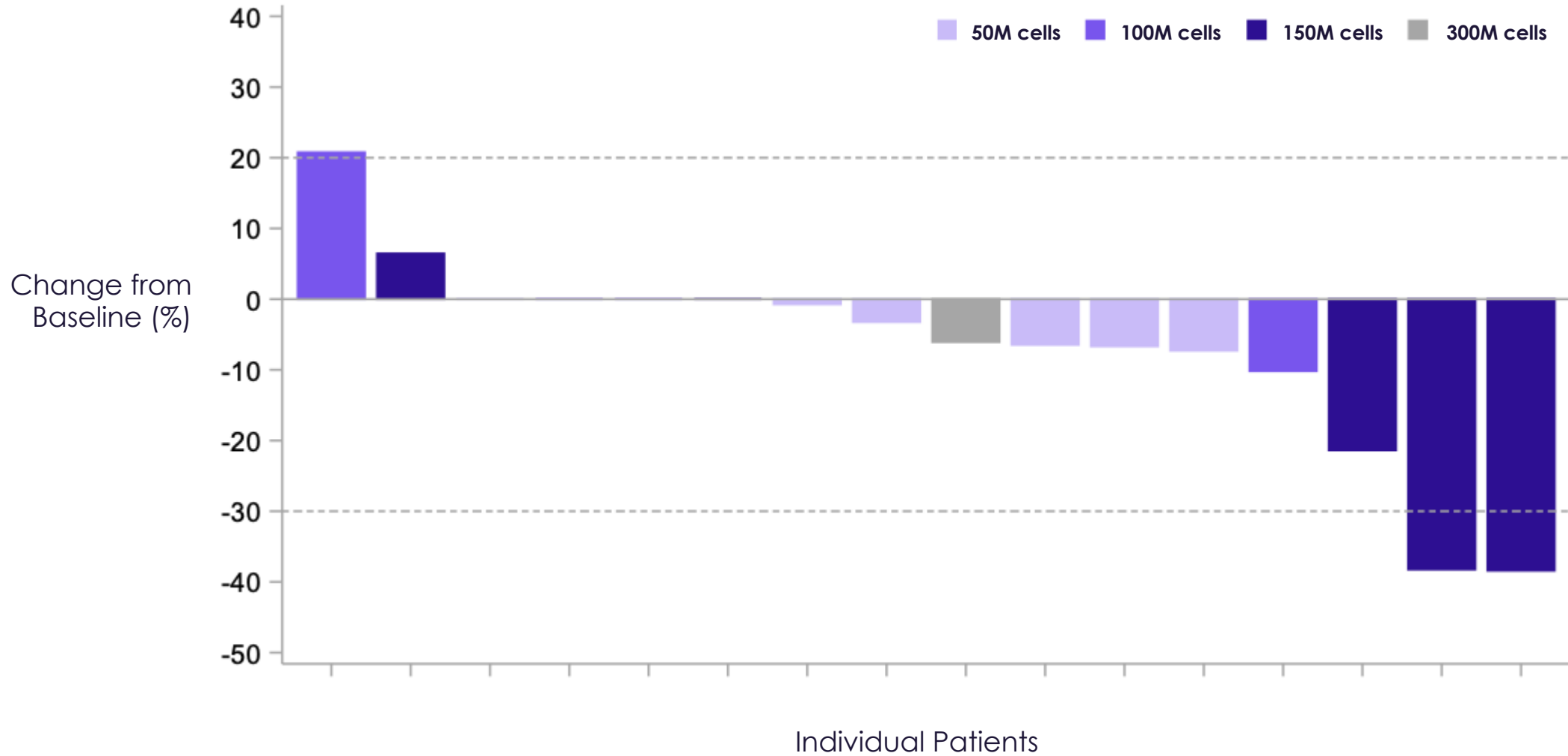


Efficacy evaluable patients, n	50 x 10 ⁶ cells n = 6	100 x 10 ⁶ cells n = 4	150 x 10 ⁶ cells n = 5*	300 x 10 ⁶ cells n = 1	Total N = 16
Patients with CR/PR, n	0	0	2	0	2
Patients with SD, n	1	1	1	1	4
ORR %	0%	0%	40%	0%	13%
Duration of Response	2 cPRs to Day 90				
Clinical Benefit Rate	17%	25%	60%	100%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

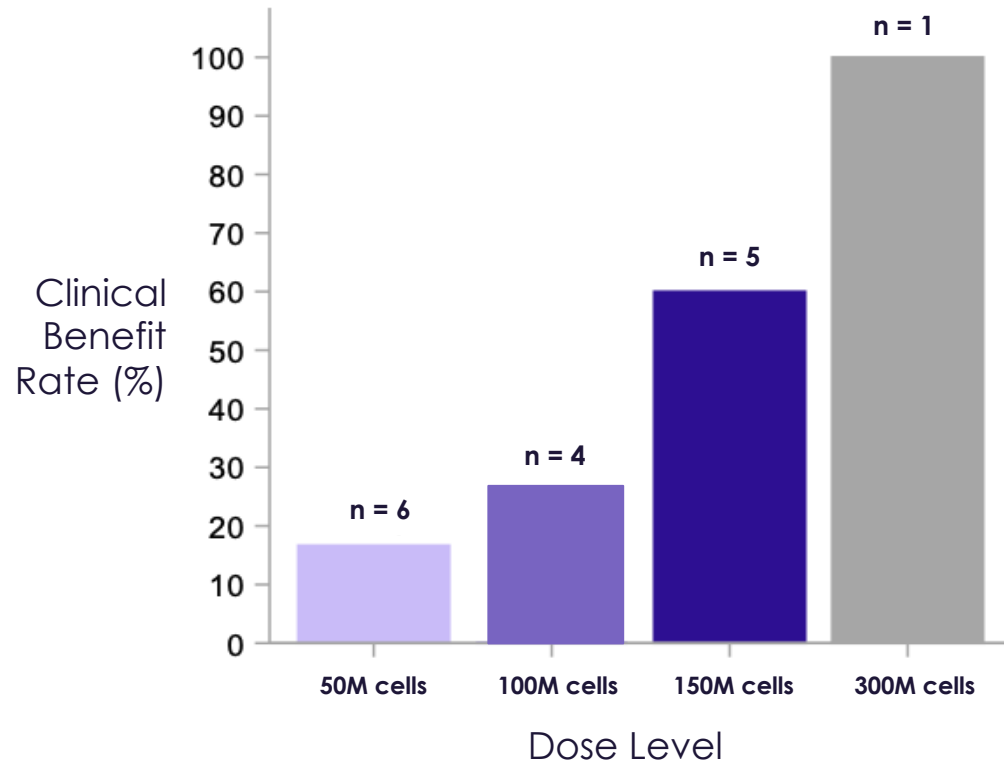
* 5 patients with TNBC; Data cutoff of 29 May 2024

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



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

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 \geq 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 \geq 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

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 300×10^6 cells for patients without lung involvement
 - Dosing at 75×10^6 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

