CAR-T-Zelltherapie:
Konzepte und Kontroversen

Dominik Schneidawind
Leitender Arzt Blutstammzelltransplantation und Zelluläre Therapien
30.11.2023

Geschichte der CAR-T-Zelltherapie

Die Entdeckung der weissen Blutkörperchen

Wikipedia

Giovanni Alfonso Borelli
* 28.01.1608 † 31.12.1679

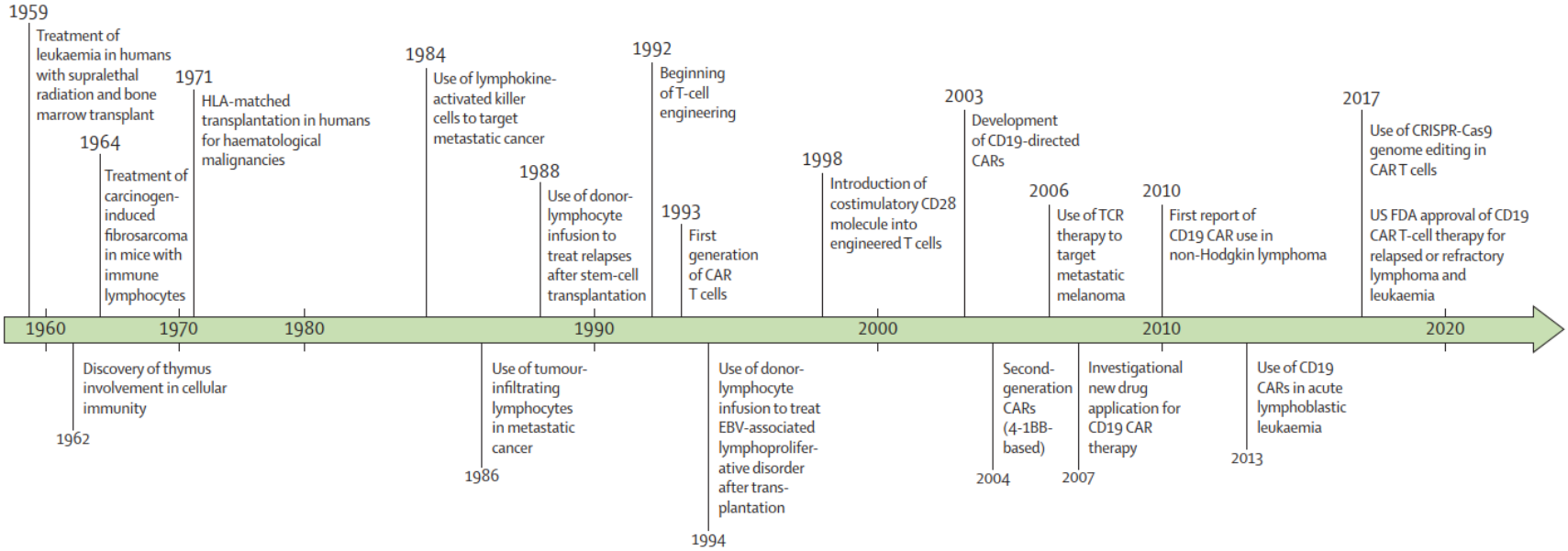
Weisse Blutkörperchen
unter dem Mikroskop

Wikipedia

Rudolf Virchow
* 13.10.1821 † 05.09.1902

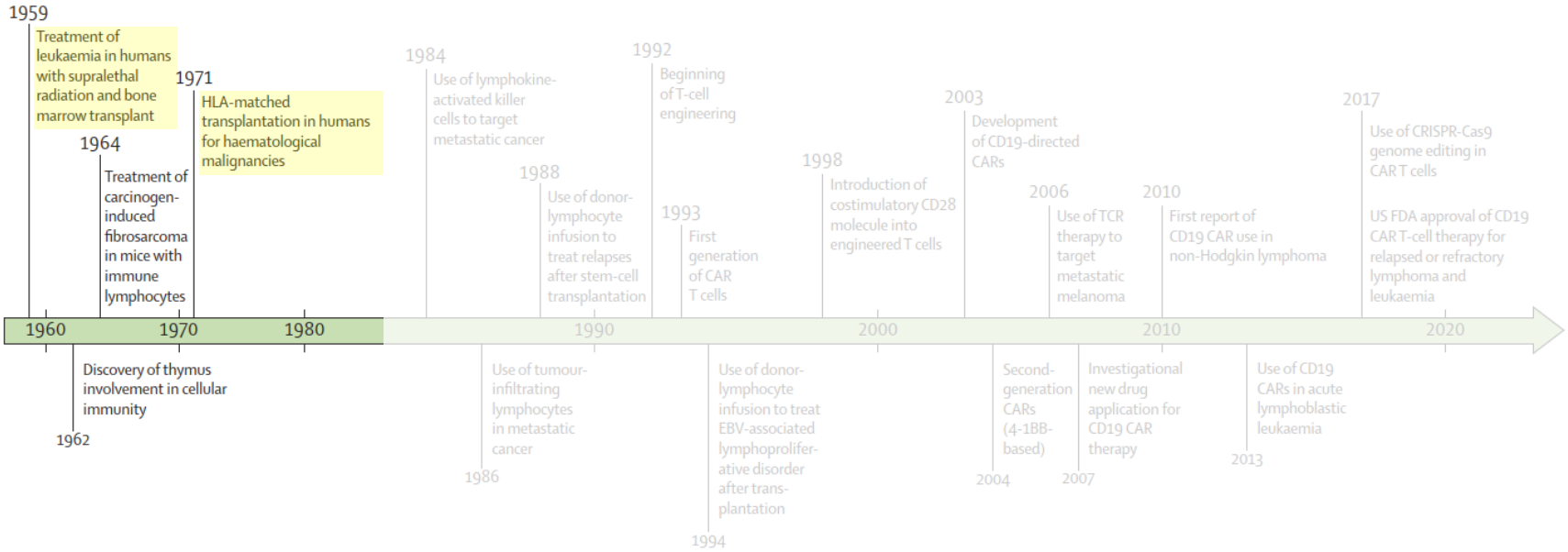
Krebs ↔ Entzündung

Zeitstrahl



Singh AK, McGuirk JP. CAR T cells: continuation in a revolution of immunotherapy. Lancet Oncol. 2020;21(3):e168-e178. doi:10.1016/

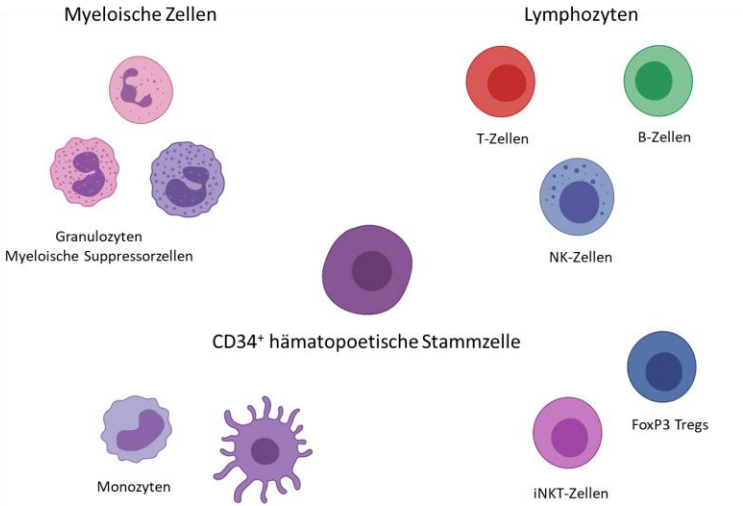
Zeitstrahl

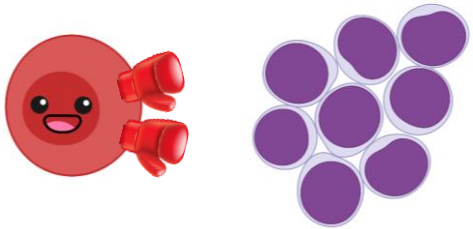


Singh AK, McGuirk JP. CAR T cells: continuation in a revolution of immunotherapy. Lancet Oncol. 2020;21(3):e168-e178. doi:10.1016/

Blutstammzelltransplantation

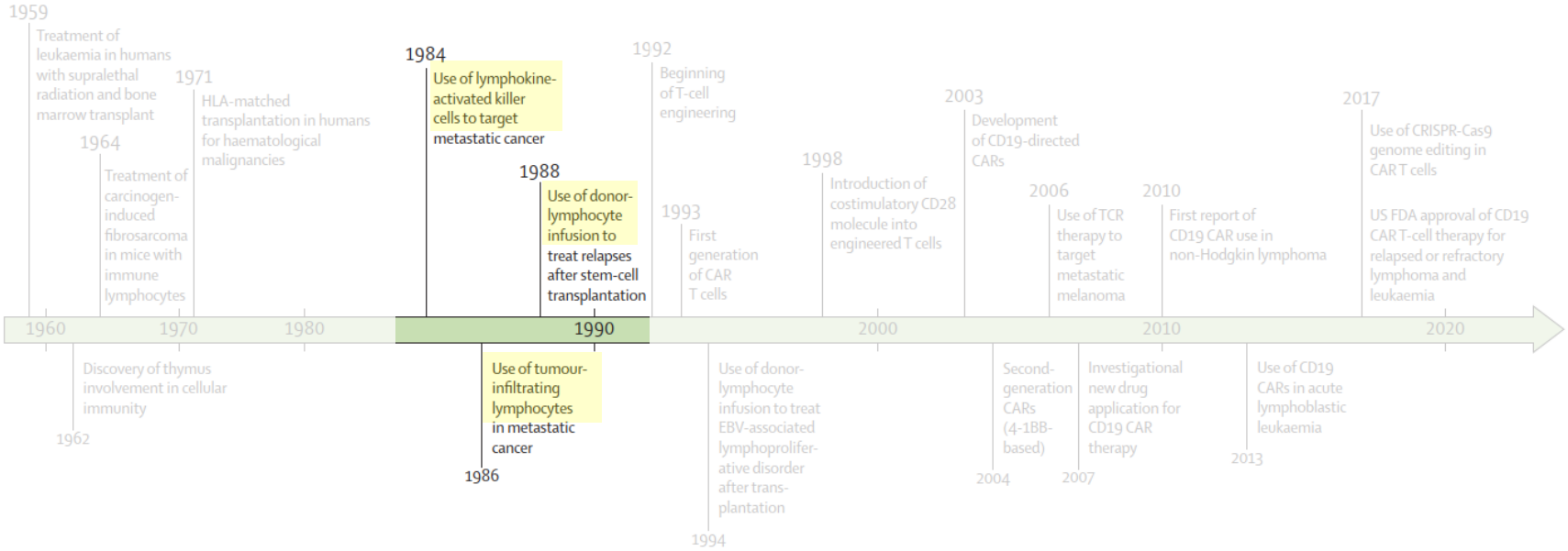
… als Prototyp der Zelltherapie





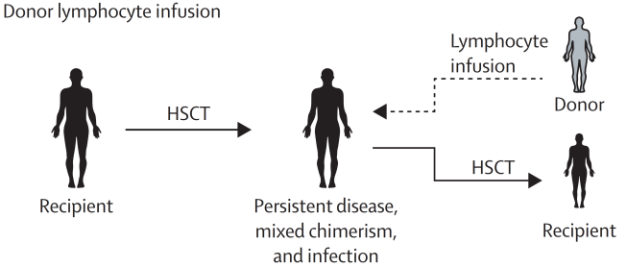
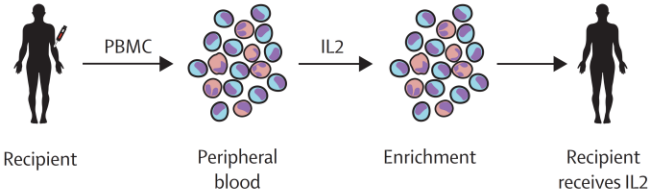
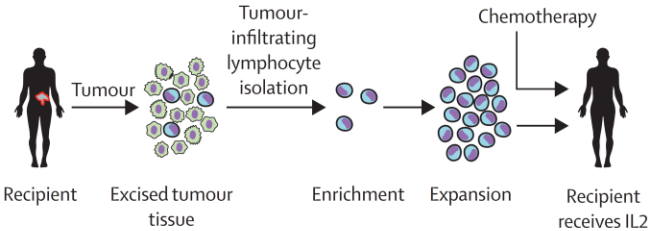
Own picture

