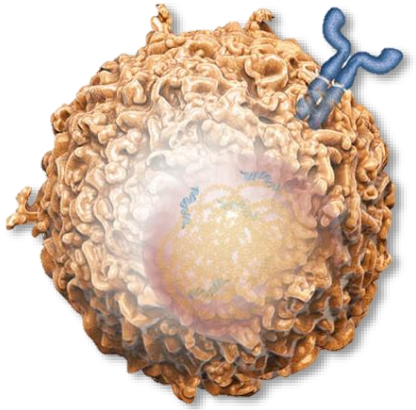
CAR T cells



voor de behandeling van diffuus grootcellig B non Hodgkin lymfoom

Mette D. Hazenberg, MD, PHD

AMC, Amsterdam

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

Communicated by Michael Sela, July 13, 1989 (received for review June 18, 1989)

into T cells from any individual. Upon returning the cells to their donors, they should manifest the specificity of the cTcR by proliferating and mediating specific effector function (cytolysis, production of lymphokines, help, or suppression) when encountering their target cells. **This approach can be exploited, for example, to direct cytotoxic T lymphocytes to kill tumor or virally infected cells. Construction of cTcRs with anti-tumor specificity will enable testing of the feasibility of this approach in combating human tumors.**

Clin Cancer Res 2006;12(20) October 15, 2006

A Phase I Study on Adoptive Immunotherapy Using Gene-Modified T Cells for Ovarian Cancer

Michael H. Kershaw,[1,3,4] Jennifer A. Westwood,[1,3] Linda L. Parker,[1] Gang Wang,[1,5] Zelig Eshhar,[6] Sharon A. Mavroukakis,[1] Donald E. White,[1] John R. Wunderlich,[1] Silvana Canevari,[7] Linda Rogers-Freezer,[1] Clara C. Chen,[2] James C. Yang,[1] Steven A. Rosenberg,[1] and Patrick Hwu[1,5]

VOLUME 24 · NUMBER 13 · MAY 1 2006

JOURNAL OF CLINICAL ONCOLOGY

CORRESPONDENCE

Treatment of Metastatic Renal Cell Carcinoma With Autologous T-Lymphocytes Genetically Retargeted Against Carbonic Anhydrase IX: First Clinical Experience

Cor H.J. Lamers, Stefan Sleijfer, Arnold G. Vulto, Wim H.J. Kruit, Mike Kliffen, Reno Debets, Jan W. Gratama, and Gerrit Stoter

Departments of Medical Oncology, Pharmacy, and Pathology, Erasmus University Medical Center–Daniel den Hoed Cancer Center, Rotterdam, the Netherlands

Egbert Oosterwijk

Department of Experimental Urology, University Medical Center, Nijmegen, the Netherlands

BLOOD, 15 SEPTEMBER 2008 • VOLUME 112, NUMBER 6

Adoptive immunotherapy for indolent non-Hodgkin lymphoma and mantle cell lymphoma using genetically modified autologous CD20-specific T cells

Brian G. Till,[1,2] Michael C. Jensen[3], Jinjuan Wang,[1] Eric Y. Chen,[1] Brent L. Wood,[4] Harvey A. Greisman,[4] Xiaojun Qian,[1] Scott E. James,[1] Andrew Raubitschek,[5] Stephen J. Forman,[6] Ajay K. Gopal,[1,2] John M. Pagel,[1,2] Catherine G. Lindgren,[2] Philip D. Greenberg,[1,2] Stanley R. Riddell,[1,2] and Oliver W. Press[1,2]

[1]Clinical Research Division of the Fred Hutchinson Cancer Research Center, Seattle, WA; [2]Department of Medicine, University of Washington, Seattle; [3]Department of Pediatric Hematology-Oncology, City of Hope National Medical Center and Beckman Research Institute, Duarte, CA; [4]Department of Laboratory Medicine, University of Washington, Seattle; and [5]Department of Radioimmunotherapy and [6]Division of Hematology and HCT, City of Hope National Medical Center and Beckman Research Institute, Duarte, CA

The New York Times

A Breakthrough Against Leukemia using altered T cells

In Girl's Last Hope, Altered Immune Cells Beat Leukemia

NY Times, 9 december 2012

Currently recruiting CAR T cell therapy trials by antigen.