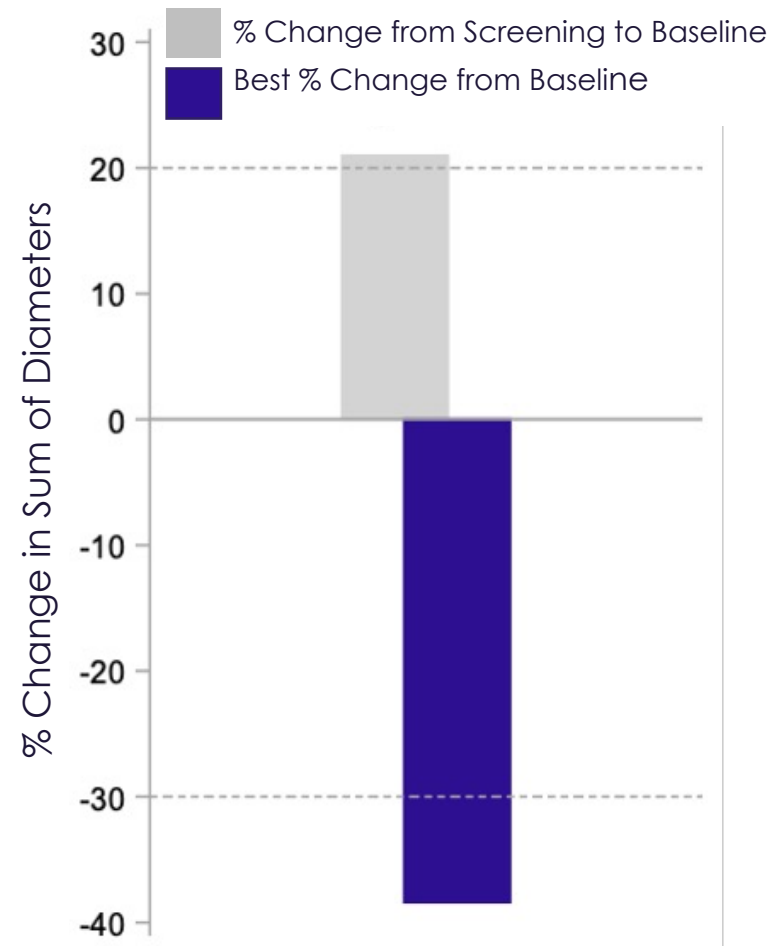
Case Report of LYL797 Clinical Activity



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 150×10^6 LYL797 CAR T cells.

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



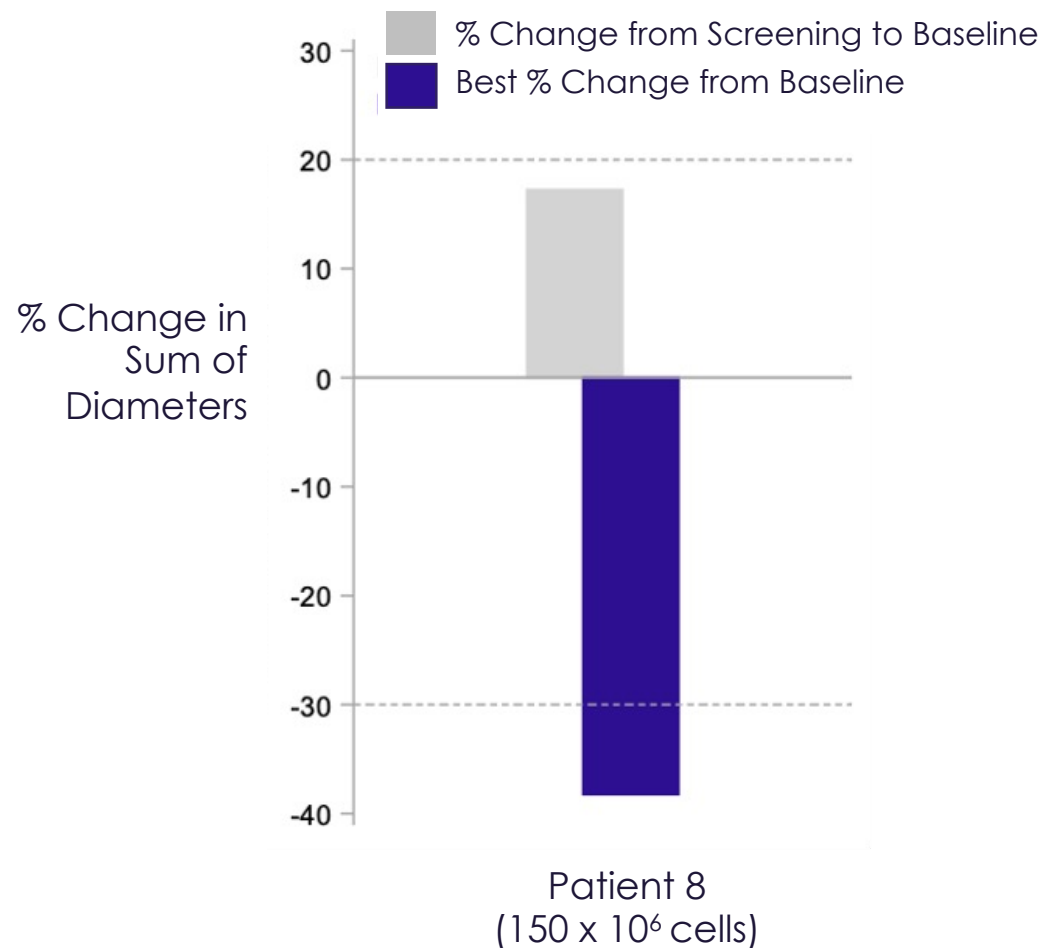
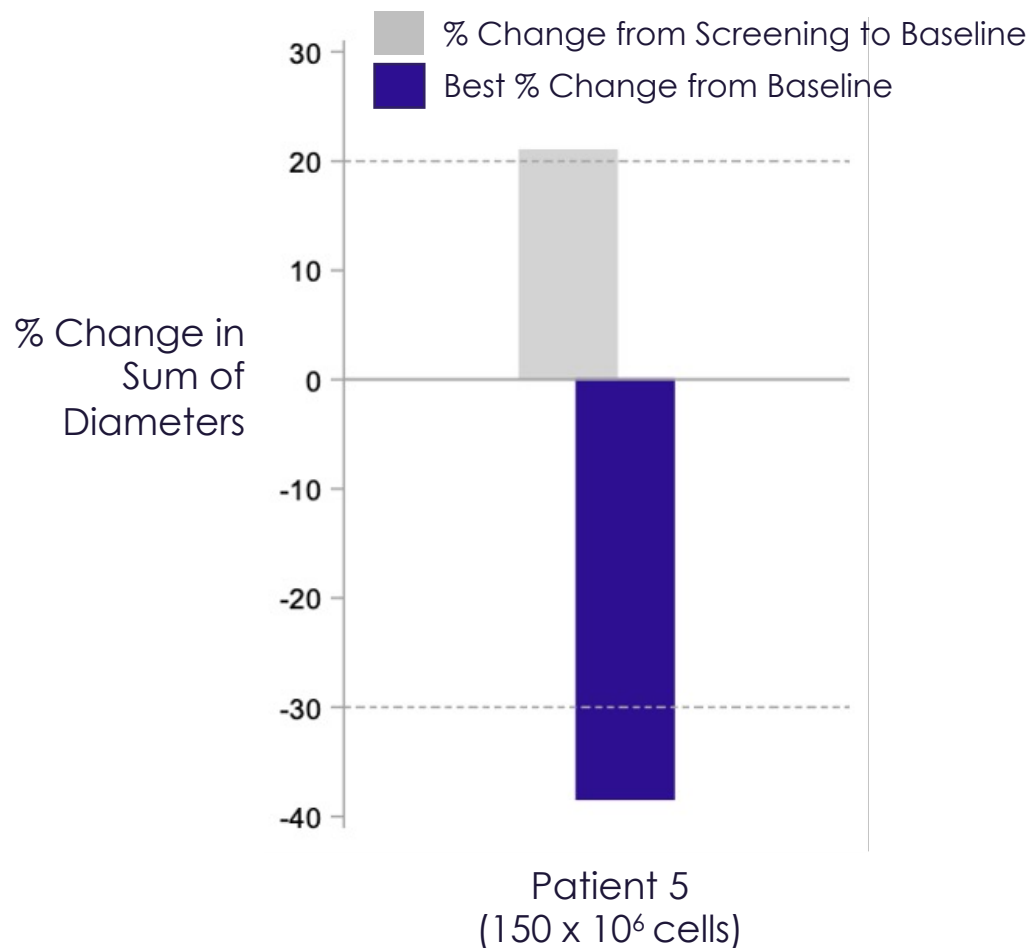
Case Report of LYL797 Clinical Activity



