Thursdays Webinars

EuroBloodNet

Management of Relapsed/Refractory Acute Lymphoblastic Leukaemia in Adult

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PARIS – FRANCE
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European Reference Network for rare or low prevalence complex diseases
Network Hematological Diseases (ERN EuroBloodNet)

Conflicts of interest

Honoraria (Consulting, advisory role)	Amgen Ariad-Incyte Bristol-Myers Squibb Celgene Jazz Pharma	Novartis Pfizer Sanofi Servier Shire
Research funding	Amgen Bristol-Myers Squibb Novartis	Jazz Pharma

Learning objectives

R/R B-ALL in adults

1. To identify the prognostic factors of adult B-ALL at relapse

2. To list the new drugs recently approved for relapsed/refractory B-ALL

3. To evaluate the benefit expected for each salvage therapy

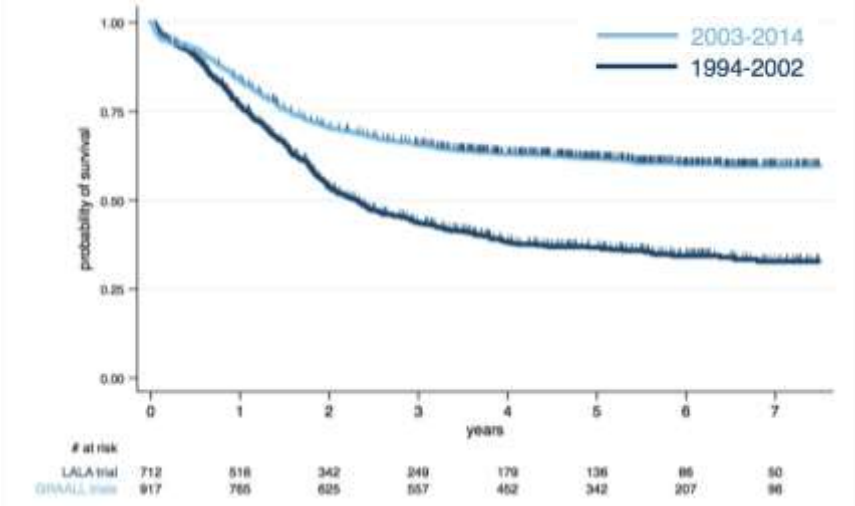
4. To evaluate the safety profile of each salvage therapy

Treatment of B-ALL in adults

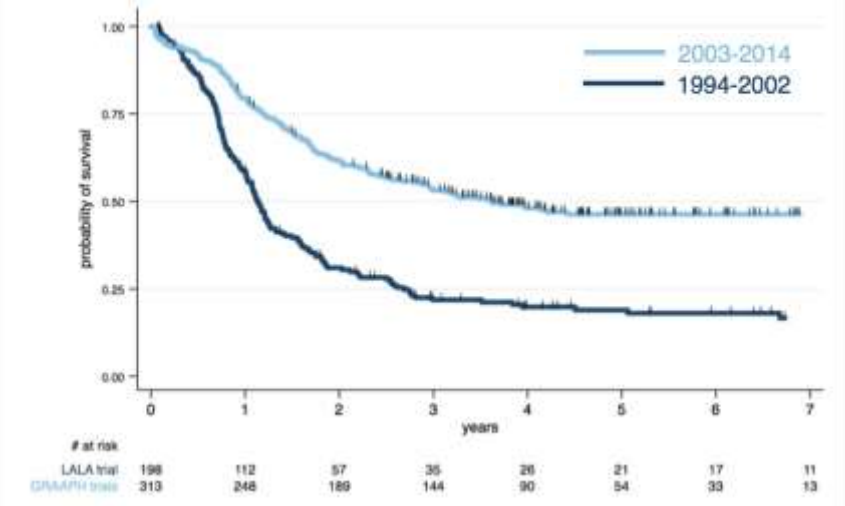
Progress and limits of conventional therapies

- Two major progressions accomplished in the last 15 years:
  - Paediatric-like approaches in young adults with Ph-negative ALL[1]
  - TKIs in Ph-positive B-ALL[2]
- Limitations:
  - Increased toxicity in patients >45 years[1]
  - About 30% of patients still relapse with very poor outcome (median survival of 3–6 months)[1,3]

Ph-negative ALL (ages 18–59 years)[4]



Ph-positive ALL (ages 18–59 years)[4]

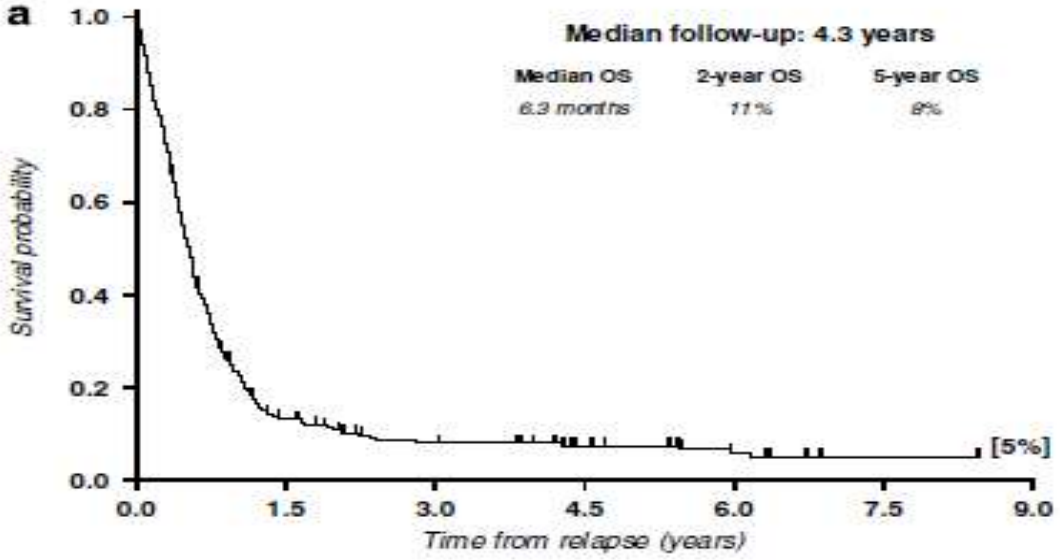


1. Huguet F, et al. J Clin Oncol 2018;36:2514–23;
2. Chalandon Y, et al. Blood 2015;125:3711–9;
3. Gökbuget N, et al. Haematologica 2016;101:1524–33; 4. GRAALL, unpublished data on file.

Adult B-ALL at relapse

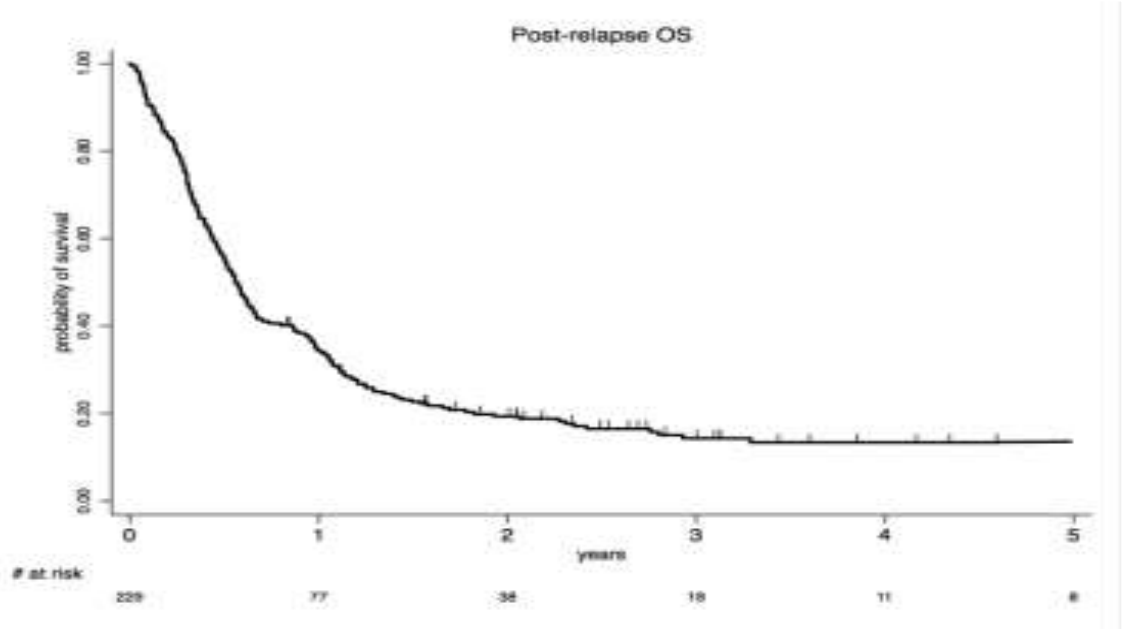
Post-relapse survival

LALA 94[1]



- Median OS: 6.3 mois
- 2y OS : 11%
- 5y OS : 9%

GRAALL 2003 & 2005[2]



- Median OS : 6.7 mois
- 2y OS : 19.3%
- 5y OS : 13.3%

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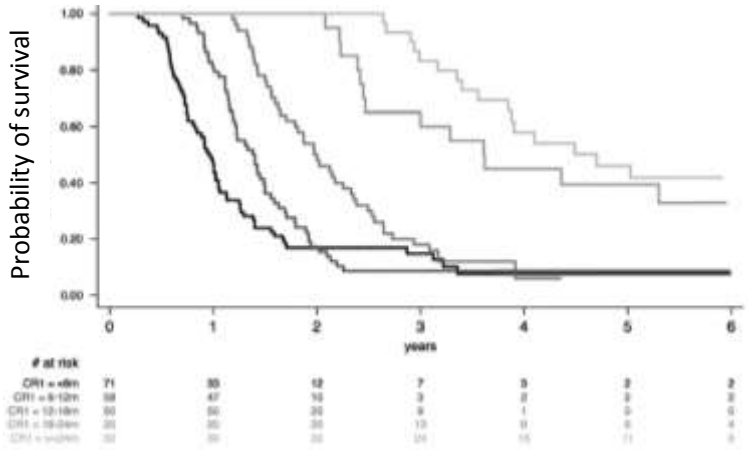
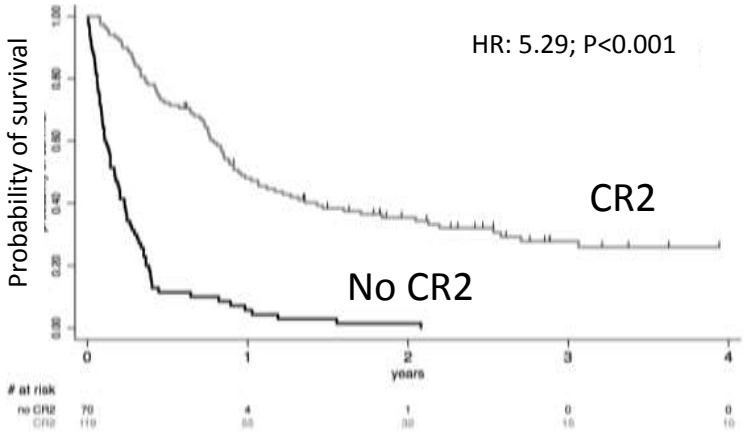
1. Tavernier E. et al. Leukemia. 2007 Sep;21(9):1907-14.
2. Desjonquères A. et al. Blood Cancer J. 2016 Dec 9;6(12):e504

