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Leaders in Developing Allogeneic γδ1 CAR T Cell Therapies to Fight Autoimmune Diseases and Cancer

γδ= Gamma delta; CAR= Chimeric antigen receptor

November 2024

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Adicet Bio: Leaders in Developing Allogeneic γδ CAR T Cell Therapies

▶ **Adicet's γδ1 CAR T Pipeline is Uniquely Positioned to Deliver Best-in-Class Cell Therapies**

Demonstrated Clinical POC	Off-the-shelf	Robust exposure	Favorable safety profile	Traffic to tissues

▶ **Differentiated pipeline offers significant commercial opportunities, with potential for short- and long-term value creation**

Autoimmune Disease / ADI-001

- Complete CD19+ B cell depletion in blood and secondary lymphoid tissue
- No significant risk of CRS, ICANS or T cell malignancies
- 6 autoimmune indications in clinical development
- **Initial ADI-001 Clinical Data in LN 1H/2025**

Oncology/ ADI-270

- Innate anti-tumor activity
- Retained potent activity in CD70-low tumors
- Engineered resilience to TGFβ in tumor
- Engineered to increase persistence
- **Initial Clinical Data in RCC in 1H/2025**

ccRCC= clear cell renal cell carcinoma; CRS= Cytokine release syndrome; ICANS= Immune effector cell-associated neurotoxicity syndrome; POC= Proof of concept

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Developing Broad Pipeline of Allogeneic γδ1 T Cell Therapies for Autoimmune Diseases and Cancer

Program	Target	Indication	Research	IND-Enabling	Clinical	Status
AUTOIMMUNE DISEASES						
ADI-001	CD20	LN & SLE	●	●	●	LN enrollment open Phase 1 • Fast Track Designation • Clinical update 1H/2025 SLE enroll Phase 1 1Q/2025
		SSc	●	●	●	Enroll Phase 1 1Q/2025 Clinical update 2H/2025
		IIM/ SPS	●	●	●	Enroll Phase 1 1Q/2025 Clinical update 2H/2025
		AAV	●	●	●	Enroll Phase 1 2H/2025 Clinical update 2H/2025
ONCOLOGY						
ADI-270	CD70 (TGFβ-DNR)	RCC & Other ST / Heme	●	●	●	RCC enrollment open Phase 1 • Fast Track Designation • Clinical update 1H/2025
ADI-xxx	PSMA (w/ Armor)	mCRPC	●	○	○	Preclinical activities

AAV= anti-neutrophil cytoplasmic autoantibody (ANCA)-associated vasculitis; ccRCC= Clear cell renal cell carcinoma; IIM= idiopathic inflammatory myopathy; IND= Investigational new drug; LN= lupus nephritis; mCRPC= Metastatic castration-resistant prostate cancer; PSMA= Prostate specific membrane antigen; SLE= systemic lupus erythematosus; SPS= stiff person syndrome; SSC= systemic sclerosis; ST= Solid tumor

Timing subject to site activation, patient enrollment, data readouts and regulatory feedback

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Adicet Bio Leadership Team

Chen Schor
President and CEO

Blake Aftab, Ph.D.
Chief Scientific Officer

Francesco Galimi, M.D., Ph.D.
Chief Medical Officer

Nancy Boman, M.D., Ph.D.
Chief Regulatory Officer

Don Healey, Ph.D.
Chief Technology Officer

Nick Harvey
Chief Financial Officer

Amy Locke
Head of Human Resources

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ADI-001
Autoimmune Diseases
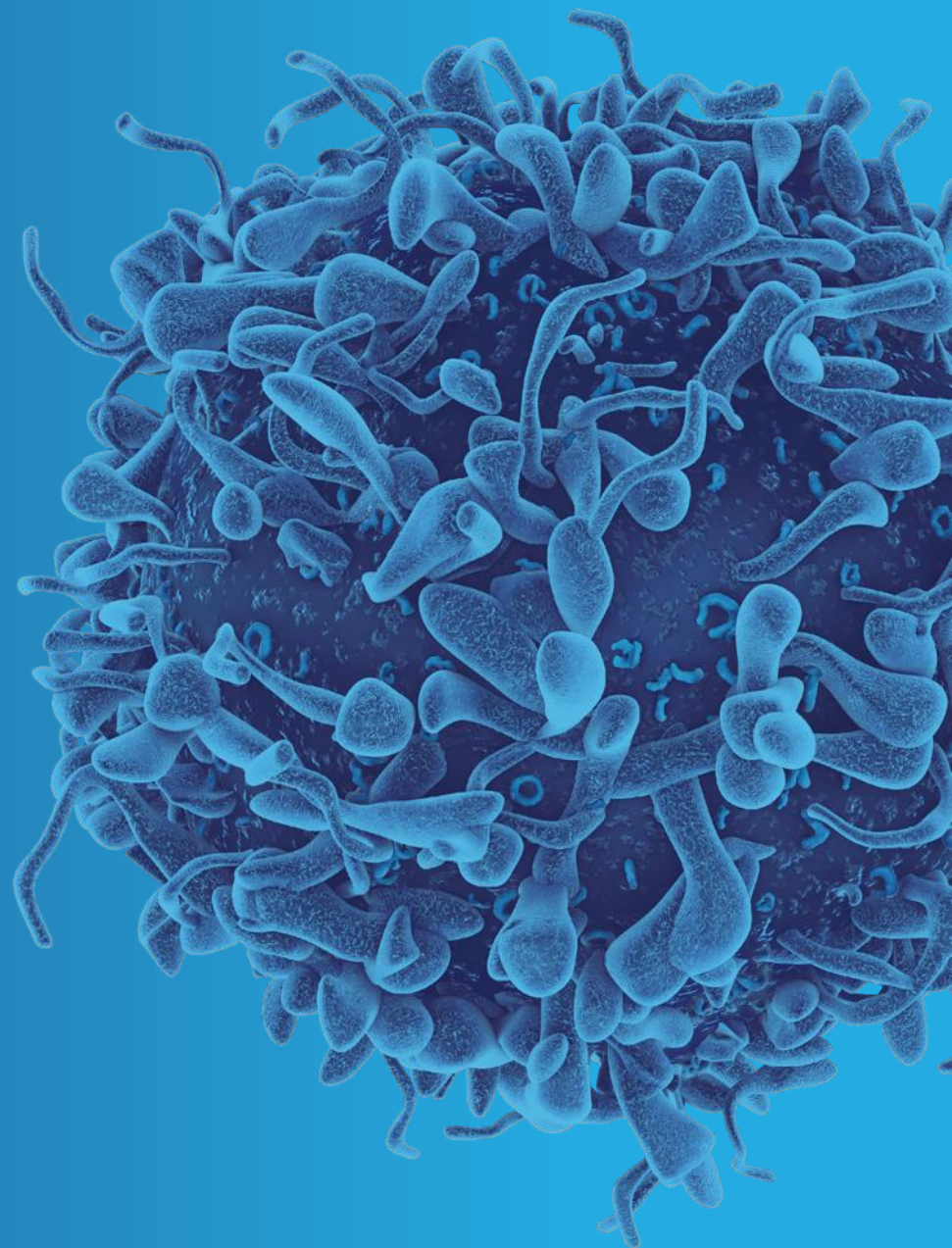
ADI-001: Multiple Levels of Evidence Support Potential in Autoimmune Disease

Multiple Levels of Evidence Supporting ADI-001
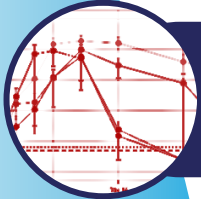
Robust PK exposure, consistent with autologous alpha-beta CAR T in autoimmune, resulting in complete CD19+ B cell depletion in blood
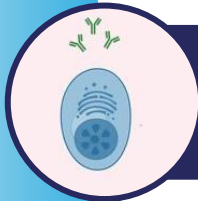
Targeting CD20 has been shown to **fully deplete the B cell lineage in the peripheral blood, including plasmablasts**[1]
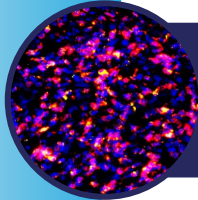
Significant tissue exposure and CAR-T activation resulting in complete CD19+ B cell depletion in secondary lymphoid tissue

Off-the-shelf; No significant risk of CRS, ICANS or T cell Malignancies; Potential to Dose in Community Setting

6 Autoimmune Indications in Clinical Development

Preliminary LN Clinical Data H1/2025

[1]Furie RA et al. Ann Rheum Dis (2022); Tur C, et al. Ann Rhum Dis (2024); CRS= Cytokine release syndrome; ICANS= Immune effector cell-associated neurotoxicity syndrome

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ADI-001's Cmax, D28 Persistence and AUC Are Consistent with Values Reported for Approved Autologous CD19 CAR T[1]

ADI-001 CAR by Flow Cytometry

Axi-cel C$_{max}$: ~44 cell/uL[2]

3E7 Dose Level
1E8 Dose Level
3E8 Dose Level
1E9 Dose Level
3E8 Dose Level^{x2}
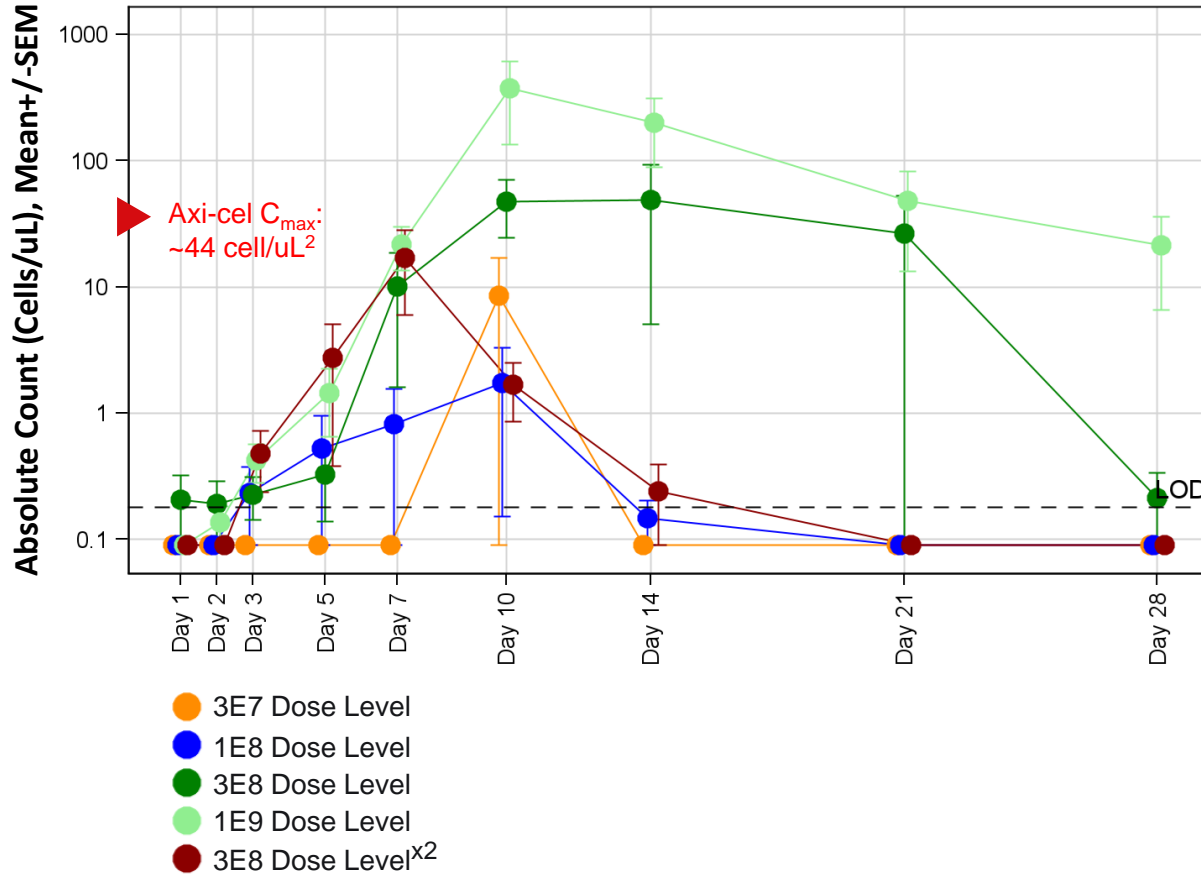
ADI-001 CAR by ddPCR
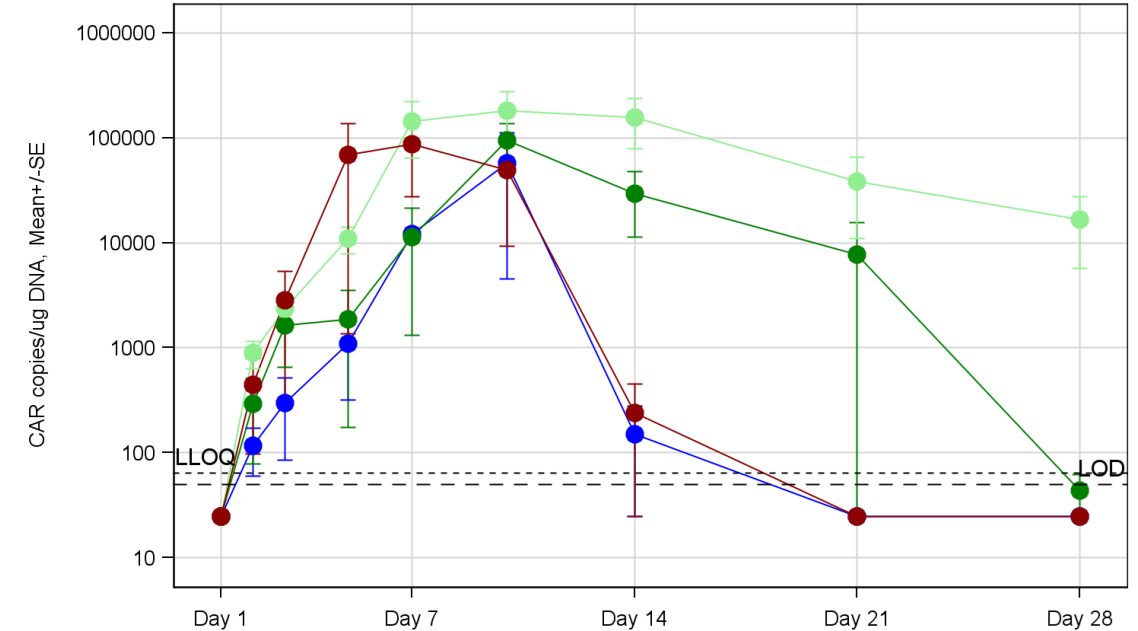
Dose Level	Mean Cmax		Mean D28	
	CAR+ Vd1 cells/ul	Copies/ug	CAR+ Vd1 cells/ul	Copies/ug
1E9	**363.80**	201,666	26.51	16,553
3E8	**56.34**	98,177	0.04	44

