Clinical results CAR-T for mantle cell lymphoma: what's next?

Michael Wang, MD

Puddin Clarke Endowed Professor
Director, Mantle Cell Lymphoma Program of Excellence
Section Chief, Rare Lymphomas
Co-PI, B-cell Lymphoma Moonshot Project
Department of Lymphoma and Myeloma
MD Anderson Cancer Center

Disclosures

Research: Pharmacyclics, Acerta Pharma, Kite Pharma, Velosbio, Inc, InnoCare, BeiGene, Loxo Oncology, AstraZeneca, Genetech, Genmab, BeiGene Aus Pty Ltd, Incyte, Lilly, BeiGene LTD, Juno Therapeutics, Janssen, Vincerx, Pharmacyclics, Nurix Therapeutics, AbbVie, Inctye, Bantam Pharmaceutical, LLC, Oncternal Therapeutics

Honoraria: AstraZeneca, BeOne, CAHON,, East Virginia Medical School,, Janssen, Kite Pharma, Mayo Clinic, MJH Life Sciences, Merck,, Pfizer,, PromCon S.R.E., Research to Practice, Studio ER Congressi, Medscape/WebMD, VJHemonc

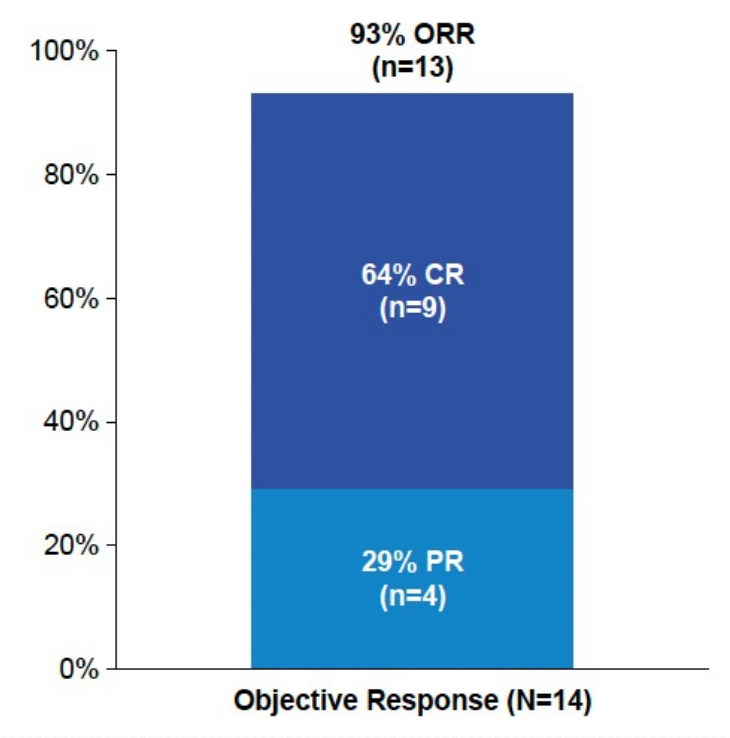
Consultancy: AstraZeneca, Galapagos NV, Genmab, InnoCare, Janssen, Kite Pharma, Lilly, Merck, PER, Pepromene Bio, Oncternal

Five-Year Outcomes of Patients With Relapsed or Refractory Mantle Cell Lymphoma Treated With Brexucabtagene Autoleucel in ZUMA-2 Cohorts 1 and 2

Michael Wang, MD[1]; Andre Goy, MD, MS[2]; Javier Munoz, MD, MS, MBA, FACP[3,4]; Frederick L. Locke, MD[5]; Caron A. Jacobson, MD, MMSc[6]; Brian T. Hill, MD, PhD[7]; John M. Timmerman, MD[8]; Ian W. Flinn, MD, PhD[9]; David B. Miklos, MD, PhD[10]; John M. Pagel, MD, PhD, DSc[11]; Marie José Kersten, MD, PhD[12]; Edouard Forcade MD, PhD[13]; Max S. Topp, MD[14]; Roch Houot, MD, PhD[15]; Amer Beitinjaneh, MD[16]; Dan Zheng, PhD[17]; Mengru Chang, MSc[17]; Rhine R. Shen, PhD[17]; Wangshu Zhang, PhD[17]; Rita Damico Khalid, DO[17]; Ioana Kloos, MD, FRCPC[17]; and Patrick M. Reagan, MD[18]

[1]The University of Texas MD Anderson Cancer Center, Houston, TX, USA; [2]John Theurer Cancer Center, Hackensack, NJ, USA; [3]Banner MD Anderson Cancer Center, Gilbert, AZ, USA; [4]Mayo Clinic, Phoenix, AZ, USA; [5]Moffitt Cancer Center, Tampa, FL, USA; [6]Dana-Farber Cancer Institute, Boston, MA, USA; [7]Cleveland Clinic Foundation, Cleveland, OH, USA; [8]UCLA David Geffen School of Medicine, Los Angeles, CA, USA; [9]Tennessee Oncology & OneOncology, Nashville, TN, USA; [10]Stanford University, Stanford, CA, USA; [11]Swedish Cancer Institute, Seattle, WA, USA; [12]Amsterdam UMC, Location University of Amsterdam, Cancer Center Amsterdam, Amsterdam, Netherlands, on behalf of HOVON/LLPC; [13]Service d'Hématologie Clinique et Thérapie Cellulaire, CHU Bordeaux, F-33000, Bordeaux, France; [14]Medizinische Klinik und Poliklinik II, Universitätsklinikum Würzburg, Würzburg, Germany; [15]CHU Rennes, University of Rennes, Inserm & EFS, Rennes, France; [16]University of Miami, Miami, FL, USA; , USA; and [18]University of Rochester School of Medicine, Rochester, NY, USA

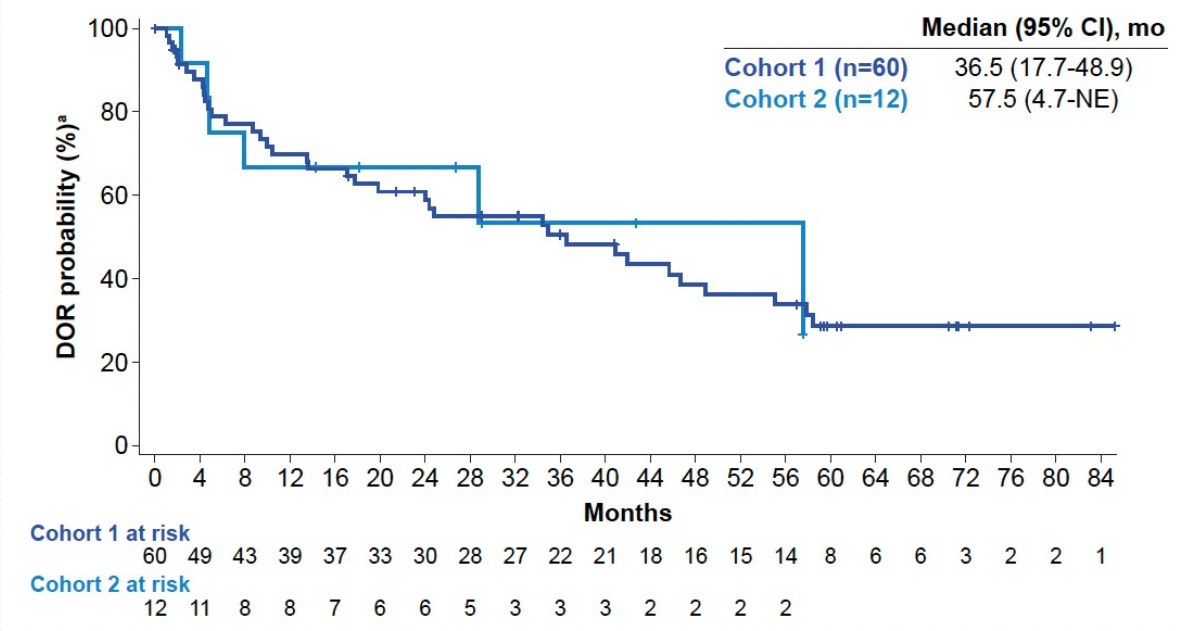
Best Objective Response by IRRC for Cohort 2 Primary Analysis



- In Cohort 2 primary analysis, ORR was 93% (95% CI, 66.1-99.8); 64% of patients had a CR and 29% had a PR
  - No patients had stable disease or progressive disease
  - One patient was not assessed at the time of analysis

CR, complete response; IRRC, independent radiology review committee; ORR, objective response rate; PR, partial response.

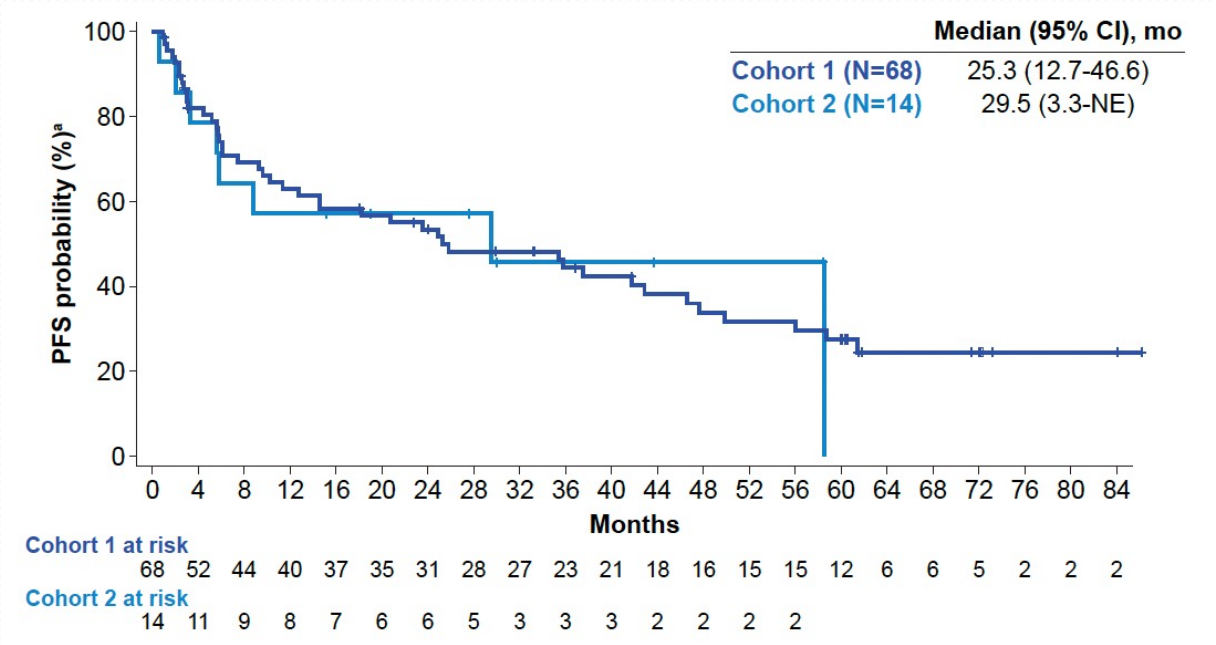
Duration of Response in ZUMA-2
5-Year Outcomes



- In Cohort 1, median investigator-assessed DOR was 36.5 months (95% CI, 17.7-48.9; n=60) with 17 patients in ongoing response at data cutoff, all CR
- In Cohort 2, median DOR was 57.5 months (95% CI, 4.7-NE; n=12) with 3 patients in ongoing response at data cutoff, all CR

[a] Per investigator assessment. CR, complete response; DOR, duration of response; NE, not estimable.

