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A Brief History of T cell Cancer Therapy: From Transplant to CARs

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T cells as anticancer agents: allogeneic T cells

Adoptive T-cell therapy of cancer refers to treatment with T cells specific to tumour cell antigens[1]

» In the allogeneic setting, this results in graft versus tumour effect[2]

1. Perica K, et al. Rambam Maimonides Med J. 2015;6:e0004;
2. Porter DL and Antin JH. Annu Rev Med. 1999;50:369–86.

Evidence of GvL effect in the setting of allo-BMT

Indirect

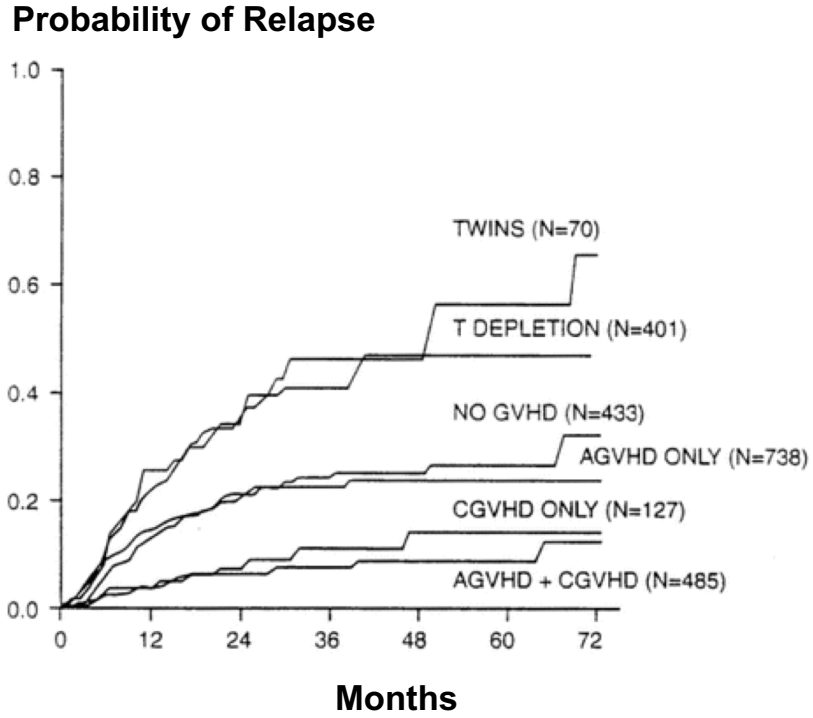
- Abrupt withdrawal of immunosuppression, or a flare of graft-versus-host disease induces complete remission in some patients with relapsed leukaemia after BMT (anecdotal)
- Syngeneic BMT is associated with a higher risk of relapse than allogeneic BMT
- Graft-versus-host disease after BMT is associated with a lower risk of relapse
- Depletion of T cells from the donor bone marrow results in an increased risk of relapse, especially for patients with CML

Direct

- Donor leukocyte infusions given to patients who relapse with haematological malignancies after allogeneic BMT will re-establish complete remissions

Porter DL and Antin JH. Annu Rev Med. 1999;50:369–86.

Relapse of disease following allo-BMT



Porter DL and Antin JH. Annu Rev Med. 1999;50:369–86.

Donor Leukocyte Infusion (DLI)

The transfer of HLA-matched allogeneic T cells from the donor to the host as a therapeutic intervention

- Infusion of EBV-specific T cells for treatment of EBV-lympho proliferative disease (EBV-LPD)
- Infusion of donor T cells in patients with relapsed CML following allo-BMT

Porter DL and Antin JH. Annu Rev Med. 1999;50:369–86.

EBV-LPD

- Malignancy commonly seen in immune-suppressed patients (transplantation, AIDS)
- Secondary to active EBV infection of B cells
- More common following T-cell depleted allo-BMT (incidence 12–25%)
- In the BMT setting, the malignant clone is invariably of donor origin
- Poorly responsive to lymphoma-based chemotherapies

Porter DL and Antin JH. Annu Rev Med. 1999;50:369–86.

DLI after BMT for EBV-LPD

Study	Cell Product	Therapy or prophylaxis	Responses	GVHD
O'Reilly *et al.* [20•]	Donor T cells	Therapy	17/19	3 acute, 8 chronic
Heslop *et al.* [42]	Donor T cells	Therapy	1/1	1/1
Gross *et al.* [37•]	Donor T cells	Therapy	0/3	NR
Lucas *et al.* [10•]	Donor T cells	Therapy	4/13*	4/13
Nagafuji *et al.* [44]	Donor T cells	Therapy	0/1	0/1
Sasahara *et al.* [43]	EBV-specific CTLs & donor T cells	Therapy	0/1	0/1
Rooney *et al.* [47•]	EBV-specific CTLs	Therapy	2/3	0/3
Rooney *et al.* [47•]	EBV-specific CTLs	Prophylaxis	0/39 developed LPD	1/39

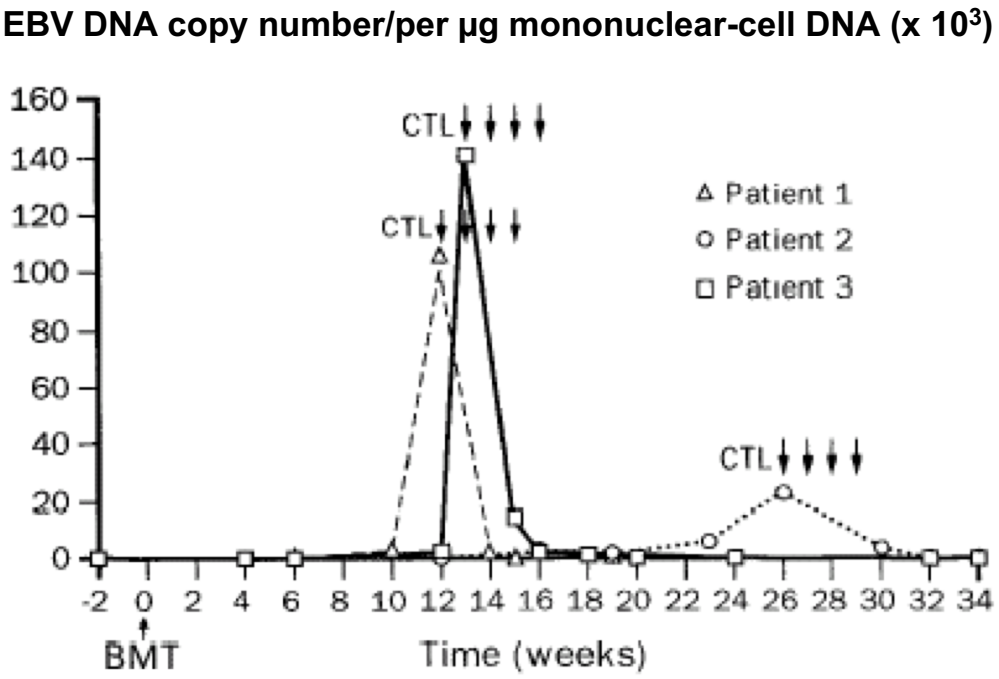
* One responding patient received EBV-specific CTLs.

Aguilar LK, et al. Curr Opin Oncol. 1999;11:96–101.

Rapid response of EBV copy number to DLI treatment

EBV DNA concentrations before and after CTL inclusions in three patients with evidence of EBV-related lymphoproliferation

CTL were given when EBV DNA rose >1000-fold



Rooney CM, et al. Lancet. 1995;345:9–13.

DLI therapy for relapsed CML after BMT

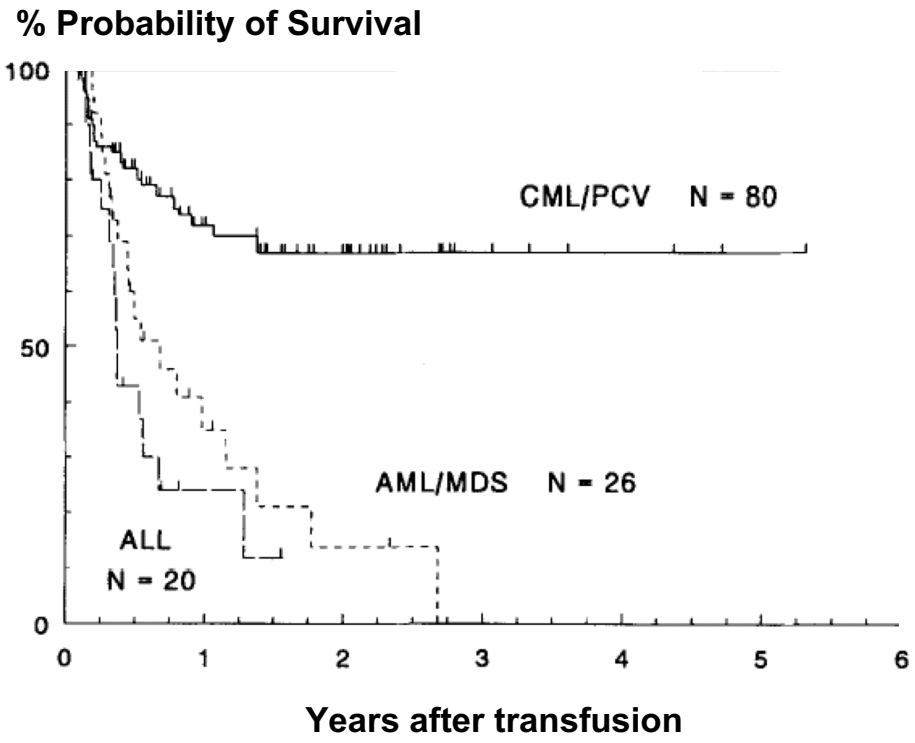
Complete remissions after donor leukocyte infusions for re-lapsed CML

CML phase	North America (26) (n=55)	EBMT (27) (n=75)
Chronic phase	76%	79%
Advanced phase	28%	12%
Total	60%	72%

Abbreviations: CML, chronic myelogenous leukemia; EBMT, European Group for Blood and Marrow Transplantation

Porter DL and Antin JH. Annu Rev Med. 1999;50:369–86.

Survival after DLI therapy



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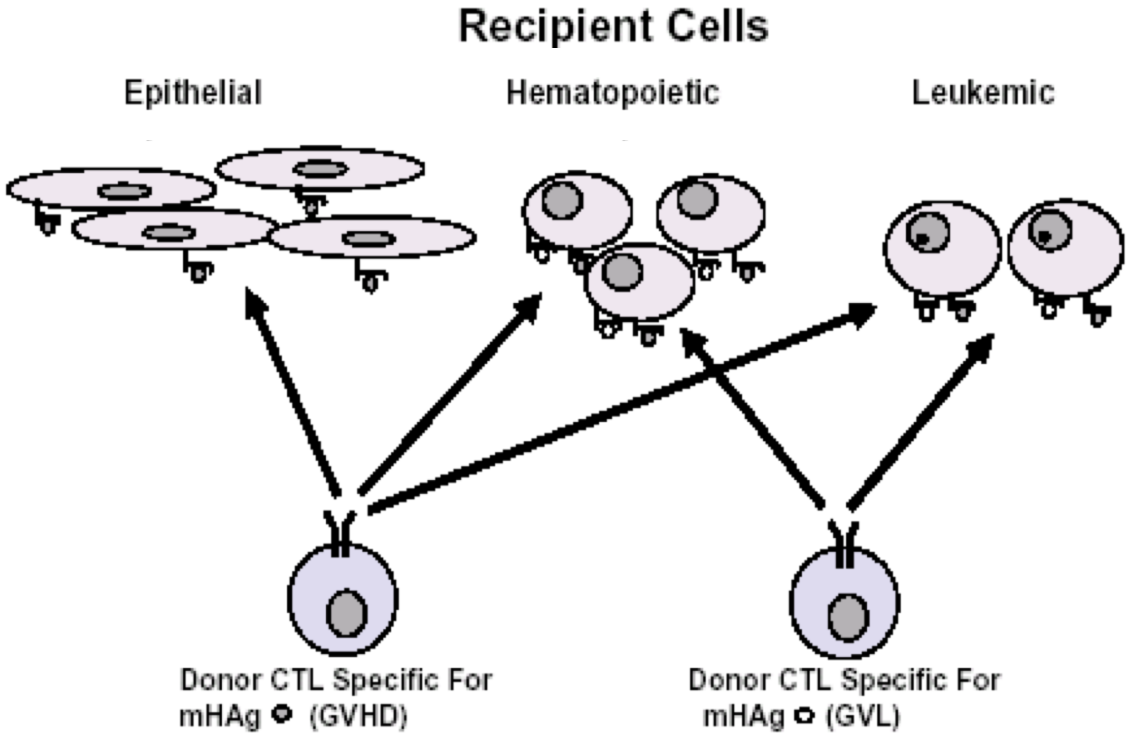
Kolb HJ, et al. Blood. 1995;86:2041–50.