[1]Badbaran, A. Cancers 2020;12, 1970; Locke et al. N Engl J Med 2022; 386:640-654; Neelapu et al. N EnglJ Med. 2017;377:2531-2544; Ogasawara et al. Clin Pharmacokinet 60, 1621–1633 (2021)
[2]YESCARTA® (axicabtagene ciloleucel) prescribing information rev. June 2024
Cmax= Mean maximum concentration of ADI-001; D28= Day 28, AUC= Area under the curve d0-28

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CD20-targeted, ADI-001, in B-NHL patients[3]

23 of 24 patients experience undetectable B cell counts in the first 3 months following treatment

Day -1/ Day 1 Pre-infusion
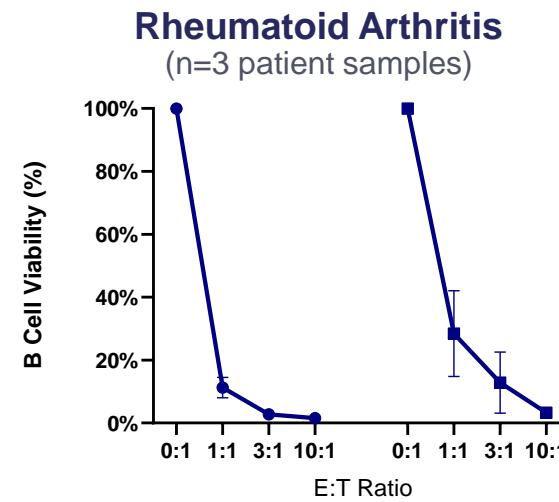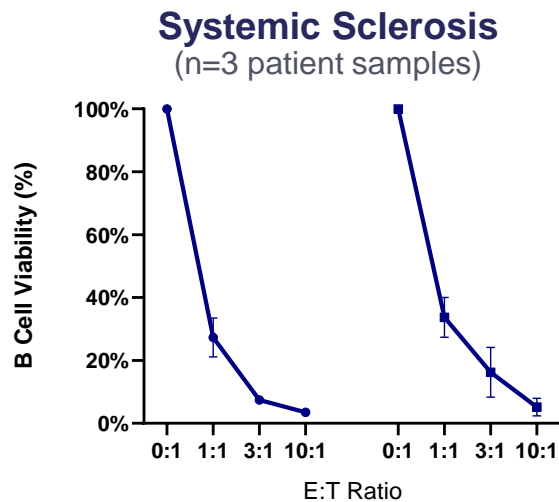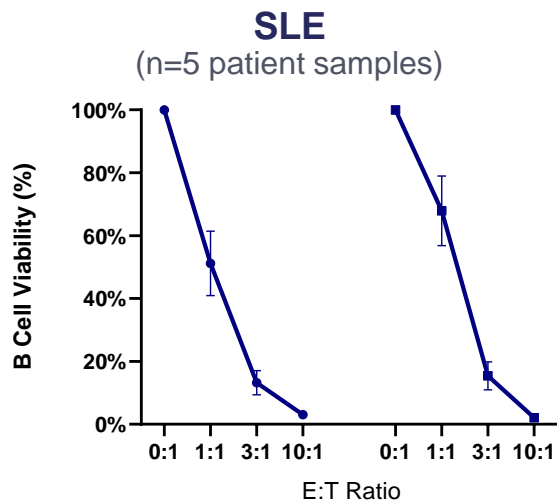
CD19-targeted CAR-T in SLE patients[1]
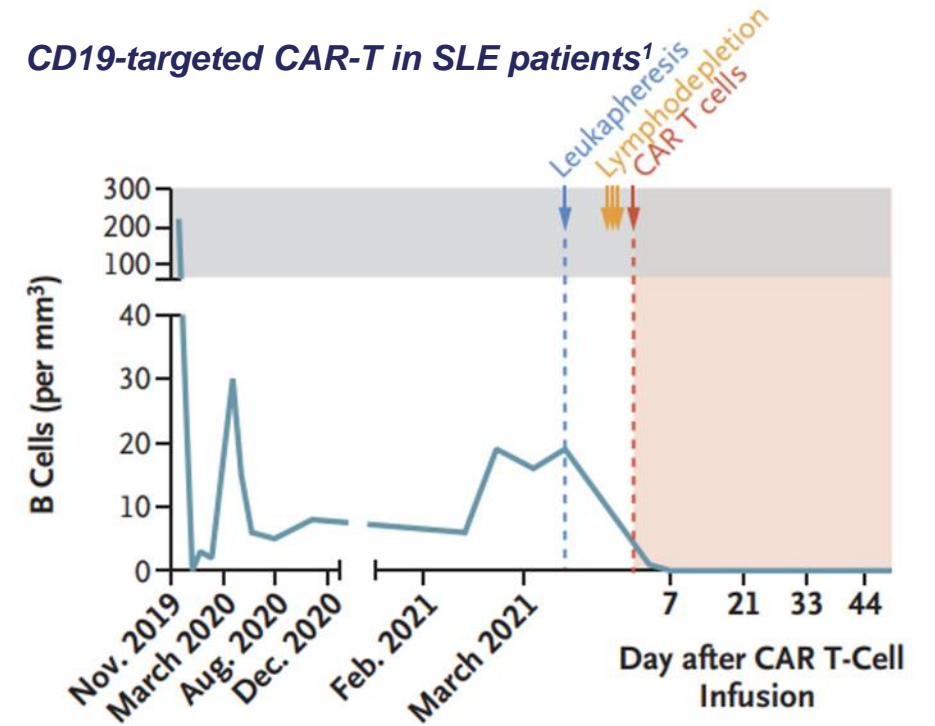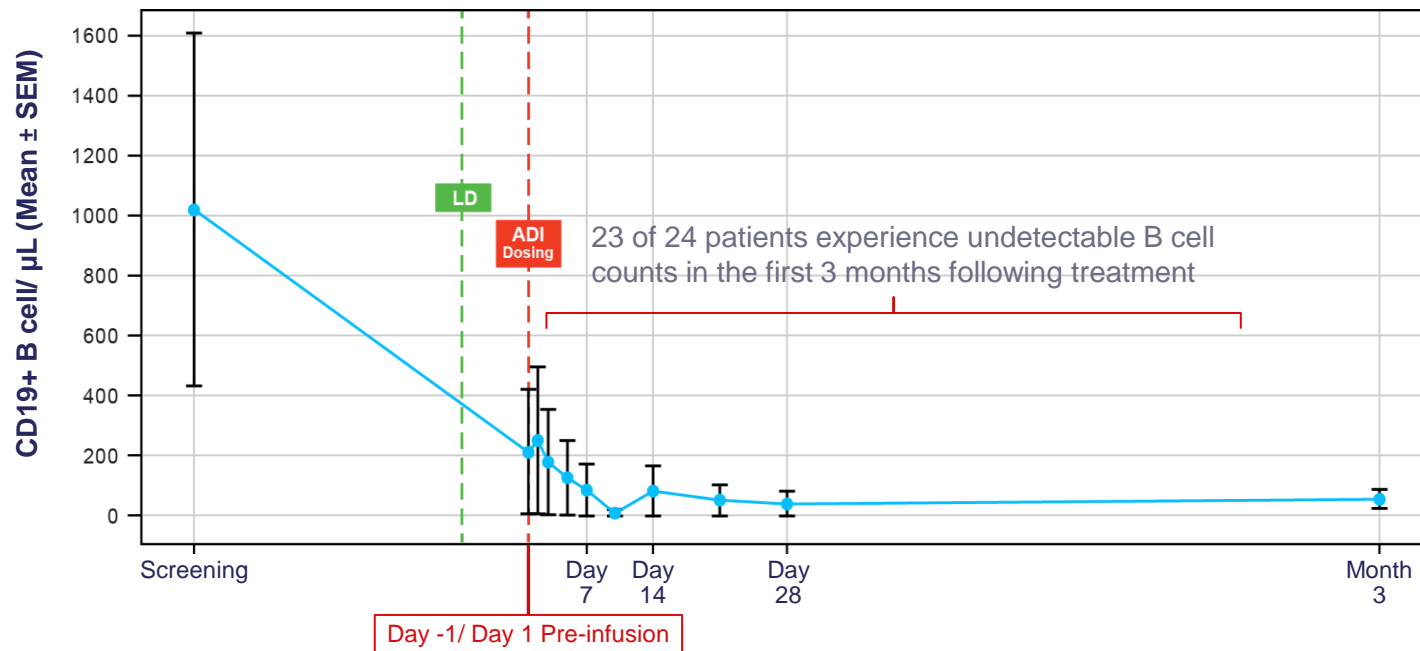
1. Mougiakakos MD et al. NEJM 2021
2. Mackensen A et al. Nature Medicine 2022
3. Adicet internal data

SOC= Standard of care

ADI-001 Exhibited Potent Killing of Patient-Derived CD19+ B Cells in Multiple Autoimmune Diseases
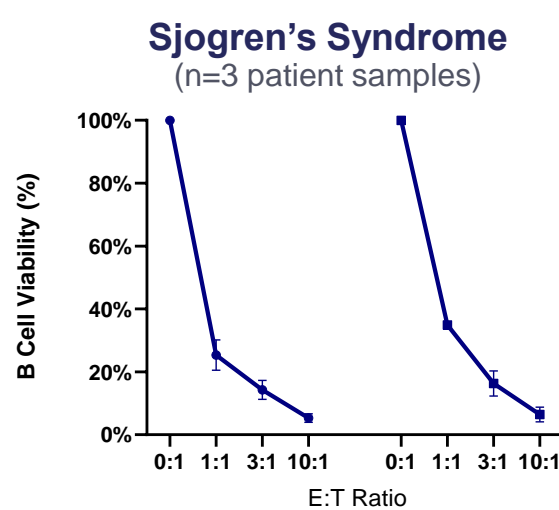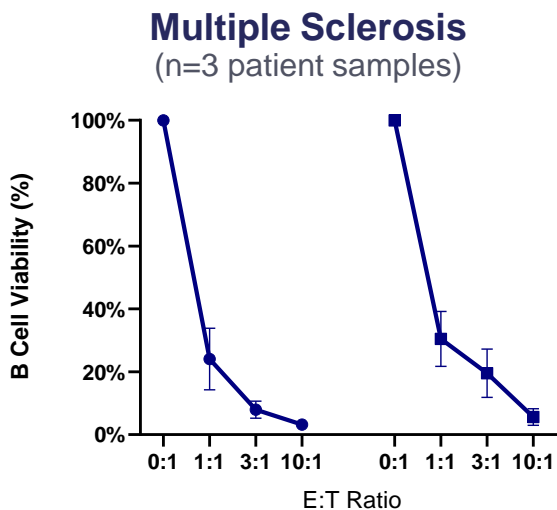
B cells from 5 SLE patients and 3 patients each for SSc, RA, Multiple sclerosis, and Sjosgren's syndrome were co-cultured with ADI-001 manufactured from two independent donors at varying effector-to-target (E:T) ratios for 24 hours and then analyzed by flow cytometry to quantify live B cells relative to negative controls.