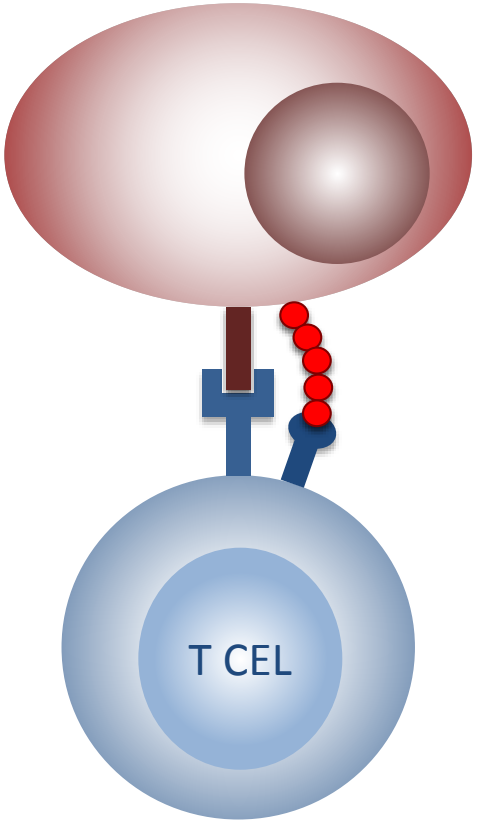
Center	Disease	Patients	Co-stimulation	Gene transfer	Notes	Clinicaltrials.gov identifier
BCMA						
NCI	MM	18–73	NA	NA		NCT02215967
CD19						
MSKCC	CLL	>18 yo	*CD28*	RV	Dose-escalation	NCT00466531
BCM	B-cell malignancy	Any	*CD28*	RV	With ipilimumab	NCT00586391
BCM	B-cell malignancy	Any	*CD28*	RV	Dose escalation	NCT00608270
BCM	B-cell malignancy	Any	*CD28*	RV	After AlloHCT, viral co-specificity	NCT00840853
NCI	B-cell malignancy	18–68	*CD28*	RV	With IL2	NCT00924326
MDACC	B-cell lymphoma	18–65			With or without IL2	NCT00968760
MSKCC	B-ALL	>18 yo	*CD28*	RV		NCT01044069
NCI	B-cell malignancy	18–75	*CD28*	RV	Post alloHCT; active GVHD not allowed	NCT01087294
MSKCC	CLL	>18 yo	*CD28*	RV	Upfront therapy	NCT01416974
MSKCC	B-ALL	<19 yo	*CD28*	RV	After AlloHCT, viral co-specificity	NCT01430390
Manchester, UK	B-cell malignancy	>18 yo	*None*	RV		NCT01493453
MDACC	B-cell malignancy	1–65			After AlloHCT	NCT01497184
NCI	B-cell malignancy	1–30 yo	*CD28*	RV		NCT01593696
CHOP	CD19 + leukemia & lymphoma	1–24 yo	*4-1BB*	LV		NCT01623495
Seattle Children's	$CD19^+$ ALL	Age 1–26			$EGFR^+$ construct (may allow deletion)	NCT01683279
Penn	CLL/SLL	>18y	*4-1BB*	LV	2 dose level comparison	NCT01747486
MSKCC	Aggressive B-NHL, relapsed/refractory	18–70	*CD28*	RV	After autologous SCT	NCT01840566
BCM	B-cell malignancy	Up to 75 yo	*CD28+/− 4-1BB*	RV		NCT01853531
MSKCC	B-ALL	<26 yo	*CD28*	RV		NCT01860937
Beijing	B-cell malignancy	5–90 yo	*4-1BB*	RV		NCT01864889
FHCRC	B-cell malignancy	>18y	*4-1BB*	LV		NCT01865617
Penn	B-cell NHL	>18 yo	*4-1BB*	LV		NCT02030834
Seattle Children's	B-ALL	NA	*4-1BB*	LV	$EGFR^+$ construct (may allow deletion)	NCT02028455
Penn	B-ALL	>18 yo	*4-1BB*	LV		NCT02030847
BCM	B-cell malignancy	NA	*CD28*	RV	After AlloHCT	NCT02050347
Beijing	Mantle cell lymphoma	50–80	*4-1BB*	RV		NCT02081937
Sweden	B-cell malignancy	>18 yo	*CD28 and 4-1BB*	RV		NCT02132624
Japan	B cell NHL	20–70	*CD28*	RV		NCT02134262
COH	ALL	>18	*CD28*	LV		NCT02146924
Beijing/Florida	B-cell lymphoma	>18	*CD27*	LV	Caspase 9 suicide gene	NCT02247609
Penn	Hodgkin	>18	*4-1BB*	RNA		NCT02277522
Kite/COH	NHL	>18	*NA*	NA		NCT02348216
Southwest Hospital, China	B-cell malignancy	18–70	*NA*	NA		NCT02349698
Shenzhen	B-cell malignancy	1–85	*CD28*	LV		NCT02456350
CD20						
Beijing	B cell NHL	18–90	*4-1BB*	RV		NCT01735604
CD22						
NCI	B-cell malignancies	1–30	*4-1BB*	LV		NCT02315612
CD30						
BCM	Hodgkin and NHL		*CD28*	RV		NCT01316146
Beijing	CD30 + lymphoma	16–80	*NA*	NA		NCT02259556
CD33						
Beijing	AML	5–90 yo	*4-1BB*	LV		NCT01864902
CD138						
Beijing	Myeloma	18–80 yo	*4-1BB*	LV		NCT01886976
CD171						
Seattle	Neuroblastoma	<18	*CD28 and 4-1BB*	LV		NCT02311621
CEA						
Southwest Hospital, China	CEA + malignancies	18–70	*NA*	NA		NCT02349724
EGFR						
Beijing	EGFR + solid tumors	18–80 yo	*4-1BB*	LV		NCT01869166
Renji Hospital	GBM	NA	*NA*	NA		NCT02331693
EGFRvIII						
NCI	GBM	18–66	*CD28*	RV		NCT01454596
Penn/UCSF	GBM	>18	*4-1BB*	LV		NCT02209376
ErbB						
London	Head & Neck cancer	>18 yo	*CD28*	RV	Intratumoral	NCT01818323
FAP						
Zurich	Mesothelioma	18–75	*NA*	RV		NCT01722149
GD2						
Kansas	Neuroblastoma	1.5–17 yo	*None*	RV	Multivirus-specific	NCT01460901
BCM	Neuroblastoma		*CD28 and OX40*		Suicide gene	NCT01822652
BCM	Sarcoma		*CD28 and OX40*	RV	Suicide gene, Co-specificity for VZV	NCT01953900
NCI	GD2 + solid tumors excluding neuroblastoma	1–35 yo	*CD28 and OX40*		Suicide gene	NCT02107963
Glypican 3						
Renji Hospital	HCC	18–70	*NA*	NA		NCT02395250
Her2						
BCM	Sarcoma		*CD28*	RV		NCT00902044
BCM	GBM		*CD28*	RV	Co-specificity for CMV	NCT01109095
BCM	Lung cancer	>3 yo			TGFbeta resistance, Co-specificity for EBV	NCT01889954
Beijing	Her2 + solid tumors	18–80 yo	*4-1BB*	LV		NCT01935843
IL13Ra2						
BCM	GBM	18–75	*4-1BB*	RV	Intracranial administration	NCT02208362
Kappa light chain						
BCM	B-cell malignancy or myeloma		*CD28*	RV		NCT00881920
Mesothelin						
Penn	Mesothelin-expressing cancer	>18	*4-1BB*	LV		NCT02159716
Penn/UCSF	Pancreatic	>18	*4-1BB*	LV	Combined with anti-CD19 CAR T cells	NCT02465983
NKG2D ligands						
DFCI	AML, MDS, MM	18 yo or older	*NA*	NA		NCT02203825

Huidige situatie:

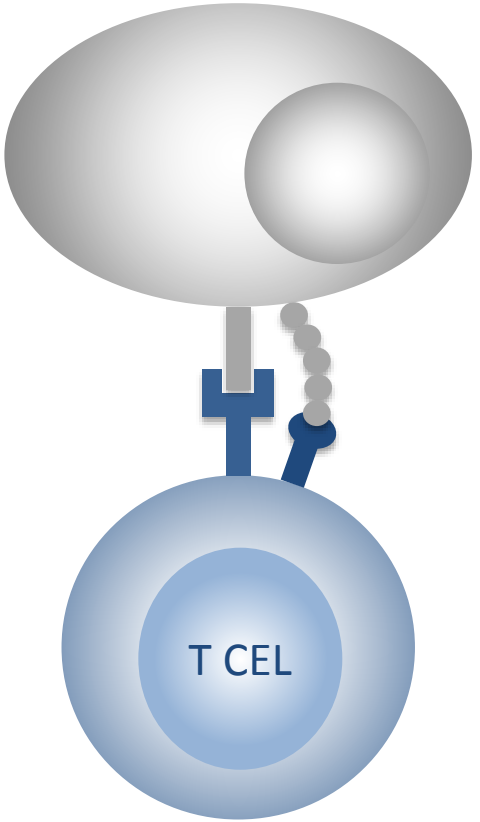
- > 65 trials
- merendeels CD19+ CAR T cells