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

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





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)

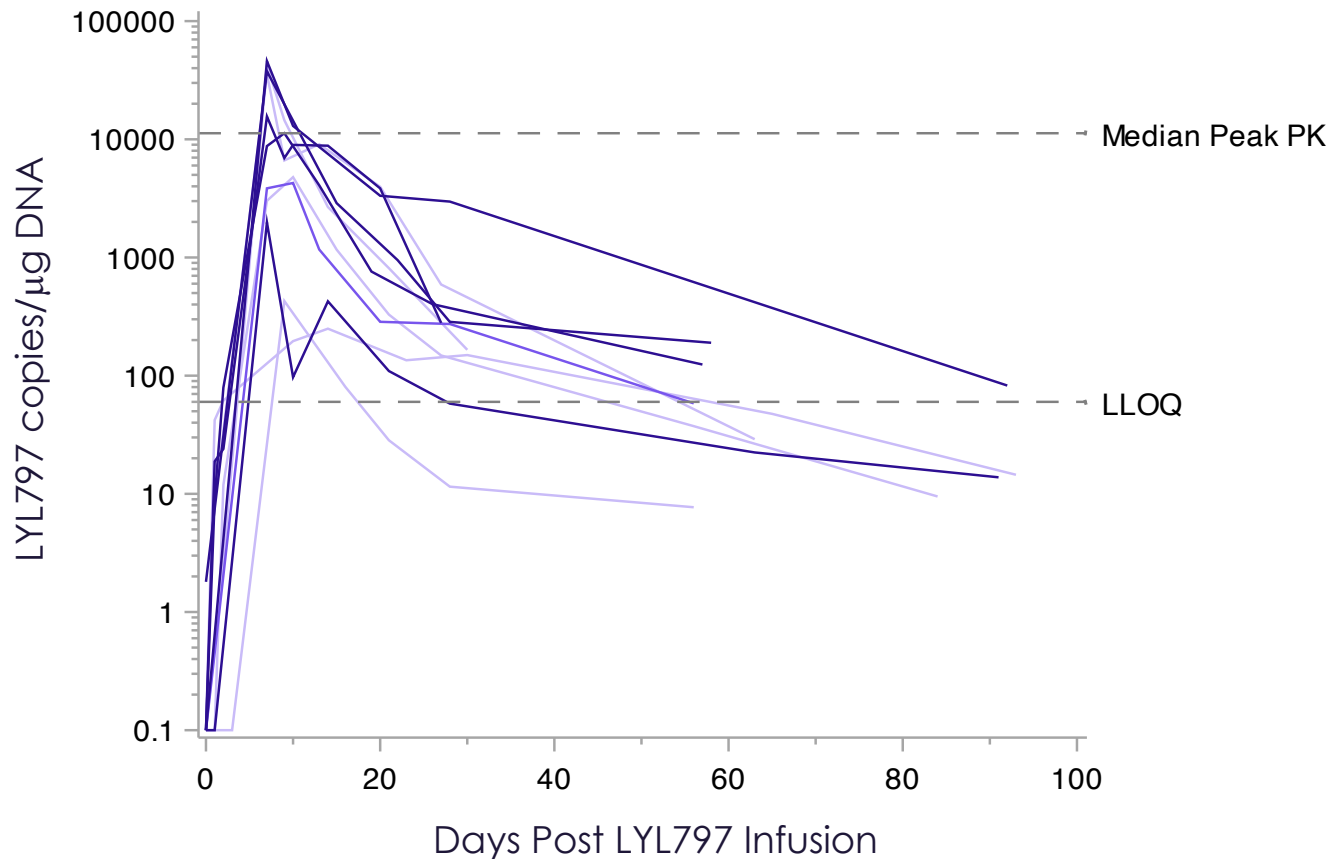
Infiltration and Tumor Lysis

- 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

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)