Prognostic factors at relapse

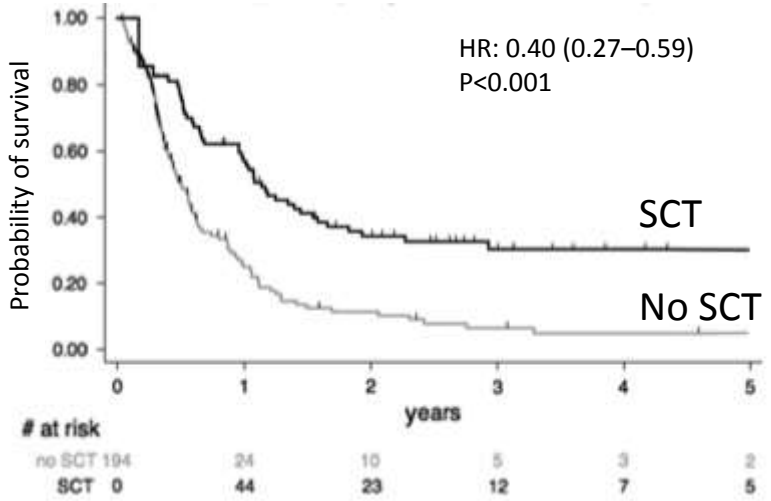
OS by CR1 duration[1]



Post-relapse OS by CR2[2]



Post-relapse OS by allogeneic SCT[1]



No standard of care!

GRAALL[1,2]	n	CR, n (%)
Total	229	121 (53%)
CR1 <18 months	179	87 (49%)*
CR1 ≥18 months	50	34 (68%)

GMALL[3]	n	CR, n (%)
Total	224	95 (42%)
CR1 <18 months	160	58 (36%)
SCT in relapse	18	10 (56%)
CR1 ≥18 months	64	37 (58%)
Standard induction	30	27 (90%)
FLAG-IDA	15	4 (27%)

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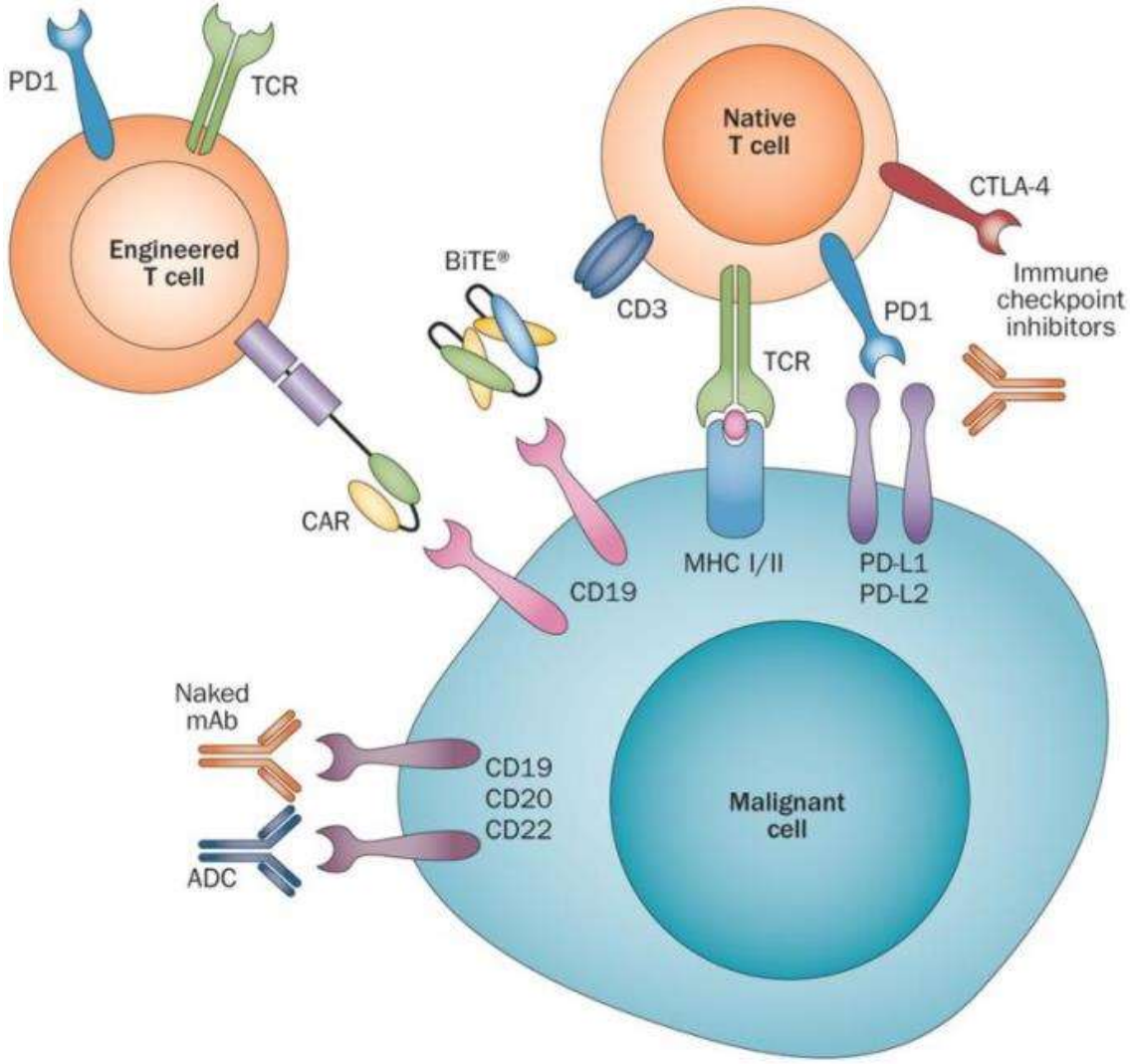
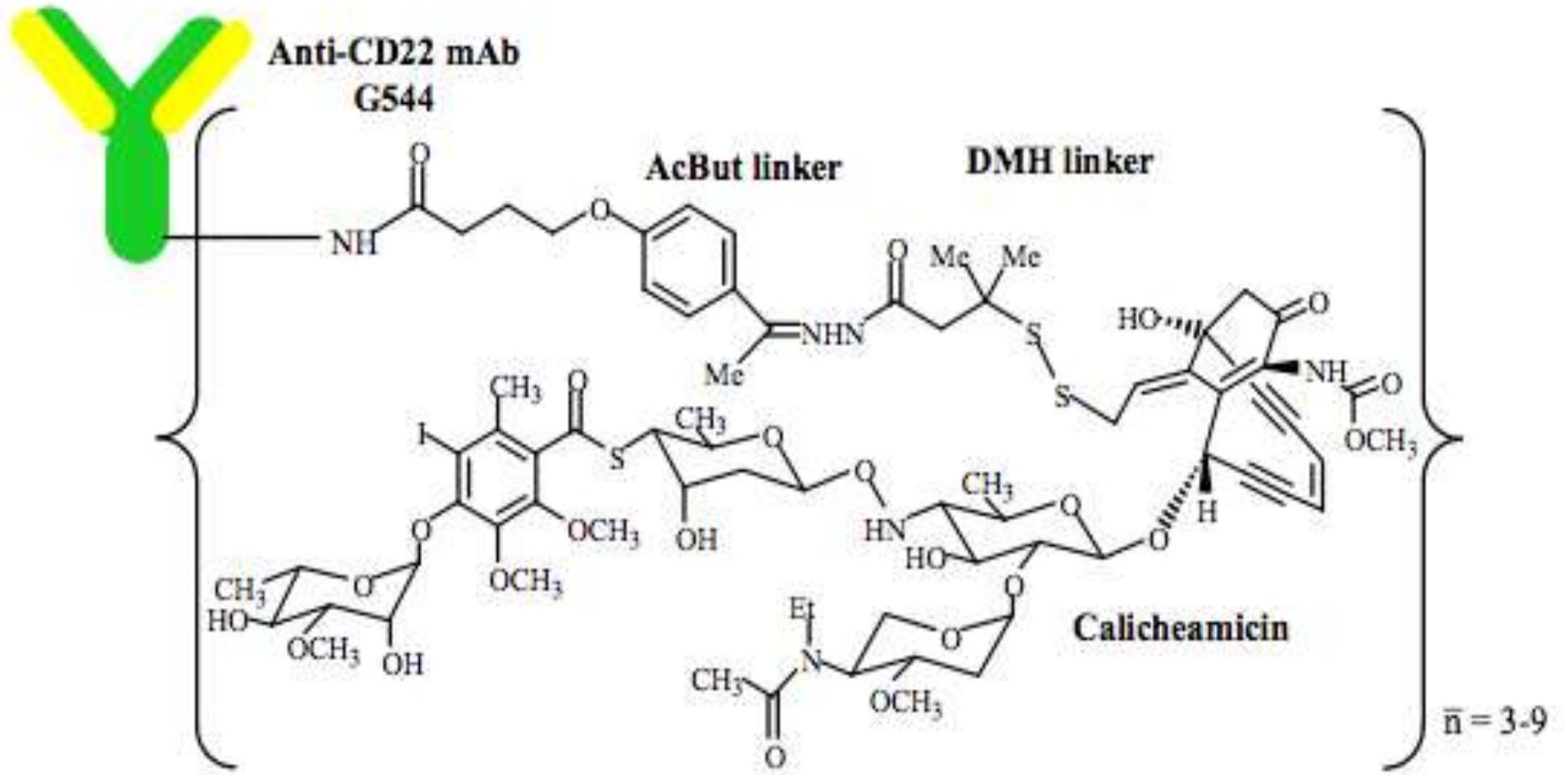
1. Desjonquères A, et al. Blood Cancer J 2016;6:e504;
2. GRAALL, unpublished data on file;
3. Adapted from Gökbuget N, et al. Blood 2012;120:2032–41.