Gill ea, Blood Reviews, 2016

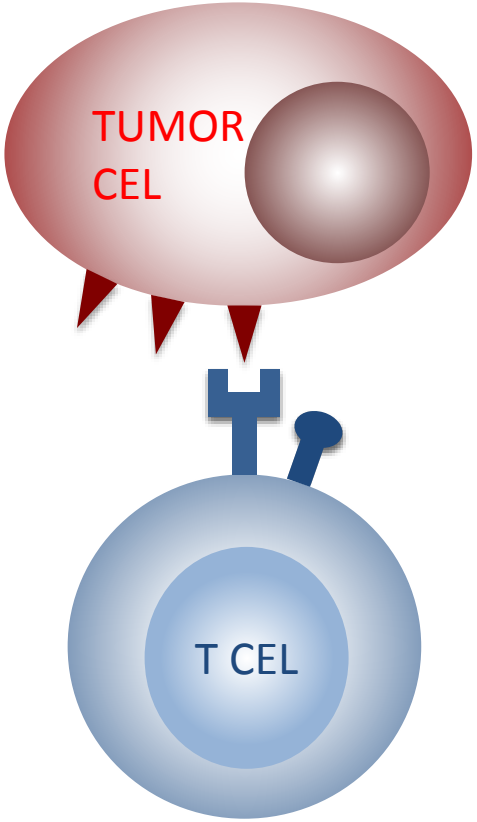
Normale T cel activatie: signaal 1 en signaal 2



Tumor cellen ontsnappen aan het immuunsysteem

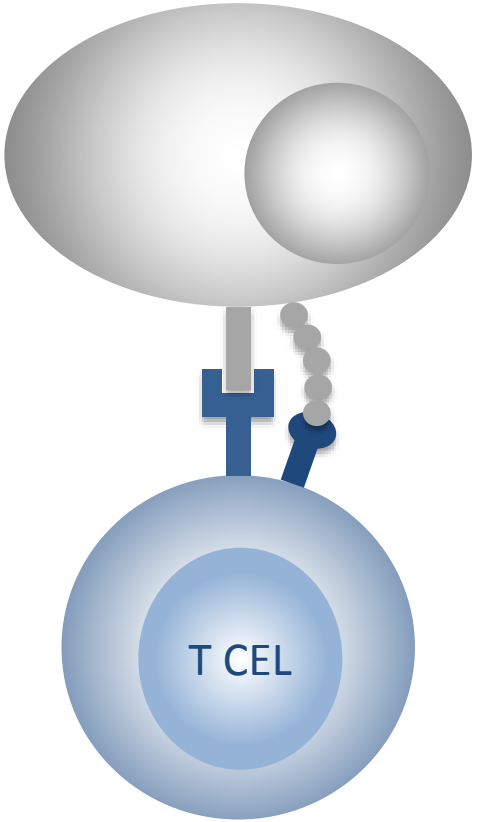


T cel activatie:
signaal 1 en 2

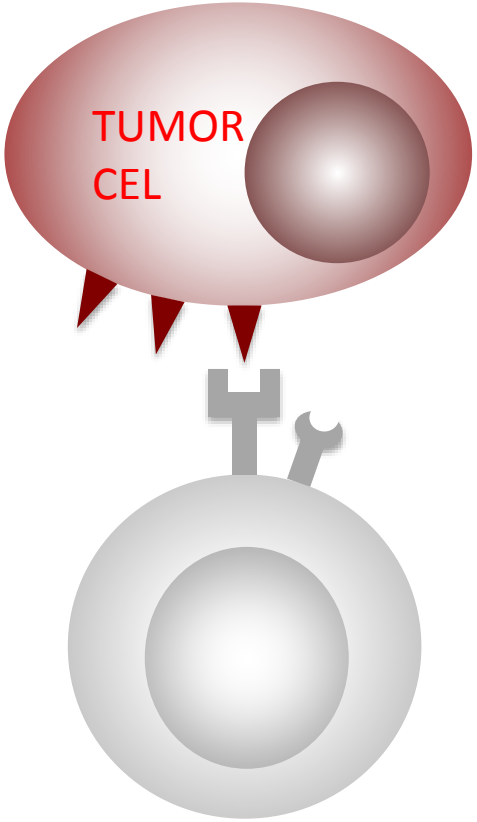


Geen signaal 1 / 2:
geen activatie

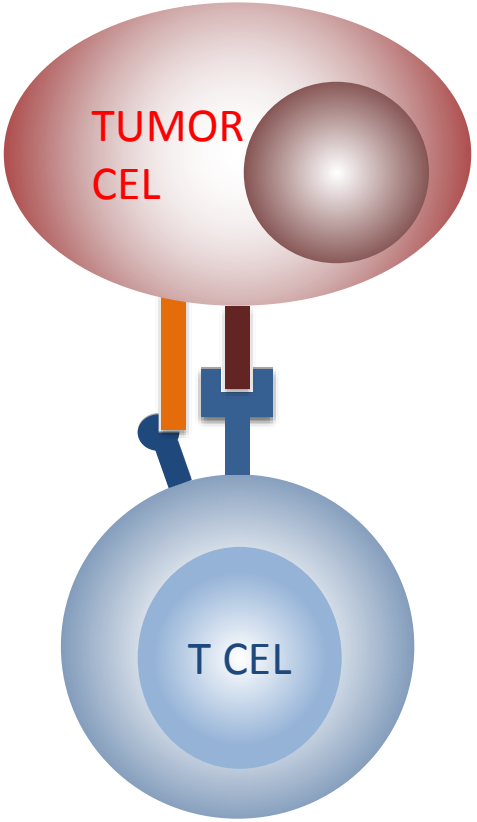
Tumor cellen ontsnappen aan het immuunsysteem



