„Immunotherapy

of Acute Lymphoblastic Leukemia”

Sebastian Giebel

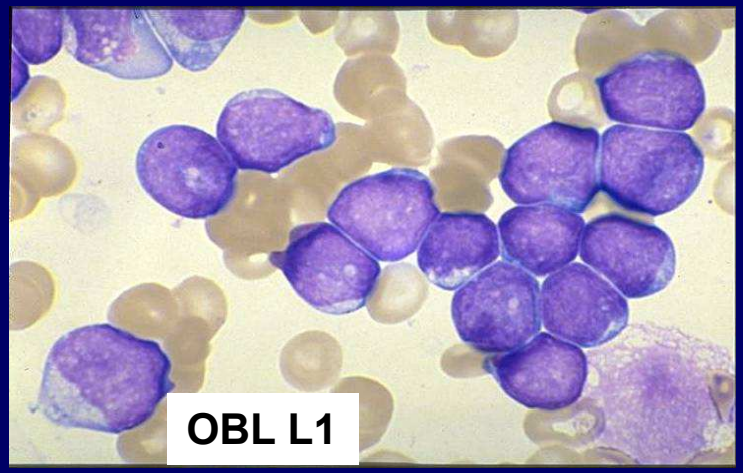
Dept. of Bone Marrow Transplantation
and Onco-Hematology

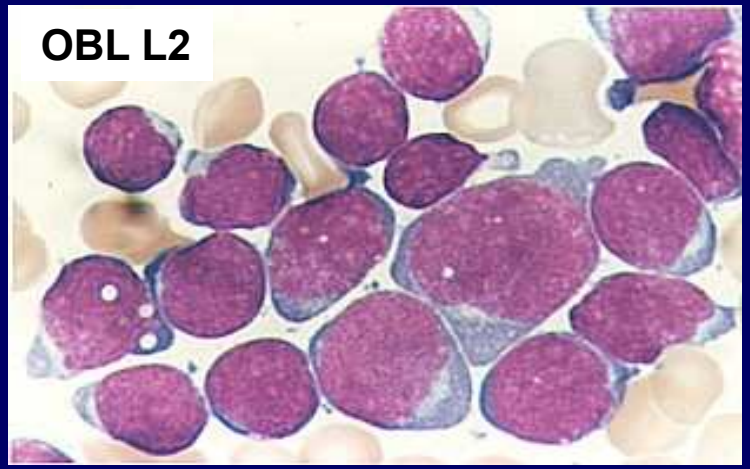
MARIA SKLODOWSKA-CURIE
INSTITUTE – ONCOLOGY CENTER
GLIWICE BRANCH

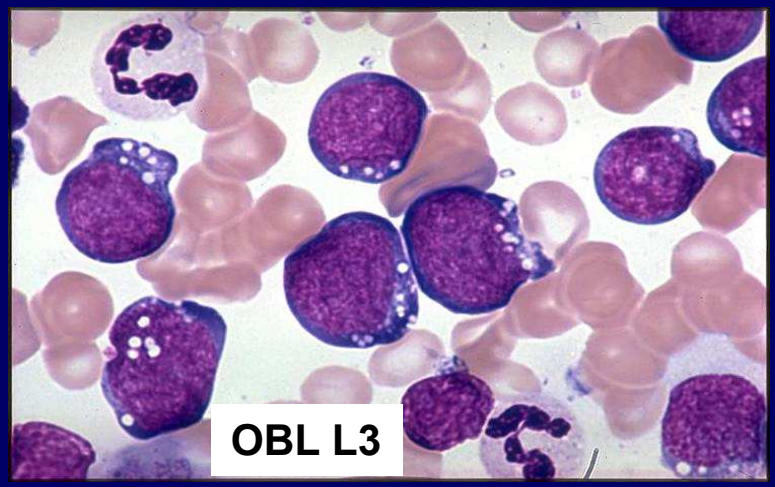
Cancer Immunotherapy

	Non-specific	Targeted
Humoral	-	Naked antibodies Immunotoxins
Humoral → Cellular	Check-point inhibitors	Bispecific antibodies
Cellular	Hematopoietic stem cell transplantation	CAR T -cells

Acute Lymphoblastic Leukemia







Atlas of Hematology, Nagoya University School of Medicine Department of Medicine The Branch Hospital, Takuji Ichihashi, December 1996

Cancer Immunotherapy

	Non-specific	Targeted
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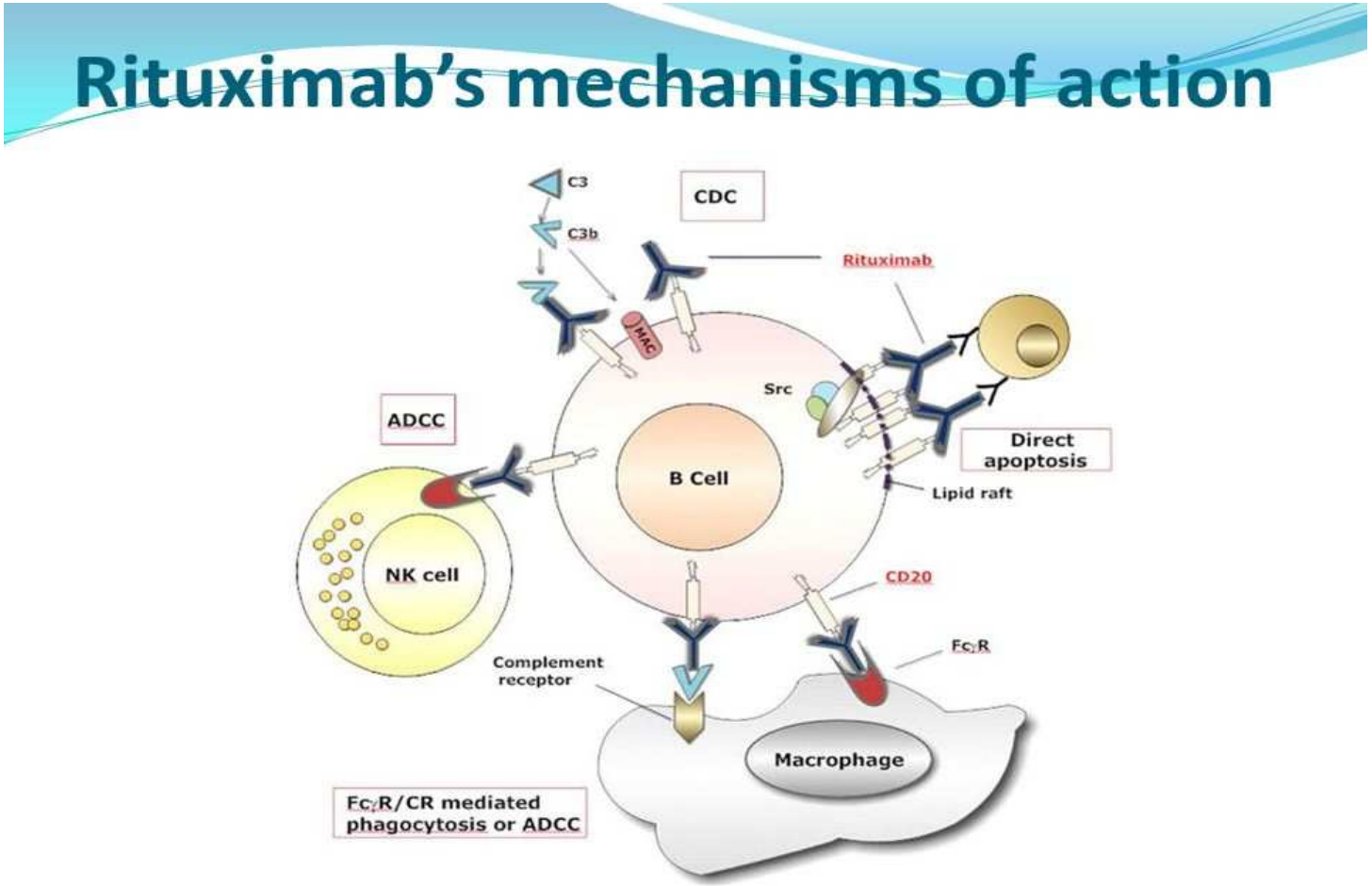
„Naked" antibodies

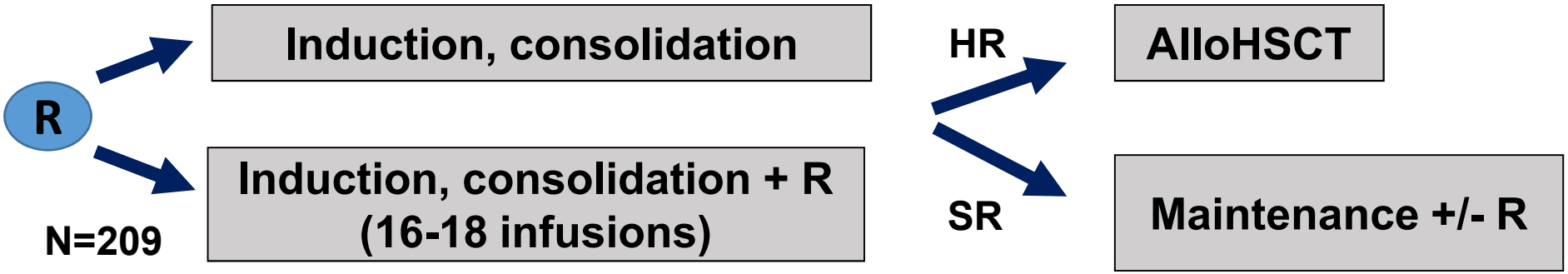
Rituximab (anti-CD20)