mHags: GvL effect in CML



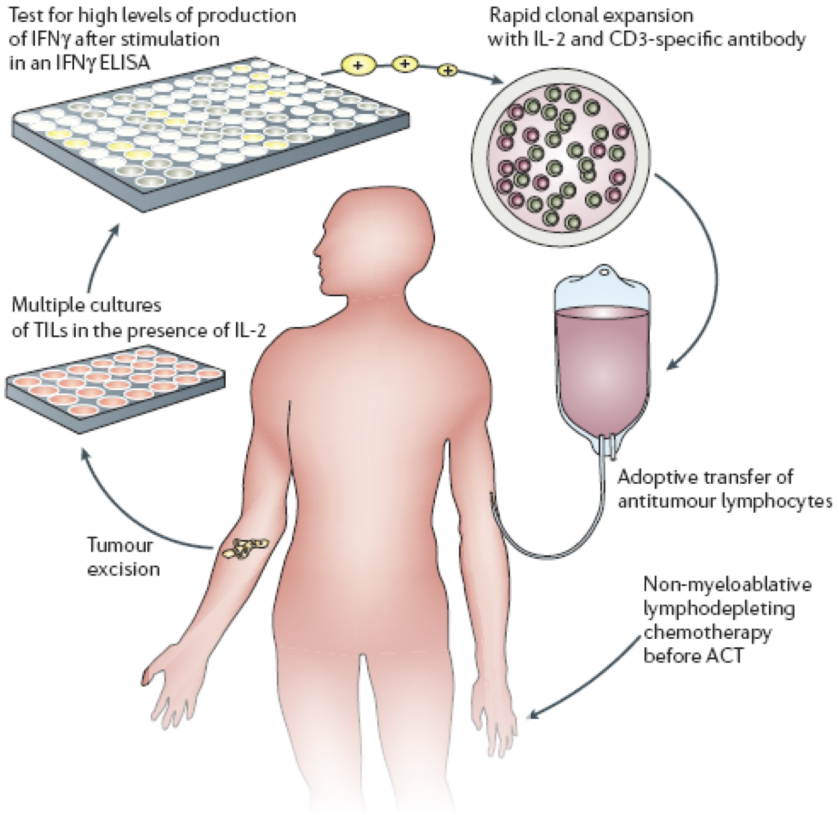
Riddell SR, et al. Cancer Control. 2002;9:114–22.

Autologous adoptive T-cell therapy: Tumour infiltrating lymphocytes

The isolation of patient T cells (presumably tumour specific), followed by ex vivo expansion and subsequent re-infusion into the patient

Gattinoni L, et al. Nat Rev Immunol. 2006;6:38–93.

TIL therapy: Melanoma



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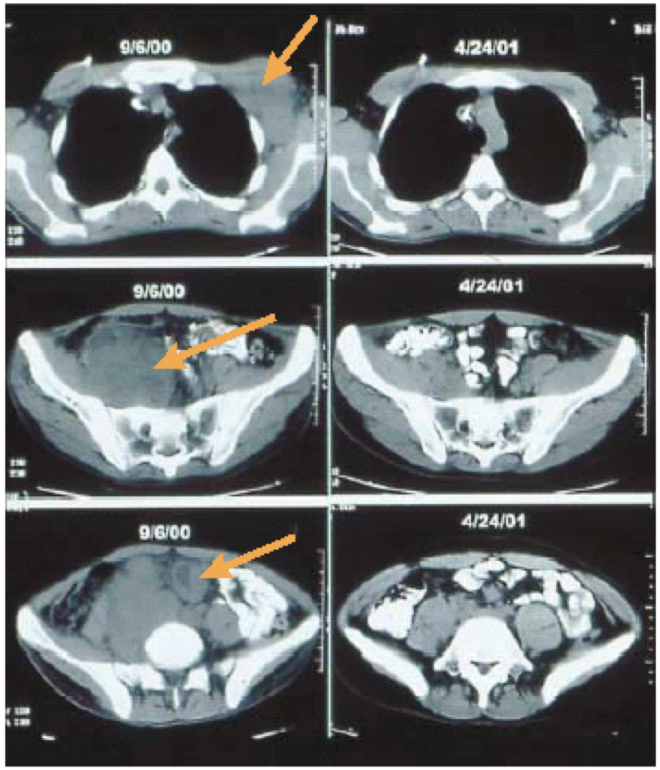
Gattinoni L, et al. Nat Rev Immunol. 2006;6:38–93.

Autologous T-cell therapy: Melanoma

Table 1. Patient demographics, treatments received, and clinical outcomes.

Patient	Age/sex	Treatment*				Sites of evaluable metastases	Response duration‖ (months)	Autoimmunity
		Cells infused† ($\times 10^{-10}$)	CD8/CD4 phenotype‡ (%)	Antigen specificity§	IL-2 (doses)			
1	18/M	2.3	11/39	Other	9	Lymph nodes (axillary, mesenteric, pelvic)	PR¶ (24+)	None
2	30/F	3.5	83/15	MART-1, gp100	8	Cutaneous, subcutaneous	PR (8)	Vitiligo
3	43/F	4.0	44/58	gp100	5	Brain, cutaneous, liver, lung	NR	None
4	57/F	3.4	56/52	gp100	9	Cutaneous, subcutaneous	PR (2)	None
5	53/M	3.0	16/85	Other	7	Brain, lung, lymph nodes	NR-mixed	None
6	37/F	9.2	65/35	Other	6	Lung, intraperitoneal, subcutaneous	PR (15+)	None
7	44/M	12.3	61/41	MART-1	7	Lymph nodes, subcutaneous	NR-mixed	Vitiligo
8	48/M	9.5	48/52	gp100	12	Subcutaneous	NR	None
9	57/M	9.6	84/13	MART-1	10	Cutaneous, subcutaneous	PR (10+)	Vitiligo
10	55/M	10.7	96/2	MART-1	12	Lymph nodes, cutaneous, subcutaneous	PR¶ (9+)	Uveitis
11	29/M	13.0	96/3	MART-1	12	Liver, pericardial, subcutaneous	NR-mixed	Vitiligo
12	37/F	13.7	72/24	MART-1	11	Liver, lung, gallbladder, lymph nodes	NR-mixed	None
13	41/F	7.7	92/8	MART-1	11	Subcutaneous	NR	None

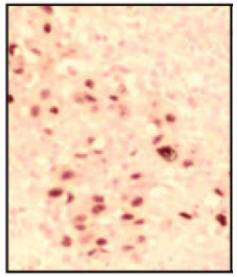
Dudley ME and Rosenberg SA. Nat Rev Cancer. 2003;3:666–75.



Autologous EBV T-cell therapy: Nasopharyngeal carcinoma

Patient No.	Treated in remission	Toxicity	Clinical Response	Outcome
729		None	N/A	Remains in remission > 27 mo
606		None	N/A	Remains in remission > 26 mo
697		None	N/A	Remains in remission > 25 mo
815		None	N/A	Remains in remission > 19 mo
Treated with relapsed or refractory disease				
845		Swelling at tumor site	No response then PR after chemotherapy	PR for 4 months then progressed and died at 12 mo
894		None	CR	Remains in remission > 23 mo after CTLs
389		None	CR	Remains in remission > 11 mo after CTLs
918		None	PR	PR for 12 mo after CTLs then relapsed
1042		None	Stable disease	Stable disease for >14 mo
1046		None	No response	Died of disease at 3 mo

Before



After

Straathof KCM, et al. Blood. 2005;105:1898–1904.

Adoptive therapy with genetically targeted autologous T cells

The isolation of patient T cells, genetic modification to recognise tumour antigen, subsequent ex vivo expansion and re-infusion

- » TCR gene-modified T cells
- » CAR-modified T cells

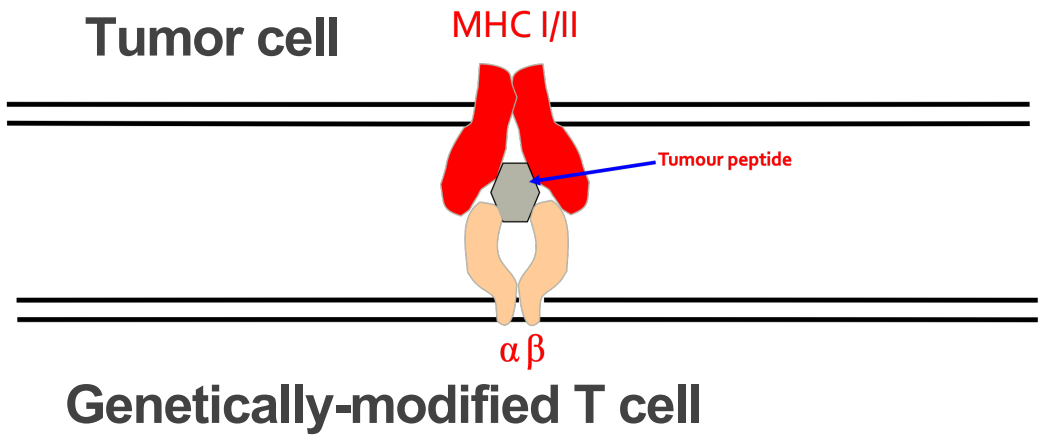
Morgan RA, et al. Science. 2006;314:126–9.

TCR-modified T cells

1. Isolate and clone T cells specific to the target tumour peptide

2. Clone the genes encoding the TCR αβ chains

3. Transduce autologous patient T cells with these genes to generate tumour-specific T cells

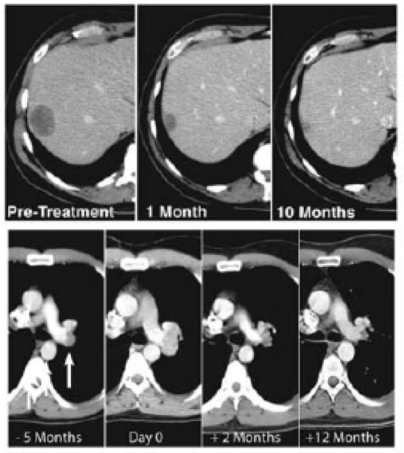


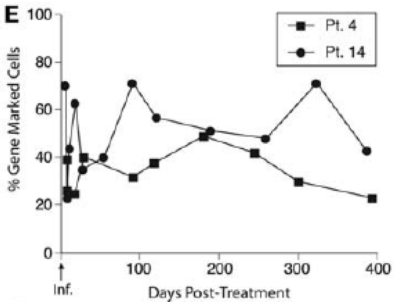
Sharp M, et al. Disease Models & Mechanisms. 2015;8:337–50.

TCR-modified T cells: Melanoma

Cohort	Patient	Age/sex	Total cells infused ($\times 10^{-9}$)	CD4/CD8 (%)	VB12 (%)	MART-1 cells infused ($\times 10^{-9}$)‡	Days in culture	Doubling time (days)†	IL-2 doses§	Sites of evaluable disease	Response (duration in months)‖
1	1	28/M	11.0	27/73	67	7.4	19	8.7	7	Ln, Cu	NR
	2a*	44/F	13.0	3/95	64	8.3	19	11.9	10	Ln, Cu	NR
	3	58/M	14.0	17/82	35	4.9	19	10.0	11	Cu, Sub	NR
2	4	52/M	1.0	50/50	42	0.5	6	1.4	9	Li, Sub	PR(21)
	5	50/M	12.0	18/82	17	2.2	8	1.0	7	Lu, Ln, Sub	NR
	6	55/F	7.0	37/72	51	3.6	7	1.3	8	Lu, Ln	NR
	7	56/M	9.0	75/21	40	3.6	7	1.0	5	Lu, Ln	NR
	8	37/M	6.1	68/40	32	1.9	7	1.3	12	Lu, Ln	NR
	9	53/M	4.2	72/24	41	1.7	7	2.0	9	Ln, Ad, Sub	MR
	10	45/M	8.6	53/30	34	2.9	6	0.6	5	Ln, Sub	
	11	45/M	6.3	7/92	45	2.8	6	0.8	5	Lu, Pa, Ln	NR
	12	32/F	4.7	30/60	61	2.9	6	0.7	5	Br, Sub	NR
	13	41/M	7.7	40/67	42	3.2	6	0.9	7	Lu, Sub	NR
	2b*	44/F	2.1	30/59	53	1.1	6	1.9	14	Ln, Cu	NR
3	14	30/M	86	11/60	40	34.4	18+9	0.9	5	Hi	PR(20)
	15	51/M	38	16/82	45	17.1	18+9	3.3	8	Lu	NR
	16	25/F	33	13/76	21	6.9	18+9	1.2	2	Lu, Li, Sub	NR
	17	20/F	23	17/78	30	6.9	17+8	1.1	3	Lu, Ln, Sub	NR

*This patient was treated twice; treatments were separated by 7 months. †Determined based on cell counts in the 2 days before infusion. ‡Total cells infused multiplied by %Vβ12. §720,000 international units/kg every 8 hours. All patients were previously refractory to treatment with IL-2 alone. ‖Based on RECIST criteria.