T cel activatie:
signaal 1 en 2



Geen signaal 1 / 2:
geen activatie



Inhiberend signaal:
geen activatie

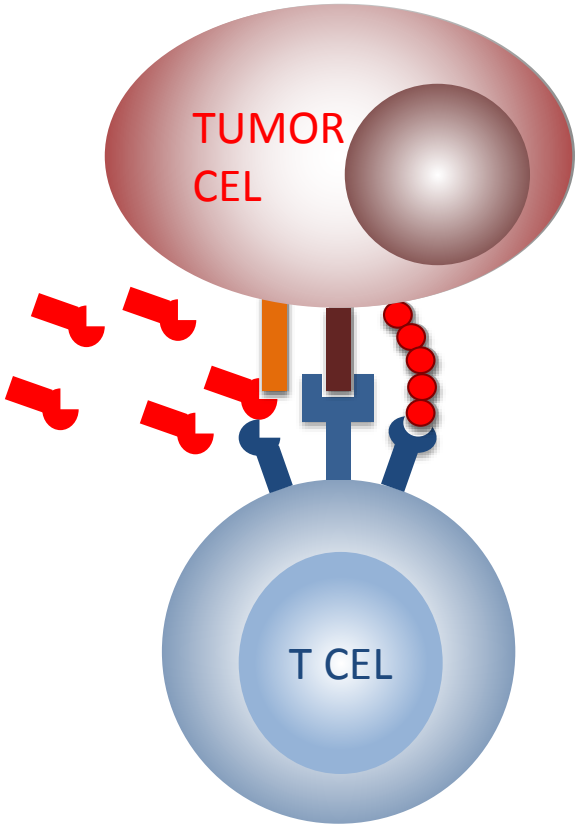
Tumor immuno-therapie (1): opheffen van de blokkade

‘Checkpoint inhibitors’ / PD1 blokkade:

- bokkeert de interactie tussen PD-1 op de T cel en PDL-1 op de tumor
- daardoor opheffing van het immuun suppressieve signaal van deze interactie → T cel activatie

Voorbeelden:

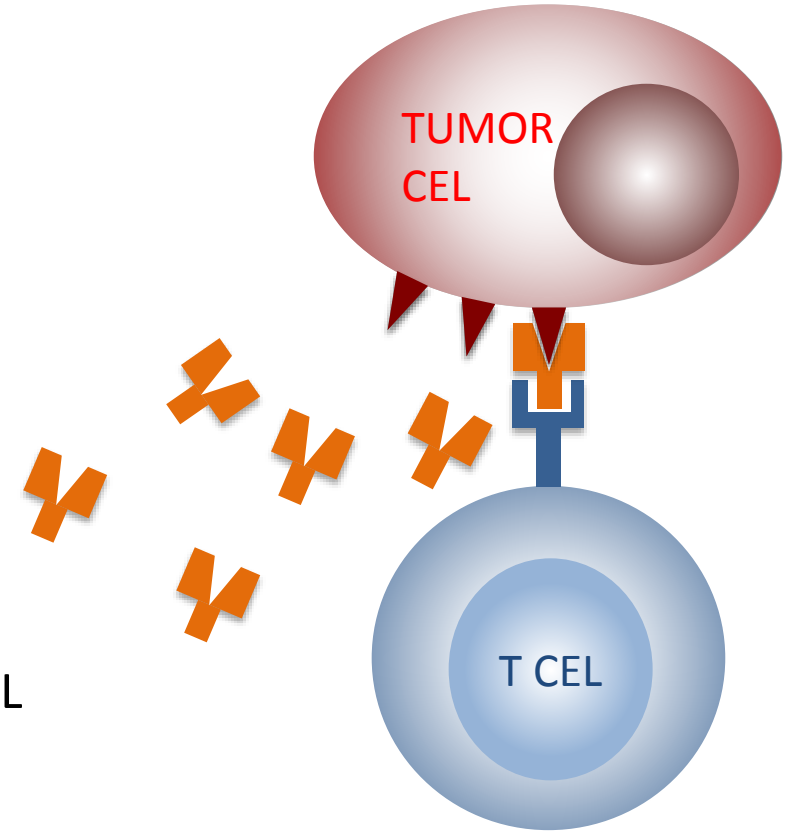
- Pembrolizumab (Keytruda)
- Nivolumab (Opdivo)



Tumor immuno-therapie (2): recruteren van T cellen

Recruteren van T cellen:

- BiTE: bispecific T cell engager
- brengt T cel bij tumor cel waardoor tumor cel gedood wordt



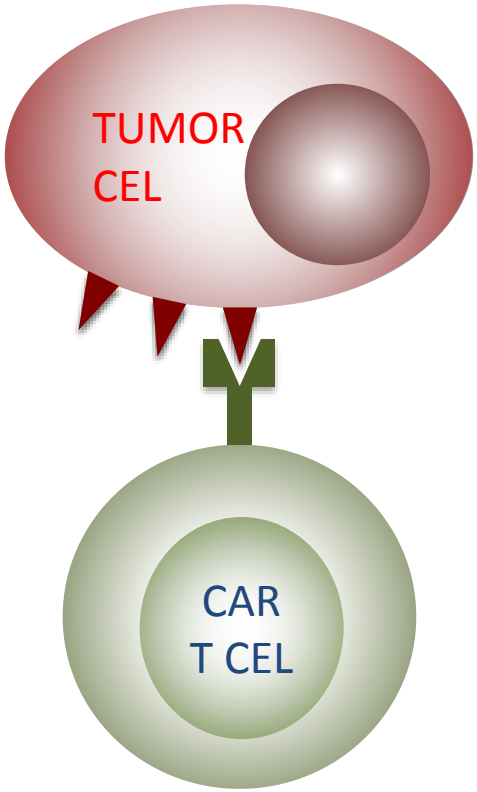
Voorbeelden:

- Blinatumomab (Blincyto): CD19+ ALL

Tumor immuno-therapie (3): CAR T cells

CAR T cells:

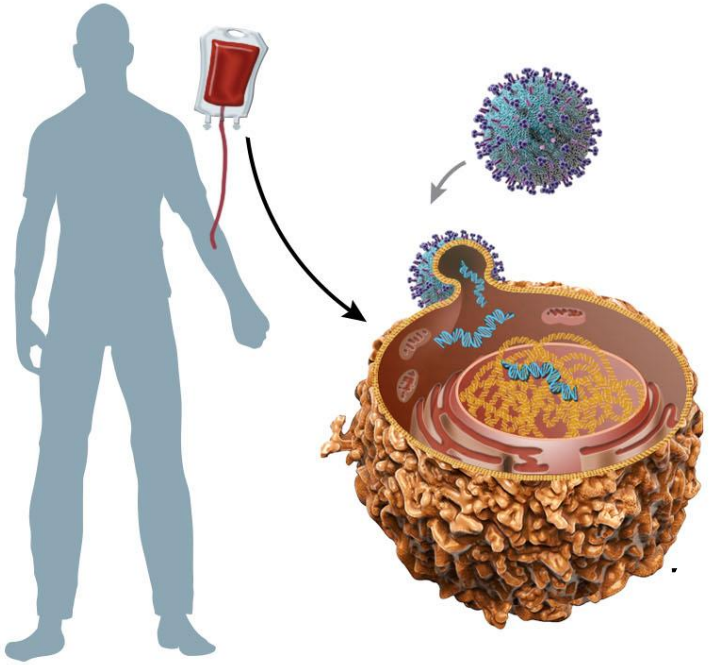
- Chimeric antigen receptor T cell
- Ex vivo genetisch gemodificeerde tumorspecifieke cytotoxische T cel



Voorbeelden:

- KTE-C19 (Kite Pharma): DLBCL
- JCAR015 & 017 (Juno): CD19+ ALL, CLL, B-NHL
- CTL019 (Novartis): CD19+ ALL, CLL, DLBCL, folliculair B-NHL

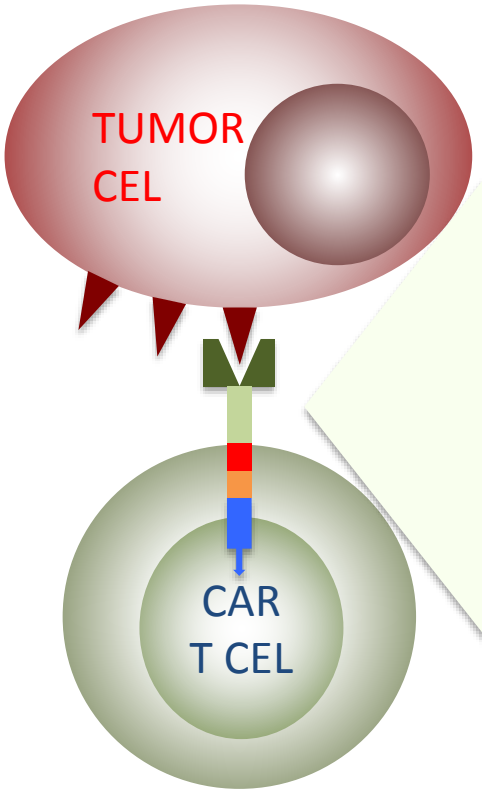
CAR T cells: productie



T cellen geïsoleerd uit patiënt

Introductie CAR proteins via virus of andere technieken in T cel

CAR T cells: design



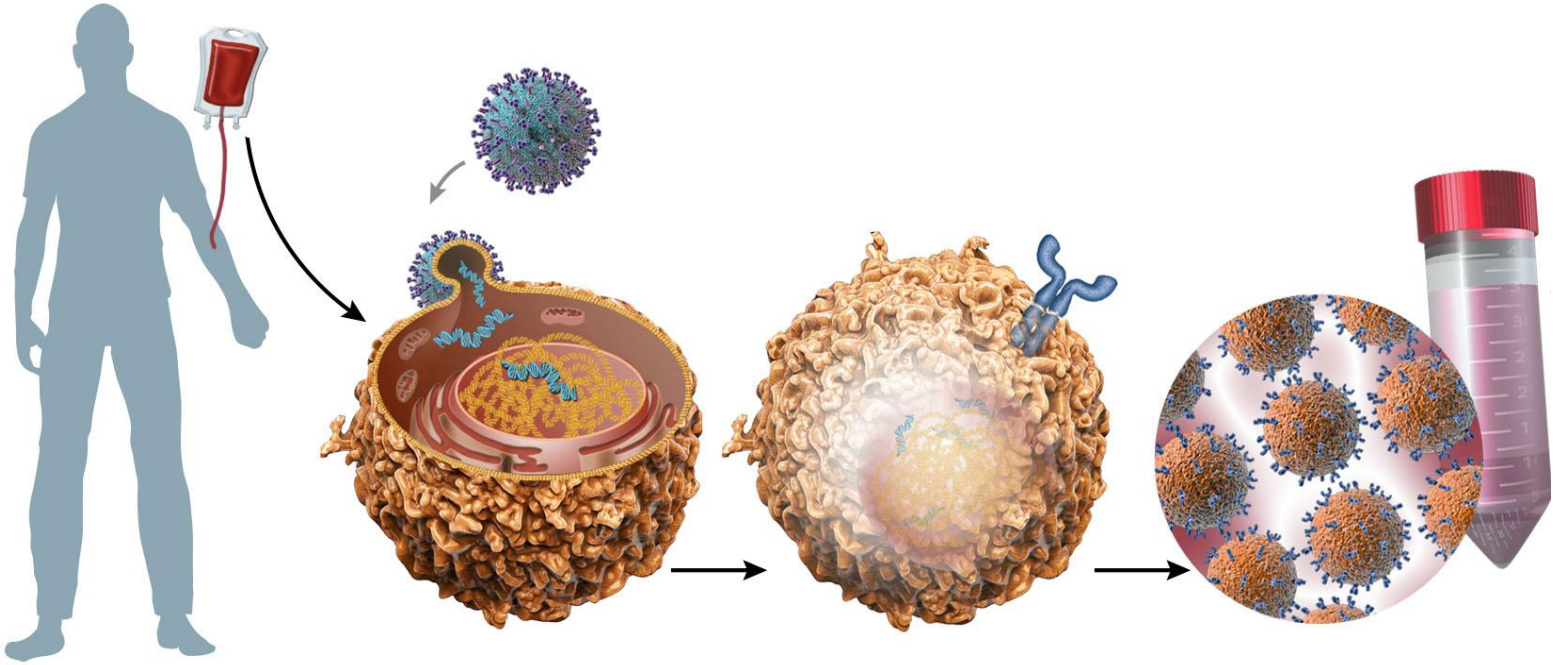
Antigeen: protein, glycoprotein, glycolipids
(niet intracellulair)

scFv: single chain variable fragments
- Linker: lengte is van belang
- Hinge: meestal van CD8 of IgG4

