Immune Effector Cells
The CAR-T revolution

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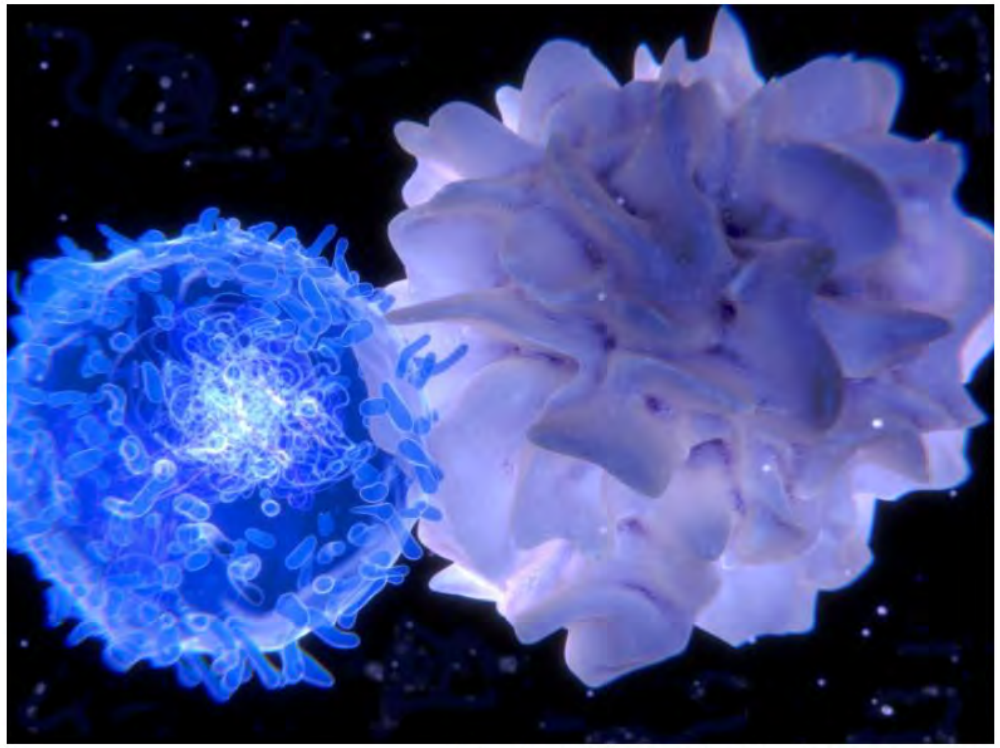
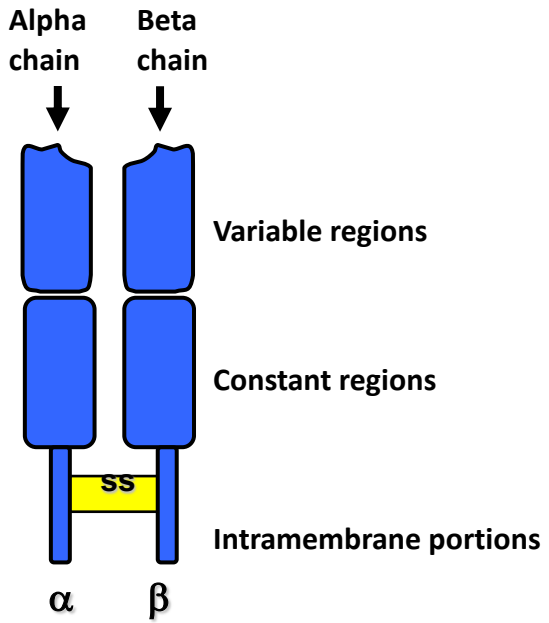
Disclosures

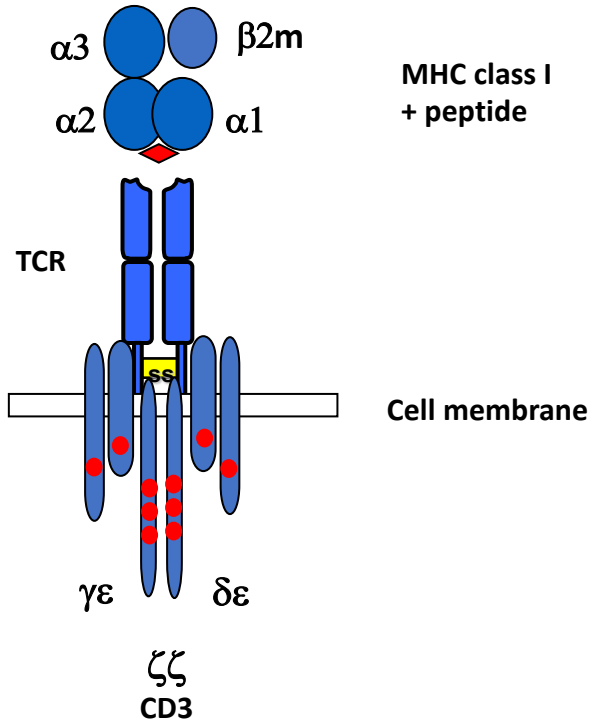
- Educational support – Kite, a Gilead Company, Novartis
- Consultancy – Sanofi, Celgene

T cell Activation & Specificity



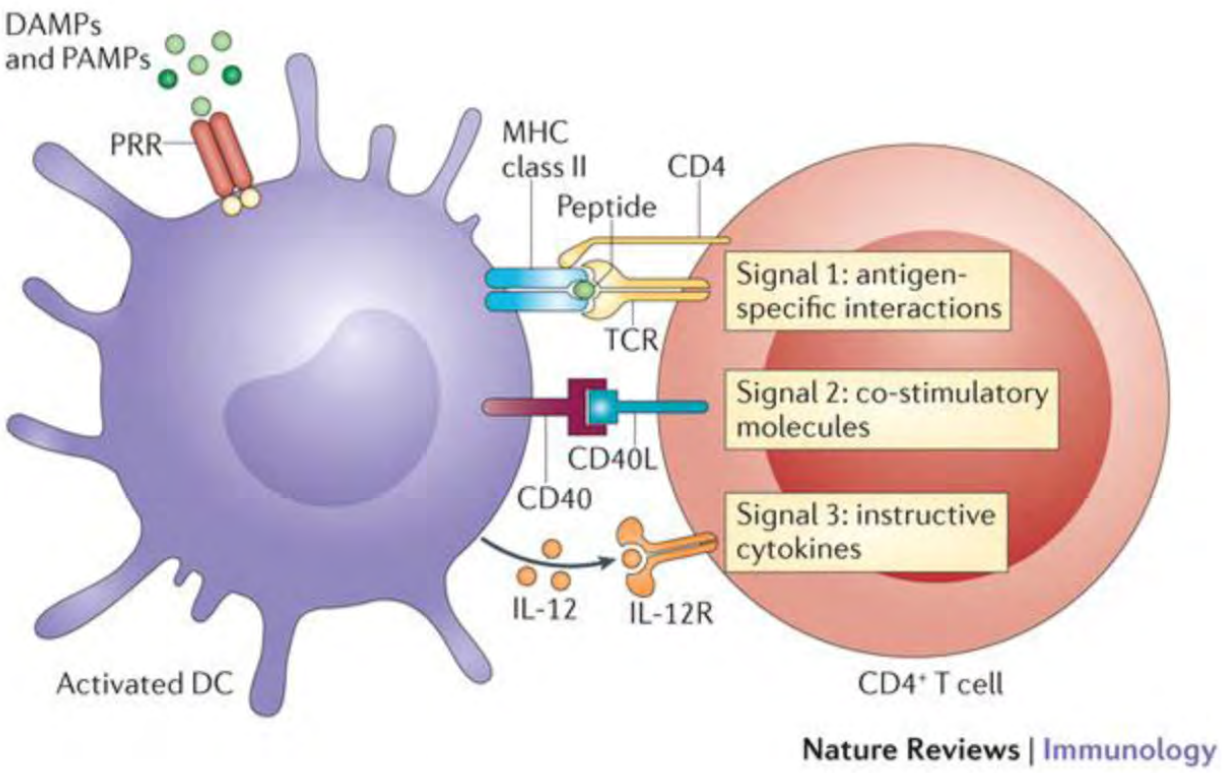
(Credited: Shutterstock - Juan Gaertner)

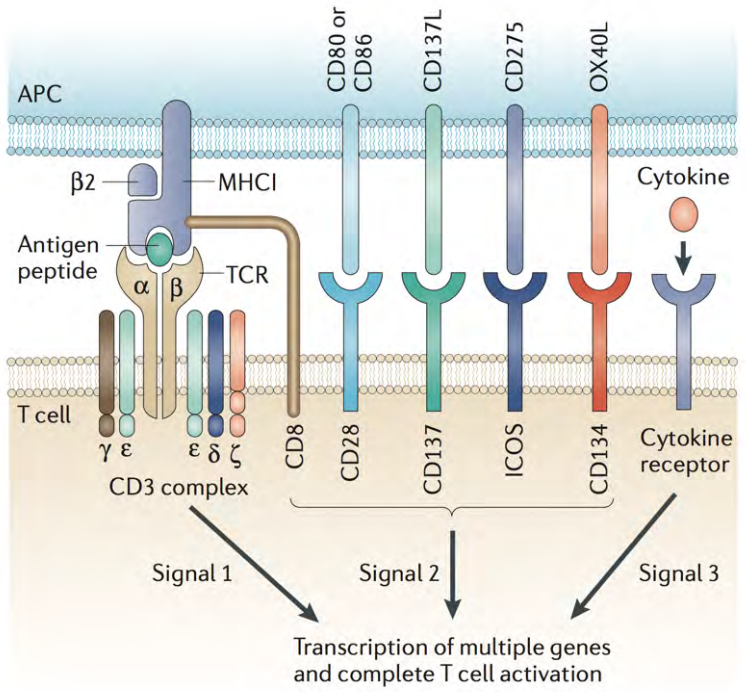




The TCR

Signals 1, 2 and 3





Nature Reviews Cancer **13**, 525–541 (2013)
Nature Reviews Immunology 14, 719-730

