



Lyell Strengthens Next-Generation CAR T-Cell Pipeline with Novel GCC-Targeted Product Candidate for Metastatic Colorectal Cancer

Lyell Immunopharma — November 10, 2025

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 the potential attributes and benefits of LYL273 and our product candidates; CRC market size and commercial opportunity; our manufacturing capacity and capabilities; our clinical trial plans and expectations; cash runway; clinical and regulatory milestones; clinical and other data updates; 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: our limited experience as a company in initiating and conducting clinical trials and lack of experience in completing clinical trials; the potential for results from clinical trials to differ from nonclinical, early clinical, preliminary or expected results; significant adverse events, toxicities or other undesirable side effects associated with our product candidates; our ability to submit planned INDs or initiate or progress clinical trials on the anticipated timelines, if at all; RMAT and Fast Track designations may not actually lead to faster development, regulatory review or approval process, and does not assure ultimate FDA approval; 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; the complexity of manufacturing cellular therapies and our ability to manufacture and supply our product candidates for our clinical trials; implementation of our strategic plans for our business and product candidates; our realization of the expected benefits of our strategic plans for our business and product candidates, including the license of LYL273; the potential reduction of our cash resources and fluctuations in our operating results and financial condition as a result of our milestone, royalty and success payment obligations for LYL273; the sufficiency of our capital resources and the need for additional capital to achieve our goals; the effects of macroeconomic conditions; other risks, including general economic conditions and regulatory developments, not within our control; and those risks described under the heading “Risk Factors” in our Quarterly Report on Form 10-Q for the quarter ended June 30, 2025, filed with the Securities and Exchange Commission (SEC) on August 12, 2025, 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.

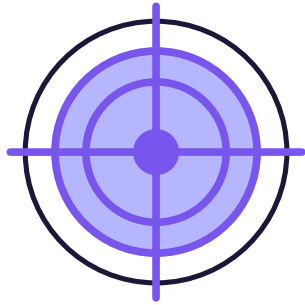
Advancing Next-Generation CAR T-Cell Therapies



**Meaningfully
improve outcomes
in hematologic
malignancies with
innovative CAR
T-cell therapies**

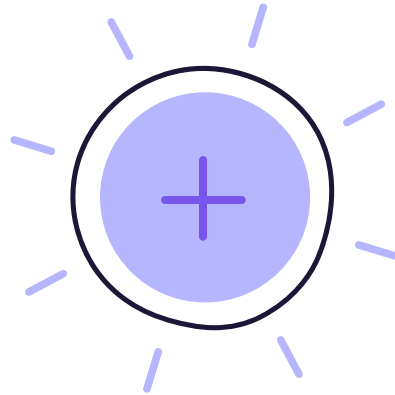
**Aggressively
progress the next
wave of cell therapy
innovation for
solid tumors**

Creating an Industry-Leading Pipeline of Next-Generation CAR T-Cell Therapies



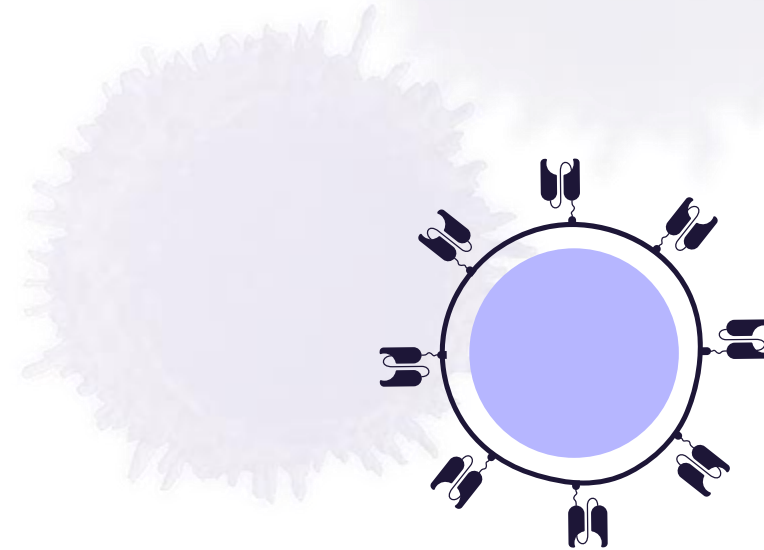
Identify promising targets

- High tumor expression to enhance benefit
- Low expression or inaccessible in normal tissue to avoid on-target, off-tumor toxicity



Arm with enhancements designed to improve the T cell's ability to fight cancer

- Expansion
- Stemness
- Anti-Exhaustion
- Infiltration
- Cytotoxicity



Develop one-time CAR T-cell therapies

- Designed to deliver lasting remission or even cure for patients with cancer

Strengthening Our Pipeline with New Solid Tumor Cell Therapy Program (LYL273)



Potentially transformative clinical-stage program in colorectal cancer (CRC)

- CRC is the 2nd leading cause of cancer deaths globally
- 67% overall response rate and 83% disease control rate at highest dose of LYL273 evaluated to date in patients with refractory mCRC in U.S. Phase 1 clinical trial; manageable safety profile
- GCC-targeted CAR T-cell product candidate enhanced with CD19 CAR expression and controlled cytokine release
 - GCC expression present on > 95% of mCRC and a majority of pancreatic cancers
 - Novel technology designed to enhance post-infusion CAR T-cell expansion, immune cell infiltration and cancer cell killing in the hostile solid tumor microenvironment
- Upfront payment of \$40 million and 1.9 million shares; additional clinical, regulatory, and commercial milestones plus tiered royalties

Colorectal Cancer Is the Second Leading Cause of Cancer Deaths Worldwide and is a Large and Growing \$6+ Billion Market

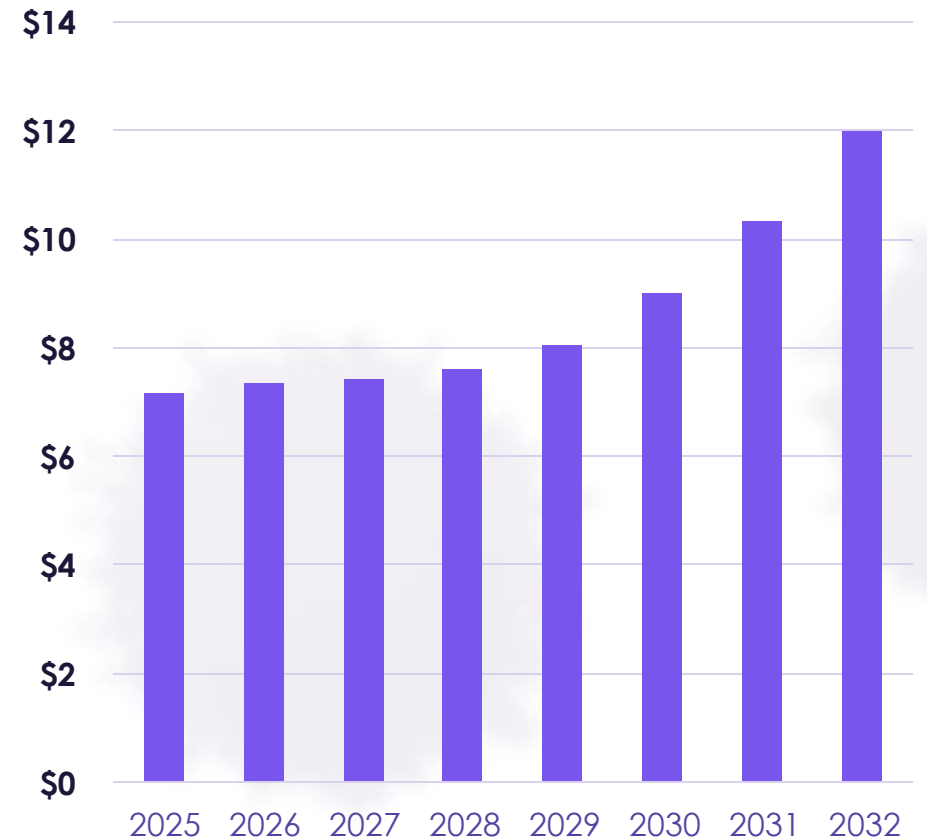
A common cancer that is often diagnosed late:

- Over 150,000 new cases and more than 50,000 deaths expected in the U.S. in 2025
- Approximately 25% of patients have metastatic disease at diagnosis
- Up to 60% of patients diagnosed with colorectal cancer will develop distant metastases at some point

More effective and safer therapies are needed:

- Median survival is < 12 months for patients treated with approved agents in the third- or later-line setting
- **Overall response rates are < 6%**

Worldwide Projected Net Sales
\$Billions (CRC)



Standard of Care Therapies in 3L+ mCRC Do Not Achieve Meaningful Response Rates or Survival Benefit



Treatment	Overall Response Rate	mPFS (months)	mOS (months)
LONSURF® (trifluridine/tipiracil) + AVASTIN® (bevacizumab) SUNLIGHT Trial (N = 246/group)	6%	6	11
LONSURF® (trifluridine/tipiracil) RECOURSE Trial (N = 534 TAS-102)	2%	2	7
FRUZAQLA® (fruquintinib) FRESCO-2 Trial (N = 461 fruquintinib)	2%	4	7
STIVARGA® (regorafenib) CORRECT Trial (N = 505 regorafenib)	1%	2	6

Grothey et al., 2013, Lancet; Mayer et al., 2015, N Engl J Med; Prager et al., 2023, N Engl J Med; Dasari et al., 2023, Lancet

mPFS, median progression-free survival; mOS, median overall survival

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LYL273 (Formerly GCC19CART) Initially Studied in China

Published in *JAMA Oncology* September 2024; single center experience

- 15 patients with refractory mCRC
- Dose Level 1: 1×10^6 CAR T cells/kg (N = 8) or Dose Level 2: 2×10^6 CAR T cells/kg (N = 7)
- Single day of lymphodepletion (fludarabine, 30 mg/m^2 and cyclophosphamide, 300 mg/m^2)

Efficacy:

- Across both dose levels, the overall response rate was 40% (6/15), with six patients achieving PRs (3 confirmed)
- Five additional patients achieved stable disease, resulting in a disease control rate of 73%
- At Dose Level 2, median OS was 25 months (95% CI, 13.4 to 26.1), median PFS was 6.0 months (95% CI, 3.0 to NA)

Additional Patient Safety Data

- Unpublished data: the prior sponsor, Innovative Cellular Therapeutics, reports 20 previously-treated patients at various doses with various manufacturing processes across multiple different centers in China. During the study treatment period, five deaths were reported at these trial sites. The study was subsequently focused at one expert center with CAR T-cell therapy experience.

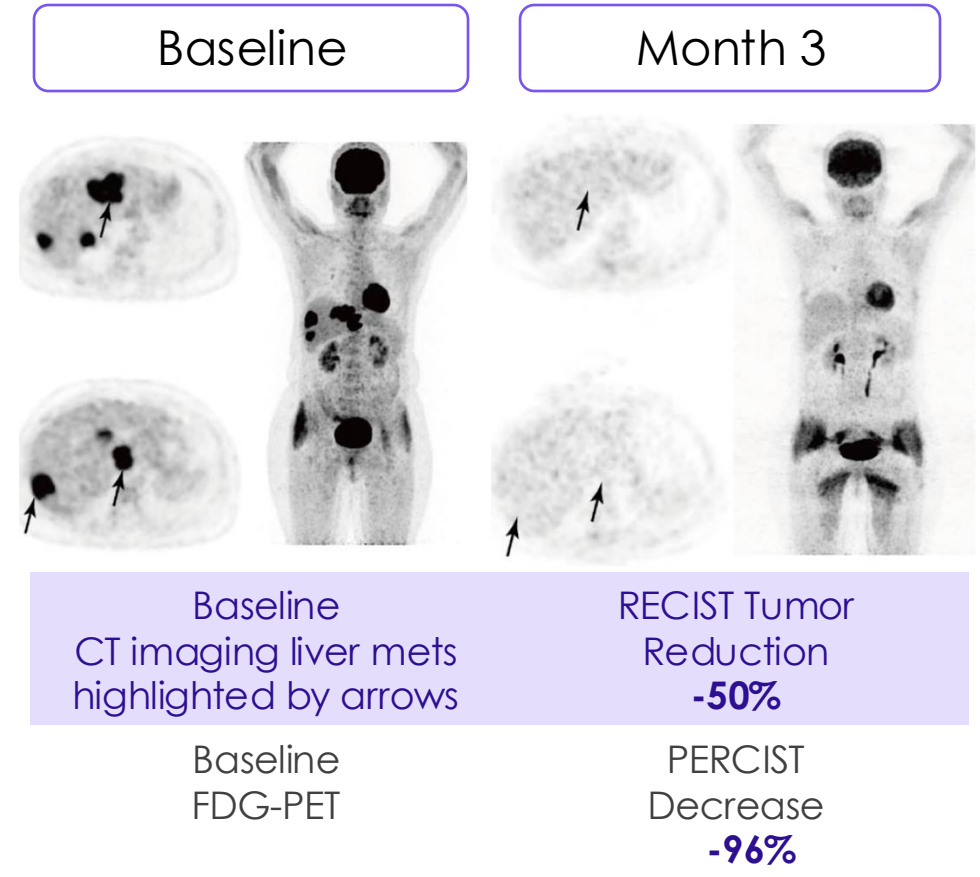
Safety – Dose Level 2:

- Cytokine release syndrome (86%, Grades 1 or 2)
- Diarrhea (57%, Grade 3), all resolved
- Leukopenia (57%, Grade 3); all patients with transient and reversible hematologic AEs
- One case of Grade 4 ICANS
- No deaths occurred during the study treatment period

Proof-of-Concept Case Study

The compelling clinical responses in Chinese patients published in *JAMA Oncology*, such as that described below, led to the initiation of an FDA-cleared clinical trial in the U.S.

- 48-year-old woman diagnosed with mCRC
- Surgical resection and four prior lines of chemotherapy
- Multiple courses of radiation to liver and lungs
- Received 2×10^6 CAR+ T cells/kg
- Grade 1 CRS, no ICANS reported, Grade 3 diarrhea
- Dramatic reduction in liver metastases as early as Month 1
- 50% tumor reduction on CT imaging and 96% reduction on on FDG-PET scan at Month 3
- Duration of partial response was 8 months and the patient lived for 46 months after CAR therapy



U.S. Phase 1 Clinical Trial of LYL273 with High Overall Response Rates and Manageable Safety

Dose-Escalation, Dose-Expansion Clinical Trial

- Four enrolling centers
- Patients with mCRC with disease progression on at least two prior lines of therapy