Zeitstrahl



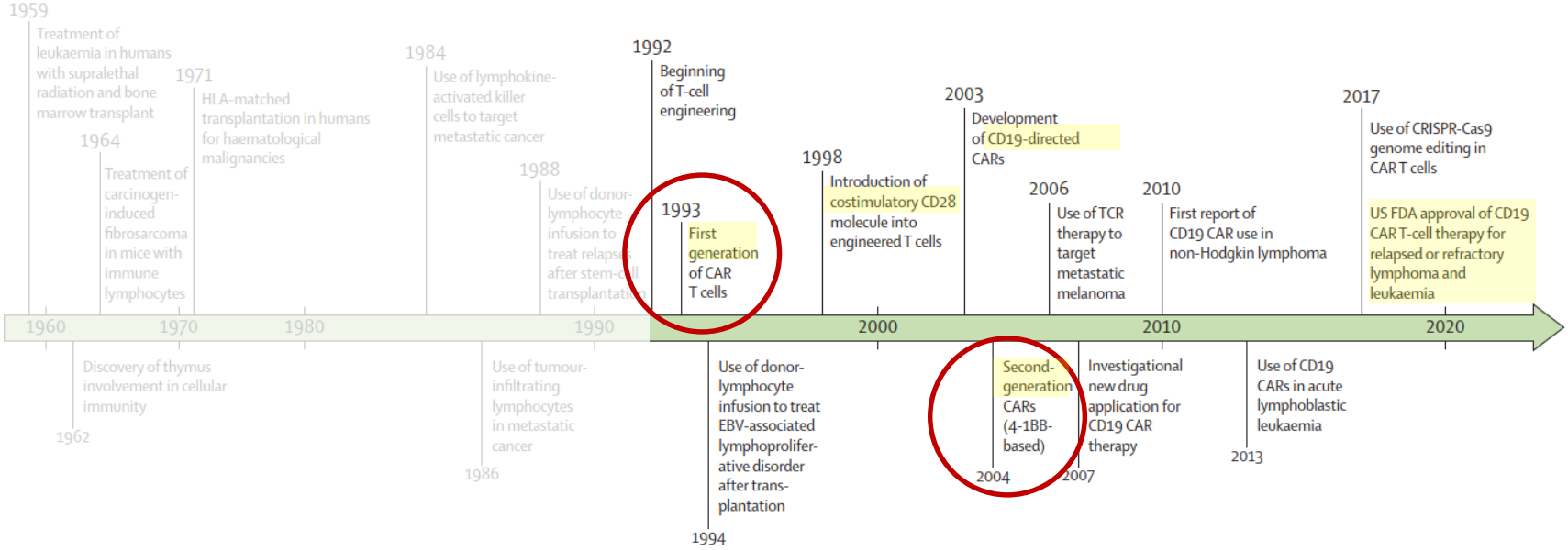
Singh AK, McGuirk JP. CAR T cells: continuation in a revolution of immunotherapy. Lancet Oncol. 2020;21(3):e168-e178. doi:10.1016/

Adoptiver T-Zell-Transfer

Adoptive T-cell therapy	Limitations
Donor lymphocyte infusion  	• Marrow aplasia • Graft-versus-host disease • Poor efficacy
Lymphokine-activated killer cells  	• Production failure • Limited efficacy
Tumour-infiltrating lymphocytes  	• Production failure • Limited efficacy

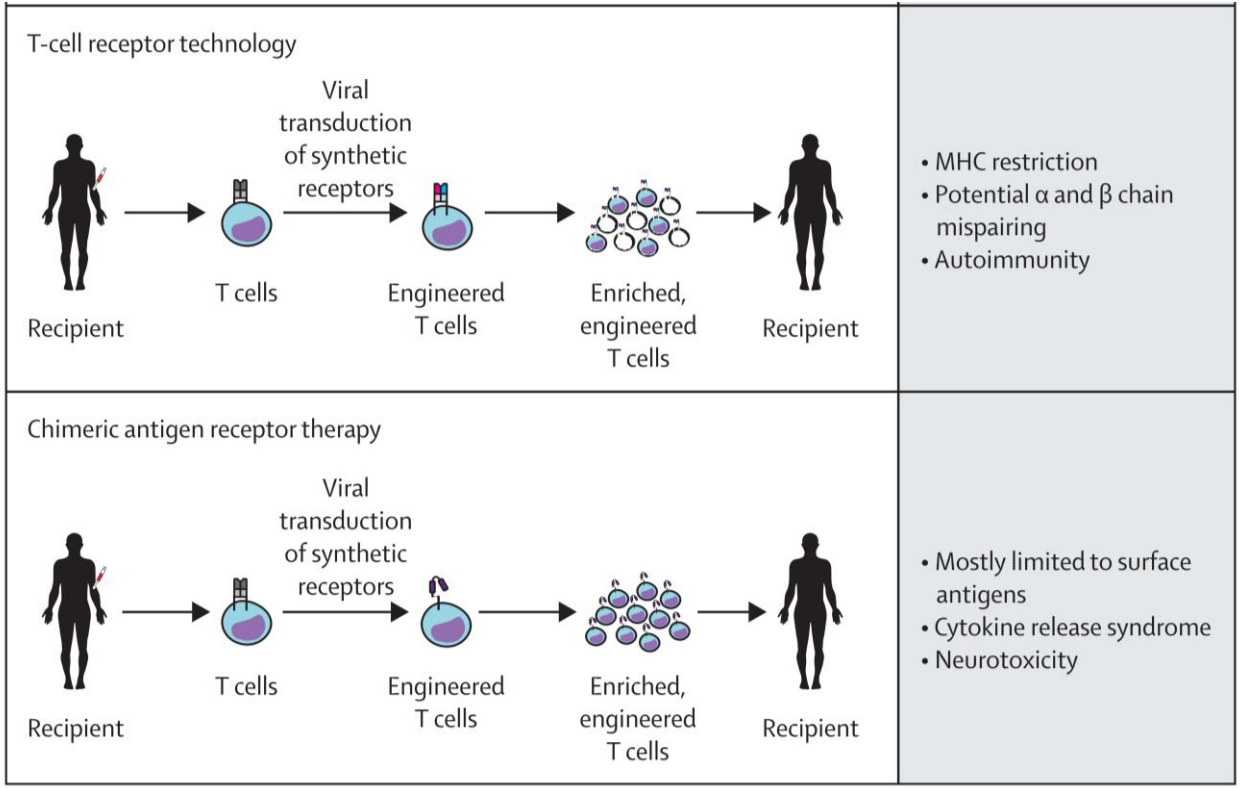
Singh AK, McGuirk JP. CAR T cells: continuation in a revolution of immunotherapy. Lancet Oncol. 2020;21(3):e168-e178. doi:10.1016/

Zeitstrahl



Singh AK, McGuirk JP. CAR T cells: continuation in a revolution of immunotherapy. Lancet Oncol. 2020;21(3):e168-e178. doi:10.1016/

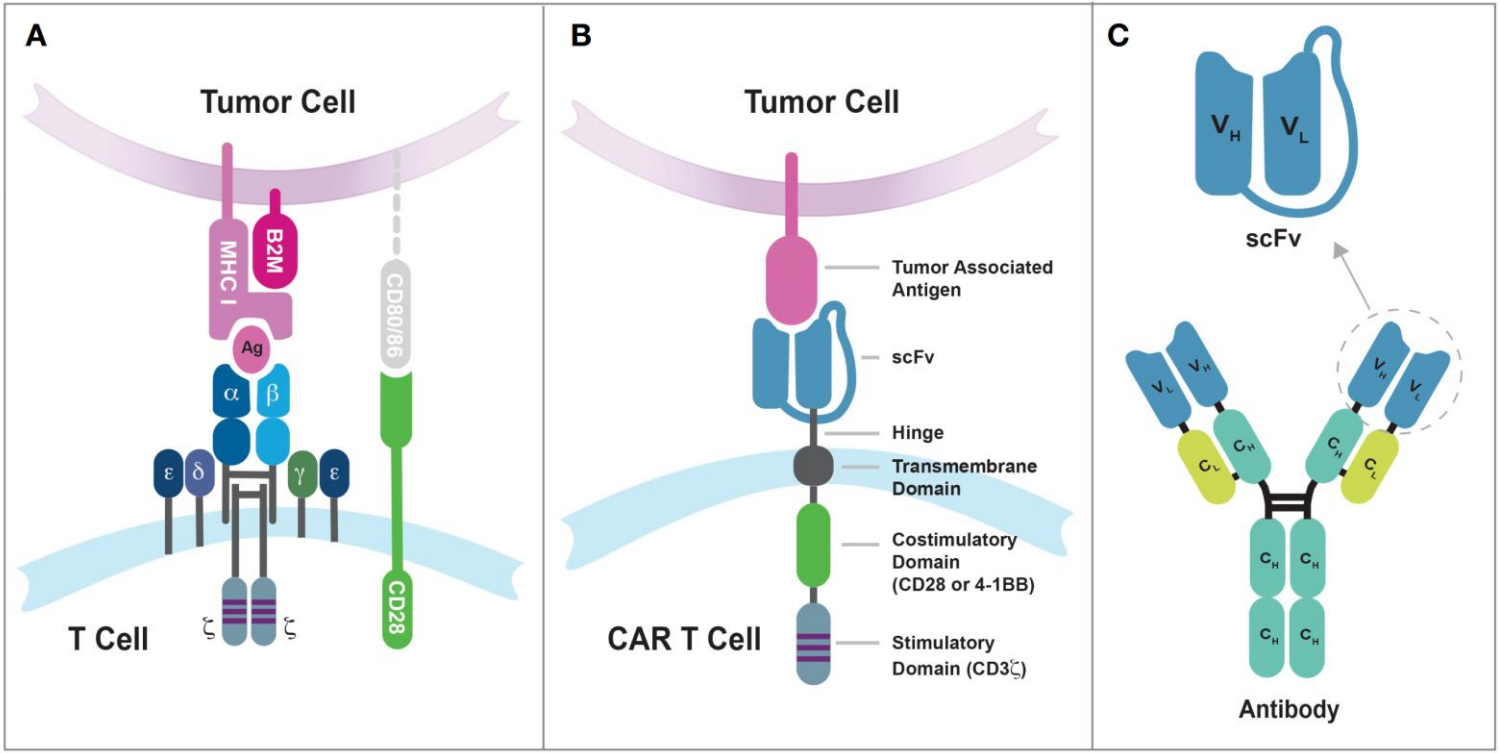
Adoptiver T-Zell-Transfer



Singh AK, McGuirk JP. CAR T cells: continuation in a revolution of immunotherapy. Lancet Oncol. 2020;21(3):e168-e178. doi:10.1016/