CLINICAL SCIENCE

B-cell depletion with obinutuzumab for the treatment of proliferative lupus nephritis: a randomised, double-blind, placebo-controlled trial

Richard A Furie,[1] Gustavo Aroca,[2] Matthew D Cascino,[3] Jay P Garg,[3] Brad H Rovin,[4] Analia Alvarez,[5] Hilda Fragoso-Loyo,[6] Elizabeth Zuta-Santillan,[7] Thomas Schindler,[8] Paul Brunetta,[3] Cary M Looney,[3] Imran Hassan,[9] Ana Malvar[10]

- In a third-party Phase 2 study in LN, obinutuzumab drove depletion of the B-cell compartment in the blood, including plasmablasts[1]

- Poor B-cell depletion in tissues is a noted challenge to efficacy of antibody-based approaches in autoimmune disorders[2,3]


Plasmablasts

Memory B-cells

Naïve B-cells
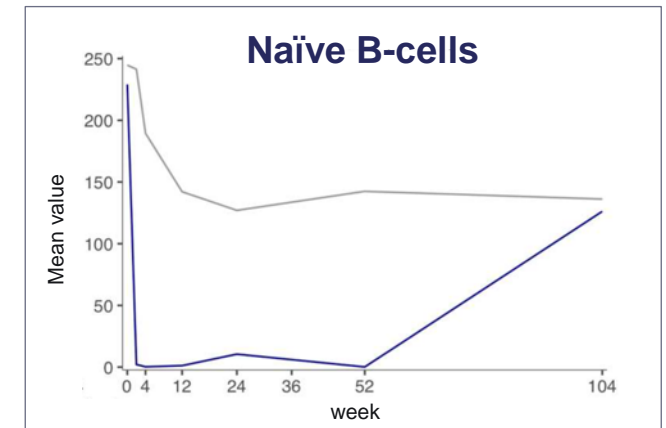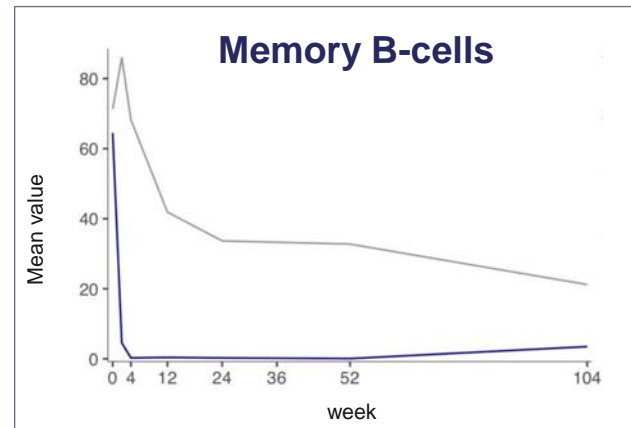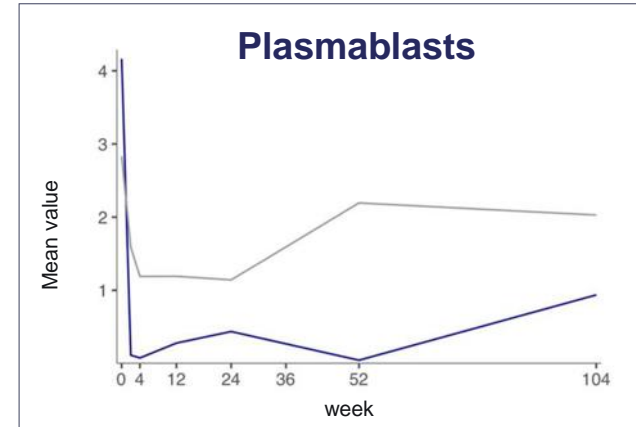
— Obinutuzumab + MMF (n=63) — Placebo + MMF (n=62)

Obinutuzumab or placebo dosed on day 1 and weeks 2, 24 and 26 in 125 LN patients

1. Furie RA et al. Ann Rheum Dis (2022)
2. Reddy VR et al. Rheumatology (2022)
3. Kamburova EG et al. American Journal of Transplantation (2013)

Memory B-cells: CD45+, CD19+, CD27+
Naïve B-cells: CD45+, CD19+, IgD+, CD27-, CD38$^{dim/-}$
Plasmablasts: CD45+, CD19+, CD27+, CD38^{bright}

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CAR T Cell Therapy But Not Antibody-Based Therapies Led to Complete Depletion of B Cells from Lymph Nodes in Autoimmune Patients
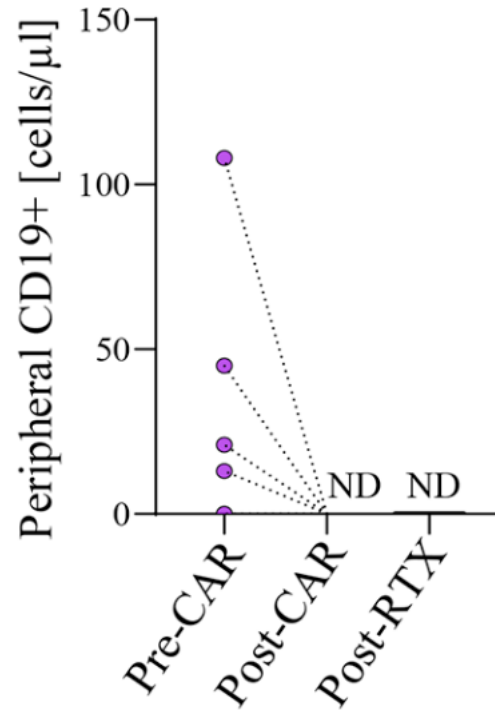
Both CD19 CAR T and CD20 Ab (Rituximab) led to complete CD19+ B cell depletion in <u>peripheral blood</u>
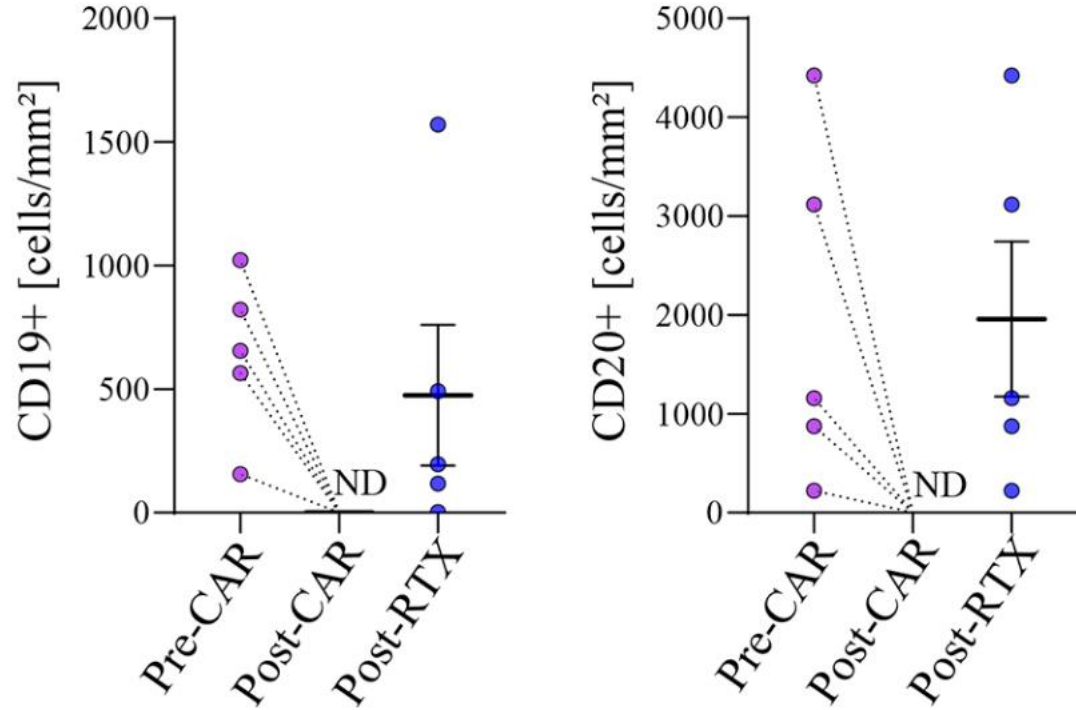
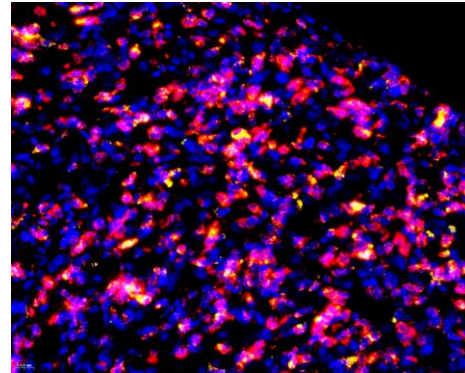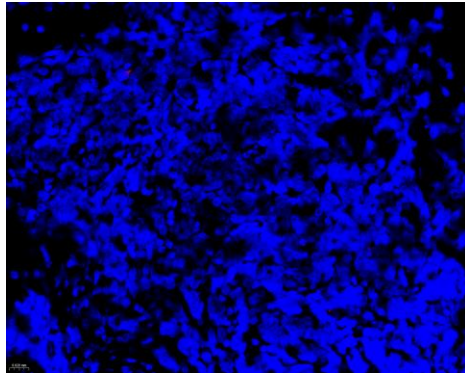**CD19 CAR T but not CD20 Ab (Rituximab) led to complete CD19+ B cell depletion in <u>lymph nodes</u>**

ADI-001 Clinical Data Demonstrated Tissue Trafficking and CAR Activation, Exceeding that Reported for Axi-cel
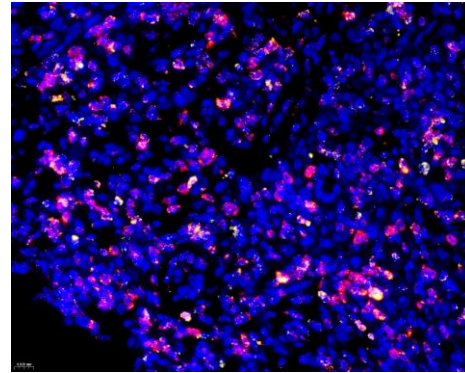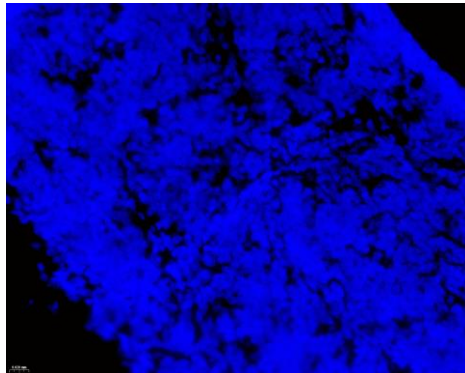
ADI-001 Clinical Tissue Analyses

	Screening Biopsy	Day 10 Post-Dose ADI-001
DLBCL Lymph Node Biopsy		
MCL Lymph Node Biopsy		

Blue : Nuclei   Yellow: ADI-001 CAR   Red: Granzyme (T Cell Activation)

ADI-001 Tissue Trafficking Exceeds Data Reported for Axi-cel[1]

Lymph Node Exposure	ADI-001 Average CAR T per Million Cells
1E8-1E9 Dose Levels	**236,701**
1E9 Dose Level	**461,867** (276,588 – 647,163)

Lymph Node Exposure[1]	Axi-cel[2]
Axi-cel Patient #011	62,948
Axi-cel Patient #014	19,647

Robust tissue tropism for ADI-001 observed in lymph node biopsies across dose levels
ADI-001 cells represent 27%-64% of total cellular material detected by ddPCR in lymph nodes at 1E9 dose level
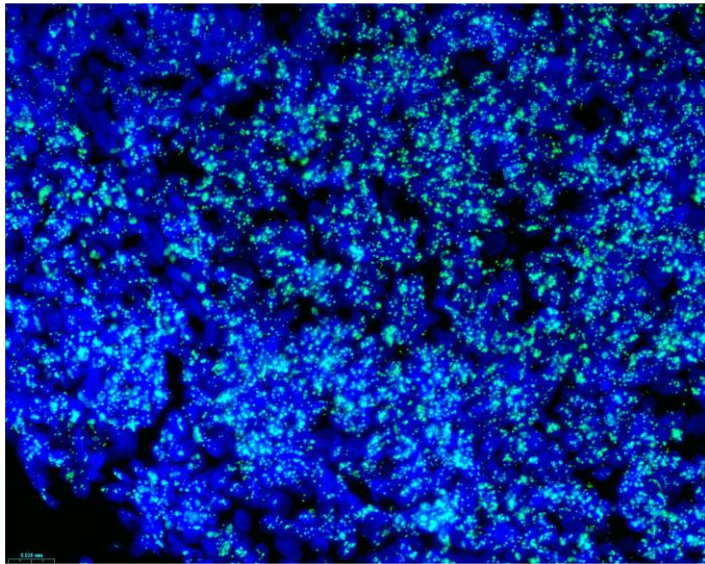
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Confirmation of CD19+ B-Cell Depletion Within Tissues