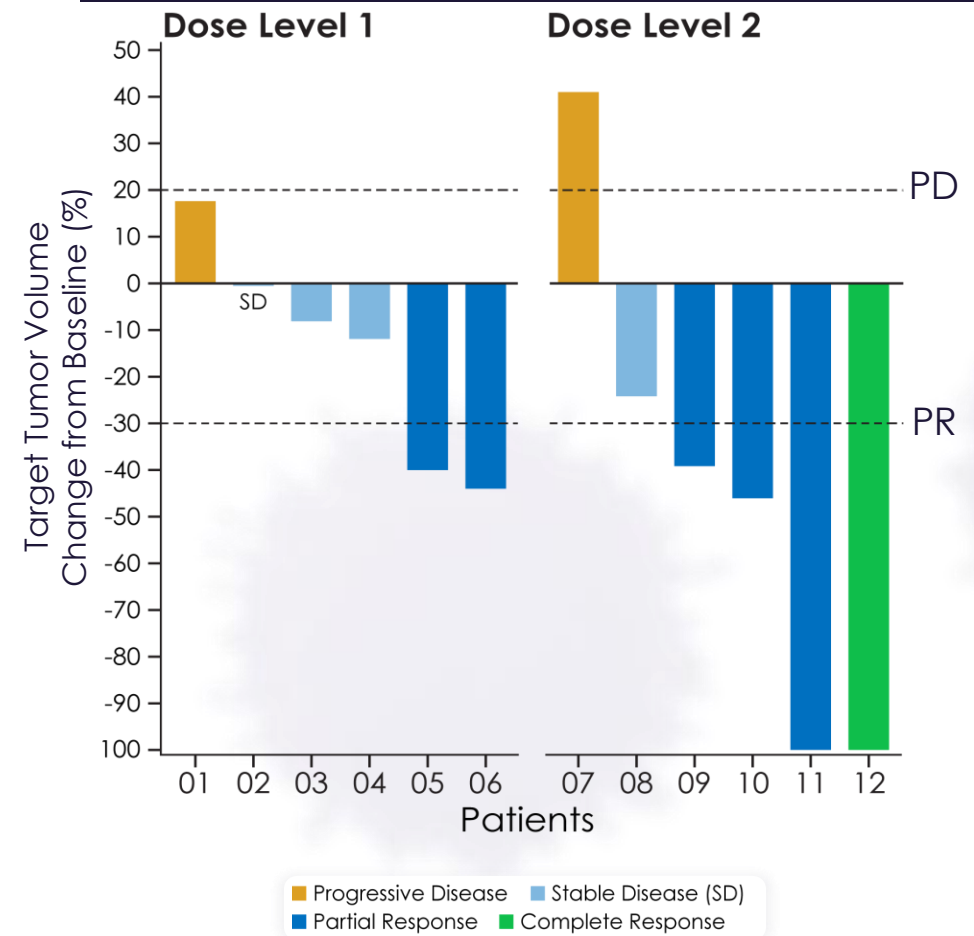
Dose-dependent increase in overall response rate

- 50% overall response rate in 12 evaluable patients
- **67% (4/6) overall response rate at Dose Level 2**
 - One pathological complete response
 - One confirmed partial response with 100% target lesion tumor reduction
 - Two additional confirmed partial responses

Manageable Safety Profile

- Optimized management protocol for diarrhea, including prophylaxis

Tumor Reduction / Best Overall Response

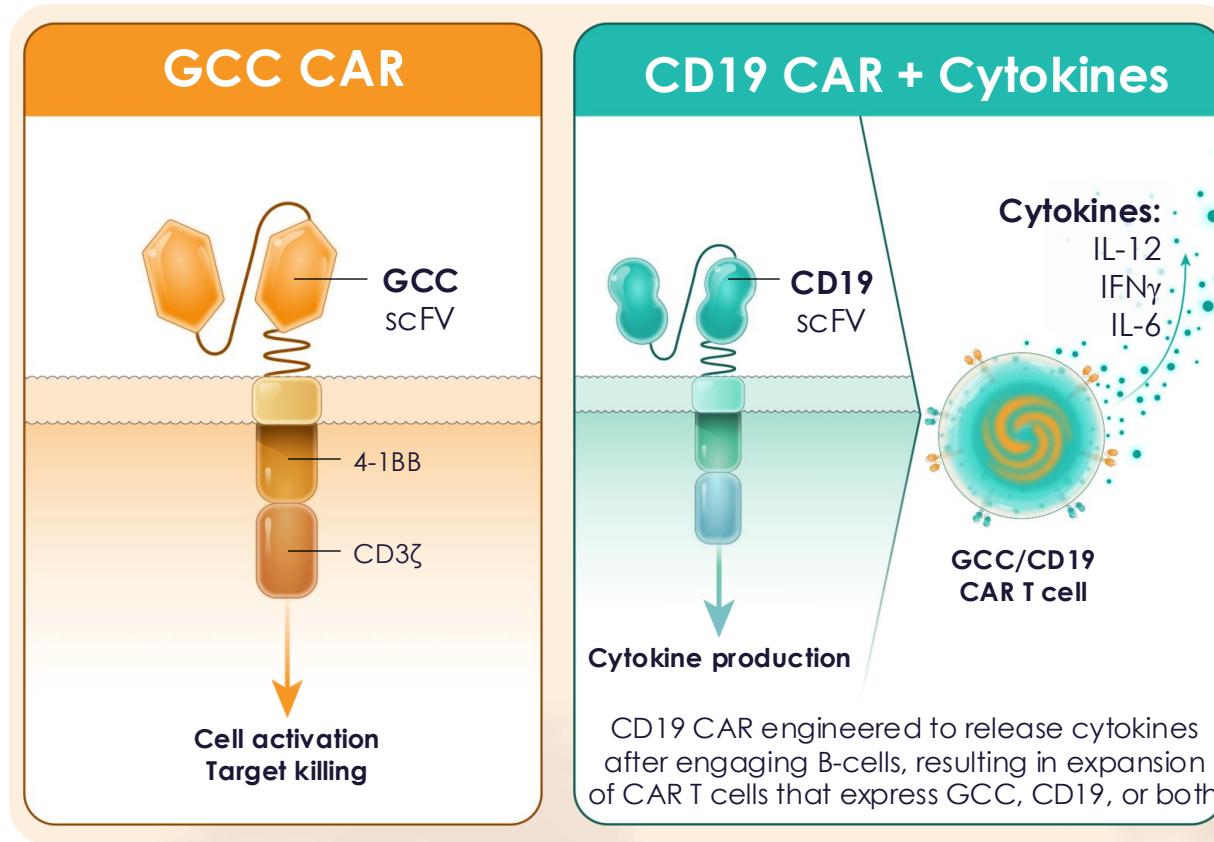


LYL273: GCC-Targeted CAR T-Cell Therapy with Novel Enhancements and Potential to be Transformational for Patients with Refractory mCRC

What is the Breakthrough?

Identify the Target: Guanylyl cyclase-C (GCC)

- Expressed on over 95% of metastatic colorectal cancers
- Regulates electrolyte balance in healthy intestinal tissue



Arm with Enhancements: CD19 CAR/Cytokines

- Patient T cells are engineered to express GCC and/or CD19 CARs
- GCC/CD19 CAR T cells expand, infiltrate and kill colorectal cancer cells



LYL273 GCC-Targeted CAR T-Cell Therapy: Data from U.S. Phase 1 Clinical Trial

David Shook, M.D.
Chief Medical Officer

U.S Phase 1 Clinical Trial of GCC-Targeted CAR T-Cell Therapy (LYL273) Armed with Enhancements for mCRC

A dose-escalation, dose-expansion trial was initiated in the U.S.