JAGLOWSKI et al, BLOOD, 11 NOVEMBER 2010 VOLUME 116, NUMBER 19

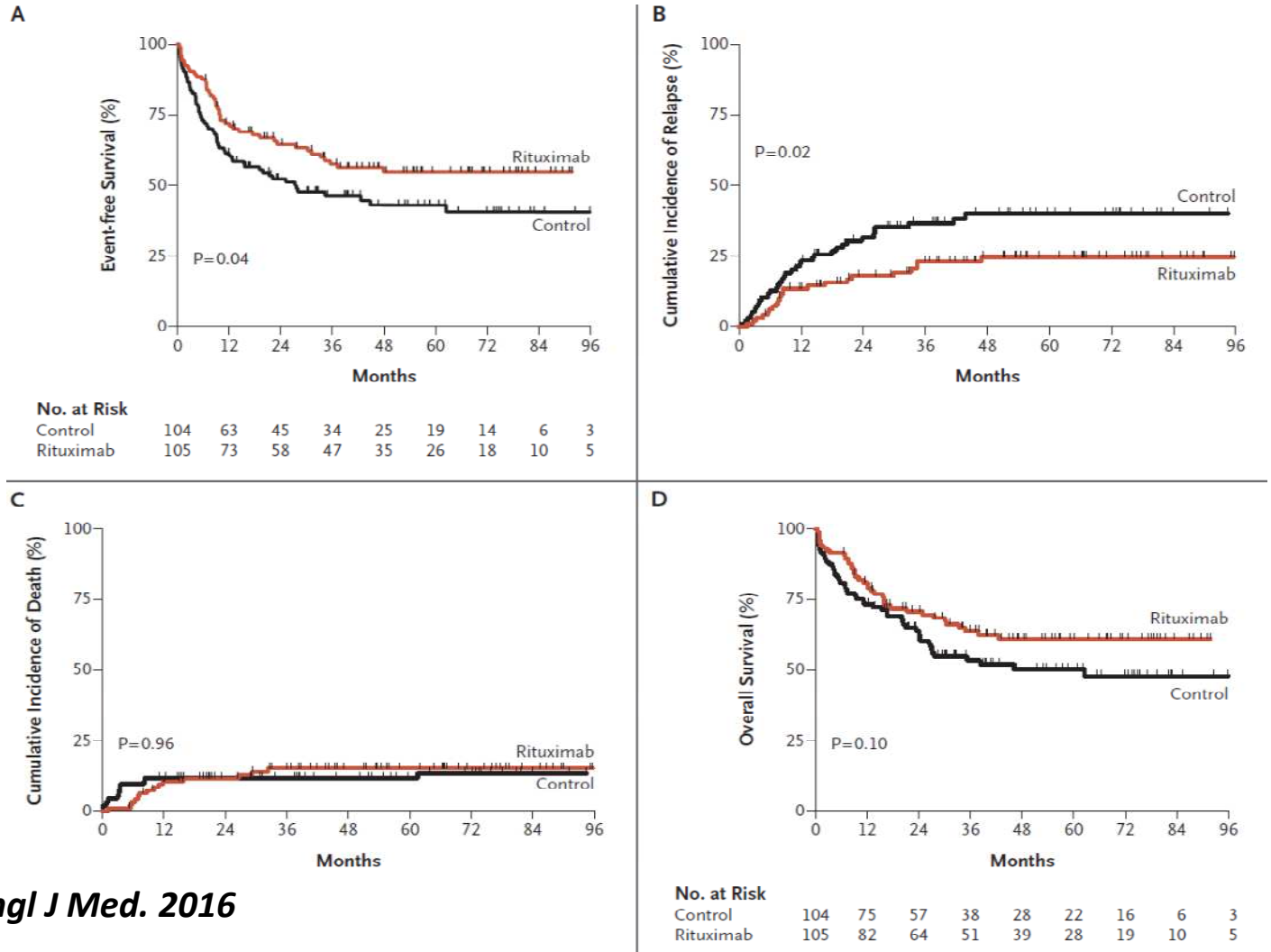
Rituximab

GRAAPH study
De novo Ph- ALL, CD20+ >20%, age 18-59 years



Maury S, et al., N Engl J Med. 2016

Rituximab



Maury S, et al., N Engl J Med. 2016

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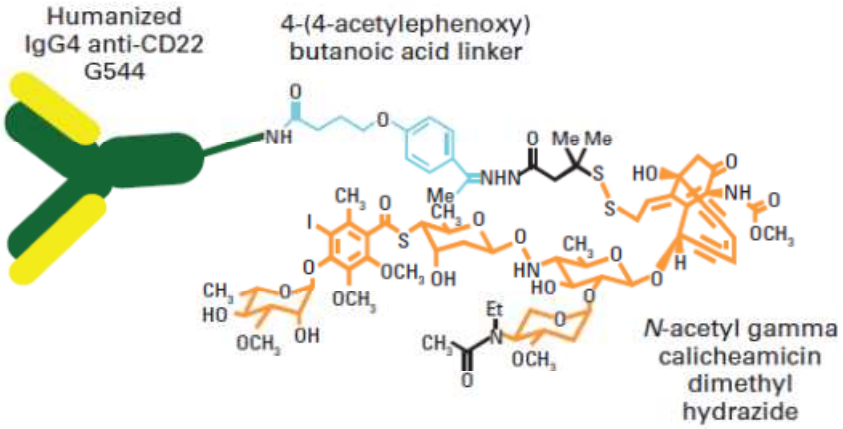
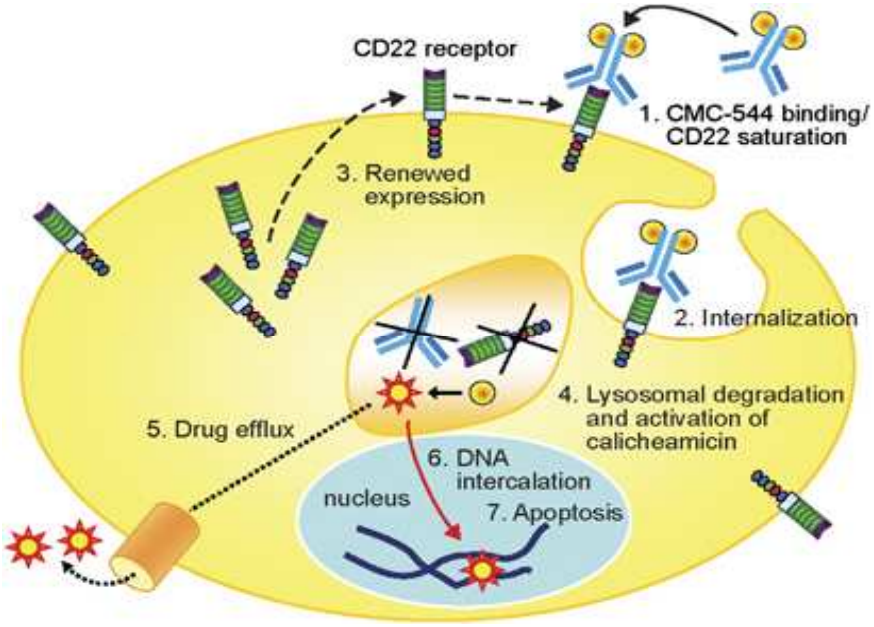
Immunotoxins

Inotuzumab ozogamycin
(anti-CD22 + calichaemicin, humanized)