1 of 2 co-stimulataire moleculen:
CD28, ICOS, 4-1BB (CD137), OX40

CD3 of FcRγ zeta keten voor signaal
transductie naar kern

CAR T cells: productie



T cellen geïsoleerd uit patiënt

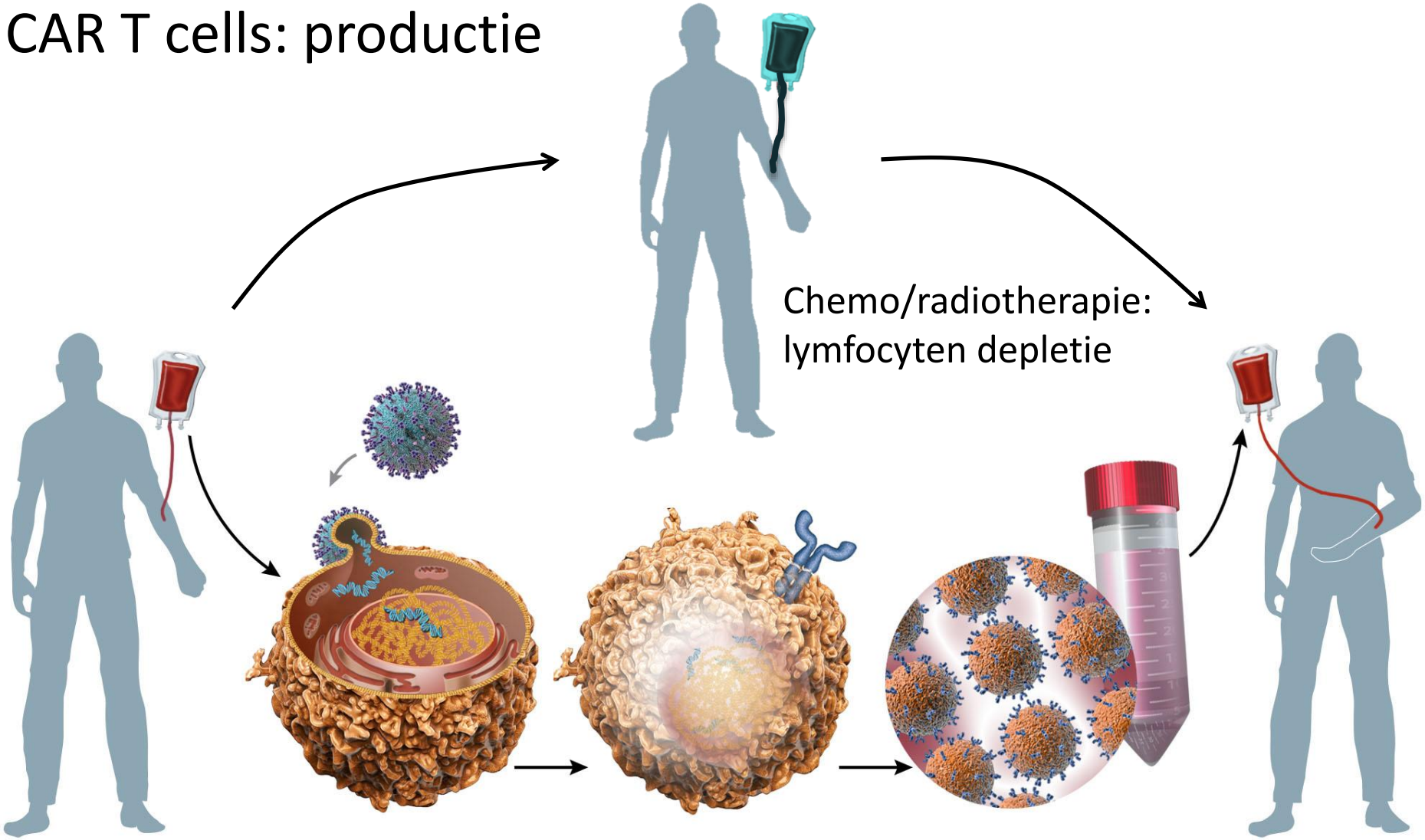
Introductie CAR proteins via virus of ander systeem in T cel

CAR T cel

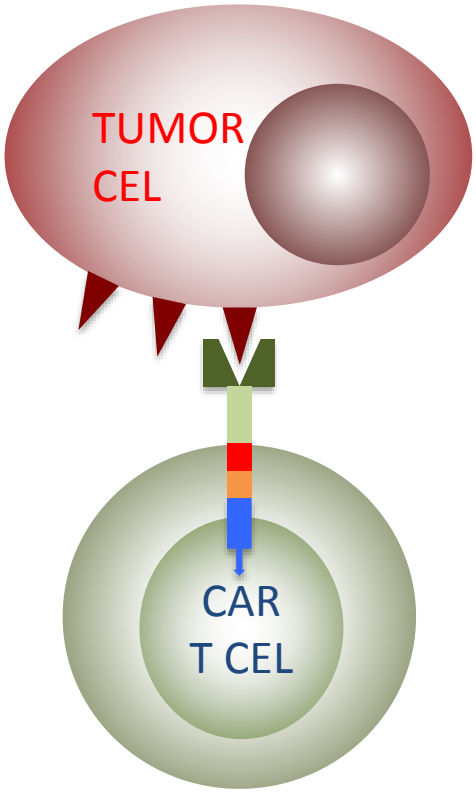
Expansie

10 dagen

CAR T cells: productie



CAR T cells: werkzaamheid

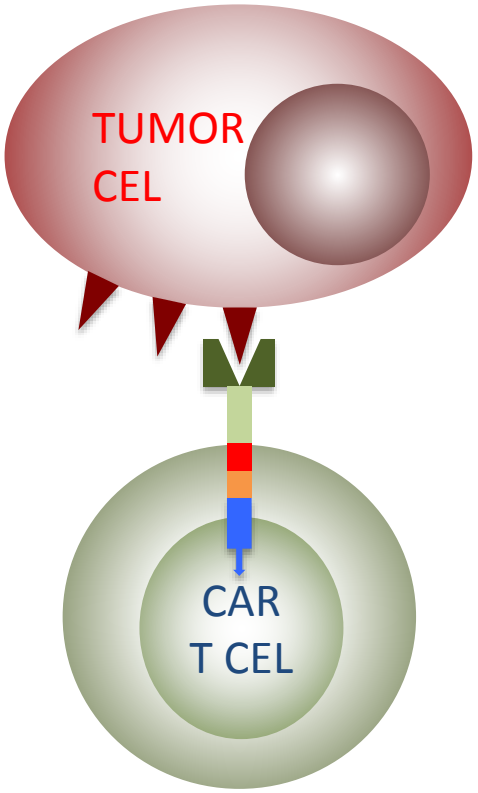


- CAR T cel design: co-stimulatie, cytokine productie, specificiteit antigeenreceptor