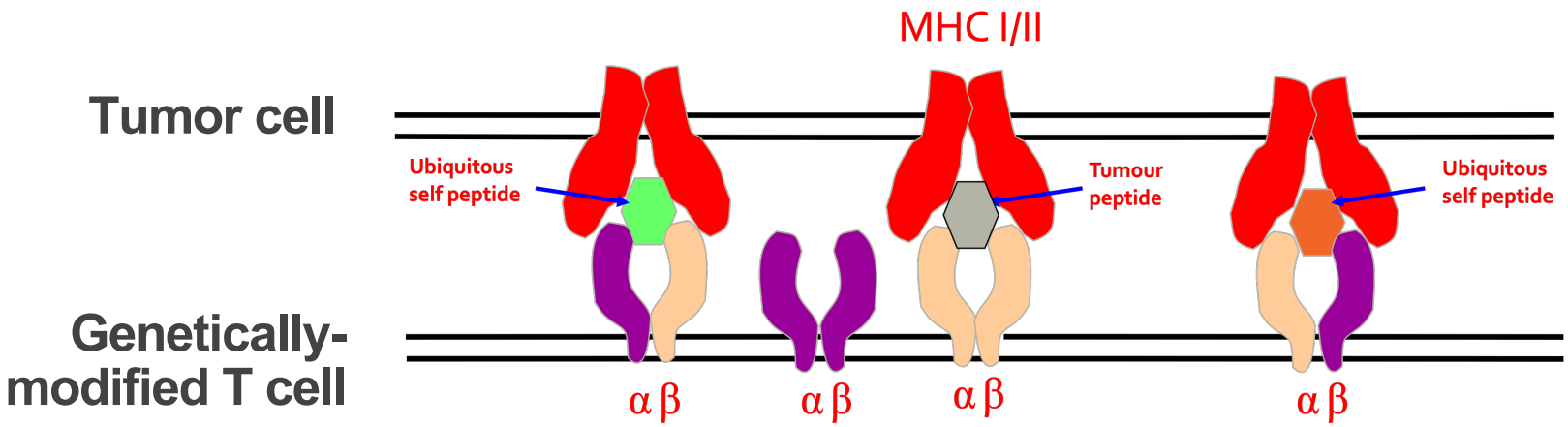
Morgan RA, et al. Science. 2006;314:126–9.

Limitations of TCR-modified T cells

- » Dependent on HLA expression
- » T-cell clones isolated for each HLA background
- » Limited to recognition of either HLA class I or class II molecules
- » Only protein (peptide) specific
- » Undesired autoimmunity

Sharp M, et al. Disease Models & Mechanisms. 2015;8:337–50.

TCR-modified T cells: Risk of autoimmunity



Sharp M, et al. Disease Models & Mechanisms. 2015;8:337–50.

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CAR T cell Therapy of Cancer

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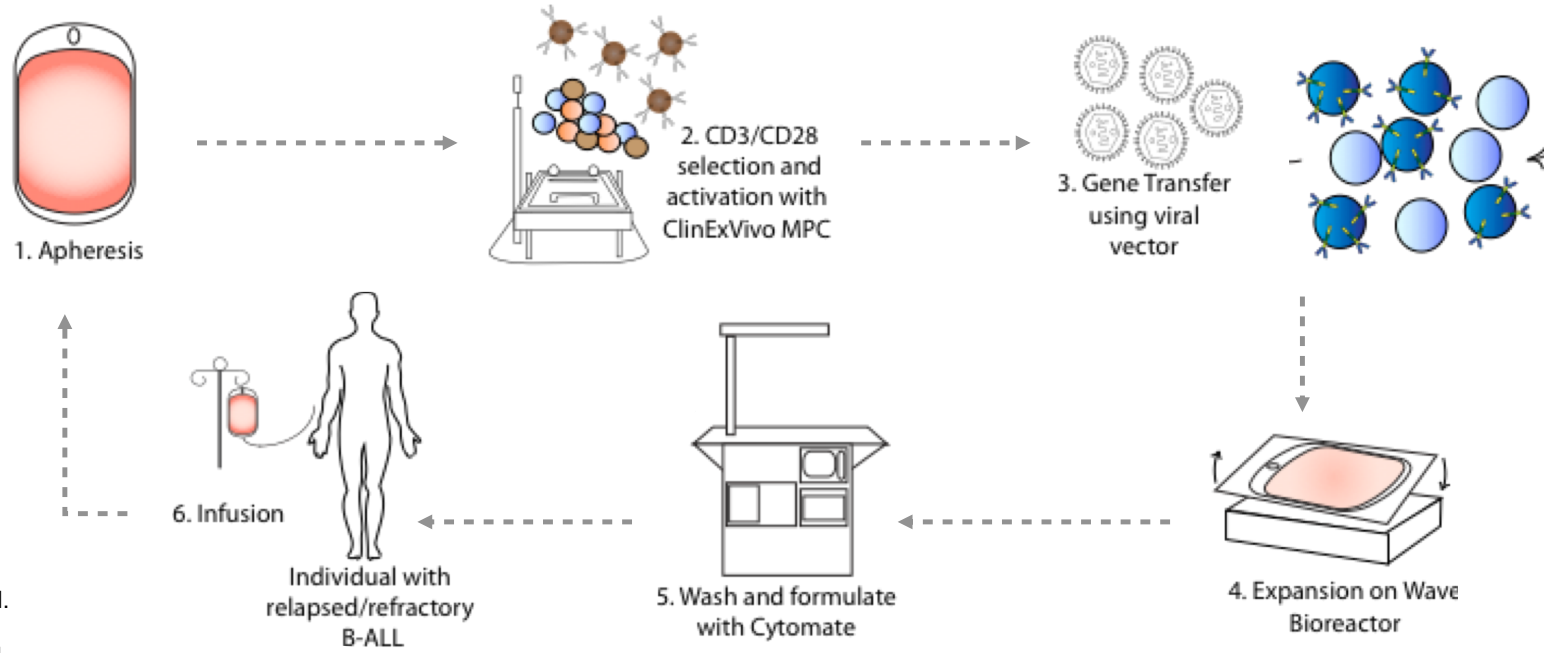
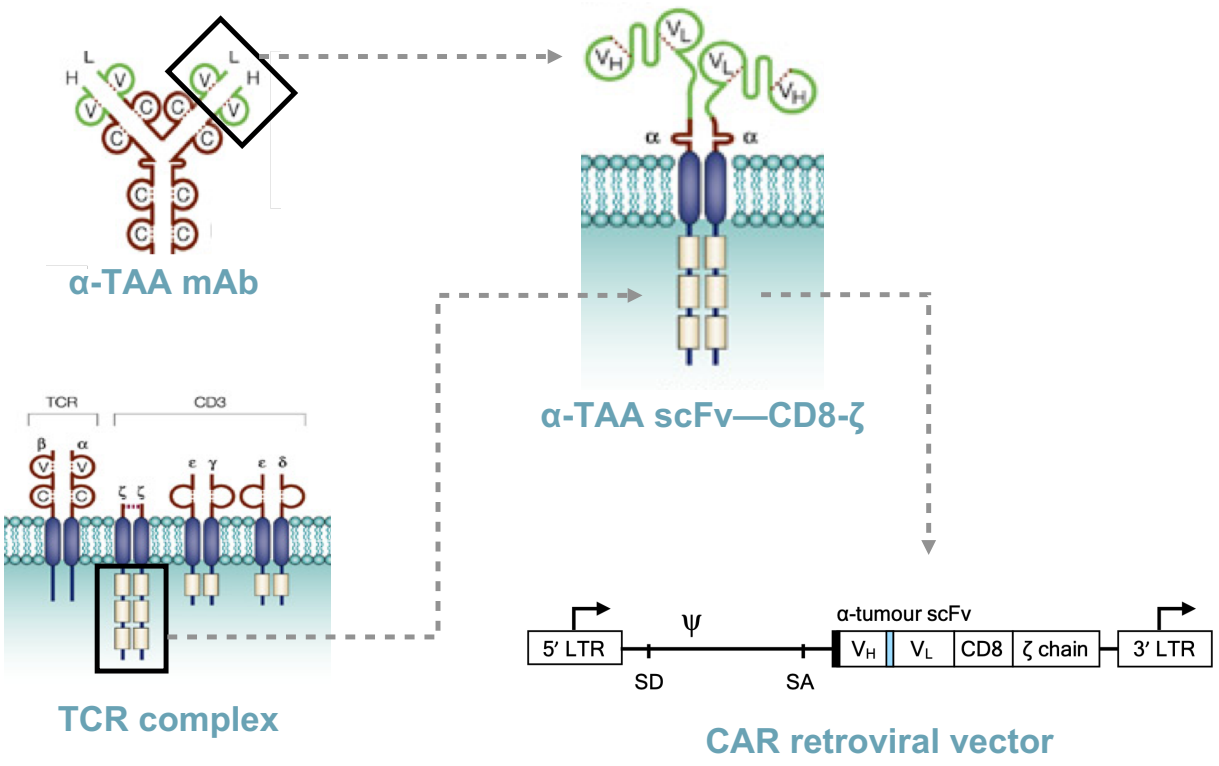
Clinical application: An overview



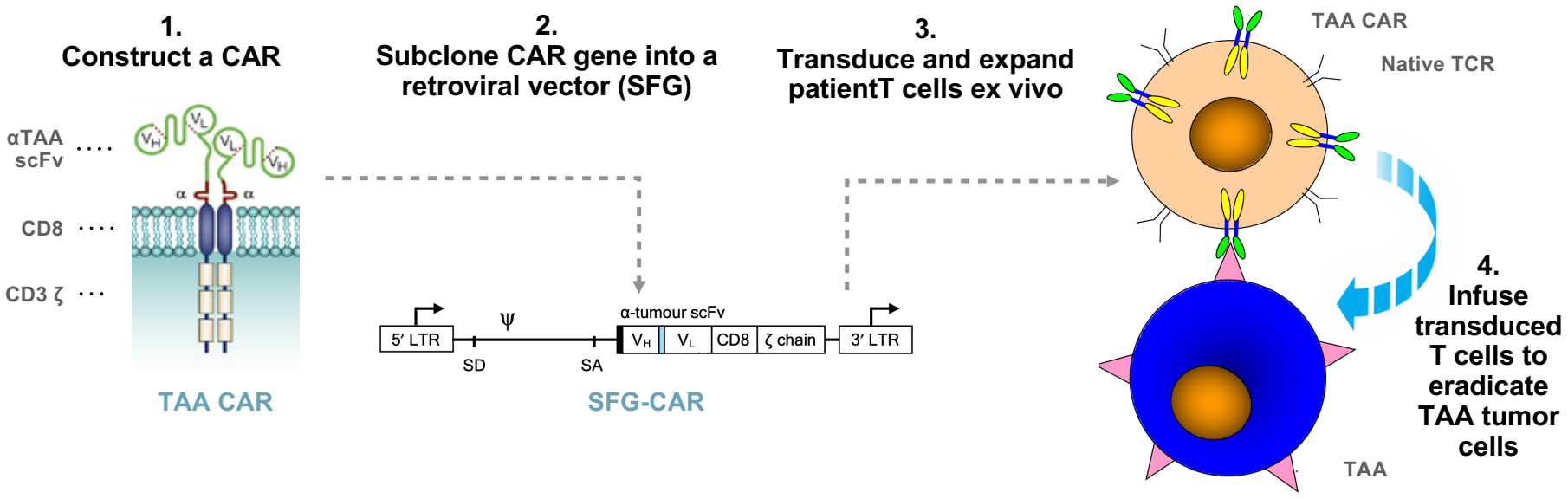
Davila ML, et. al.
Int J Hematol.
2014;99:361–71.

Generation of a tumour-targeted CAR



Sadelain M, et al.
Nat Revs Cancer.
2003;3:35–45.

Generation of TAA-targeted T cells for treatment of cancer



Sadelain M, et al. Nat Revs Cancer. 2003;3:35–45.

What is the ideal TAA?

Qualities of the "ideal" tumour antigen:

- » Expression restricted to the tumour cell population alone
- » Restricted expression to tumour and otherwise non-vital tissues
- » Expressed by all tumour cells
- » Expressed on the tumour cell surface
- » The target antigen is required by the tumour cell for survival

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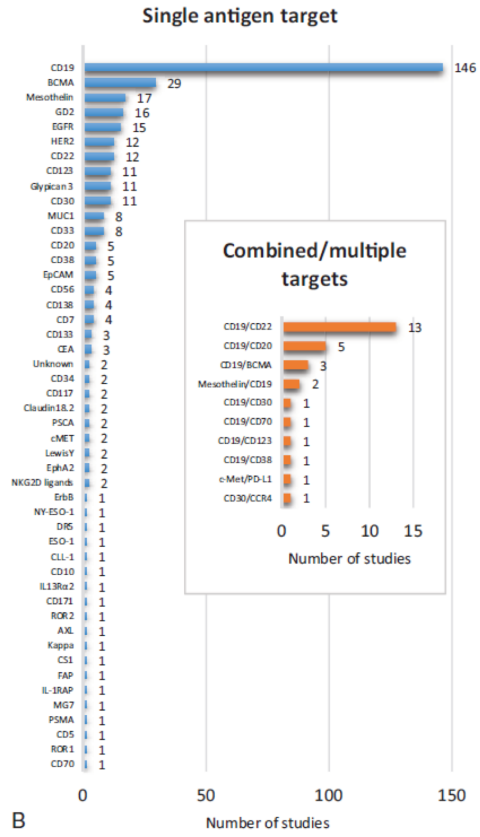
Cheever MA, et al. Clin Cancer Res. 2009;15:5323–37.