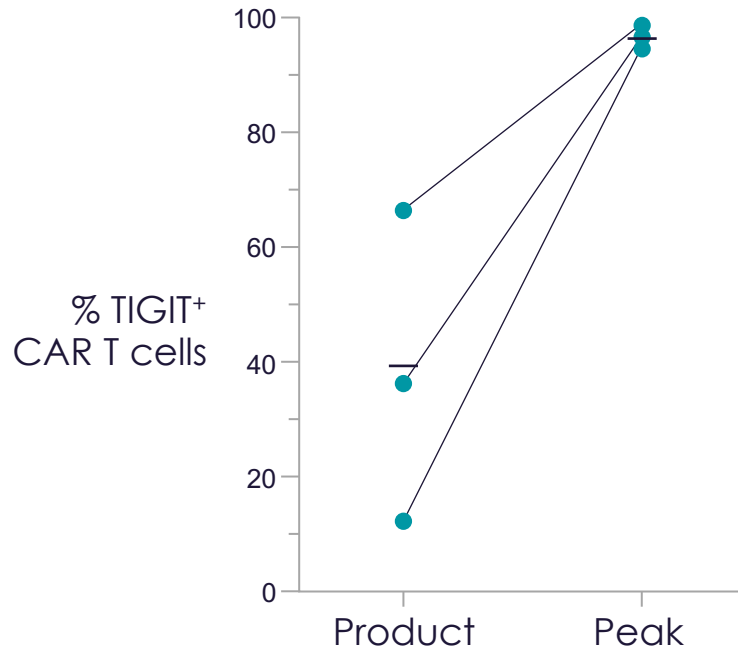
Median peak PK = 11,251 copies/ μg DNA

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

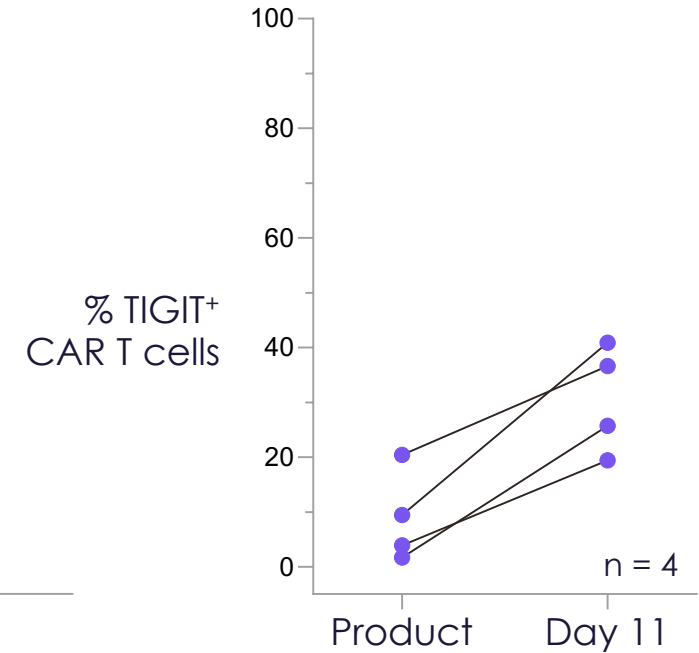
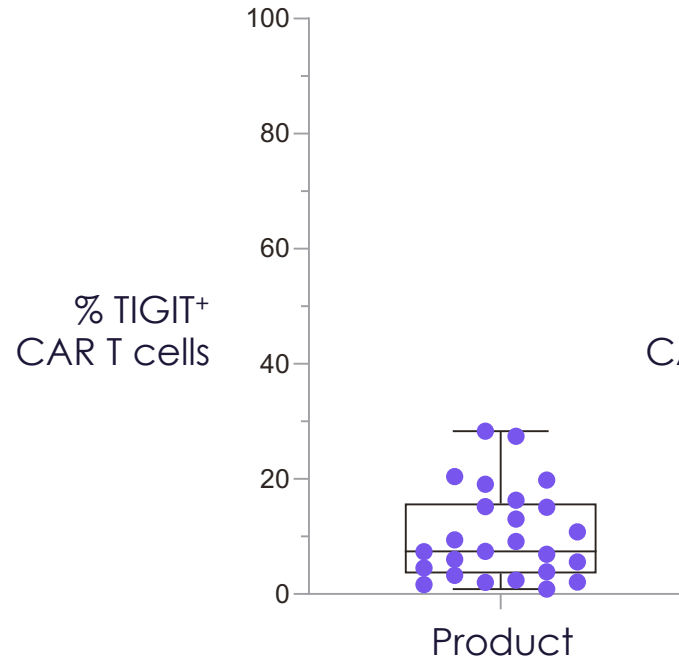
Infusion Products and LYL797 in Day 11 Peripheral Blood Samples Had Significantly Lower Percent TIGIT+ Cells (Exhaustion Marker)



Fred Hutch Cancer Center: Solid Tumor Patients



LYL797 CAR T Cell Data



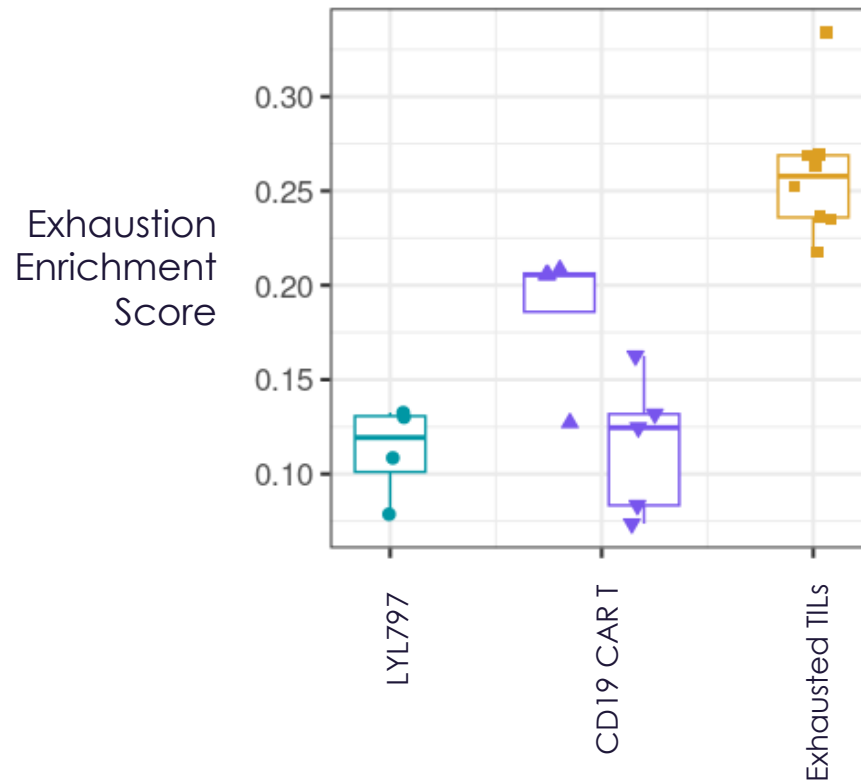
Data cutoff of 29 May 2024; CAR, chimeric antigen receptor; TIGIT, T cell immunoreceptor with immunoglobulin and ITIM domain
Specht J. Jan 31 2020, EHA
*LYL797 defined by CD8+ EGFR+

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



Exhaustion related gene set consistent among multiple tumor types (N = 18 genes)



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

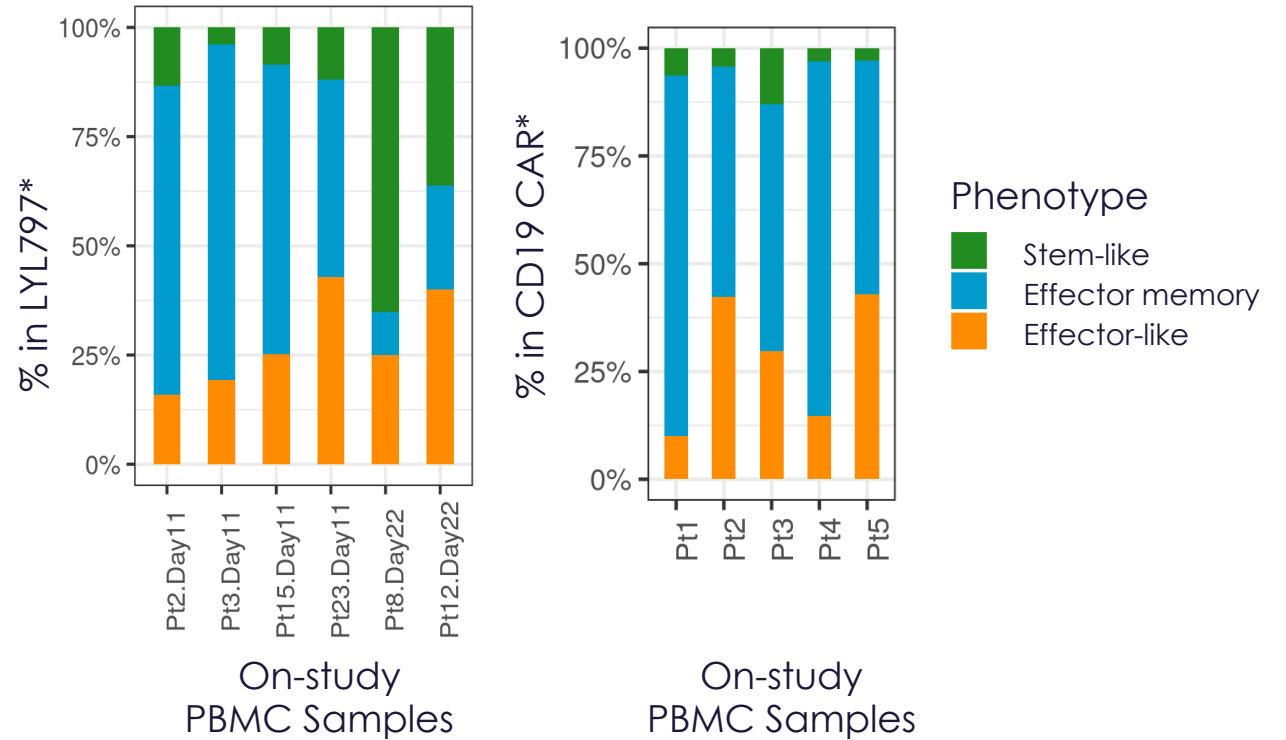
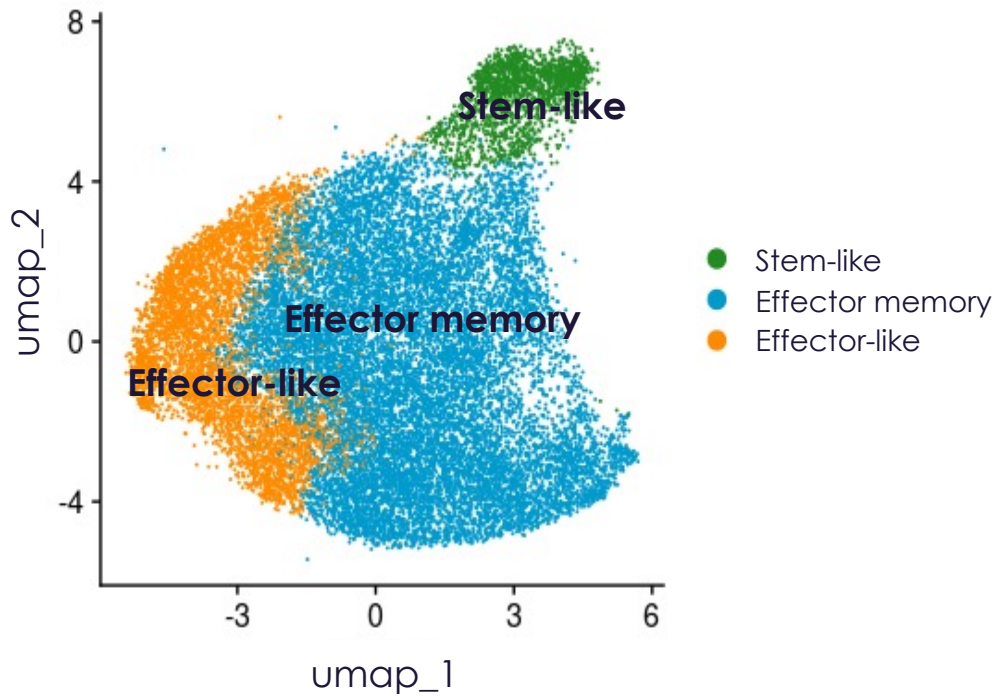
LYL797 Cells from Day 11 and Day 22 PBMC Samples Had a Significant Proportion of Cells with Stem-like and Effector-memory Phenotype