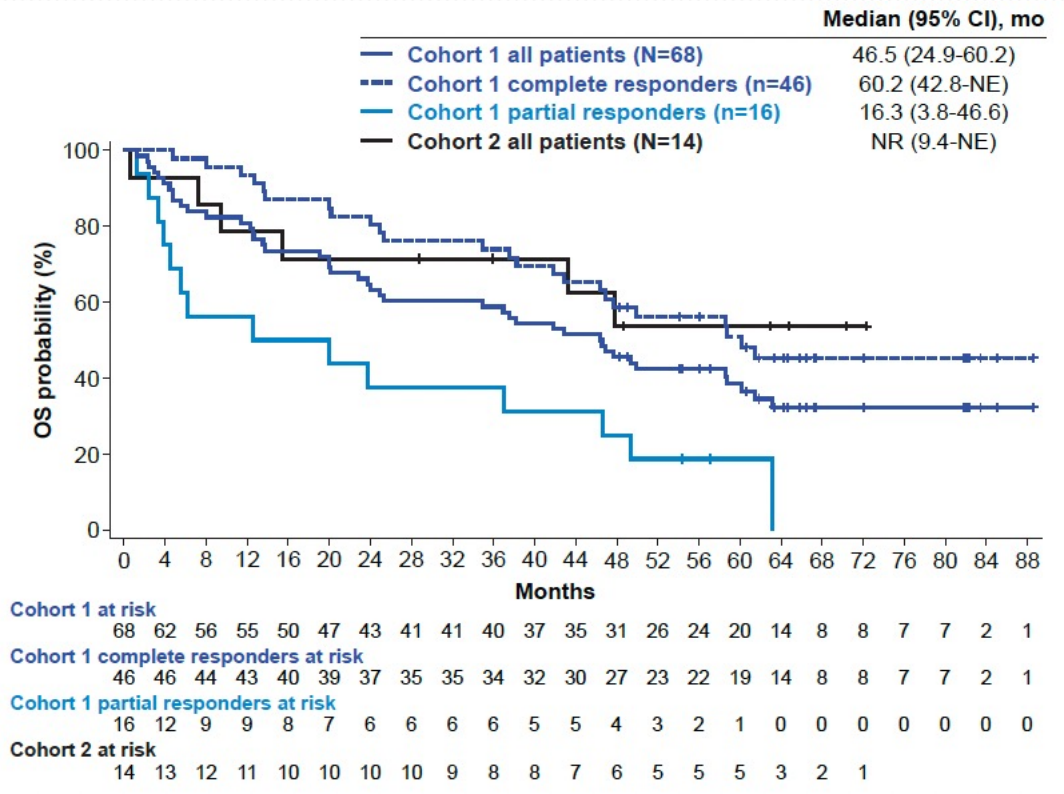
Progression-Free Survival in ZUMA-2 5-Year Outcomes



- Median investigator-assessed PFS was 25.3 months (95% CI, 12.7-46.6; N=68) and 54-month PFS rate was 32% (95% CI, 20.0-44.2) in Cohort 1
- In Cohort 2, median PFS was 29.5 months (95% CI, 3.3-NE) and 54-month PFS rate was 46% (17.3-70.5; N=14)

[a] Per investigator assessment. NE, not estimable; PFS, progression-free survival.

Overall Survival in ZUMA-2 5-Year Outcomes



- In Cohort 1, the median OS was 46.5 months (95% CI, 24.9-60.2) and 60-month OS rate was 39% (95% CI, 26.7-50.1)
- In Cohort 2, median OS was not reached (95% CI, 9.4-NE) and 60-month OS rate was 54% (95% CI, 23.8-76.2)

NE, not estimable; NR, not reached; OS, overall survival.

Lisocabtagene maraleucel in R/R MCL: primary analysis results from the MCL cohort of the single-arm, multicenter, seamless design TRANSCEND NHL 001 study

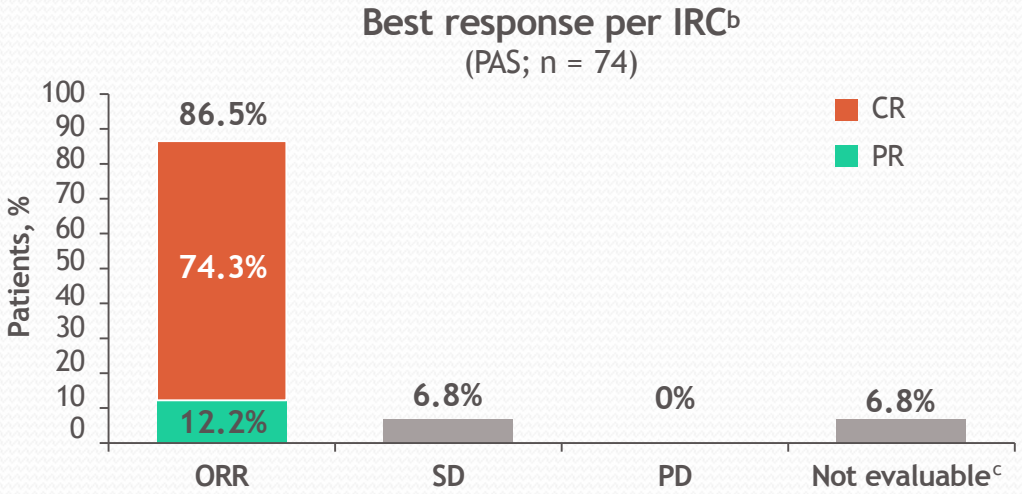
Michael Wang,[1] Tanya Siddiqi,[2] Leo I. Gordon,[3] Manali Kamdar,[4] Matthew Lunning,[5] Alexandre V. Hirayama,[6] Jeremy S. Abramson,[7] Jon Arnason,[8] Nilanjan Ghosh,[9] Amitkumar Mehta,[10] Charalambos Andreadis,[11] Scott R. Solomon,[12] Ana Kostic,[13] Christine Dehner,[13] Ricardo Espinola,[14] Lily Peng,[13] Ken Ogasawara,[15] Amy Chattin,[13] M. Lia Palomba[16]

[1]The University of Texas MD Anderson Cancer Center, Houston, TX, USA; [2]City of Hope National Medical Center, Duarte, CA, USA; [3]Northwestern University, Feinberg School of Medicine, Robert H. Lurie Comprehensive Cancer Center, Chicago, IL, USA; [4]University of Colorado Cancer Center, Aurora, CO, USA; [5]University of Nebraska Medical Center, Omaha, NE, USA; [6]Fred Hutchinson Cancer Center, Seattle, WA, USA; [7]Massachusetts General Hospital Cancer Center, Harvard Medical School, Boston, MA, USA; [8]Beth Israel Deaconess Medical Center, Boston, MA, USA; [9]Levine Cancer Institute, Atrium Health, Charlotte, NC, USA; [10]University of Alabama at Birmingham, Birmingham, AL, USA; [11]University of California, San Francisco, San Francisco, CA, USA; [12]Northside Hospital Cancer Institute, Atlanta, GA, USA; [13]
[16]Memorial Sloan Kettering Cancer Center, New York, NY, USA

ICML 2023, Presentation LBA3

Liso-cel delivers high ORR and CR rates in patients with R/R MCL

- Primary (ORR) and key secondary (CR rate) per IRC efficacy endpoints[a] were met based on the PAS (n = 74)
  - ORR: **86.5%** (95% CI, 76.5–93.3); CR rate: **74.3%** (95% CI, 62.8–83.8); *P* < 0.0001 for both
- Consistently high ORR and CR rate were observed in the efficacy analysis set (n = 83)
  - Median (range) time to first CR or PR was 0.95 (0.7–3.0) months



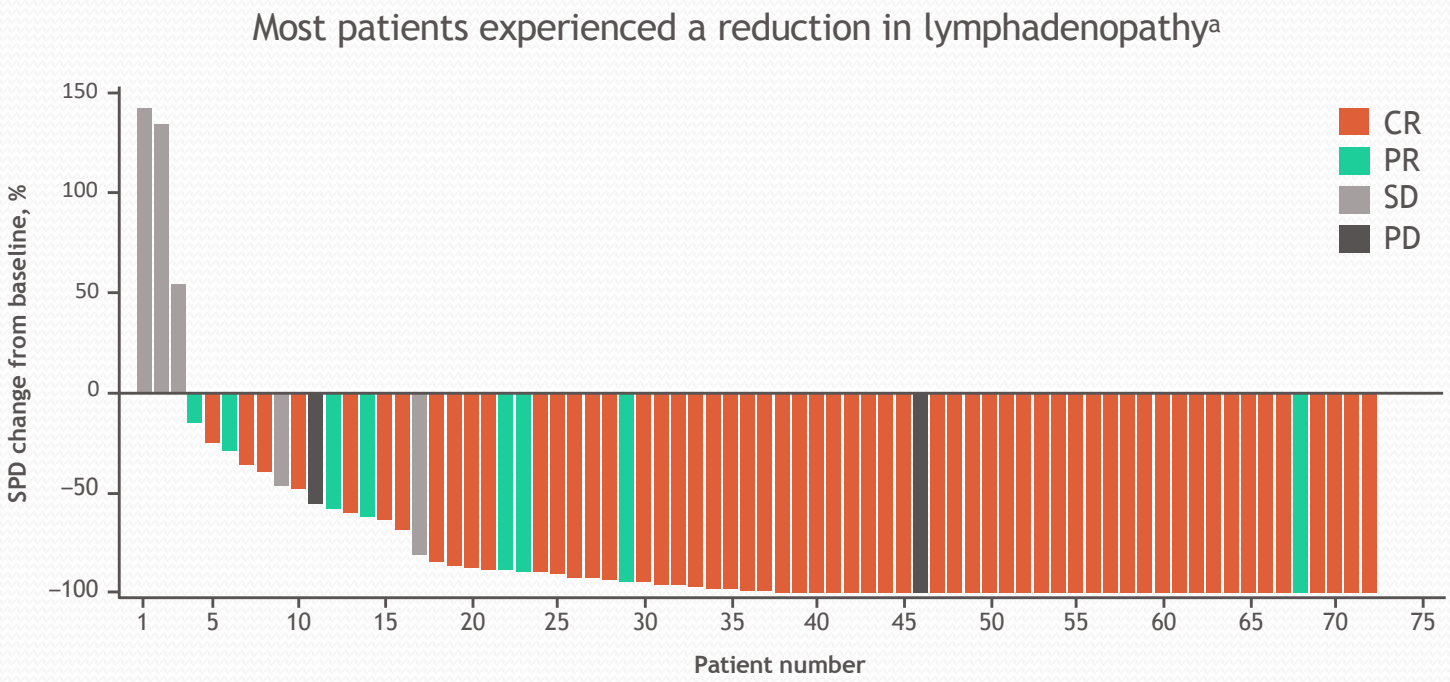
Efficacy analysis set (n = 83)	
ORR per IRC	CR rate per IRC
83.1% (95% CI, 73.3–90.5)	72.3% (95% CI, 61.4–81.6)

[a]Primary and key secondary efficacy hypotheses were tested hierarchically in the PAS in the order of the following: H_0: ORR ≤ 40%, H_0: CR rate ≤ 18%, one-sided p-value; [b]Best disease response per IRC by Lugano 2014 criteria from the time of liso-cel infusion until disease progression, end of study, start of another anticancer therapy, or HSCT; [c]No postbaseline scans were submitted to IRC for evaluation. H_0, null hypothesis.

Wang M, et al. ICML 2023 [Abstract #LBA3]

Change in tumor burden and response status per IRC[a] (efficacy analysis set)

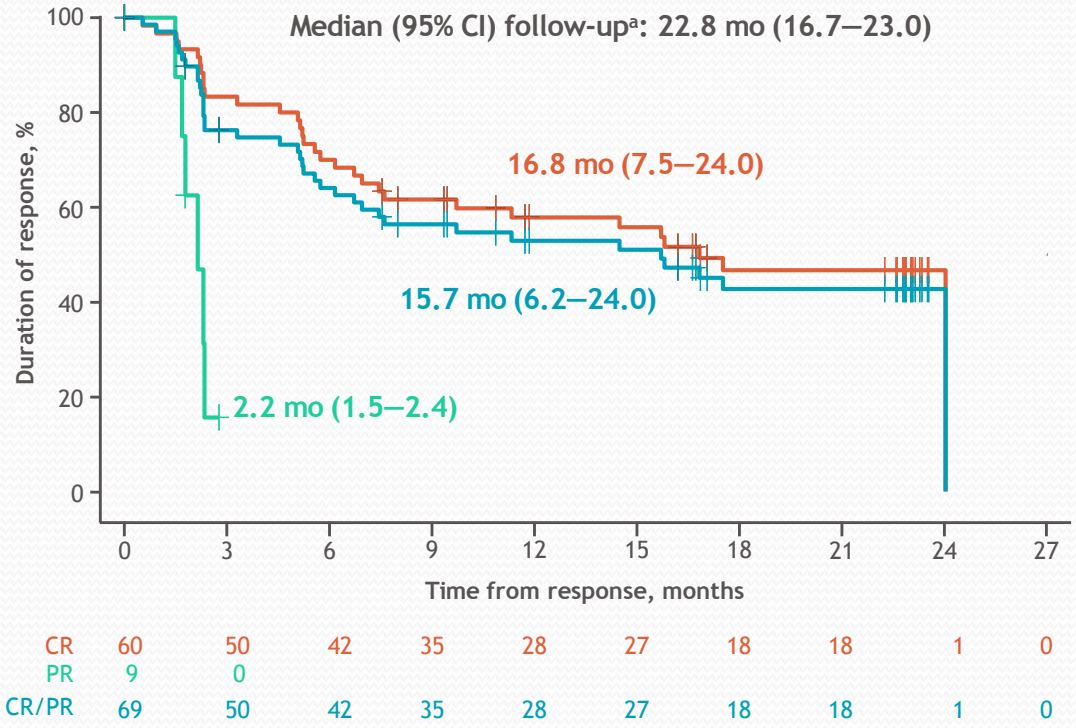
TRANSCEND NHL 001: MCL cohort



[a]Maximum change from baseline in SPD per IRC assessment for all patients in the efficacy analysis set with baseline and ≥1 postbaseline target lesion measurement. 11 patients were excluded due to lack of measurable target lesions at baseline (n = 5), or missing scans postbaseline (n = 6).