Evidence for T cell immunotherapies

The allo response

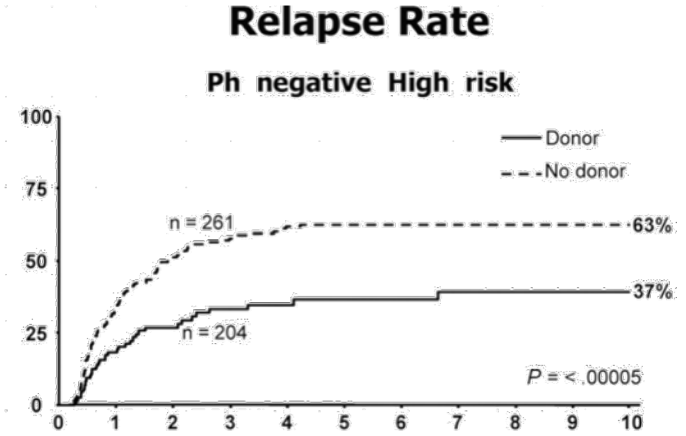
Long term remissions post allo-HSCT

Ag-specific T cells

Effective vs viruses (eg. CMV, Adeno, EBV)

Immune surveillance

Increased malignancies; Checkpoint inhibitors

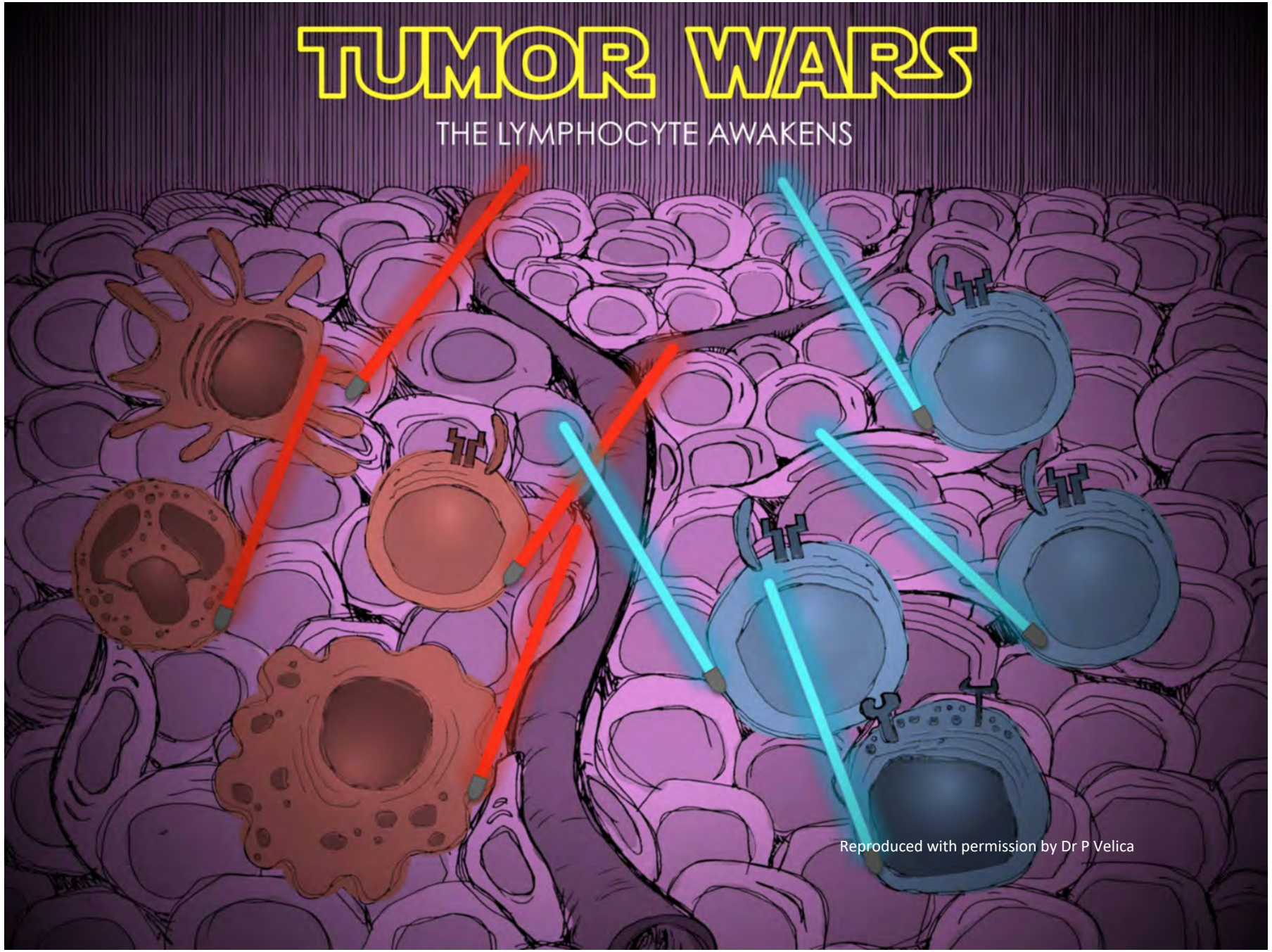


Donor-attributable reduction in relapse

GVL effect mediated by Donor T cells

Goldstone et al, Blood 2008 (UKALLXII/ECOG2993)

Current Therapy for Cancer


TUMOR WARS
THE LYMPHOCYTE AWAKENS
Reproduced with permission by Dr P Velica

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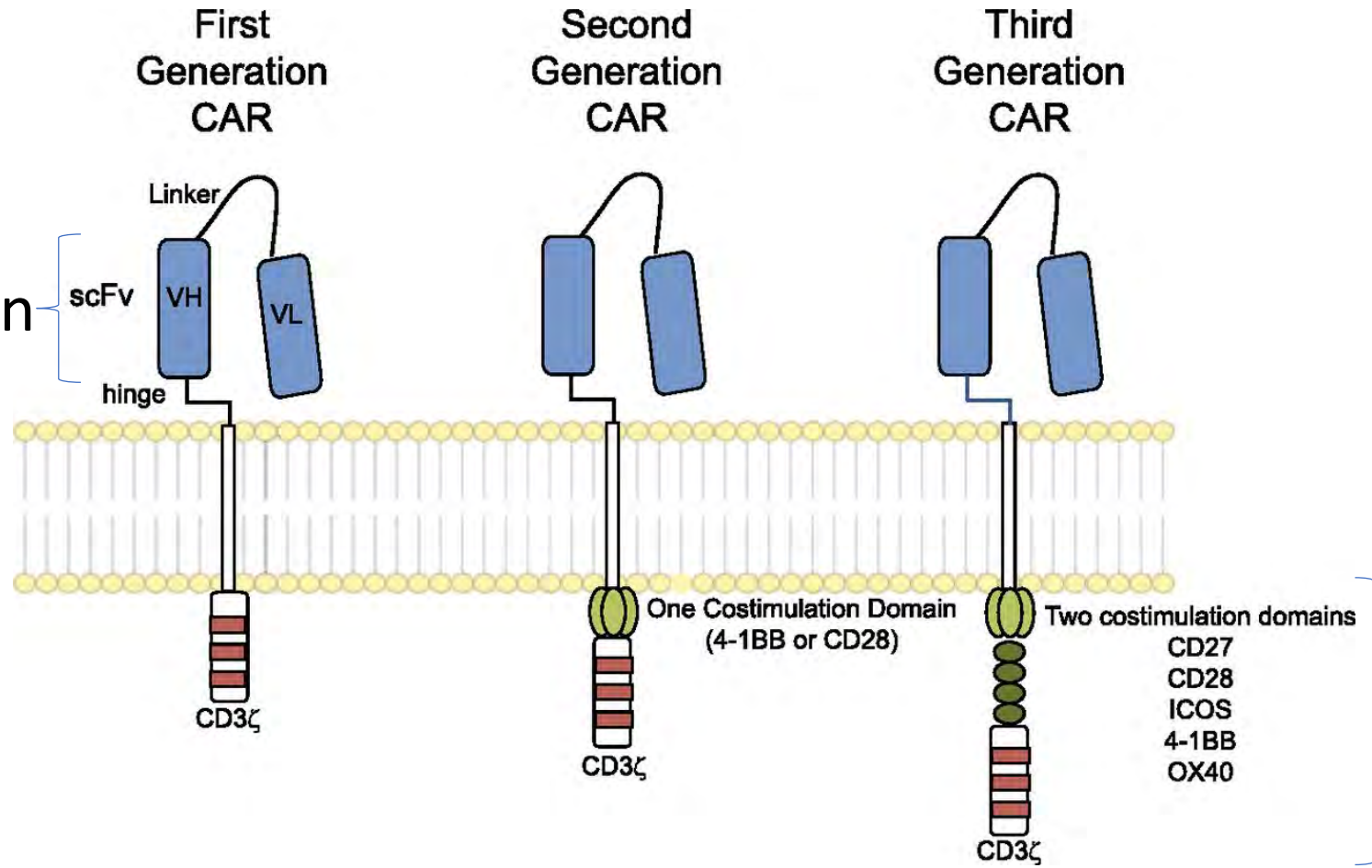
Why genetically modify T cells?