mRNA by RNAseq/ transcriptomic analyses

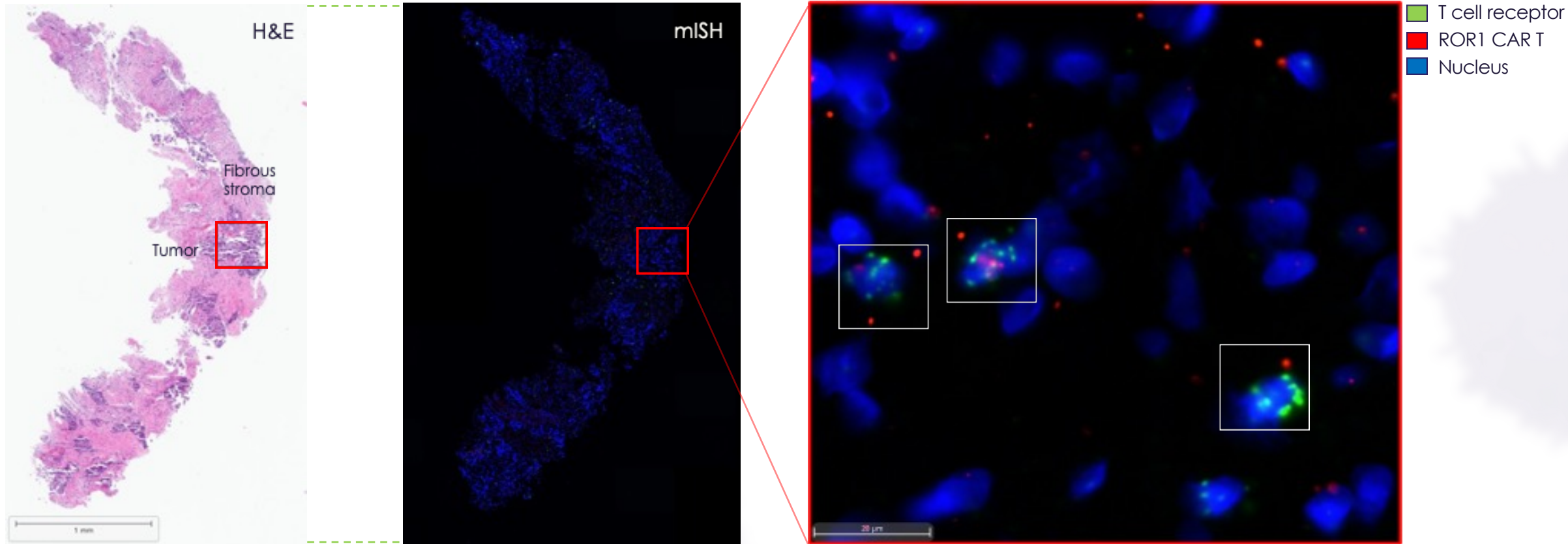
LYL797* Compared to CD19 CAR

LYL797* from Day 11 PBMC Samples



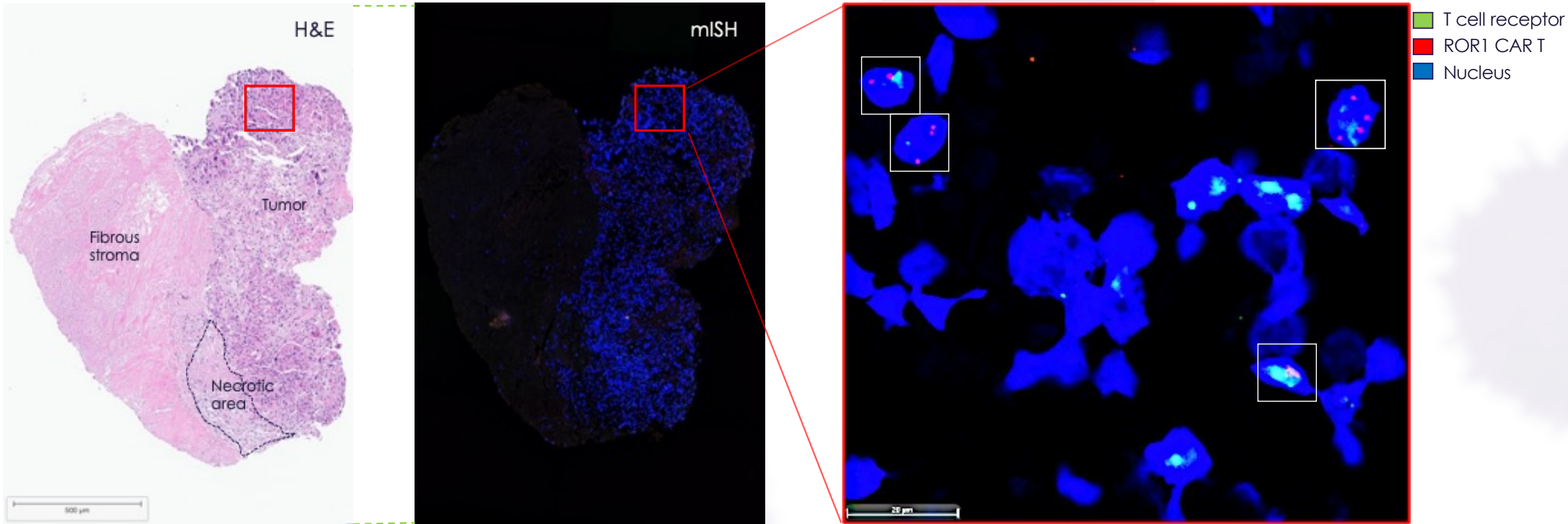
Detection of LYL797 CAR T Cell Infiltration in All Evaluable (N=9) On-study Tumor Biopsies (Days 21-30)