- Four experienced cell therapy centers
 - Dana Farber Cancer Institute; University of California, San Francisco Comprehensive Cancer Center; University of Colorado Cancer Center; City of Hope Comprehensive Cancer Center
- Data presented from 12 patients:
 - Dose Level 1 (1×10^6 CAR T cells/kg) (N = 6)
 - Dose Level 2 (2×10^6 CAR T cells/kg) (N = 6)
- One day of lymphodepletion (cyclophosphamide, 300 mg/m², fludarabine, 30 mg/m²)

Key Inclusion/Exclusion Criteria

- Refractory mCRC that progressed following at least two prior lines of therapy
- One measurable lesion per RECIST 1.1
- Liver metastases included, but limited to no more than seven lesions with the largest lesion less than 3 cm
- No surgical options with curative intent

Baseline Patient Demographics and Disease Characteristics



Characteristics	Dose Level 1 (N = 6)	Dose Level 2 (N = 6)	Overall (N = 12)
Age, year			
Median (range)	46 (39-52)	53 (46-57)	49 (39-57)
Sex, n, %			
Male	3 (50%)	3 (50%)	6 (50%)
Female	3 (50%)	3 (50%)	6 (50%)
Prior Therapies			
Median prior lines, n (range)	3 (2-6)	3 (1-5)	3 (1-6)
Median 5-FU combo regimens e.g., FOLFOX/FOLFIRI, n (range)	2 (1-3)	2 (1-4)	2 (1-4)
LONSURF® (trifluridine/tipiracil), n (%)	1 (17%)	2 (33%)	3 (25%)
AVASTIN® (bevacizumab), n (%)	6 (100%)	6 (100%)	12 (100%)
Disease Sites			
Median (range)	2.5 (1-3)	2 (1-3)	2 (1-3)
Mutations			
MSS/pMMR	6 (100%)	6 (100%)	12 (100%)
RAS mutated	1 (17%)	3 (50%)	4 (33%)

FOLFOX, folinic acid (leucovorin), fluorouracil (5-FU), and oxaliplatin; FOLFIRI, folinic acid (leucovorin), 5-fluorouracil (5-FU), and irinotecan.

MSS, microsatellite stable; pMMR, proficient mismatch repair; RAS, rat sarcoma

LONSURF is a registered trademark of Taiho Pharmaceutical Co., Ltd., AVASTIN is a registered trademark of Genentech, Inc.

Manageable Safety Profile

Treatment-Related Adverse Events

Adverse Events of Interest, N (%)

CRS	Dose Level 1 (N = 6)	Dose Level 2 (N = 6)
Grade 1	4 (67%)	4 (67%)
Grade 2	2 (33%)	1 (17%)
Grade 3	0	0
ICANS		
Grade 1	0	0
Grade 2	0	1 (17%)
Grade 3	0	1 (17%)

Diarrhea	Dose Level 1 (N = 6)	Dose Level 2 (N = 6)
Grade 1	2 (33%)	2 (33%)
Grade 2	1 (17%)	2 (33%)
Grade ≥ 3	1 (17%)	1 (17%)
Other Common Adverse Events		
Fatigue	3 (50%)	4 (67%)
Nausea	3 (50%)	5 (83%)

- One patient treated at Dose Level 2 experienced a dose-limiting toxicity of Grade 3 diarrhea, Grade 4 colitis, and died from fungal sepsis 48 days after infusion.
- No Grade 3 or higher diarrhea occurred in the three patients enrolled since establishing an optimized management protocol for diarrhea, including prophylaxis.

Best Overall Response Rates

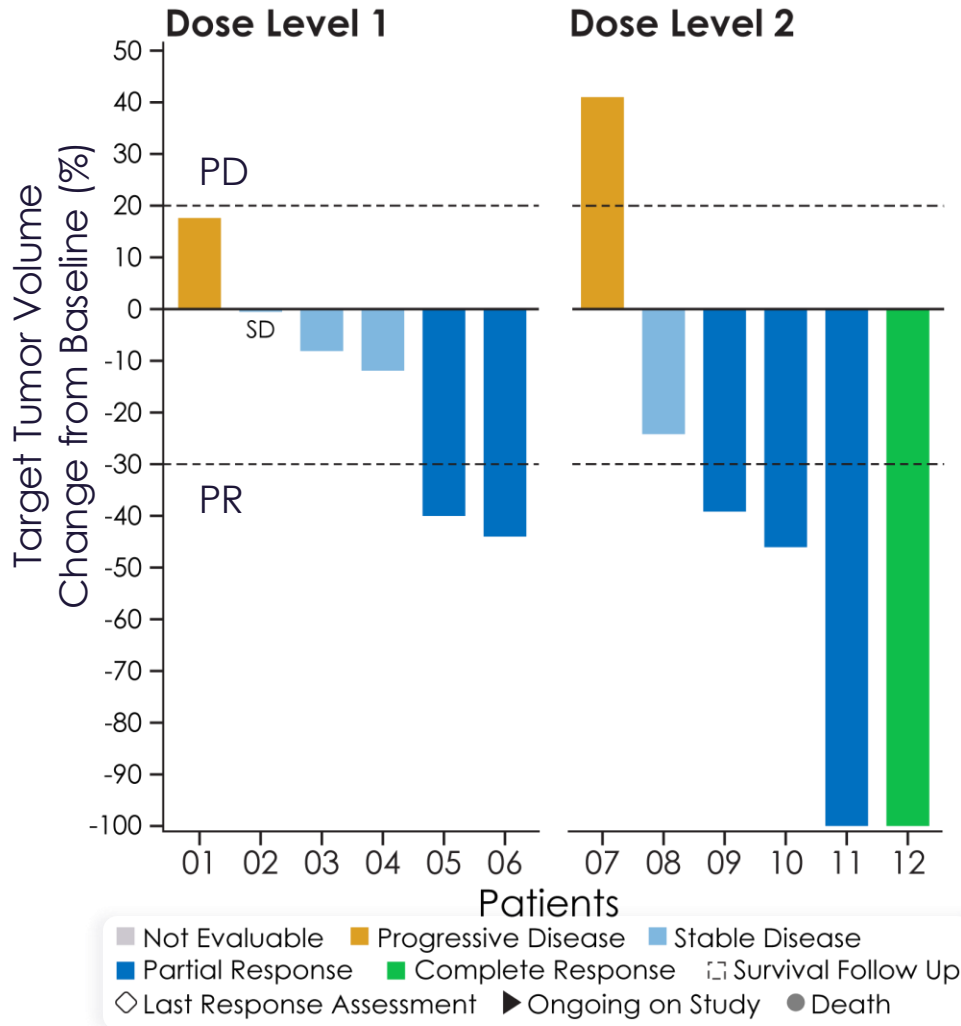
Best Overall Response	Dose Level 1 (1 x 10 ⁶ CAR T cells/kg) N = 6	Dose Level 2 (2 x 10 ⁶ CAR T cells/kg) N = 6	Total N = 12
Overall Response Rate n (%)	2 (33%)	4 (67%)	6 (50%)
Complete Response	0	1 (17%)*	1 (8%)*
Partial Response	2 (33%)	3 (50%)	5 (42%)
Stable Disease	3 (50%)	1 (17%)	4 (33%)
Progressive Disease	1 (17%)	1 (17%)	2 (22%)
Disease Control Rate (CR + PR + SD)	5 (83%)	5 (83%)	10 (83%)
Median Follow Up (months)	17.0	10.2	11.2
Median PFS (months)	5.0	7.8	6.2
Median Overall Survival (months)	17.0	NR	NR