MCL Patient Lymph Node Biopsies

Intramuscular DLBCL

Screening Biopsy **Day 10 Post ADI-001 Dose**

Baseline **Day 28 Post ADI-001**
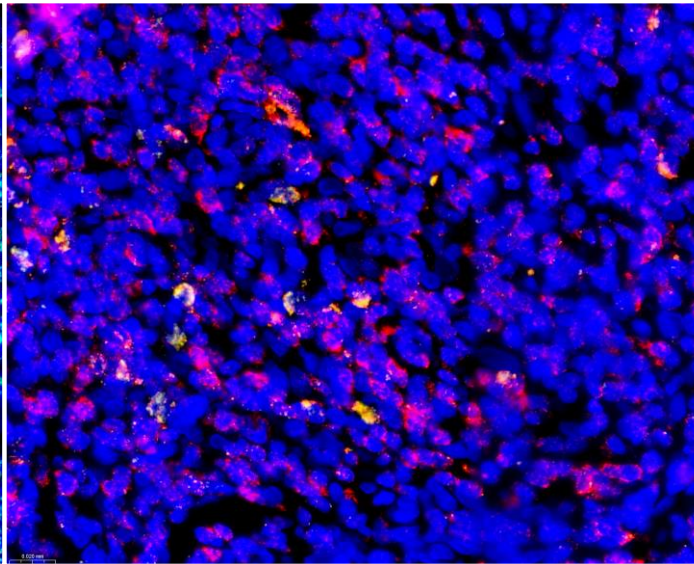
Blue : Nuclei Green: CD19+ cells Yellow: ADI-001 CAR Red: Granzyme B (T Cell Activation)

73y M, 4 prior lines (including rituximab and SCT), 1E9 Dose Level CR

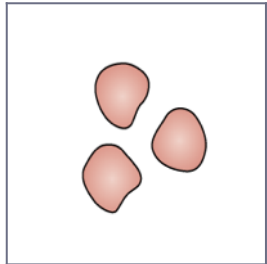**Complete depletion of CD19+ B cells observed at day 10 within secondary lymphoid tissue**

75y M, 5 prior lines (incl. CD19 CAR-T); Sagittal view of the right leg
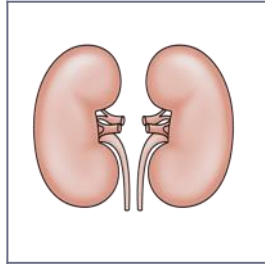
Clinical responses observed in extra-nodal tissue

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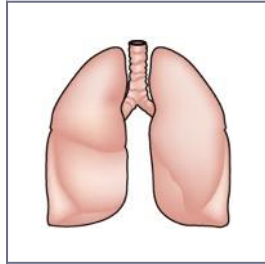# γδ1 T Cells Preferentially Traffic to Solid Tissues: Addressing a Source of Resistance to Antibody Therapies

lymph node[1,2]

CD27+

CD62L+

Vδ1+ ↑↑

Vδ2+ ↓↓

kidney[3]

tissue: **>3X**

γδ vs αβ

~3X more **Vδ1 vs Vδ2+**

lung[4]

issue/blood: **9X**
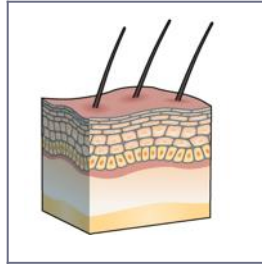
skin[5]

tissue/blood: **8X**
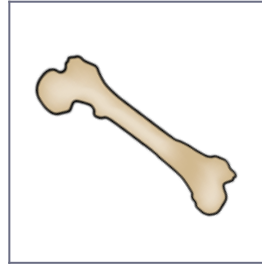
bone marrow[6]

tissue/blood: **4X**
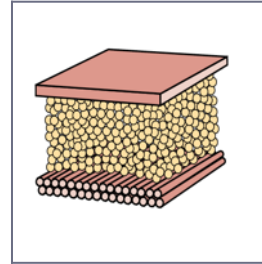
breast[7]

tissue/blood: **~15X**

adipose tissue/blood: **9X**
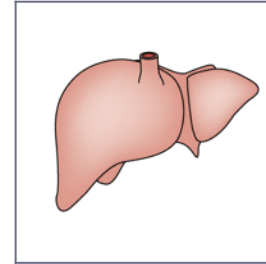
liver[8]

tissue/blood: **3X**
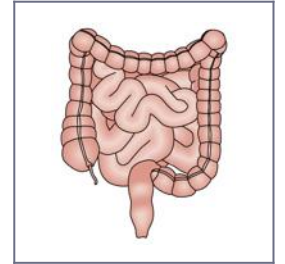
GI[9]

tissue/blood: **11X**

Ratios empirically calculated or approximated from proportion of %CD3 from literature reports in relative compartment[3,6]

Images adapted from Hunter et al J Hepatol (2018) and Ribot et al Nat Rev Immunol (2021)

[1]Davey et al Trends Immunol (2018)
[2]Uger et al Sci Rep (2018)
[3]Rancan et al Nat Immunol (2023)
[4]Wisnewski et al Am J Respir Cell Mol Biol (2000)
[5]Toulon et al J Exp Med (2009)
[6]Brauneck et al Front Med (2021)
[7]Wu et al Sci Transl Med (2019)
[8]Melo et al Clin Immunol (2021)
[9]Deutsch et al Eur J Immunol (1991)

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Preclinical Data Highlights γδ1 T Cells Tissue Residence

Homing
γδ1 actively homed and biodistributed to relevant tissues

Expansion
Tissue residence of γδ1 and selective expansion within target lesions

Herrman et. al. SITC (2022)

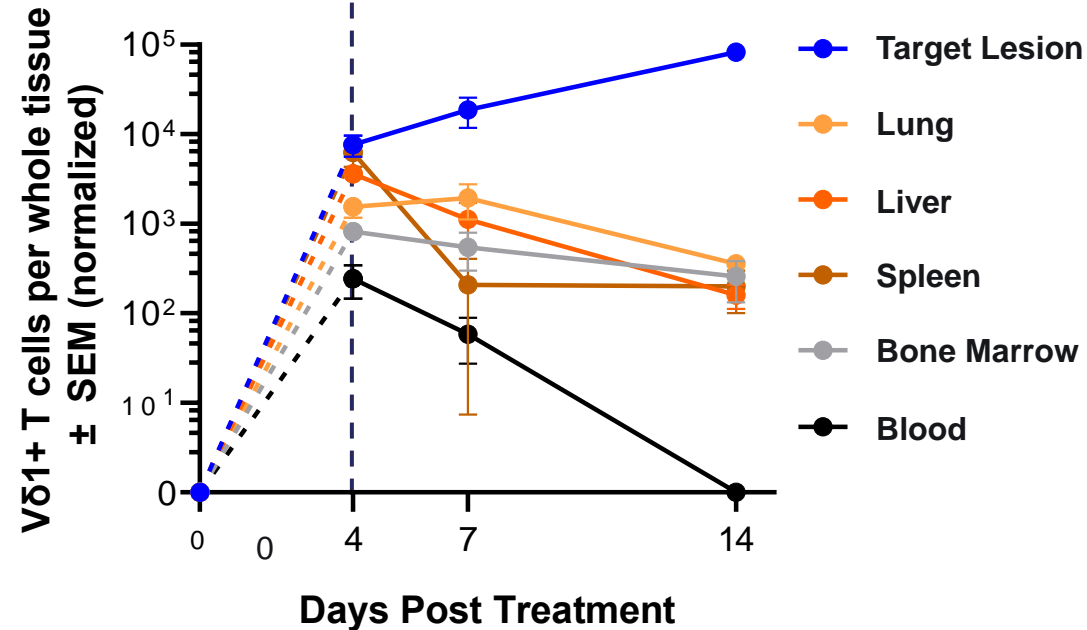# Expanding ADI-001 Autoimmune Development Across Six Indications

US Prevalence (thousand patients)

SPS [5]

AAV [4] ~60

IIM [3] ~60

Systemic Sclerosis [2] ~85

SLE [1] ~242

~40% with LN[6]

500 · 400 · 300 · 200 · 100 · 0
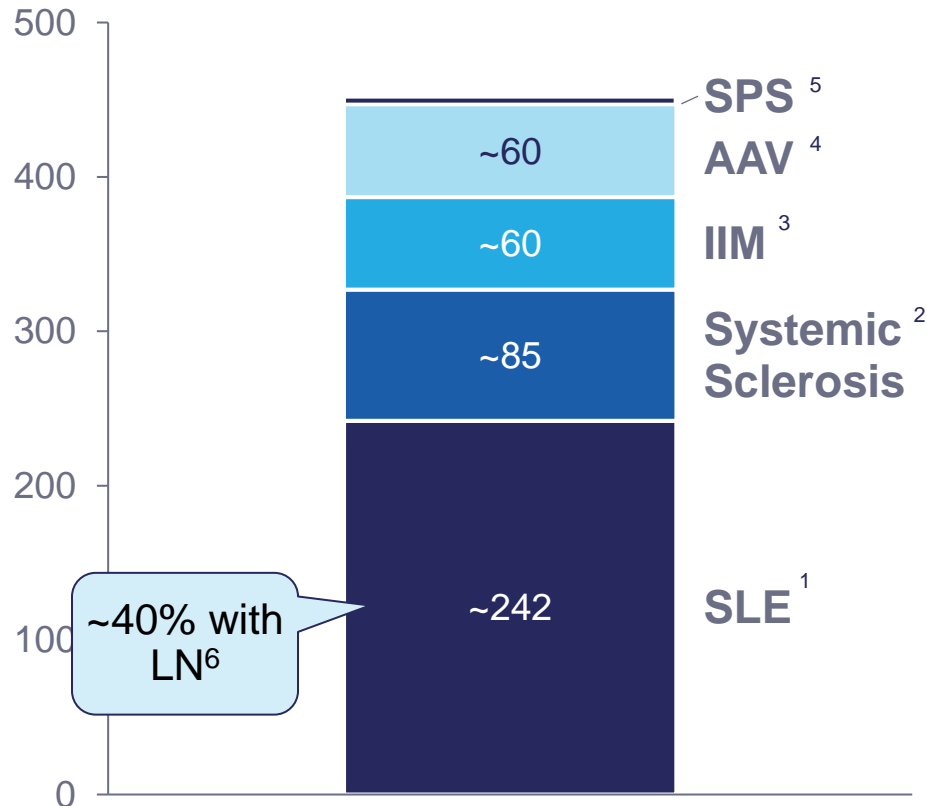
Prioritized indications where:

- ADI-001 has the potential to materially impact patient outcomes

- Probability of success viewed favorably given validated role of B-cell depletion

- Opportunity to leverage expanding clinical footprint in rheumatology

1. Helmick CG et al. Arthritis & Rheumatism (2008)
2. Bairkdar M et al. Rheumatology (2021)
3. Lundberg IE et al. Nature Reviews (2021)
4. Berti A et al. Arthritis & Rheumatology (2017)
5. Ortiz JF et al. Cureus (2020); U.S. prevalence <1K
6. Morales E et al. Nephron (2021)

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ADI-001: Phase 1 Autoimmune Study Design

Consent Day -28 → **Screening** → (Enrollment) → **Lymphodepletion** → **Treatment DLT Period (28 days)** → **Follow Up** → **LTFU Study**

- Consent Day -28
- Enrollment
- Single ADI-001 Infusion Day 0
- Response/Safety Assessments Day 28
- Response/Safety Assessments Months 3-6-9-12-18-24

