ADI-001: An allogeneic CD20-targeted γδ CAR T cell therapy with potential for improved tissue homing in autoimmune indications

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- *I have the following relevant financial relationship(s) to disclose: Shareholder, Employee, Inventor on related patents: Adicet Therapeutics*
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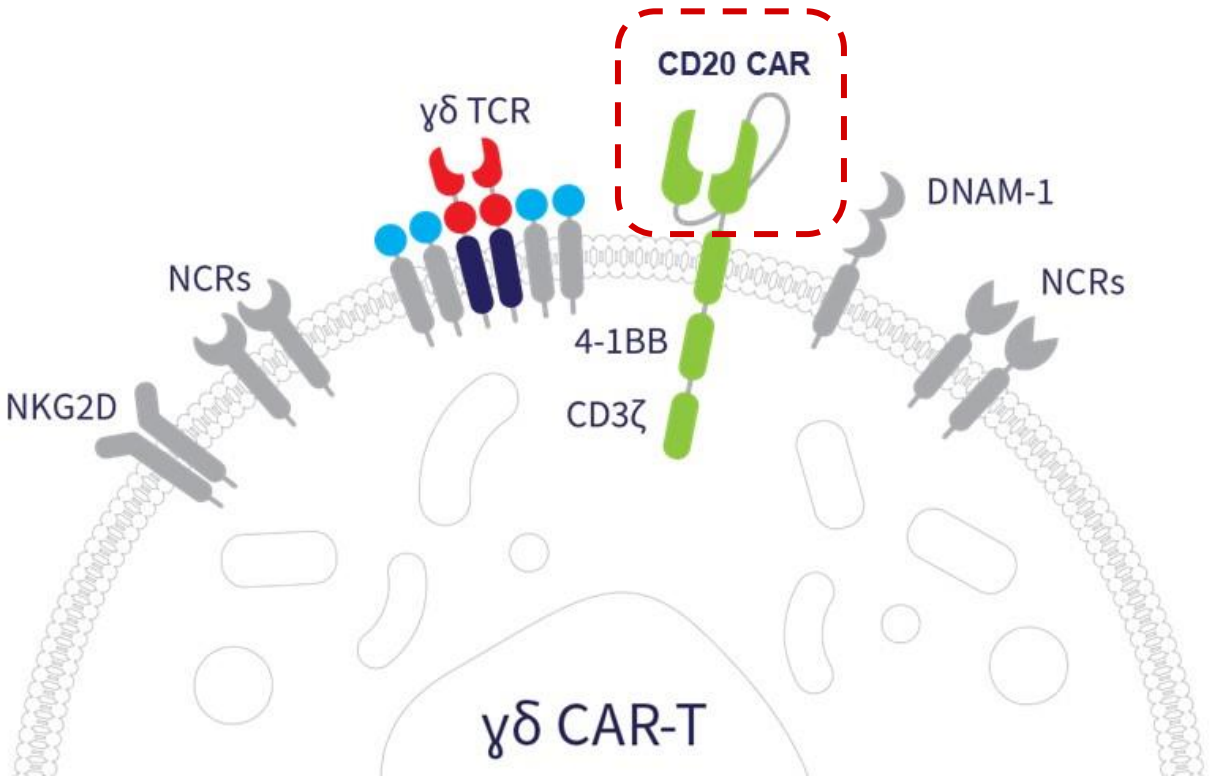
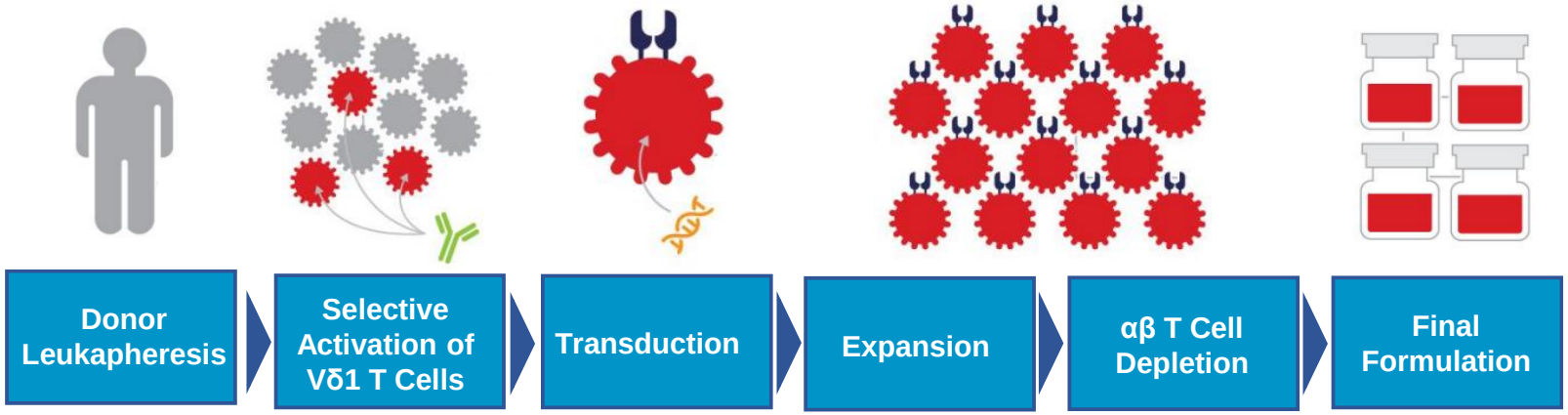
ADI-001: A First Allogeneic CAR γδ T Cell Therapy