CAR T cell targets for the treatment of haematological malignancies

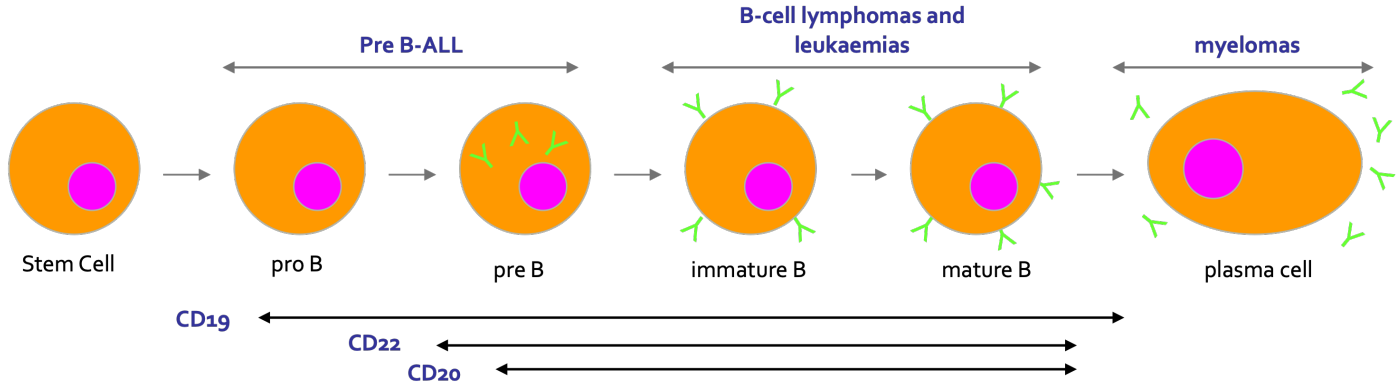
Antigen target	CAR structure	Malignancy
CD19	CD3ζ and CD28 or CD3ζ and 4-1BB	B-ALL, CLL, DLBCL, FL, MCL
CD22	CD3ζ and CD28	B-ALL, DLBCL, FL, NHL
CD20	CD3ζ or and CD3ζ and 4-1BB	CD20-positive malignancies
ROR1	CD3ζ and 4-1BB	CLL, SLL
Igk	CD3ζ and CD28	CLL, low-grade malignancies
CD30	CD3ζ and CD28	HL, NHL
CD123	CD3ζ and CD28	AML
CD33	CD3ζ and 4-1BB	AML
LeY	CD3ζ and CD28	AML
BCMA	CD3ζ and 4-1BB	MM
CD138	CD3ζ and 4-1BB	MM

1. Jackson HJ, et al. Nat Rev Clin Oncol. 2016;13:370–83; 2. Charrot S and Hallam S. Hemasphere. 2019;3:e188.



CD19

- CD19 expression is restricted to B cells and possibly follicular dendritic cells
- CD19 is not expressed on pluripotent bone marrow stem cells

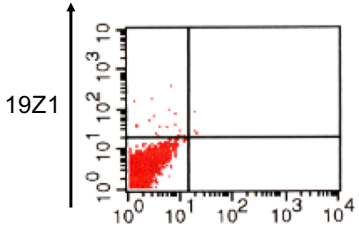


- CD19 is expressed on the surface of most B-cell malignancies
- Antibodies against CD19 inhibit growth of tumour cells

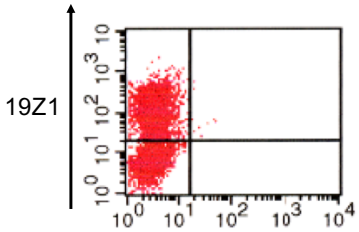
Mostolizadeh R, et al. Numer Algebra Control Optim. 2018; 8:63–80; Wang K, et al. Exp Hematol Oncol. 2012;1:36.

19z1+ T cells lyse CD19+ tumour cells in vitro and in vivo

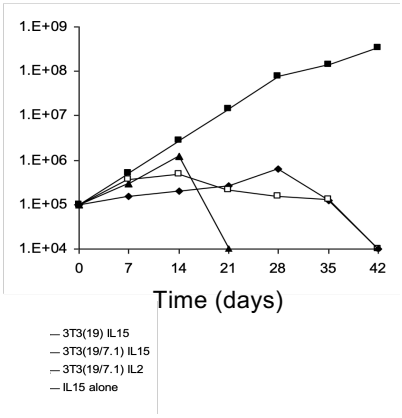
A. **Un-transduced T cells**



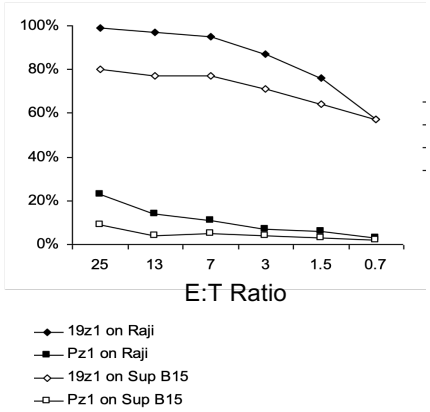
19Z1 transduced T cells



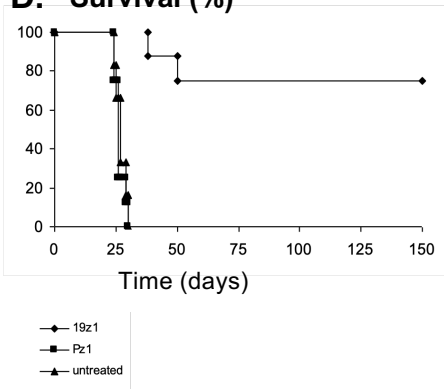
B. **Cell count**



C. **Lysis**



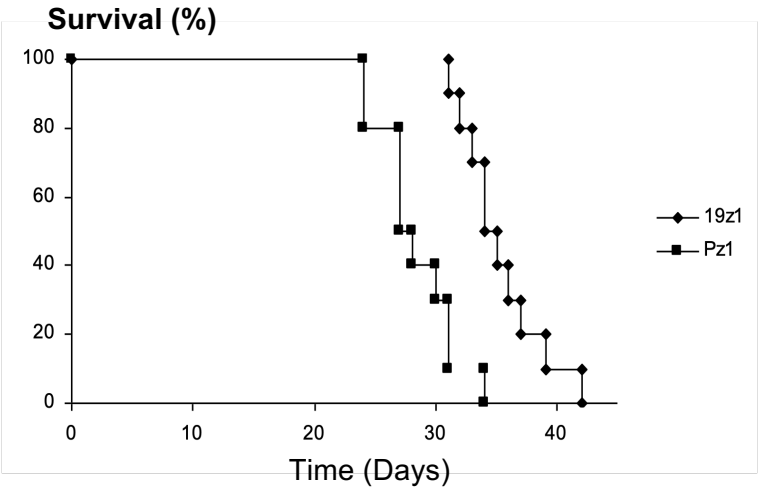
D. **Survival (%)**



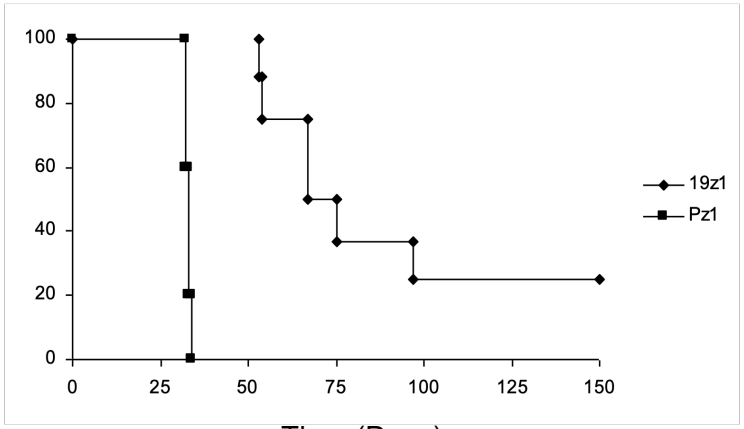
Brentjens RJ, et al. Nat Med. 2003;9:279–86.

19z1+ T cells require in vivo co-stimulation

NALM6



NALM6/CD80



Brentjens RJ, et al. Nat Med. 2003;9:279–86.

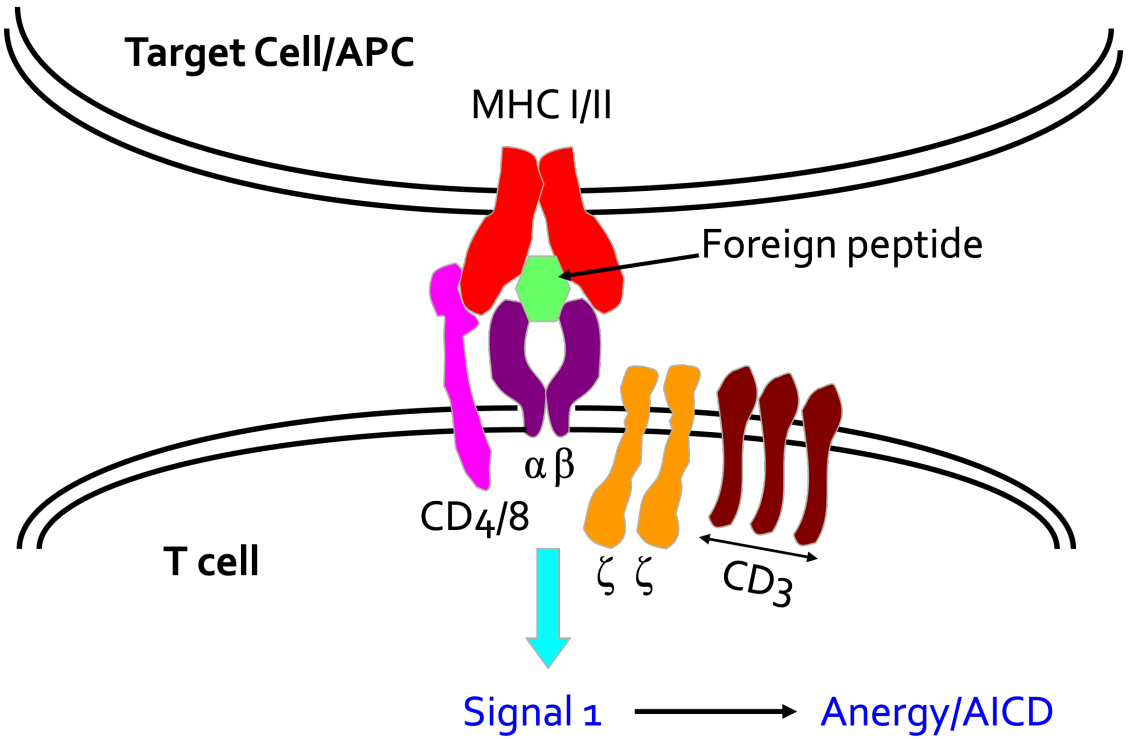
T-cell co-stimulation

T-cell activation and proliferation requires both signaling through the TCR (signal 1) and signaling through a co-stimulatory receptor (signal 2) (CD28, 4-1BB, OX-40)[1]

In the absence of co-stimulation (signal 2), the T cell will either become unresponsive (anergic) or undergo activation-induced cell death (AICD/apoptosis)[2]

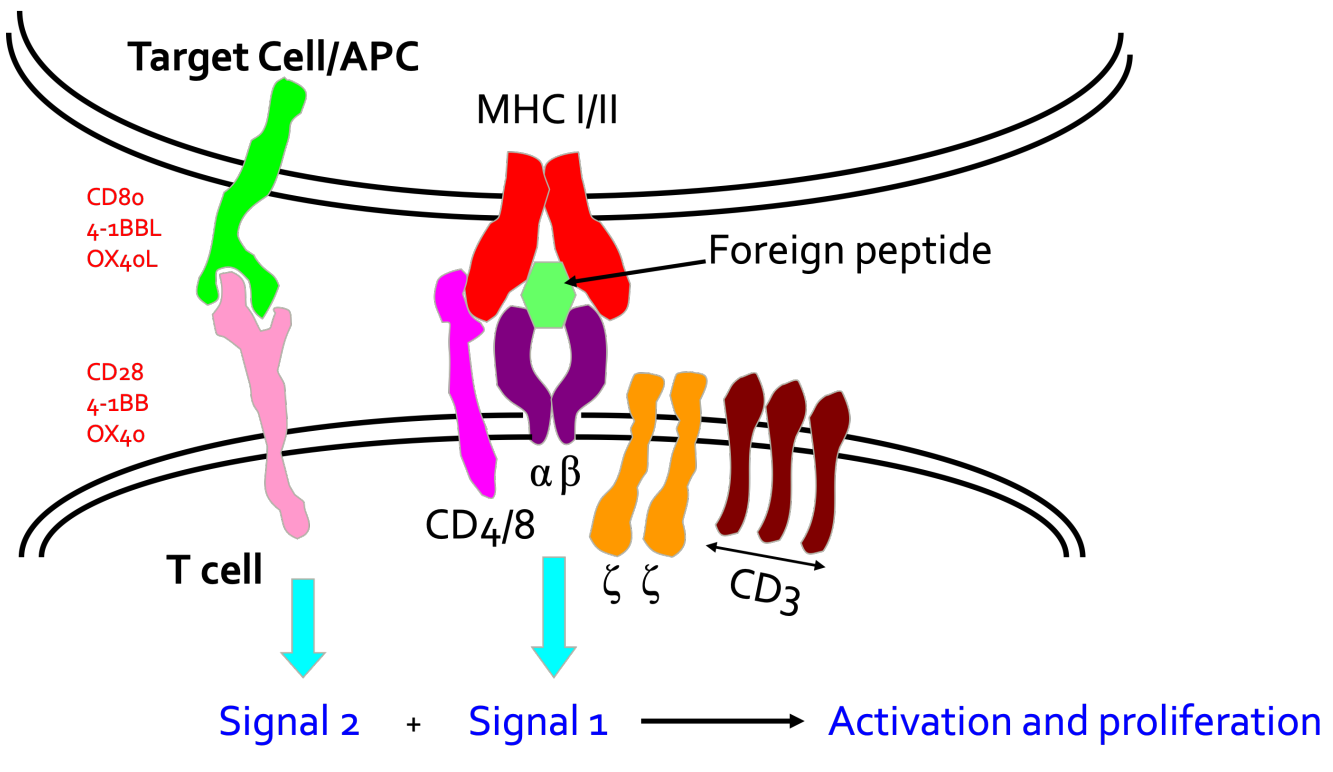
1. Cavanagh M. Bitesized Immunology: T cell activation. British Society for Immunology. Available at https://www.immunology.org/public-information/bitesized-immunology/systems-and-processes/t-cell-activation. Accessed August 2020;
2. Arlen P, et al. Future Oncol. 2009;5:187–96.