*This patient was a pathological complete response at autopsy

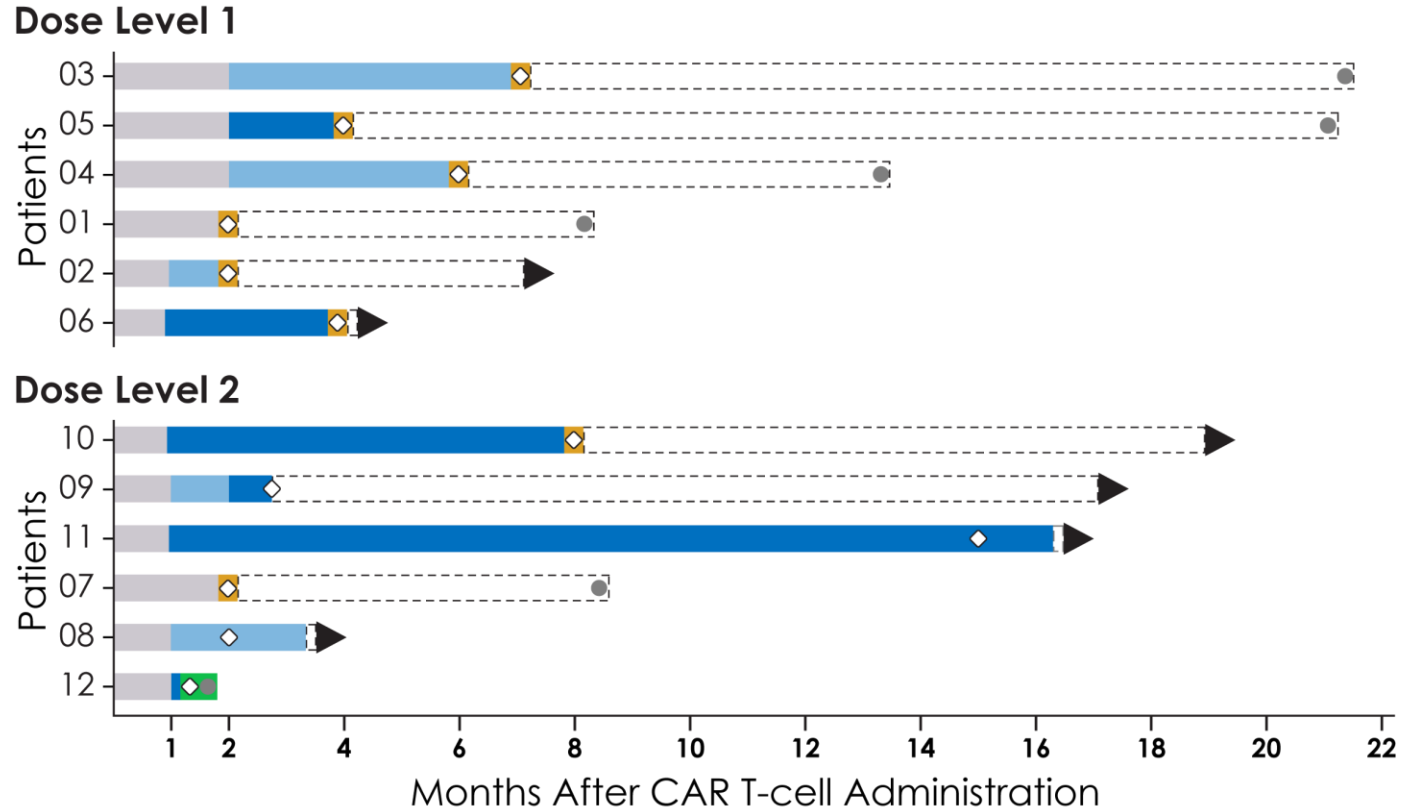
LYL273: High Overall Response Rates in Patients with Refractory Metastatic Colorectal Cancer



Tumor Reduction: Best Overall Response



Swimmer Plot of Each Patient's Response



Patient 09: Censored after receiving radiation to slightly enlarging lesions (non PD)
 Patient 11: Resolution of target lesions and complete metabolic response by PERCIST, but non-target pulmonary lesion received radiation therapy for micro-foci of adenocarcinoma on biopsy so PR rather than CR by RECIST
 Patient 12: Pathological complete response on autopsy; patient had more than 600 pulmonary lesions at baseline

LYL273 Patient 11 Case Study

54-year-old woman diagnosed with Stage IVB colorectal adenocarcinoma after mass detected on first screening colonoscopy

- Microsatellite stable and with KRAS G12D mutation on molecular testing

Disease progression after 3 prior lines of therapy

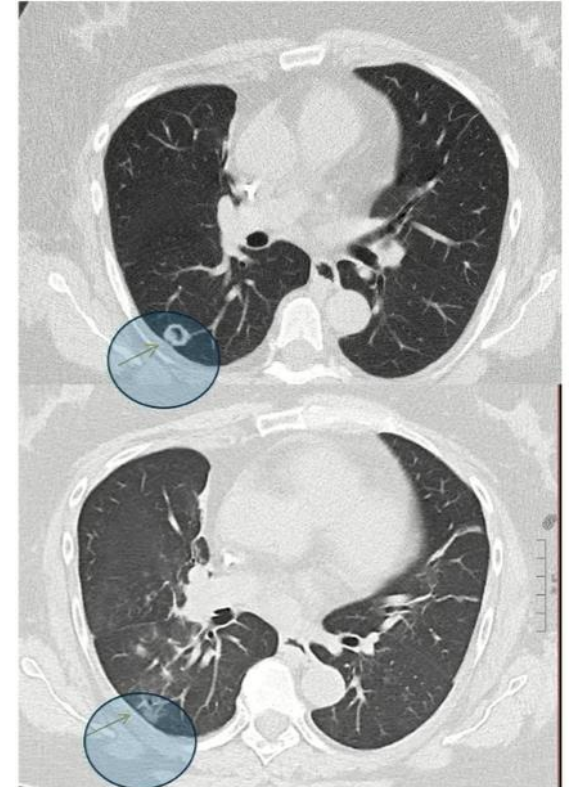
- FOLFOXIRI + AVASTIN® (bevacizumab) and hepatectomy; developed liver and lung metastases less than 6 months after resection
- FOLFIRI + AVASTIN® (bevacizumab)
- LONSURF® (trifluridine/tipiracil) + AVASTIN® (bevacizumab)

Received LYL273 at Dose Level 2 following one day of lymphodepletion (fludarabine, 30 mg/m² and cyclophosphamide, 300 mg/m²)

- Grade 1 CRS and no ICANS
- Grade 1 diarrhea
- Discharged on Day 15, no reported serious adverse events

LYL273 Patient 11 Case Study: Partial Response at Day 28 Deepening to 100% PR by Month 10

- Partial response by RECIST 1.1 at Month 1 disease assessment
- Persistent and increasingly deeper response at subsequent scans
- Now with complete elimination of target lesions



Assessment (month)	1	2	4	8	10	15
Change from Baseline	-38%	-41%	-83%	-83%	-100%	-100%
Response	PR	PR	PR	PR	PR*	PR*

* This does not meet RECIST criteria for a complete response due to resection of and radiotherapy to the site of a non-target lesion