Immuno-strategies in BCP-ALL

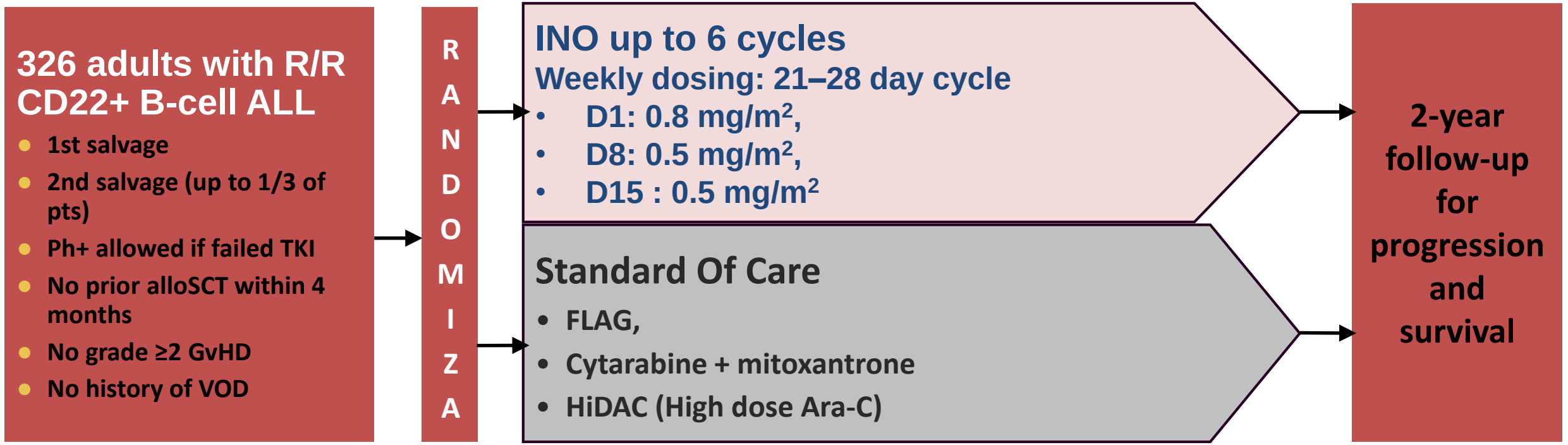


Batlevi et al., Nat Rev Clin Oncol. 2016 Jan;13(1):25-40.

Inotuzumab Ozogamicin



Inotuzumab phase III (INO-VATE)



- INO reduced to 1.5 mg/m2/cycle once the patient achieved CR/CRi
- Primary endpoint: CR (CR + CRi)

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Kantarjian, N Engl J Med. 2016 Aug 25;375(8):740-53

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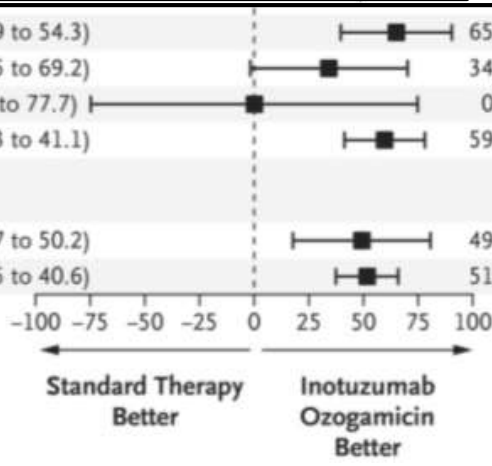
Inotuzumab phase III (INO-VATE)

BCP-ALL, R/R

Subgroup	No. of Patients		Complete Remission		Between-Group Difference (97.5% CI)	P Value
	Inotuzumab Ozogamicin Group	Standard-Therapy Group	Inotuzumab Ozogamicin Group	Standard-Therapy Group		
			% (95% CI)		percentage points	
All patients	109	1			51.4 (38.4 to 64.3)	<0.001
Normal	20	20	95.0 (75.1 to 99.9)	30.0 (11.9 to 54.3)	65.0 (39.6 to 90.4)	<0.001
Ph-positive	14	18	78.6 (49.2 to 95.3)	44.4 (21.5 to 69.2)	34.1 (–1.8 to 70.1)	0.08
t(4;11)-positive	3	6	33.3 (0.8 to 90.6)	33.3 (4.3 to 77.7)	0.0 (–74.7 to 74.7)	1.00
Other abnormalities	49	46	85.7 (72.8 to 94.1)	26.1 (14.3 to 41.1)	59.6 (41.3 to 78.0)	<0.001
Previous stem-cell transplantation						
Yes	17	22	76.5 (50.1 to 93.2)	27.3 (10.7 to 50.2)	49.2 (17.8 to 80.6)	0.004
No	92	87	81.5 (72.1 to 88.9)	29.9 (20.5 to 40.6)	51.6 (37.4 to 65.9)	<0.001

MRD < 0.01% in patients with CR

Inotozumab: 78.4% *vs.* SOC: 28.1%, P<0.001



Kantarjian, N Engl J Med 2016 Aug 25;375(8):740-53

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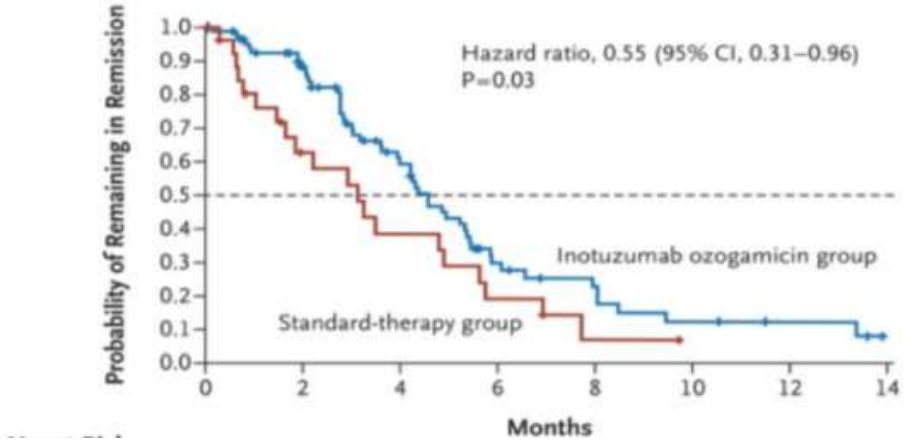
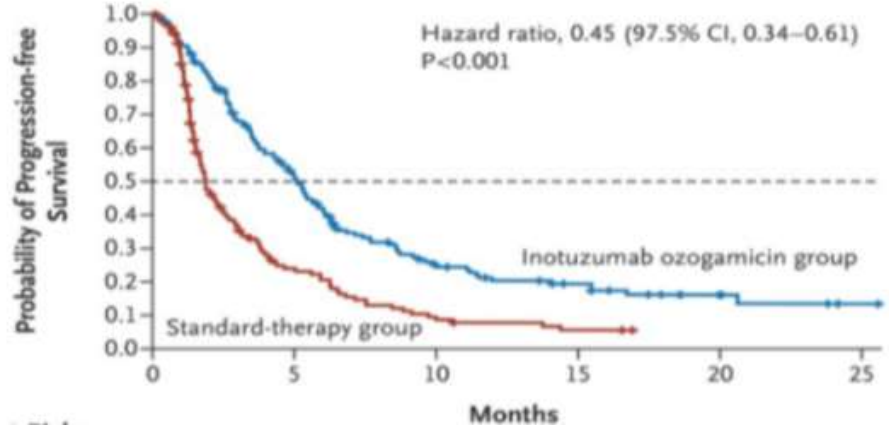
Inotuzumab phase III (INO-VATE)

BCP-ALL, R/R

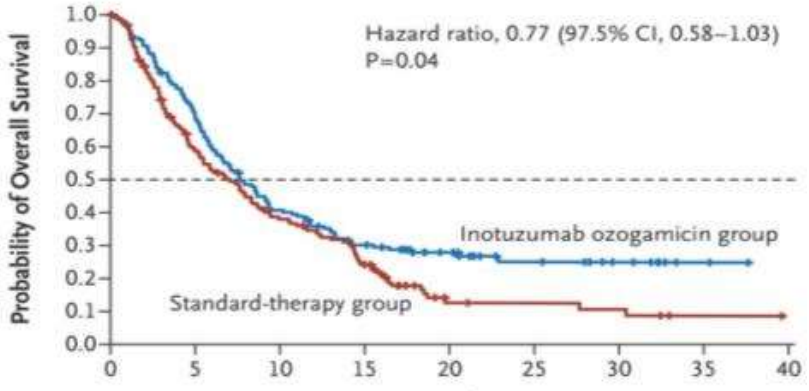
Duration of remission



Progression-free Survival



Overall Survival



No. at Risk									
Inotuzumab ozogamicin group	164	112	62	41	24	13	8	2	0
Standard-therapy group	162	85	51	30	6	5	4	1	0

2-year survival rate:
InO **23%** (95% CI 16–30) vs SOC **10%** (95% CI 5–16)

Kantarjian, N Engl J Med. 2016 Aug 25;375(8):740-53

Inotuzumab phase III (INO-VATE)

Liver toxicity, sinusoidal obstruction syndrome (SOS)

	Inotuzumab ozogamicin (n=164)				Standard care (n=143)			
	Any grade	Grade 1 or 2	Grade 3	Grade 4	Any grade	Grade 1 or 2	Grade 3	Grade 4
Any adverse event	83 (51%)	35 (21%)	33 (20%)	10 (6%)	49 (34%)	28 (20%)	18 (13%)	3 (2%)
Aspartate aminotransferase increased	37 (23%)	30 (18%)	6 (4%)	1 (<1%)	16 (11%)	11 (8%)	2 (1%)	3 (2%)
γ-glutamyltransferase increased	35 (21%)	17 (10%)	16 (10%)	2 (1%)	12 (8%)	5 (3%)	7 (5%)	0
Hyperbilirubinaemia	35 (21%)	25 (15%)	9 (5%)	1 (<1%)	24 (17%)	15 (10%)	8 (6%)	1 (<1%)
Alanine aminotransferase increased	25 (15%)	19 (12%)	6 (4%)	0	18 (13%)	11 (8%)	6 (4%)	1 (<1%)
Blood alkaline phosphatase increased	22 (13%)	19 (12%)	2 (1%)	1 (<1%)	10 (7%)	10 (7%)	0	0
Sinusoidal obstruction syndrome (veno-occlusive disease; total)*	22 (13%)	4 (2%)	7 (4%)	6 (4%)	1 (<1%)	0	1 (<1%)	0

Inotuzumab and HSCT

- **SOS in 17/77 (22%)**
- **5 deaths**

	Number of patients in each subset	Odds ratio (95% CI)	p value
Multivariate analysis (n=62)‡			
Conditioning regimen with two alkylating agents (two vs one)	11 vs 51	8·606 (1·516–48·861)	0·015
Pre-HSCT bilirubin concentration (≥ULN vs <ULN)	11 vs 51	15·308 (1·950–120·206)	0·009
Pre-HSCT AST or ALT concentration (>1·5 × ULN vs ≤1·5 × ULN)	11 vs 51	0·027 (<0·001–0·833)	0·039
History of liver disease or hepatitis (yes vs no)	15 vs 47	5·133 (0·907–29·060)	0·064