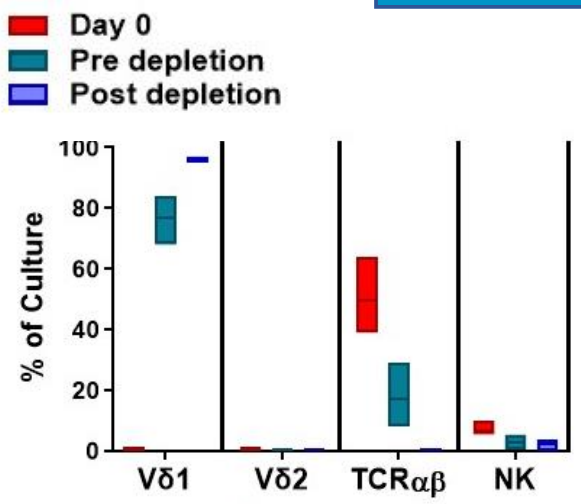


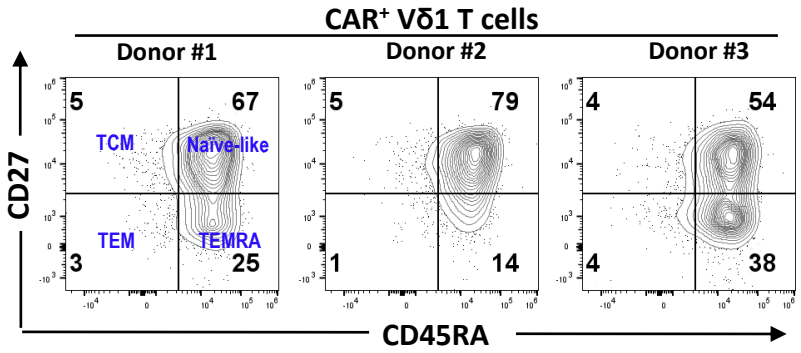
ADI-001

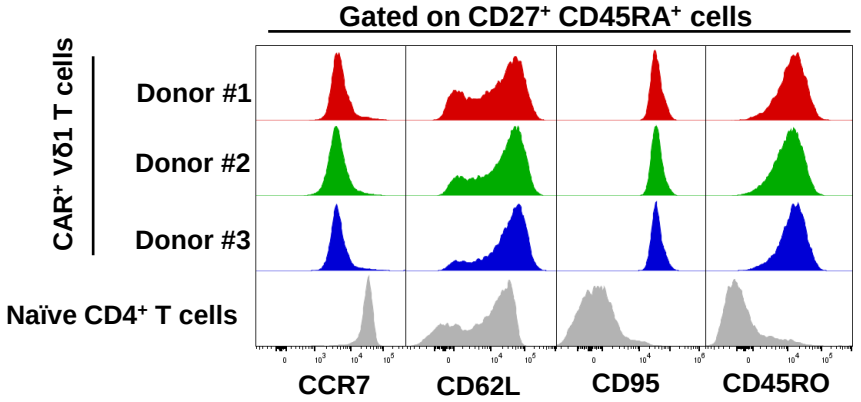
- ADI-001 is a first-in-class, allogeneic CAR γδ T cell therapy targeting the B-cell antigen CD20 with a novel human binder
- ADI-001 expresses MHC-independent γδ T cell receptors, thus lowering the risk of graft-versus-host disease (GvHD) without the need for gene editing
- Demonstrated high rates of expansion after antigen engagement
- Confirmed tropism to tissues, providing significant differentiation with potential for improved tissue homing in autoimmune indications
- Readily available, “off-the-shelf” product candidate with scalable cGMP manufacturing process
- Clinical experience in oncology demonstrates no significant CRS, ICANS, GvHD

ADI-001 is Highly Enriched for Vδ1 CAR+ T Cells That Possess a Favorable Phenotype







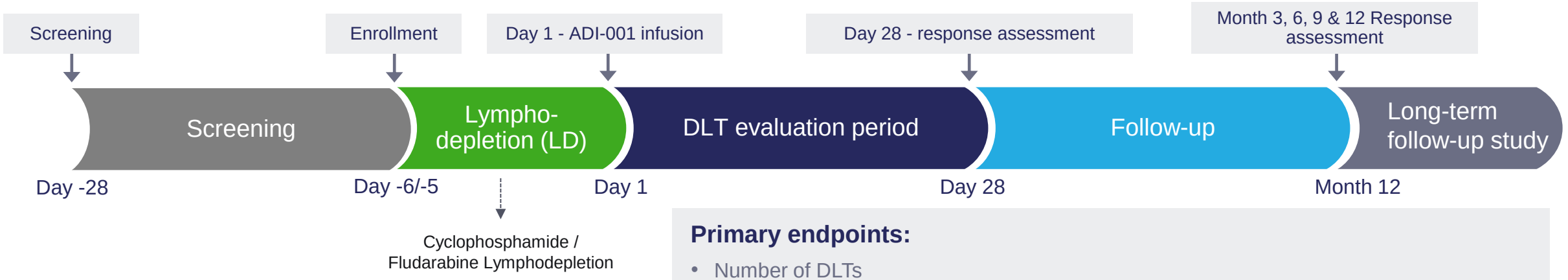


ADI-001 is highly enriched for Vδ1 CAR T cells

ADI-001 cells co-express markers associated with both naïve (CD27, CD45RA, CD62L) and memory T cells (CD95, CD45RO)

K. Nishimoto et al. **Clin & Trans Immunol** Jan 2022

GLEAN: Phase 1 First in Human Study of ADI-001 (anti-CD20 gamma-delta 1 CAR T) in Patients with Previously Treated B-cell Non-Hodgkin's Lymphoma



ADI-001 Dose (CAR+ Cells) (3 + 3 escalation design)

DL1	DL2	DL3	DL4
3E7	1E8	3E8	1E9

Primary endpoints:

- Number of DLTs
- Treatment emergent and treatment-related AEs

Secondary endpoints:

- ORR, DOR, PFS, TTP, and OS
- PK, immunogenicity

Study Status:

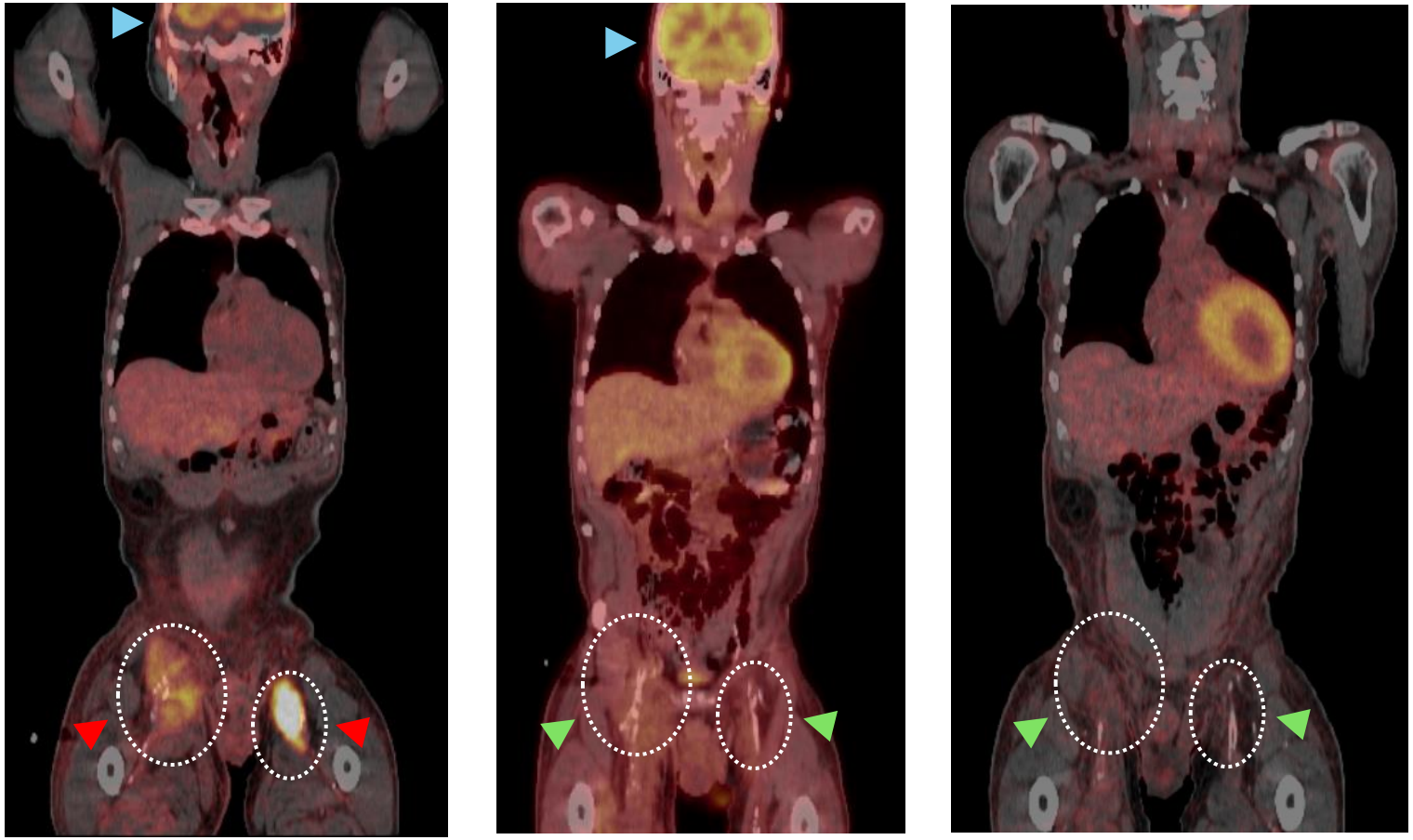
- Dose escalation with ADI-001 up to 1E9 CAR+ cells is complete
- No unexpected safety signals were observed in patients with R/R B cell NHL dosed with ADI-001 at any dose level
- Enrollment in study ADI-20200101 has been closed

AEs= Adverse events; Cy= Cyclophosphamide; DL= Dose level; DOR= Duration of response; Flu= Fludarabine; GLEAN= Gamma deLta adoptive thErApy for Nhl-1; OS= Overall survival; PFS= Progression-free survival; PK= Pharmacokinetics; R/R= Relapsed or refractory; TTP= Time to progression

GLEAN Trial Case Study (1E8 cells): Clinical Response Observed with No ICANS, CRS or GvHD

- 62-year-old male
- Mantle Cell Lymphoma
- MIPI score 4, Stage IV
- SPD 6,404 mm^2 at baseline
- 5 prior lines of therapy
  - Bendamustine + rituximab
  - Zanubrutinib
  - Bendamustine + obinutuzumab
  - Bendamustine + rituximab
  - Rituximab + gemcitabine + dexamethasone + carboplatin

- Efficacy Data:
  - **CR at Day 28 and maintained through Month 9**
- Safety Data:
  - No ICANS, CRS, or GvHD
  - No ADI-001 related adverse events or adverse events meeting dose limiting toxicity criteria



Baseline | Day 28 | Month 6

FDG uptake by normal tissues

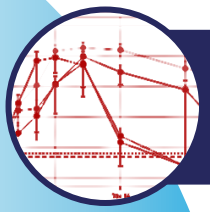
Baseline FDG uptake by tumor lesions

Sites of tumor response

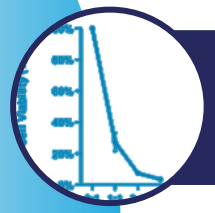
MIPI: mantle cell lymphoma international prognostic index; SPD: sum of the product of the perpendicular diameters; ICANS: immune effector cell-associated neurotoxicity syndrome; CRS: cytokine release syndrome; GvHD: graft versus host disease; CR: complete response per the 2014 Lugano classification

Assessment of CK and PD profile of ADI-001

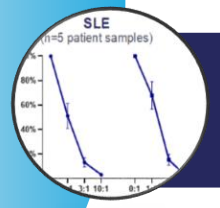
Multiple Levels of CK/PD support



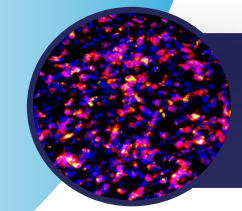
Peripheral CK exposure by ddPCR and flow



Pharmacodynamic assessment of CD19+ B cells by flow



Ex vivo assessment of **potent killing of patient-derived CD19+ B cells** in Multiple **Autoimmune Diseases**