T-cell activation and anergy/cell death



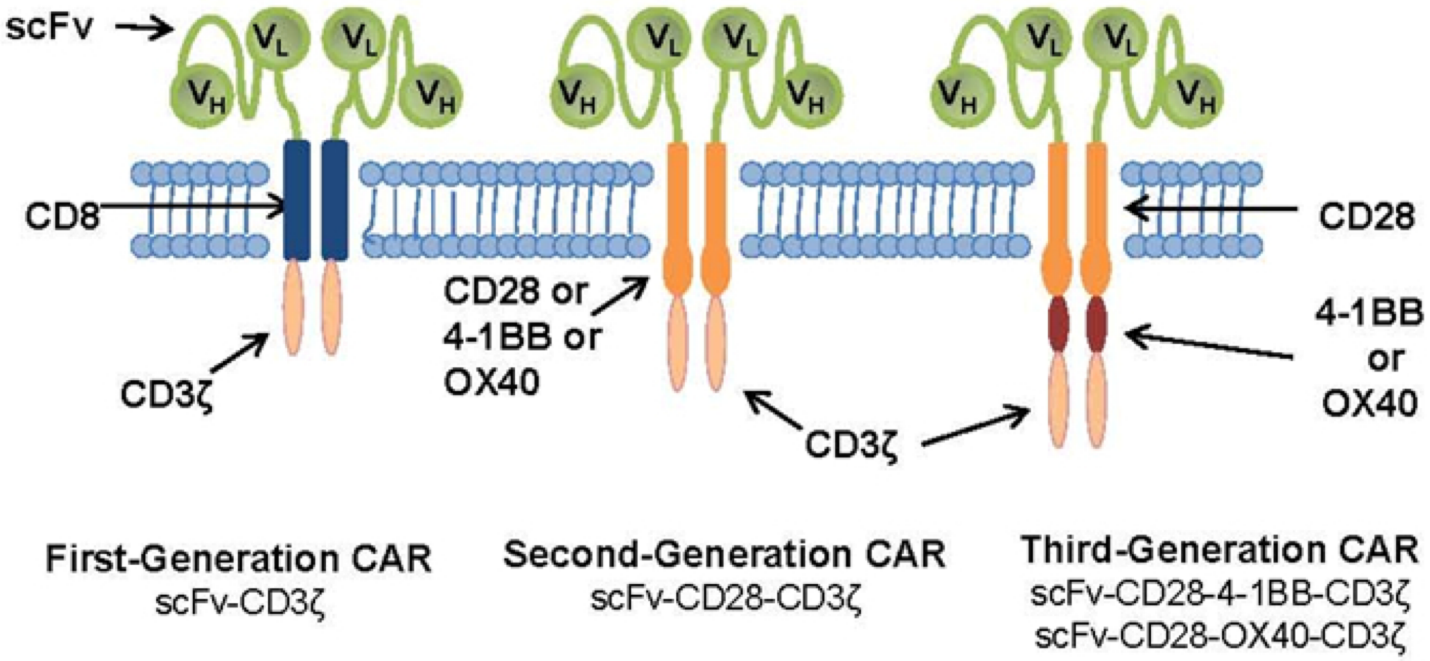
Cavanagh M. Bitesized Immunology: T cell activation. British Society for Immunology. Available at https://www.immunology.org/public-information/bitesized-immunology/systems-and-processes/t-cell-activation. Accessed August 2020;
Arlen P, et al. Future Oncol. 2009;5:187–96.

T-cell activation and anergy/cell death



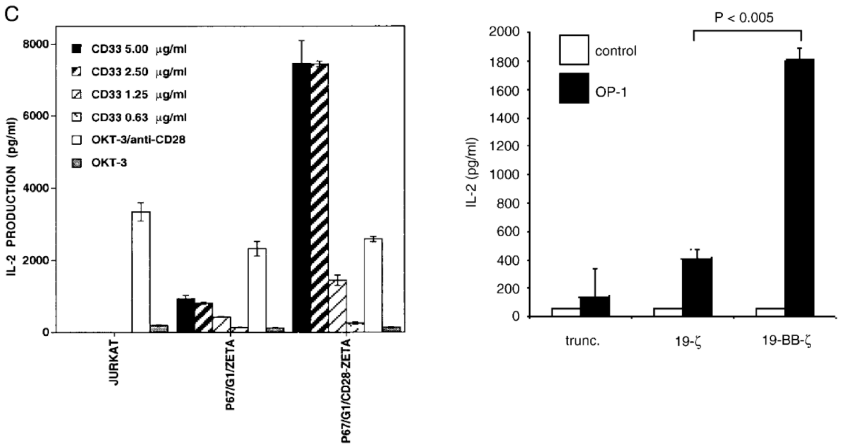
Cavanagh M. Bitesized Immunology: T cell activation. British Society for Immunology. Available at https://www.immunology.org/public-information/bitesized-immunology/systems-and-processes/t-cell-activation. Accessed August 2020;
Arlen P, et al. Future Oncol. 2009;5:187–96.

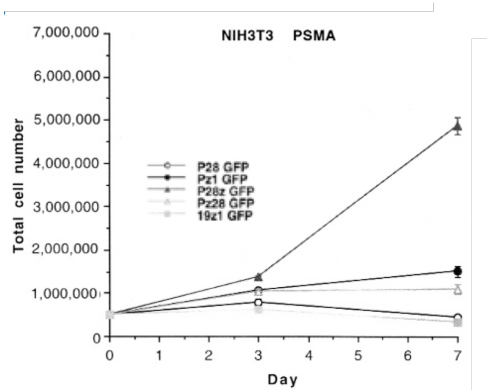
Evolution in CAR design



Park JH and Brentjens RJ. Discov Med. 2010;9:277–88.

Second-generation CARs: in vitro



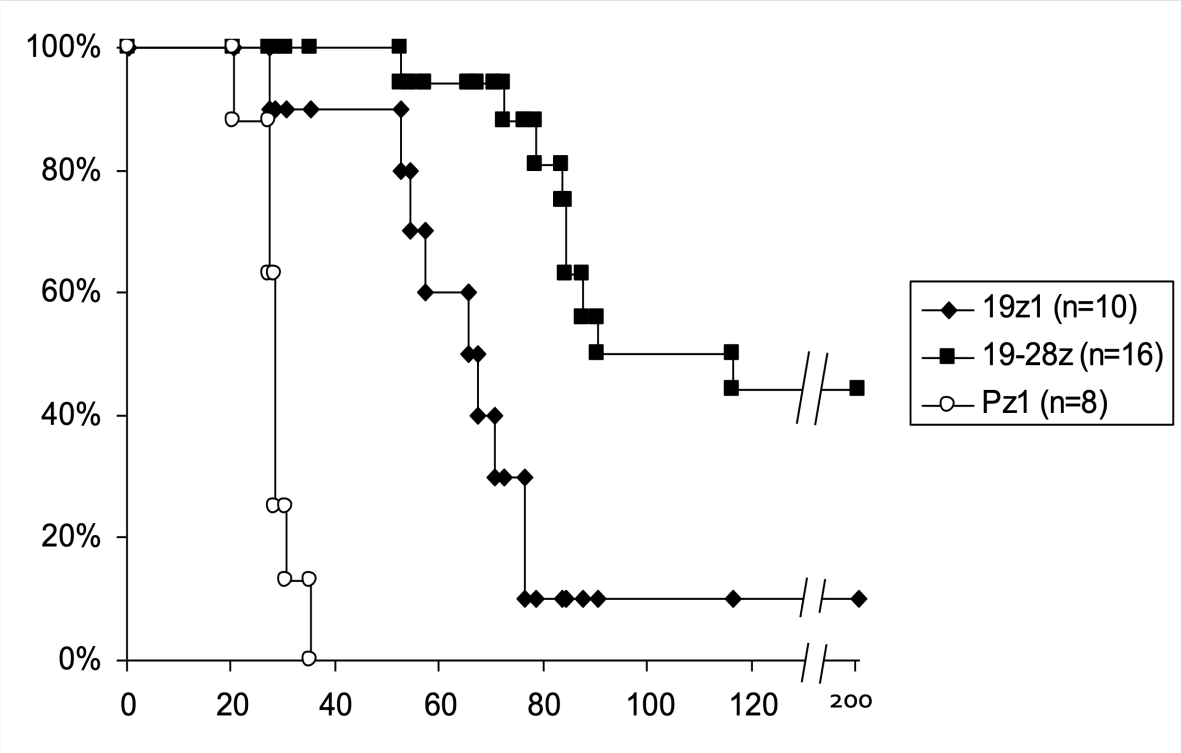


Finney HM, et al. J Immunol. 1998;168:2791–97;
Imai C, et al. Leukemia. 2004;18:676–84;
Maher J, et al. Nat Biotechnol. 2002;20:70–5.

Table 1. Interleukin-2 production by human PBL transduced with different CD3ζ–CD28 fusion receptors[a]

Fibroblast feeder	PSMA-specific receptor			
	P28	Pz1	P28z	Pz28
Unmodified NIH3T3	<50 (–)	<50 (–)	<50 (–)	<50 (–)
B7.1	<50 (–)	<50 (–)	<50 (–)	<50 (–)
PSMA	<50 (–)	<50 (–)	21,900 (1,153)	<50 (–)
PSMA + B7.1	<50 (–)	164,236 (3,285)	52,936 (2,786)	29700 (958)

Second-generation CARs: in vivo



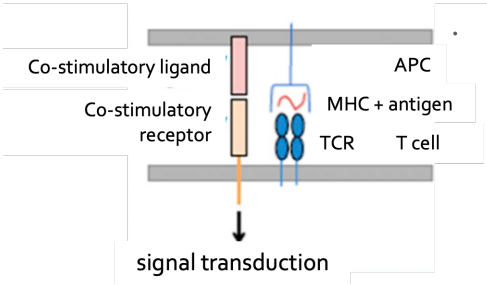
Memorial Sloan Kettering Cancer Center

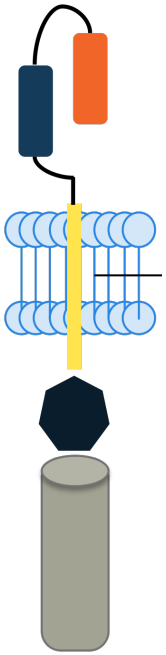
Brentjens RJ, et al. Clin Can Res. 2007;13:5426–35.