Kantarjian, Lancet Haematol. 2017 Aug;4(8):e387-e398

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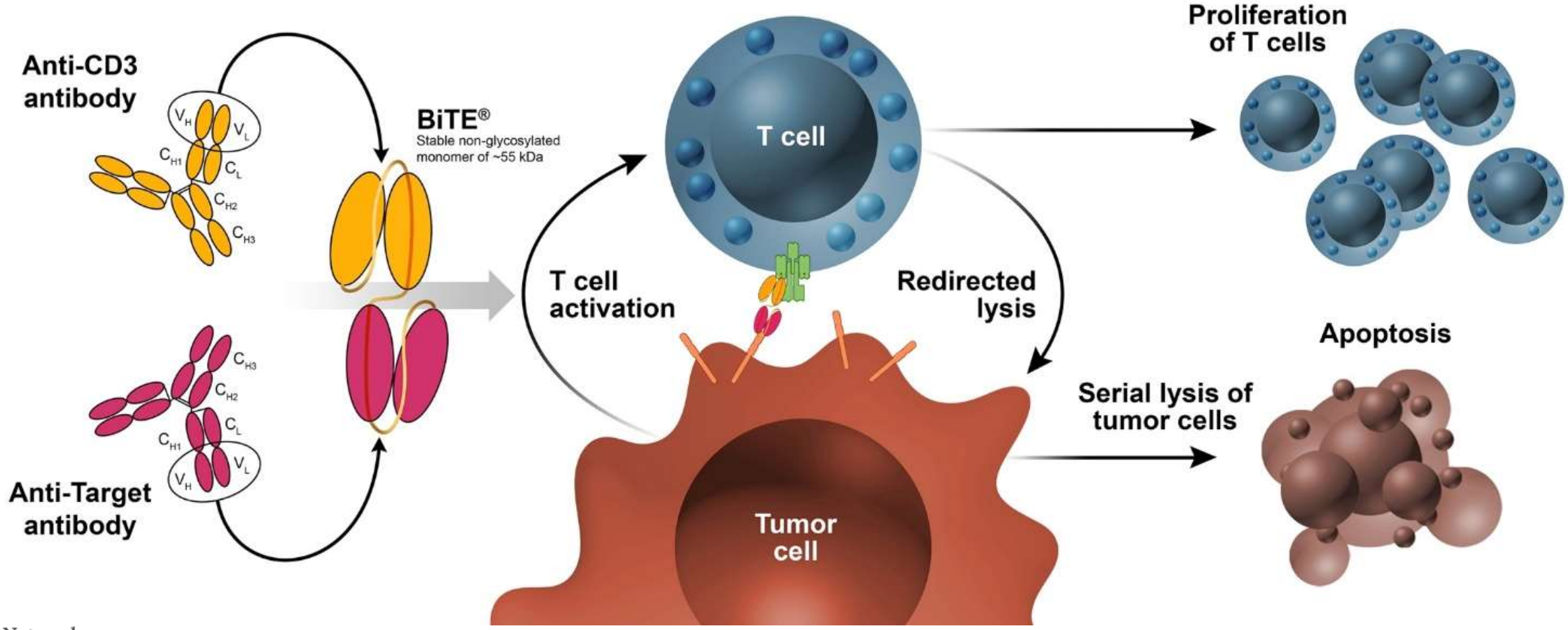
Blinatumomab: CD19xCD3 bispecific T-cell engager

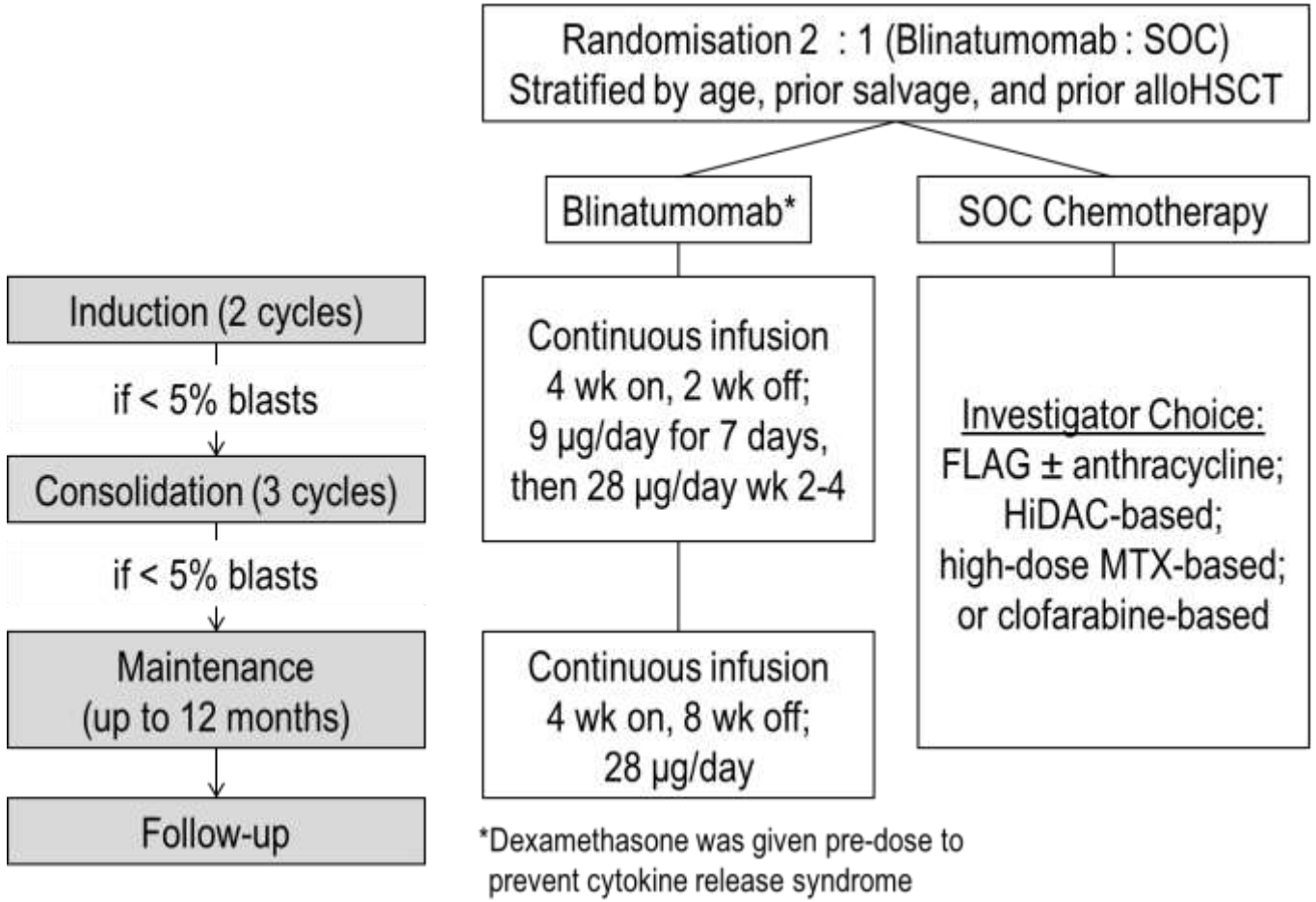


Baeuerle PA, et al. Curr Opin Mol Ther 2009;11:22–30;
Nagorsen D, et al. Exp Cell Res 2011;317:1255–60.

Blinatumomab, R/R Ph-negative B-ALL

Confirmatory Phase 3 study (TOWER)

Inclusion	• Refractory disease • 1st relapse <12 months • >2nd relapse • Any relapse after alloHSCT
Exclusion	• Clinically relevant CNS pathology • AutoHSCT <6 weeks • AlloHSCT <12 weeks • Active GvHD (Grade 2–4) or GvHD treatment in previous 2 weeks