Advani A, et al., J Clin Oncol 2010

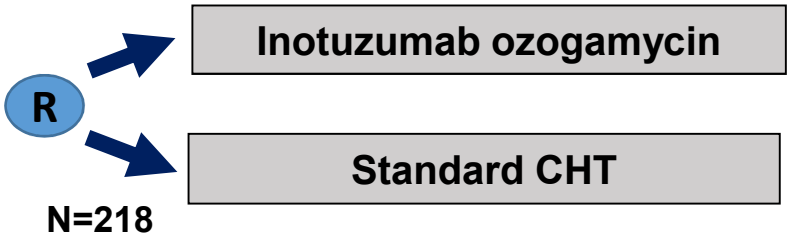


Cortes JE, et al., N Eng J Med 2013

Immunotoxins

Inotuzumab ozogamycin

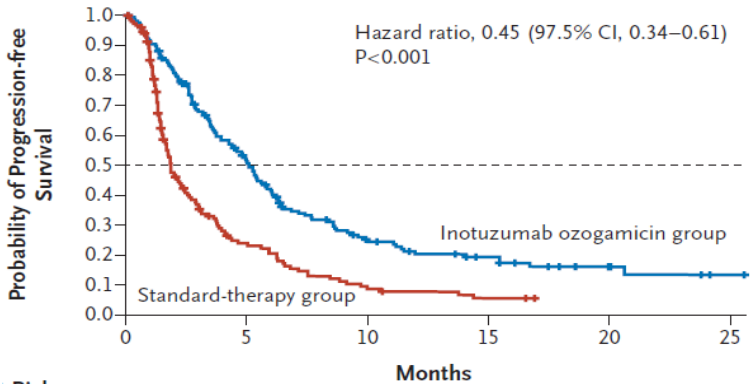
Rel/Ref B-ALL

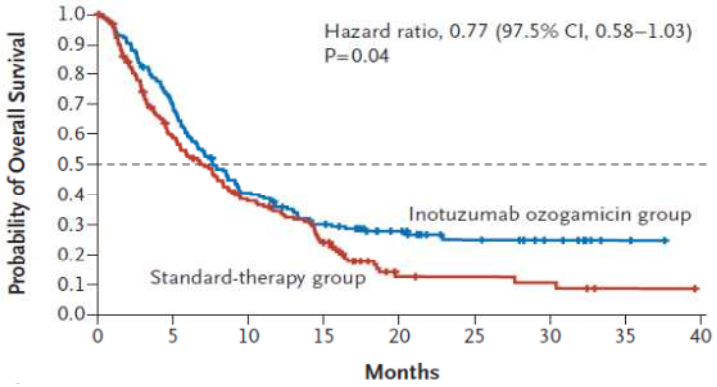


N=218

Kantarjian H, et al., N Engl J Med 2016

	INO	CHT	P
CR	81%	29%	<0.001





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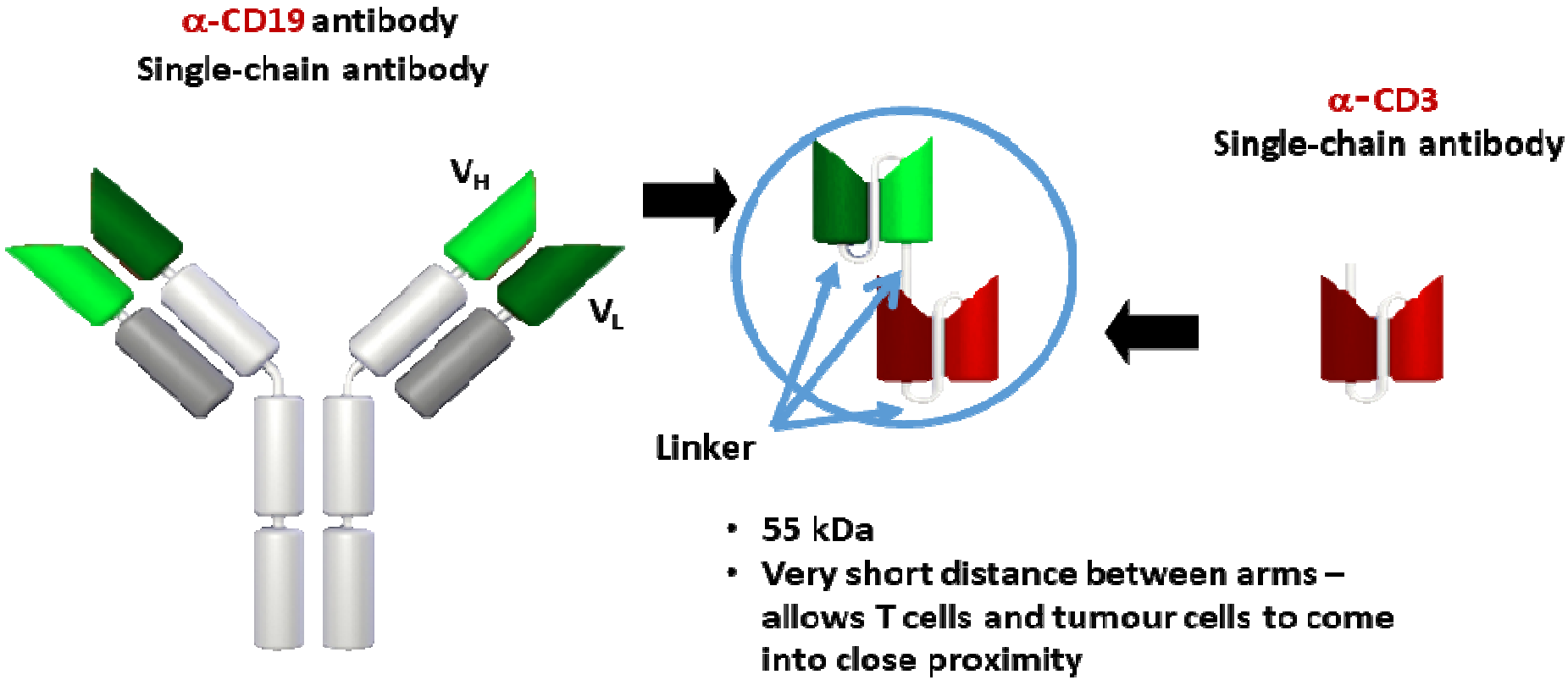
Bisepecific antibodies

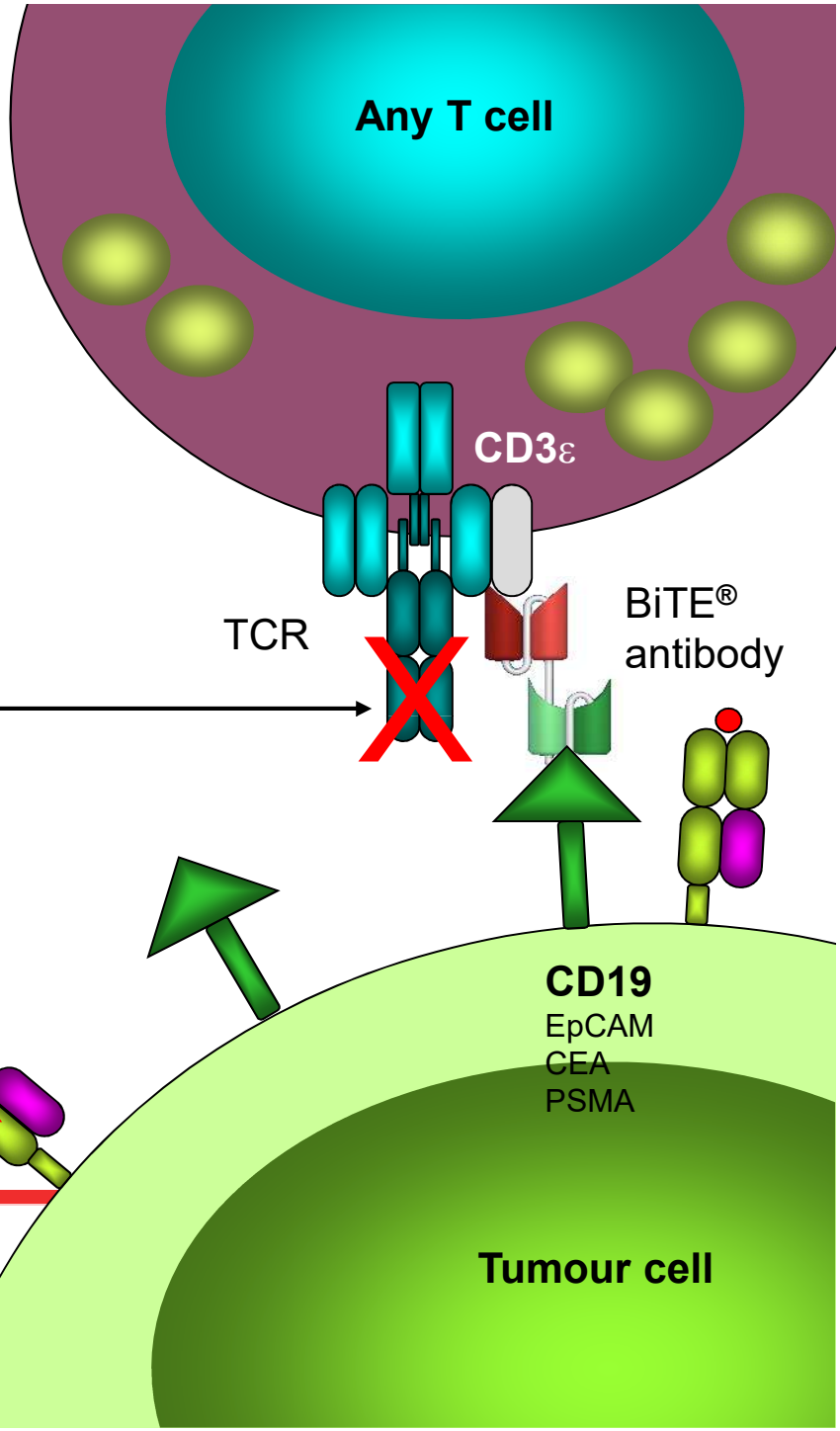
Blinatumomab
(anti-CD19/anti-CD3)



- 55 kDa
- Very short distance between arms – allows T cells and tumour cells to come into close proximity

Blinatumomab mechanize of action:

- T-cells are engaged in immune response against CD19+ cells



No need for specific receptor

No need for MHC expression and peptide presentation

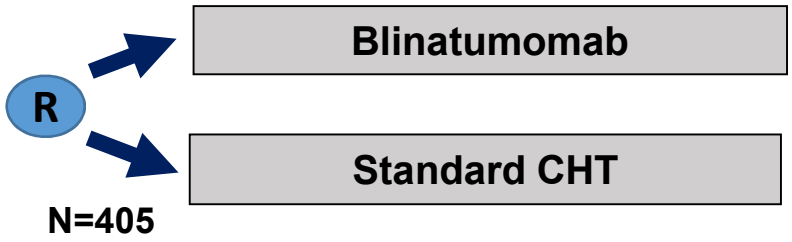
MARIA SKLODOWS
INSTITUTE – ONCOLO
GLIWICE BRANCH

Adapted from Baeuerle PA & Reinhardt C. Cancer Res 2009;69:4941–4944

Bispecific antibodies

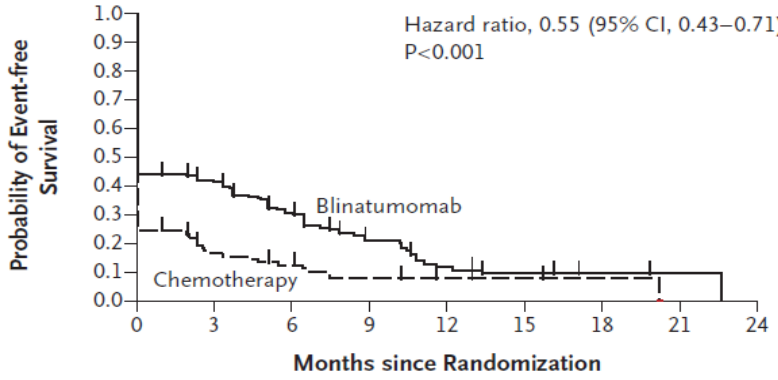
Blinatumomab

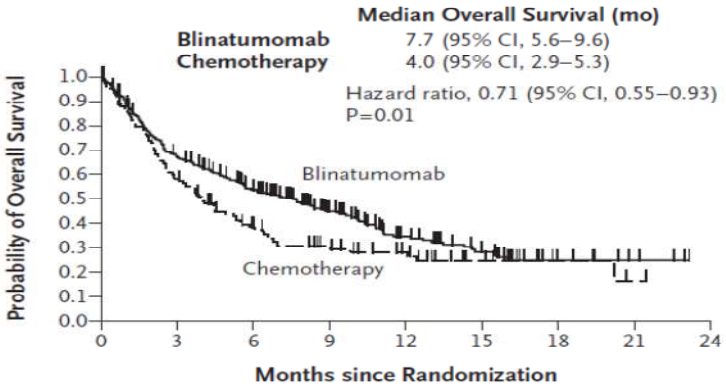
Rel/Ref B-ALL



N=405

	BLINA	CHT	P
CR/CRi	44%	25%	<0.001





Kantarjian H, et al., N Engl J Med 2017

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Annals of Hematology

September 2017, Volume 96, Issue 9, pp 1569–1572

Low-dose nivolumab-induced responses in acute lymphoblastic leukaemia relapse after allogeneic haematopoietic stem cell transplantation

Chan T.S.Y, Sim J.P.Y., Kwong Y.L.