- Generate large numbers of Ag-specific T cells of known avidity
- **Redirect specificity towards known Ag (eg TAA; viral epitope)**
- **Augment T cell function**
- **Enhance *in vivo* persistence**
- Alter homing *in vivo*
- Include suicide switches
- Influence differentiation status
- Overcome tolerance to self
- Ability to test specific T cell subtypes (eg, Tregs, Tcm)
- Generate the “universal T cell”

Chimeric antigen receptors

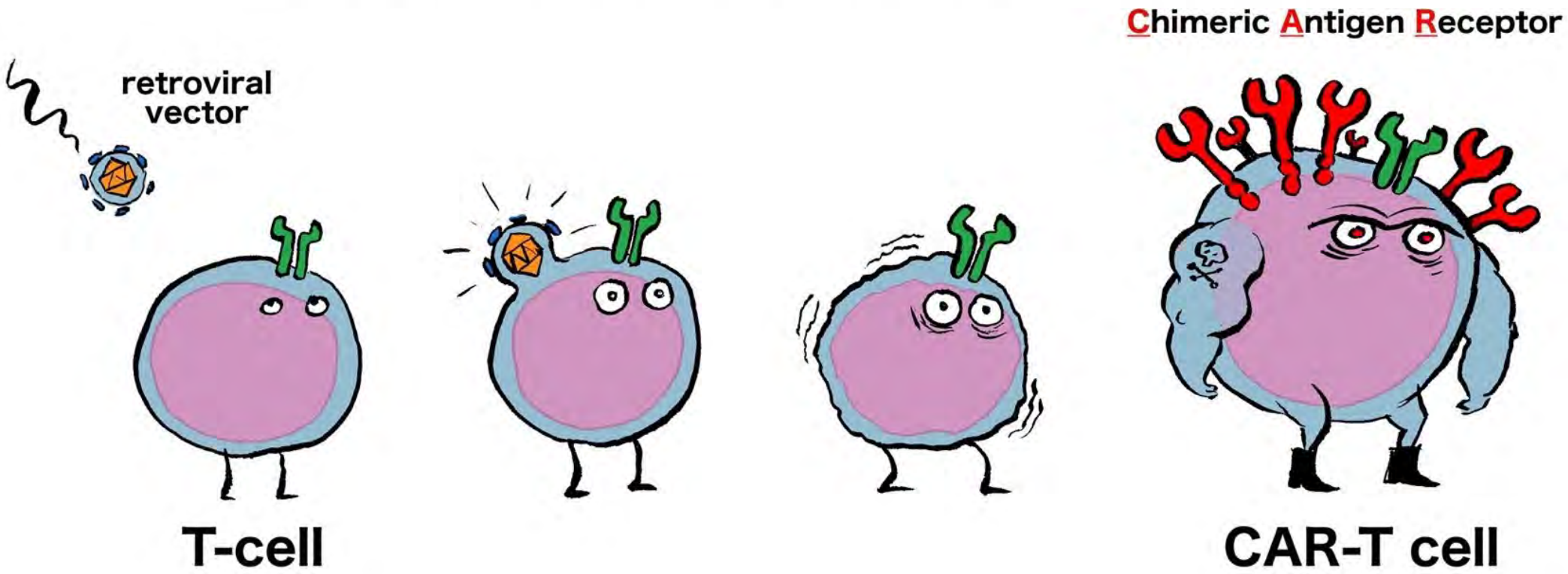


Recognition

Signalling
→ activation
→ survival

Maus M V et al. Blood 2014;123:2625-2635

Generating Super-soldiers



Reproduced with permission from Pedromics

What Do You Need

- Cells – facility, machine, staff
- Logistics/cold chain
- GMP facility
- Gene for receptor
- Mechanism to insert gene (usually viral vector)
- Culture facilities to increase the number of cells/select transduced cells
- Hospital, pharmacy, ITU etc.
- Regulation, Quality Assurance

BRIEF REPORT

The NEW ENGLAND JOURNAL of MEDICINE

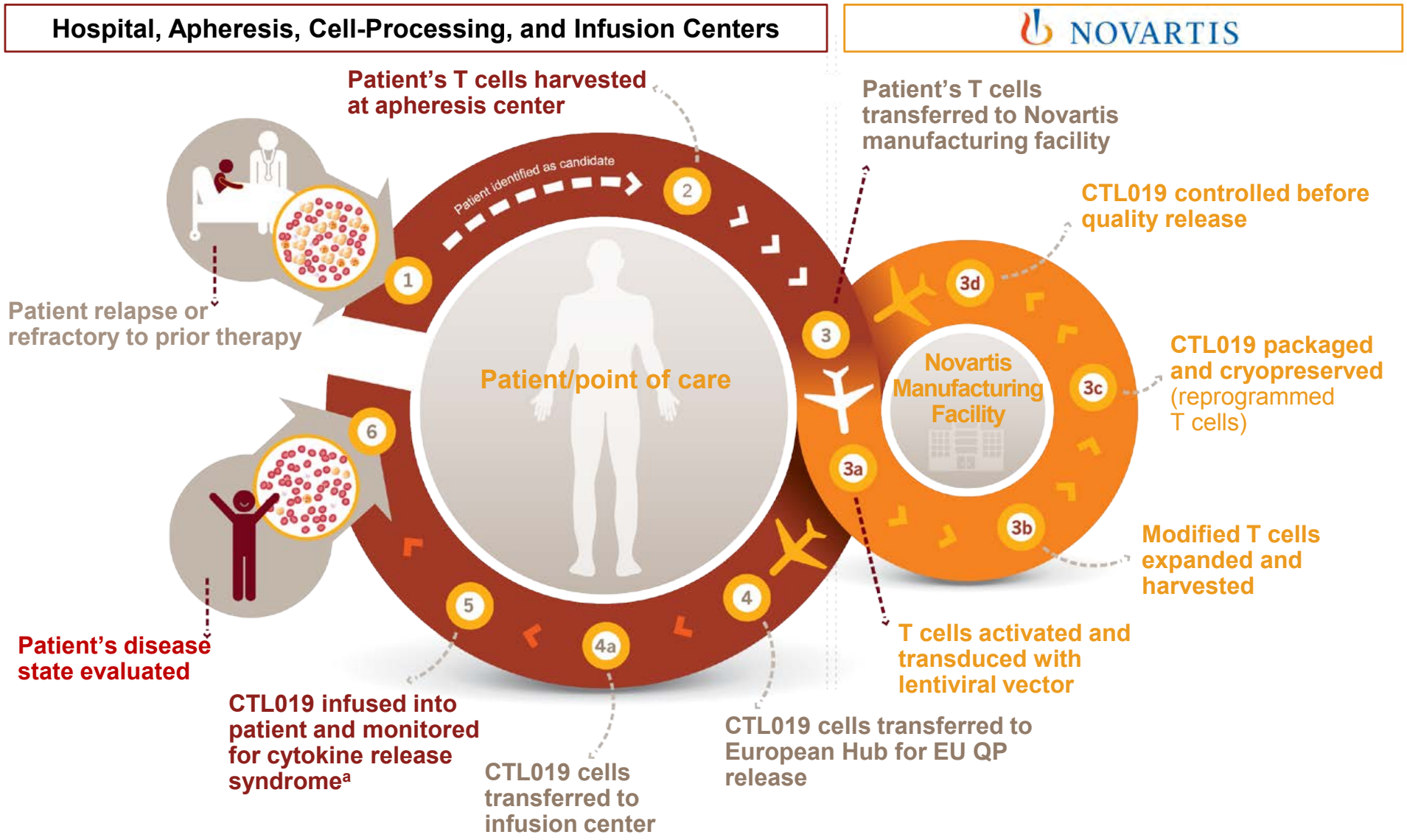
Chimeric Antigen Receptor–Modified T Cells for Acute Lymphoid Leukemia

Stephan A. Grupp, M.D., Ph.D., Michael Kalos, Ph.D., David Barrett, M.D., Ph.D., Richard Aplenc, M.D., Ph.D., David L. Porter, M.D., Susan R. Rheingold, M.D., David T. Teachey, M.D., Anne Chew, Ph.D., Bernd Hauck, Ph.D., J. Fraser Wright, Ph.D., Michael C. Milone, M.D., Ph.D., Bruce L. Levine, Ph.D., and Carl H. June, M.D.

- Two children with relapsed and refractory pre–B-cell ALL
- CAR-T cells expanded to a level that was more than 1000 times as high as the initial engraftment level
- Eight grade 3 or 4 adverse events were noted. The cytokine-release syndrome and B-cell aplasia developed in both patients
- Complete remission was observed in both patients

CARs hitting the headlines

Complex production



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HTA Human Tissue Authority
The regulator for human tissue and organs