U.S. Phase 1 Clinical Data Summary for LYL273

High response rates and manageable safety profile in mCRC

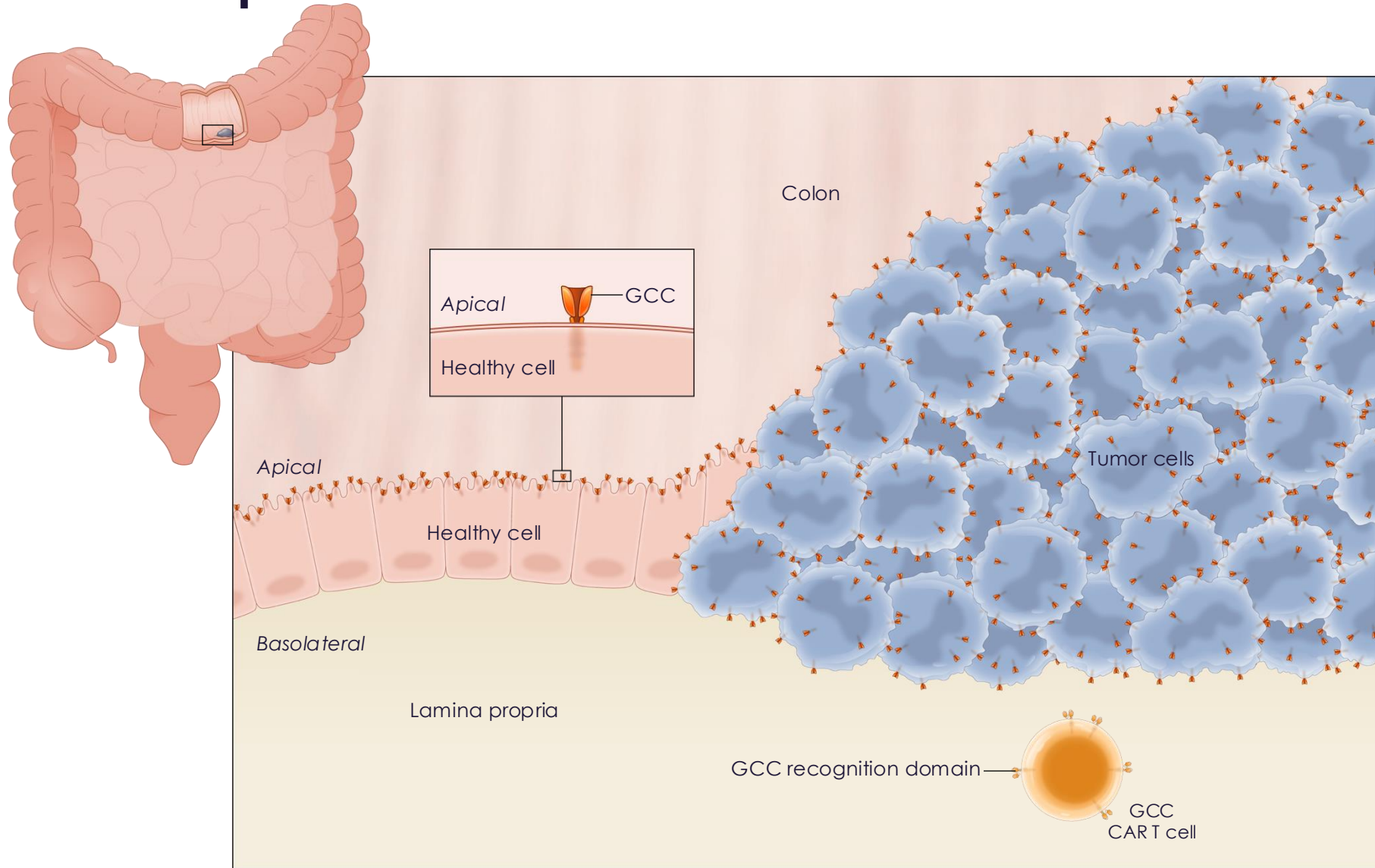
- LYL273 (formerly GCC19CAR T) exhibits significant and durable anti-tumor activity in patients with refractory mCRC
 - **67% overall response rate at highest dose studied**
- The safety profile is manageable and consistent with the GCC-targeted mechanism of action and CAR T-cell therapy (diarrhea, CRS, ICANS)
- Enrollment is continuing in the Phase 1 trial to select the recommended Phase 2 dose
- The next data update for LYL273 expected in first half of 2026



LYL273 GCC-Targeted CAR T-Cell Therapy: Mechanism of Action

Gary Lee, Ph.D.
Chief Scientific Officer

Colorectal Cancer is an Immunologically Cold Cancer that Expresses GCC



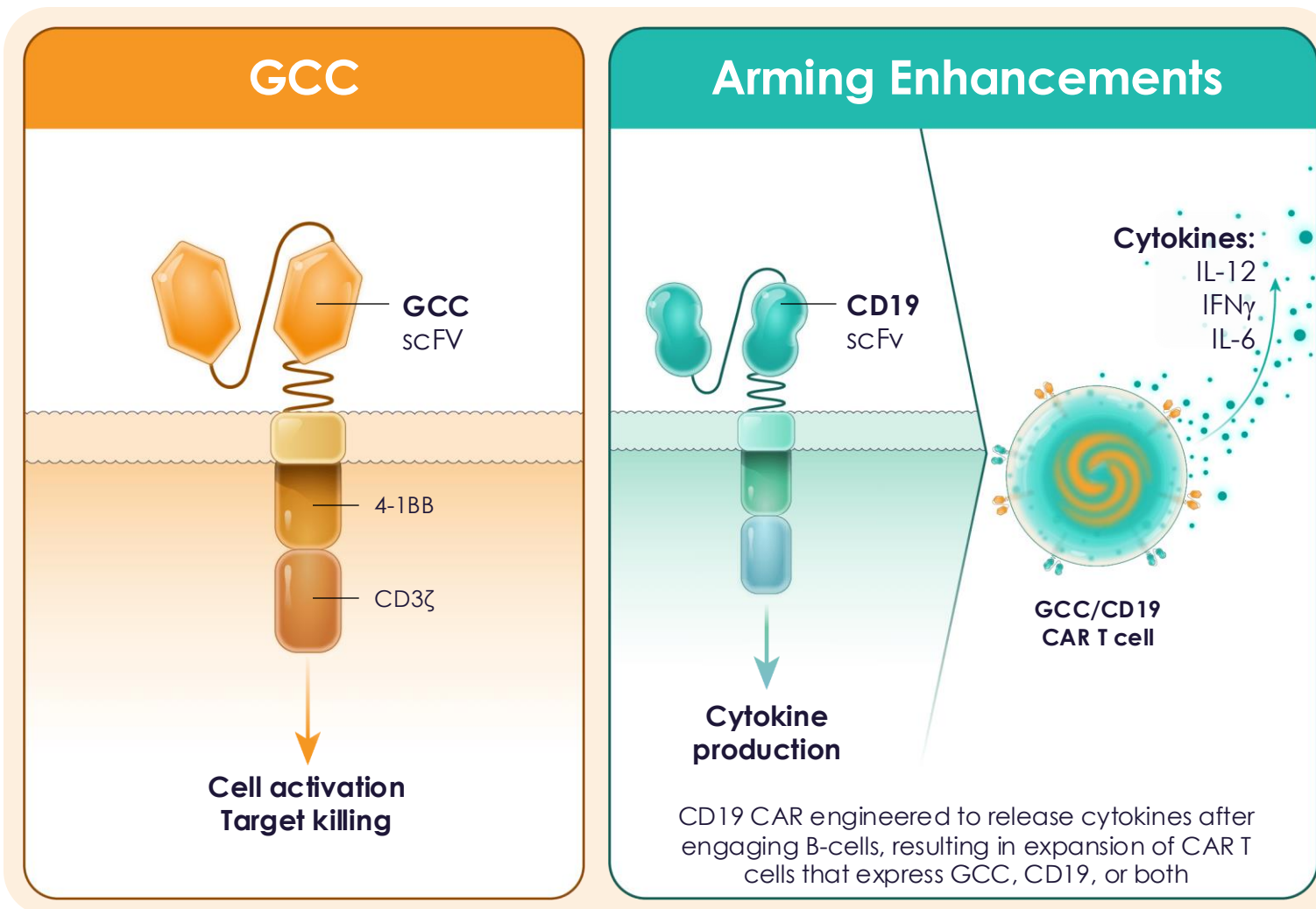
Guanylyl Cyclase-C (GCC)

- Expressed in > 95% of patients with colorectal cancer
- Expression in normal tissue limited to GI tract, but inaccessible to CAR T cells

Two critical barriers to successful CAR T-cell therapy in solid tumors

- Lack of in vivo CAR T-cell expansion
- Hostile immunosuppressive tumor microenvironment limits cancer cell killing

LYL273 is a GCC-Targeted CAR T-Cell Product Candidate Armed with Enhancements to Improve CAR T-Cell Expansion and Cancer Cell Killing