Chimäre Antigenrezeptoren

T-Zellaktivierung **MHC-unabhängige Antigenbindung**



Mitra A, Barua A, Huang L, et al.. From bench to bedside: the history and progress of CAR T cell therapy. Front Immunol. 2023;14:1188049. doi:10.3389/fimmu.2023.1188049

Erste Beschreibung von CARs

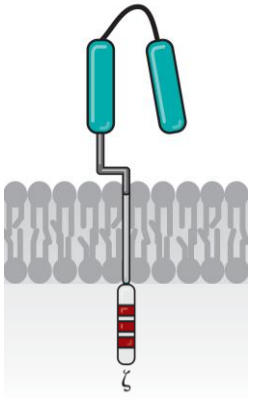
Vol. 149, No. 3, 1987
December 31, 1987

BIOCHEMICAL AND BIOPHYSICAL RESEARCH COMMUNICATIONS
Pages 960-968

EXPRESSION OF CHIMERIC RECEPTOR COMPOSED OF IMMUNOGLOBULIN-DERIVED V RESIONS AND T-CELL RECEPTOR-DERIVED C REGIONS

Yoshihisa Kuwana[1], Yoshihiro Asakura[1,2], Naoko Utsunomiya[2], Mamoru Nakanishi[2], Yohji Arata[2], Seiga Itoh[3], Fumihiko Nagase[4] and Yoshikazu Kurosawa[1*]

[1]Institute for Comprehensive Medical Science, Fujita-Gakuen Health University, Toyoake, Aichi, 470-11



Adapted from: June CH, O'Connor RS, Kawalekar OU, et al. CAR T cell immunotherapy for human cancer. Science. 2018;359(6382):1361-1365. doi:10.1126/science.aar6711

Proc. Natl. Acad. Sci. USA
Vol. 86, pp. 10024–10028, December 1989
Immunology

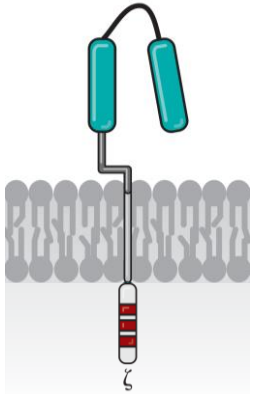
Expression of immunoglobulin-T-cell receptor chimeric molecules as functional receptors with antibody-type specificity

(chimeric genes/antibody variable region)

GIDEON GROSS, TOVA WAKS, AND ZELIG ESHHAR*

Department of Chemical Immunology, The Weizmann Institute of Science, Rehovot 76100, Israel

First generation CARs



Adapted from: June CH, O'Connor RS, Kawalekar OU, et al. CAR T cell immunotherapy for human cancer. Science. 2018;359(6382):1361-1365. doi:10.1126/science.aar6711

Brief Definitive Report

Lysis of Ovarian Cancer Cells by Human Lymphocytes Redirected with a Chimeric Gene Composed of an Antibody Variable Region and the Fc Receptor γ Chain

By P. Hwu,* G. E. Shafer,* J. Treisman,* D. G. Schindler,‡ G. Gross,‡ R. Cowherd,* S. A. Rosenberg,* and Z. Eshhar‡

*From the *Surgery Branch, National Cancer Institute, National Institutes of Health, Bethesda, Maryland 20892; and the ‡Department of Chemical Immunology, Weizmann Institute of Science, Rehovot 76100, Israel*

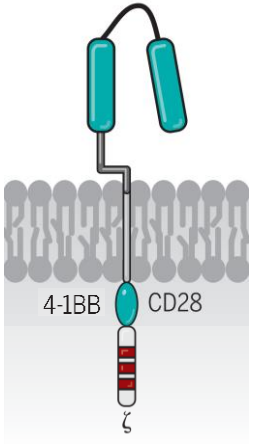
[CANCER RESEARCH 55, 3369–3373, August 1, 1995]

In Vivo Antitumor Activity of T Cells Redirected with Chimeric Antibody/T-Cell Receptor Genes

P. Hwu,[1] J. C. Yang, R. Cowherd, J. Treisman, G. E. Shafer, Z. Eshhar, and S. A. Rosenberg

Surgery Branch, National Cancer Institute, Bethesda, Maryland 20892 [P. H., J. C. Y., R. C., J. T., G. E. S., S. A. R.]; and Department of Chemical Immunology, Weizmann Institute of Science, Rehovot 76100, Israel [Z. E.]

Second generation CARs



Adapted from: June CH, O'Connor RS, Kawalekar OU, et al. CAR T cell immunotherapy for human cancer. Science. 2018;359(6382):1361-1365. doi:10.1126/science.aar6711

Antigen-dependent CD28 Signaling Selectively Enhances Survival and Proliferation in Genetically Modified Activated Human Primary T Lymphocytes

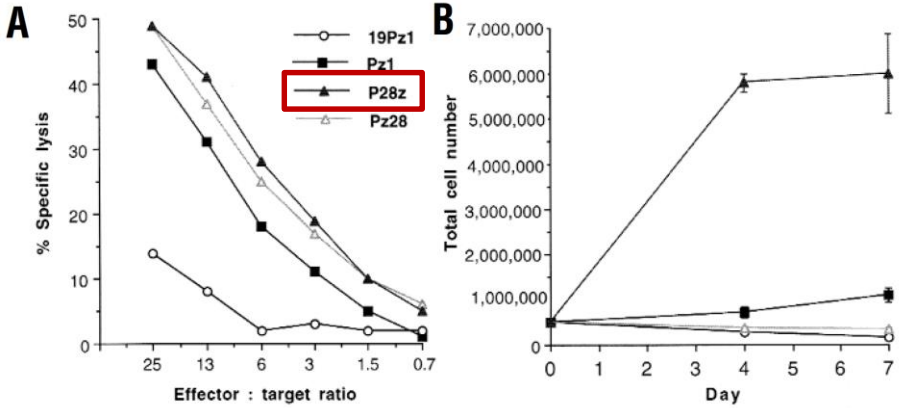
By Anja Krause,* Hong-Fen Guo,‡ Jean-Baptiste Latouche,* Cuiwen Tan,* Nai-Kong V. Cheung,‡ and Michel Sadelain*§

J. Exp. Med. © The Rockefeller University Press • 0022-1007/98/08/619/08 $2.00
Volume 188, Number 4, August 17, 1998 619–626

Human T-lymphocyte cytotoxicity and proliferation directed by a single chimeric TCRζ /CD28 receptor

John Maher, Renier J. Brentjens, Gertrude Gunset, Isabelle Rivière, and Michel Sadelain*

nature biotechnology • VOLUME 20 • JANUARY 2002



CAR-T-Zellen für die Behandlung der CLL

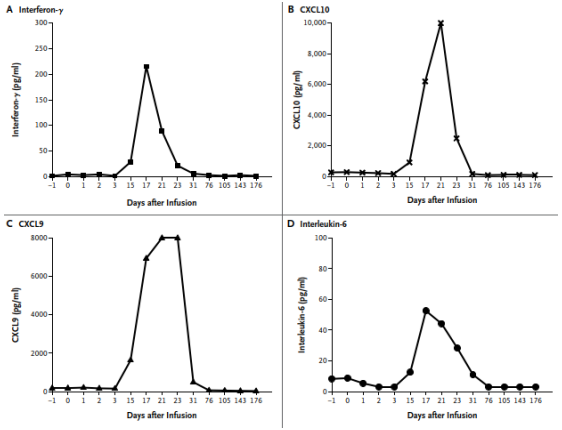
The NEW ENGLAND JOURNAL of MEDICINE

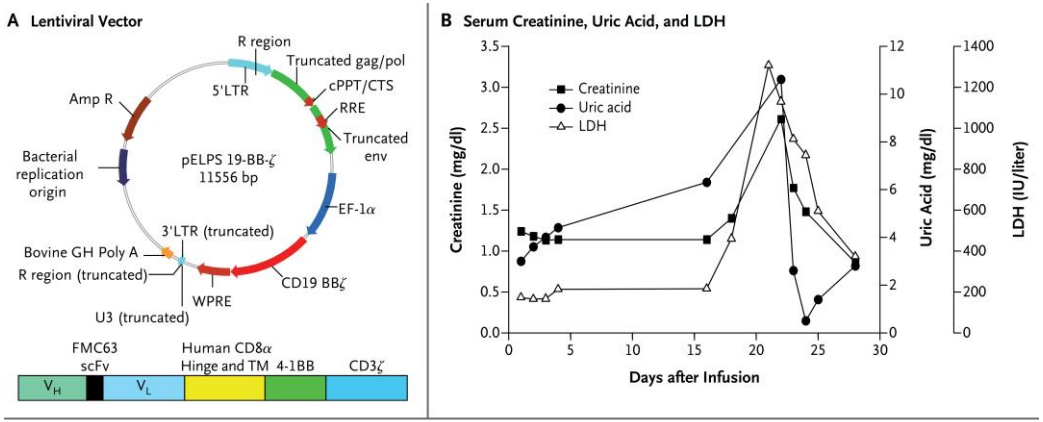
BRIEF REPORT

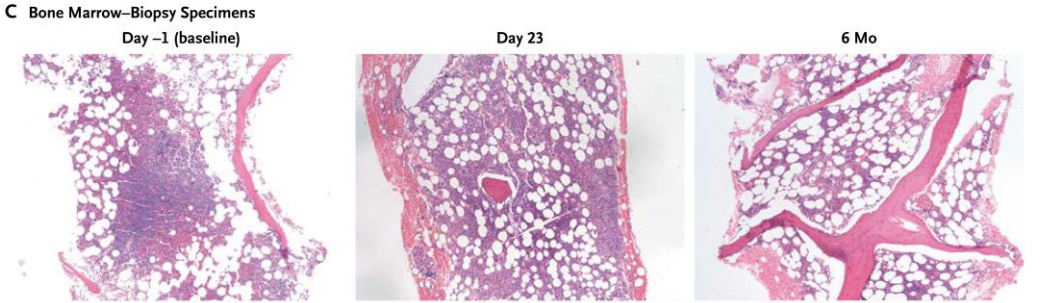
Chimeric Antigen Receptor–Modified T Cells in Chronic Lymphoid Leukemia

David L. Porter, M.D., Bruce L. Levine, Ph.D., Michael Kalos, Ph.D., Adam Bagg, M.D., and Carl H. June, M.D.