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; 100×10^6 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

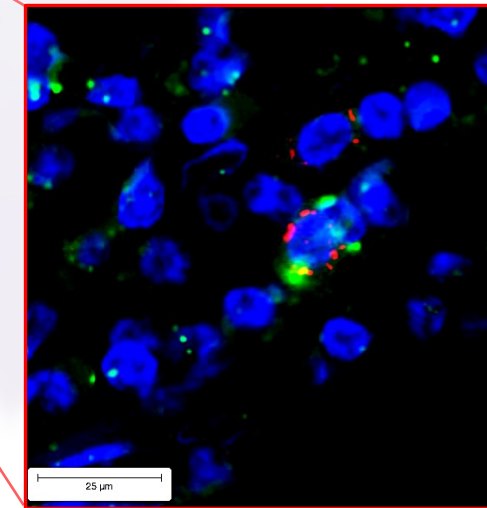
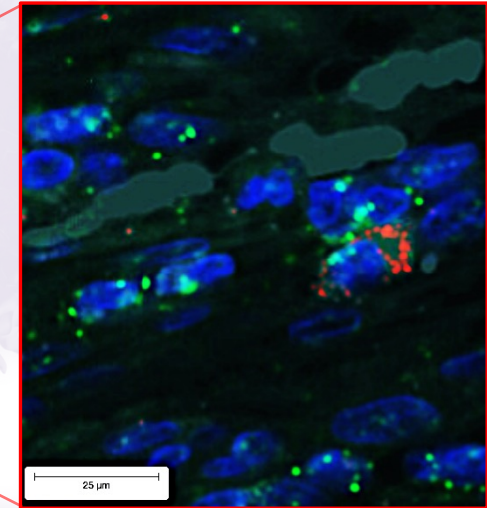
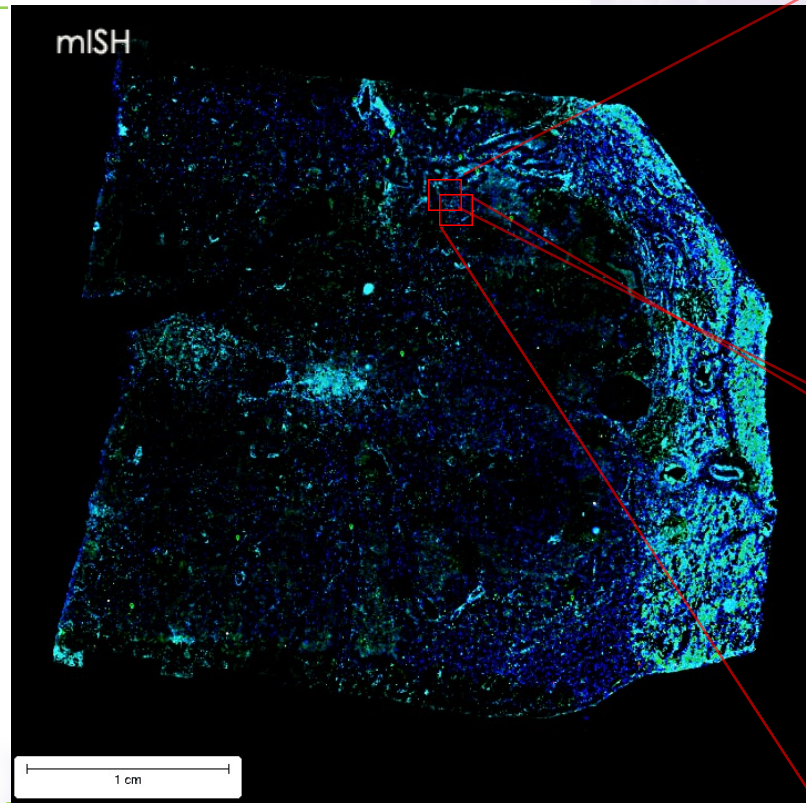
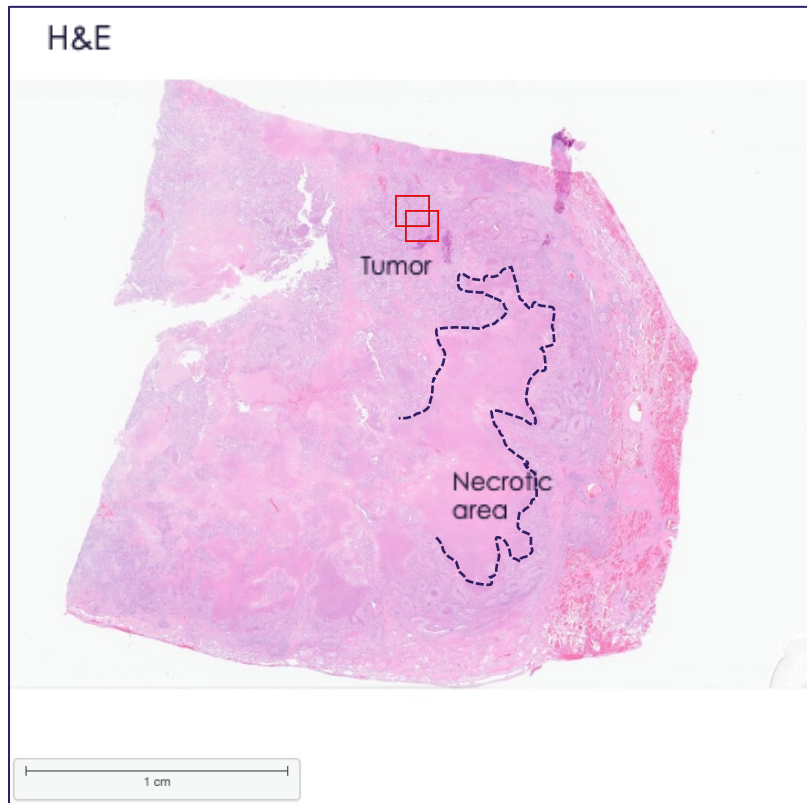
LYL797 CAR T Cell Infiltration in Patient with Confirmed Partial Response (Patient 8)



Data cutoff of 29 May 2024; Patient 8; TNBC; 150×10^6 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