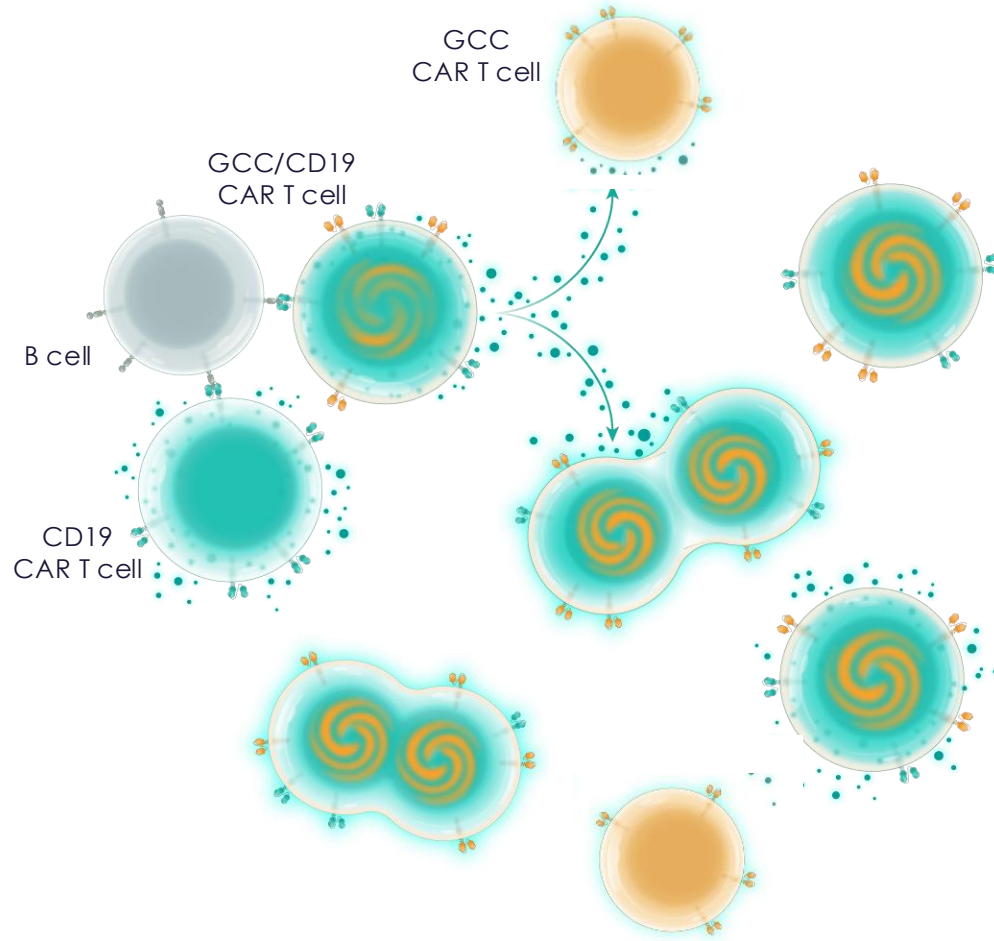
CD19 CAR Arming

- Jump starts CAR T-cell activation and expansion upon infusion by engaging B-cells

Controlled Release of Multiple Cytokines Upon T-Cell Activation

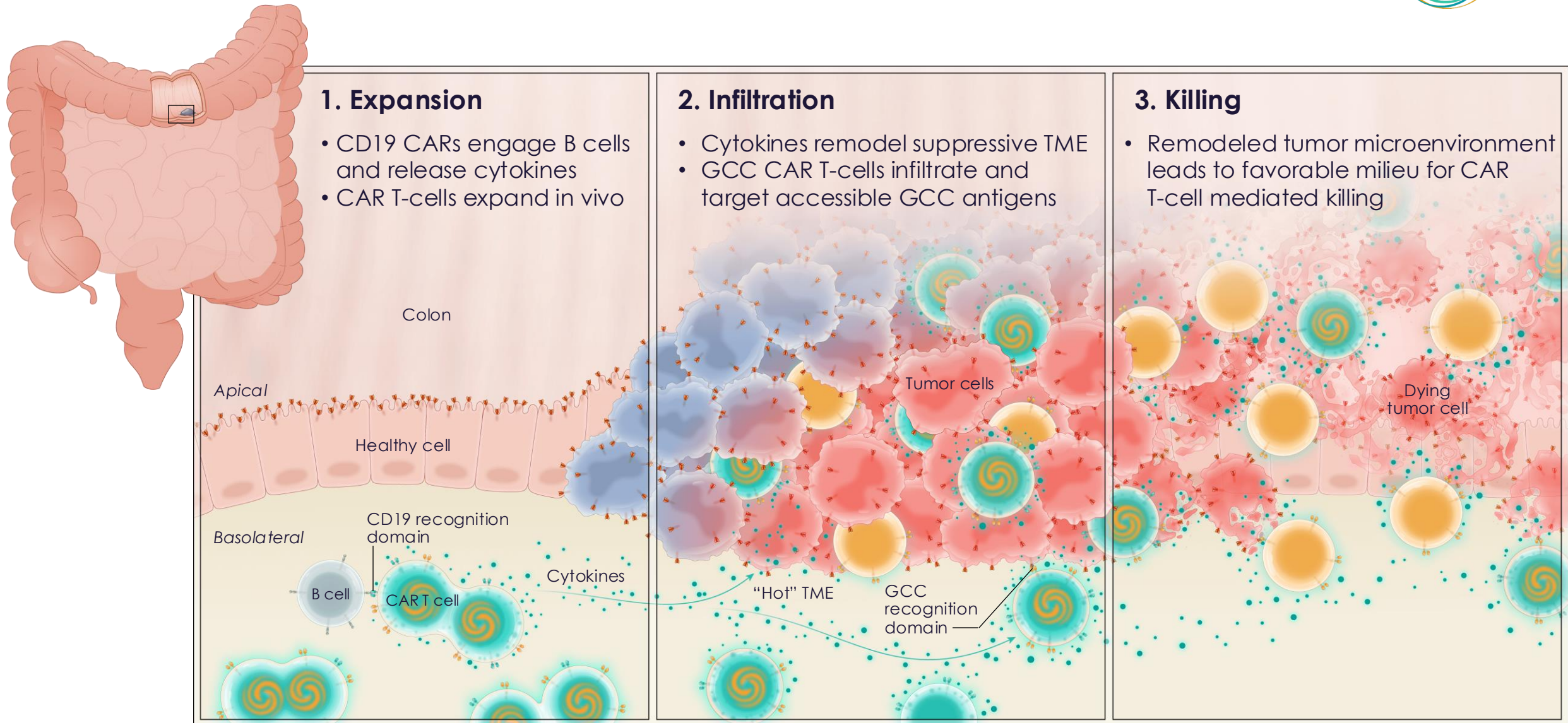
- Level of cytokines regulated by specific vector design and usage during manufacturing
- Cytokines enhance CAR T-cell expansion, remodel the suppressive tumor microenvironment and enhance immune cell infiltration and cancer cell killing