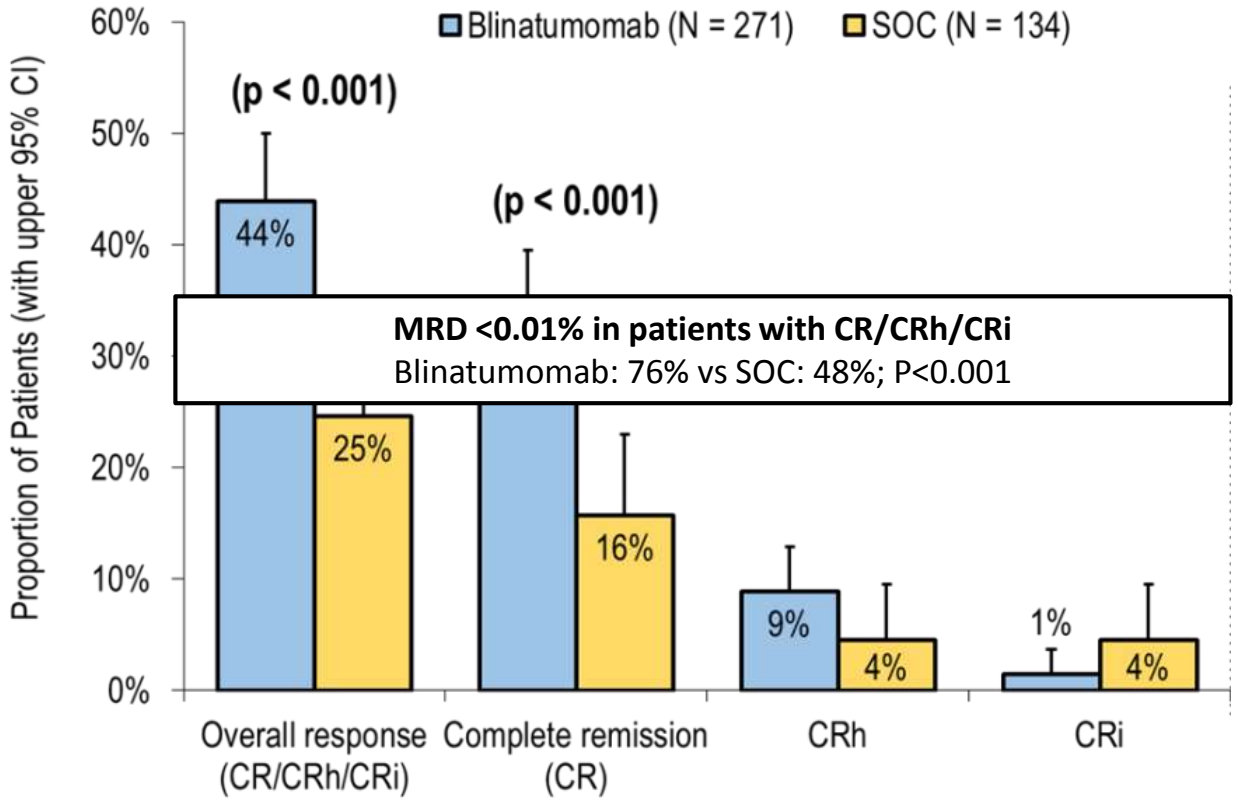


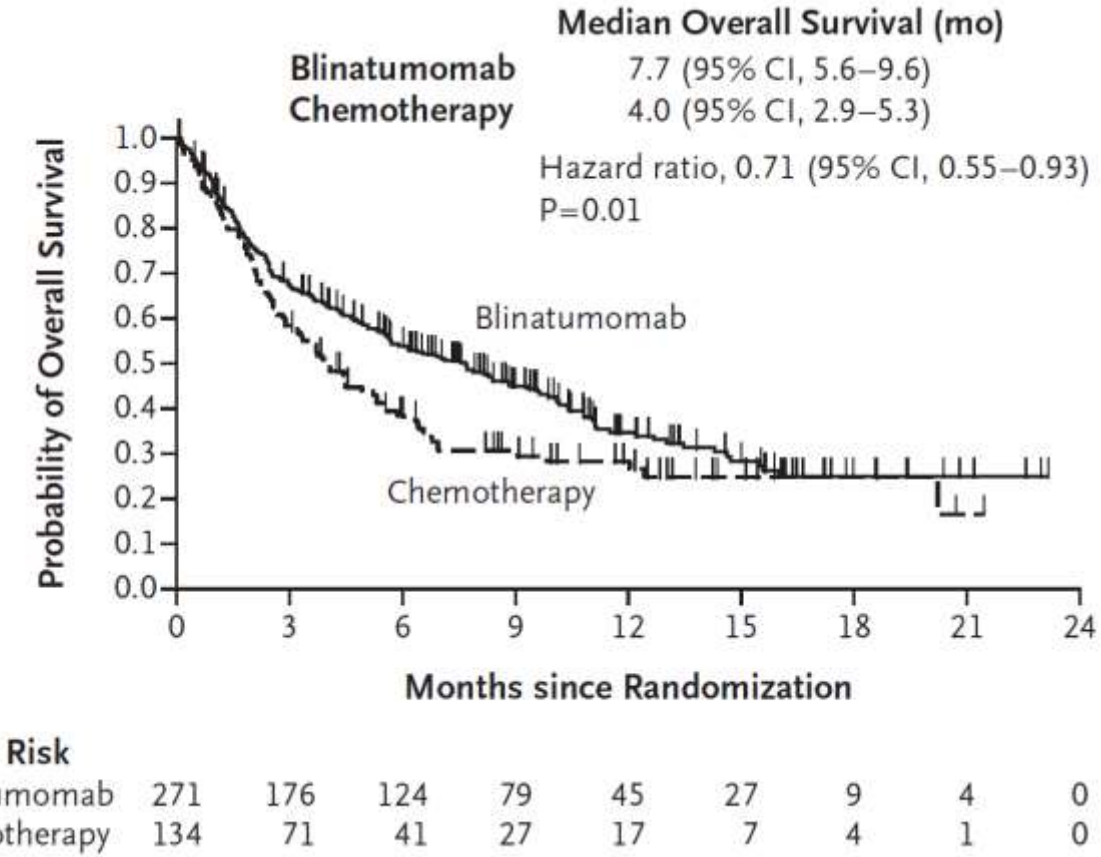
FLAG, fludarabine, cytarabine and G-CSF; GvHD, graft vs host disease; HiDAC, high-dose cytarabine; MTX, methotrexate; SOC, standard of care.

Katarjian H, et al. N Engl J Med 2017;376:836–47.

Blinatumomab Phase 3 (TOWER); R/R Ph-negative B-ALL

Complete remission and overall survival





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Katarjian H, et al. N Engl J Med 2017;376:836–47.

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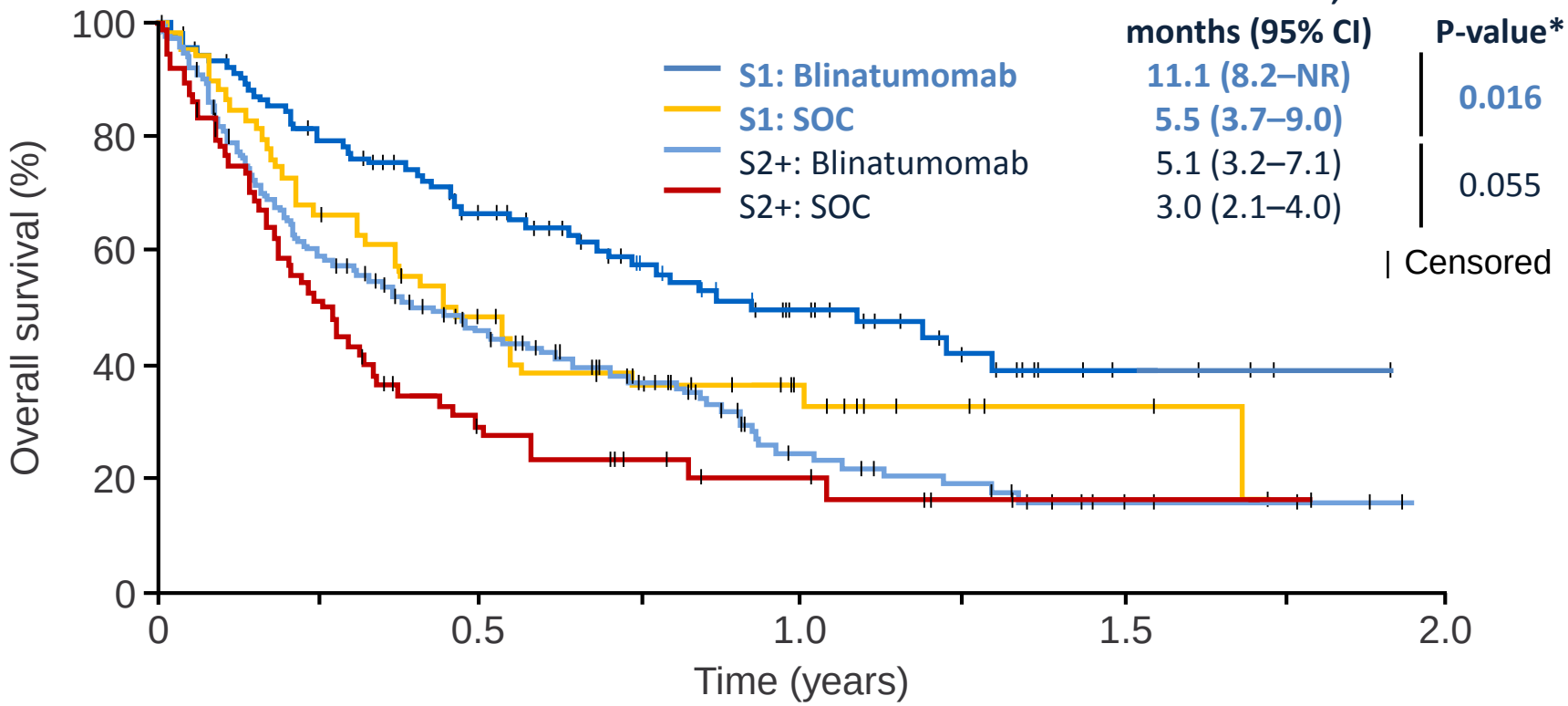
Blinatumomab Phase 3 (TOWER); R/R Ph-negative B-ALL

Overall survival according to salvage status



Patients at risk:									
S1: blinatumomab	104	80	59	39	26	14	5	1	0
S1: SOC	63	39	26	18	11	5	3	0	0
S2+: blinatumomab	167	96	65	40	19	13	4	3	0
S2+: SOC	71	32	15	9	6	2	1	1	0

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Dombret H, et al. Leuk Lymphoma 2019;60:2214–22.

Blinatumomab Phase 3 (TOWER); R/R Ph-negative B-ALL

Exposure-adjusted AE rates

	Blinatumomab (N=267)	SOC (N=109)	P-value*
Total treatment exposure, years	89.0	14.8	
Median treatment duration (range)	2 cycles (1–9)	1 (1–4)	
	eaAE rate†	**eaAE rate†**	
Any AE	46.16	137.64	**<0.001**
Grade ≥3 AEs	10.73	45.27	**<0.001**
All serious AEs	3.49	6.41	NR
Specific AEs of interest			
Cytokine release syndrome	**0.16**	0	**0.038**
Neurological events	0.38	**0.95**	**0.008**
Tumour lysis syndrome	0.09	0.07	**0.780**
Gastrointestinal disorders	0.28	1.49	**<0.001**
Infections	1.63	**6.49**	**<0.001**
Cytopenias	3.64	**20.07**	**<0.001**
Elevated liver enzymes	0.65	1.89	**<0.001**

*P-value comparing blinatumomab vs SOC from a Poisson regression model using number of AEs as the dependent variable and log(exposure time) as offset.

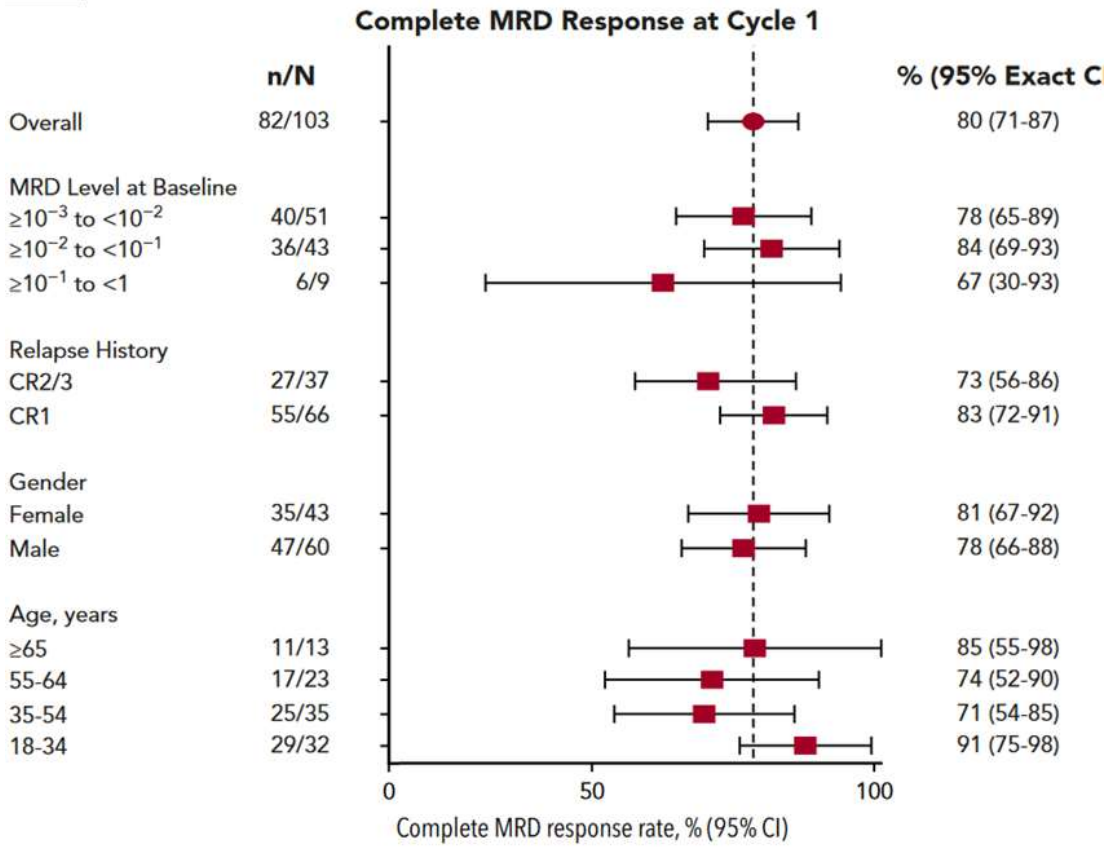
Green favours blinatumomab arm; **Blue** favours SOC chemotherapy arm; †events per patient-year.