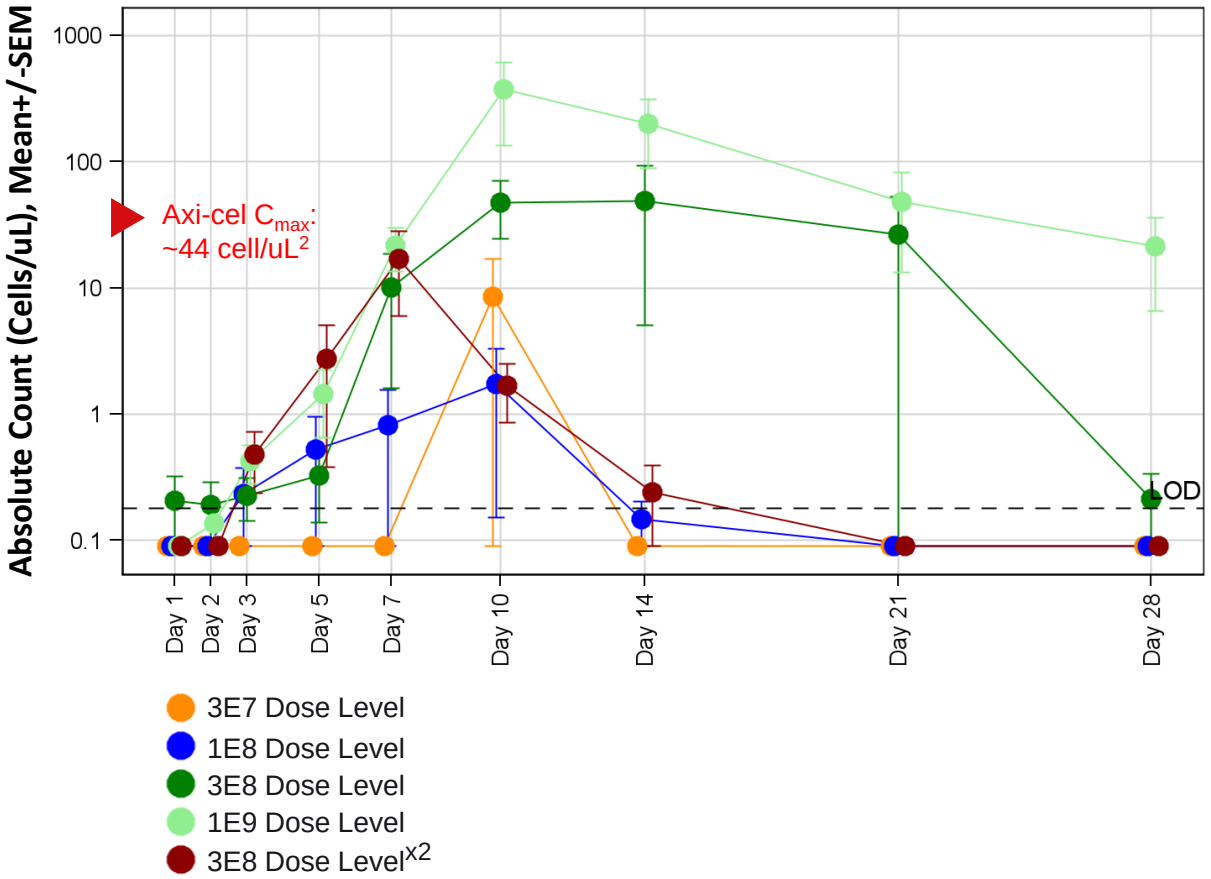


Tissue CK/PD assessment of exposure, CAR-T activation and CD19+ B cells by ddPCR and ISH

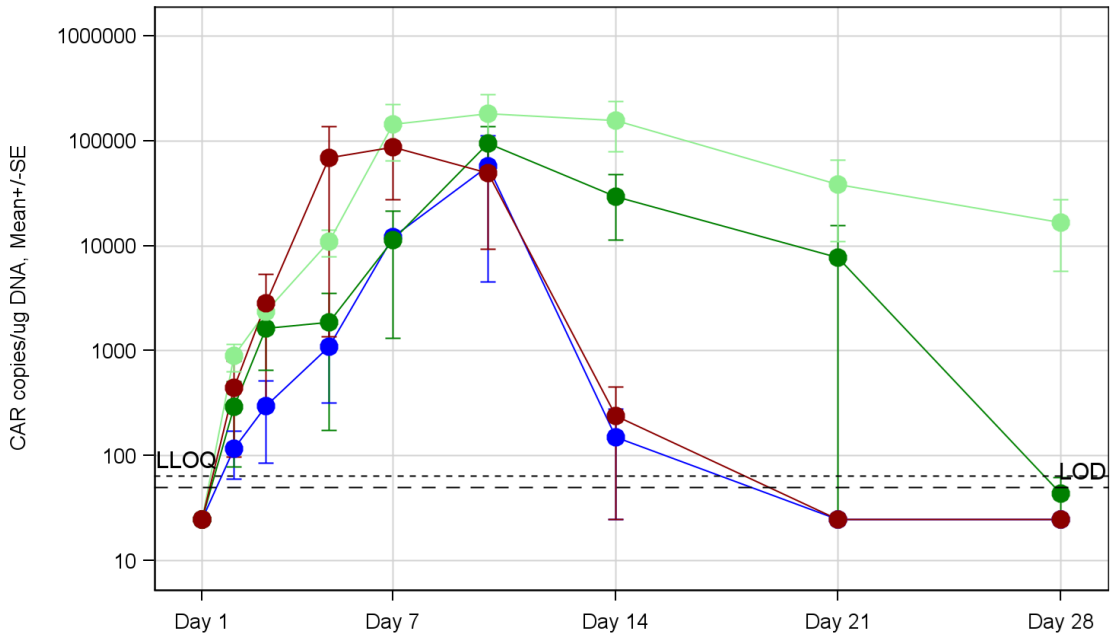
CK = cellular kinetics; PD = pharmacodynamic

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



ADI-001 CAR by ddPCR

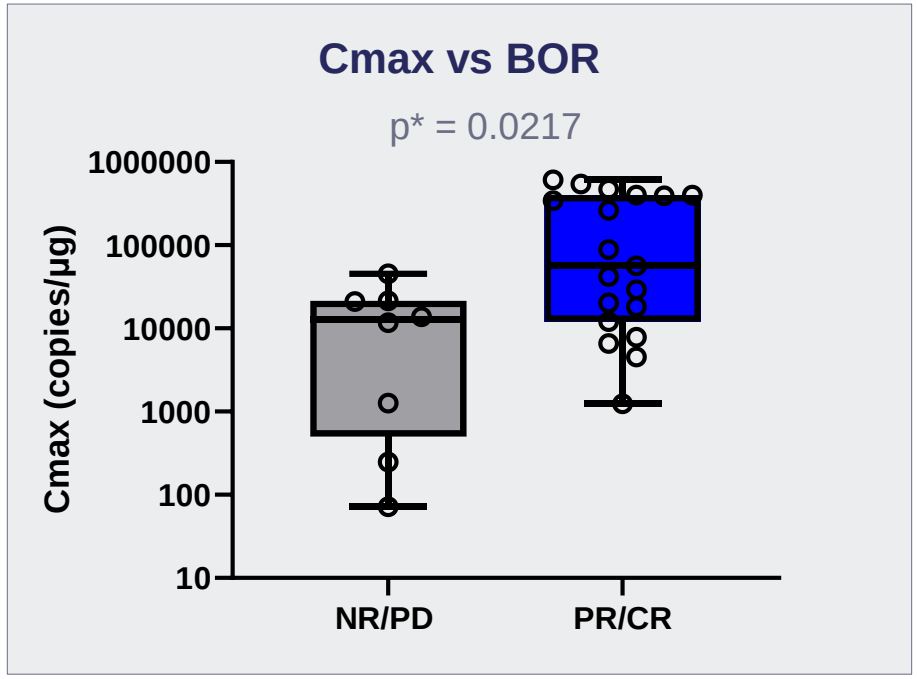


Dose Level	Mean Cmax		Mean D28	
	CAR+ Vd1 cells/ul	Copies/ug	CAR+ Vd1 cells/ul	Copies/ug
1E9	**363.80**	201,666	26.51	16,553
3E8	**58.15**	98,177	0.04	44