LYL273: A Single Product with 3 Key CAR T-Cell Types



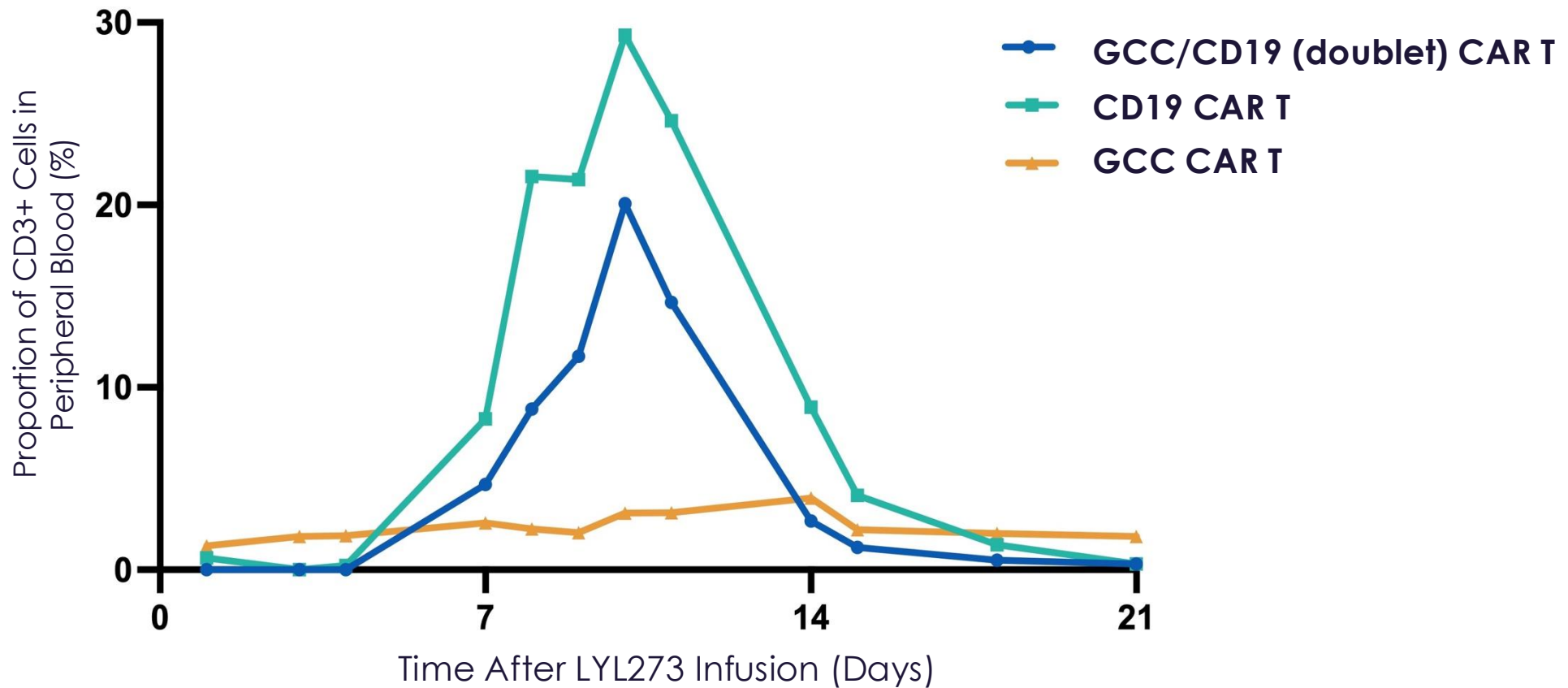
- **GCC CAR T cells:** kill GCC-positive tumor cells
- **CD19 CAR T cells:** activate and expand upon engagement of B cells; release cytokines to support CAR T-cell expansion
- **GCC/CD19 (doublet) CAR T cells:** activate and expand upon engagement of B cells, release cytokines, kill GCC-positive tumor cells; doublets represent the majority of anti-GCC CAR T cells at peak expansion
- **Three cytokines** released based on proportional control
 - Multi-vector co-transduction at a defined ratio
 - Cytokines include IL-12, IFN γ , and IL-6

LYL273 is Designed To Enhance In Vivo Cell Expansion and Remodel the Tumor Microenvironment to Improve Tumor Infiltration and Cell Killing



Translational Data Revealed Expansion of GCC/CD19 Doublet CAR T-Cells in Patient 11 with 100% Partial Response

GCC/CD19 doublet accounts for > 80% of all GCC CAR-expressing T-cells at peak



LYL273 Automated Manufacturing Process Fits Easily into the LyFE Manufacturing Facility Footprint

LyFE capable of commercial launch with capacity for >1,200 doses/year at full capacity

- Miltenyi CliniMACS Prodigy[®] closed, automated manufacturing system
- Standardized 7-day manufacturing process
- Easily transferable and scalable





Strategic Rationale and Terms of License Agreement

Strategic Rationale and Deal Terms

Strategic Rationale

- Alignment with Lyell's mission to develop next-generation CAR T-cell therapies that give patients with cancer the gift of time
- Strengthens pipeline with a second clinical-stage program with compelling Phase 1 data in area of high unmet need
- Targets large and growing metastatic colorectal cancer market with potential for substantially improved efficacy over currently approved therapies in refractory disease
- Potential to expand into other GCC-expressing tumor types (pancreatic)

Deal Terms

- Upfront payment of \$40mm and 1.9mm shares
- Additional cash milestones
 - \$30mm clinical milestone
 - \$115mm in late-stage regulatory milestones
 - \$675mm in commercial milestones
- Additional equity consideration of up to 1.85mm shares for clinical and regulatory milestones
- Tiered royalties on annual net sales
 - Mid single-digit up to 10% in the U.S.
 - Low to mid-single-digit in other countries

Advancing Novel, Next Generation CAR T-Cell Therapies



Cash runway into 2027, through multiple clinical milestones

Product	Target	Target Indications	Enhancements	Preclinical	Phase 1	Pivotal	Next Expected Milestone
Ronde-cel (LYL314)	CD19/CD20	3L+ Aggressive LBCL <ul style="list-style-type: none"> Regenerative Medicine Advanced Therapy Designation Fast Track Designation 	<ul style="list-style-type: none"> CD62L+ 	3L+ CAR T Naïve			<ul style="list-style-type: none"> Updated PiNACLE clinical data at ASH BLA submission in 2027
Ronde-cel (LYL314)	CD19/CD20	2L Aggressive LBCL	<ul style="list-style-type: none"> CD62L+ 	2L CAR T Naïve			<ul style="list-style-type: none"> Updated clinical data at ASH Initiate pivotal trial by early-2026
LYL273	GCC	Metastatic CRC <ul style="list-style-type: none"> Fast Track Designation 	<ul style="list-style-type: none"> CD19 CAR with controlled cytokine release 	3L+			<ul style="list-style-type: none"> Updated clinical data in first half 2026
Solid Tumor Programs	Undisclosed	Undisclosed	<ul style="list-style-type: none"> Anti-exhaustion Stemness TME functional enhancement 				<ul style="list-style-type: none"> First IND in 2026

2L, second-line; 3L+, third- or later-line; BLA, Biologics License Application; CAR, chimeric antigen receptor; CD62L+, CD62L or L-selectin positive T cells; CRC, colorectal cancer; GCC, guanylyl cyclase-C; IND, Investigational new drug application; LBCL, large B-cell lymphoma; TME, tumor microenvironment

Ronde-Cel Progress

FDA has granted ronde-cel Regenerative Medicine Advanced Therapy (RMAT) designation for large B-cell lymphoma in the 2L setting

Two oral presentations at ASH – December 7th :

Updated clinical data from the Phase 1/2 results from patients in the 2L and 3L+ settings:

Rondecabtagene Autoleucel, an Autologous, Dual-Targeting CD19/CD20 CAR T-Cell Candidate Manufactured from CD62L+ Enriched T Cells, Achieves Durable Responses in Patients with Large B-Cell Lymphoma

Translational data from patients evaluating CD62L enrichment:

CD62L Enrichment Achieves Robust Expansion and Memory Phenotype Post-infusion in Patients with LBCL Treated with Rondecabtagene Autoleucel, an Autologous, Dual-targeting CD19/CD20 CAR T-cell Candidate

Advancing Next-Generation CAR T-Cell Therapies



Late-stage clinical company targeting large patient populations

Rondecabtagene autoleucel (ronde-cel), a dual-targeting CD19/CD20 CAR T-cell candidate with potential to be a new standard of care for relapsed and/or refractory large B-cell lymphoma

- High response rates in high-risk patients, with a safety profile appropriate for outpatient administration
- First of two planned pivotal trials underway (PiNACLE), second to begin enrollment by early 2026 (PiNACLE – H2H)

LYL273 (formerly GCC19CART), a GCC-targeted CAR T cell candidate for metastatic colorectal cancer

- High response rates in refractory patients with a manageable safety profile

Scalable wholly-owned LyFE manufacturing facility capable of commercial launch

- >1,200 doses/year at full capacity

Cash runway into 2027 through multiple clinical readouts



Q&A