Wang M, et al. ICML 2023 [Abstract #LBA3]

DOR per IRC (efficacy analysis set)

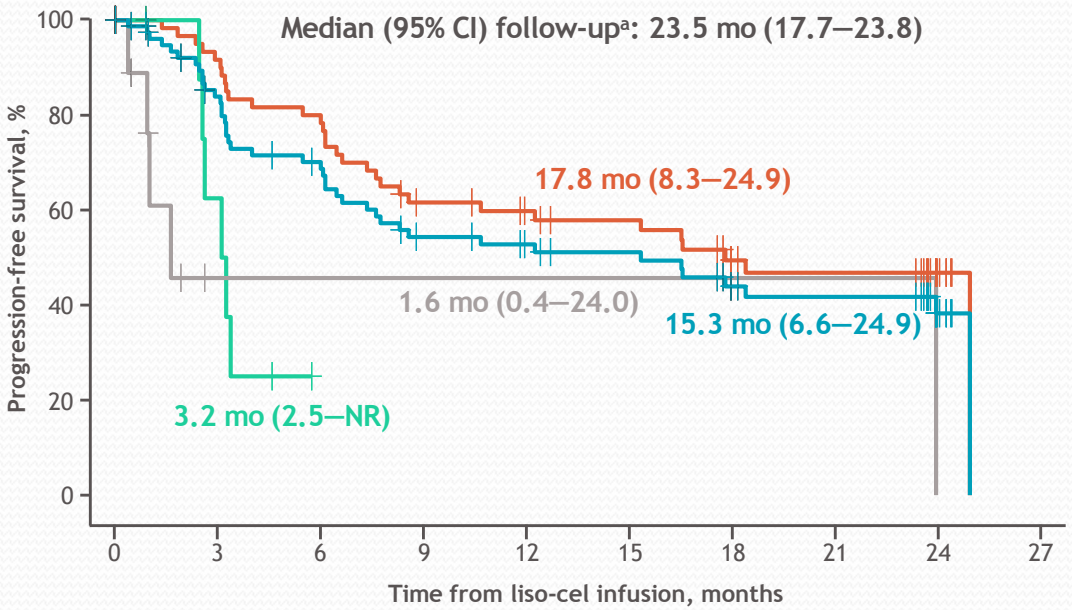


	Continued response rate	
	Responders (n = 69)	Patients with CR (n = 60)
12-mo rate (95% CI)[b]	52.9% (40.1–64.2)	57.8% (44.2–69.2)
18-mo rate (95% CI)[b]	42.7% (29.9–54.9)	46.7% (32.8–59.4)

[a]Reverse Kaplan-Meier method was used to obtain median follow-up and its 95% CI; [b]Kaplan-Meier method was used to obtain 2-sided 95% CI intervals.

Wang M, et al. ICML 2023 [Abstract #LBA3]

PFS per IRC (efficacy analysis set)



CR	60	55	48	35	31	28	20	18	6	0
PR	9	5	0							
Nonresponder	14	1	1	1	1	1	1	1	0	
Total	83	61	49	36	32	29	21	19	6	0

	PFS rate	
	Total (n = 83)	Patients with CR (n = 60)
12-mo rate (95% CI)[b]	52.8% (40.6–63.6)	59.8% (46.3–71.0)
18-mo rate (95% CI)[b]	43.9% (31.8–55.4)	49.4% (35.7–61.8)

[a]Reverse Kaplan-Meier method was used to obtain median follow-up and its 95% CI; [b]Kaplan-Meier method was used to obtain 2-sided 95% CI intervals.
NR, not reached.

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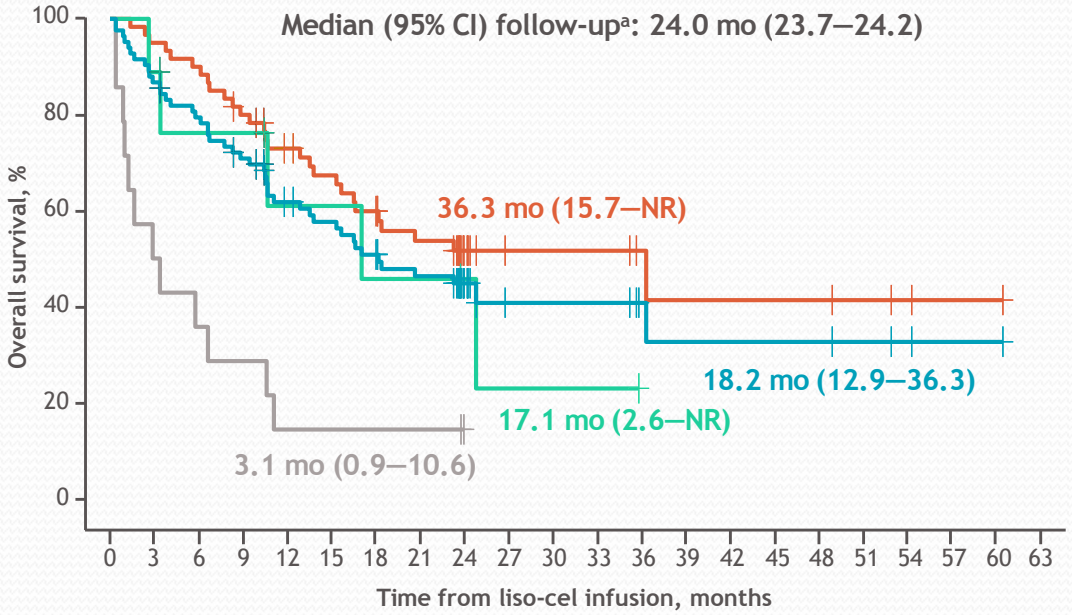
OS (efficacy analysis set)



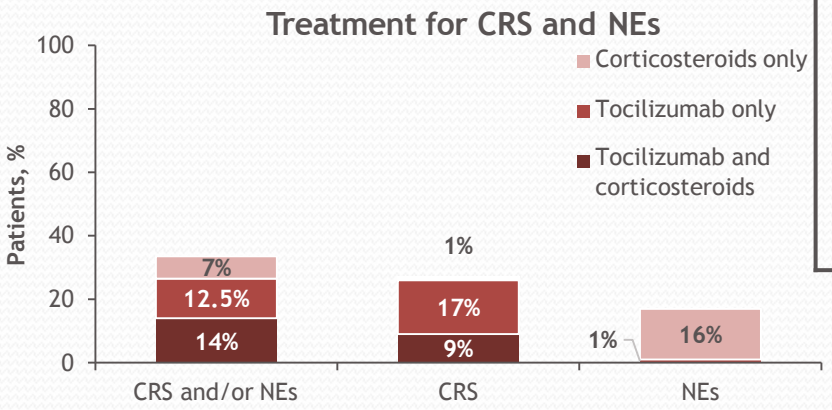
	OS rate	
	Total (n = 83)	Patients with CR (n = 60)
12-mo rate (95% CI)[b]	61.8% (50.2—71.4)	72.9% (59.6—82.5)
18-mo rate (95% CI)[b]	50.8% (39.2—61.2)	59.8% (45.9—71.3)

[a]Reverse Kaplan-Meier method was used to obtain median follow-up and its 95% CI; [b]Kaplan-Meier method was used to obtain 2-sided 95% CI intervals.

Wang M, et al. ICML 2023 [Abstract #LBA3]

Treatment-emergent AESIs and management of CRS and NEs

Other AESIs	Liso-cel–treated set (n = 88)
Prolonged cytopenias,[c] n (%)	35 (40)
Grade ≥ 3 infections,[d] n (%)	13 (15)
Hypogammaglobulinemia, n (%)	6 (7)



Patients with CRS and NEs	Liso-cel–treated set (n = 88)
CRS,[a] n (%)	
Any grade	54 (61)
Grade 1/2	53 (60)
Grade 3	0
Grade 4	1 (1)
Grade 5	0
Median (range) time to onset, days	4.0 (1–10)
Median (range) time to resolution, days	4.0 (1–14)
NEs,[b] n (%)	
Any grade	27 (31)
Grade 1/2	19 (22)
Grade 3	7 (8)
Grade 4	1 (1)
Grade 5	0
Median (range) time to onset, days	8.0 (1–25)
Median (range) time to resolution, days	5.0 (1–45)

[a]CRS was graded based on the Lee 2014 criteria; [b]NEs were defined as investigator-identified neurological AEs related to liso-cel; [c]Defined as grade ≥ 3 laboratory abnormalities of neutropenia, anemia, and/or thrombocytopenia at Day 30 after liso-cel infusion; [d]Includes grade ≥ 3 TEAEs from the infections and infestations (system organ class) by AE high-level group term.
AESI, adverse event of special interest; NE, neurological event.

Wang M, et al. ICML 2023 [Abstract #LBA3]

ROR1 (Receptor Tyrosine Kinase-Like Orphan Receptor 1)
Compelling Tumor-Specific Target

- Expressed on **most B-cell malignancies**, including
  - Mantle cell lymphoma (MCL), diffuse large B-cell lymphoma (DLBCL), chronic lymphocytic leukemia (CLL)
- Expressed on **many solid tumors**
  - Increased ROR1 expression associated with more aggressive tumors, shorter PFS and OS
- ROR1 activity associated with **aggressive phenotype**
  - Invasion, metastasis, stem cell-like behavior, and resistance to treatment
- Subject of **large pharma acquisitions**
  - ROR1-ADCs:
- **Oncternal ROR1 pipeline differentiated and advancing**
  - Deep target biology expertise & immunotherapy experience

ROR1 Expressed on Multiple Solid and Liquid Tumors

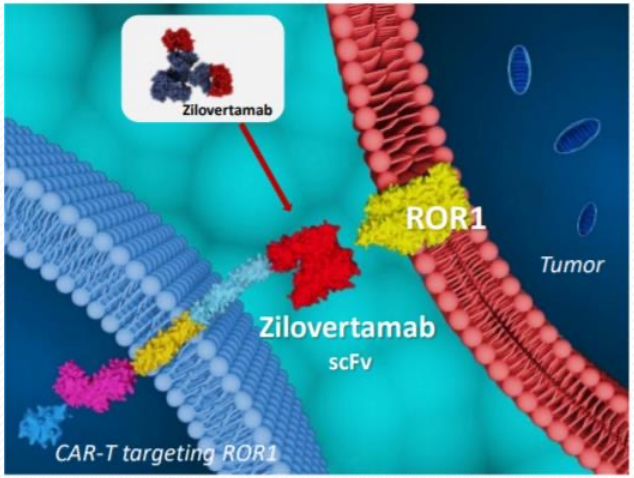
MCL	95%
CLL	95%
Uterus	96%
Lymphoma	90%
Prostate	90%
Skin	89%
Pancreatic	83%
Adrenal	83%
Lung	77%
Breast	75%
Testicular	73%
Colon	57%
Ovarian	54%

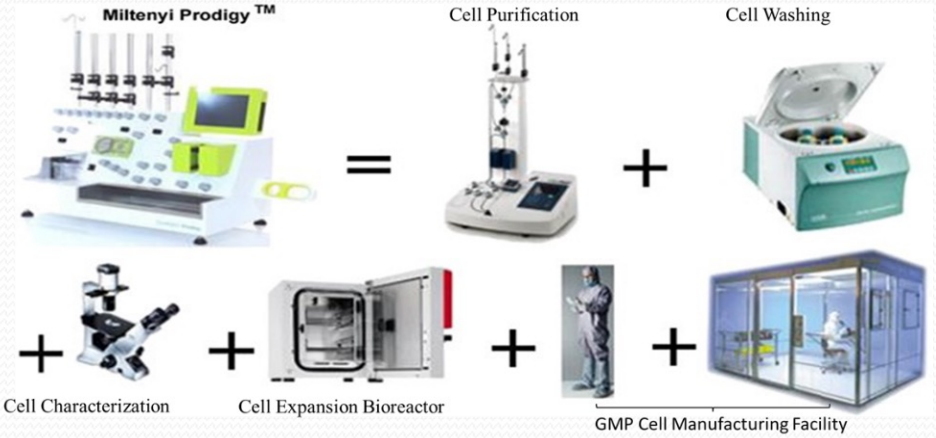
Zhang 2012
AJP

Green 2008 Trends Cell Biol. 2008; Matsuda T 2001 Mech Dev.; Fukuda 2008 PNAS;
Hudecek 2010 Blood; Zhang 2012 Am J Pathology; Zhang 2014 PNAS