Department of Medicine, Queen Mary Hospital, Pokfulam, Road, Hong Kong

Cancer Immunotherapy

	Non-specific	Targeted
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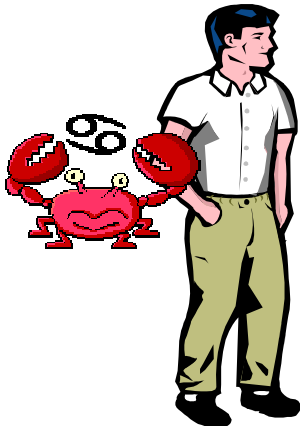
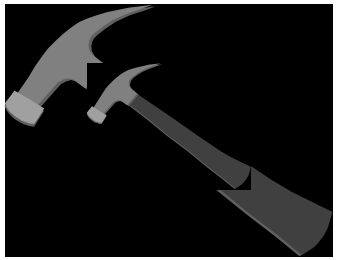
Allogeneic hematopoietic stem cell transplantation (ALLO-HSCT)

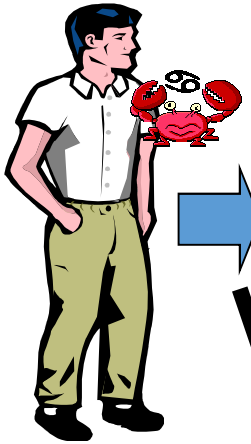
Stem cell collection
after G-CSF stimulation



CONDITIONING
(Cht or TBI)



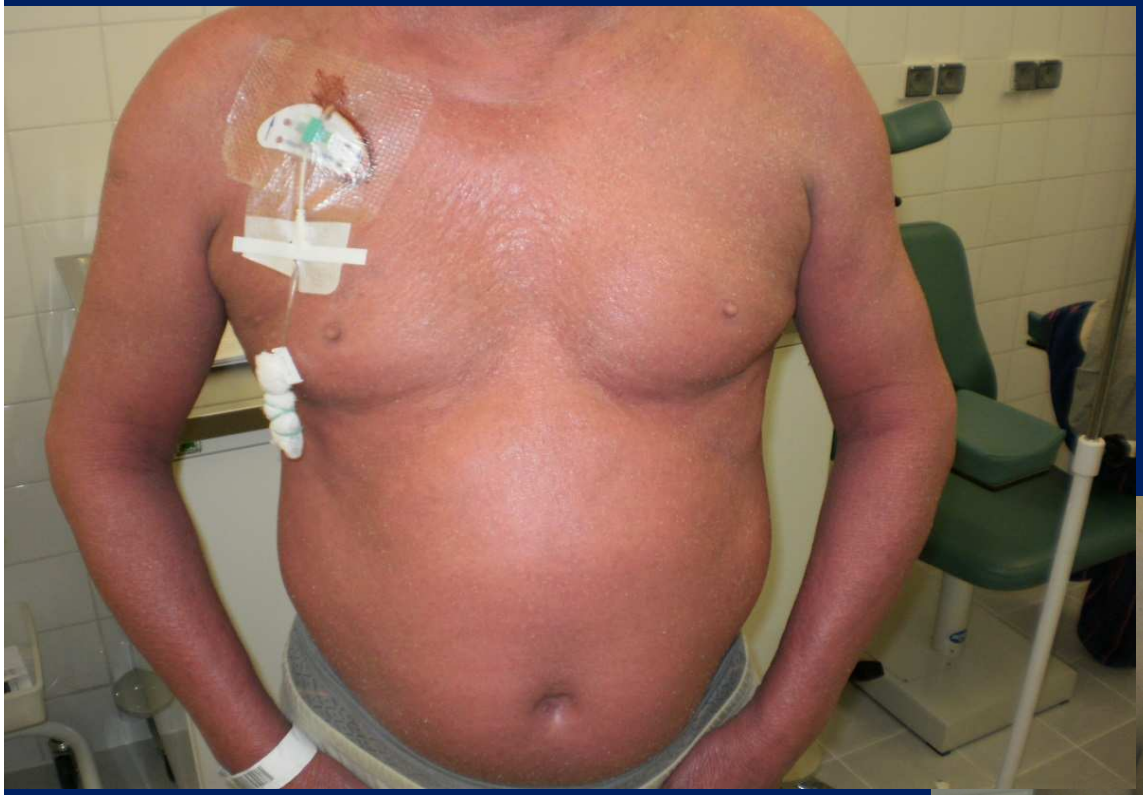
HSCT
(i.v. infusion)



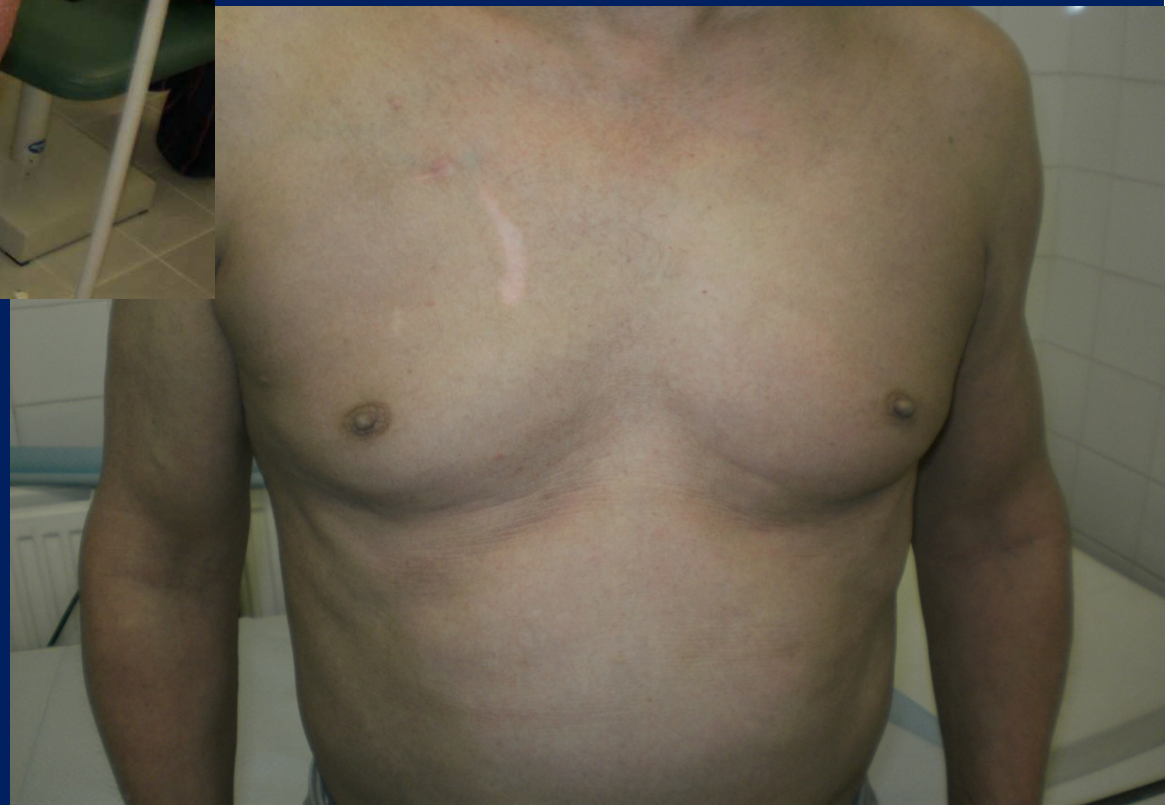
Graft-vs. tumor
(T, NK)

APLASIA
(sterile room)