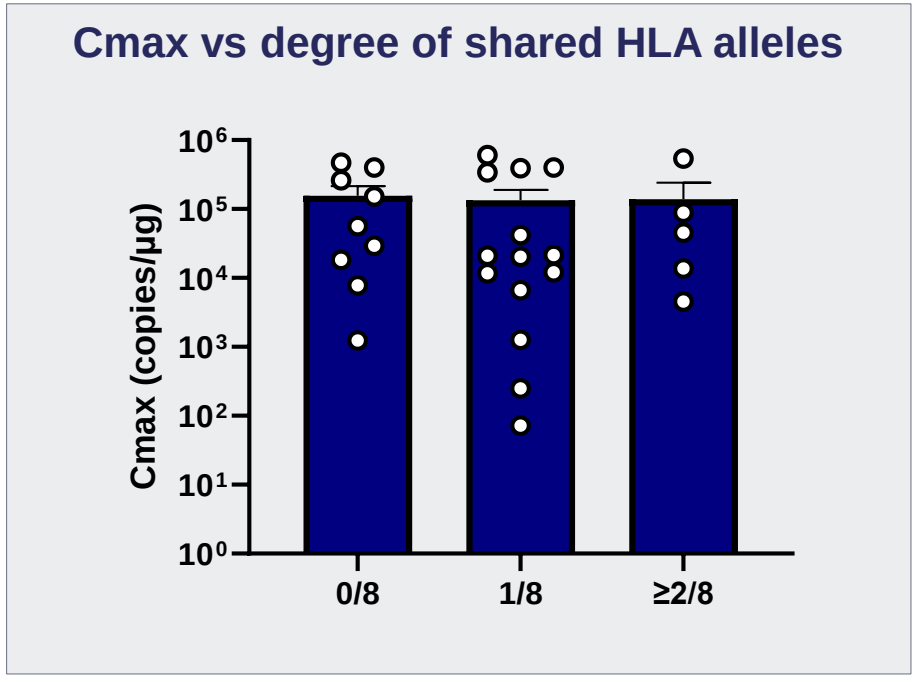
[1]Badbaran, A. Cancers 2020;12, 1970; Locke et al. N Engl J Med 2022; 386:640-654; Neelapu et al. N EnglJ Med. 2017;377:2531-2544; Ogasawara et al. Clin Pharmacokinet 60, 1621–1633 (2021)
[2]YESCARTA® (axicabtagene ciloleucel) prescribing information rev. June 2024
Cmax= Mean maximum concentration of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

ADI-001 Cmax is Associated with Clinical Response in the GLEAN Study

Expansion correlated with the degree of response



High Cmax observed irrespective of degree of shared HLA alleles between ADI-001 and patients



Clinical biomarkers of response for ADI-001 do not require HLA matching

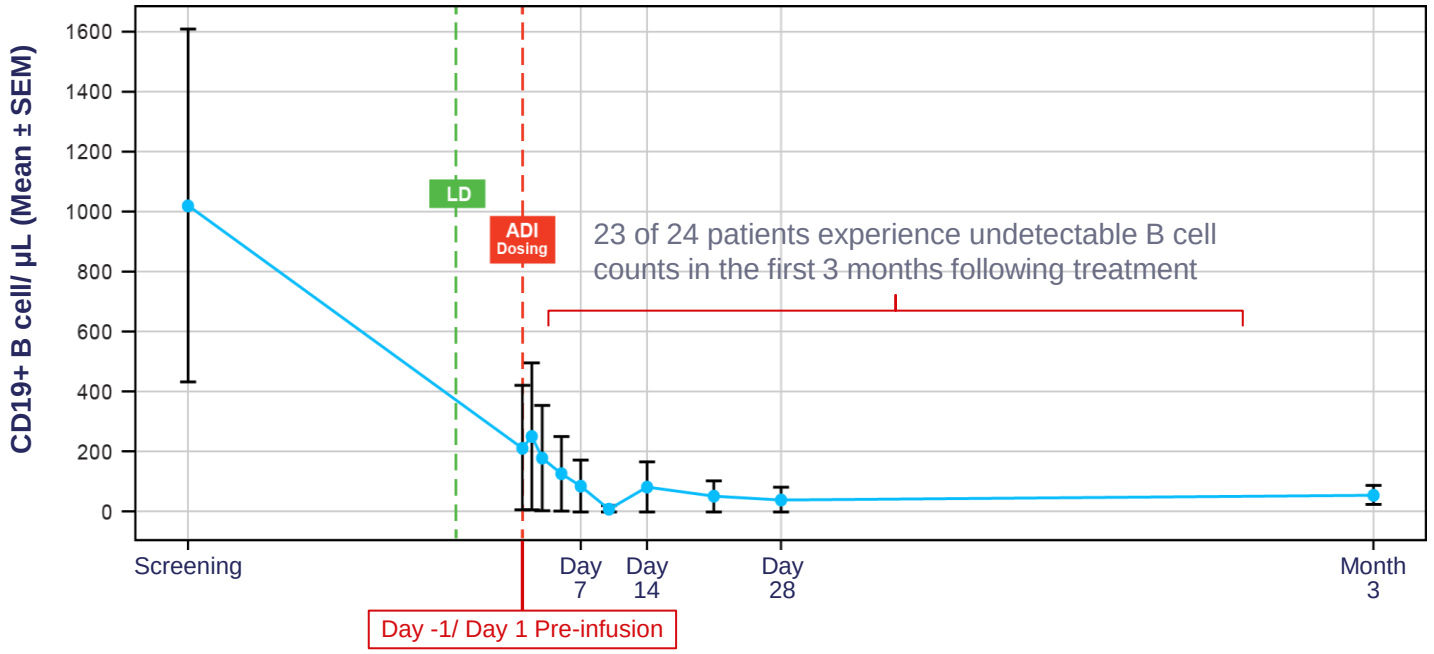
*Wilcoxon Rang Sum test; BOR = best overall response; NR = no response; PD = progressed disease; PR = partial response; CR = complete response; Data snapshot 22AUG2024

ADI-001: B-Cell Depletion Observed in GLEAN Trial Consistent with Autologous CD19 CAR T in SLE Academic Studies