CAR structure: Mechanism of action

The scFv recognises target antigens for **tumour specificity**

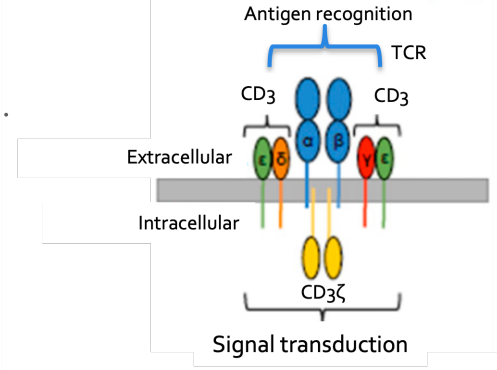
Signalling through a co-stimulatory domain increases **T-cell function, survival and proliferation**





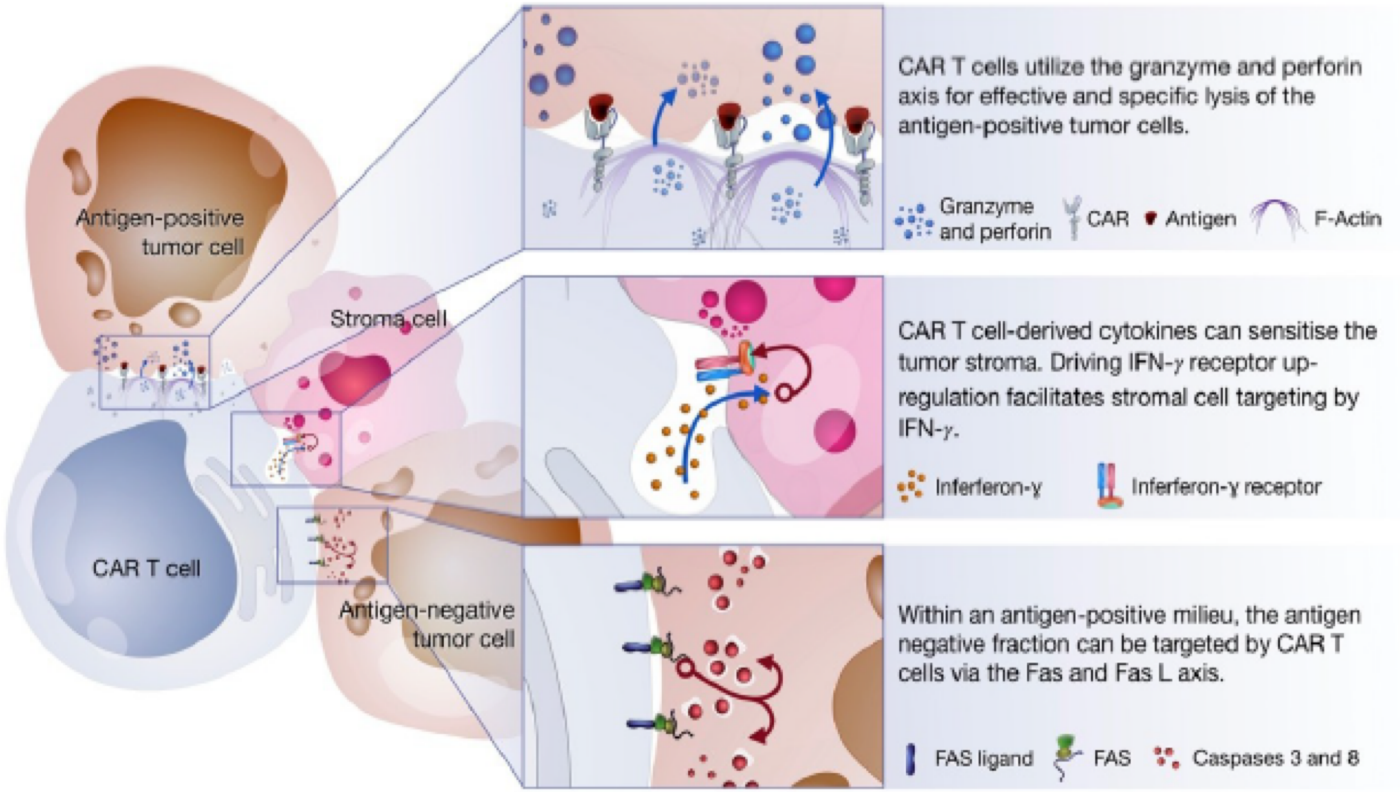
The hinge provides sufficient **flexibility** to overcome steric hindrance and adequate **length** to facilitate access to target antigen

The CD3ζ chain allows **activation** of T-cell signalling



Gills S, June C. Immunol Rev 2015; 263:68–89;
Maus MV and Levine BL. Oncologist. 2016;21:608–17.

CAR T cell: Mechanism of action (2)



Benmebarek MR, et al.
Int J Mol Sci.
2019;20:1283.

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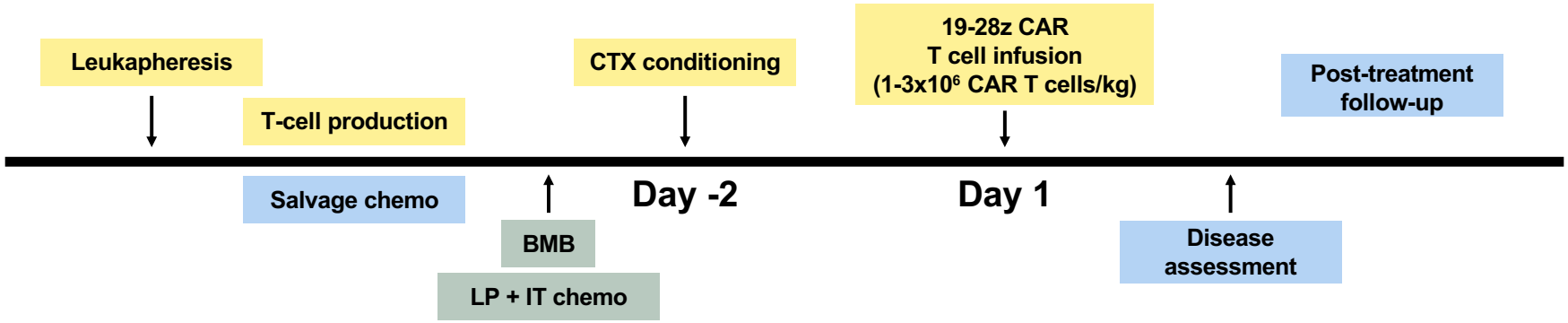
Clinical Trial Outcomes:

CD19-targeted CAR T cells to treat R/R B-cell ALL

Memorial Sloan Kettering Cancer Center

A Phase 1 trial of precursor B-ALL treated with autologous T cells genetically targeted to the B-cell-specific antigen CD19



Inclusion Criteria

- Adult patients, age ≥18
- R/R CG19+ B-ALL
- Relapsed after allogeneic HSCT allowed

Exclusion Criteria

- Active CNS disease
- Active GvHD requiring immunosuppressants
- Significant heart disease (MI ≤ 6 months or NYHA III/IV CHF or EF < 40%)

Brentjens R et al. Sci Transl Med. 2013;5:177ra38; Clinical trials. NCT01044069. Available at: https://clinicaltrials.gov/ct2/show/NCT01044069. Accessed August 2020.

Patient characteristics and treatment outcomes

*MSK-ALL02 patient was removed from the study prior to the planned T-cell infusion because they deferred T-cell infusion for an allo-SCT.

**Disease status within 1 week of infusion with CD19-targeted T cells.

***This patient's T cells were harvested while in remission. All other patients listed had their T cells harvested while they had relapsed disease.

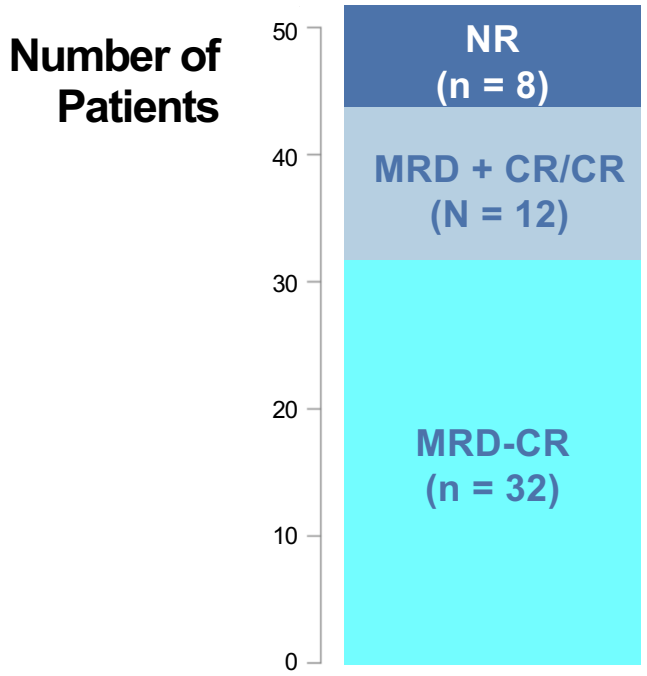
Brentjens R, et al. Sci Transl Med. 2013;5:177ra38.

Patient ID*	Age	FISH/Cyto genetics	Initial therapy	Duration of CR1	Salvage therapy	Disease response to salvage therapy**	Disease response	Steroids	Outcome
MSK-ALL01	66	Normal karyotype	Mito/Cy → Vinc/Pred → Cy → Etop/Cy	27 weeks	Vinc/Pred/Peg	MRD+	MRD-	N	Allo-SCT
MSK-ALL03	56	Normal karyotype	HyperCVAD	45 weeks	Inotuzumab ozogamicin → Vinc/Pred/Peg	MRD-	MRD-	N	Allo-SCT
MSK-ALL04	59	t(9;11), 9p21 deletion	ECOG2993(24)	5 weeks	Vinc/Pred	Refractory disease, 63% blasts in BM	MRD-	Y	Ineligible for Allo-SCT, relapse 90 days
MSK-ALL05***	58	9p21 deletion	ECOG2993	28 weeks	HIDAC/Mito	Refractory disease, 70% blasts in BM	MRD-	Y	Allo-SCT
MSK-ALL06	23	Normal karyotype	NYII ref (25)	34 months	Modified NYII Consolidation I ref (25)	MRD+	MRD-	N	Allo-SCT

Study outcome: Complete remission rates

MRD was assessed by multiparameter flow cytometry with a sensitivity of 10-4.

MRD assessment available in 48 patients with available BMA samples.



» Overall CR rate: **84.6%** (44 of 52 pts)

» MRD-CR rate: **66.6%** (32 of 48 evaluable pts)

Park J, et al. ASCO 2017; Abstract 7008.

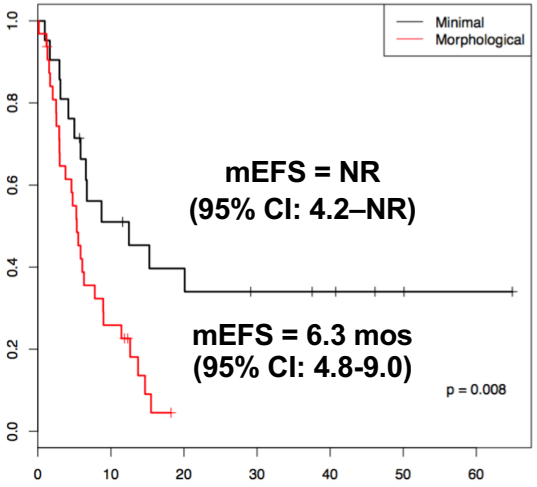
Long-term outcome: By pretreatment disease burden

Memorial Sloan Kettering Cancer Center

Park J, et al. ASCO 2017; Abstract 7008.

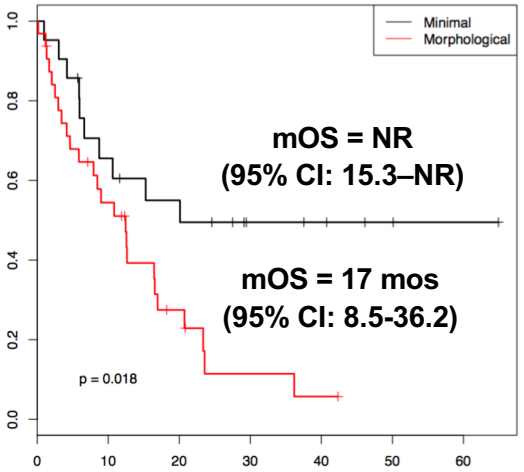
EFS

Proportion surviving



Time from T cell

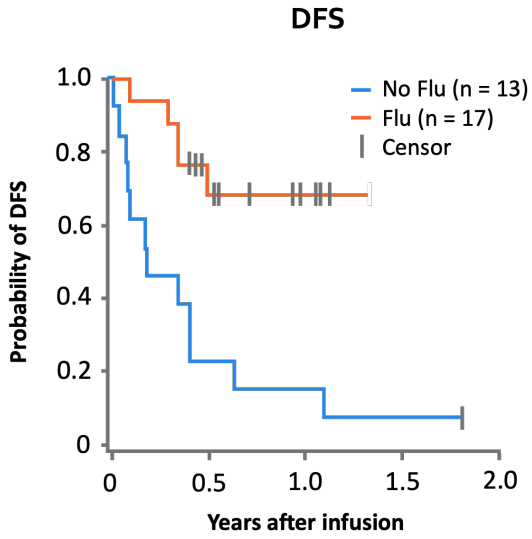
OS



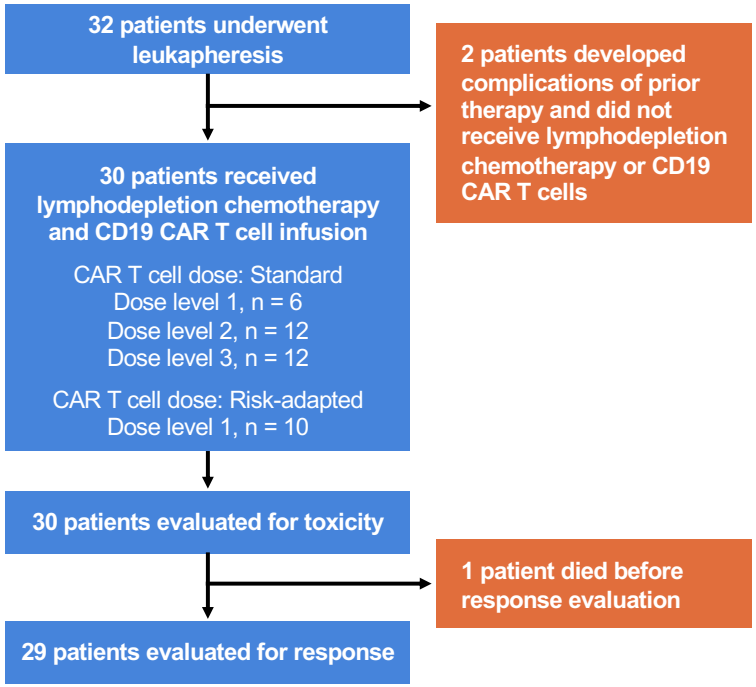
Time from T cell

Median follow-up = 29 months (range, 1-65)