Cyclophosphamide / Fludarabine Lymphodepletion

Part 1

- LN / SLE Arm — LN
- SSc Arm
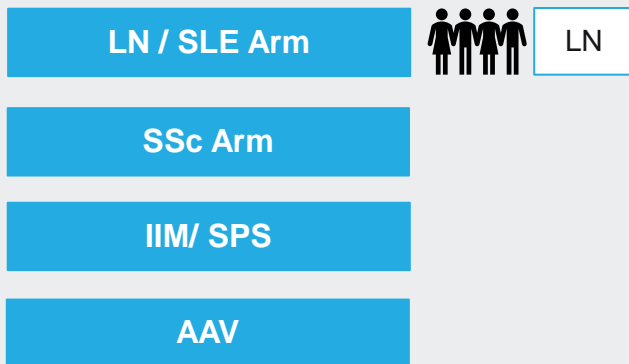- IIM/ SPS
- AAV
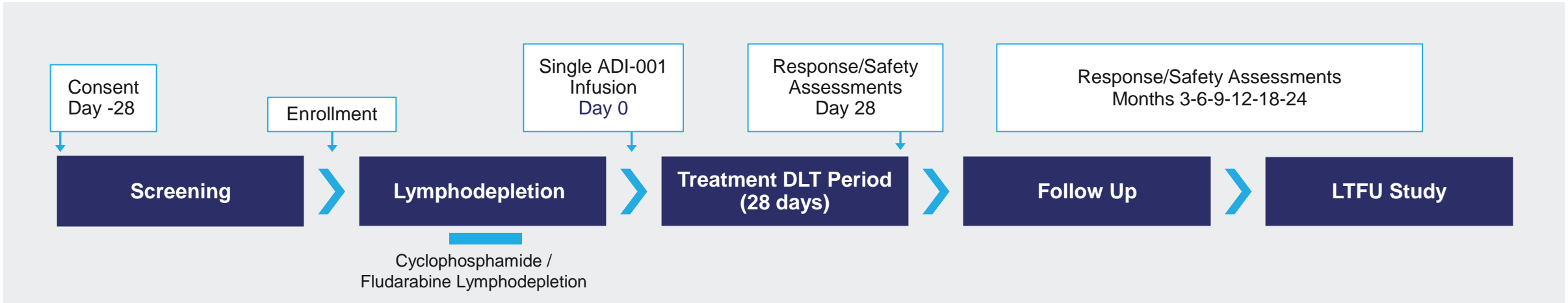
3+3 design
3E8 starting dose

Part 2

Dose Expansion Cohorts

Some patients may be initially dosed with 1E8 until amendment for starting dose of 3E8 becomes effective; For each indication starting dose is 3E8 with potential to escalate up to 1E9 (based on 3+3 design) or de-escalate down to DL1 of 1E8 (in all cases CAR+ cells); LTFU= Long term follow up

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ADI-001 Phase 1 Autoimmune Study Endpoints

Primary Endpoints

Incidence of treatment-emergent adverse events (TEAEs), including severity, seriousness, and relatedness

Incidence of DLTs at each dose (in Part 1 only)

Secondary & Exploratory Endpoints

Cellular Kinetics: Levels of ADI-001 cells in peripheral blood

Pharmacodynamics after treatment with ADI-001:
- Dynamics of B cell depletion and reconstitution
- Dynamics of host immune cell recovery in peripheral blood
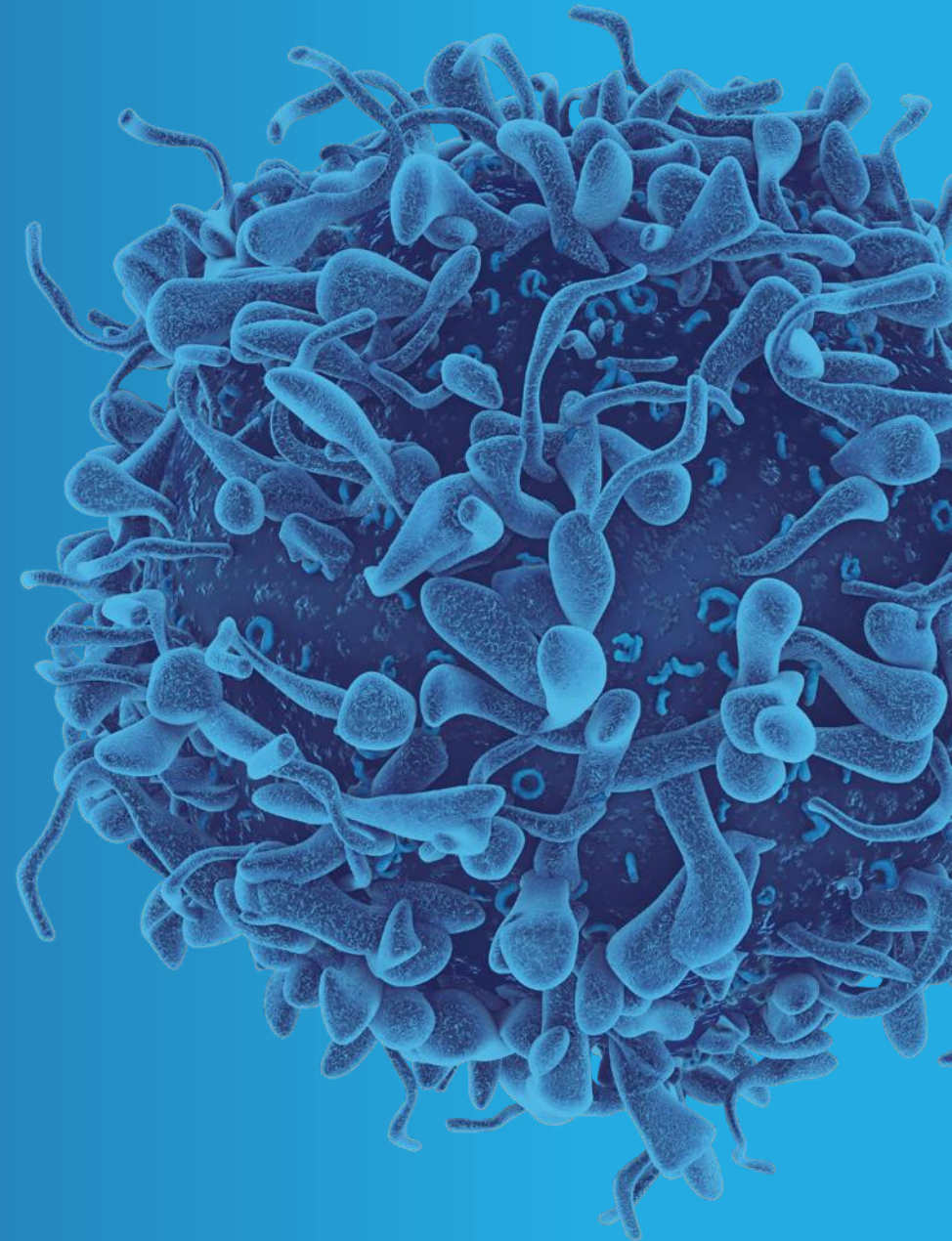- Autoantibody titers

Efficacy endpoints:
- LN: CR/PR based on kidney function
- SLE: SLEDAI-2K/DORIS remission
- SSc: CRISS score, mRSS in diffuse cutaneous, FVC% predicted in ILD
- IIM: changes in MMT-8 and muscle enzymes, Total Improvement Score
- DM: CDASI
- SPS: Distribution of Stiffness Index, Timed 25 foot walk, Rankin scale
- AAV: CR per BVAS

DORIS = definition of remission in systemic lupus erythematosus; SLEDAI-2K = systemic lupus erythematosus disease activity index 2000; CR/PR = complete/partial response; CRISS = American College of Rheumatology Composite Response Index in Systemic Sclerosis; mRSS = modified Rodnan Skin Score; FVC% predicted = percent predicted forced vital capacity; BVAS = Birmingham Vasculitis Activity Score; IIM= idiopathic inflammatory myopathies; MMT-8 = Manual Muscle Test-8; DM=dermatomyositis; CDASI = Cutaneous Dermatomyositis Disease Area and Severity Index; SPS = stiff person syndrome

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ADI-270
Renal Cell Carcinoma & Other CD70+ Diseases

ADI-270: Designed to Address Multiple Refractory Cancers
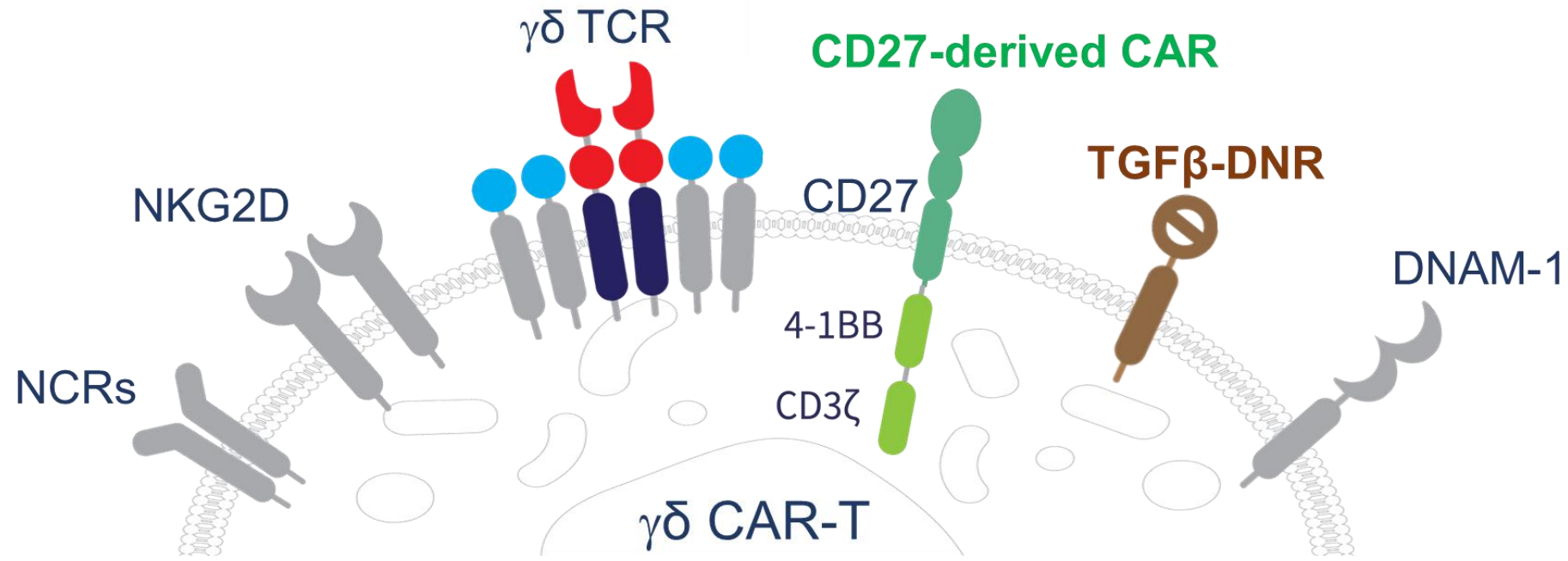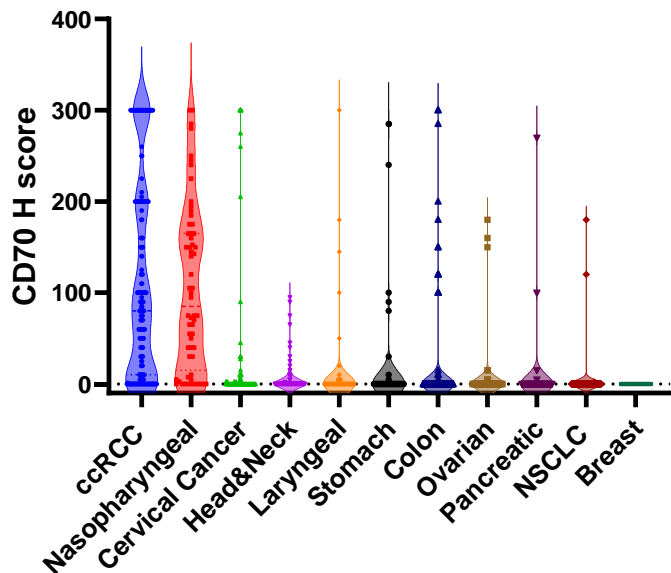

- CAR utilizes CD27 as binding domain; contains CD27 and 4-1BB costimulatory domains plus CD3ζ (3rd gen)
- Inactive form of TGFβ receptor II to mitigate the immunosuppressive effects of TGFβ within the tumor microenvironment
- Host vs graft armoring against alloreactive activated CD70+ T cells to increase persistence
- Combines endogenous γδ innate and adaptive mechanisms to recognize and kill malignant cells