- inhiberende factoren in tumor environment (PD1, Tregs)

- levensduur CAR T cells

CAR T cells: bijwerkingen



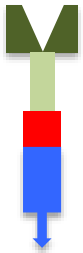
Cytokine release syndrome (CRS):
- koorts, hypotensie, vascular leakage, spierpijnen, gewrichtspijnen
- te behandelen met IL-6 inhibitor tocilizumab

Tumorlysis syndroom

Neurologische klachten:
- afasie, verwardheid, parese, insulten
- oorzaak onduidelijk
- i.h.a. spontaan en volledig herstel

CAR T cells:
1e gepubliceerde trial diffuus grootcellig B- NHL

Patiënt	Leeftijd (jr)	Cyclofosfamide (mg/kg)	Aantal CAR T ($x10^6$/kg)	Respons e	Duur (mnd)
1	43	60	5		22+
2	30	120	2.5	CR	
3	42	60	2.5	NE	9+
4	44	60	2.5	CR	12+
5	38	120	2.5	CR	1
6	58	60	1	SD	1
7	60	60	1	PR	
8	43	60	1	NE	6
9	64	60	1	CR	6+
				PR	

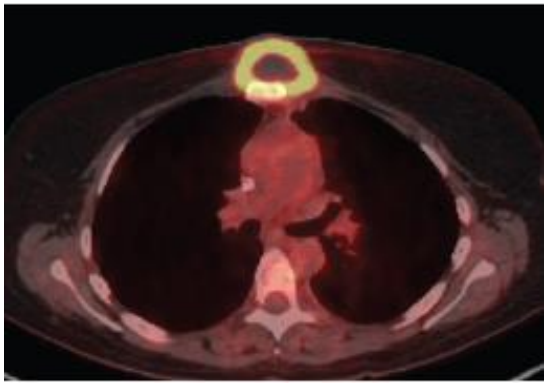


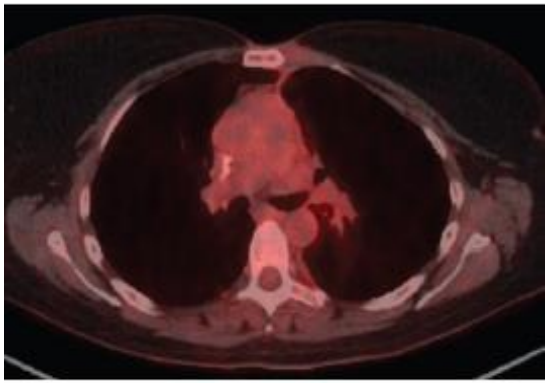
co-stimulatoir signaal: CD28

Kochendorfer ea, JCO, 2015

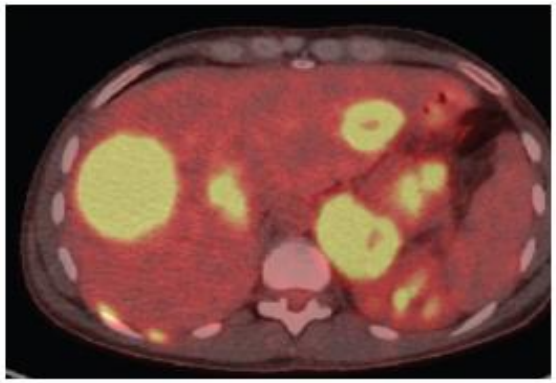
CAR T cells:
4 van de 7 evalueerbare patiënten complete remissie