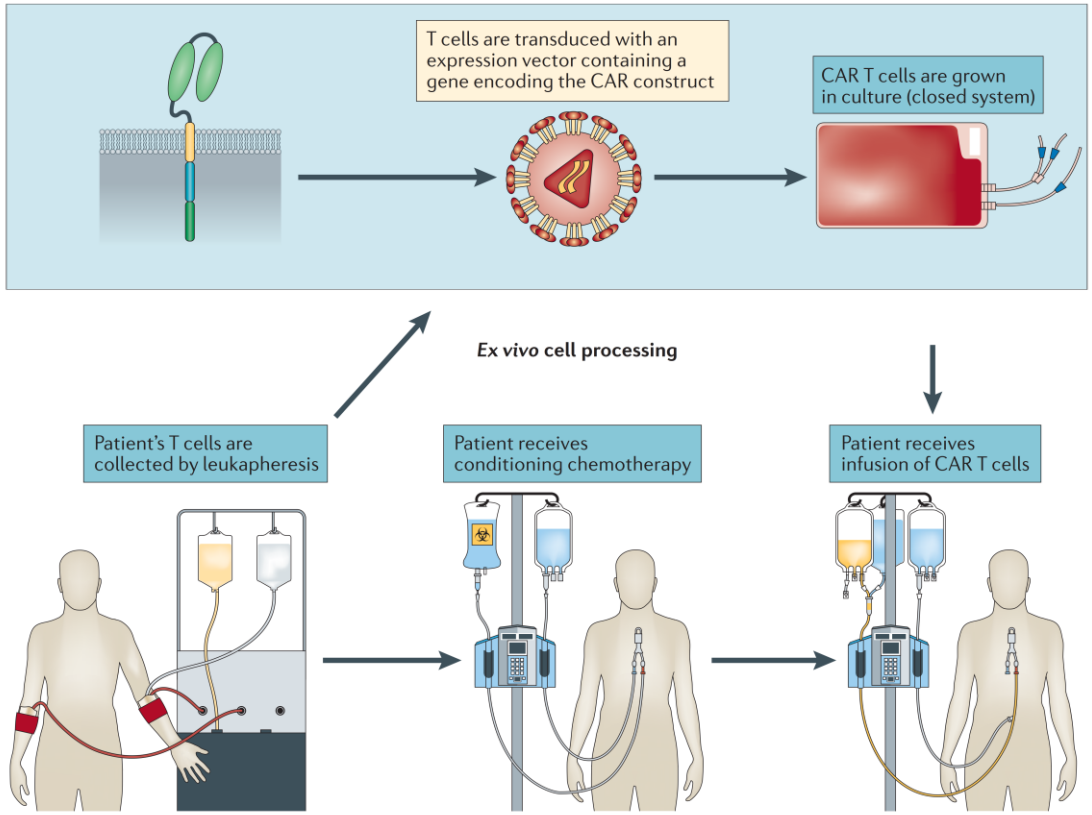
N Engl J Med 2011;365:725-33.







Herstellung von CAR-T-Zellen



Adapted from: Brudno JN, Kochenderfer JN. Chimeric antigen receptor T-cell therapies for lymphoma. Nat Rev Clin Oncol. 2018;15(1):31-46. doi:10.1038/nrclinonc.2017.128

Zugelassene Therapien für Leukämien, Lymphome und das Myelom

Überblick

TABLE 1 Summary of FDA-approved CAR T cell therapies for B cell malignancies and multiple myeloma.

Company name Brand name Generic name	Date of approval	Target antigen/ Antibody	Hinge/ transmembrane	Costimulatory domains	Vector/ promoter	Targeted cancers	Pivotal trial	No. of Patients	Outcomes
Novartis Kymriah Tisagenlecleucel	Aug 30, 2017	CD19 Mouse FMC63	CD8α/CD8α	4-1BB + CD3ζ	Lentiviral EF1α	R/R CAYA B-ALL	ELIANA (NCT02228096)	75	81% overall remission rate
Kite Yescarta Axicabtagene ciloleucel	Oct 18, 2017	CD19 Mouse FMC63	CD8α/CD8α	CD28 + CD3ζ	Gammaretroviral LTR	R/R LBCL	ZUMA-1 (NCT02348216)	108	58% complete response
Kite Tecartus Brexucabtagene autoleucel	Jul 24, 2020	CD19 Mouse FMC63	CD28/CD28	CD28 + CD3ζ	Gammaretroviral LTR	R/R MCL	ZUMA-2 (NCT02601313)	68	67% complete response
Juno Breyanzi Lisocabtagene maraleucel	Feb 5, 2021	CD19 Mouse FMC63	IgG4/CD28	4-1BB+ CD3ζ	Lentiviral EF1α	R/R LBCL	Transcend NHL001 (NCT02631044)	269	53% complete response
Bluebird Abecma Idecabtagene vicleucel	Mar 26, 2021	BCMA Mouse BB2121	CD8α/CD8α	4-1BB+ CD3ζ	Lentiviral MND	R/R MM	KarMMa (NCT03361748)	128	33% complete response
J&J and Legend Carvykti Ciltacabtagene autoleucel	Feb 28, 2022	BCMA dual camel single-domain antibodies	CD8α/CD8α	4-1BB + CD3ζ	Lentiviral EF1α	R/R MM	CARTITUDE-1 (NCT03548207)	97	82.5% complete response

R/R, relapsed or refractory. CAYA, children and young adults. LBCL, large B-cell lymphoma. MCL, mantle cell lymphoma. MM, multiple myeloma.

Mitra A, Barua A, Huang L, et al.. From bench to bedside: the history and progress of CAR T cell therapy. Front Immunol. 2023;14:1188049. doi:10.3389/fimmu.2023.1188049

Akute lymphatische Leukämie

Entity	Product	Details	Trial
B-ALL	Tisa-cel	≤25 years refractory, relapsed after transplantation, relapsed after at least two lines of therapy	ELIANA
B-ALL	Brexu-cel	Adults relapsed or refractory B-ALL after two or more lines of systemic therapy	ZUMA-3

according to "http://www.swissmedicinfo.ch", Sep 2023

Non-Hodgkin-Lymphom (I)

Entity	Product	Details	Trial
DLBCL	Tisa-cel	Adults relapsed or refractory DLBCL after two or more lines of systemic therapy	JULIET
DLBCL PMBCL	Axi-cel	Adults relapsed or refractory DLBCL/PMBCL after two or more lines of systemic therapy	ZUMA-1
DLBCL PMBCL	Liso-cel	Adults relapsed or refractory DLBCL/PMBCL after two or more lines of therapy	TRANSCEND
DLBCL HGBL	Axi-cel	Adults refractory to first line chemoimmunotherapy or relapsed within 12 months after first line chemoimmunotherapy	ZUMA-7
DLBCL PMBCL HGBL	Liso-cel	Adults refractory to first line chemoimmunotherapy or relapsed within 12 months after first line chemoimmunotherapy	TRANSFORM

according to "http://www.swissmedicinfo.ch", Nov 2023

Non-Hodgkin-Lymphom (II)

Entity	Product	Details	Trial
MCL	Brexu-cel	Adults relapsed or refractory MCL after two or more lines of systemic therapy incl. BTK inhibitor	ZUMA-2
FL	Axi-cel	Adults relapsed or refractory FL after three or more lines of systemic therapy	ZUMA-5
FL	Tisa-cel	Adults relapsed or refractory FL after three or more lines of systemic therapy	ELARA

according to "http://www.swissmedicinfo.ch", Sep 2023

Multiples Myelom

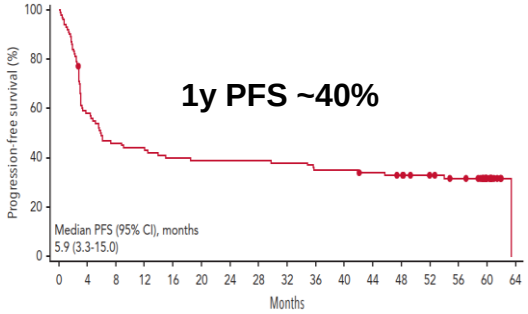
Entity	Product	Details	Trial
MM	Ide-cel	Adults relapsed and refractory MM after three or more lines of therapy incl. immunomodulator, proteasome inhibitor and anti-CD38	KarMMa
MM	Cilta-cel	Adults relapsed and refractory MM after three or more lines of therapy incl. immunomodulator, proteasome inhibitor and anti-CD38	CARTITUDE-1

according to "http://www.swissmedicinfo.ch", Sep 2023
Swissmedic

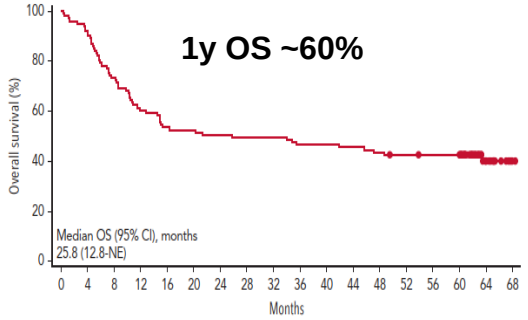
Real World Experience

Grosszelliges B-Zelllymphom (≥3. Linie): Axi-cel und Tisa-cel

ZUMA-1 follow-up (n=101)
Neelapu et al. Blood 2023
Bridging nicht erlaubt.



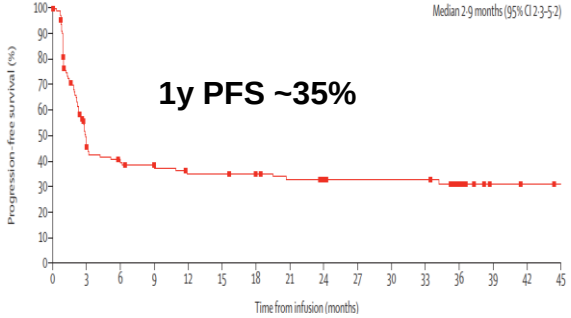
1y PFS ~40%



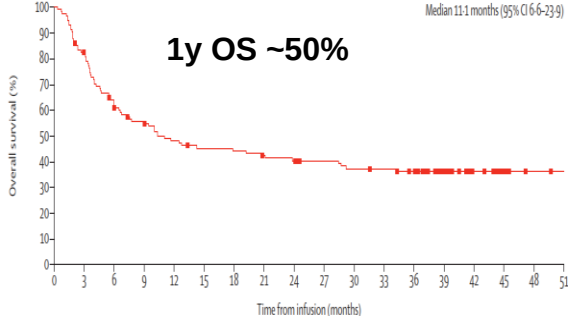
1y OS ~60%

Neelapu SS, Jacobson CA, Ghobadi A, et al. Five-year follow-up of ZUMA-1 supports the curative potential of axicabtagene ciloleucel in refractory large B-cell lymphoma. Blood. 2023;141(19):2307-2315. doi:10.1182/blood.2022018893

JULIET follow-up (n=115)
Neelapu et al. Blood 2023
Bridging erlaubt.