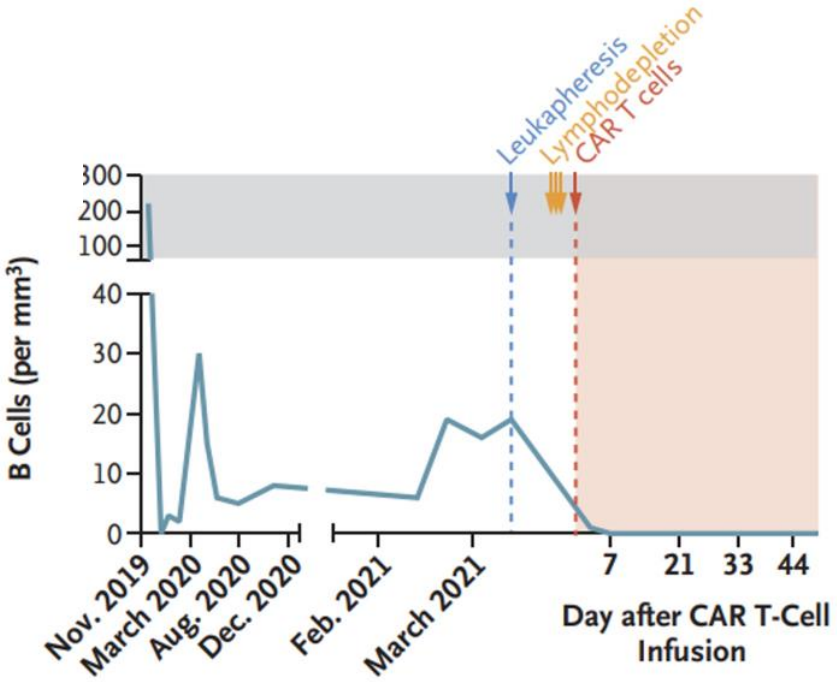
B-cell Depletion

- B-cell depletion data from ADI-001 trial in GLEAN study mirrored experience of autologous CD19 CAR T in SLE[1,2]
- B-cell depletion via CD20 targeting validated by CD20-targeted antibody (obinutuzumab) which demonstrated efficacy on top of SOC in lupus nephritis patients[3]

CD20-targeted, ADI-001, in B-NHL patients[4]



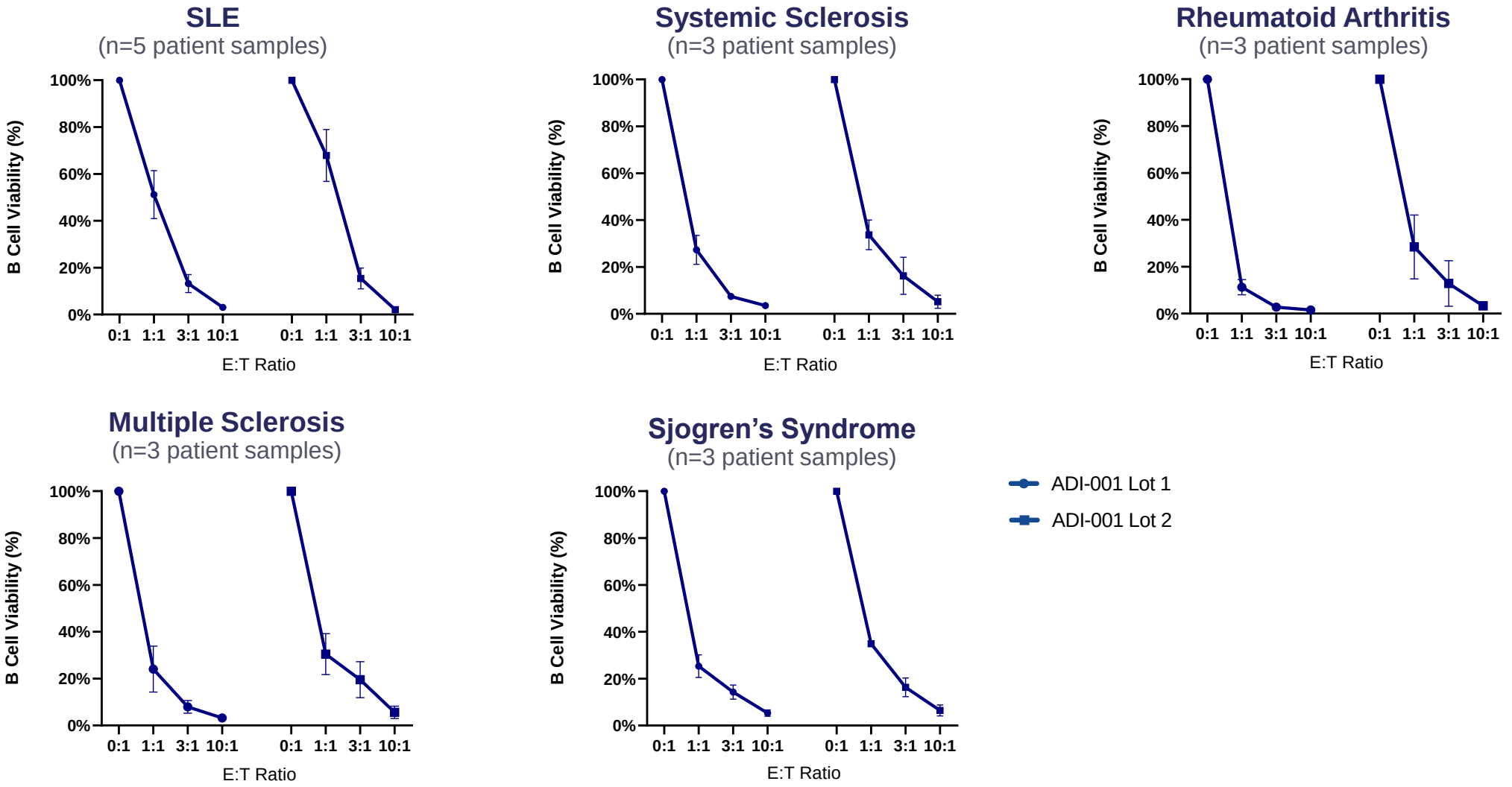
CD19-targeted CAR-T in SLE patients[1]



1. Mougiakakos MD et al. NEJM 2021
2. Mackensen A et al. Nature Medicine 2022
3. Furie RA et al. Ann Rheum Dis. 2022
4. Adicet internal data