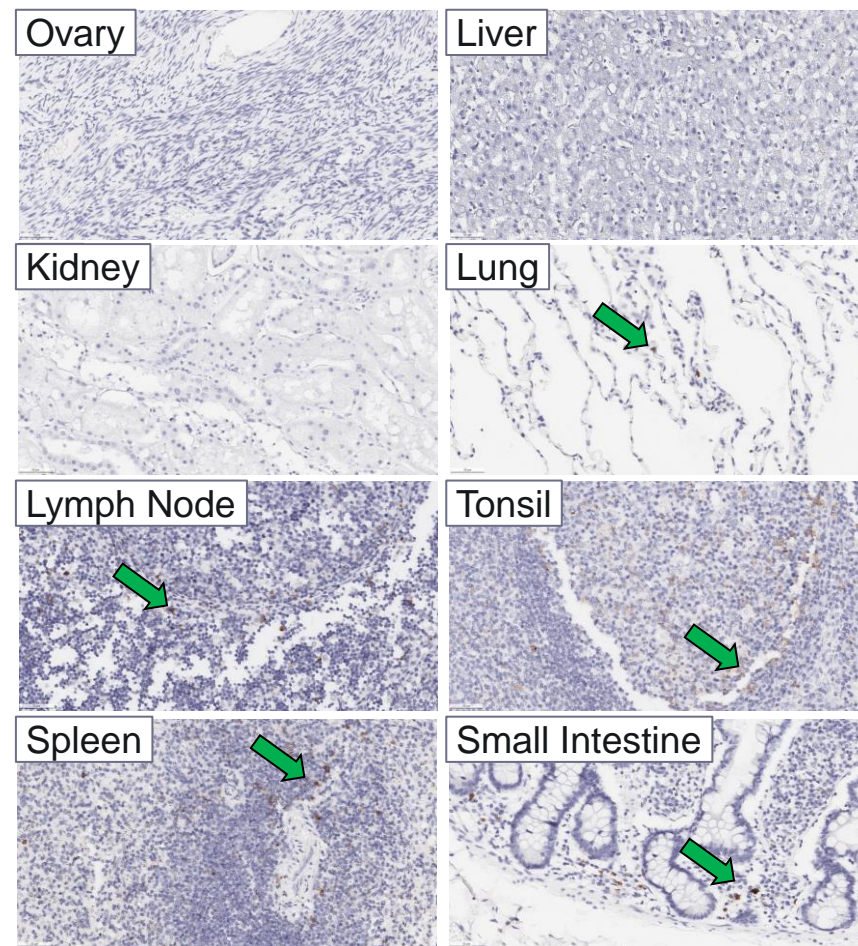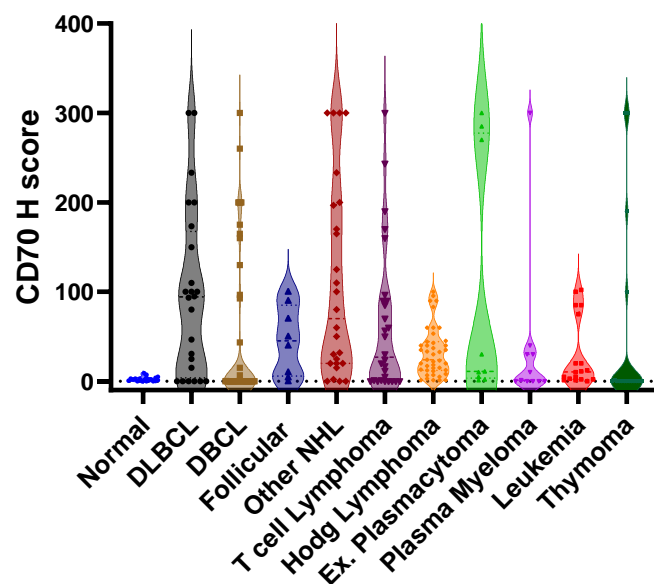# CD70 is Expressed on Multiple Solid and Hematological Cancers with Limited Expression in Normal Tissues

- High expression in multiple solid and heme malignancies
  - Beyond ccRCC and NPC, multiple solid tumors are of interest when paired with CD70 screening

- Minimal expression on normal tissues (activated lymphocytes)

- Target has clinical safety experience

Solid tumors

Hematological malignancies

Representative images from a normal tissue array stained for CD70

Adicet Bio internal data
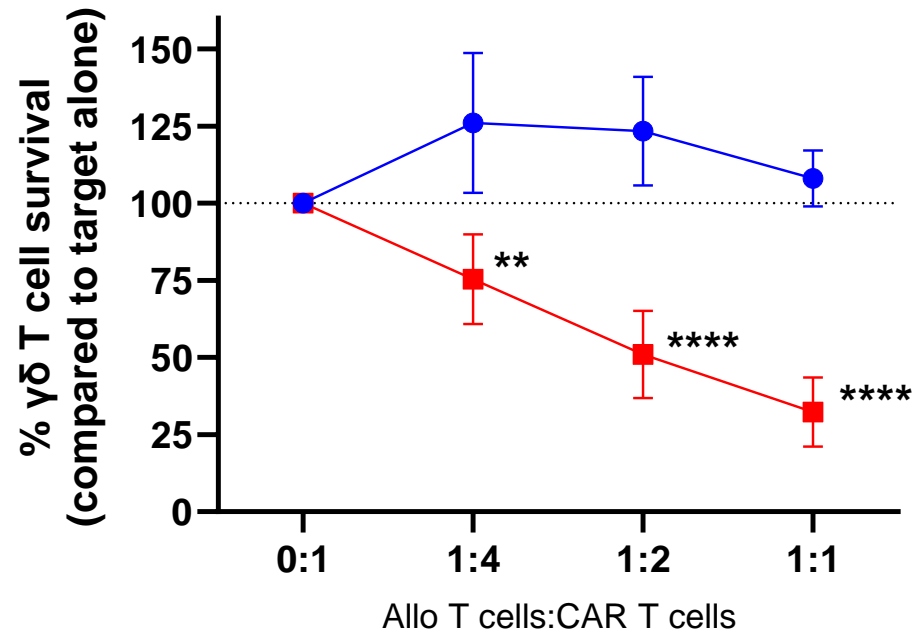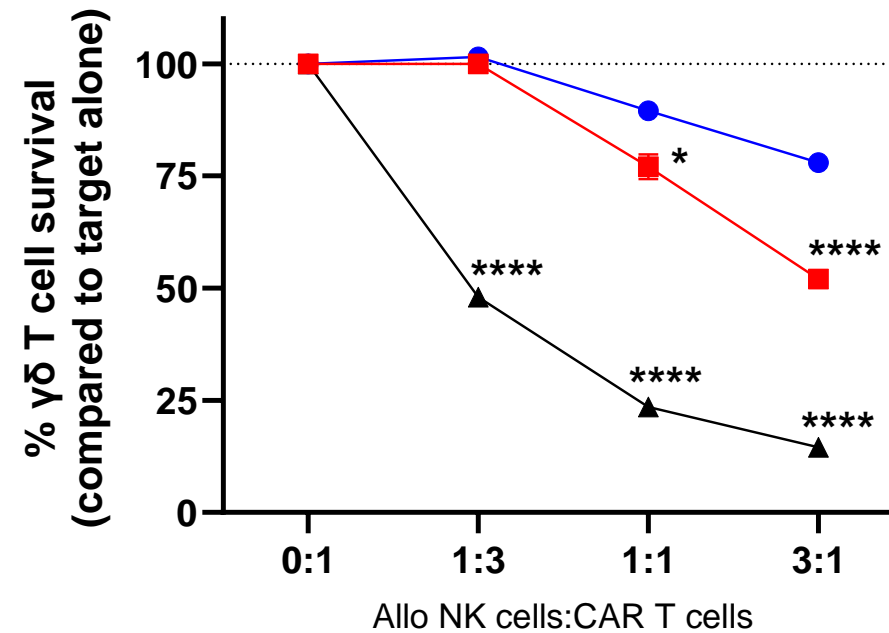ccRCC= Clear cell renal cell carcinoma; NPC= Nasopharyngeal carcinoma

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ADI-270 May Be Less Susceptible to T and NK Rejection by Host

CD70 targeting less susceptible to T cell rejection

y-axis: % γδ T cell survival (compared to target alone)
x-axis: Allo T cells:CAR T cells — 0:1, 1:4, 1:2, 1:1

** at 1:4 (Control); **** at 1:2 (Control); **** at 1:1 (Control)

- ● ADI-270 CAR T cells
- ■ Control γδ CAR T cells

γδ1 CAR T cells less susceptible to NK rejection

y-axis: % γδ T cell survival (compared to target alone)
x-axis: Allo NK cells:CAR T cells — 0:1, 1:3, 1:1, 3:1

**** at 1:3 (black); * at 1:1 (red); **** at 1:1 (black); **** at 3:1 (red); **** at 3:1 (black)

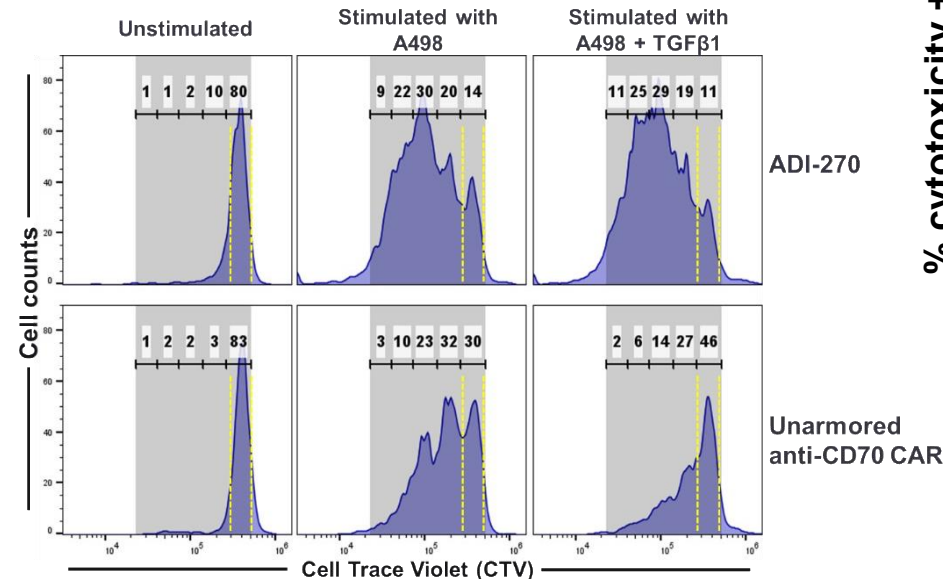- ● γδ CAR T cells
- ■ β2M^{KO} HLA-E^{KI} CAR T cells
- ▲ β2M^{KO} HLA-E^{neg} CAR T cells