Stem Cell Transplant teams

Medicines & Healthcare products Regulatory Agency

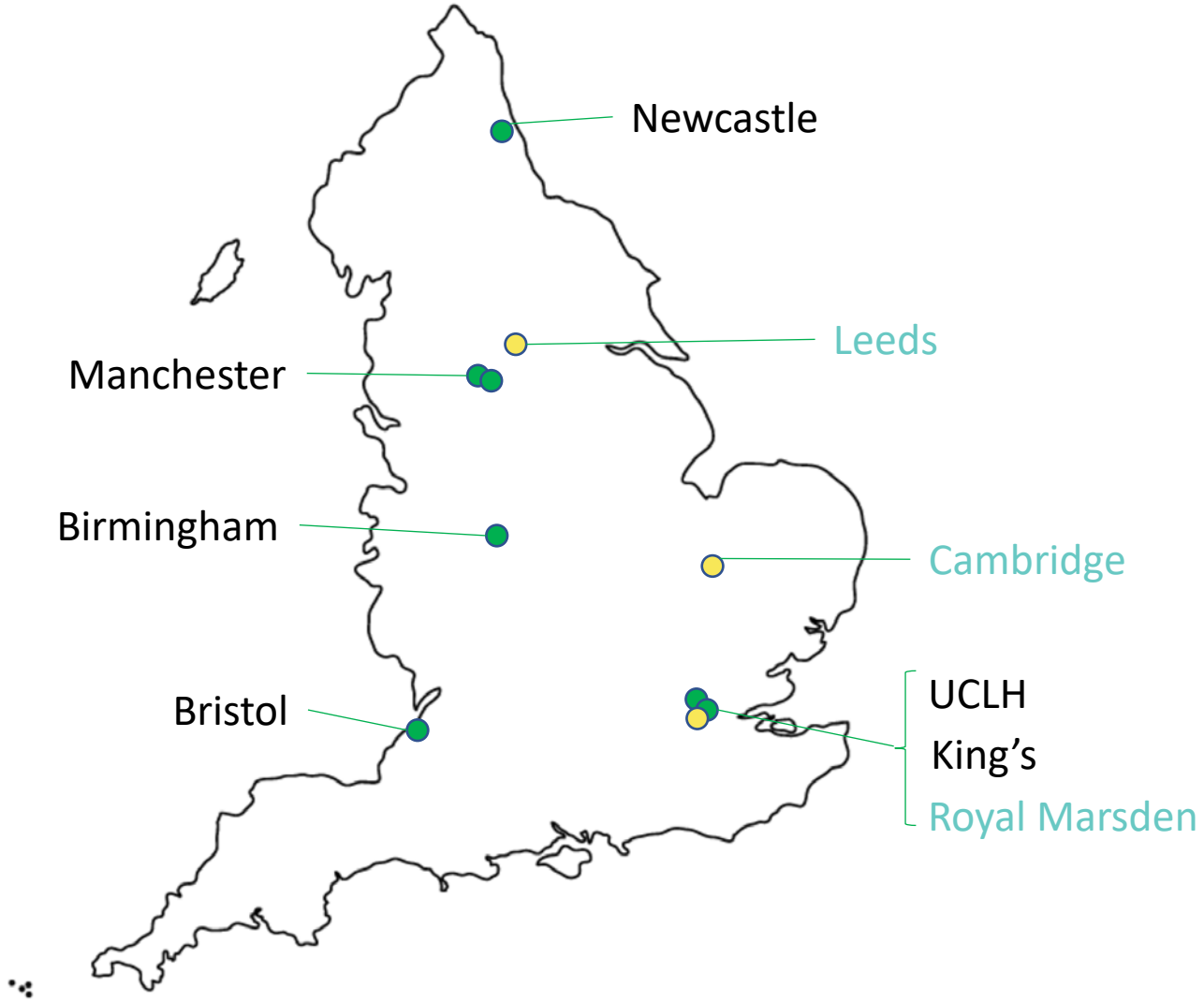
Pharmaceutical companies

How to name a CAR

Prefix Random	Infix1 Manipulation	Infix2 Cell type				Suffix -cel
To ensure a distinctive name	To specify manipulation the cells have undergone e.g. -gen- (transduced, genetic modification) -fus- (fusion to a cell)	To identify the primary cell type e.g.				To name all cellular ATMP
		-den- -isle- -mio(b)- -co(n)- -fi(b)- -ker(a)- -end(o)- -ep(a)- -mestro- -ret-	denritic cells islet cells Myoblasts chondrocytes fibroblasts keratinocytes endothelial cells hepatocytes mesenchymal stromal cells retinal epithelial cells	-ren- -pla(c)- -ur- -ova- -tesi- -cor- -leu- -tem- -deftim- -tu-	renal tubular cells placenta cells urothelial cells ovary cells testis cells umbilical cord cells lymphocytes stem cells differentiated stem cells tumour cells	

WHO, INN 2015

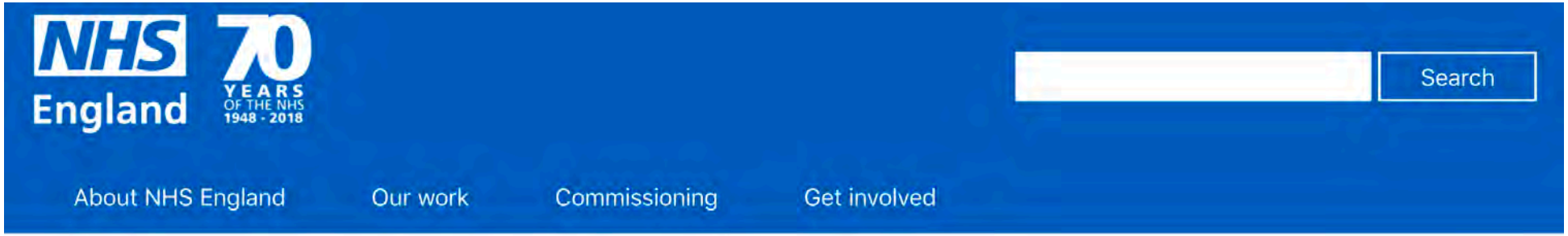
NHS England CAR-T centres



Current Licenced/Commissioned products

KYMRIAH
(tisagenlecleucel)

YESCARTA
(axicabtagene ciloleucel)



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News

NHS England announces groundbreaking new personalised therapy for children with cancer

5 September 2018

Cancer | Children and young people | Medicine

NHS patients to benefit from Europe's first full access deal on breakthrough CAR-T therapy.

NHS England chief executive Simon Stevens has announced today that children and young people in England will receive a groundbreaking cancer treatment, the first in what is expected to be a rapidly expanding class of personalised cancer therapies available on the NHS.

NHS England's commercial deal with the manufacturer Novartis is the first in Europe, and comes less than 10 days after the treatment was granted its European marketing authorisation. It represents one of the fastest funding approvals in the 70 year history of the NHS.

NICE rejects Gilead's CAR-T, immediately after EU approval

Richard Staines

August 28, 2018

Novartis and Gilead's CAR-T therapies have been approved in Europe – and the UK's NICE immediately slapped down the latter, saying it is too expensive for regular NHS use in England and Wales.

Novartis' CAR-T, Kymriah (tisagenlecleucel) has not yet been reviewed by NICE's committees, as the cost-effectiveness body received the manufacturer's dossier much later.

But if NICE's decision on Gilead's CAR-T (chimeric antigen receptor T-cell) therapy, Yescarta (axicabtagene ciloleucel) is anything to go by, Novartis may also have difficulties securing market access on England's NHS.

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Gilead strikes deal with NHS England on Yescarta access

8th October 2018

ELIANA

KYMRIAH (tisagenlecleucel)

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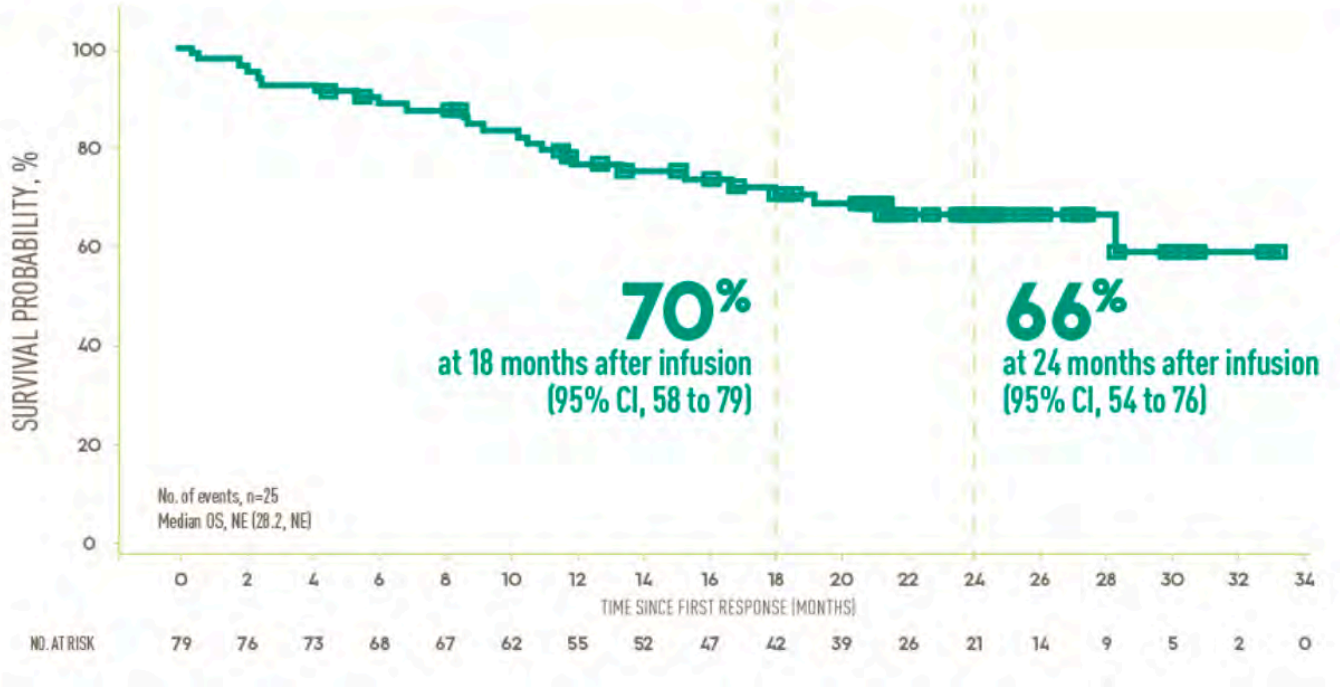
82%
ORR WITHIN 3 MONTHS[1]*

(n=65/79)
ASH 2018: 24-month analysis

98%
MRD– WITHIN 3 MONTHS[1†]

(n=64/65)