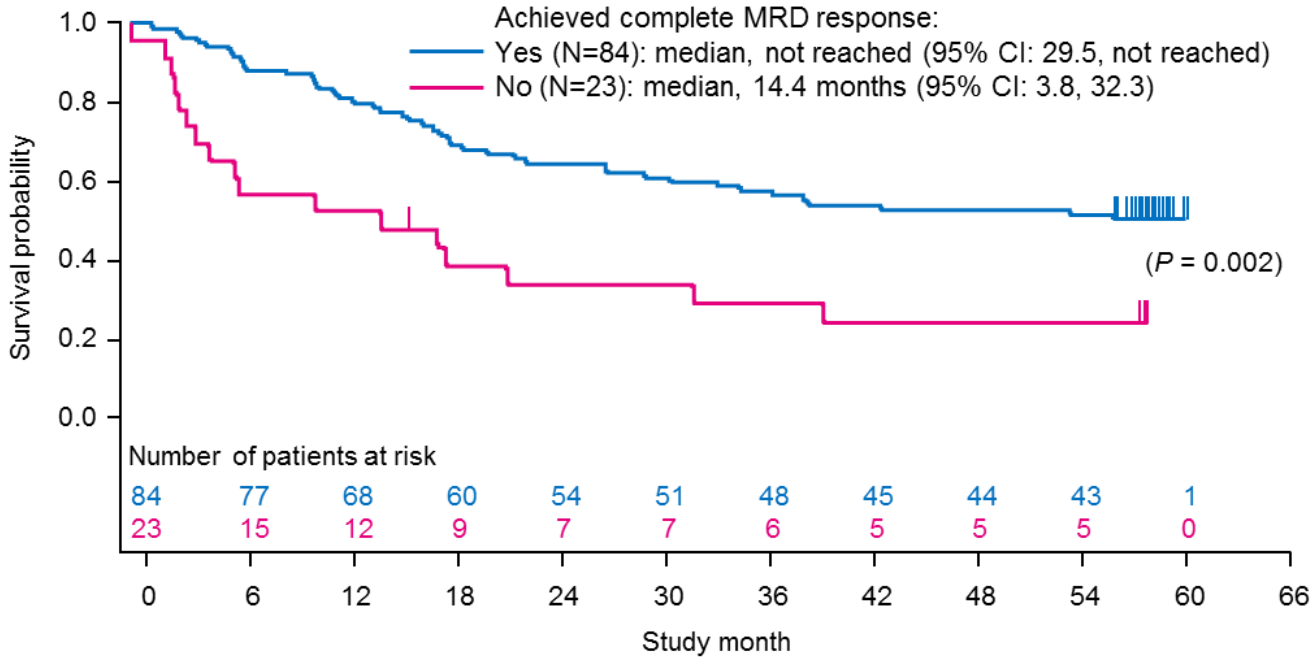
eaAE rate, exposure adjusted event rate; NR, not reported.

Stein AS, et al. Blood Adv 2018;2:1522–31.

Blinatumomab, B-ALL, MRD+

BLAST Study, MRD response and OS by CMR



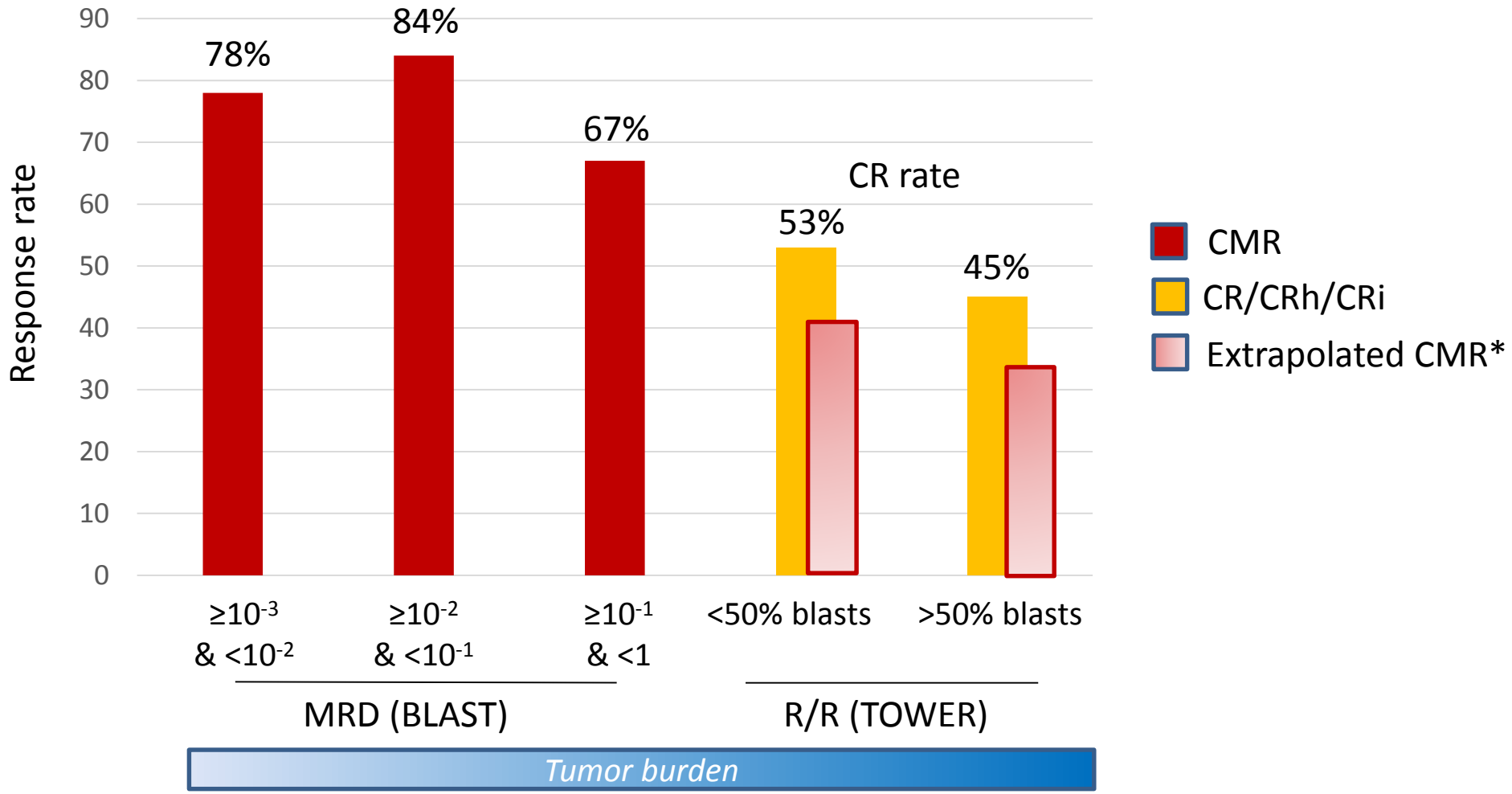


- Median follow-up for survival was 59.8 months (5 years)
- Estimated 5-year survival for complete MRD responders: 50% (95% CI: 39–60%)

Gökbuget N, et al. ASH 2018, abstract 554

Early response after blinatumomab

Impact of tumor burden



* Considering a 76% CMR rate in CR/CRh/Cri patients

Katarjian H, N Engl J Med. 2017 Mar 2;376(9):836-847
Gökbuget et al., ASH2015, #680