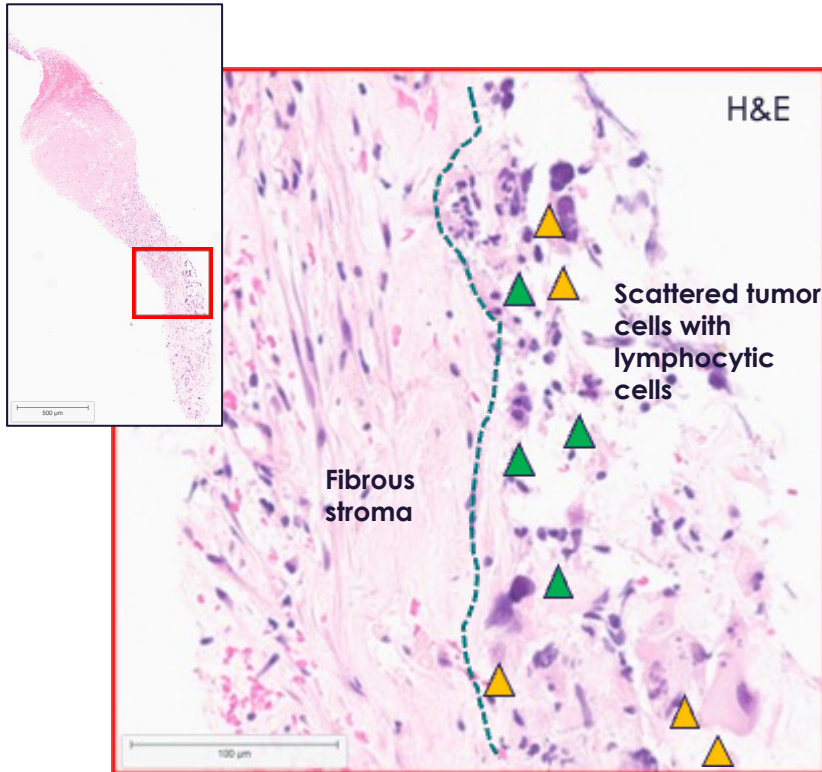
- T cell receptor
- ROR1 CAR T
- Nucleus

Data cutoff of 29 May 2024; Patient 8; TNBC; 150×10^6 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

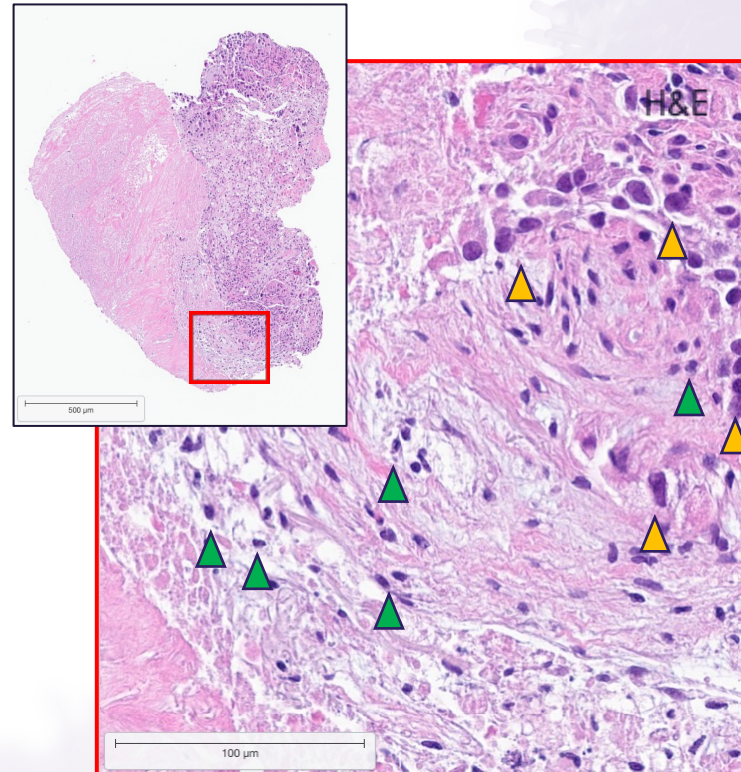
Multiple Tumor Biopsies Had Features Consistent with T Cell-mediated Tumor Lysis Including T Cell-rich Inflammation with Scattered Tumor Cells



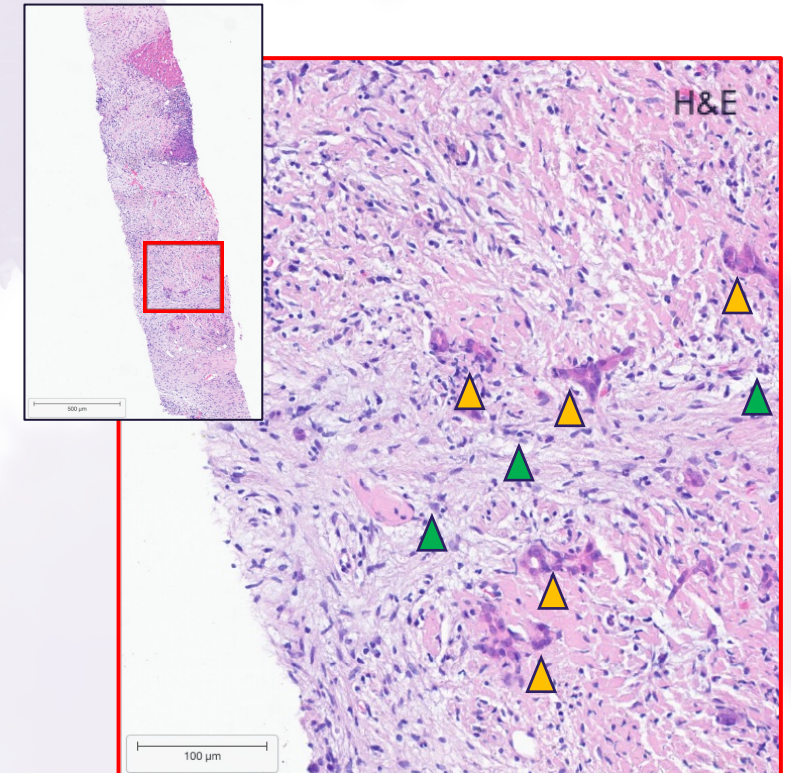
▲ Tumor cells ▲ Lymphocytic cells



Patient 3, TNBC
50 x 10⁶ cells, Day 26 liver biopsy



Patient 5, TNBC
150 x 10⁶ cells, Day 23 liver biopsy



Patient 8, TNBC
150 x 10⁶ cells, Day 28 lung biopsy

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

Next Steps for ROR1 CAR T Cell Program

Demonstrated clinical activity supports expanded development of LYL797 and LYL119