CD19 CAR T cells: Adult B-ALL (FHCRC, 19-41BBz)



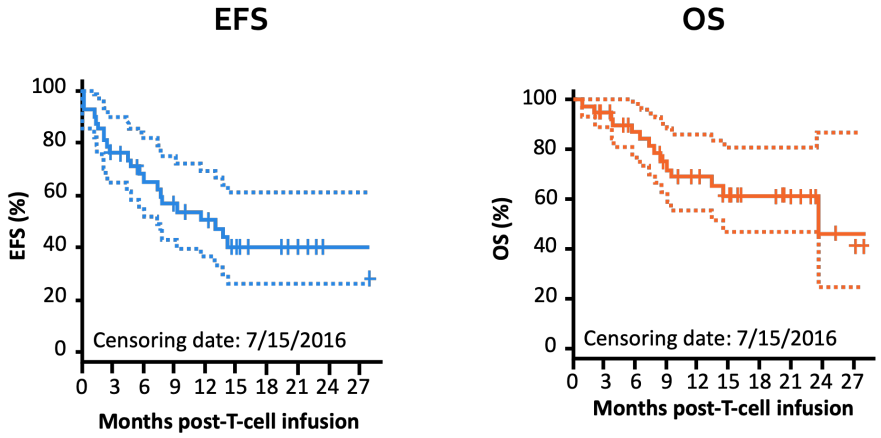
Patient disposition



Turtle CJ, et al. J Clin Invest. 2016;126:2123–38.

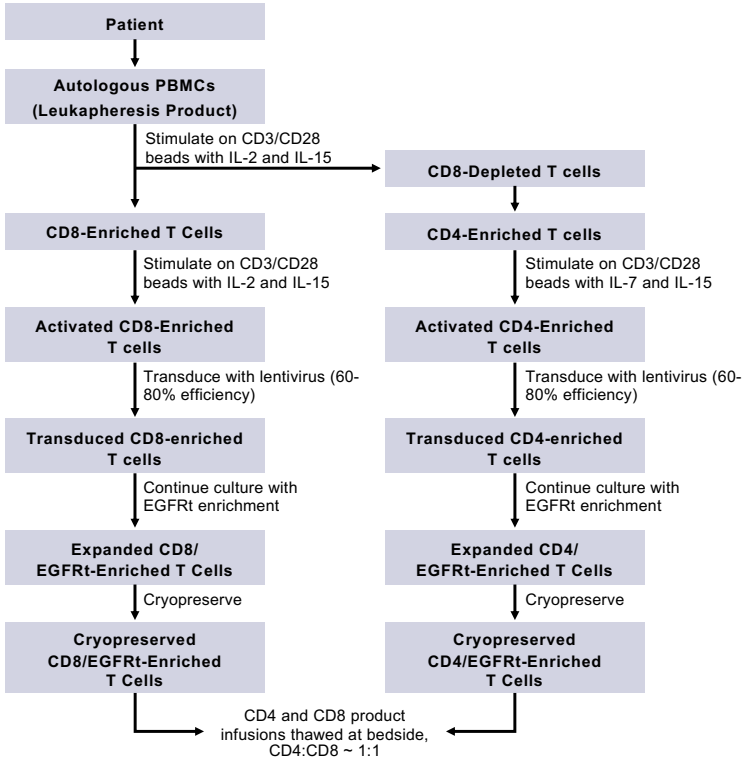
Slide credit: clinicaloptions.com

CD19 CAR T cells: Paediatric B-ALL (SCH/FHCRC, 19-41BBz)

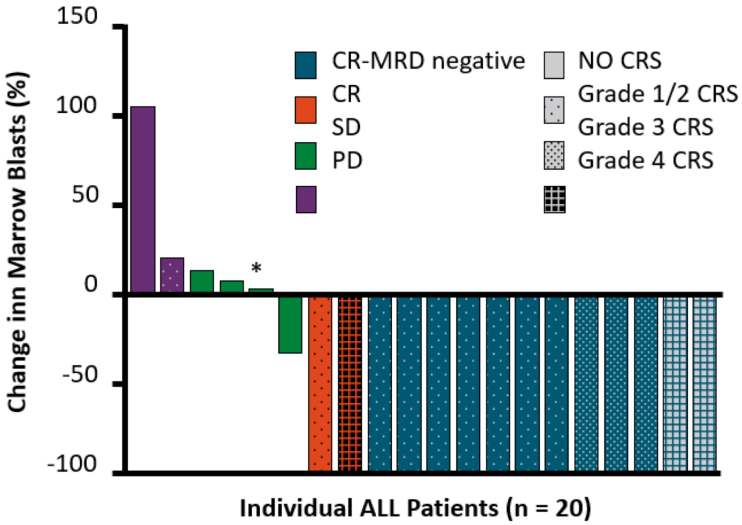


Gardner RA, et al. Blood. 2017;129:3322–31.

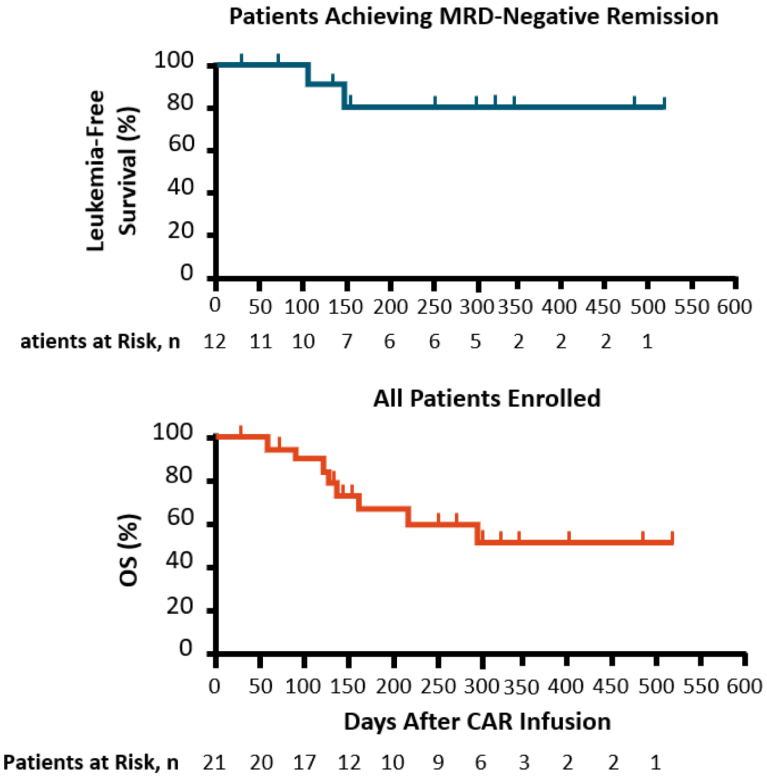
Patient disposition



CD19 CAR T cells: Paediatric B-ALL (NCI, 19-28z)



Lee DW, et al. Lancet. 2015;385:517–28.



Tisagenlecleucel in children and young adults with R/R B-ALL

Phase 2, global, 25-centre study

- Primary endpoint: Overall response in 3 months

92 pts enrolled and 75 pts (82%) treated

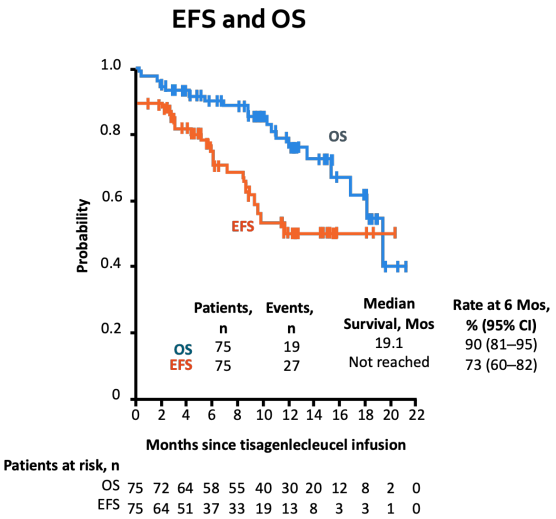
- Median age: 11 (range, 3–23)
- Median prior # of tx: 3 (range, 1–8)
- Prior alloHSCT: 61%

Conditioning regimen: Cy and Flu

T-cell dose (median): 3.1x106 CAR T cells/kg

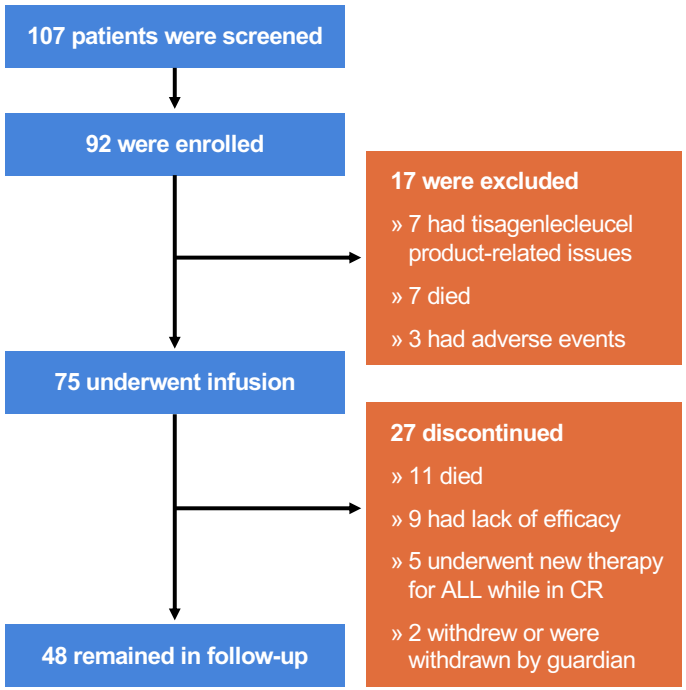
Maude S, et al. N Engl J Med. 2018;378:439–48.

Tisagenlecleucel in children and young adults with R/R B-ALL



Maude S, et al. N Engl J Med. 2018;378:439–48.

Patient disposition



Approved CAR therapy in B-cell ALL

FDA approved tisagenlecleucel (Kymriah) August 2017 for treatment of patients up to age 25 years with B-cell precursor ALL that is refractory or in second or later relapse

- First CAR T-cell immunotherapy approved by FDA
- No CAR T cells approved for adults with ALL older than 25

1. KYMRIAH. FDA Prescribing information. 2018; 2. FDA press release. 2018. Available at: https://www.fda.gov/drugs/resources-information-approved-drugs/fda-approves-tisagenlecleucel-b-cell-all-and-tocilizumab-cytokine-release-syndrome#:~:text=On%20August%2030%2C%202017%2C%20the,in%20second%20or%20later%20relapse. Accessed August 2020.

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Clinical Trial Outcomes:

CD19-targeted CAR T cells to treat DLBCL

Memorial Sloan Kettering
Cancer Center

Axicabtagene ciloleucel in R/R DLBCL [ZUMA-1]

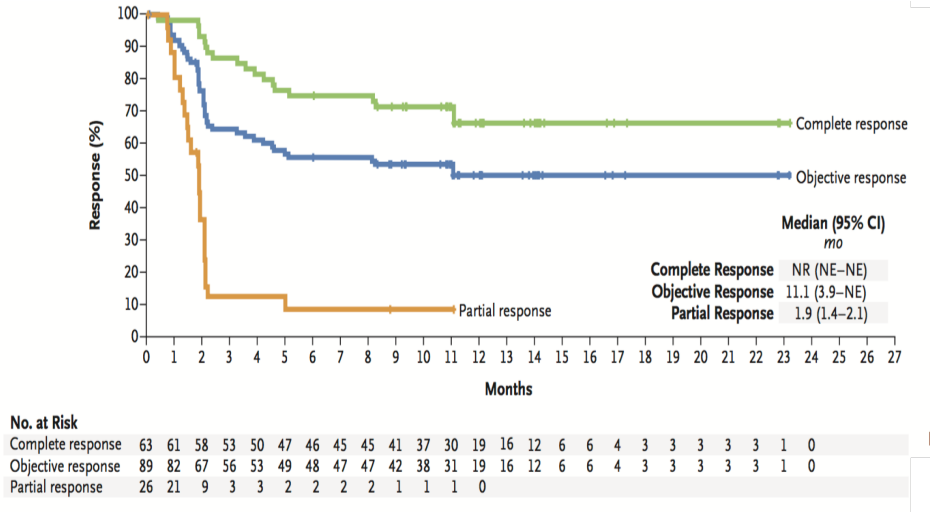
Baseline patient characteristics

- Primary endpoint: ORR
- Conditioning regimen: Flu 30 mg/m2 and Cy 500 mg/m2 x 3d
- CAR T cell dose: 2x106 CAR T cells/kg

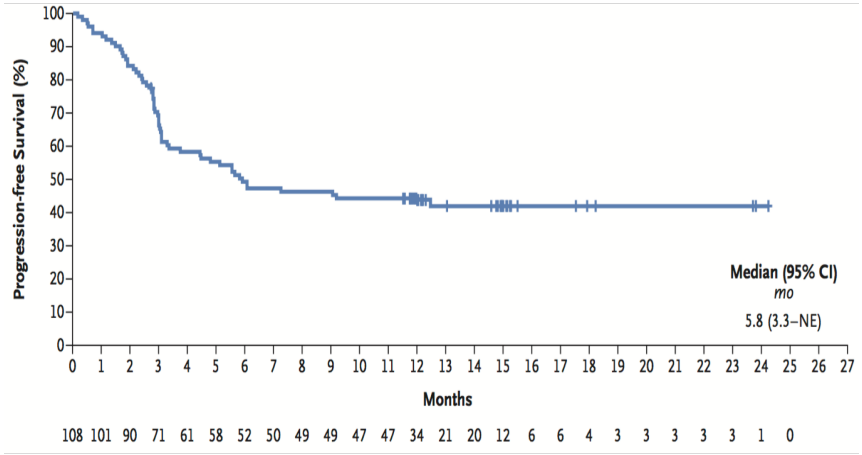
Baseline characteristics	Pts (n = 111)
Median age, yrs (range) §≥ 65 yrs, %	58 (23-76) 24
Histology, % §DLBCL §Transformed FL	 73 27
No. prior lines of antineoplastic tx §≥ 3	 69
Prior autoHSCT	21

Neelapu S, et al. N Engl J Med. 2017;377:2531–44.