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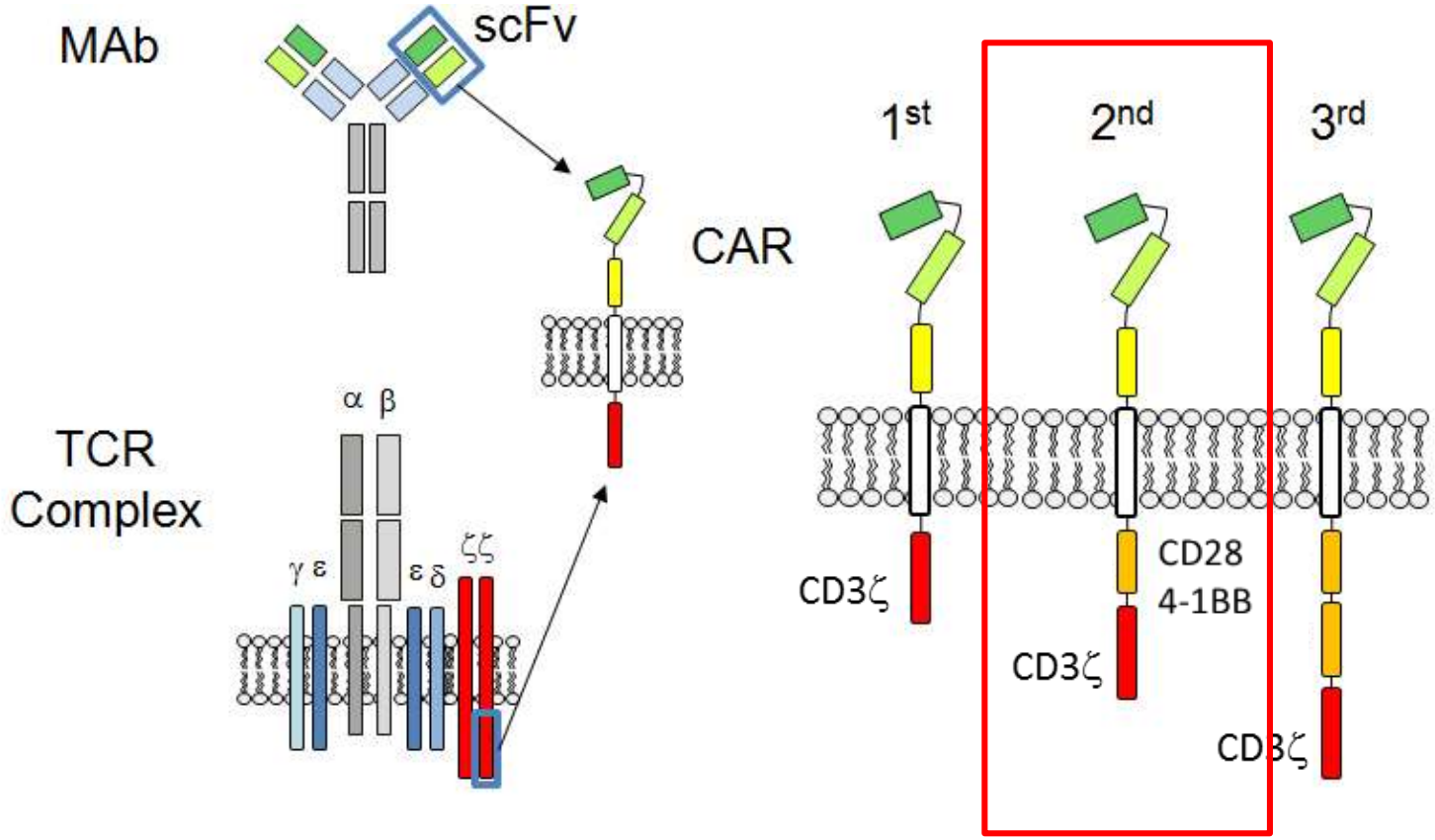
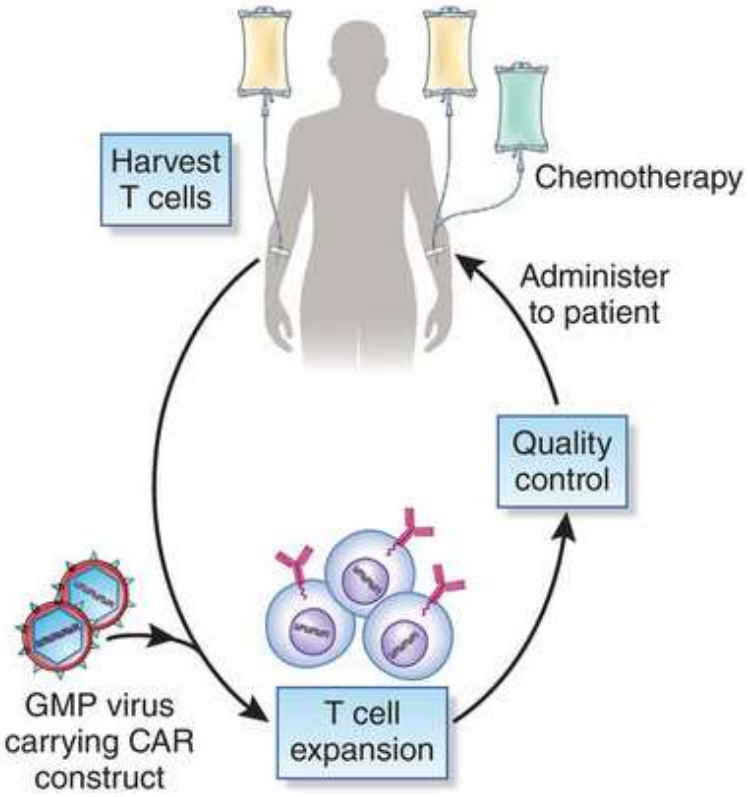
Chimeric antigen receptor generations



Autologous CAR-T



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Heczey A, Louis CU. Discov Med 2013;16:287–94.
Adapted from Olweus J, Nat Biotechnol. 2017 Jun 7;35(6):520-521.

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Autologous CD19 CAR-T in R/R B-ALL

Phase 1/2 studies

Study	Population	CD19-CAR	V	N	Cond.	T-cells	ORR
Maude, 2013[1]	Ped+adult	4-1BB	LV	30	CyF	unselected	90%
Lee, 2015[2]	Ped+YA	CD28	gRV	21	Cy	unselected	68%
Gardner, 2017[3]	Ped+YA	4-1BB	LV	45	CyF	1:1 CD4/8	93%
Maude, 2018[4]	Ped+YA	4-1BB	LV	75	CyF	unselected	81%
Park, 2018[5]	Adult	CD28	gRV	53	Cy/CyF	unselected	83%
Hay, 2019[6]	Adult	4-1BB	LV	53	Cy/CyF	1:1 CD4/8	85%

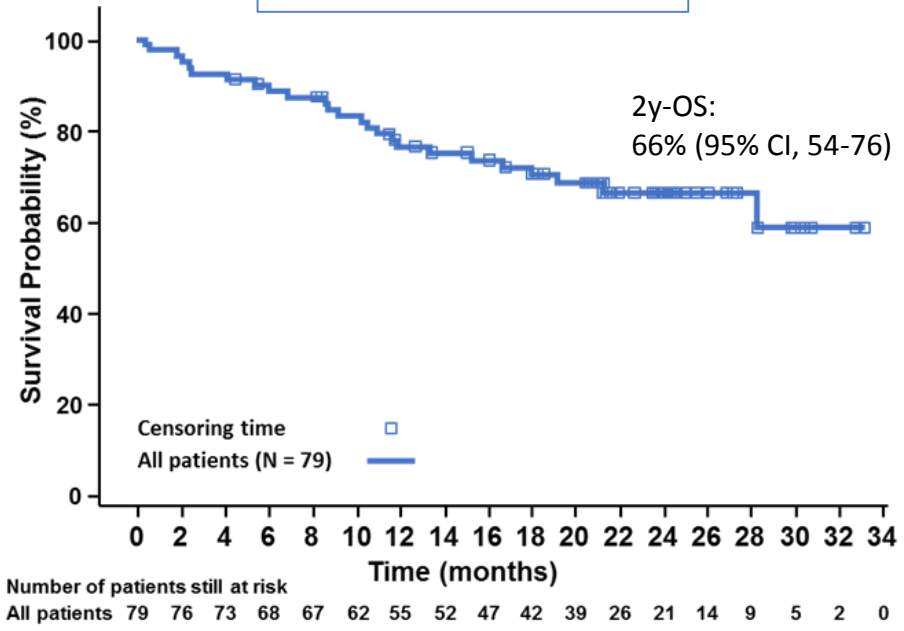
Cy, cyclophosphamide; CyF, cyclophosphamide + fludarabine; Ped, paediatric; YA, young adults;
LV, lentivirus; gRV, gamma-retrovirus; Auto, autologous.

1. Maude SL, et al. N Engl J Med 2014;371:1507–17;
2. Lee DW, et al. Lancet 2015;385:517–28;
3. Gardner RA, et al. Blood 2017;129:3322–31;
4. Maude SL, et al. N Engl J Med 2018;378:439–48;
5. Park JH, et al. N Engl J Med 2018;378:449–59;
6. Hay KA, et al. Blood. 2019 Apr 11;133(15):1652-1663.

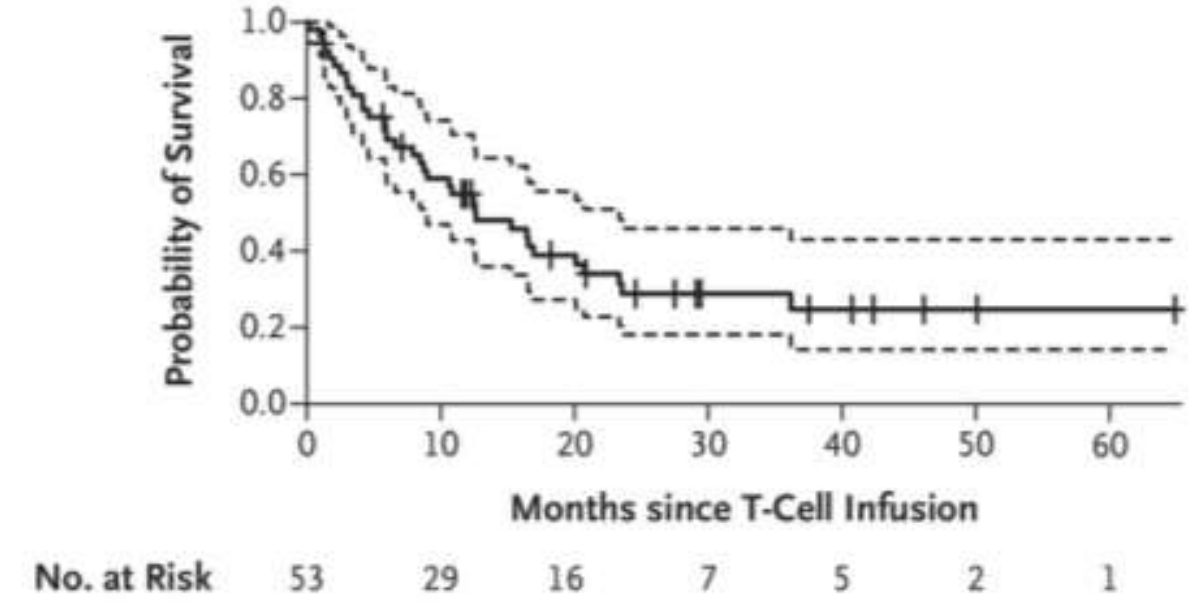
Long-term outcome after CD19 CAR-T

in R/R B-ALL

ELIANA study
R/R B-ALL
3-21 years
CD19/4-1BB/CD3z



MSKCC
R/R B-ALL
>18 years
CD19/CD28/CD3z



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Maude SL, N Engl J Med. 2018 Feb 1;378(5):439-448 + Grupp S, ASH 2018

Park JH, N Engl J Med. 2018 Feb 1;378(5):449-459.