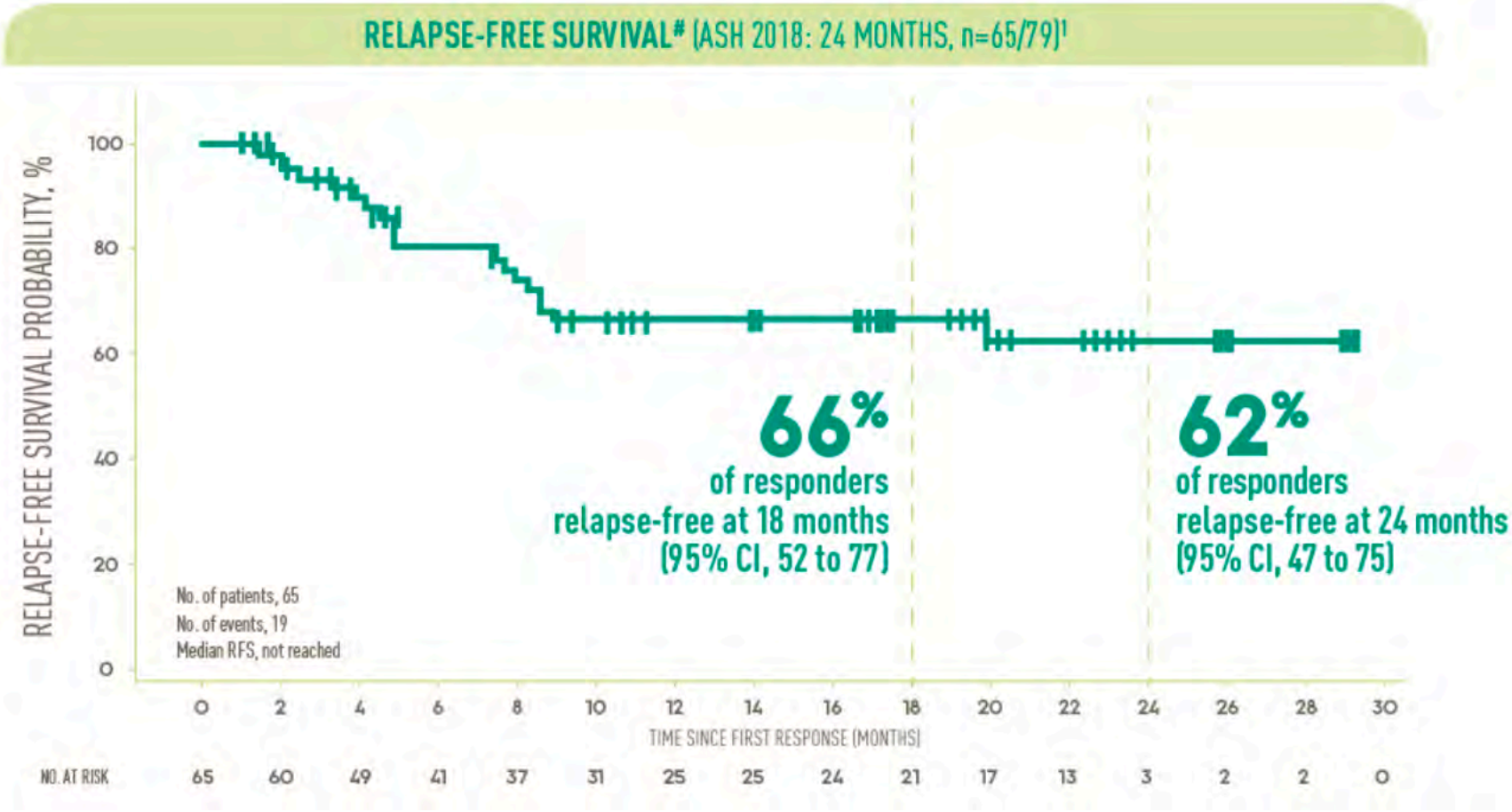
OVERALL SURVIVAL (ASH 2018: 24 MONTHS, N=79)[1]



ELIANA

KYMRIAH (tisagenlecleucel)

BBTS 2019

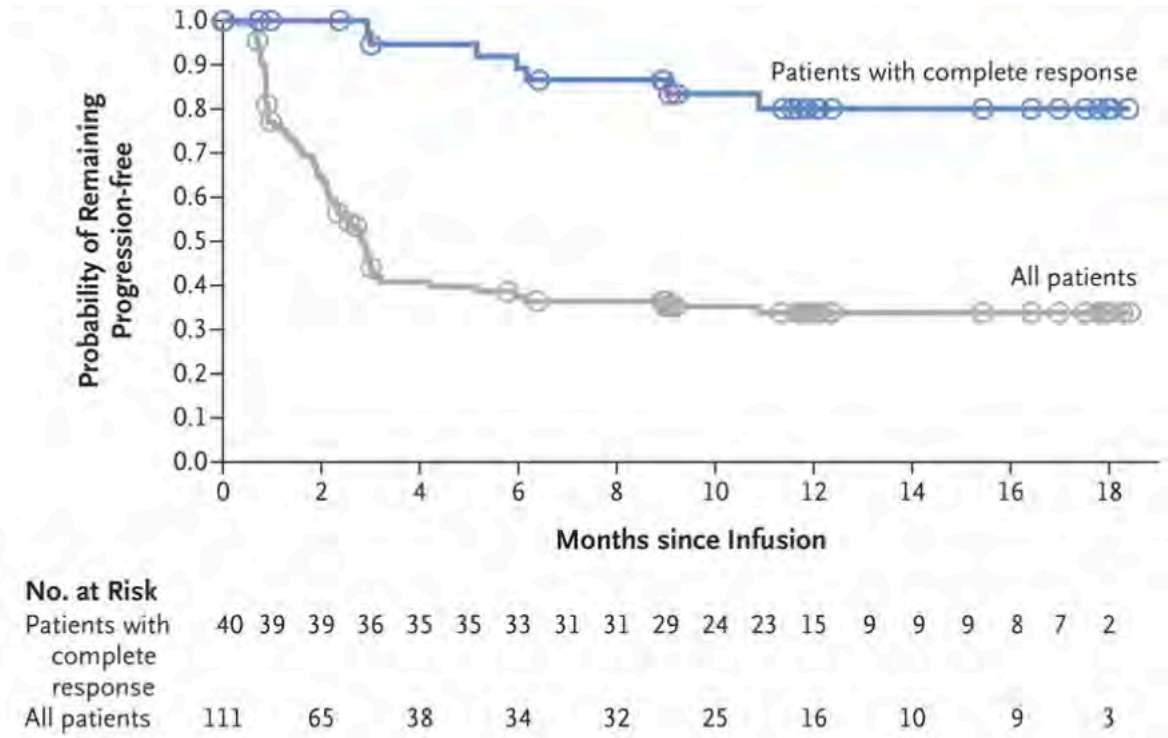


JULIET

KYMRIAH (tisagenlecleucel)

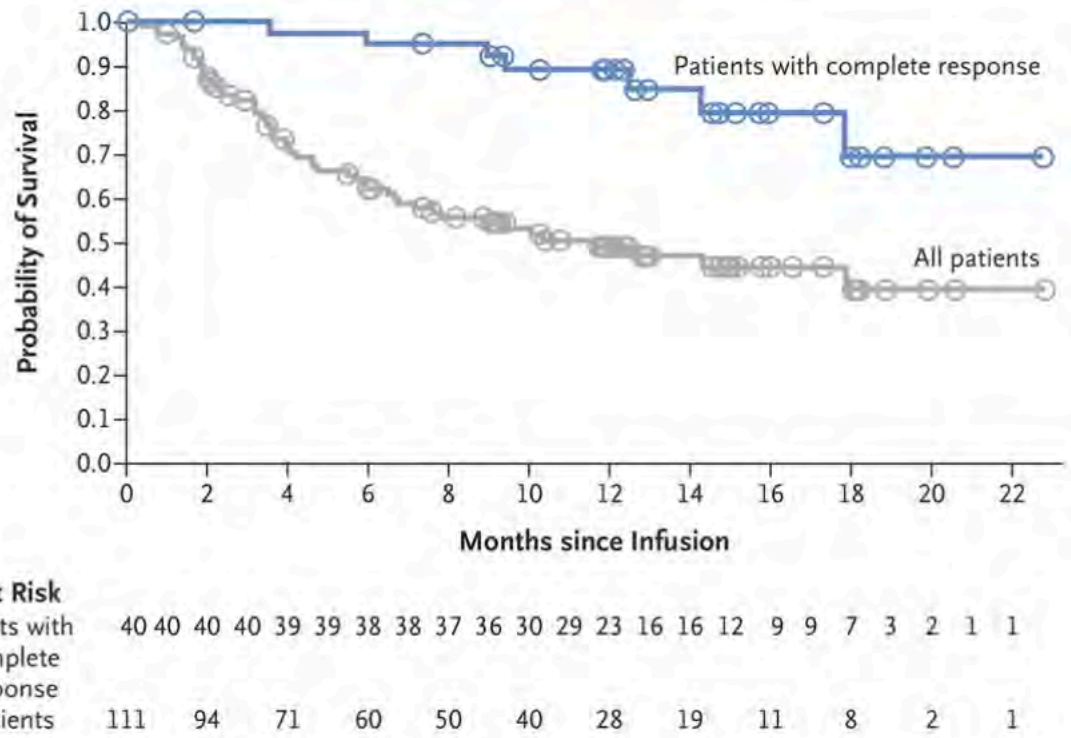
BBTS 2019

PFS



No. at Risk																		
Patients with complete response	40	39	39	36	35	35	33	31	31	29	24	23	15	9	9	9	8	7	2
All patients	111		65		38		34		32		25		16		10		9		3