Axicabtagene ciloleucel in R/R DLBCL: Survival



No. at Risk																								
Complete response	63	61	58	53	50	47	46	45	45	41	37	30	19	16	12	6	6	4	3	3	3	3	1	0
Objective response	89	82	67	56	53	49	48	47	47	42	38	31	19	16	12	6	6	4	3	3	3	3	1	0
Partial response	26	21	9	3	3	2	2	2	2	1	1	1	0											



Neelapu S, et al. N Engl J Med. 2017;377:2531–44.

Tisagenlecleucel in R/R DLBCL [JULIET]: Baseline patient characteristics

238 pts screened → 165 enrolled → 111 pts treated

- Primary endpoint: ORR
- Conditioning: Flu 25 mg/m2 + Cy 250 mg/m2 x 3d or Benda 90 mg/m2 x2d
- CAR T cell dose: median, 3x108 CAR T cells (0.1–6.0x108)

Baseline characteristics	Pts (n = 111)
Median age, yrs (range)	56 (22–76)
§≥ 65 yrs, %	23
Histology, %	
§DLBCL	79
§Transformed FL	19
No. prior lines of antineoplastic tx	
§≥ 3	52
Prior autoHSCT	49

Schuster S, et al. N Engl J Med. 2019;380:45–56.

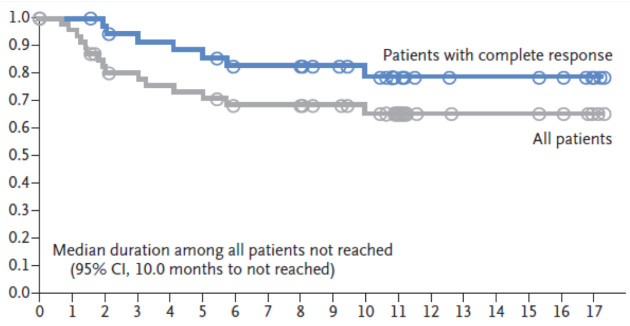
Tisagenlecleucel in R/R DLBCL: Response and survival

ORR: 52%

(40% CR + 12% PR)

Duration of response

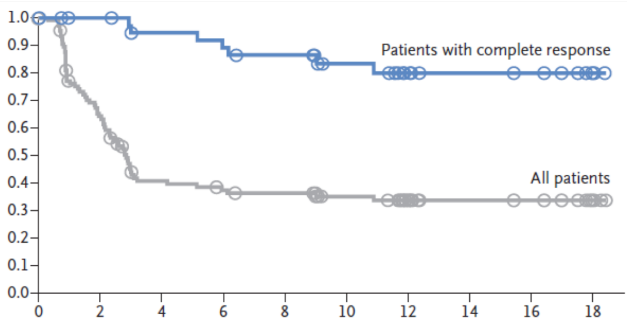
Probability of Maintaining Response



No. at Risk																	
Patients with complete response	37	36	35	32	31	30	26	26	26	23	21	15	9	8	8	8	7	4
All patients	48		37		32		27		27		22		10		9		8	

Progression-free survival

Probability of Remaining Progression-Free



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

Schuster S, et al. N Engl J Med. 2019;380:45–56.

Approved CAR therapy in B-cell ALL

FDA approved axicabtagene in October 2017 for treatment of adult patients with R/R large B-cell lymphoma after ≥ 2 lines of systemic therapy, including DLBCL not otherwise specified, primary mediastinal large B-cell lymphoma, high-grade B-cell lymphoma, and DLBCL arising from follicular lymphoma[1,2]

FDA approved tisagenlecleucel May 2018 for treatment of adult patients with R/R large B-cell lymphoma after ≥ 2 lines of systemic therapy, including DLBCL not otherwise specified, high-grade B-cell lymphoma, and DLBCL arising from follicular lymphoma

- FDA approved with a Risk Evaluation and Mitigation Strategy3,4

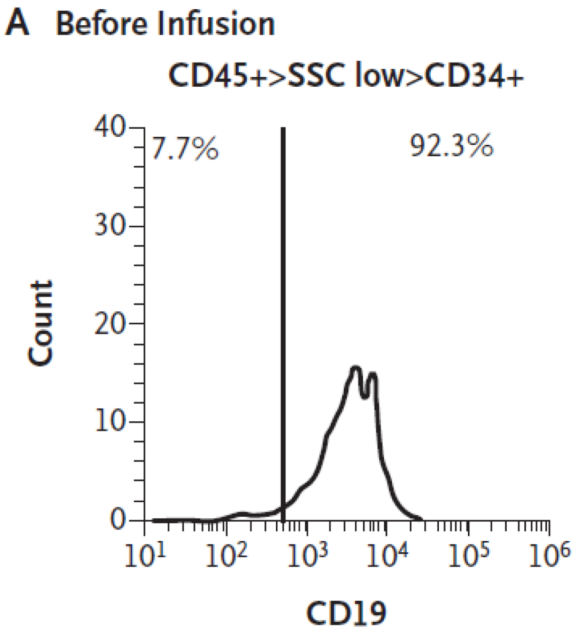
1. YESCARTA. FDA Prescribing information. 2017;
2. FDA press release. 2017. Available at: https://www.fda.gov/drugs/resources-information-approved-drugs/fda-approves-axicabtagene-ciloleucel-large-b-cell-lymphoma. Accessed August 2020;
3. KYMRIAH. FDA Prescribing information. 2018;
4. FDA press release. 2018. Available at: https://www.fda.gov/drugs/resources-information-approved-drugs/fda-approves-tisagenlecleucel-adults-relapsed-or-refractory-large-b-cell-lymphoma. Accessed August 2020.

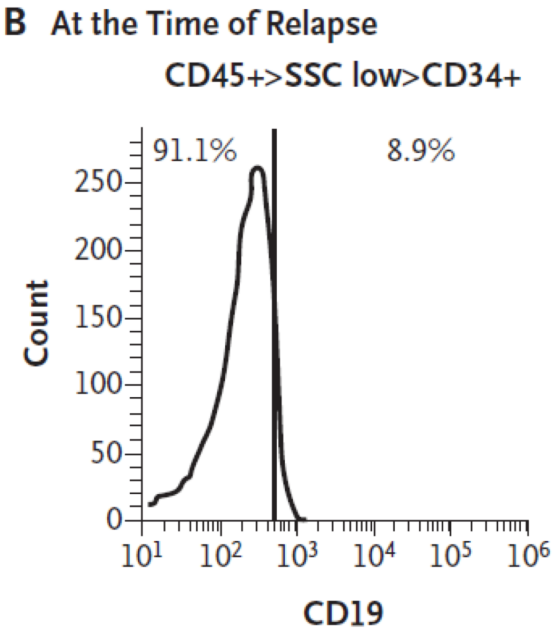
CD19-targeted CAR T cells and DLBCL

	Axicabtagene ciloleucel	Tisagenlecleucel	Lisocabtagene maraleucel
Study populations	DLBCL, TFL, PMBCL	R/R DLBCL	CORE DL2*
Target antigen	CD19	CD19	CD19
Lymphodepletion	Flu/Cy	Flu/Cy	Flu/Cy
Costimulatory domain	CD28	4-1 BB	4-1 BB
T cell composition	Unspecified	Unspecified	1:1 CD4:CD8
Cell dose	2 x 10^6 cells/kg	5 x 10^8	1 x 10^8
OR (best)	82% (n = 108)	53% (n = 81)	81% (n = 27)
OR (6 mo)	41% (n = 101)	37% (n = 46)	50% (n = 14)
CR (best)	58% (n = 108)	40% (n = 81)	63% (n = 27)
CR (6 mo)	36% (n = 101)	30% (n = 46)	50% (n = 14)
Any grade CRS/NT†	94%/87% (n = 108)	58%/21% (n = 99)	24%/17% (n = 29)
≥Grade 3 CRS†	12% (n = 108)	23% (n = 99)	0% (n = 29)
≥Grade 3 NT†	31% (n = 108)	12% (n = 99)	7% (n = 29)
Grade 5 AEs	4% (n = 108)‡	None	—

Chow VA, et al. Blood. 2018;132:7 77–81.

Relapsed disease with loss of CD19 expression: UPenn trial





Memorial Sloan Kettering Cancer Center

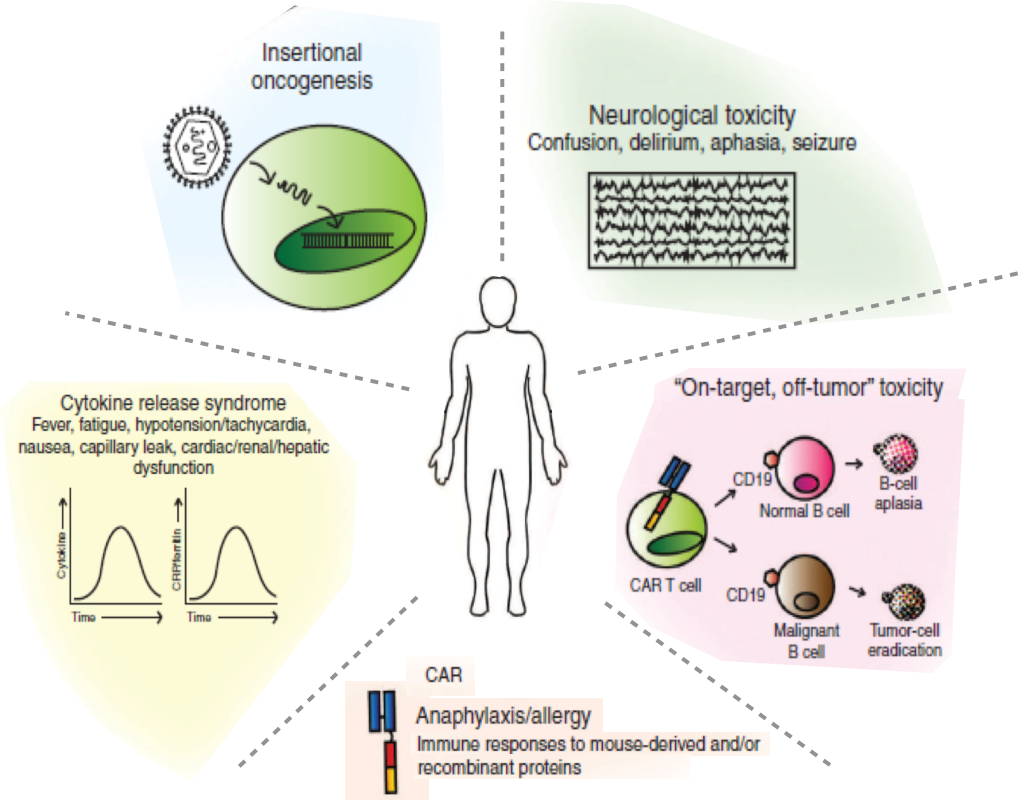
Grupp SA, et al. N Engl J Med. 2013;368:1509–18.

Anti-CD22 CAR T cells in R/R B-ALL

- Nine paediatric and young adult patients with R/R B-ALL patients treated
- Seven patients previously treated with a CD19 CAR T cell, six with loss or dim CD19 expression on relapsed tumor cells
- 22-4-1BBz CAR design
- 44% CR in BM, all MRD-
- CRs seen in both CAR T cell-naïve patients as well as patients with CD19 relapse after CD19 CAR T cell therapy

Shah NN, et al. Blood. 2016;128:650

CAR T cell associated toxicities



Maude S, et al. N Engl J Med. 2018;378:439–48.

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A Brief History of T cell Cancer Therapy: From Transplant to CARs

Questions