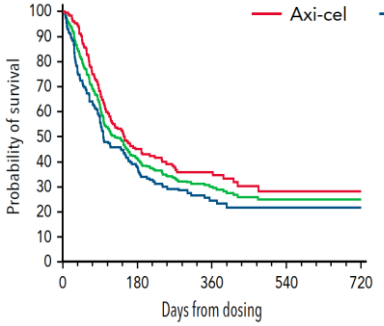
1y PFS ~35%



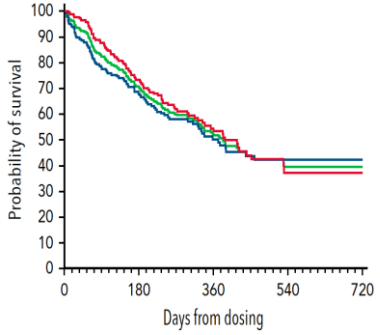
1y OS ~50%

Schuster SJ, Tam CS, Borchmann P, et al. Long-term clinical outcomes of tisagenlecleucel in patients with relapsed or refractory aggressive B-cell lymphomas (JULIET): a multicentre, open-label, single-arm, phase 2 study. Lancet Oncol. 2021;22(10):1403-1415. doi:10.1016/S1470-2045(21)00375-2

Real-world Axi-cel and Tisa-cel (n=356)
Bethge et al. Blood 2022
Bridging bei 80% der Patienten.



1y PFS 30%
35% Axi
24% Tisa
***p*=0.015**

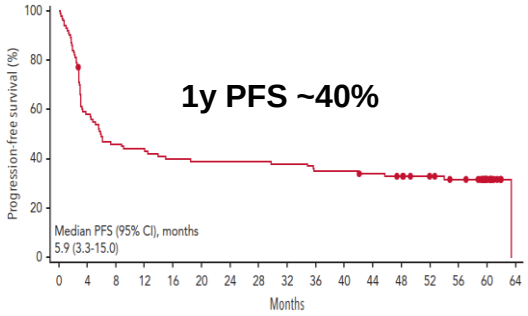


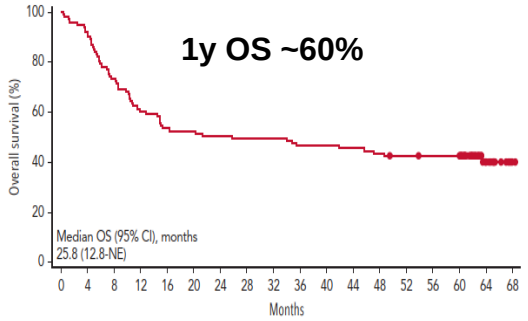
1y OS 52%

Bethge WA, Martus P, Schmitt M, et al. GLA/DRST real-world outcome analysis of CAR T-cell therapies for large B-cell lymphoma in Germany. Blood. 2022;140(4):349-358. doi:10.1182/blood.2021015209

Grosszelliges B-Zelllymphom (≥3. Linie): Axi-cel und Tisa-cel

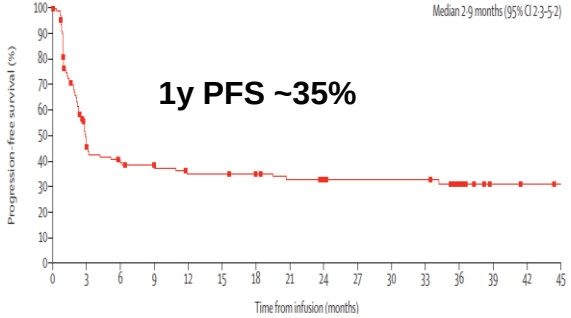
ZUMA-1 follow-up (n=101)
Neelapu et al. Blood 2023
Bridging nicht erlaubt.

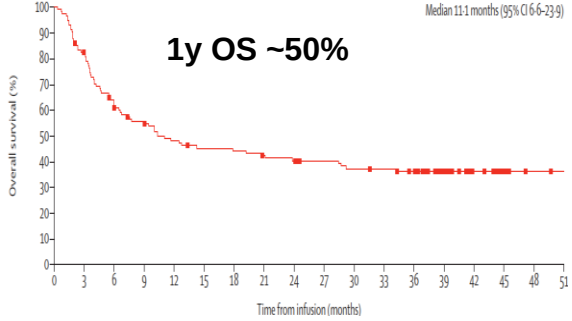




Neelapu SS, Jacobson CA, Ghobadi A, et al. Five-year follow-up of ZUMA-1 supports the curative potential of axicabtagene ciloleucel in refractory large B-cell lymphoma. Blood. 2023;141(19):2307-2315. doi:10.1182/blood.2022018893

JULIET follow-up (n=115)
Neelapu et al. Blood 2023
Bridging erlaubt.

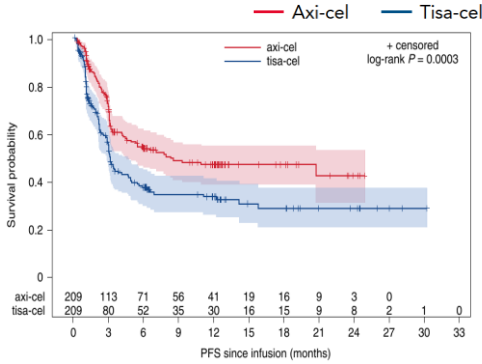




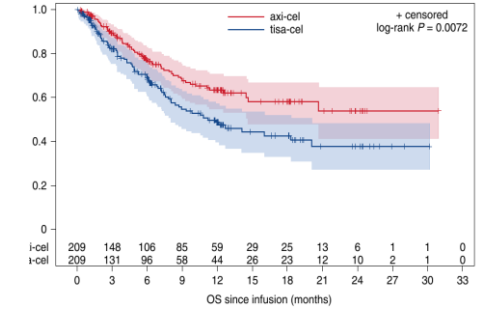
Schuster SJ, Tam CS, Borchmann P, et al. Long-term clinical outcomes of tisagenlecleucel in patients with relapsed or refractory aggressive B-cell lymphomas (JULIET): a multicentre, open-label, single-arm, phase 2 study. Lancet Oncol. 2021;22(10):1403-1415. doi:10.1016/S1470-2045(21)00375-2

Propensity score matching (PSM)

Real-world Axi-cel and Tisa-cel (n=809->418)
Bachy et al. Nat Med 2022



1y PFS ~40%
47% Axi
33% Tisa
***p*<0.0001**



1y OS ~60%
64% Axi
49% Tisa
***p*=0.007**

Bachy E, Le Gouill S, Di Blasi R, et al. A real-world comparison of tisagenlecleucel and axicabtagene ciloleucel CAR T cells in relapsed or refractory diffuse large B cell lymphoma. Nat Med. 2022;28(10):2145-2154. doi:10.1038/s41591-022-01969-y

Grosszelliges B-Zelllymphom (≥3. Linie): Axi-cel und Tisa-cel

Real-world Axi-cel and Tisa-cel (n=356)
Bethge et al. Blood 2022

	All, n (%)	Axi-cel, n (%)	Tisa-cel, n (%)	P
CRS 1-4	259 (73)	141 (81)	118 (65)	.003
CRS ≥3	42 (12)	18 (10)	24 (13)	n.s.
CRS 5	1 (0.3)	0	1 (0.5)	—
ICANS 1-4	116 (33)	76 (44)	40 (22)	<.0001
ICANS ≥3	40 (11)	28 (16)	12 (7)	.004
ICANS 5	1 (0.3)	1 (0.6)	0	—

Real-world Axi-cel and Tisa-cel (n=809)
Bachy et al. Nat Med 2022

Table 3 | Toxicity after CAR T infusion according to CAR T product in the PSM cohorts

	axi-cel		tisa-cel		P
	n = 209		n = 209		
CRS of any grade	180	(86.1%)	158	(75.6%)	0.006
Grade 1–2	169	(80.9%)	139	(66.5%)	<0.001
Grade ≥3	11	(5.3%)	19	(9.1%)	0.130
ICANS of any grade	102	(48.8%)	46	(22.0%)	<0.001
Grade 1–2	73	(34.9%)	40	(19.1%)	<0.001
Grade ≥3	29	(13.9%)	6	(2.9%)	<0.001

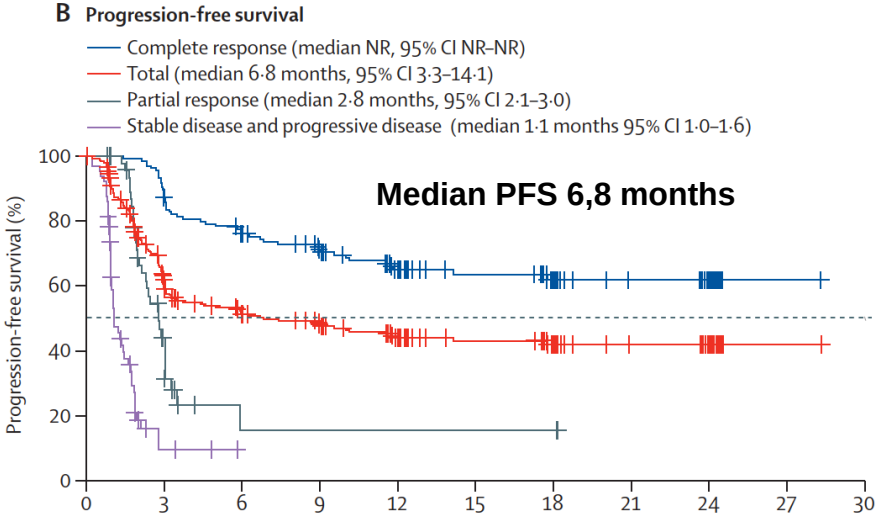
Bachy E, Le Gouill S, Di Blasi R, et al. A real-world comparison of tisagenlecleucel and axicabtagene ciloleucel CAR T cells in relapsed or refractory diffuse large B cell lymphoma. Nat Med. 2022;28(10):2145-2154. doi:10.1038/s41591-022-01969-y

	All, n (%)	Axi-cel	Tisa-cel	P
Eligibility ZUMA-I	45 (13)	31 (18)	14 (8)	.004
Eligibility JULIET	318 (89)	149 (86)	169 (92)	n.s.