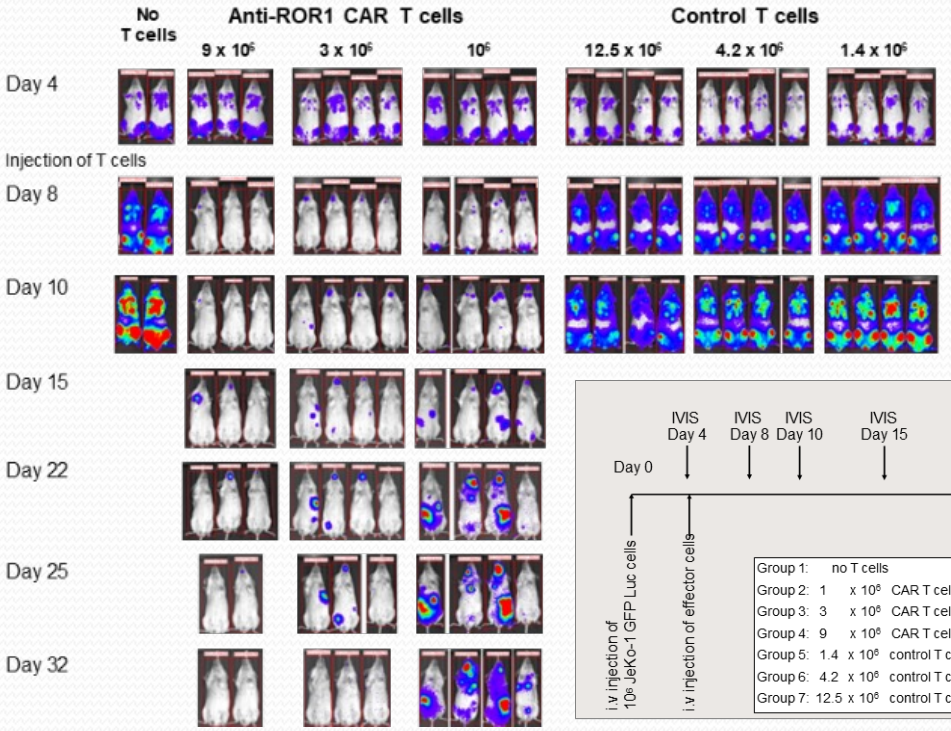
ONCT-808 – CMC and Manufacturing

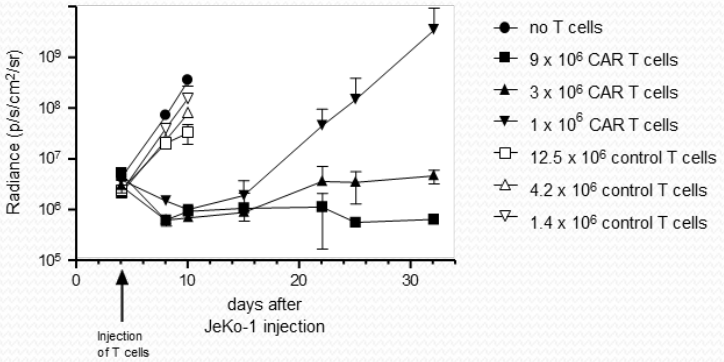
1. **Lead ROR1 CAR construct optimized and selected with demonstrated high potency against ROR1+ cancer cell lines**
2. **Lentivirus production process confirmed**
3. **Oncternal ROR1 CAR-T cell product process optimized and confirmed**
   - Leveraging a flexible, closed fully-automated platform
   - 8-day production process post-activation
   - Greater than 2 billion CAR+ T cells produced with over 60% CAR+ expression
   - Majority of CAR T cells with juvenile phenotypes (CD4 and CD8 stem central memory T cells)
4. **Harvard/Dana Farber CMCF (Cell Manipulation Core Facility) agreed for Phase 1 manufacturing**





ONCT-8o8 – Strong Anti-tumor Activity in Preclinical Xenograft Model





Data generated in collaboration with Dr. Evren Alici (Karolinska Institutet).

Data were presented at EHA 2022.

- **Strong anti-tumor activity of ROR1 CAR-T cells demonstrated in MCL xenograft mouse model**
- **Data from additional IND-supporting in vivo studies will be presented at upcoming scientific conferences**

MCL: Single Center (MCW) Study Using Anti- CD20/Anti-CD19 CAR

Original Reports | Hematologic Malignancy

Check for updates

Phase I/II Study of Adaptive Manufactured Lentiviral Anti-CD20/Anti-CD19 Chimeric Antigen Receptor T Cells for Relapsed, Refractory Mantle Cell Lymphoma

Nirav N. Shah, MD, MS[1]; Alfredo S. Colina, BA[2]; Bryon D. Johnson, PhD[1]; Aniko Szabo, PhD[3]; Fateeha Furqan, MD[1]; Tyce Kearl, MD, PhD[1]; Dina Schneider, PhD[4]; Marlenny Vargas-Cortes, BS[5]; Jessica L. Schmeling, BS[5]; Michael B. Dwinell, PhD[2]; Katie Palen, BS[1]; Walter Longo, MD[1]; Peiman Hematti, MD[1]; Anthony E. Zamora, PhD[2]; Parameswaran Hari, MD, MS[1]; Daniel Bucklan, MD[6]; Ashley Cunningham, MD[7]; Mehdi Hamadani, MD[1]; and Timothy S. Fenske, MD[1]

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Shah NN, Colina AS, Johnson BD, et al. Phase I/II Study of Adaptive Manufactured Lentiviral Anti-CD20/Anti-CD19 Chimeric Antigen Receptor T Cells for Relapsed, Refractory Mantle Cell Lymphoma. *Journal of Clinical Oncology*. Published online March 31, 2025. Accessed April 3, 2025. https://ascopubs.org/doi/10.1200/JCO-24-02158

MCL: Patient Characteristics

TABLE 1. Patients With MCL (N = 17)

Baseline Patient Characteristic	Phase I = 3, Phase II = 14
Age, years, median (range)	63 (50-74)
Male sex, No. (%)	15 (88)
Previous auto-HCT, No. (%)	8 (47)
Previous allo-HCT, No. (%)	2 (12)
LDH >normal on day 0, No. (%)	6 (35)
Marrow involvement before CAR infusion, No. (%)	14 (82)
BTKi exposed, No. (%)	16 (94)
BTKi progressed, No. (%)	13 (76)
Noncovalent (pirtobrutinib) BTKi progressed, No. (%)	6 (35)
Previous lines (including transplant), median (range)	4 (2-8)
Previous bendamustine, No. (%)	13 (76)
Previous bendamustine <1 year, No. (%)	2 (12)
MIPI at diagnosis (n = 14), No. (%)	
Low	6 (35)
Intermediate	4 (31)
High	4 (31)
Missing	3 (18)
Complex cytogenetics, No. (%)	3 (18)
p53 aberrations, No. (%)	8 (47)
p53 mutation	6 (35)
17p deletion by FISH or cytogenetics	3 (18)

Supplemental Table 1: p53 Aberrations and Complex Cytogenetics by Subject

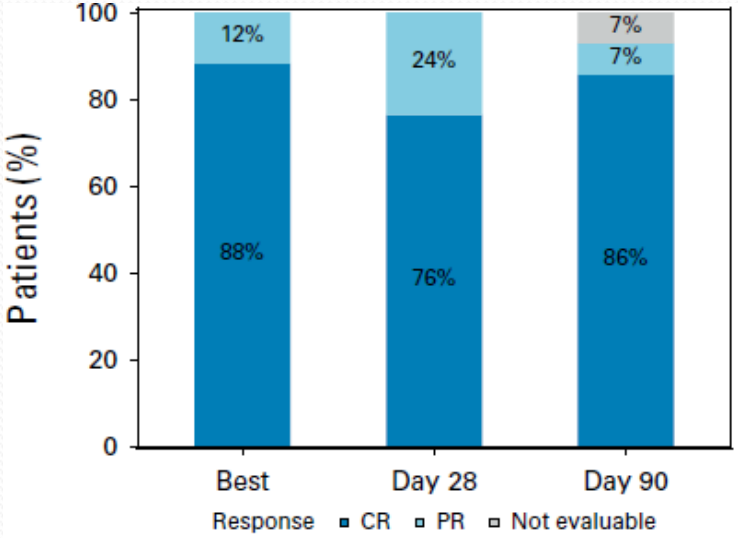
Subject Number	P53 aberration	Karyotype
3	Loss of chromosome 17	Complex Karyotype
5	N/A	N/A
7	Positive for TP53 mutation	N/A
12	N/A	-Y/Not Complex
15	Negative for TP53 mutation	Not Complex
16	Negative for TP53 mutation	N/A
19	Negative for TP53 mutation	Not Complex
20	TP53 deletion by FISH Positive for TP53 mutation	Not Complex
30	N/A	Complex karyotype
31	TP53 deletion by FISH	Complex karyotype
40	Positive for TP53 mutation	-Y/Not Complex
42	Negative for TP53 mutation	Del(13q)/Not Complex
43	N/A	Not Complex
49	Positive for TP53 mutation	Not Complex
55	N/A	Not Complex
56	Positive for TP53 mutation	N/A
57	Positive for TP53 mutation	Not Complex

N/A- Not available or unable to assess

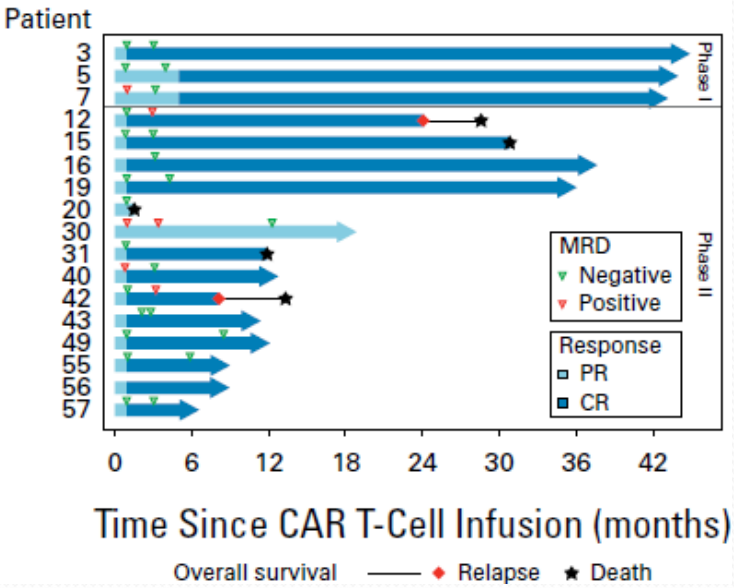
Shah NN, Colina AS, Johnson BD, et al. Phase I/II Study of Adaptive Manufactured Lentiviral Anti-CD20/Anti-CD19 Chimeric Antigen Receptor T Cells for Relapsed, Refractory Mantle Cell Lymphoma. *Journal of Clinical Oncology*. Published online March 31, 2025. Accessed April 3, 2025. https://ascopubs.org/doi/10.1200/JCO-24-02158

MCL: Clinical outcomes for patients treated with LV20.19 CAR T cells

Percentages of the 17 patients who had clinical response at day 28, day 90, and best overall response



Patient identification on the y-axis and demarcation for MRD status and response



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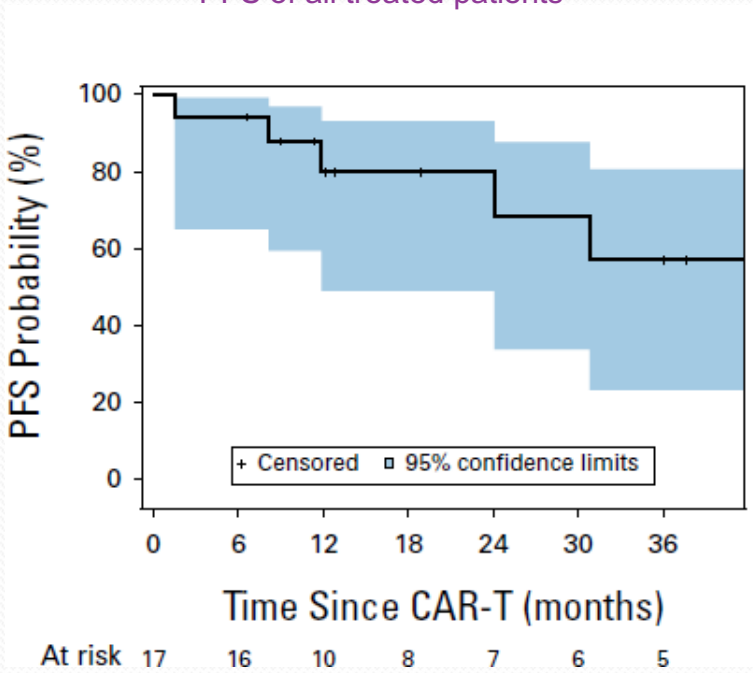
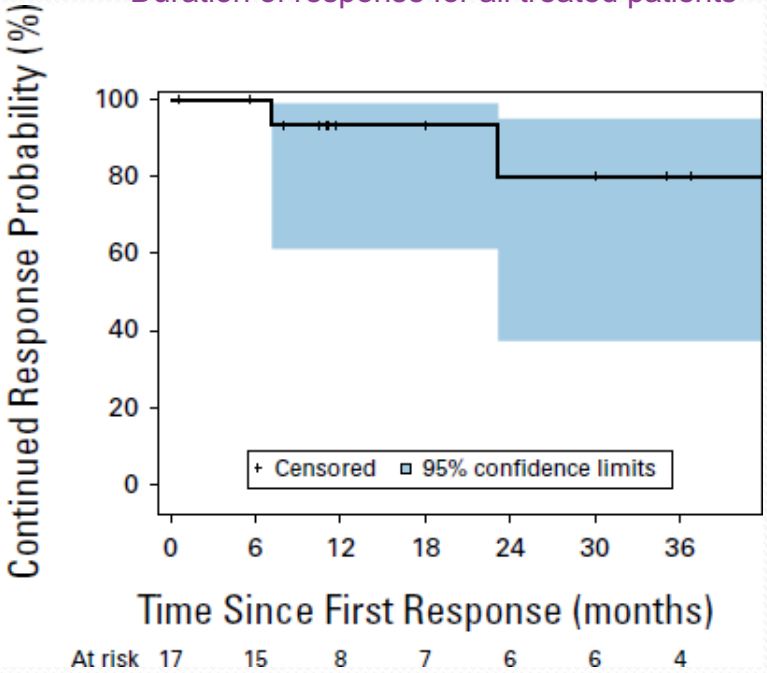
MCL: Clinical outcomes for patients treated with LV20.19 CAR T cells