ADI-270 is Resilient to the Inhibitory Effects of TGFβ

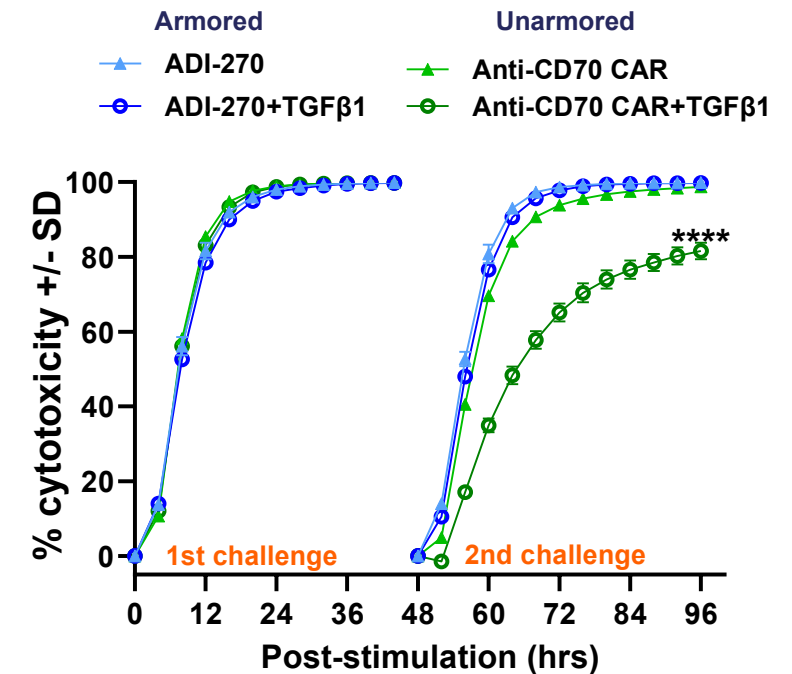**ADI-270 showed _resilience_ to transcriptional changes driven by TGFβ signaling**
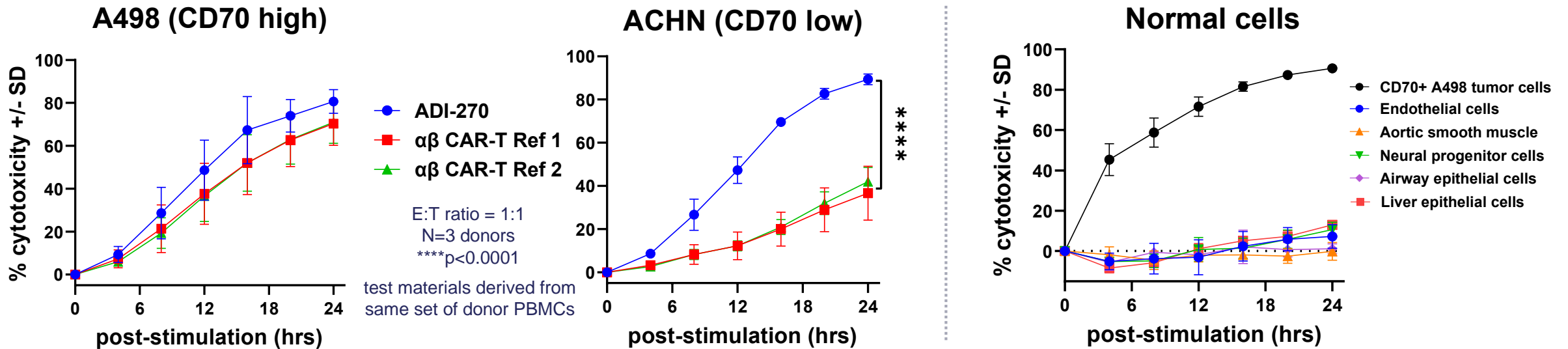
ADI-270 maintained _cytotoxicity_ in the presence of TGFβ
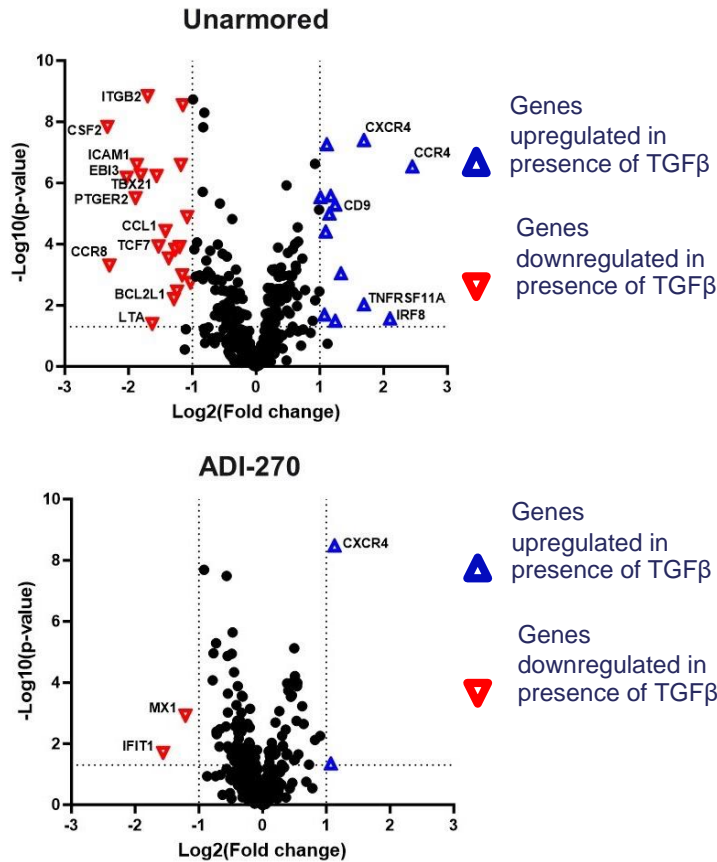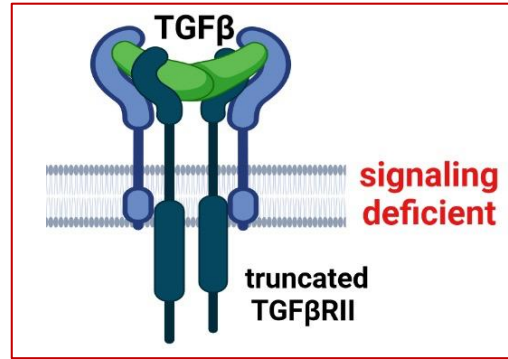
ADI-270 maintained _proliferation_ in the presence of TGFβ

Adicet Bio internal data

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ADI-270 Retained Potent Activity in the Context of CD70-Low Tumors Compared to Clinically Relevant CD70-Targeting αβ CAR T Cell Benchmarks

Adicet Bio internal data
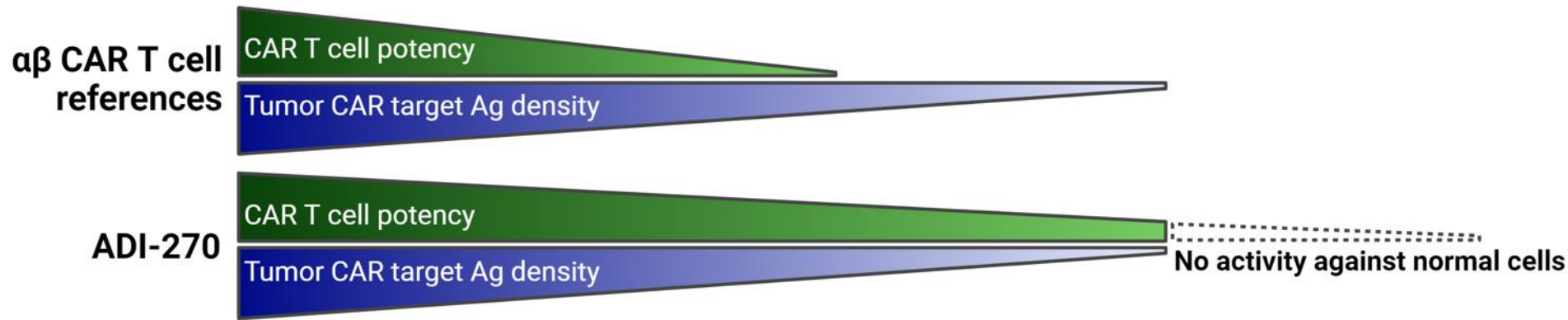
ADI-270 Demonstrated Higher Innate Cytolytic Activity Against CD70 Negative Tumor Cells Compared to CAR-T Cell References
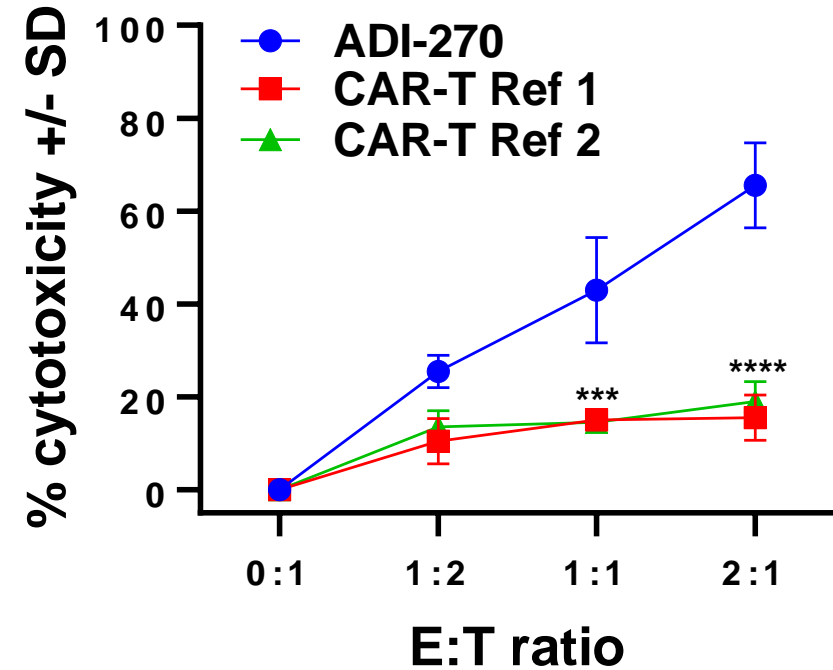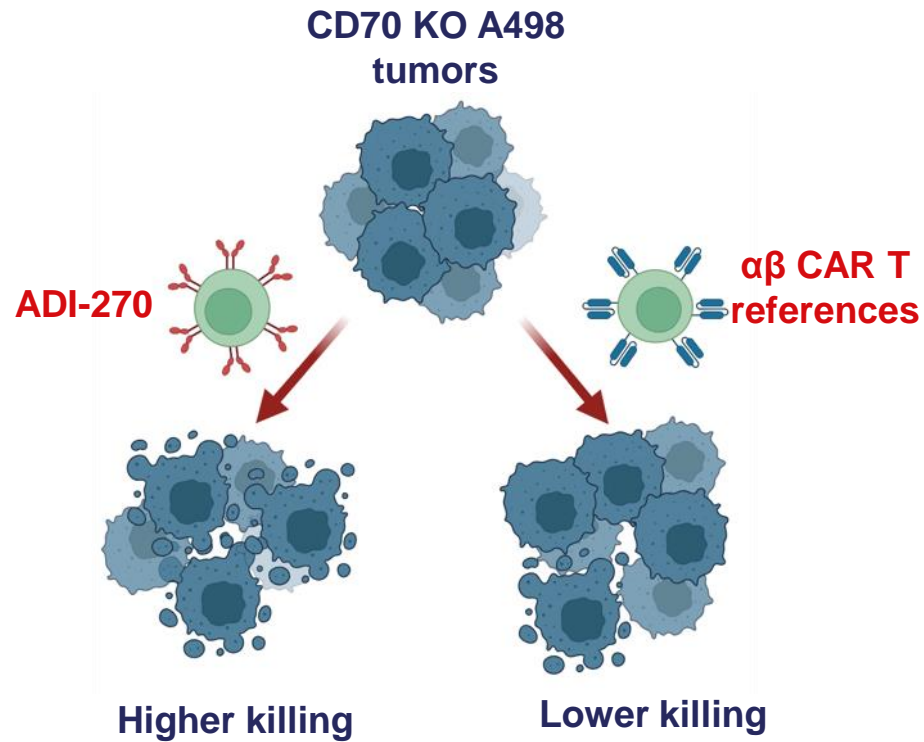
***p<0.001, ****p<0.0001

test materials derived from same donor PBMCs

A single dose of ADI-270 showed potent efficacy in A498 tumors, rapidly eradicating CD70+ cells

ADI-270 Day 3

DAPI +CD3 (cyan)+ Ki67 (orange) + Granzyme B (red)
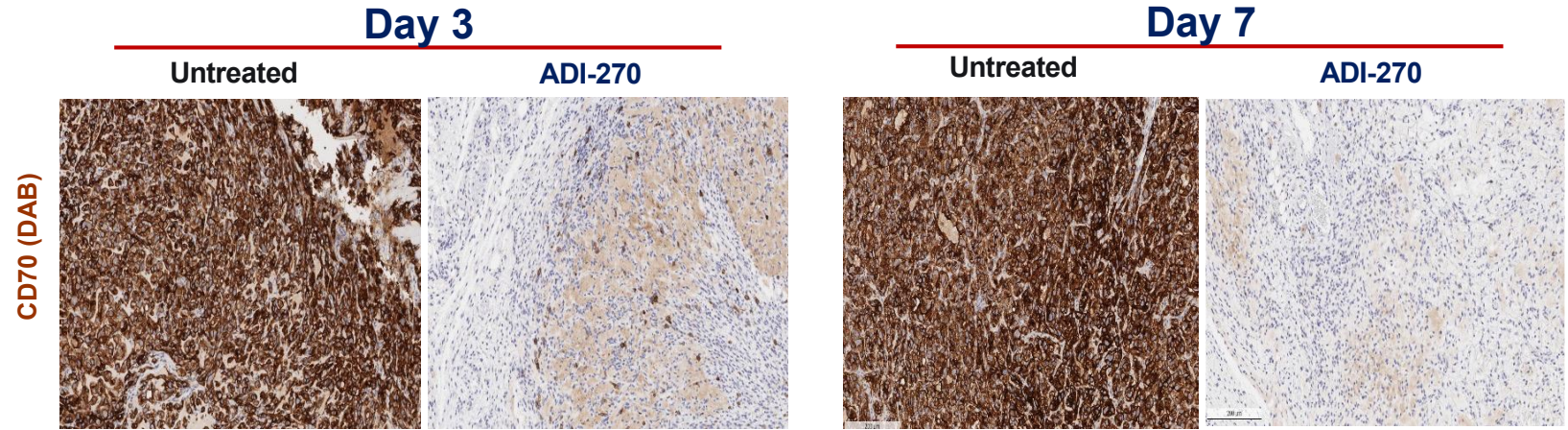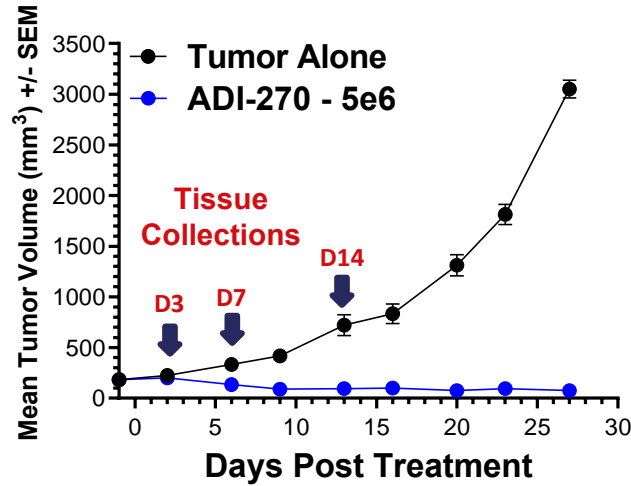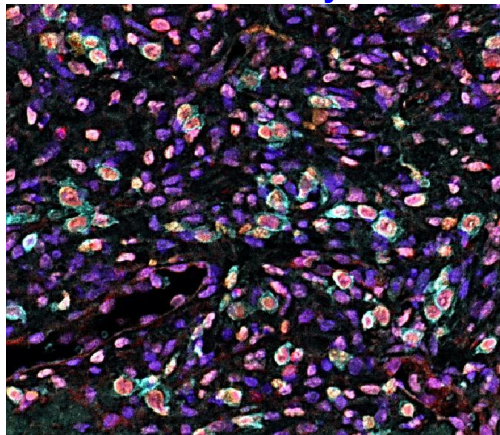
ADI-270 infiltrates, proliferates, and has effector function as early as Day 3