OS

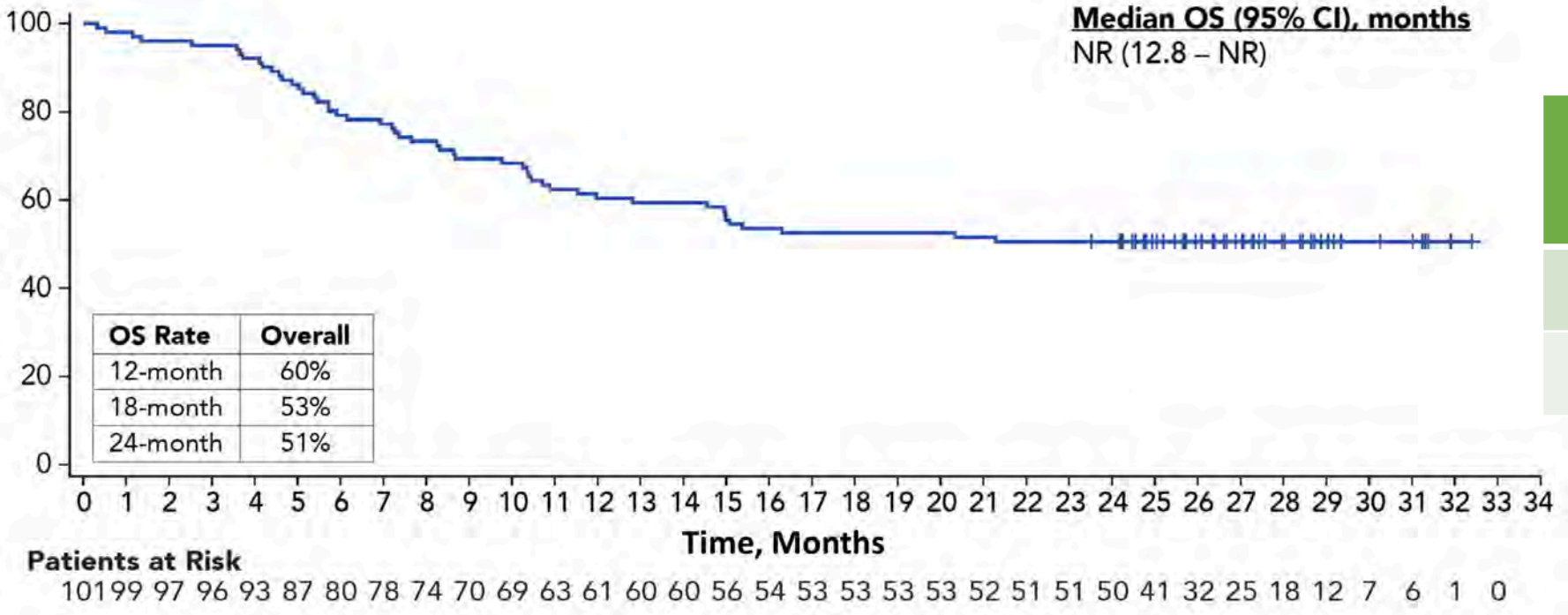


No. at Risk																							
Patients with complete response	40	40	40	40	39	39	38	38	37	36	30	29	23	16	16	12	9	9	7	3	2	1	1
All patients	111		94		71		60		50		40		28		19		11		8		2		1

N Engl J Med 2019; 380:45-56

ZUMA-1

YESCARTA
(axicabtagene ciloleucel)

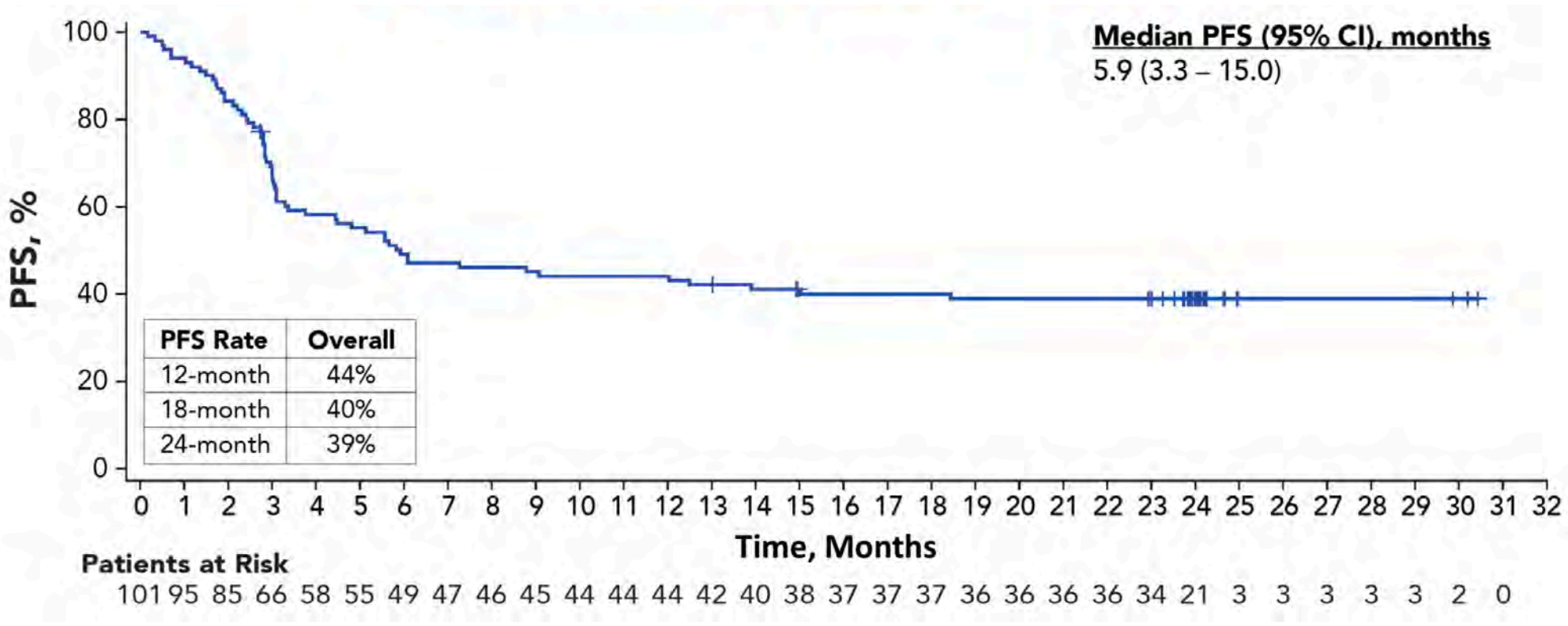


Best Overall Response	
ORR	CR
74%	54%

Neelapu SS, et al. *Blood.* 2018;132: Abstract 2967

ZUMA-1

YESCARTA
(axicabtagene ciloleucel)



ZUMA-1

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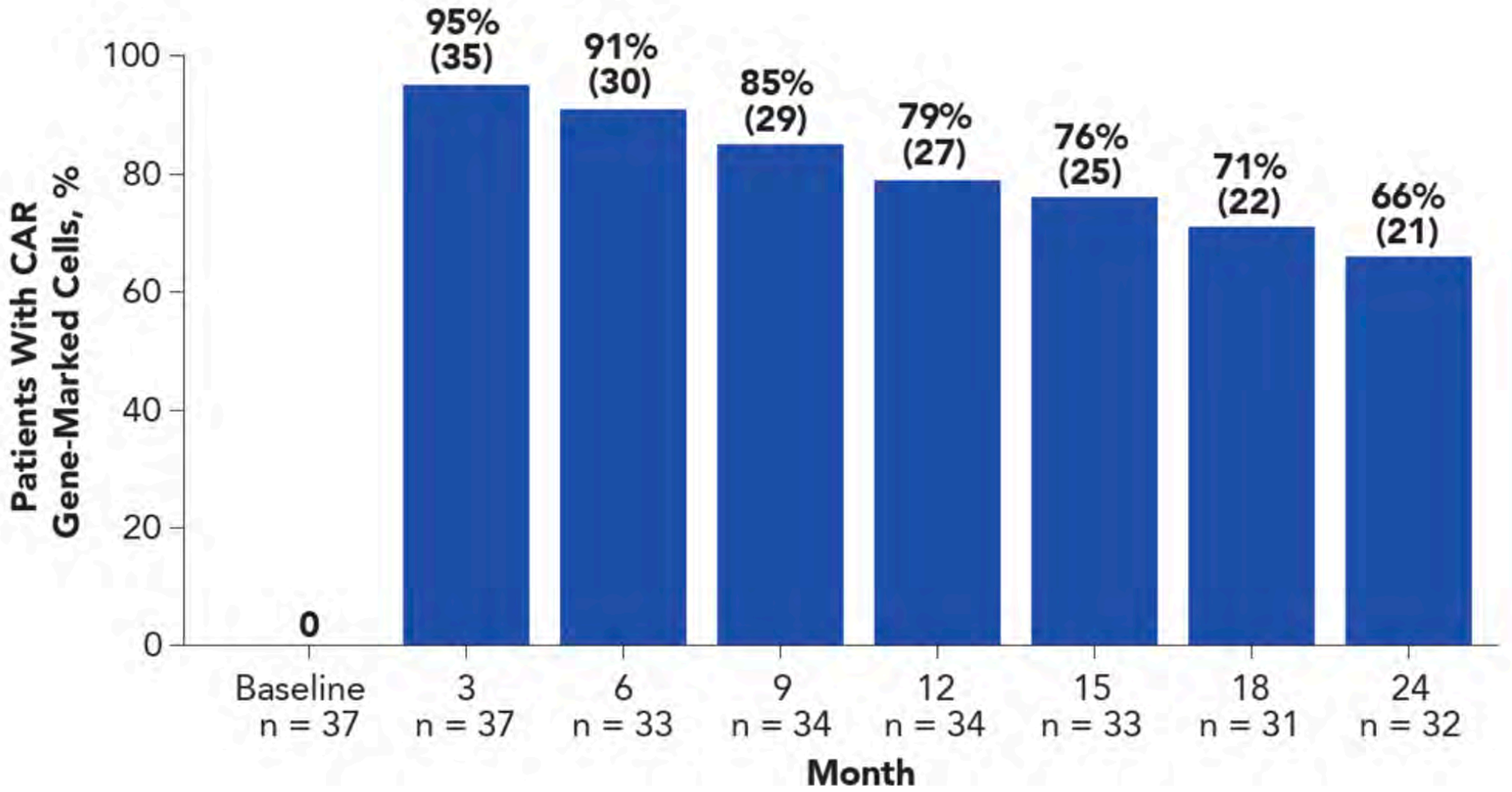