PFS of all treated patients



Duration of response for all treated patients



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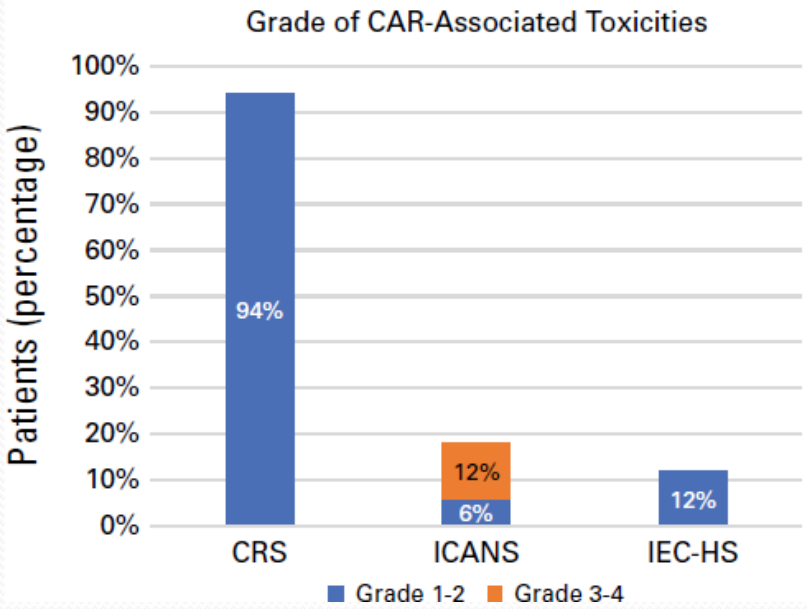
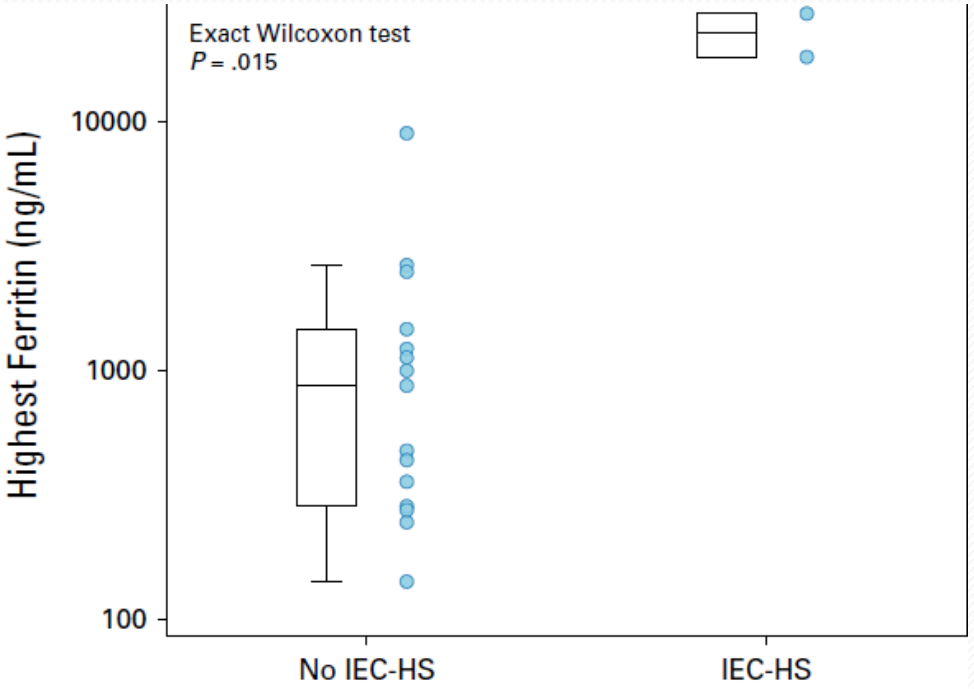
MCL: Safety data for patients treated with LV20.19 CAR T cells

Percentages of patients (n=17) who experienced CRS, ICANS, or IEC-HS



Peak ferritin levels are depicted on the basis of presence or absence of IEC-HS



Shah NN, Colina AS, Johnson BD, et al. Phase I/II Study of Adaptive Manufactured Lentiviral Anti-CD20/Anti-CD19 Chimeric Antigen Receptor T Cells for Relapsed, Refractory Mantle Cell Lymphoma. *Journal of Clinical Oncology*. Published online March 31, 2025. Accessed April 3, 2025. https://ascopubs.org/doi/10.1200/JCO-24-02158

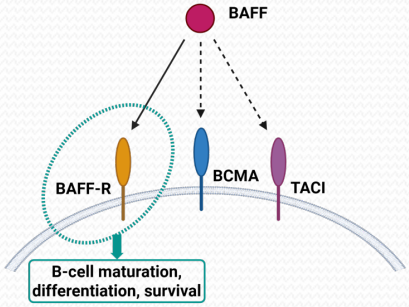
BAFFR CAR T Cells (PMB-CT01) Demonstrate Durable Responses and Manageable Toxicities in Relapsed/Refractory B-Cell Lymphomas with Prior CD19-Directed Therapy Failure or CD19-Negative Disease

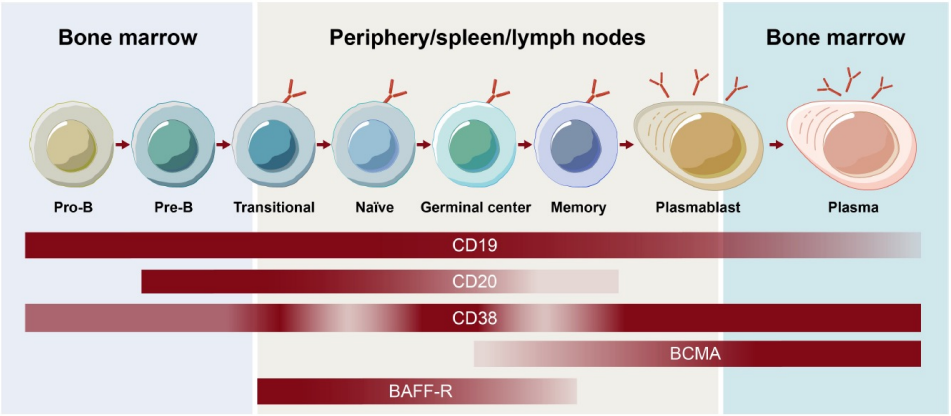
L.Elizabeth. Budde, Marissa M. Del Real, John H. Baird, Lu Chen, Joo Y. Song, Xiuli Wang, Swetha Thiruvengadam, Marie Hu, Alan Macias, Emanuela Marcucci, Soungchul Cha, Zhenyuan Dong, Teresa Kim, Baishakhi Barva, Sandrine Puverel, Qing Liu-Michael, Hazel (Ting-Ying) Cheng, Stephen J. Forman, and Larry W. Kwak

City of Hope National Medical Center
Duarte, CA, USA

BAFF-R as a novel therapeutic target in B-cell lymphomas

- BAFF-R (B-cell activating factor receptor) is a member of the TNF superfamily and the main receptor for BAFF.
- It is selectively expressed on B cells and on most subtypes of B-cell non-Hodgkin lymphomas





Robinson *et al.*, Front Immunol. 2024;15:1454747

B-cell malignancy	BAFF-R positive cases (%)
Hairy cell leukemia	10/10 (100)
Chronic lymphocytic leukemia	21/21 (100)
Mantle cell lymphoma	7/7 (100)
Follicular lymphoma	13/16 (81)
Diffuse large B-cell lymphoma	14/18 (78)
Marginal zone lymphoma	10/11 (91)

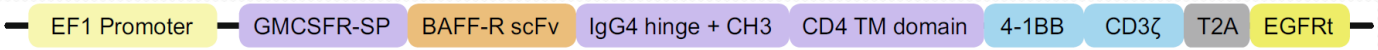
Rodig *et al.*, Hum Pathol. 2005;36(10):1113-9

BAFF-R as a novel therapeutic target in B-cell lymphomas

- BAFF-R signaling promotes normal B-cell proliferation and is required for survival
- In lymphoid malignancy, BAFF-R signaling activates NF-κB pathways and contribute to malignant lymphoid cell survival and proliferation (ALL, MCL).
- This critical feature may limit the capacity of B-cell tumors to escape therapy by down-regulation of BAFF-R expression, as this would compromise their viability
- CD19-negative primary ALL tumors retained BAFF-R expression

Rodig *et al.*, Hum Pathol. 2005;36(10):1113-9; Novak *et al.*, Blood 2004;104(8):2247-53; Maia *et al.*, PLoS One 2011;6(6):e20787; Pham *et al.*, Blood 2011;117(1):200-10

- Kwak's group at COH generated a humanized BAFF-R Ab and incorporated the scFv into a CAR.



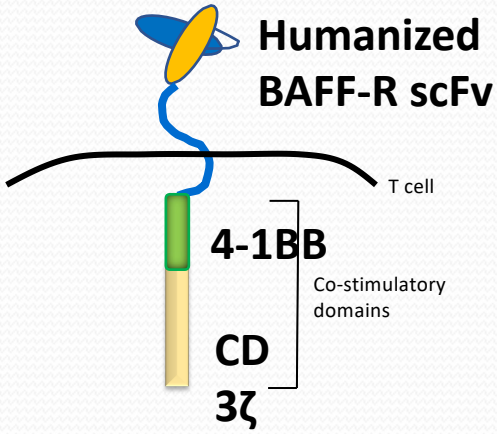
Published OnlineFirst November 27, 2017; DOI: 10.1158/1078-0432.CCR-17-1193

Cancer Therapy: Preclinical

Clinical Cancer Research

Novel BAFF-Receptor Antibody to Natively Folded Recombinant Protein Eliminates Drug-Resistant Human B-cell Malignancies *In Vivo*

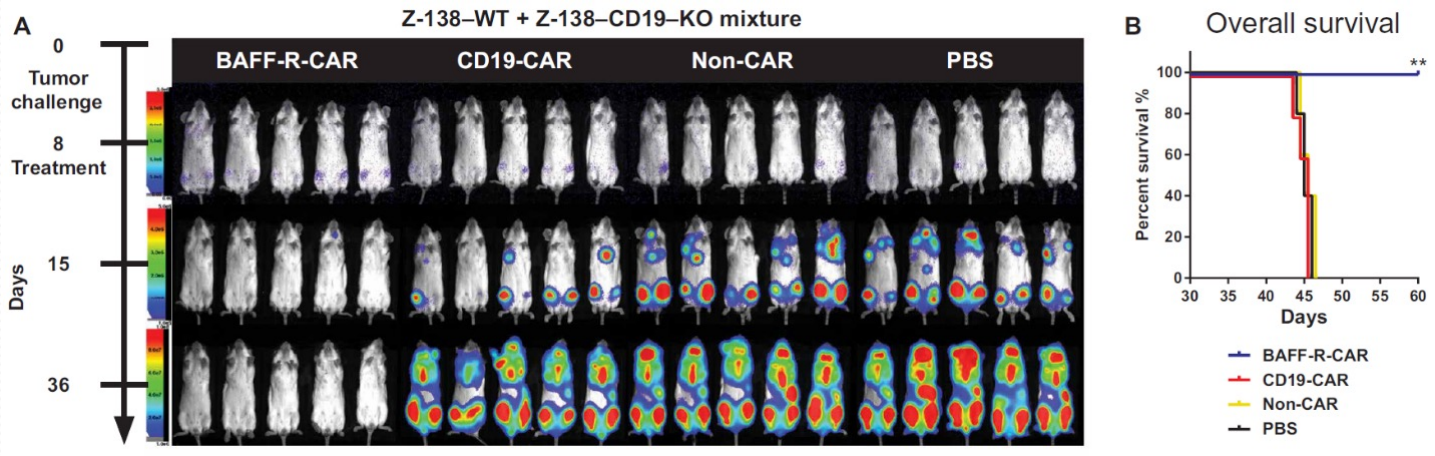
Hong Qin[1], Guowei Wei[1], Ippei Sakamaki[2], Zhenyuan Dong[1], Wesley A. Cheng[1], D. Lynne Smith[1], Feng Wen[1,3], Han Sun[1], Kunhwa Kim[4], Soungchul Cha[4], Laura Bover[5], Sattva S. Neelapu[4], and Larry W. Kwak[1]