SOC= Standard of care

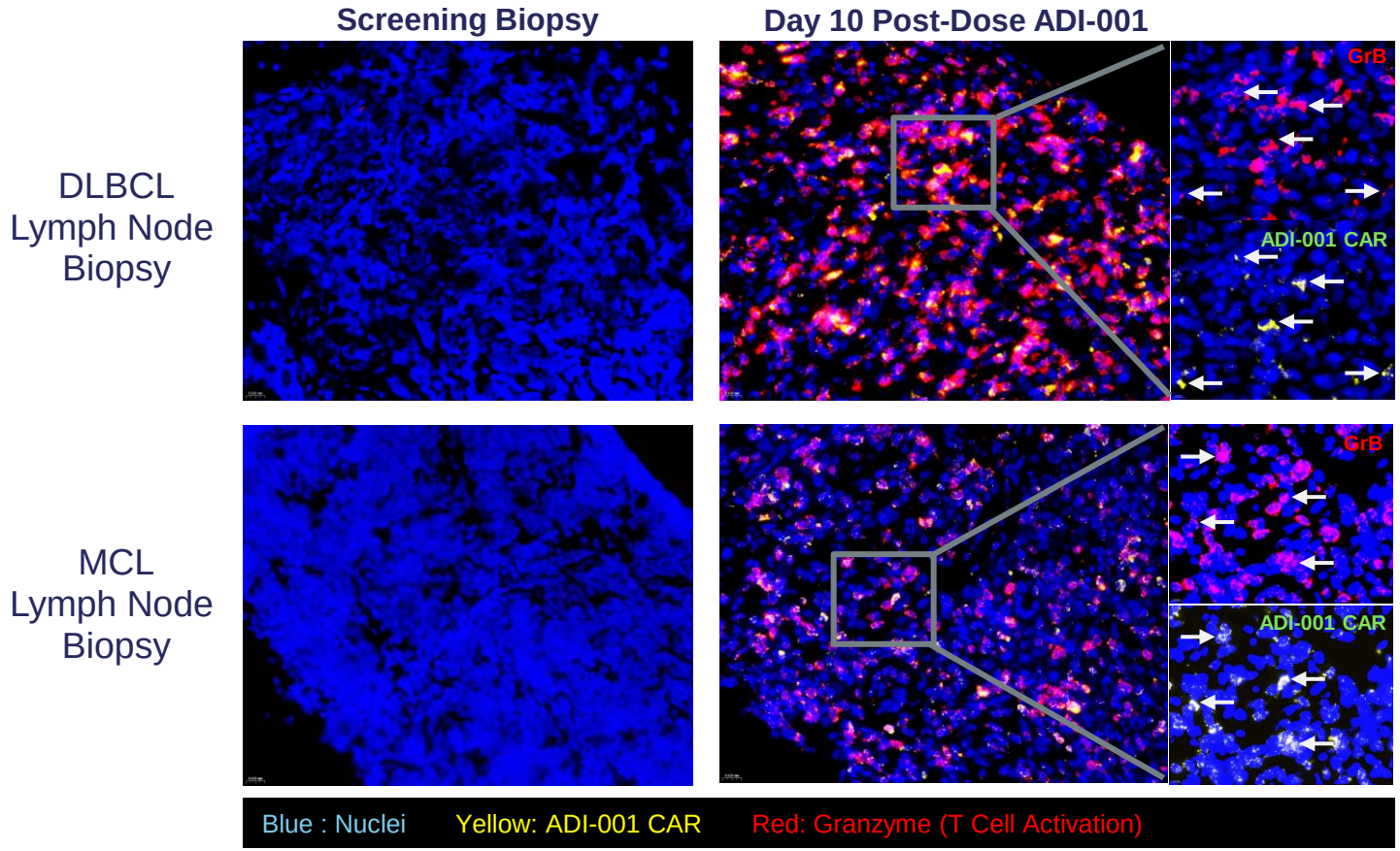
ADI-001 Exhibited Potent Killing of Patient-Derived CD19+ B Cells in Multiple Autoimmune Diseases



B cells from 5 SLE patients and 3 patients each for SSc, RA, Multiple sclerosis, and Sjogren'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.

ADI-001 Clinical Data Demonstrated Tissue Trafficking and CAR Activation

ADI-001 Clinical Tissue Analyses



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

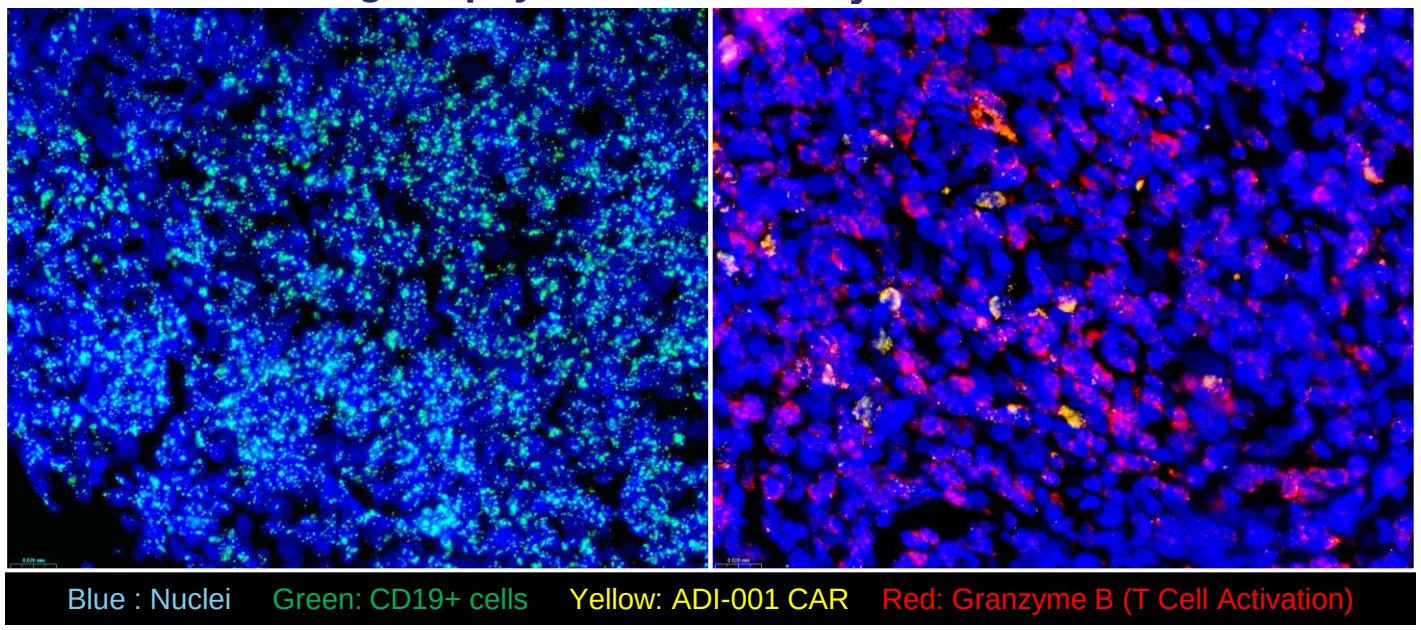
Robust tissue tropism for ADI-001 observed in lymph node biopsies across dose levels
ADI-001 cells represent 27%-64% of total cellular material detected by ddPCR in lymph nodes at 1E9 dose level

Axi-cel= Axicabtagene ciloleucel
[1]Head-to-head studies have not been conducted
[2]Table 3. Excerpt for Axi-cel assay. Badbaran, A et al., Cancers (2020)