Bethge WA, Martus P, Schmitt M, et al. GLA/DRST real-world outcome analysis of CAR T-cell therapies for large B-cell lymphoma in Germany. Blood. 2022;140(4):349-358. doi:10.1182/blood.2021015209

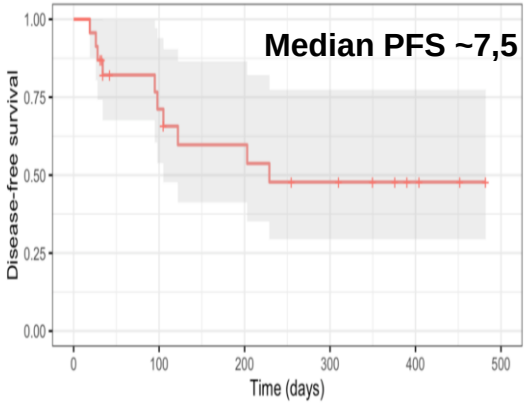
Grosszelliges B-Zelllymphom (3. Linie): Liso-cel

TRANSCEND (n=344)
Abramson et al. Lancet 2020



Abramson JS et al. Lisocabtagene maraleucel for patients with relapsed or refractory large B-cell lymphomas (TRANSCEND NHL 001): a multicentre seamless design study. Lancet. 2020;396(10254):839-852.

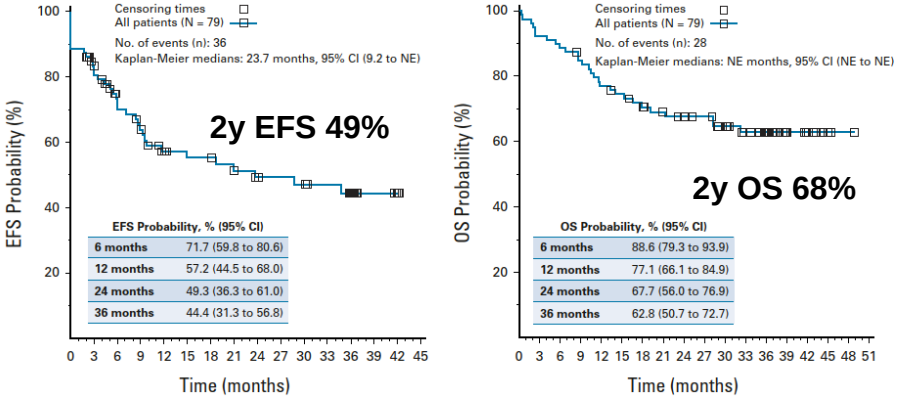
Real-world Liso-cel (n=26)
Portuguese et al. EBMT 2023



Portuguese AJ et al. Lisocabtagene maraleucel for relapsed or refractory large B-cell lymphoma: feasibility, safety and efficacy in a real-world setting. Poster presented at the 49th EBMT; April 23-26, 2023; Paris.

B-ALL: Tisa-cel

ELIANA follow-up (n=79)
Laetsch et al. JCO 2022



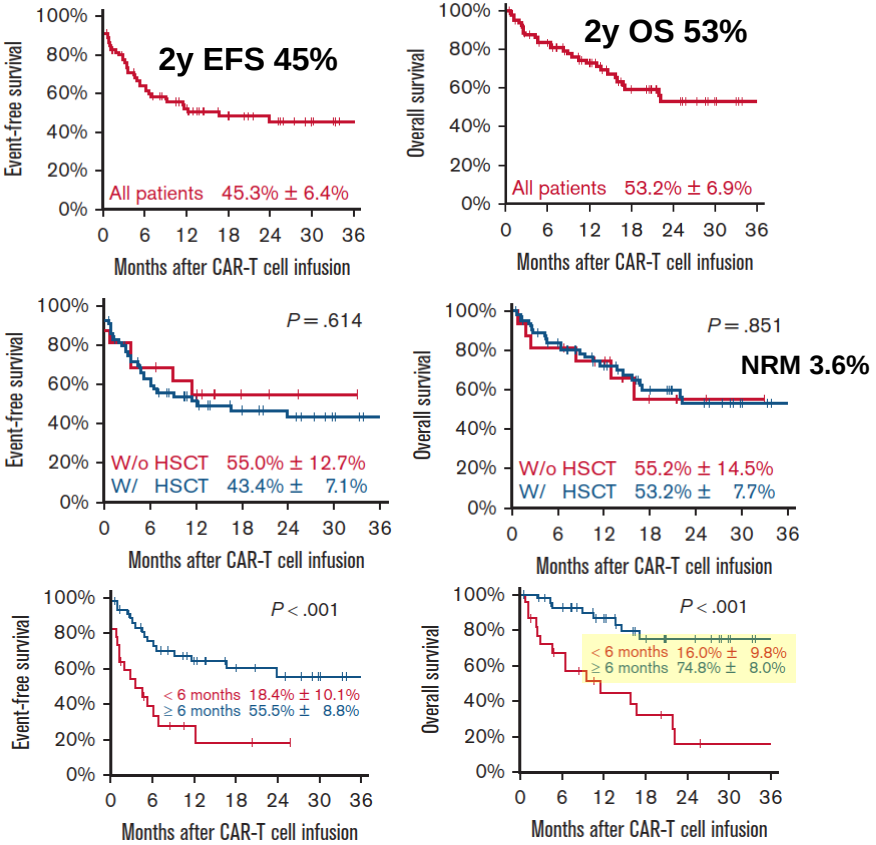
Characteristic	All Patients (N = 79)	Post-Infusion alloSCT (n = 17)	No Post-Infusion alloSCT (n = 62)
Age, years, median (range)	11 (3-24)	9 (4-21)	12 (3-24)
Sex, male, No. (%)	45 (57)	13 (77)	32 (52)
Prior HSCT, No. (%)	48 (61)	6 (35)	42 (68)
Previous lines of therapy, No., median (range)	3 (1-8)	2 (2-4)	3 (1-8)
Disease status, No. (%)			
Primary refractory	6 (8)	1 (6)	5 (8)
Relapsed	73 (92)	16 (94)	57 (92)

Laetsch TW, Maude SL, Rives S, et al. Three-Year Update of Tisagenlecleucel in Pediatric and Young Adult Patients With Relapsed/Refractory Acute Lymphoblastic Leukemia in the ELIANA Trial. J Clin Oncol. 2023;41(9):1664-1669. doi:10.1200/JCO.22.00642

"It is of special interest that **only 1 patient was consolidated with allo-HSCT** after having achieved remission with CAR T cells."

Bader P, Rossig C, Hutter M, et al. CD19 CAR T cells are an effective therapy for posttransplant relapse in patients with B-lineage ALL: real-world data from Germany. Blood Adv. 2023;7(11):2436-2448. doi:10.1182/bloodadvances.2022008981

Real-world Tisa-cel (n=81, 80% prior allo-HCT)
Bader et al. Blood Advances 2022



B-ALL: Tisa-cel

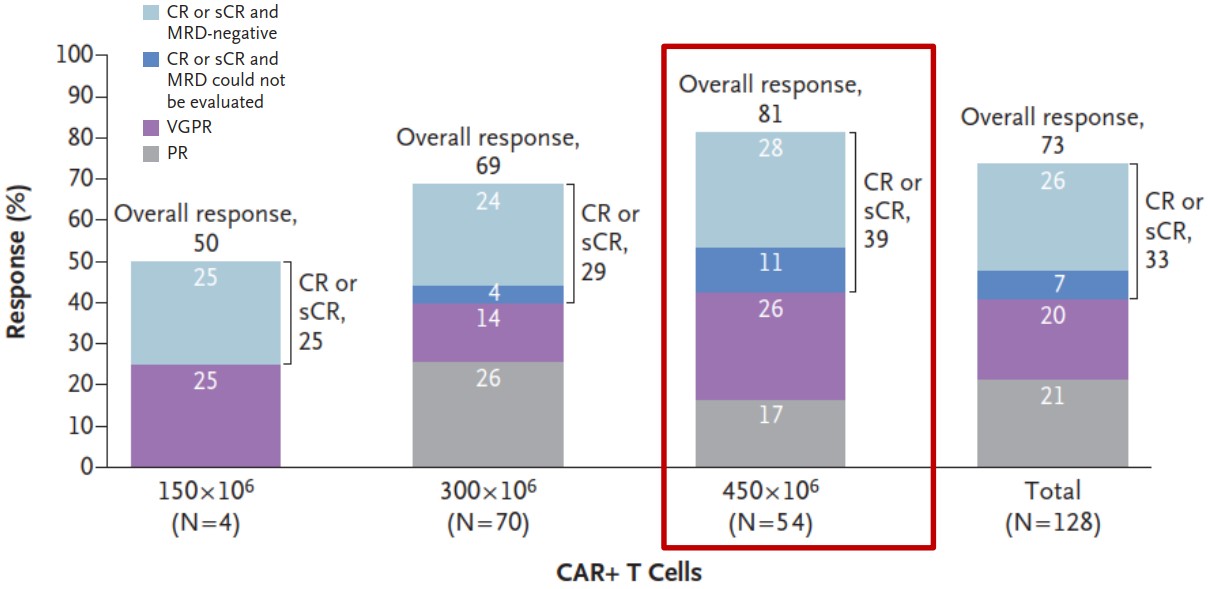
Table 2. Adverse events after CAR T-cell infusion

	All patients (N = 81)	With HSCT (N = 65)	Without HSCT (N = 16)	*P* value	<5% blasts (N = 44)	≥5% blasts (N = 37)	*P* value	ELIANA (N = 75)	*P* value
CRS (1-5), n (%)	55 (67.9)	42 (64.6)	13 (81.2)	.202	26 (59.1)	29 (78.4)	.064	58 (77.3)	.188
CRS (≥3), n (%)	5 (6.2)	4 (6.2)	1 (6.2)	.989	0 (0.0)	5 (13.5)	.012	35 (46.7)	<.001
CRS (5), n (%)	2 (2.5)	2 (3.1)	0 (0.0)	.477	0 (0.0)	2 (5.4)	.118	0 (0.0)	.171
ICANS (1-5), n (%)	6 (7.4)	5 (7.7)	1 (6.2)	.844	2 (4.5)	4 (10.8)	.283	30 (40.0)	<.001
ICANS (≥3), n (%)	4 (4.9)	3 (4.6)	1 (6.2)	.787	1 (2.3)	3 (8.1)	.227	10 (13.3)	.067
ICANS (5), n (%)	0 (0.0)	0 (0.0)	0 (0.0)	NA	0 (0.0)	0 (0.0)	NA	0 (0.0)	NA

Bader P, Rossig C, Hutter M, et al. CD19 CAR T cells are an effective therapy for posttransplant relapse in patients with B-lineage ALL: real-world data from Germany. Blood Adv. 2023;7(11):2436-2448. doi:10.1182/bloodadvances.2022008981