- **Bench to Bedside Development of a Novel, Personalized Cellular Therapy for Blood Cancers**

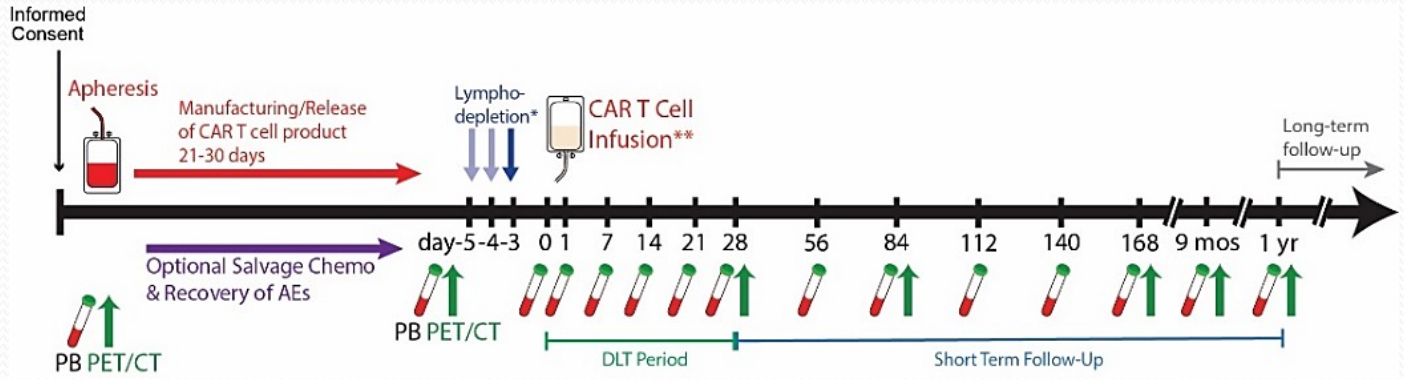
Preclinical studies support BAFF-R as a B-NHL target

- Head-to-head comparisons with CD19 CAR T cells in preclinical models suggest superior efficacy with BAFF-R CAR T cells
- BAFF-R CAR T cells can eliminate lymphoma cells regardless of CD19 expression



Qin H *et al.* Sci Trans Med. 2019;11(511):eaaw9414

First-in-human, multicenter phase 1 trial (NCT05370430)



Dose level	Dose of BAFFR-CAR T Cells*
-1 (de-escalation)	20 x 10^6 cells
1 (starting dose)	**50 x 10^6 cells**
2	200 x 10^6 cells
3	600 x 10^6 cells

* ≤20% lower cell dose permitted

- Dose-finding cohort (3+3) (***completed***)
- Three histology expansion cohorts (12 pts each) (MCL, LBCL, FL) at RP2D

6 sites: City of Hope Duarte, Stanford University, University of Minnesota, Atrium Health Levine Cancer Institute, Providence Swedish Cancer Institute, University of Kansas Cancer Center

Eligibility and Study objectives

Inclusion

- BAFF-R+ B-NHL
- ≥ 18 years old
- Measurable disease
- ECOG ≤2
- Prior CAR T allowed, ≥ 90 days from leukapheresis

Exclusion

- Active CNS involvement
- Prior allo-HCT
- Auto-HCT within 6 months
- Steroids and immunosuppressants

Primary objectives

- Safety
- MTD/RP2D

Secondary objectives

- Response
- Duration of B-cell aplasia
- PFS, OS

Exploratory objectives

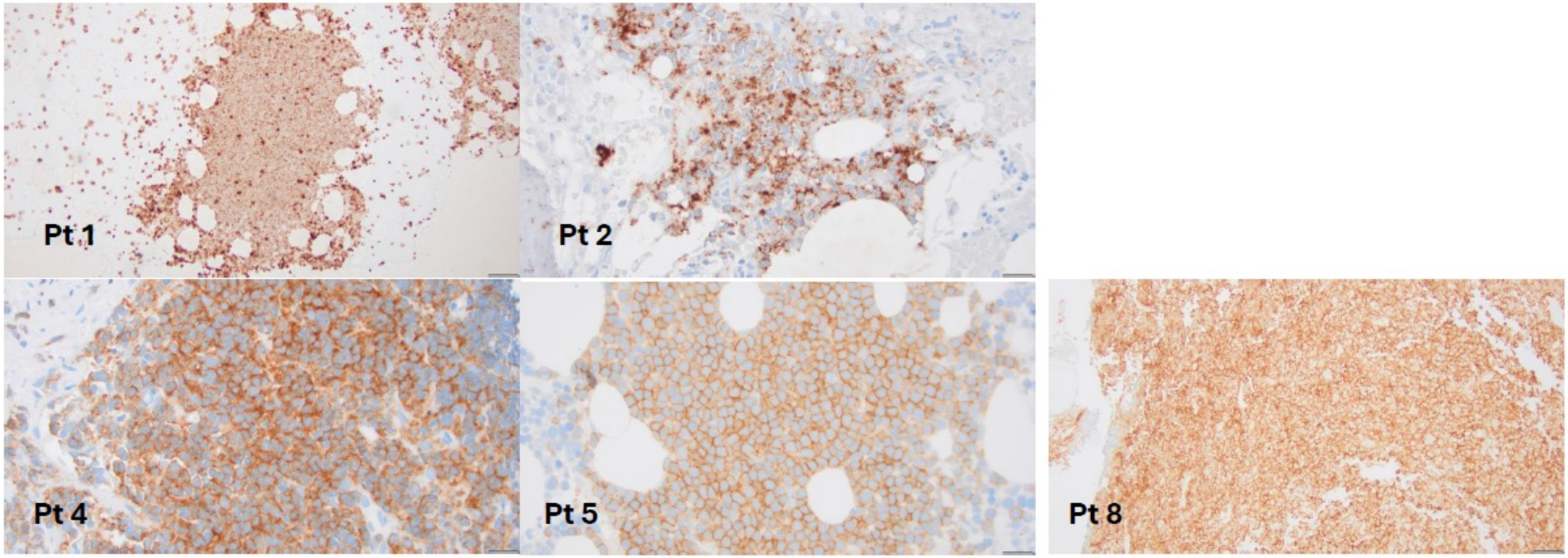
- Expansion, persistence
- MRD-negative rate
- Cytokines
- BAFF-R expression post-relapse or progression
- CAR T polyfunctionality

Baseline characteristics

- Nine patients were infused

Characteristic	Dose Level 1			Dose Level 2					
	Patient 1	Patient 2	Patient 3	Patient 4	Patient 5	Patient 6	Patient 7	Patient 8	Patient 9
Gender	M	M	M	M	M	M	F	M	M
Age	56	75	41	62	72	74	62	57	58
Histology	*MCL*	*MCL*	*THRBCL*	*MCL*	*MCL*	*MZL*	*FL*	*MCL*	*MCL*
• Stage at baseline	IV	IV	III	IV	IV	IIA	III	IV	IV
• # Prior lines	4	10	3	3	3	1	7	3	6
• Prior CD19 CAR T	Yes	Yes	No	No	Yes	No	Yes	Yes	Yes
• Prior HCT	No	No	Yes	No	No	No	No	Yes	No
• Prior TCE	No	Yes	No	Yes	No	No	Yes	No	No
• CD19 expression	Yes	Yes	No	Yes	Yes	Yes	Yes	Yes	Yes
• CD20 expression	Yes	Yes	No	Yes	Yes	Yes	No	Yes	Yes
• TP53 mutation	Yes	No	No	No	Yes	No	No	Yes	n/a

BAFF-R Expression



Treatment safety

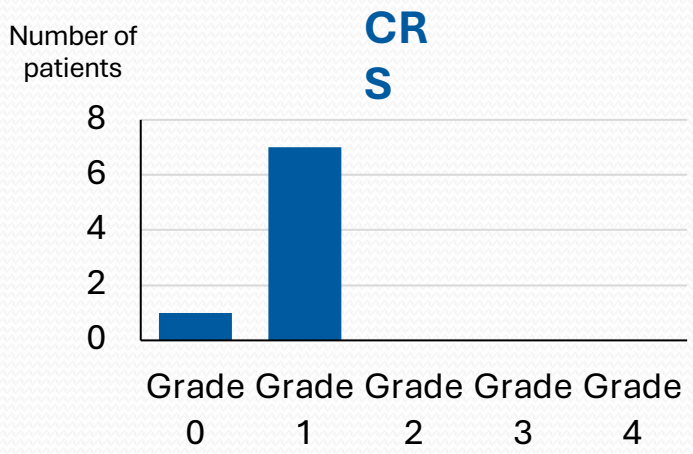
No DLTs

CTCAE grade ≥3 AE considered at least possibly related to the BAFF-R CAR T cells

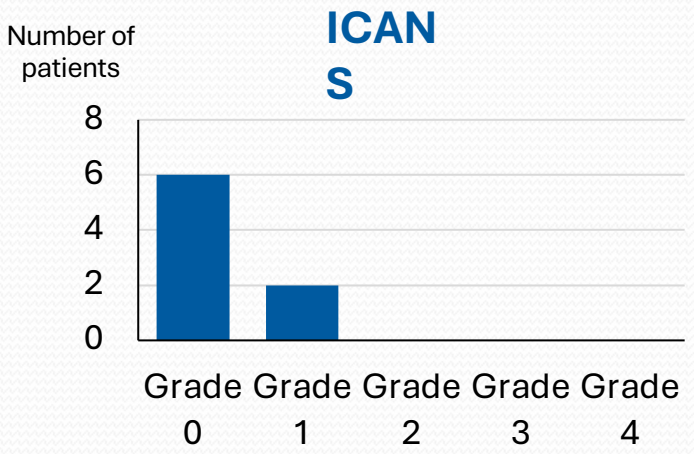
	Grade	
	Grade 3	Grade 4
Cardiac disorders		
Sinus tachycardia	1	0
Infections and infestations		
Pneumonia viral	1	0
Hematologic events		
Lymphocyte count decreased	3	4
Neutrophil count decreased	1	2
Platelet count decreased	1	2
While blood cell count decreased	4	0
Metabolism and nutrition disorders		
Hypophosphatemia	1	0
Skin and subcutaneous tissue disorders		
Rash	1	0

One patient developed a myelodysplastic syndrome that was deemed unrelated to study treatment

Treatment safety



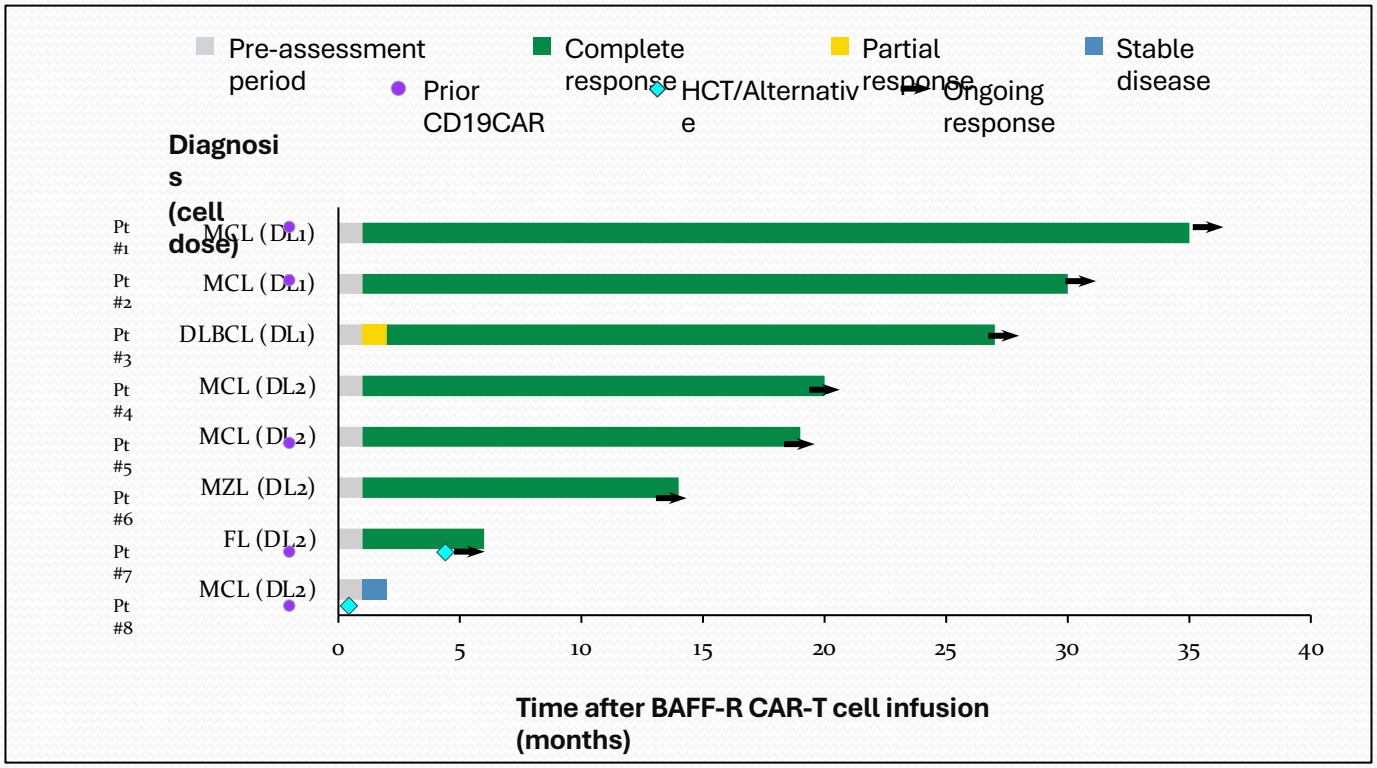
87.5% grade 1 CRS (7/8 patients)
No grade >1 CRS