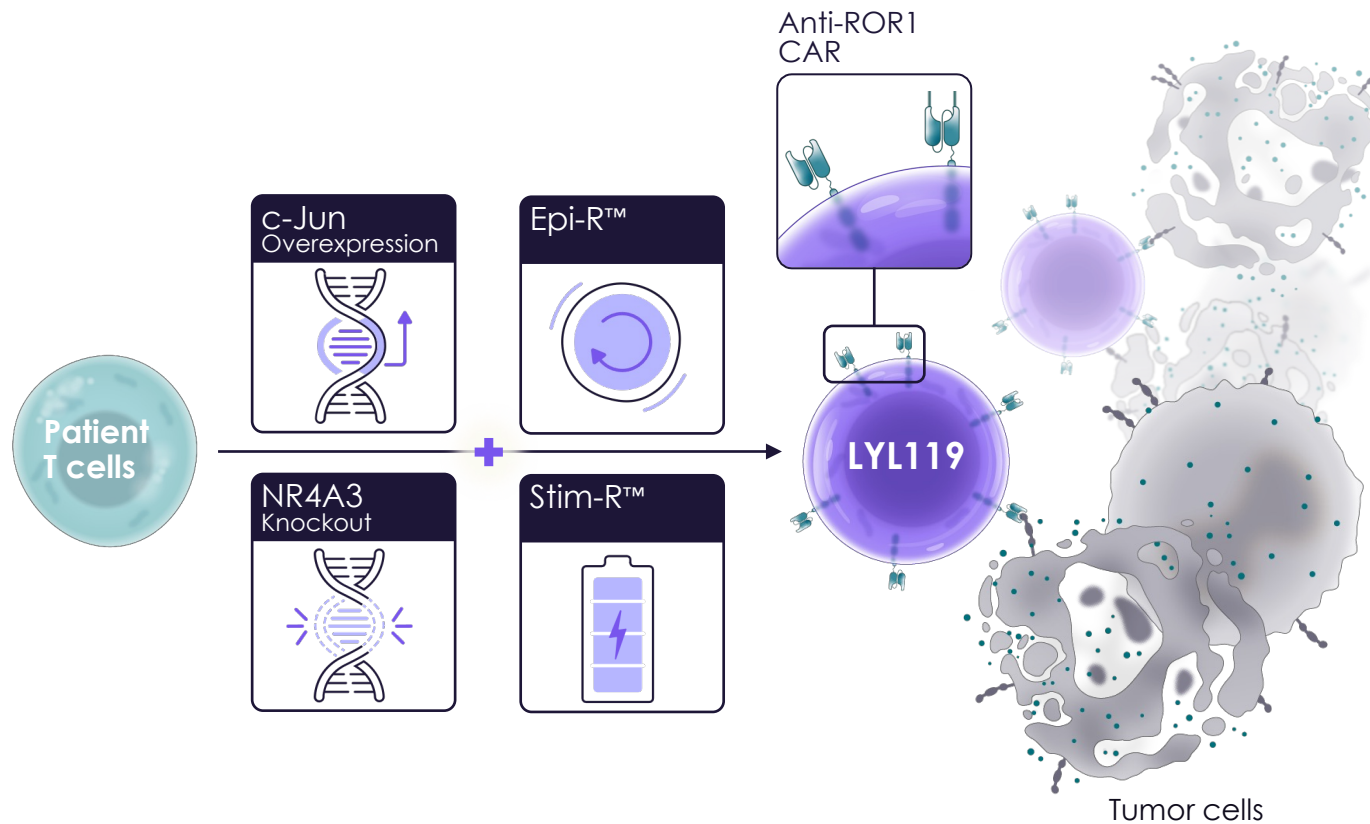
LYL797

- 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

LYL119: Incorporates Novel Stackable Technologies Designed to Improve Potency

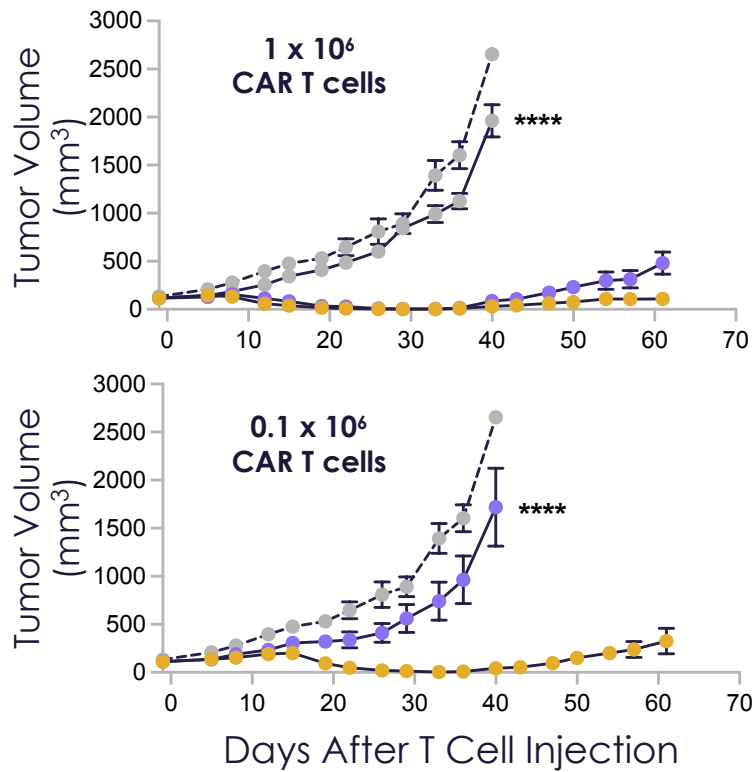


CAR, chimeric antigen receptor; NR4A3, The nuclear receptor 4A3; ROR1, receptor tyrosine kinase-like orphan receptor 1
NR4A3 knockout with CRISPR/Cas9

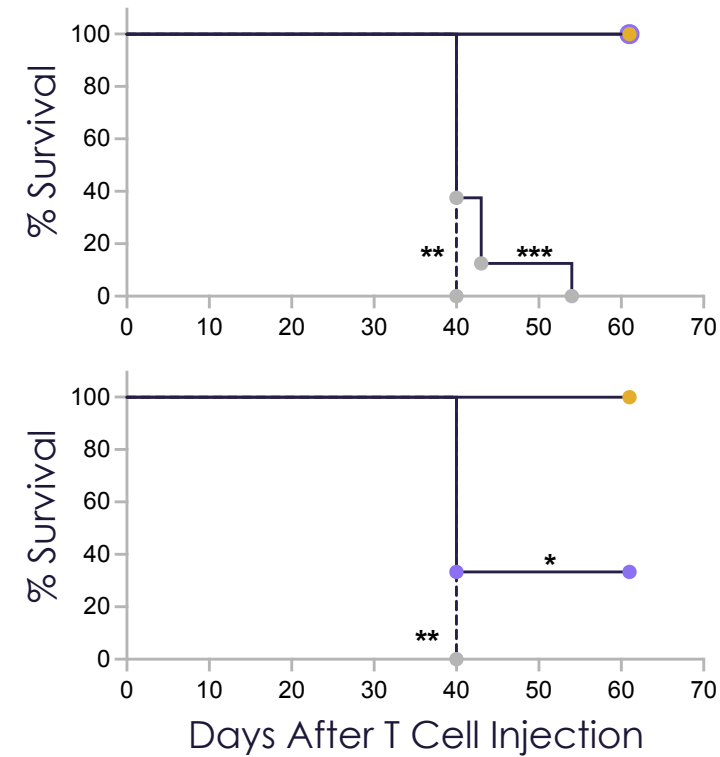
LYL119, Next-generation ROR1-targeted CAR T, Demonstrated More Potent Anti-tumor Activity In Vivo



Significantly Improved Elimination of Xenograft Tumors at the Lower 0.1 x 10⁶ CAR T-cell Dose



Significantly Improved Animal Survival at the Lower 0.1 x 10⁶ CAR T-cell Dose







● - PBS
 ● Mock non-transduced (Epi-R + Stim-R) 1.42 x 10⁶ 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
	<input type="checkbox"/> Begin enrolling patients with ovarian or endometrial cancers
2H24	<input type="checkbox"/> Submit IND for trial in patients with multiple myeloma or CLL
	<input type="checkbox"/> Clinical data update including initiation of dose expansion (late-2024/early-2025)
1H25	<input type="checkbox"/> 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	<input type="checkbox"/> IND clearance
1H25	<input type="checkbox"/> Progress update on Phase 1 trial
2H25	<input type="checkbox"/> Initial clinical data
LYL845	TIL + Epi-R
2H24	<input type="checkbox"/> 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