Confirmation of CD19+ B Cell Depletion Within Tissues

MCL Patient Lymph Node Biopsies

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



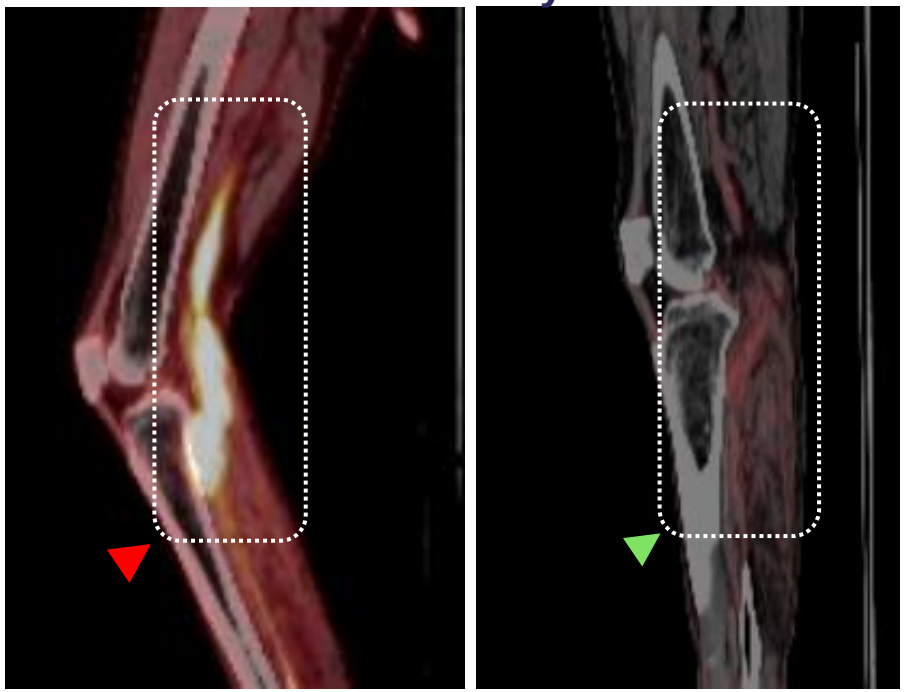
Blue : Nuclei Green: CD19+ cells Yellow: ADI-001 CAR Red: Granzyme B (T Cell Activation)

73y M, 2 prior lines (including SCT), 1E9 Dose Level CR

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

Intramuscular DLBCL

Baseline | **Day 28 Post ADI-001**

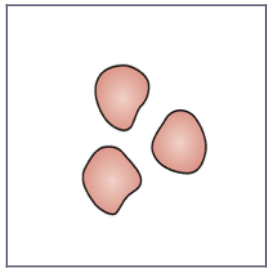


75y M, 5 prior lines (incl. CD19 CAR-T); Sagittal view of the right leg

Clinical responses observed in extra-nodal tissue

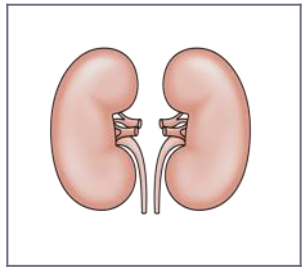
Staining for CD138 in lymph node biopsies demonstrated low levels at baseline and absence of CD138+ cells on day 10. DLBCL= Diffuse large B-cell lymphoma; MCL= Mantle cell lymphoma

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



lymph node[1,2]

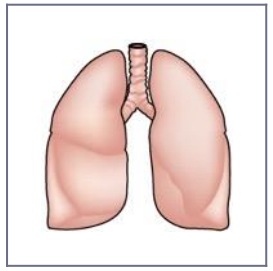
CD27+
CD62L+
Vδ1+ ↑↑
Vδ2+ ↓↓



kidney[3]

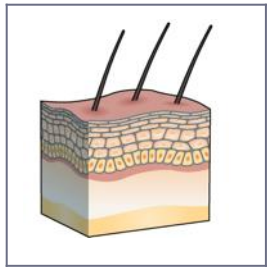
tissue: **>3X** γδ vs αβ

~3X more **Vδ1 vs Vδ2+**



lung[4]

issue/blood: **9X**

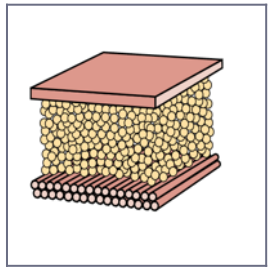


skin[5]

tissue/blood: **8X**

bone marrow[6]

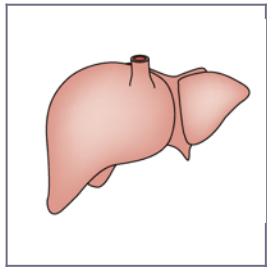
tissue/blood: **4X**



breast[7]

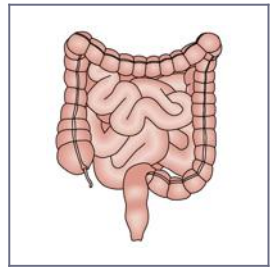
tissue/blood: **~15X**

adipose tissue/blood: **9X**



liver[8]

tissue/blood: **3X**



GI[9]

tissue/blood: **11X**

Observations of ADI-001 tissue trafficking and CAR activation, accompanied by demonstrated functional clinical responses is well aligned with the established function of gamma delta 1 T cells

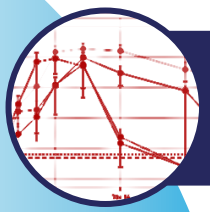
Ratios empirically calculated or approximated from proportion of %CD3 from literature reports in relative compartment[3,6]

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

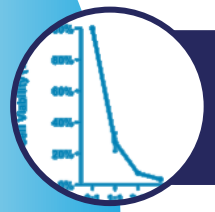
[1]Davey et al Trends Immunol (2018)
[2]Uger et al Sci Rep (2018)
[3]Rancan et al Nat Immunol (2023)
[4]Wisnewski et al Am J Respir Cell Mol Biol (2000)
[5]Toulon et al J Exp Med (2009)
[6]Brauneck et al Front Med (2021)
[7]Wu et al Sci Transl Med (2019)
[8]Melo et al Clin Immunol (2021)
[9]Deutsch et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

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

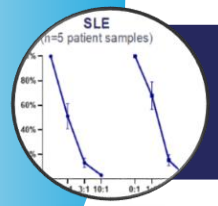
Multiple Levels of Evidence Supporting ADI-001



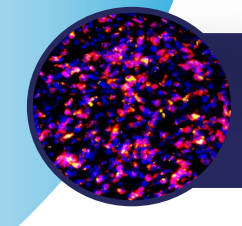
Robust CK and exposure in blood, consistent with autologous alpha-beta CAR T in autoimmune diseases



Deep CD19+ B cell depletion below detectable levels in peripheral blood



Exhibited ex vivo **depletion of patient-derived CD19+ B Cells** in Multiple **Autoimmune Diseases**



Significant tissue exposure and CAR-T activation resulting in complete CD19+ B cell depletion in secondary lymphoid tissue

ADI-001 is being evaluated in patients with LN / SLE, SSc, AAV, IIM, and Stiff-Person Syndrome