25% grade 1 ICANS (2/8 patients) that resolved without corticosteroids
No grade >1 ICANS

67% of patients (6/9) received LD and CAR T infusion in the outpatient setting

Response to treatment



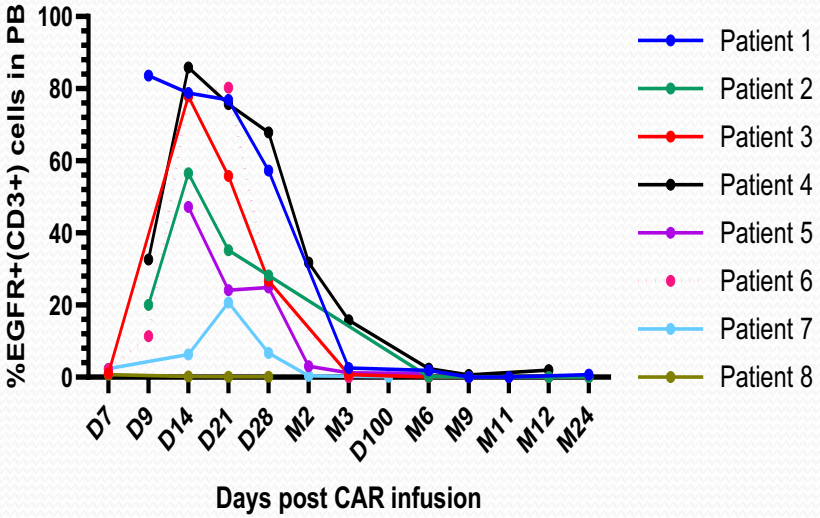
87.5% CR at 3 months (7/8 patients)

All 4 MCL CR patients were MRD-negative by flow and NGS

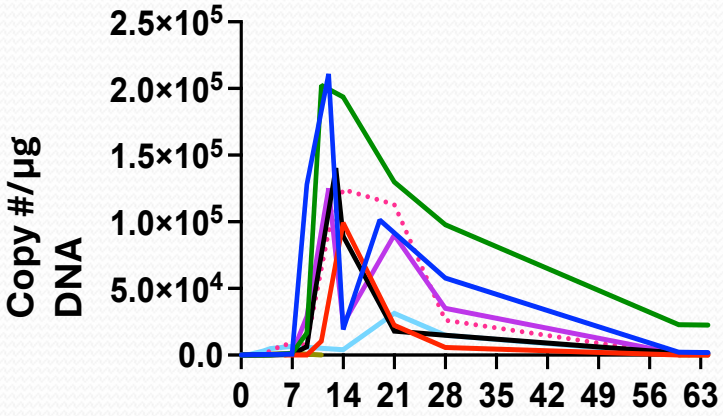
No relapses

Robust BAFF-R CAR T expansion

CAR%

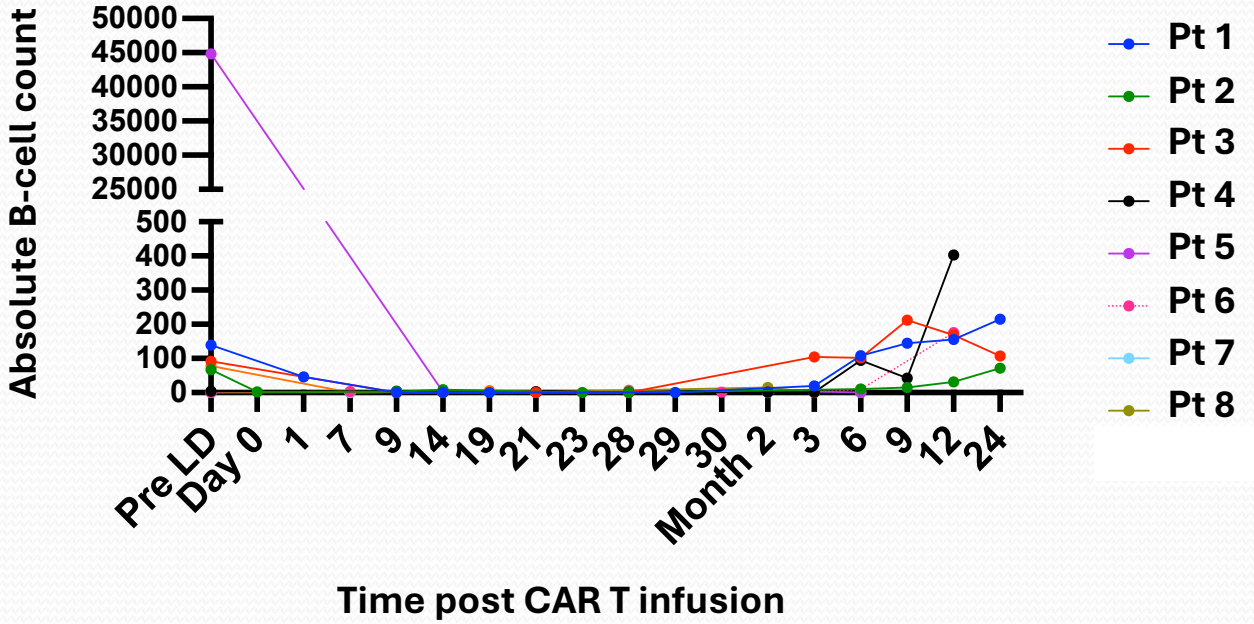


WPRE Copy #/µg DNA



- **Robust CAR-T cell expansion** was observed in all responders with peak of expansion on day 12-21

B-cell recovery after BAFF-R CAR T cell infusion



Advances in In Vivo CAR T-Cell Therapy

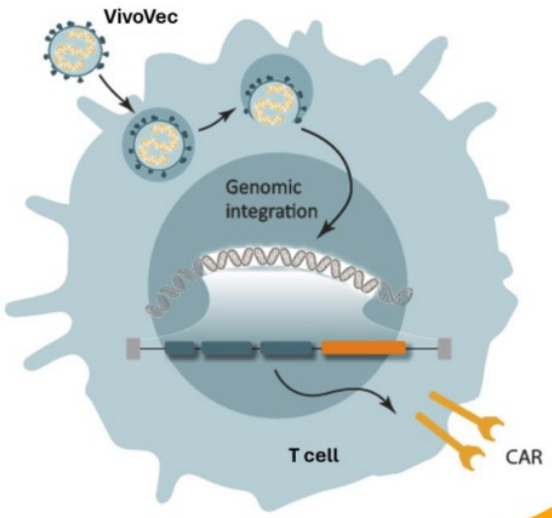
01/15/2026

In Vivo CAR-T Therapy

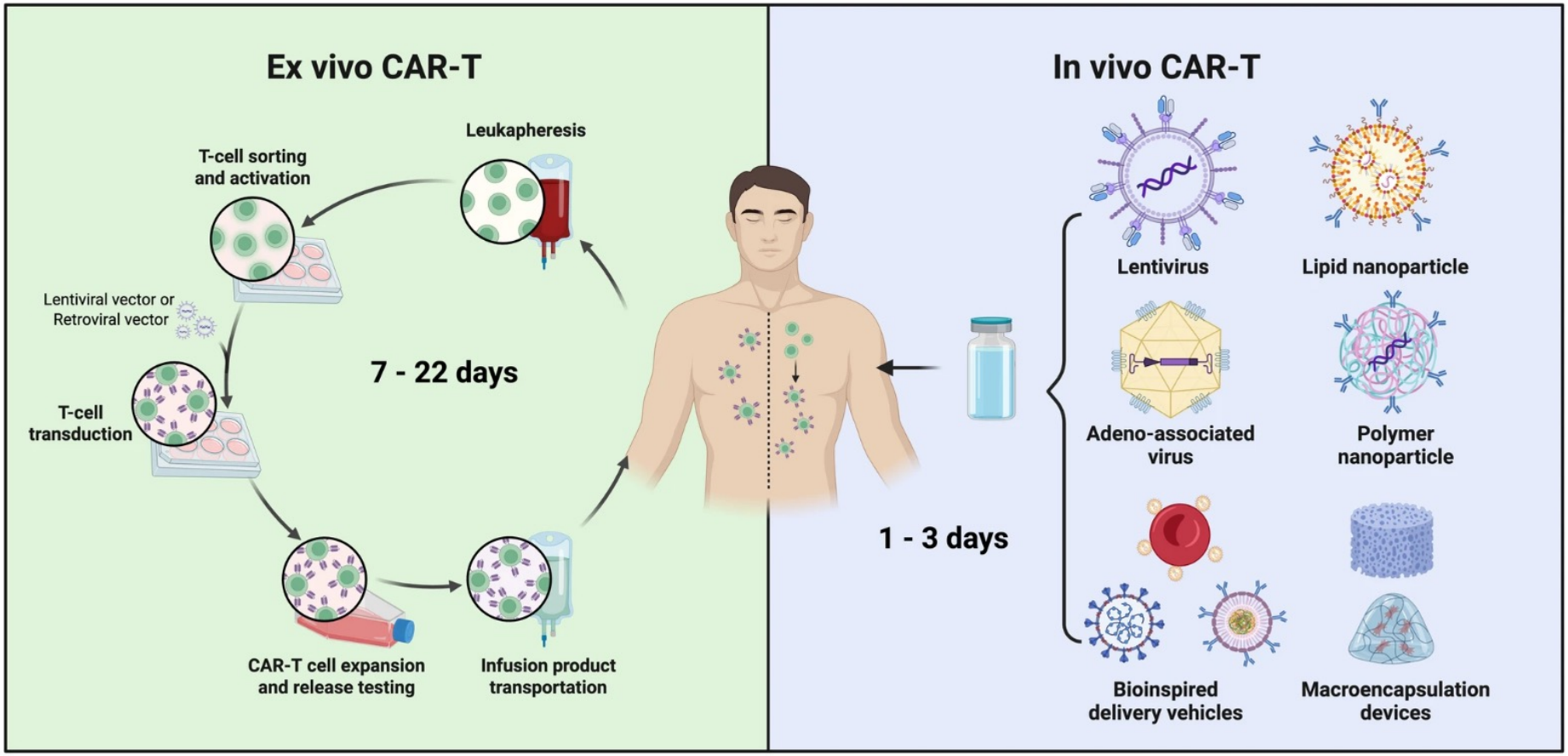
- **In vivo CAR-T therapy is an emerging approach in which CAR constructs are delivered directly into patients, enabling T cells to be engineered in situ without ex vivo manufacturing.**
- **Using platforms such as engineered viral vectors or targeted nanoparticles, this strategy aims to improve accessibility, reduce cost, and accelerate treatment, while introducing distinct challenges in delivery and safety.**

In vivo CAR T cell therapy =

T cells are genetically altered *within* the body to enhance their effectiveness at fighting against disease (eg, cancer); drug product is available immediately to patients instead of within weeks or months.[19,20]



From Multi-Step Ex Vivo Manufacturing to Streamlined In Vivo CAR-T Therapy



Xu J, et al, J Hematol Oncol. 2025;18(1):105.