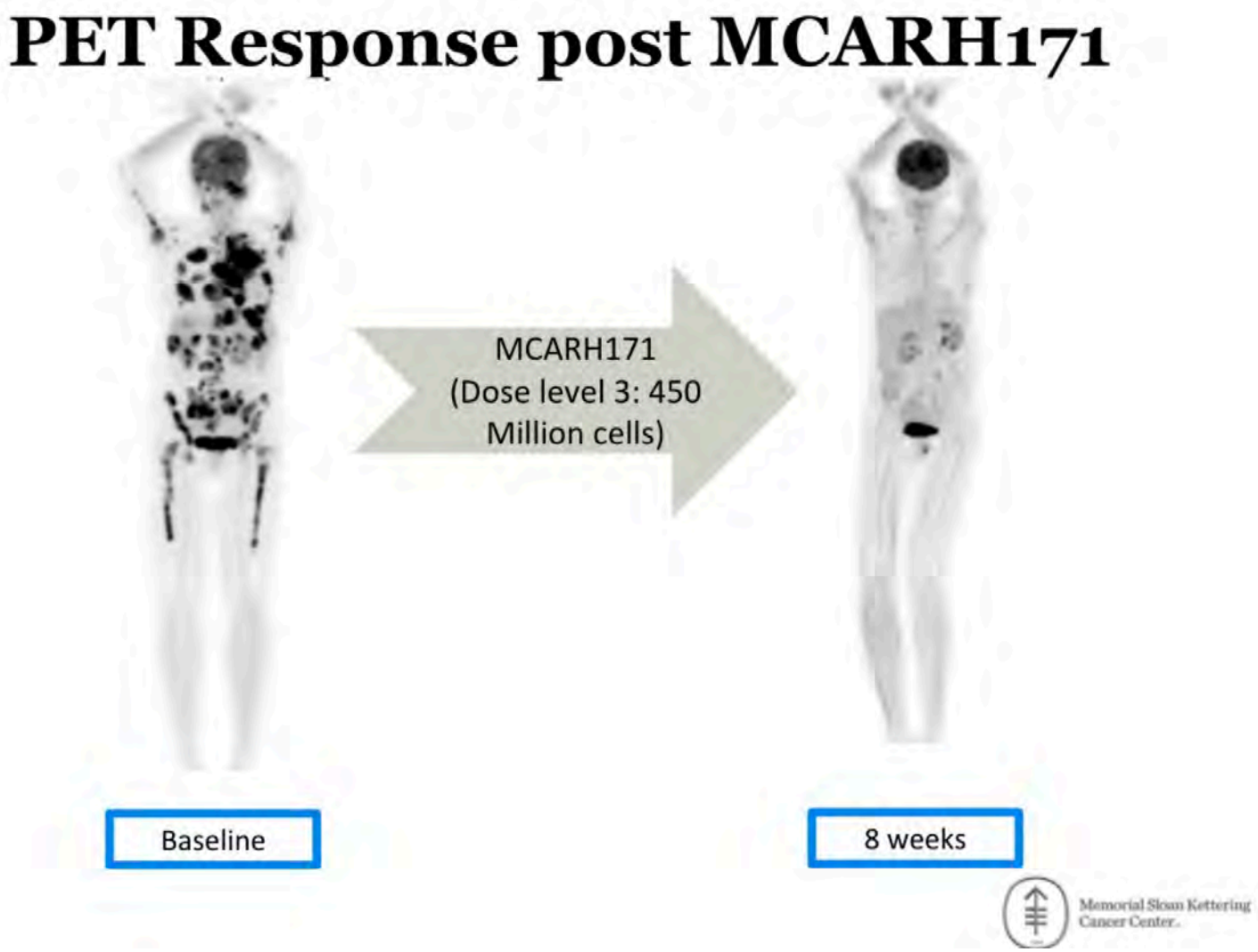
The growing trial landscape

Dual Specific – ALL, Myeloma
BCMA – Myeloma
CD44v6 – AML & Myeloma

GD2 – Neuroblastoma

Allo CAR

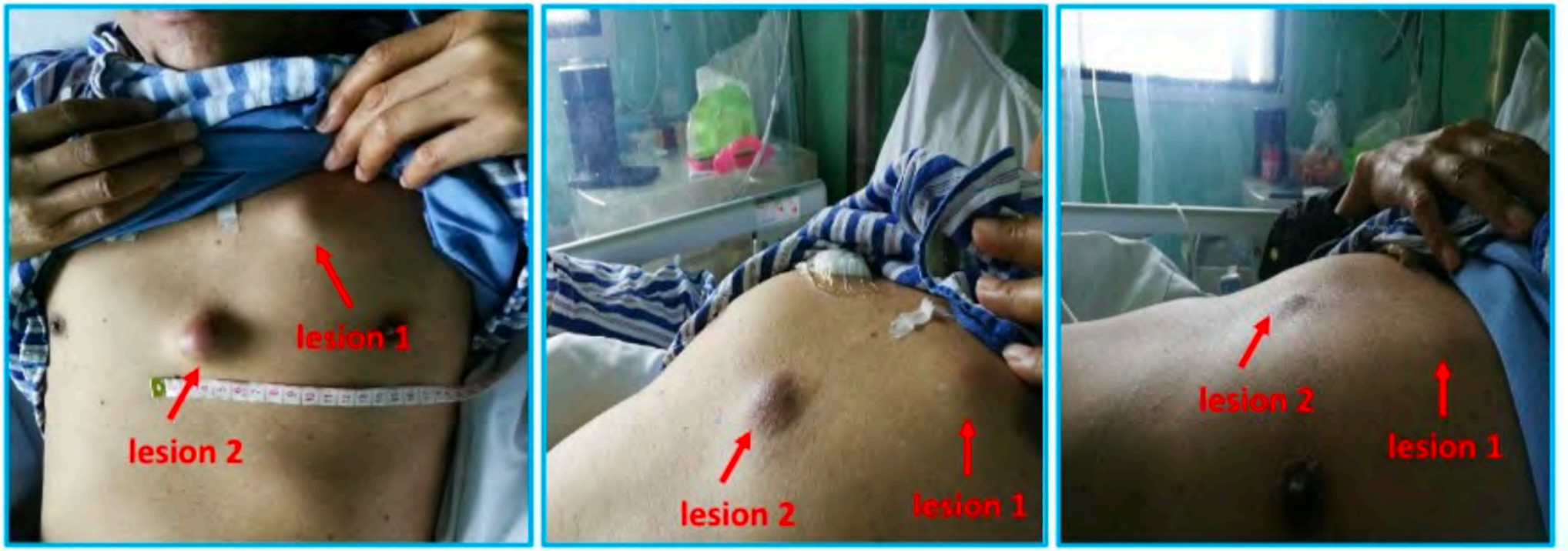
959 Clinical Responses and Pharmacokinetics of MCARH171, a Human-Derived BCMA Targeted CAR T Cell Therapy in R/R MM: Final Results of a Phase I Clinical Trial



ASH 2018

960 Low Dose of Human scFv-Derived BCMA-Targeted CAR-T Cell Achieved Fast Response and High CR in Patients with R/R MM

Pt # 8 : Male, 65yrs. MM(λ type).
Achieved CR at week 4.



Day 1 after CT053 treatment | Day 5 after CT053 treatment | Day 6 after CT053 treatment