Relapsed/refratory mycosis fungoides/Sezary syndrome



Before alloHSCT



5 months after alloHSCT

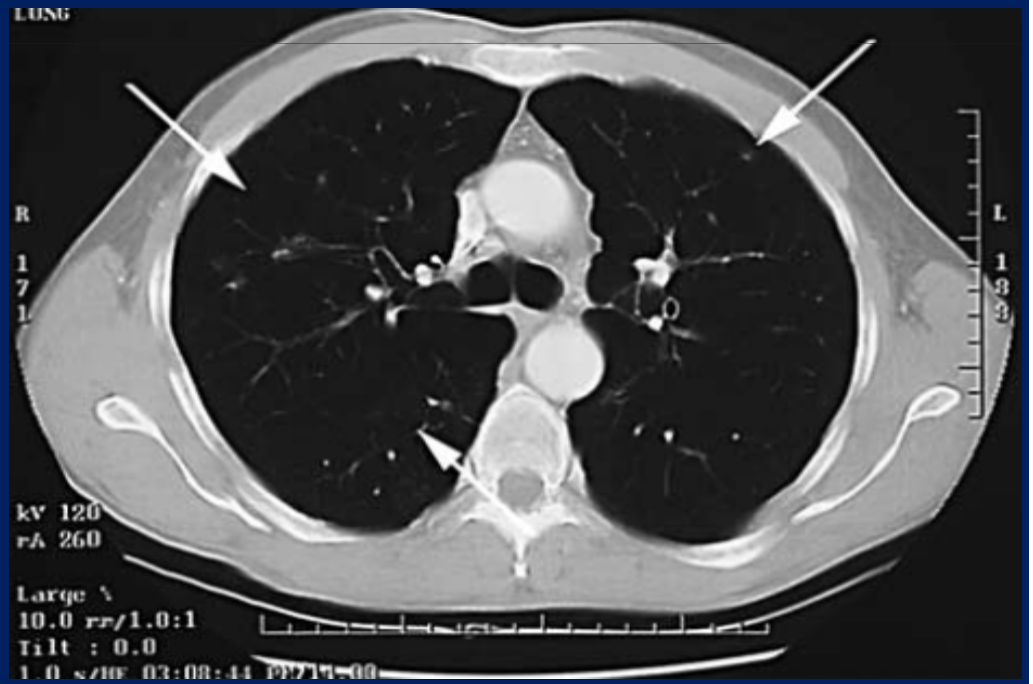
AlloHSCT – renal cancer

Metastatic renal cancer, resistant to CHT

N=19

Cy 60 mg/kg d. -7,-6
Fludara 25 mg/m2 d. -5,-4,-3,-2,-1
+ alloHSCT

Childs et al., NEJM 2000



AlloHSCT for relapsed/refractory ALL

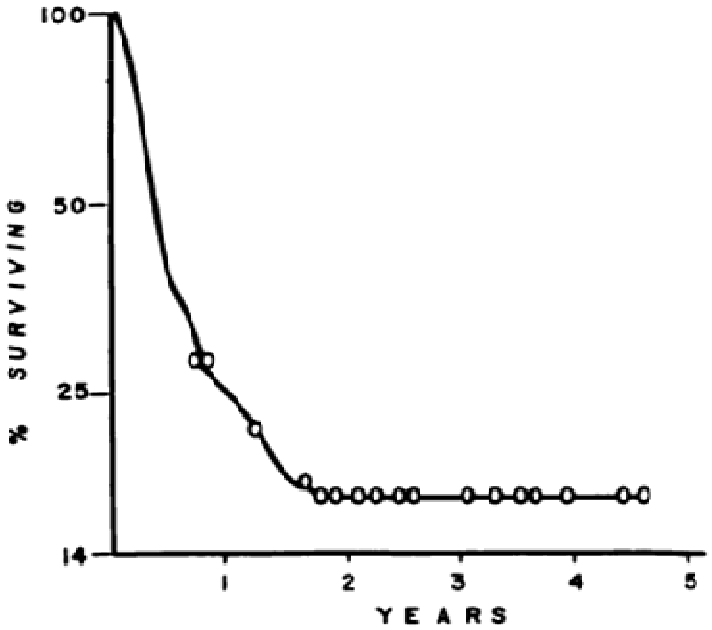
blood 1977 49: 511-533

One hundred patients with acute leukemia treated by chemotherapy, total body irradiation, and allogeneic marrow transplantation

ED Thomas, CD Buckner, M Banaji, RA Clift, A Fefer, N Flournoy, BW Goodell, RO Hickman, KG Lerner, PE Neiman, GE Sale, JE Sanders, J Singer, M Stevens, R Storb and PL Weiden

End-stage disease

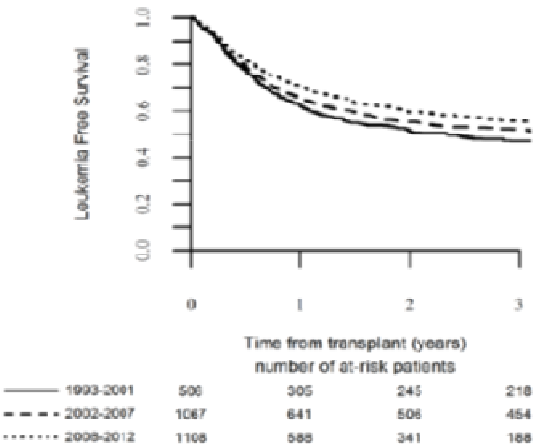
	Diagnosis	
	ALL	AML
Number of patients	46	54
Patient characteristics		
Age median (range) (yr)	13.5 (4–36)	24.5 (1–56)
Sex: female/male	17/29	22/32
Race: white/nonwhite	41/5	50/4
Status of disease		
Number of remissions before marrow transplant (range)	3 (0–5)	1 (0–5)
Number of patients with:		
Relapse at time of transplant	38	52
History CNS disease	20	4
Active CNS disease	6	6



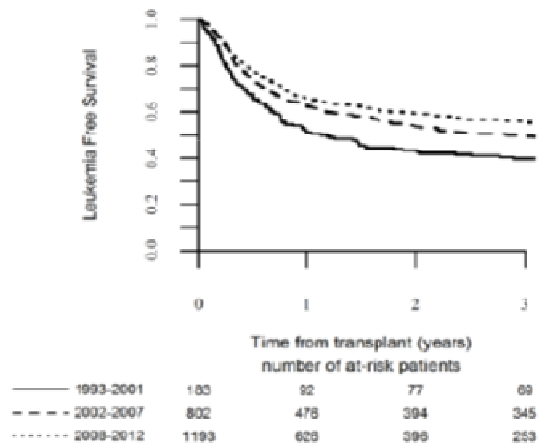
Improving results of HSCT for adults with ALL

Retrospective analysis (EBMT)

Matched sibling HSCT



URD-HSCT



NON-RELAPSE MORTALITY

	MSD	URD
1993-2001	18.8%	28.2%
2002-2007	20%	24.4%
2008-2012	14.7%	22.4%

Giebel S, et al., Haematologica 2017;102:139-49

Graft-versus-leukemia in ALL

CIBMTR – retrospective analysis: association of GvHD with outcome alloHSCT in CR1/CR2; N=5215

Relapse	HR (95%CI)	p
aGVHD 1-2 / no cGVHD	0.7 (0.58-0.84)	**0.0001**
aGVHD 3-4 /no cGVHD	0.61 (0.45-0.82)	**0.001**
cGVHD / no aGVHD	0.66 (0.51-0.85)	**0.0001**
cGVHD with aGVHD 1-2	0.57 (0.45-0.73)	**<0.0001**
cGVHD with aGVHD 3-4	0.49 (0.35-0.71)	**0.0001**

Overall survival	HR (95%CI)	p
aGVHD 1-2 / no cGVHD	0.83 (0.7-0.98)	**0.025**
aGVHD 3-4 /no cGVHD	2.43 (2.04-2.89)	0.001
cGVHD with aGVHD 3-4	1.46 (1.18-1.81)	0.0001