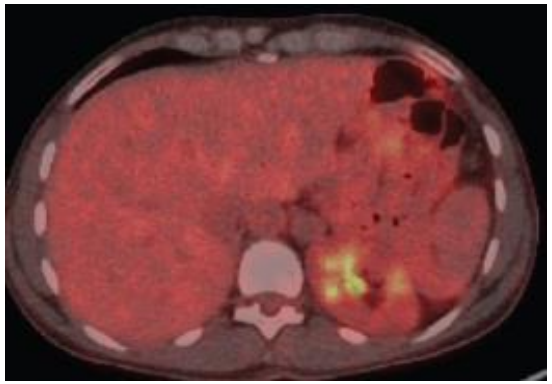
patient 1



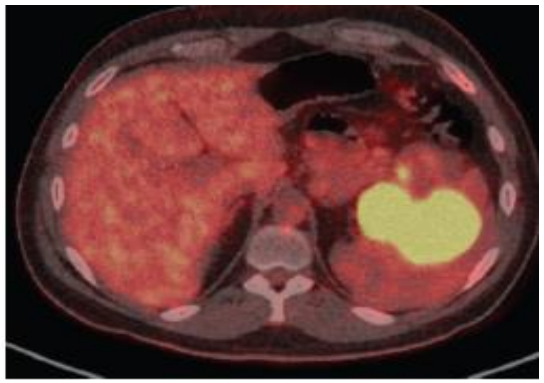


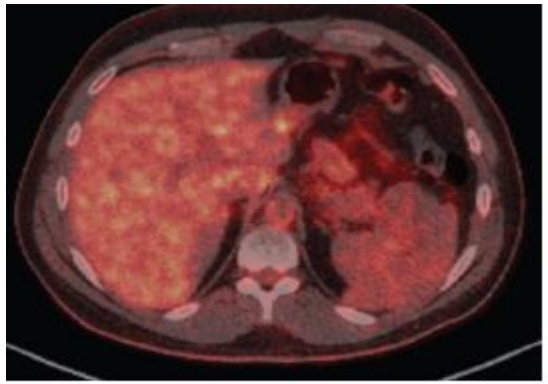
patient 4





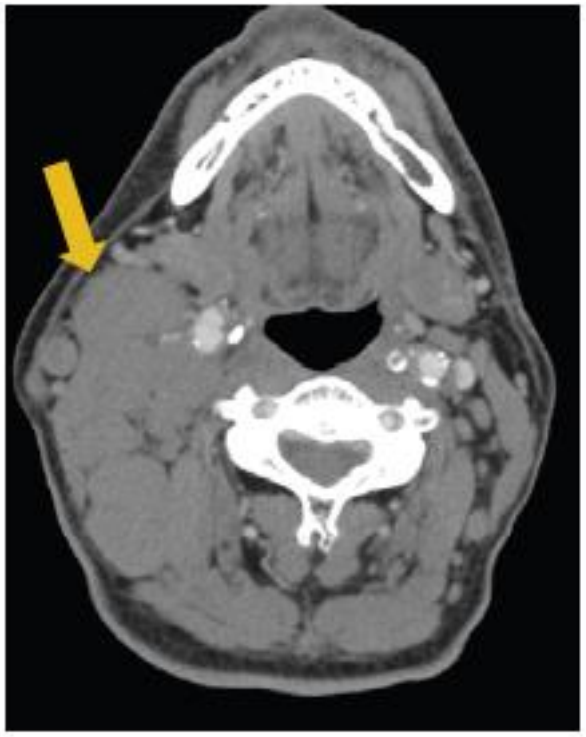
patient 8

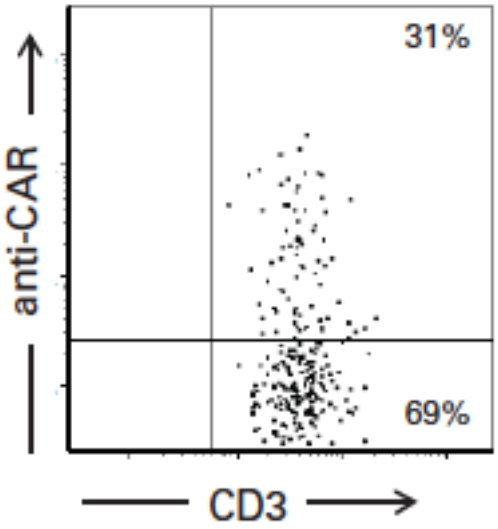




Kochendorfer ea, JCO, 2015

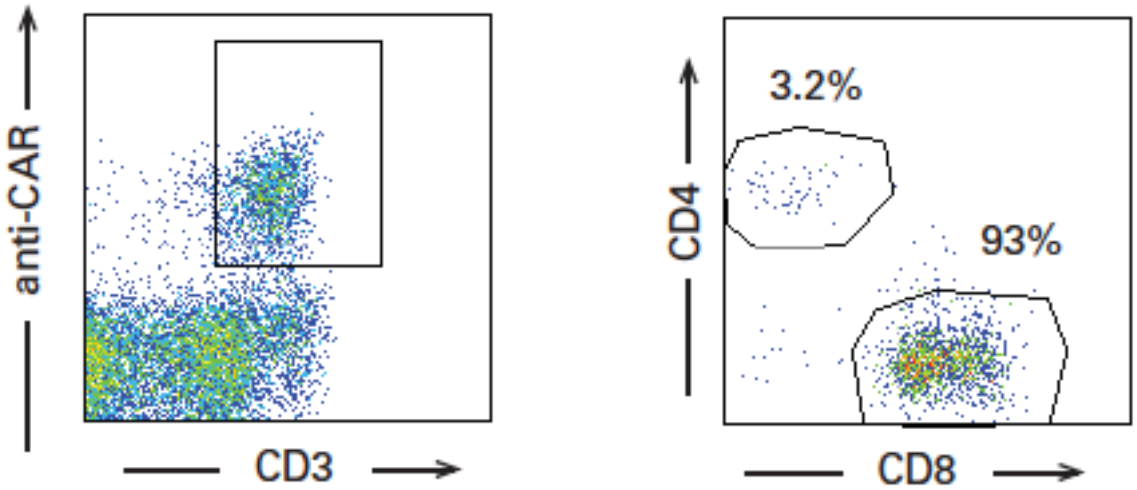
CAR T cells: aantoonbaar in tumor





Kochendorfer ea, JCO, 2015

CAR T cells: merendeels cytotoxische T cellen



Kochendorfer ea, JCO, 2015

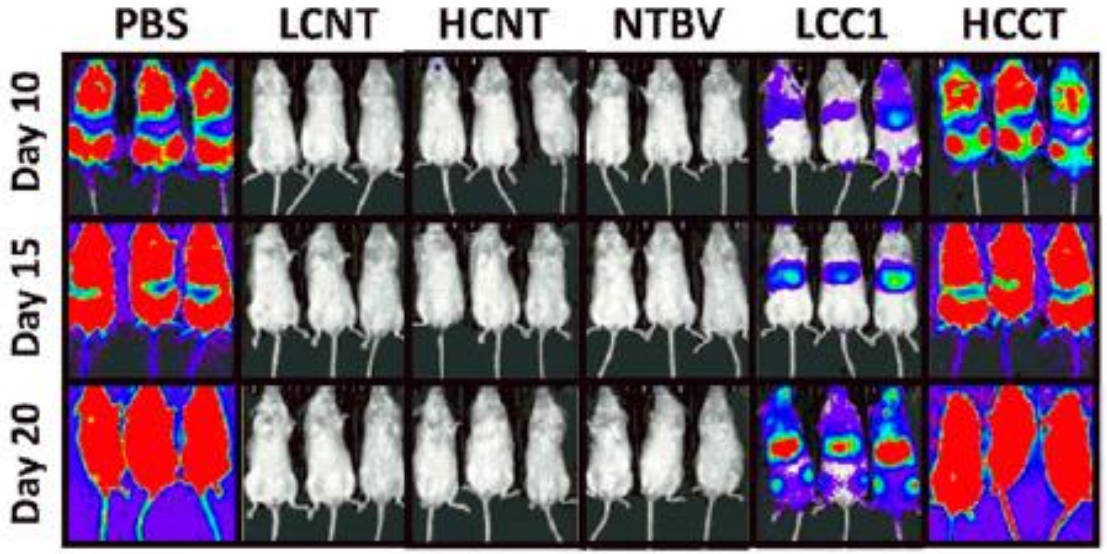
CAR T cells: de toekomst

Verbeteren en verbreden werkzaamheid

- door combinatie therapie met checkpoint inhibitors (bv CLL)
- post-allogene hematopoietische stamceltransplantatie
- ‘bridge to..’?

Toepassing voor CD19^{-} hematologische maligniteiten

- identificatie van tumor-specifieke targets (AML, myeloom)
- ‘uitzetten’ van CAR T cellen d.m.v. ‘switch’



Rodgers ea, PNAS, 2016