ASH 2018

BCMA CAR T-cell Therapies for Myeloma

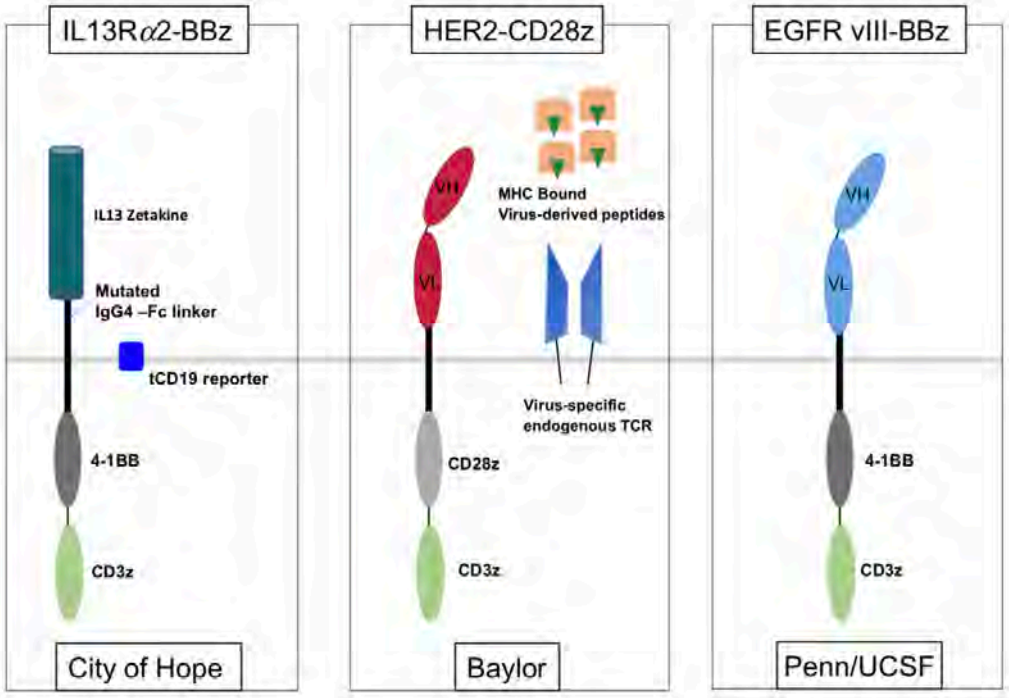
	Anti-BCMA CAR[1] NCT02215967	Bb2121[2] NCT02658929	CART-BCMA[3] NCT02546167	LCAR-B38M[4] NCT03090659
Group/company	***NIH***	***Bluebird/Celgene***	***University of Pennsylvania/ Novartis***	***Nanjing Legend Biotech***
Patients	**16** patients at 9x10^6/kg dose level	22 (>150 x 10^6 cells)	**21 (3 cohorts)**: 9 (10-500 x 10^6, No Cyt) 5 (10–50 x 10^6 · Cyt) 7 (5 (100–500 x 10^6 · Cyt)	**57**
BCMA expression required?	Yes	Yes; ≥ 50% BCMA expression	No	Yes
Median prior lines of therapy	7	7	7 (3–11)	3
Reported efficacy	ORR 14/16 (**81%**) 11/14 (**79%**) MRD- EFS: **7.2 months**	**86.4%** ≥VGPR (**50%** sCR/CR) **PFS: 11.8 months**	#1: **67%** (1 sCR, 1VGPR) #2: (**40%**) 1 PR, 1 MR both PD #3: (**83%**) 1 CR, 3 PR, 1 MR	ORR: **88%** **CR: 74%** **MRD-: 93% of CR** **PFS:15m**
Safety data	CRS all grades:100%, 37%G3-4	CRS all grades: 63% 2 events of CRS grade ≥3 resolved within 24 hours	CRS: 17 pts (grade 3: 32%) Neurotoxicity: 3 (2 grade 4) 1 death – PD candidaemia	Transient CRS (5,7% G3) No neurotoxicity

This slide is provided for ease of vie
BCMA, B-cell maturation antigen; C
partial response

1. Ali A, *et al.* Presented at ASH 2015. Abstract LBA 1; 2. Raje NS, *et al. JCO.* 2018;36:(suppl; abstr 8007); 3. Cohen AD, *et al. Blood* 2017;130:505.; 4. Zhang W, *et al.* Presented at EHA 2017. Abstract S103.

Abstracts ASH 2018: 488, 955-7, 959, 960, 1009, 1011-14

CAR-T in non-Haem malignancy



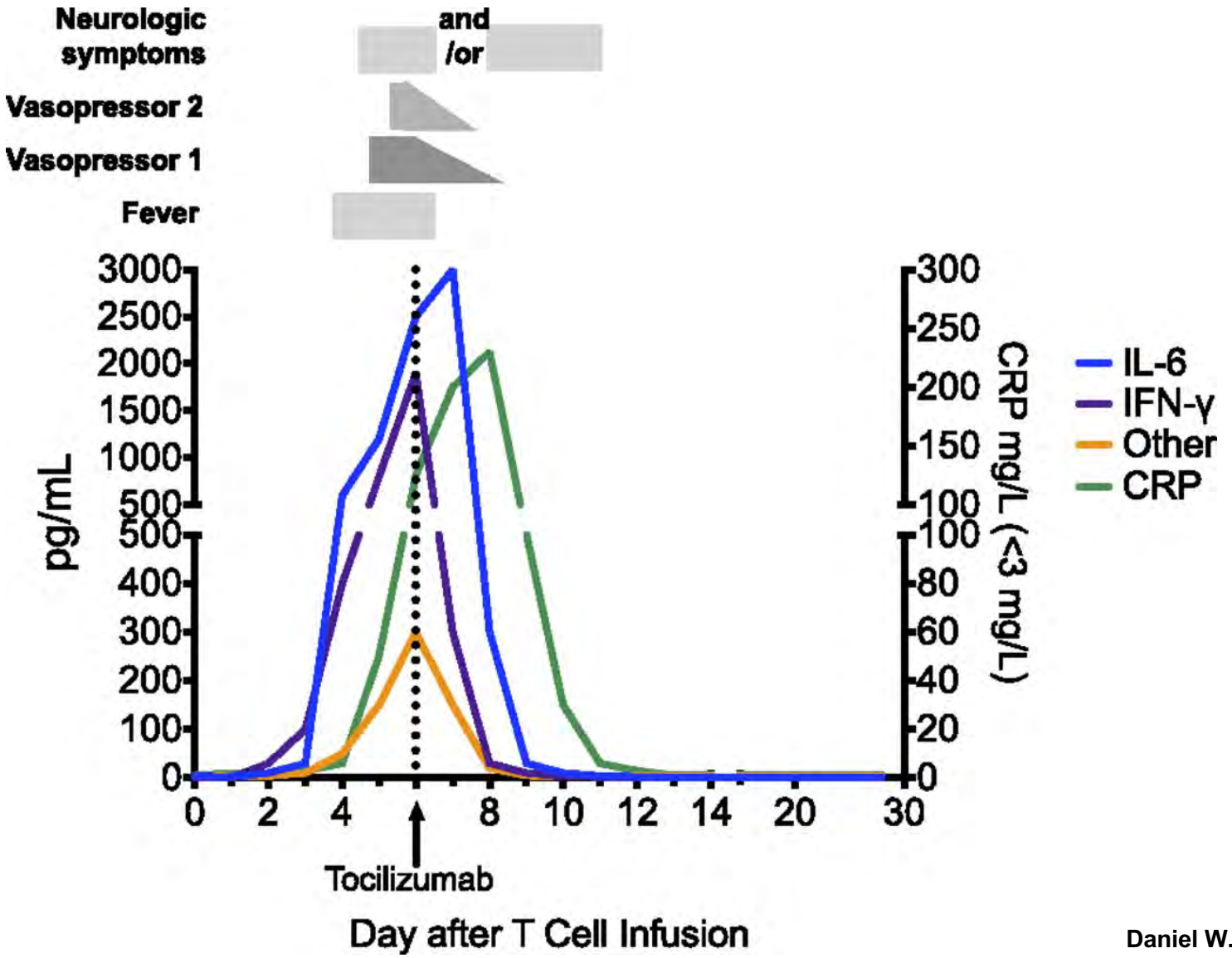
Target TAA	Solid tumors expressing target TAA	Type of CAR	Clinical trials*	Phase
CD44v6	(Metastasized) colon cancer, soft tissue sarcoma (STS), possible marker for many metastasizing tumors (12, 13)	28ζ CAR-CIK/ HSV-TK suicide gene	Preclinical	–
CAIX (carbonic anhydrase IX)	Metastatic clear cell renal cell carcinoma (ccRCC) (14, 15)	$CD4_{TM}$-γ	Study stopped	I/II
CEA (carcinoembryonic antigen)	Ovarian, gastrointestinal, colorectal, hepatocellular carcinoma (HCC) (16–18)	CD3ζ	NCT02959151	I/II
			NCT02850536	Ib
			NCT02349724	I
			NCT03267173	Early I
CD133	Ovarian, glioblastoma (GBM), HCC (17–19)	BBζ	NCT02541370	I/IIa
		–	NCT03423992	I
c-Met (Hepatocyte growth factor receptor)	Breast (50%), melanoma, HCC	BBζ mRNA	NCT01837602	Early I
			NCT03060356	Early I
	(20)	c-Met/PDL-1	NCT03672305	Early I
EGFR (epidermal growth factor receptor)	NSCLC, GBM, sarcoma, malignant pleural mesothelioma (MPM) (79.2%), retinoblastoma, glioma, medulloblastoma, osteosarcoma, Ewing sarcoma (21–23)	28/BBζ	NCT03152435	I/II
		α-CTLA-4/PD-1	NCT03182816	I/II
		IL12	NCT03542799	I
		BBζ/EGFR806/ tEGFR suicide gene	NCT03638167	I
			NCT03618381	I
EGFRvIII (type III variant epidermal growth factor receptor)	GBM (24–67%), glioma, colorectal, sarcoma, pancreatic	–	NCT03283631	I
		tEGFR suicide gene	NCT02844062	I
		–	NCT01454596	I/II
		–	NCT03267173	Early I
		BBζ+pembrolizumab	NCT03726515	I
	(16, 24)	–	NCT03423992	I
Epcam (epithelial cell adhesion molecule)	HCC, lung, ovarian, colorectal, breast, gastric, stomach, esophogeal, pancreatic, liver, prostate, gynecological cancers, nasopharyngeal carcinoma	–	NCT02915445	I
		–	NCT03563326	I
		28ζ	NCT03013712	I/II
		–	NCT02729493	I/II
	(16, 25)	–	NCT02725125	I/II
EphA2 (Erythropoetin producing hepatocellular carcinoma A2)	GBM, glioma (26, 27)	–	NCT03423992	I
Fetal acetylcholine receptor	Osteosarcoma, rhabdomyosarcoma (28)	CD3ζ	Preclinical	–
FRα (folate receptor alpha)	Ovarian (90%), urothelial bladder carcinoma (14)	4SCAR (4th gen)	NCT03185468	II


Not
Everything is
perfect

Toxicity

- Cytokine Release Syndrome (CRS)
- Neurological (ICANS)
- B cell aplasia
- Tumour escape

CRS



blood

Daniel W. Lee et al. Blood 2014;124:188-195

B cell Aplasia

Tumour escape

Summary

- Treatments utilizing the power of the immune system are producing complete responses in patients with refractory disease
- CAR-T cells are complex ‘living drugs’
- Toxic, high cost therapy but NHS has rapidly embraced them