Yeshurun M et al., ASH 2017, abstract #518

Cancer Immunotherapy

	Non-specific	Targeted
Humoral	-	„Naked" antibodies Immunotoxins
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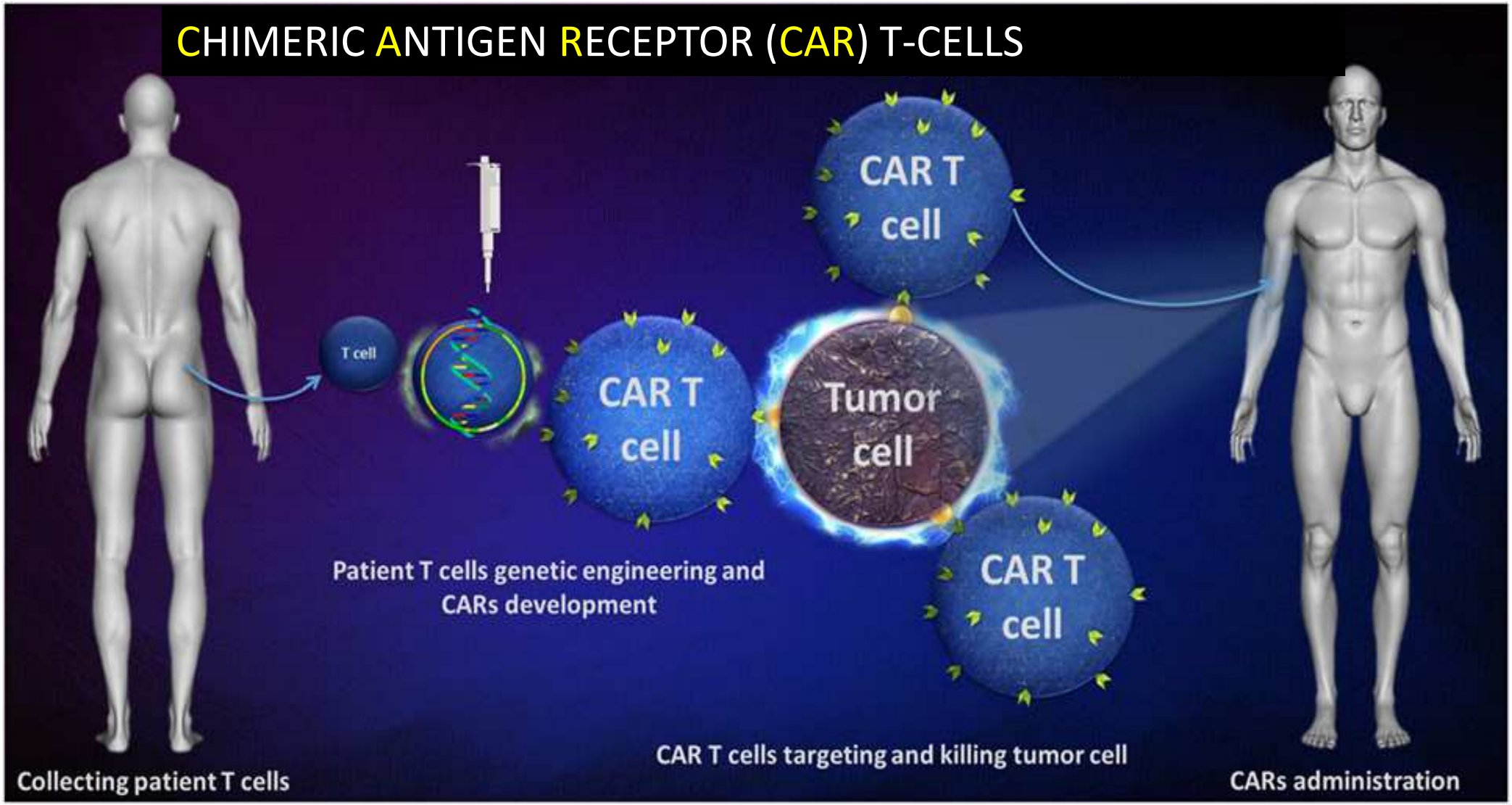
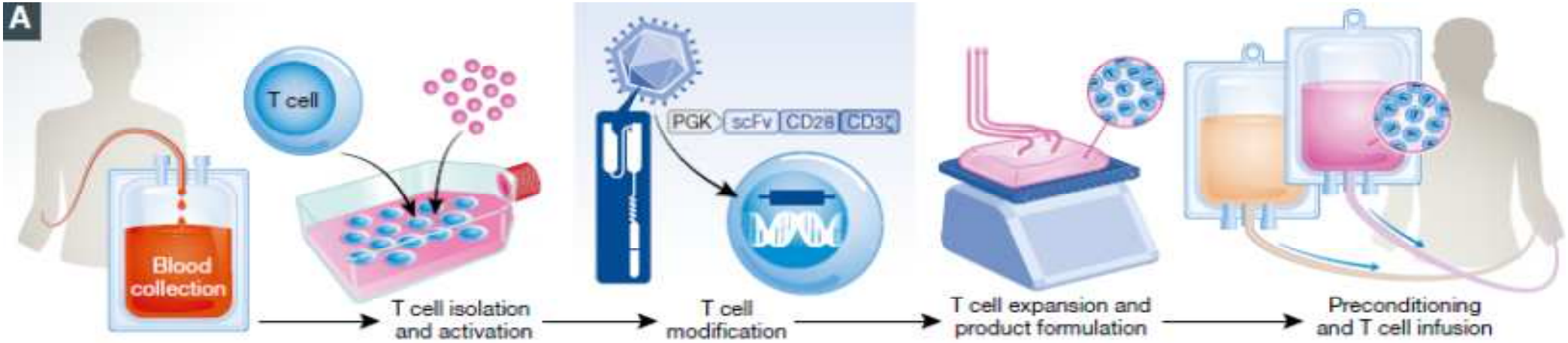
CHIMERIC ANTIGEN RECEPTOR (CAR) T-CELLS