Lentiviral-based in vivo CAR-T cell platforms in development

Company	Targeting mechanism	Therapeutic payloads	Lead indications	Preclinical evidence	Development stage
	Anti-CD7 scFv-decorated particles (T cell and natural killer cell engineering)	Anti-CD20 CAR, anti-CD19 CAR	B cell malignancies, autoimmunity	Proof of principle in mice and NHPs[84]	Clinical (phase I enrolling in 2024 with anti-CD20 CAR)[78,85]
	Multi-domain anti-CD3, CD80, CD58 decorate particles (T cell engineering)	Anti-CD19 CAR, anti-CD22 CAR, anti-CD20 CAR	B cell malignancies, autoimmunity	Proof of principle in mice and NHPs[81,88,91]	Clinical (phase I initiated in 2024 with anti-CD19 CAR, the others in 2024, 2026)[90]
	Anti-CD3 decorated particles	Anti-CD19 CAR	B cell malignancies	Not disclosed	Investigator-sponsored trial, first responder in a patient with lymphoma[95,96]
	Targeted lentiviral particles	Anti-BCMA CAR, undisclosed	Multiple myeloma, autoimmunity, solid tumours	Proof of principle in mouse model[95]	Phase I initiation in 2025, first clinical response in myeloma, acquisition[98,101,148]
	Anti-CD3 decorated particles	Anti-BCMA CAR	Multiple myeloma	Proof of principle in mice and NHPs[102,103]	Phase I initiation mid 2025
	Anti-CD8 fusogen-decorated particles	Anti-CD19 CAR	Undisclosed	Proof of principle in mice and NHPs[78,109,111]	Undisclosed
	CD46-targeted viral-like particles (multilineage)	Anti-HER2 CAR	Multiple solid tumours	Proof of principle in preclinical models[112]	Undisclosed
	CD3-targeted lentiviral vector	Anti-CD19 CAR	B cell malignancies	Proof of principle, mouse models[114]	Undisclosed

BCMA, B cell maturation antigen; CAR, chimeric antigen receptor; NHP, non-human primate.

Bot A, et al. Nat Rev Drug Discov. 2025 Sep 30.

LNP-RNA-based in vivo CAR-T cell platforms in development

Company	Targeting mechanism	Therapeutic payloads	Lead indications	Preclinical evidence	Development stage
	LNPs – macrophage tropic	Anti-Trop2 CAR, anti-GPC3 CAR, anti-HER2 CAR, anti-gp75 CAR (CD89 and natural killer cell p44-based CAR constructs)	Multiple solid tumours and hepatocellular carcinoma	Multiple preclinical models[122,124]	Clinical (phase I initiated in 2024 with anti-TROP2 and GPC3 CARs) and first clinical response[125,127]
	Anti-CD8 monoclonal antibody-decorated LNPs (CTL engineering)	Anti-CD19 CAR and undisclosed	Autoimmunity and undisclosed	Mouse and NHP proof of principle[135–137]	Phase I initiated (NCT06917742)
	tLNPs (T cells, myeloid cells and natural killer cells)	B cell-targeted CAR (RNA format)	$CD19^+$ B cell malignancies	Undisclosed	Phase I initiated with first patient dosed[140]
	CD8 T cell tLNPs	Anti-CD19 CAR (mRNA format)	Systemic lupus erythematosus	Mouse and NHP proof of principle[142]	Phase 1 initiated and evidence of activity reported[140,143]
	LNPs containing immunotropic lipids (pan-T cell engineering)	Anti-CD19 CAR (circular RNA format)	B cell malignancies and autoimmunity	Mouse and NHP proof of principle[148]	Phase I initiation by 2026
	tLNPs (T cell engineering)	Anti-CD22 and anti-CD19 CAR (mRNA)	Oncology, autoimmunity	Mouse and NHP proof of principle[152,154]	Undisclosed
	LNPs – macrophage tropic	Anti-GPC3 CAR and not disclosed	Hepatocellular carcinoma	Preclinical mouse models[161,162]	Preclinical stage; strategic changes announced[164]
	tLNPs	Anti-CD19, CD20, BCMA using RNA writer (integrating payload)	Oncology, autoimmunity	Preclinical modelling[171–173]	Undisclosed
	tLNPs and viral-like particles	CAR (circular RNA format) – details not disclosed	Undisclosed	Undisclosed	Undisclosed

BCMA, B cell maturation antigen; CAR, chimeric antigen receptor; CTL, cytotoxic T cell lymphocyte; GPC3, glypican 3; LNP, lipid nanoparticle; NHP, non-human primate; tLNP, targeted LNP.

Bot A, et al. Nat Rev Drug Discov. 2025 Sep 30.

Clinical Trials

Company	Product name	Targeting Mechanism and Payloads	Disease	ClinicalTrials .gov ID	Phase	Study Start	Collaborators and Investigators
	UB-VV111	CD3-Cocal-LV-CD19 CAR	R/R large B-cell lymphoma (LBCL) and chronic lymphocytic leukemia (CLL).	NCT06528301	Phase 1	2024-11	• City of Hope • The David and Etta Jonas Center for Cellular Therapy • Washington University School of Medicine/Siteman Cancer Center • University of Nebraska Medical Center • University of Cincinnatti Medical Center • Fred Hutch Cancer Center • Royal North Shore Hospital • St. Vincent's Hospital Melbourne
Myeloid Therapeutics	MT-303	LNP-GPC3 scFv/CD89 (mRNA)	Advanced or Metastatic GPC3-Expressing Cancers, Including HCC	NCT06478693	Phase 1	2024-07-01	• CREATE Medicines • Australia (4 locations) • South Korea (3 locations) • Taiwan (2 locations) *https://clinicaltrials.gov/*

First-in-Human Validation of Viral In Vivo CAR-T: ESO-T01

Key Findings

- **Patients treated**: 4
- **Dose**: single dose, 2.0×10^8 TU
- **Overall response rate (ORR):** 100%
  - 2 CR, 2 PR
- **Extramedullary lesion clearance observed**
  - Indicates effective CAR-T infiltration into the TME
- **Acceptable safety profile**
  - No adverse events > Grade 3 (except hematologic toxicities)
- **CAR-T cellular kinetics**
  - Comparable to commercial ex vivo CAR-T products

ELSEVIER

The Lancet

Volume 406, Issue 10500, 19–25 July 2025, Pages 228-231

Correspondence

In-vivo B-cell maturation antigen CAR T-cell therapy for relapsed or refractory multiple myeloma

Jia Xu [a], Lin Liu [a], Philippe Parone [b], Wei Xie [a], Chunyan Sun [a], Zhaozhao Chen [a], Jishuai Zhang [c], Chunrui Li [d], Yu Hu [a], Heng Mei [a] ✉

[a] Institute of Hematology, Union Hospital, Tongji Medical College, Huazhong University of Science and Technology, Wuhan 430022, China

[b] EsoBiotec, Mont-Saint-Guibert, Belgium

[c] Shenzhen Pregene Biopharma, Shenzhen, China

[d] Department of Hematology, Tongji Hospital, Tongji Medical College, Huazhong University of Science and Technology, Wuhan, China

Xu J, et al. Lancet. 2025;406(10500):228-231.

blood

Minimal residual disease (MRD)-negative outcomes following a novel, in vivo gene therapy generating anti-B-cell maturation antigen (BCMA) chimeric antigen receptor (CAR)-T cells in patients with relapsed and refractory multiple myeloma (RRMM): Preliminary results from inMMyCAR, the first-in-human phase 1 study of KLN-1010

Simon Harrison[1], Phoebe Joy Ho[2,3], Sueh-Li Lim[4,5], Stephanie Talam[6], Hannah Pahl[7], Dharmesh Dingar[8], Scott Currence[8], Travis Quigley[8], Andrew Spencer[4]

[1] Peter MacCallum Cancer Centre, Centre of Excellence for Cellular Immunotherapy, Melbourne, Australia
[2] Royal Prince Alfred Hospital, Camperdown, Australia
[3] University of Sydney, Camperdown, Australia
[4] Monash University, Australian Centre for Blood Diseases, Melbourne, Australia
[5] Alfred Hospital, Malignant Haematology, Transplantation and Cellular Therapies Service, Melbourne, Australia
[6] Royal Prince Alfred Hospital, Institute of Haematology, Camperdown, Australia
[7] Peter MacCallum Cancer Centre, Parkville Cancer Clinical Trials Unit, Melbourne, Australia
[8] ., Boston, United States

Key Findings

- **Patients**
  - N = 3
  - Heavily pretreated RRMM (≥3 prior lines, high-risk cytogenetics)
  - No prior BCMA-targeted therapy
- **Efficacy**
  - 100% MRD-negative in bone marrow at month 1 (10^{-5}–10^{-6} sensitivity)
  - All achieved PR at month 1, deepening to VGPR by month 3
  - Responses ongoing with no disease progression
- **CAR-T Expansion & Persistence**
  - Robust in vivo T-cell expansion despite no lymphodepletion
  - CAR^+ cells up to 72% of $CD3^+$ T cells at peak (~day 15)
  - Memory-phenotype CAR-T cells detected in blood and BM through ≥3 months
- **Safety**
  - Grade 2 CRS in 2/3 patients; no ICANS
  - Limited cytopenias, no treatment-emergent infections
  - Toxicity profile comparable to ex vivo CAR-T, with milder hematologic effects

Blood 2025; 146 (Supplement 2): LBA–1

In Vivo CD19 CAR-T via LNP in Refractory SLE (HN2301)

The NEW ENGLAND JOURNAL of MEDICINE

CURRENT ISSUE SPECIALTIES TOPICS

CORRESPONDENCE

In Vivo CD19 CAR T-Cell Therapy for Refractory Systemic Lupus Erythematosus

Published September 17, 2025 | N Engl J Med 2025;393:1542-1544 | DOI: 10.1056/NEJMc2509522

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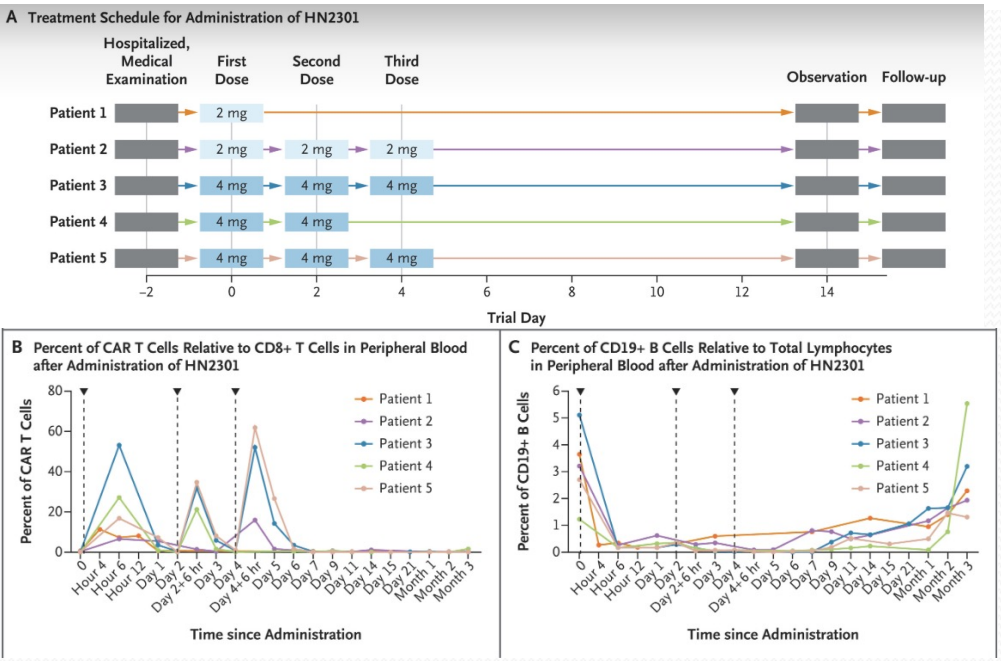

Key Findings

- **Rapid in vivo CAR-T generation**: CD19 CAR-T detectable within 6 h, transient expression (baseline by 2–3 days)
- **Efficient B-cell depletion**: dose-dependent, complete depletion at 4 mg, lasting 7–10 days
- **Favorable safety**: no Grade ≥3 CRS, no ICANS; only low-grade, manageable cytokine release
- **Biologic & clinical activity**: reduced autoantibodies, normalized complement, SLEDAI-2K improved in all patients

Wang Q, et al. *N Engl J Med*. 2025;393(15):1542-1544.

Safety Challenges in In Vivo CAR-T Development

- **Limited clinical experience**: in vivo CAR-T remains early in development, requiring reliance on preclinical models and cautious clinical translation.
- **Platform-dependent risk profiles**: safety considerations differ fundamentally between delivery technologies
  - **Viral vector–based CARs**: genomic integration and persistent CAR expression limit control over expansion and durability, increasing risks of delayed inflammatory toxicities and chronic on-target effects.
  - **LNP–RNA–based CARs**: transient CAR expression may necessitate repeat dosing, introducing risks of innate immune activation, liver toxicity, and anti-vector immune responses.

Bot A, et al. Nat Rev Drug Discov. 2025 Sep 30.

Last Supper