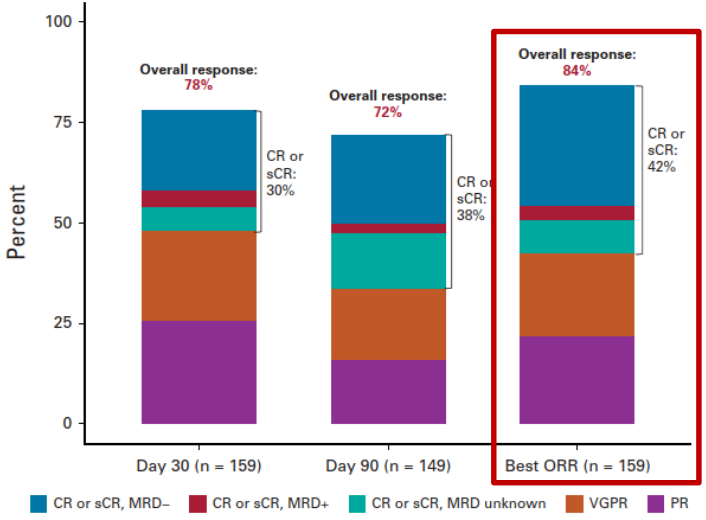
Multiples Myelom: Ide-cel

KARMMA (n=128)
Munshi et al. NEJM 2021



Munshi NC, Anderson LD Jr, Shah N, et al. Idecabtagene Vicleucel in Relapsed and Refractory Multiple Myeloma. N Engl J Med. 2021;384(8):705-716. doi:10.1056/NEJMoa2024850

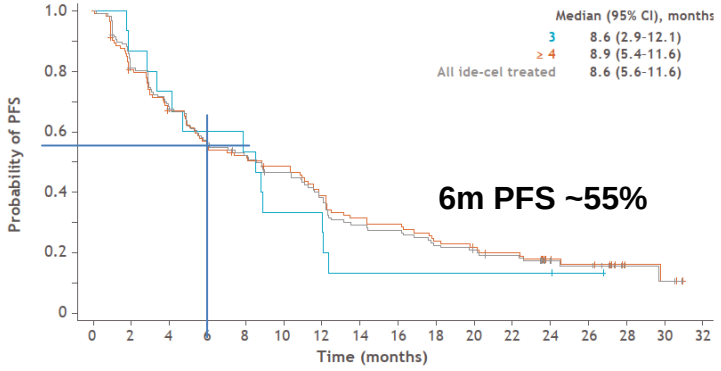
Real-world Ide-cel (n=159)
Hansen et al. JCO 2022

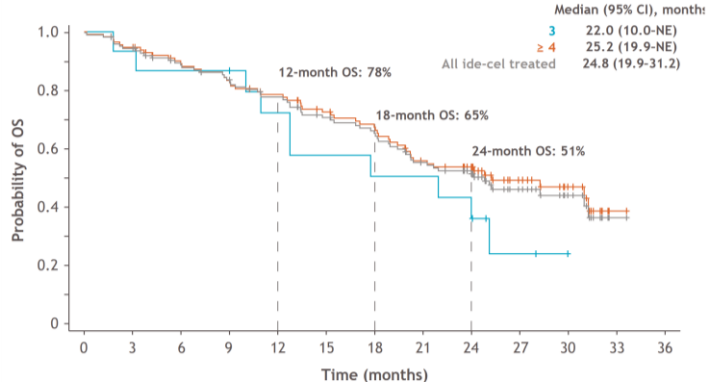


Hansen DK, Sidana S, Peres LC, et al. Idecabtagene Vicleucel for Relapsed/Refractory Multiple Myeloma: Real-World Experience From the Myeloma CAR T Consortium. J Clin Oncol. 2023;41(11):2087-2097. doi:10.1200/JCO.22.01365

Multiples Myelom: Ide-cel

KARMMA follow-up (n=128)
Oriol et al. EHA 2021
Keine BCMA-gerichtete Vortherapie erlaubt

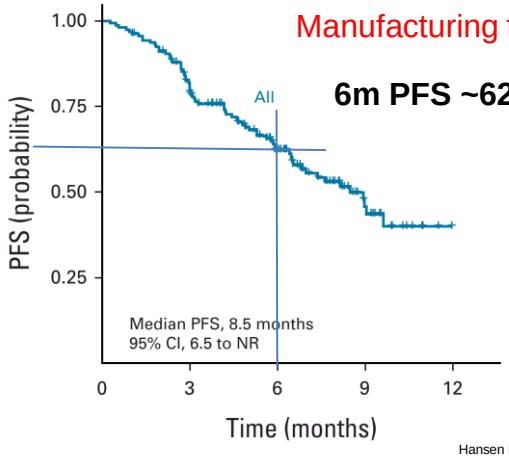


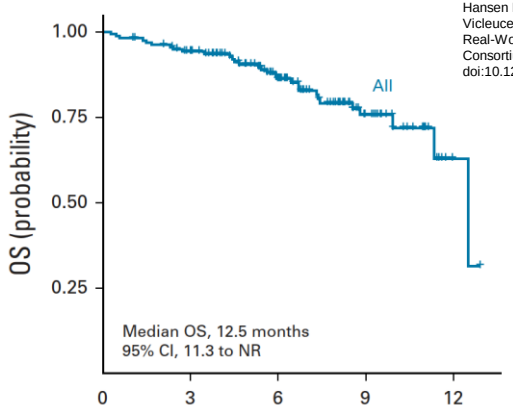


Oriol et al. Idecabtagene vicleucel (ide-cel, bb2121), a BCMA-directed CAR T cell therapy, in patients with relapsed and refractory multiple myeloma: updated KarMMa results. Poster presented at European Hematology Association; June 9-17, 2021; Virtual congress

Real-world Ide-cel (n=159)
Hansen et al. JCO 2022

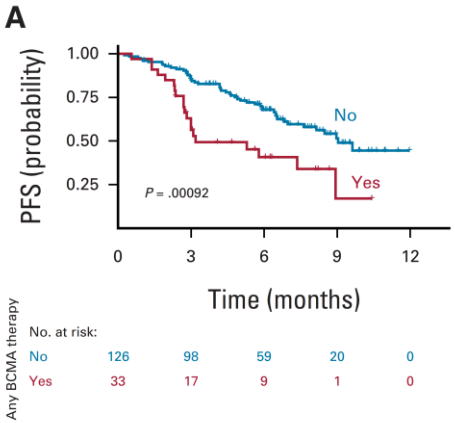
Manufacturing failure **6%** vs 0.6%



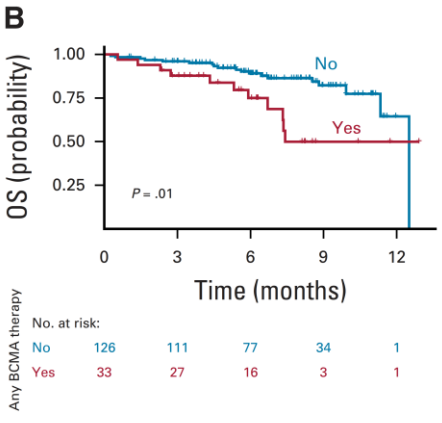


Hansen DK, Sidana S, Peres LC, et al. Idecabtagene Vicleucel for Relapsed/Refractory Multiple Myeloma: Real-World Experience From the Myeloma CAR T Consortium. J Clin Oncol. 2023;41(11):2087-2097. doi:10.1200/JCO.22.01365

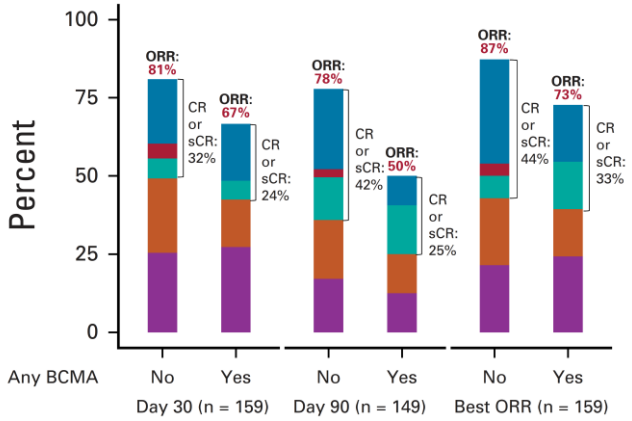
Multiples Myelom: Ide-cel (vorgängig BCMA-gerichtete Therapie)



No BCMA therapy: Median PFS, 9.0 months (95% CI, 7.6 to NR)
BCMA therapy: Median PFS, 3.2 months (95% CI, 2.8 to NR)



No BCMA therapy: Median OS, 12.5 months (95% CI, 11.3 to NR)
BCMA therapy: Median OS, 7.4 months (95% CI, 7.3 to NR)

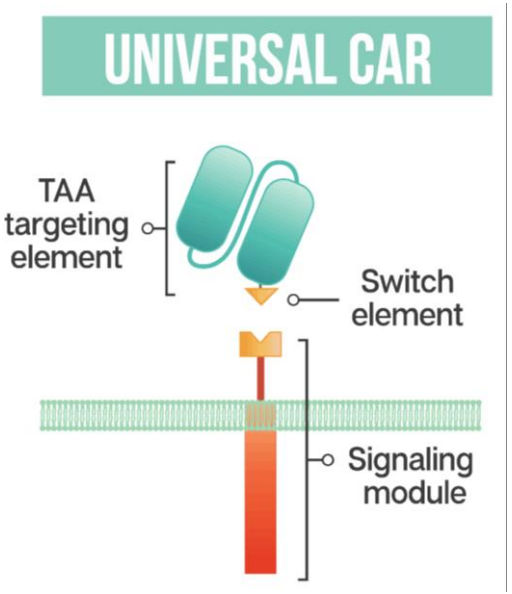


Hansen DK, Sidana S, Peres LC, et al. Idecabtagene Vicleucel for Relapsed/Refractory Multiple Myeloma: Real-World Experience From the Myeloma CAR T Consortium. J Clin Oncol. 2023;41(11):2087-2097. doi:10.1200/JCO.22.01365

Versorgung

Entwicklungsfelder

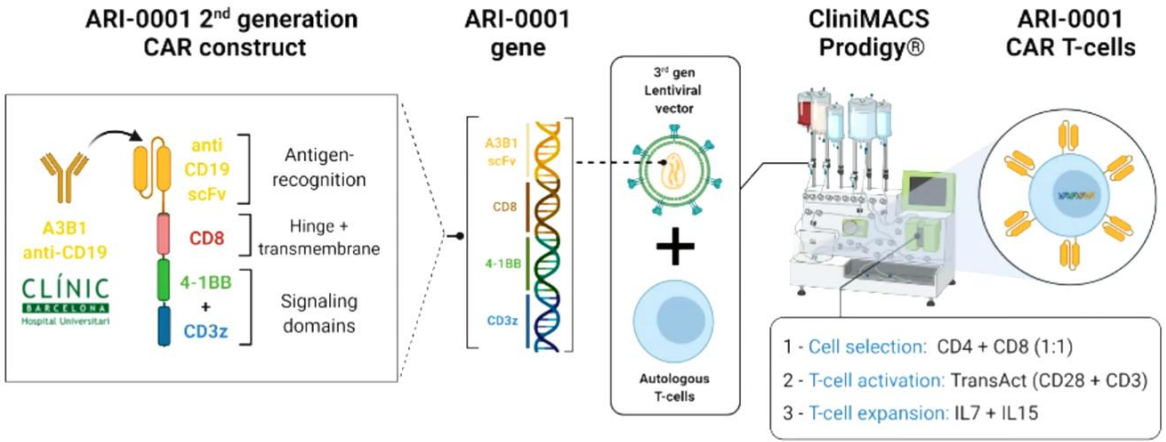
- Neue Antigene
- Neue Indikationen, z.B. solide Tumoren, Autoimmunität, Infekte
- Neue Effektorzellen, z.B. NK-Zellen, iNKT-Zellen
- Kontrolle über die CAR-T-Zellfunktion, z.B. Suicide Gene, modularer Aufbau
- Neue Herstellungsmethoden, z.B. Sleeping Beauty
- Kombinationstherapien
- Und, und, und



Sutherland, A.R.; Owens, M.N.; Geyer, C.R. Modular Chimeric Antigen Receptor Systems for Universal CAR T Cell Retargeting. Int. J. Mol. Sci. 2020, 21, 7222.