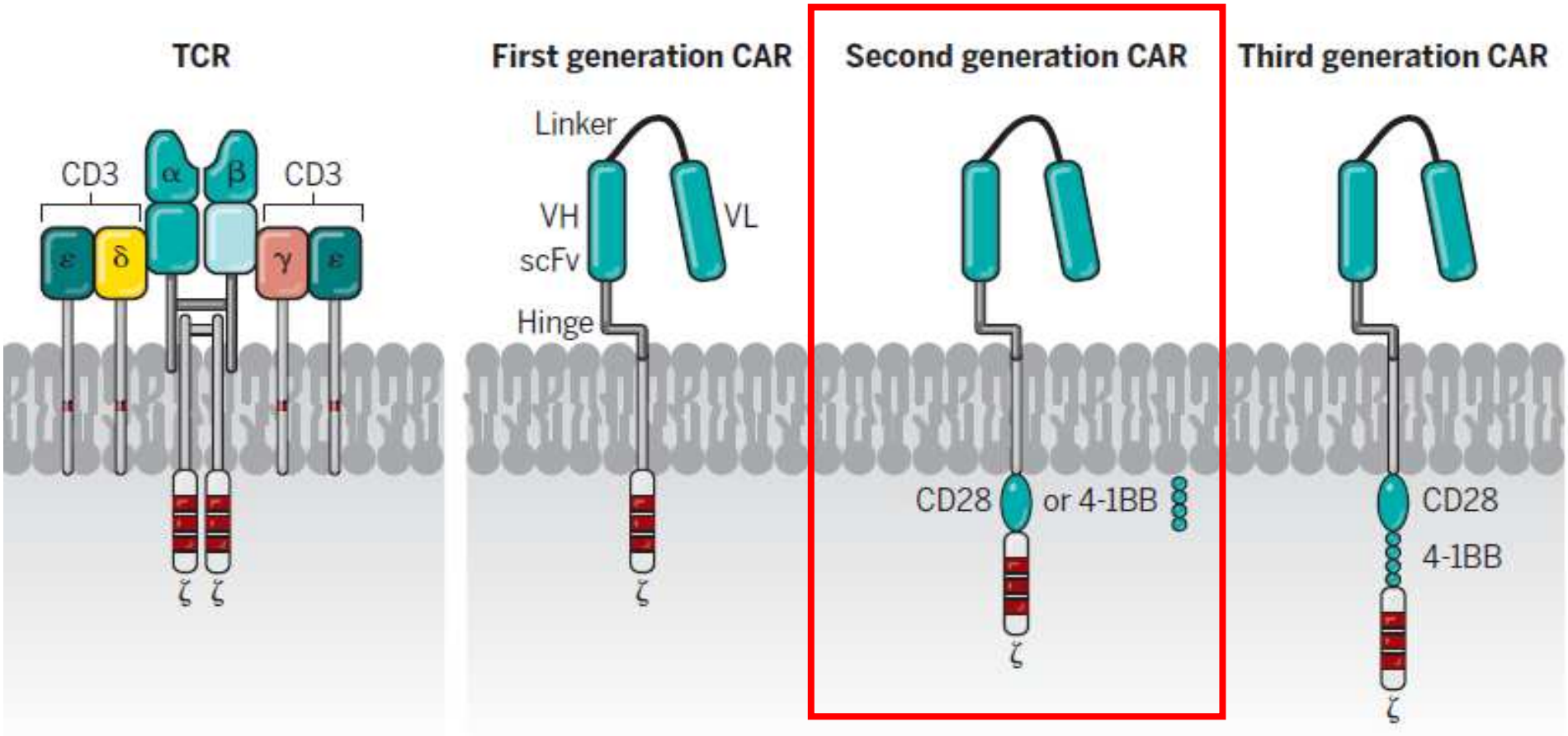


June CH, et al., Front Immunol 2018

CAR T-cells production



Hartman J, et al., EMBO Molecular Medicine 2017

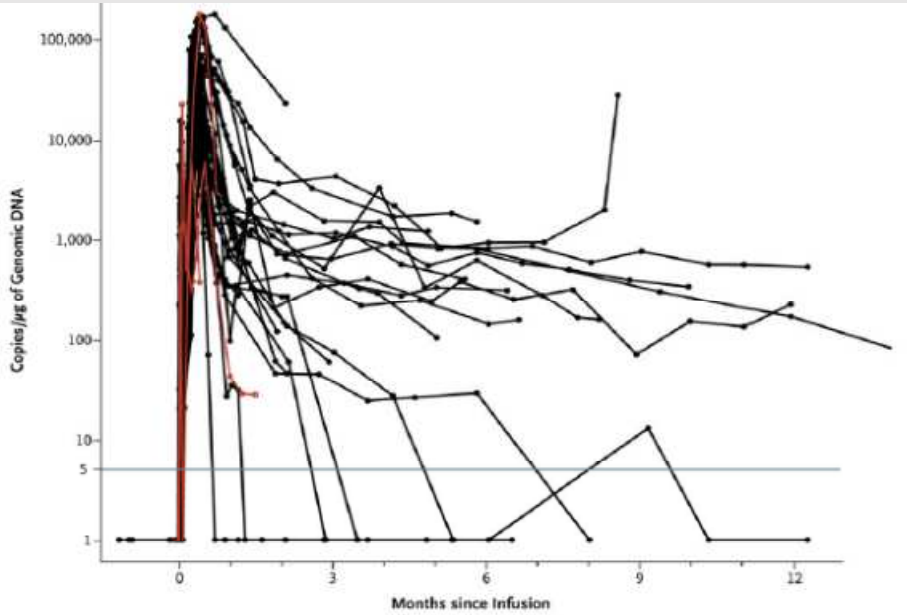


June CH, et al., Science 2018

CAR T-cells: B-ALL

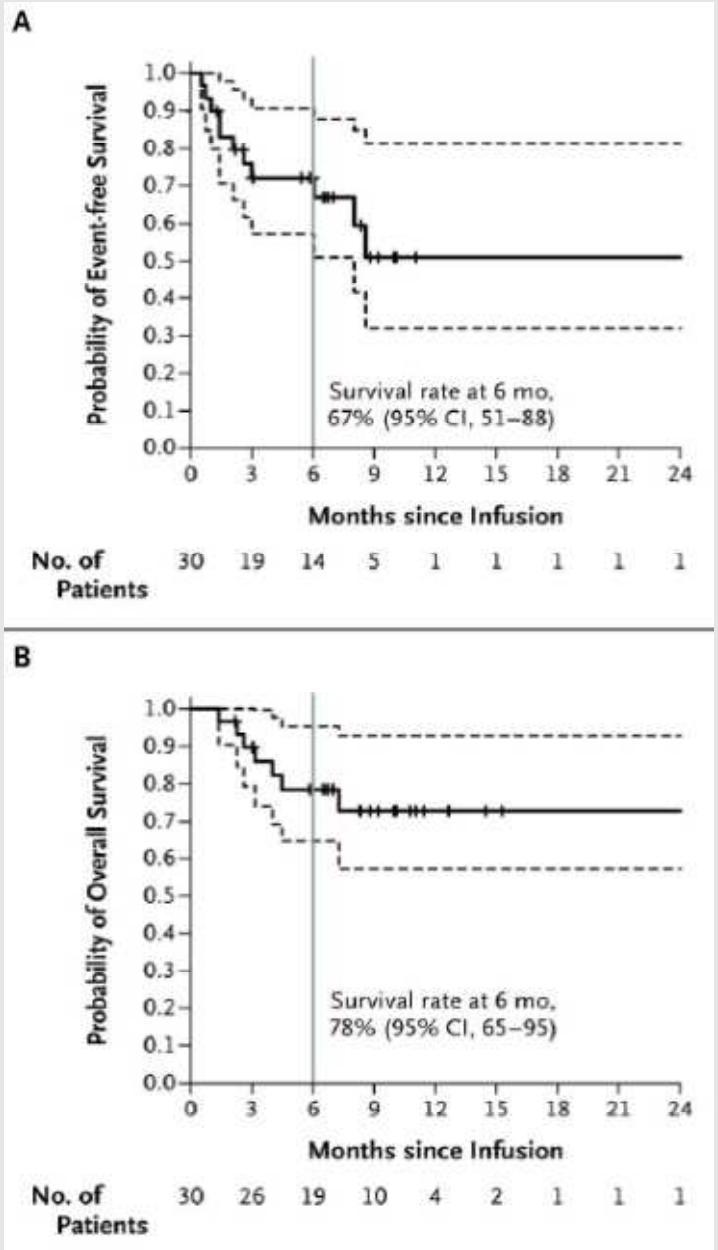
Relapsed/refractory B-ALL
N=30; Age 5-60 years

Lentivirus vector
CTL019



N	30
CR mol	90%

Maude SL, et al., N Eng J Med. 2014

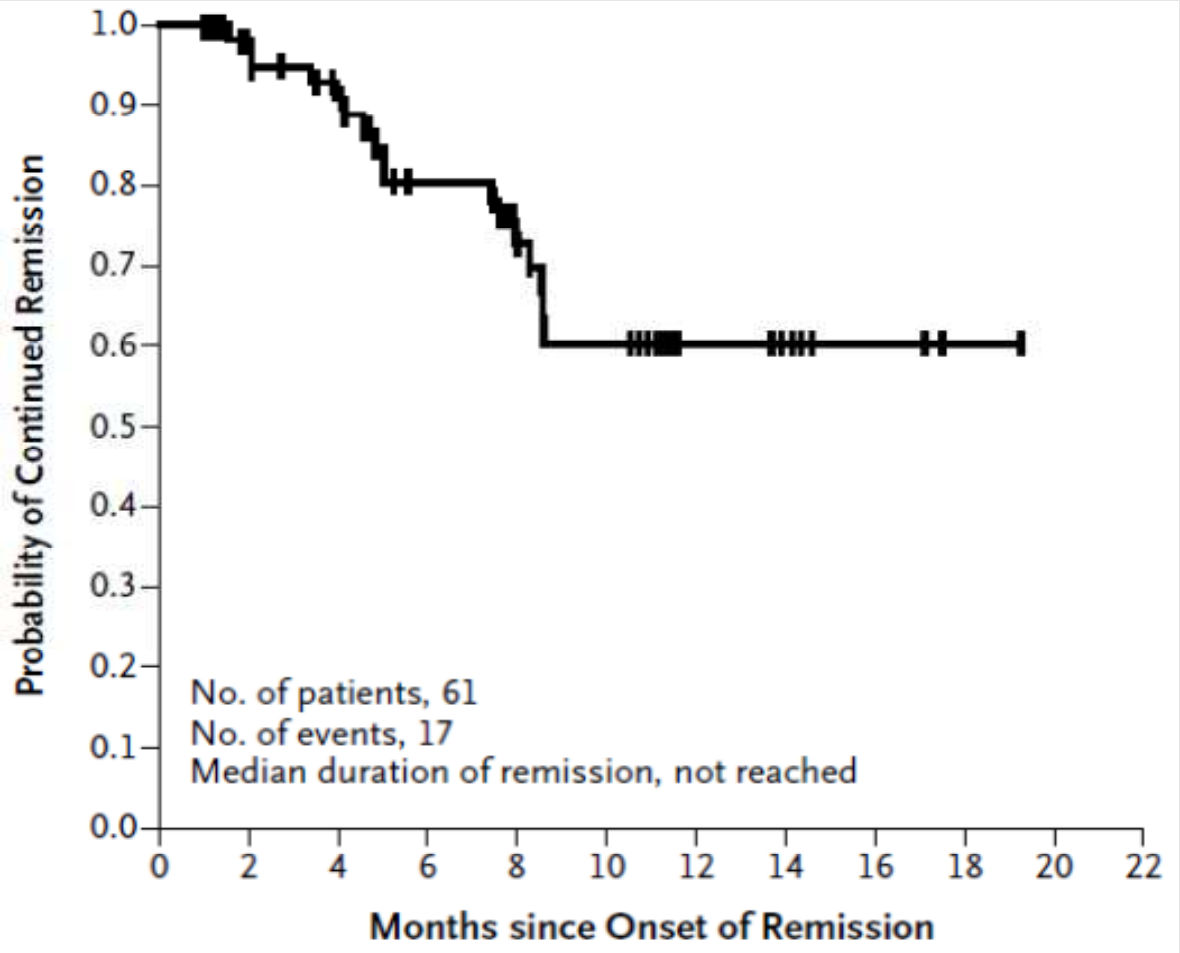


CAR T-cells: B-ALL

Relapsed/refractory B-ALL
N=75; Age 3-23 years

Lentivirus vector
CTL019 (Tisagenlecleucel)

N	75
CR mol	81%

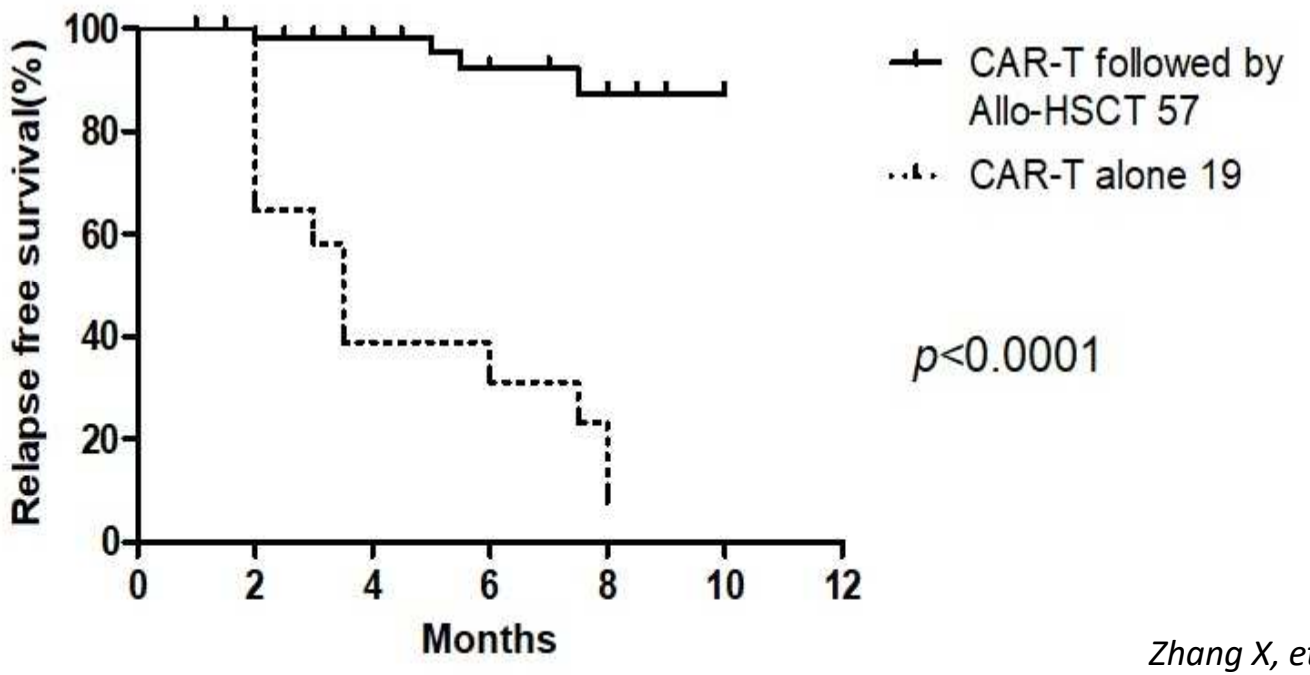


Maude SL, et al., N Eng J Med. 2018

CAR T-cells as a bridge to alloHSCT ?