Adicet Bio internal data

Adicet Bio
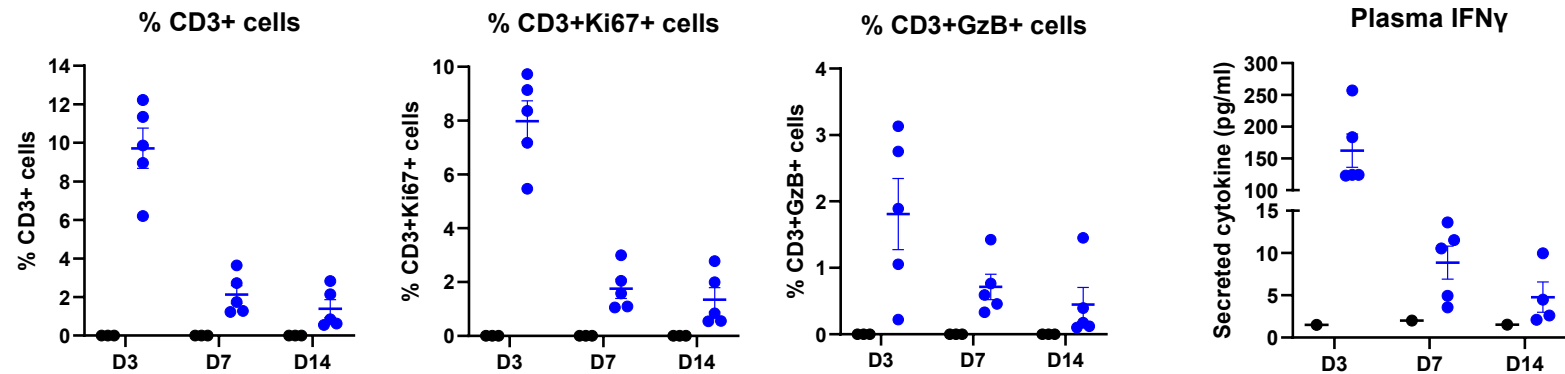
A Single Dose of ADI-270 Showed Potent Regression and Sustained Systemic Anti-Tumor Activity in ccRCC Xenograft Models
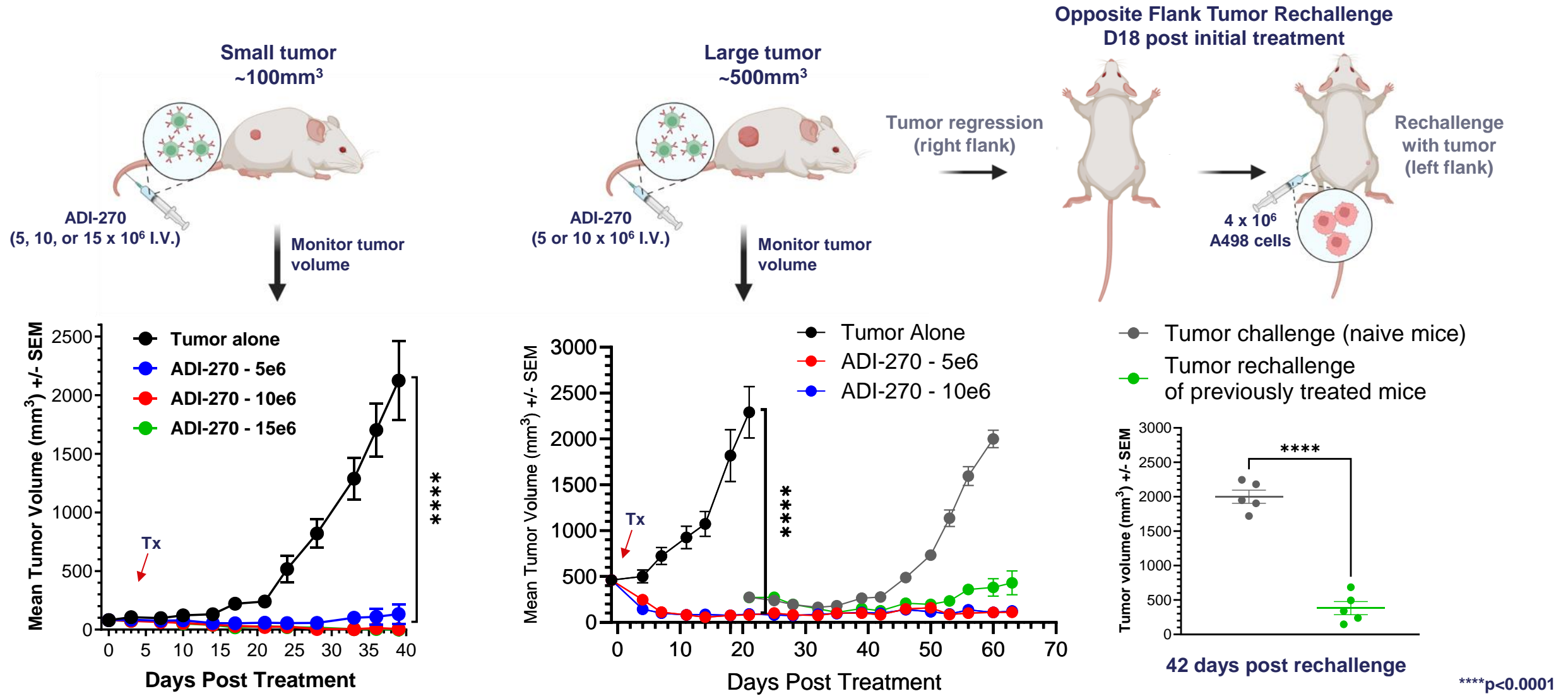
Renal Cell Carcinoma: A Critical Unmet Need

Substantial Addressable Patient Population

- **Kidney cancer incidence of ~80K in the US[1] and ~71K in the EU5[2], clear cell RCC (ccRCC) makes up approximately 80% of cases[3]**
- **High expression of CD70 in ccRCC (80%)** and expression is maintained in primary and metastatic disease[4,5]
- Approximately 25% of patients receive first-line systemic treatment for metastatic disease and of those approximately 50% will receive second-line therapy[6,7]

Critical Unmet Need

- In the US approximately 14K deaths due to renal cancer in 2024[1]
- **5-year survival for stage IV kidney cancer ~ 15%[8]**

Poor Treatment Options in Advanced Setting

- Therapies post early-line treatment options of VEGF TKI inhibitors and checkpoint inhibitors (CPI) offer limited benefit to patients
- Significant share of patients receive TKI combined with PD-1 in 1L setting
- **Post VEGF TKI and CPI therapies offer response rates of ~20% with mPFS of <6 months[9,10,11]**

1. SEER
2. Globocan
3. https://www.cancer.gov/pediatric-adult-rare-tumor/rare-tumors/rare-kidney-tumors/clear-cell-renal-cell-carcinoma#:~:text=How%20common%20is%20ccRCC?,young%20adult%20kidney%20cancer%20cases.
4. Adam PJ et al. Br J Cancer (2006)
5. Huang RR et al. Clin Genitourin Cancer (2024)
6. Mori K et al. Cancer Immunol Immunother (2020)
7. Stukalin I et al. Kidney Cancer (2018)
8. Cancer Research UK
9. Rini BI et al. Lancet oncology (2020)
10. Albiges et al. ESMO 2023
11. FDA labels for tivozanib and belzutifan

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ADI-270 Phase I Study (CD70-dnTGFβ CAR+ γδ1 T cells)

Consent Day -28

Enrollment

Single ADI-270 Infusion Day 1

Response/Safety Assessments Day 28

Response/Safety Assessments Every 2-3 Months Through Month 24

Screening → **Lymphodepletion** → **Treatment DLT Period (28 days)** → **Follow Up** → **LTFU Study**

Cyclophosphamide / Fludarabine Lymphodepletion

Dosing Arms:

DL2: 1E9 CAR+ cells

DL1: 3E8 CAR+ cells

3+3 design
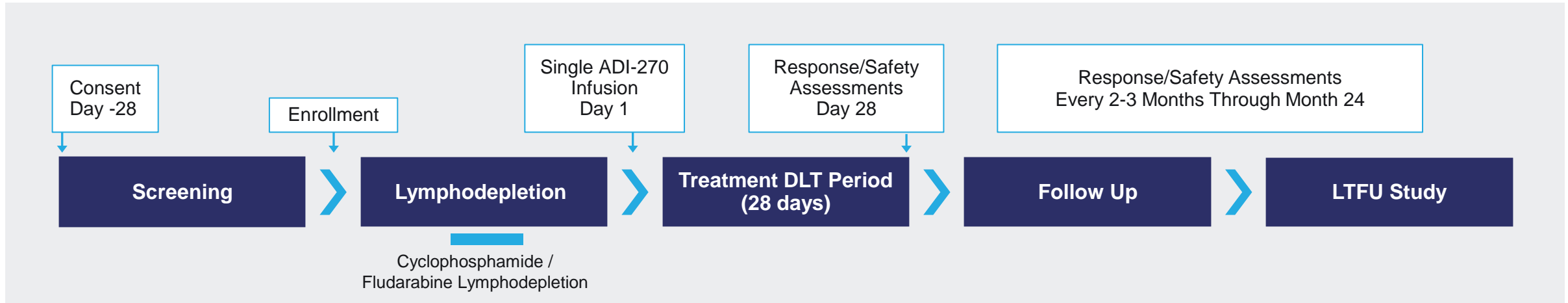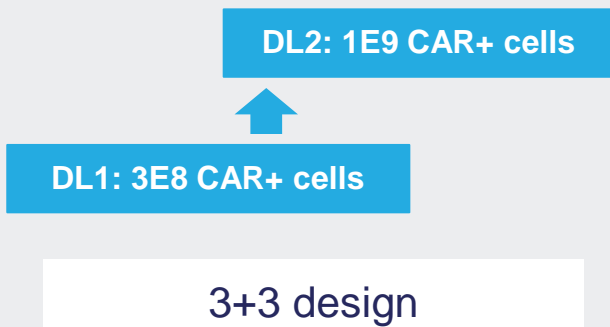
Primary endpoints:
- Number of DLTs
- Treatment emergent and treatment-related AEs

Secondary endpoints:
- ORR, DCR, DOR, PFS, TTP, and OS
- PK, host immune cell recovery

Dose Expansion:
- RCC
- Other CD70+ tumors

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ADI-270 Summary

- ADI-270 represents potential evolution of γδ CAR T cell-based therapeutics

- CD27-based 3rd gen CAR demonstrated significant potency advantages[1,2,3,4]

- Armoring against TGFβ and alloreactive T cells confirmed and characterized preclinically

- Robust efficacy maintained across multiple relevant tumor models of varying stringency

- Desirable preclinical safety profile with lower potential for CRS and macrophage activation syndrome

- IND cleared and Fast Track Designation received for metastatic/advanced ccRCC

- Enrollment open in Phase 1 study; Preliminary clinical data expected 1H/2025

[1]Shaffer et al., Blood 2011
[2]Acharya et al., Blood 2023
[3]Leick et al., Cancer Cell 2022
[4]Kasap et al., BioRxiv 2024

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Potential Near-Term Milestones

	2024	**2025**	
	4Q	**1H**	**2H**
ADI-001 **LN, SLE, SSc,** **AAV**	☑ Expand ADI-001 Autoimmune development; activate sites	Clinical Update: LN	Clinical Update: Multiple Autoimmune Indications
	☑ Initiate enrollment LN	Initiate enrollment – SLE, SSc, IIM/SPS	Initiate enrollment AAV
ADI-270 **RCC**	☑ Activate sites / Initiate enrollment in Phase 1	Clinical Update: RCC	Clinical Update: RCC Potential Expansion to additional CD70+ Tumors

Cash and cash equivalents: ~$202.1M (9/30/24)
Projected cash runway into 2H/2026

Subject to site activation, patient enrollment, data readouts and regulatory feedback

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Leaders in Developing Allogeneic γδ1 CAR T Cell Therapies to Fight Autoimmune Diseases and Cancer

γδ= Gamma delta; CAR= Chimeric antigen receptor

November 2024