Academic CAR-T-cell production

ARI-0001 cells *(varnimcabtagene autoleucel [var-cel])*



Creatio | Production and validation center of advanced therapies UNIVERSITAT DE BARCELONA

Castella M, et al. *Mol. Ther.* 2019

EHA 2023: Presentation ID p296-3

Verfügbarkeit in Osteuropa

Availability & reimbursement

Country	Kymriah	Yescarta	Tecartus	First use	Centres	Pts treated*	NHL	p ALL
Bulgaria				--	--	--	--	--
Croatia				2020	1	28	24	4
Czech R.				2019	7	128	118	10
Estonia				--	--	--	--	--
Hungary				2023	2	1	0	1
Latvia				--	--	--	--	--
Lithuania				--	--	--	--	--
Poland				2021	6	82	57	25
Romania				2022	1	15	10	5
Slovakia				2023	3	0	0	0
Slovenia				2021	1	9	7	2

*By December 2022

Hajek. Presented at EHA-EBMT CART-cell meeting. Rotterdam. February 2023

EHA 2023: Presentation ID p296-3

SOHC
SWISS ONCOLOGY & HEMATOLOGY CONGRESS

BCMA-directed bispecific antibodies in plasmablastic lymphoma

Category: Clinical hemato-oncology

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1. Department of Medical Oncology and Hematology, University Hospital Zürich, Zürich, Switzerland, 2. Department of Hematology, Oncology, Clinical Immunology and Rheumatology, University Hospital Tübingen, Tübingen, Germany, 3. Infection Biology Laboratory, Department of Biomedicine, University of Basel, Basel, Switzerland, 4. Department of Pathology and Molecular Pathology, University Hospital Zürich, Zürich, Switzerland, 5. Department of Infectious Diseases and Hospital Epidemiology, University Hospital Zürich, Zürich, Switzerland, 6. Institute of Medical Virology, University of Zürich, Zürich, Switzerland, 7. Division of Infectious Diseases and Hospital Epidemiology, University and University Hospital Basel, Basel, Switzerland. *equally contributing senior authors.

Introduction

Plasmablastic lymphoma (PBL) is a rare and aggressive subtype of large B-cell lymphoma that primarily affects individuals with immunodeficiency, most of which are HIV positive. The prognosis of PBL is dismal as current treatment options have limited efficacy with reported median overall survival estimates of 6-32 months. PBL cells are characterized by immunoblastic or plasmablastic morphology and are thought to originate from plasmablasts, B-cells that have undergone somatic hypermutation and are differentiating to plasma cells. Their immunophenotype has features of terminal B-cell differentiation but is notable for the loss of the B-cell differentiation markers CD19, CD20, and PAX5, with frequent expression of IRF4/MUM1, CD38, CD138, BLIMP1, and XBP1.

In relapsed and refractory myeloma, bispecific antibodies that allow tumor cell killing by recruiting and activating T cells to BCMA and other antigens have emerged as very effective salvage treatment options. As PBL cells share many surface markers with plasma cells such as the B-cell maturation antigen (BCMA), which is present in almost all cases of PBL, these agents appear promising for the treatment of PBL as well. However, due to the rarity of the disease and exclusion of HIV-infected patients from most clinical trials, prospective studies on this treatment option are unlikely to be undertaken and efficacy might be hampered by the diminished quantitative and qualitative T-cell activity in these individuals.

Case report

A 33-year-old man with no previous medical history presented with exophytic oral lesions and axillary and cervical lymphadenopathy. Histopathological analysis of a palatinal biopsy revealed the diagnosis of PBL with EBV (EBER) association. Concomitantly, a diagnosis of HIV infection was made (C3, 181'000 HIV copies/ml, 108/µl CD4+ T helper cells). Antiretroviral therapy with bictegravir/emtricitabine/tenofovir was initiated together with V-DA-EPOCH (bortezomib plus dose-adjusted etoposide, prednisone, vincristine, cyclophosphamide and doxorubicin) resulting in complete remission after six cycles. Three months later, the palatal lesion recurred with lymphoma infiltration of the maxillary sinus (confirmed by biopsy, **Figure 1A-D**), as well as cervical lymph node and skeletal manifestations (**Figure 2A-C**).

As the PBL was refractory to second-line chemotherapy (ifosphosphamide, carboplatin, etoposide) and subsequent PD-L1 inhibitor treatment over 3 months despite 100% expression of PD-L1 on immunostaining (**Figure 1E**) and normalized CD4 cell counts, off-label treatment with teclistamab 1500 µg/kg weekly was initiated. However, BCMA expression on immunohistochemistry (clone E6D7B) stainings was low (**Figure 1F and G**). Apart from a grade II cytokine release syndrome after the first ramp-up dose, the treatment was well tolerated and resulted in complete remission after 6 weekly applications of the target dose (**Figure 2D**).

The patient proceeded to allogeneic stem cell transplantation (alloSCT). There was no human leukocyte antigen (HLA)-matched sibling, but seven HLA-matched, unrelated donors were identified, of which an HLA-matched unrelated donor (CMV D+/R+, EBV D+/R+) with heterozygous CCR5 Δ32 mutation with a high EBV T-cell response determined by IFN-γ Elispot was selected (donor 4, **Figure 3A**). The patient received alloSCT after reduced intensity conditioning with fludarabine and busulfan. Prophylaxis against graft-versus-host disease (GVHD) consisted of anti-thymocyte globuline, mycophenolate mofetil and cyclosporine. The patient engrafted successfully and post-transplant follow-up showed sustained complete remission with no GVHD at 6 months. Donor-derived EBV T-cell response showed high reactivity 27 days after alloSCT (**Figure 3B**).

Discussion

Given its rarity and aggressive behavior, treatment of PBL remains challenging with no clearly established standard of care. Here, we present the successful use of teclistamab in a refractory patient with HIV-associated EBV+ PBL as bridging therapy to alloSCT. Of note, in contrast to other reports expression of BCMA on immunohistochemical stainings was low, which might be due to technical issues or low levels of expression.

Currently, there is insufficient data to consider donor EBV serostatus in alloSCT for EBV-related lymphoma. However, donor-derived EBV-specific T-cell therapy has demonstrated remarkable success in treating highly immunogenic type 3 latency tumors, such as post-transplantation lymphoproliferative disorders, but is potentially less effective in less immunogenic type 1 and 2 latency lymphoma. Remarkably, our strategy yielded high donor EBV T-cell responses as early as one month after alloSCT.

Conclusion

- This case highlights the potential efficacy of teclistamab in relapsed and refractory HIV- and EBV-associated PBL and the importance of donor selection for alloSCT in EBV-positive lymphomas.
- Further research and prospective clinical trials are needed to define the most effective treatment strategies for this aggressive lymphoma subtype.

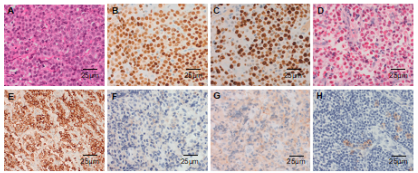

Figure 1. Histologic stains of plasmablastic lymphoma with (**A**) plasmablastic and immunoblastic morphology with enlarged nuclei and prominent nucleoli, H&E (400x). Immunohistochemistry demonstrates (**B**) high IRF4/MUM1 expression (400x), (**C**) high Ki-67 proliferation rate (400x), (**D**) EBER in situ hybridisation positivity (400x), (**E**) strong PD-L1 expression (400x) and (**F-G**) heterogenous low BCMA expression (400x). In contrast, a positive control of a different patient for BCMA in plasma cells of a reactive tonsil (**H**).

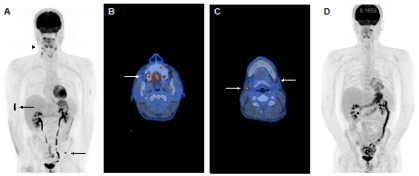

Figure 2. (**A**) PET-CT before teclistamab with PBL manifestations in the cervical lymph nodes and osseous lesions of the humerus, maxilla and iliac bone (arrows). Axial image of the primary lesions in the maxillary bone (**B**) and cervical lymph nodes (**C**, arrows). (**D**) PET-CT after treatment with almost complete normalization of the FDG-signal of all previously described lesions.

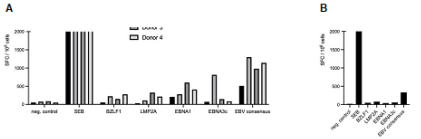

Figure 3. EBV T-cell response of (**A**) the 4 potential stem cell donors and (**B**) the patient 27 days after alloSCT as determined by IFN-γ Elispot using BZLF1, LMP2A, EBNA1, EBNA3c and EBV consensus (pool of 43 lyophilized MHC class I and class II restricted peptides, derived from 13 different EBV proteins). EBV peptide pools. Staphylococcal enterotoxin B (SEB) was used as positive control. SFC, spot forming cells.

USZ Universitäts Spital Zürich

Presented at SOHC 2023 from 22 – 24 November 2023

Zusammenfassung

- Die Entwicklung von zellulären Immuntherapien und CAR-T-Zellen blickt auf eine lange Geschichte zurück, hat aber in letzter Zeit stark an Dynamik gewonnen.

- 6 CAR-T-Zell-Produkte sind derzeit in der Schweiz für die Behandlung von lymphatischen Malignomen und des multiplen Myeloms zugelassen.

- Die Real World-Ergebnisse sind ähnlich wie die Daten der Zulassungsstudien, obwohl die Unterschiede hinsichtlich der Studienpopulation bemerkenswert sind.

- Die Versorgung mit CAR-T-Zellen ist komplex und der Zugang beschränkt.

Vielen Dank für die Aufmerksamkeit

Dominik Schneidawind
Leitender Arzt Blutstammzelltransplantation und Zelluläre Therapien
30.11.2023