CHINA (Langfang)

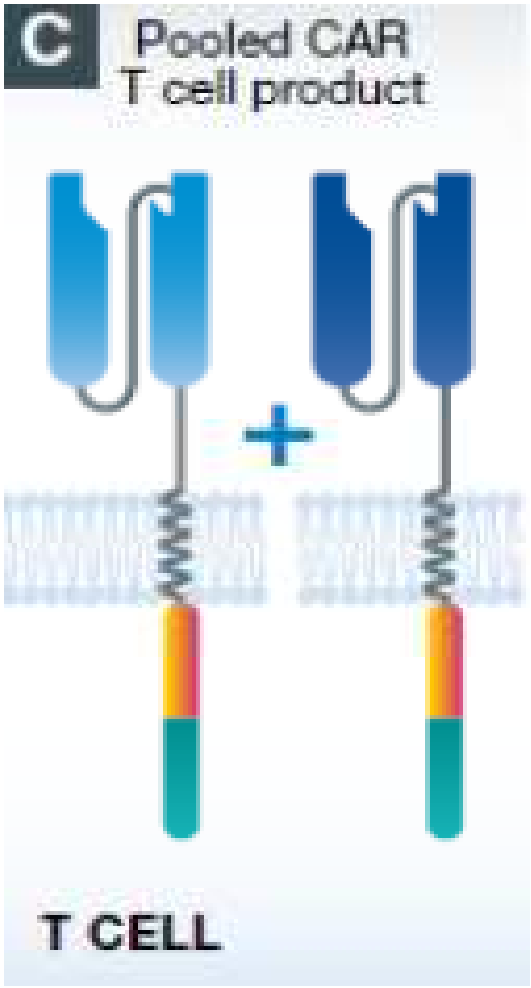
R/R B-ALL
N=83
Age: 10 (2-61) years
CD19:28.3z-CAR



Zhang X, et al., ASH 2018, abstract #280

„Pooled” CAR T-cells

UK (Londyn)
R/R B-ALL,
N=8
Age: 1-24 years
CD19 + CD22

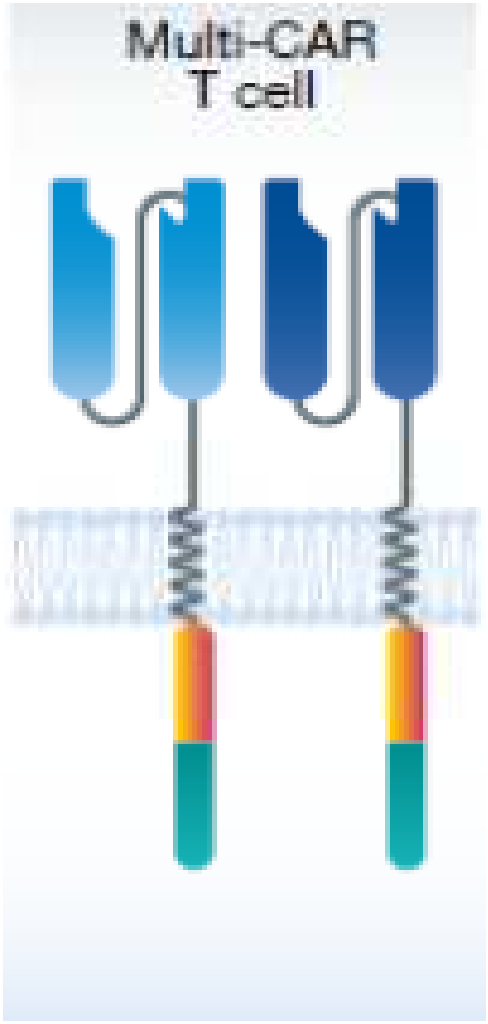


	N=8
CR	75%

Amorolia PJ, et al., ASH 2018, abstract #279

Multi-CAR T-cells

USA (Seattle)
R/R/MRD+ B-ALL,
N=7
Age: 1-26 years
CD19xCD22

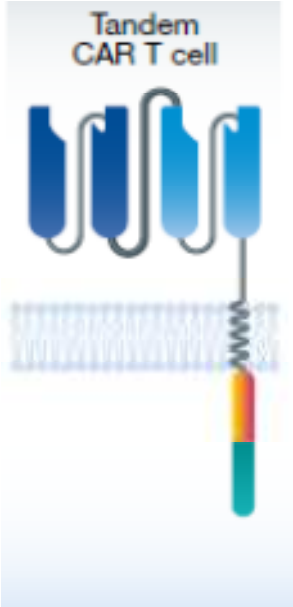


	N=7
CR	71%

Gardner R, et al., ASH 2018, abstract #278

Tandem „Bispecific" CAR T-cells

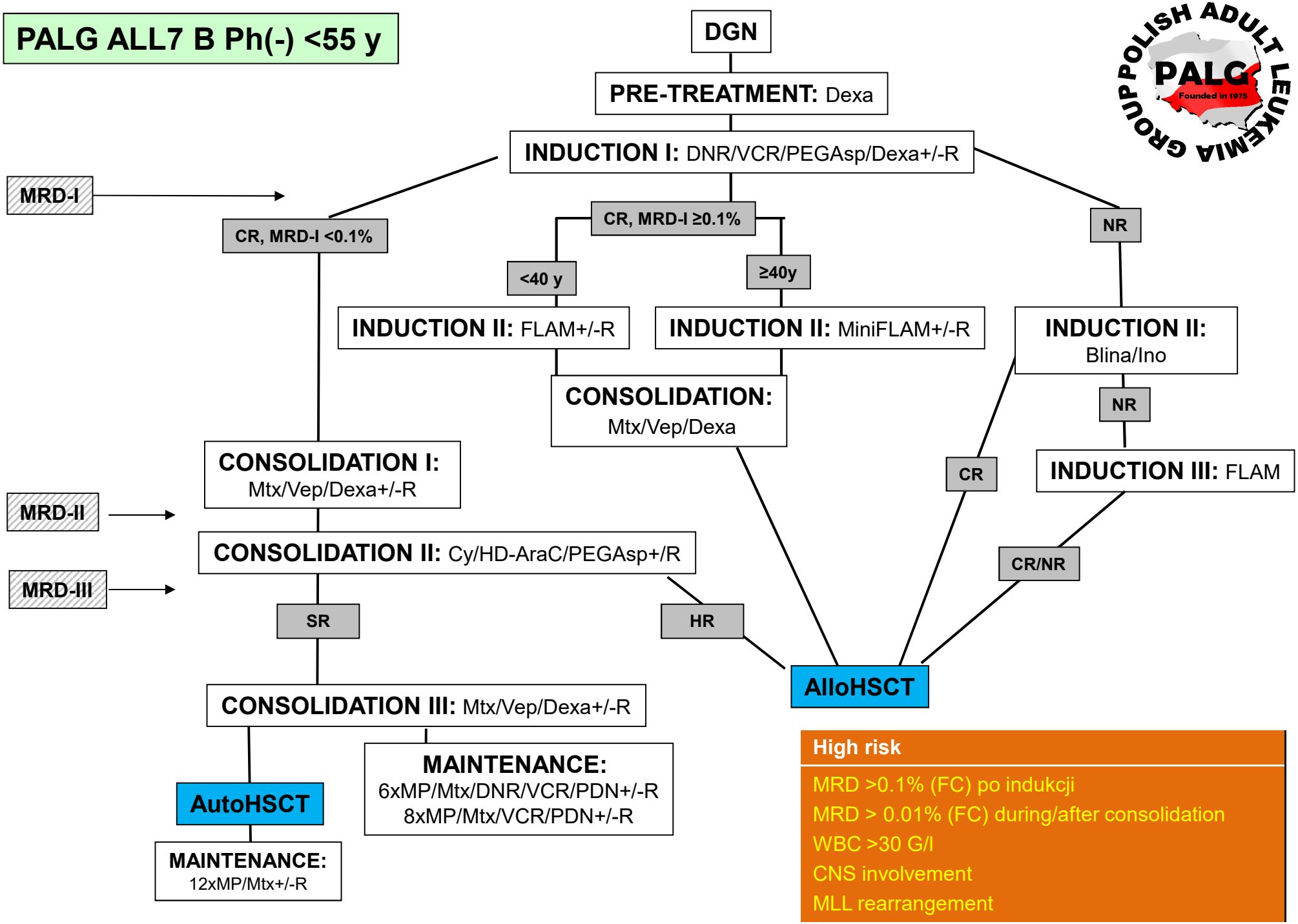
USA (Stanford)
R/R B-ALL/NHL,
N=7
Wiek: 35-75 years
CD19/CD22



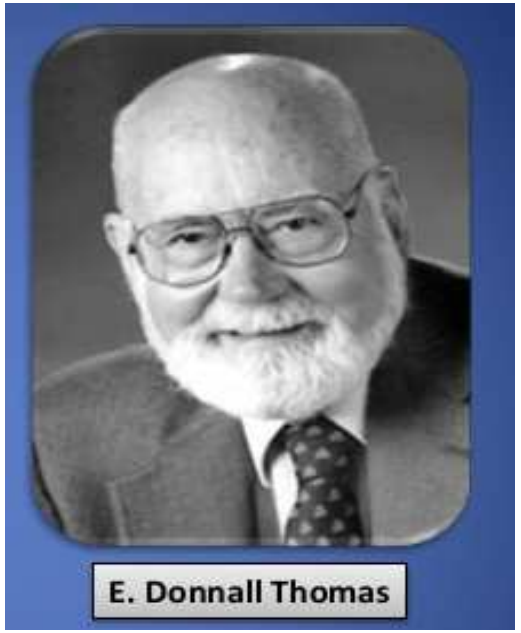
Ptn ID	Age	Gender	Disease	Markers	Previous Lines of Therapy	History of AlloSCT	Max CRS	Max CRES	Best Response
001	71	M	DLBCL-NOS	Double Hit (MYC,BCL2)	3	No	2	2	SD
002	54	M	tDLBCL	Triple Expresser	3	No	0	0	PR
002-2nd infusion	54	M	tDLBCL	Triple Expresser	4	No	0	0	SD
003	67	M	DLBCL-NOS	Non Double Hit	4	No	1	0	CR
004	50	F	ALL	Ph negative	4	Yes	N/A	N/A	N/A
005	75	M	DLBCL-NOS	Non Double Hit	2	No	1	0	CR
006	67	M	DLBCL-NOS	Non Double Hit	2	No	1	1	PR
007	35	F	ALL	Ph Positive	7	Yes	1	1	CR

Schultz L, et al., ASH 2018, abstract #898

PALG ALL7 B Ph(-) <55 y



Nobel prize in Medicine and Physiology was awarded to Köhler, Milstein and Jerne in 1984



Tasuku Honjo

James Allison

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MARIA SKLODOWSKA-CURIE
INSTITUTE – ONCOLOGY CENTER
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