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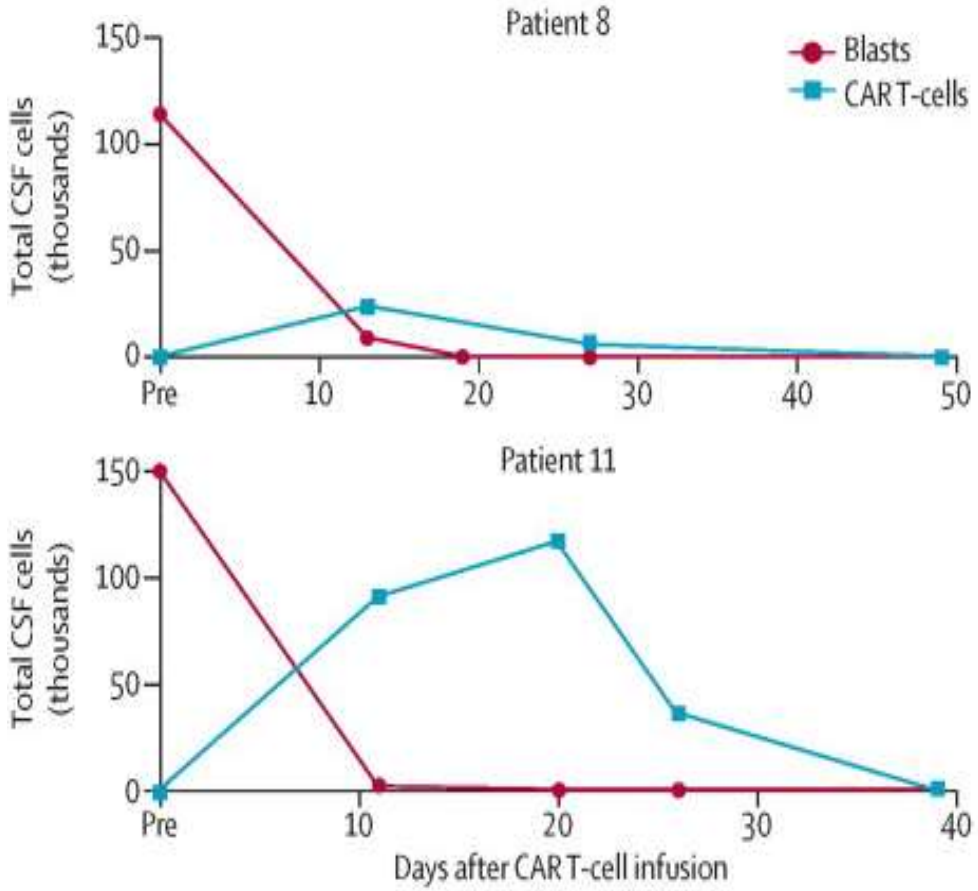
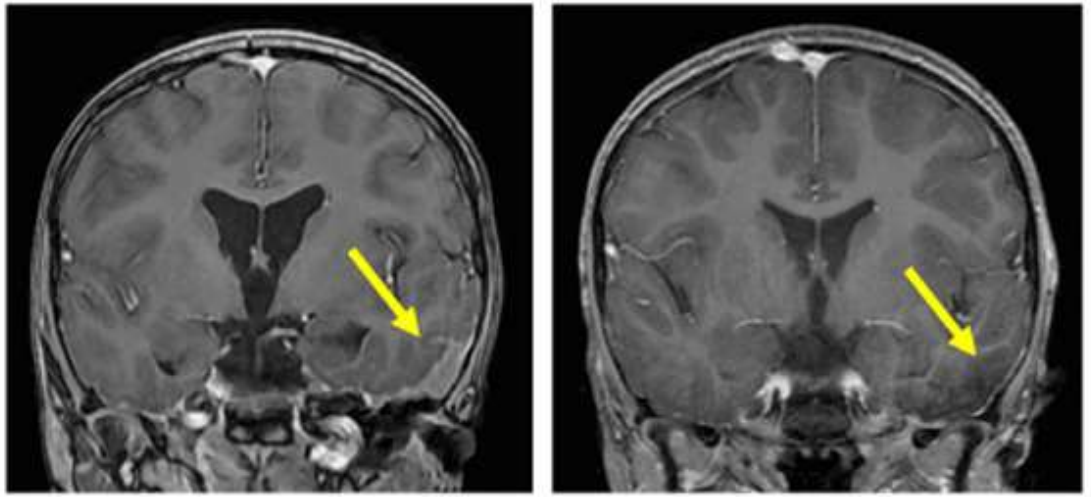
CAR-T cells cross the blood-brain barrier





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

Jacoby E, et al. Am J Hematol 2018;93:1485–92.

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CRS* and ICANS** in CD19 CAR-T ALL studies

Study	CD19-CAR	N	Population	CR	CRS*	ICANS**
Maude, 2013[1]	4-1BB	30	Ped+Adult	90%	**100% 27% severe**	**43% encephalopathy, seizure, aphasia**
Lee, 2015[2]	CD28	21	Ped+YA	68%	**76% 28% severe**	**29% encephalopathy, hallucination**
Gardner, 2017[3]	4-1BB	45	Ped+YA	93%	**93% 23% severe**	**49% 21% severe**
Maude, 2018[4]	4-1BB	75	Ped+YA	81%	**77% 46% severe**	**40% 13% severe**
Park, 2018[5]	CD28	53	Adult	83%	**85% 26% severe**	**43% 42% severe**
Hay, 2019[6]	4-1BB	53	Adult	85%	**75% 19% severe**	**23% severe**

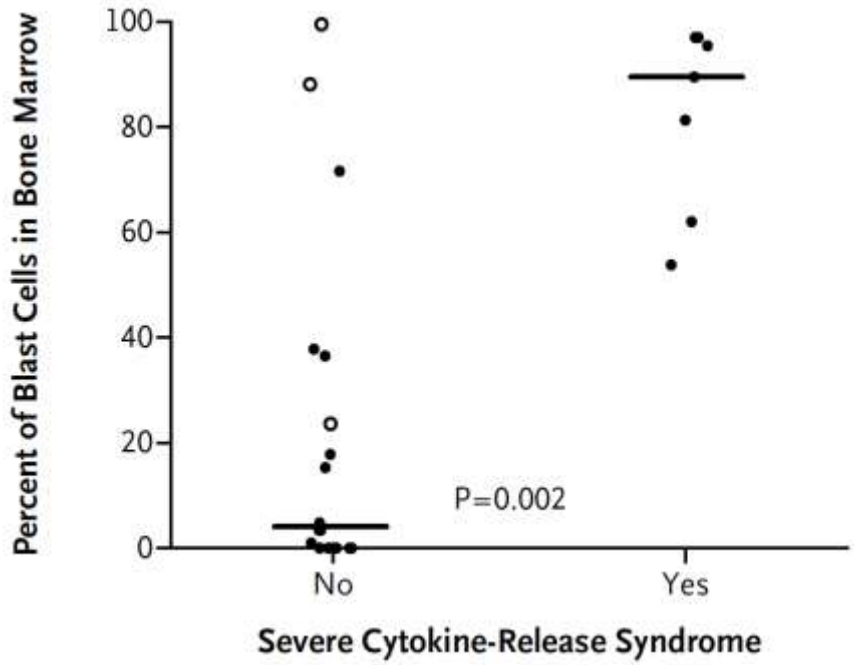
*Cytokine release syndrome
**Immune effector cell-associated neurotoxicity syndrome

1. Maude SL, et al. N Engl J Med 2014;371:1507–17;
2. Lee DW, et al. Lancet 2015;385:517–28;
3. Gardner RA, et al. Blood 2017;129:3322–31;
4. Maude SL, et al. N Engl J Med 2018;378:439–48;
5. Park JH, et al. N Engl J Med 2018;378:449–59;
6. Hay KA, et al. Blood. 2019 Apr 11;133(15):1652-1663.

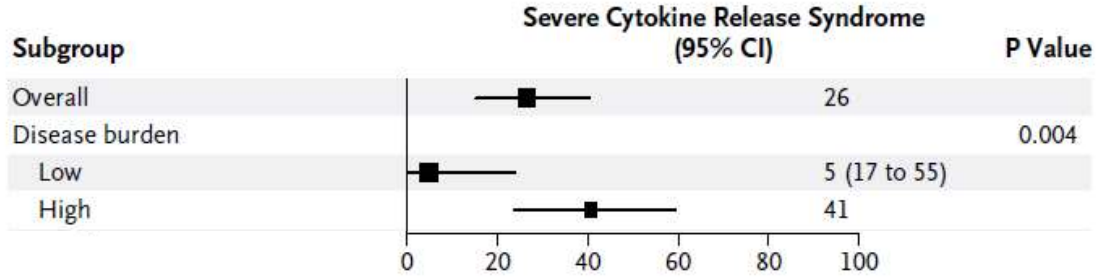
Should we bridge to CAR-T?

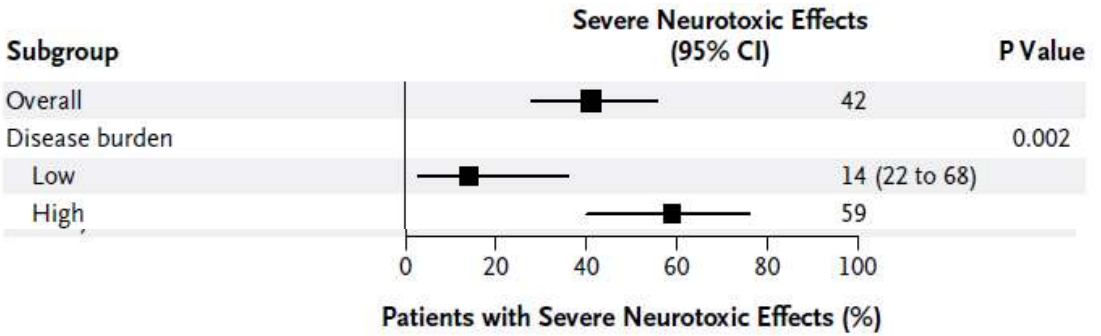
Impact on toxicity

UPENN[1]
5–60 years
CD19/4-1BB/CD3z



MSKCC[2]
>18 years
CD19/CD28/CD3z





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1. Maude SL, et al. N Engl J Med 2014;371:1507–17;
2. Park JH, et al. N Engl J Med 2018;378:449–59.

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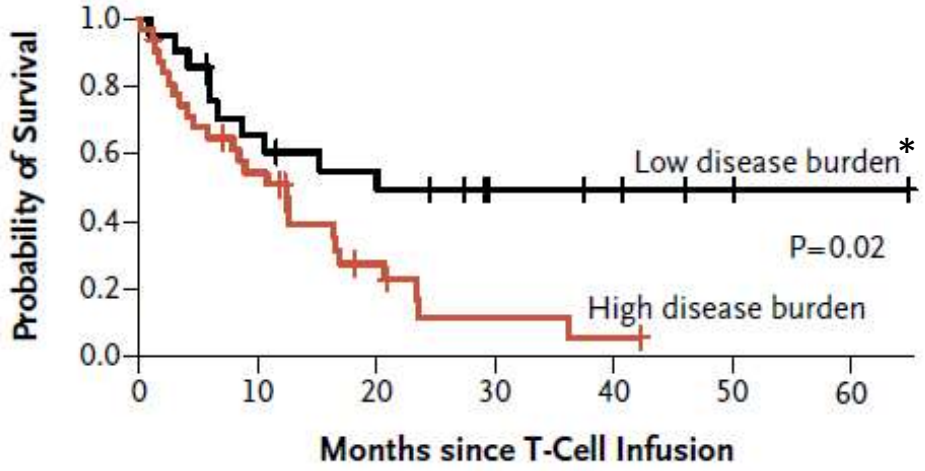
Should we bridge to CAR-T?

Impact on outcome

MSKCC[1]
>18 years
CD19/CD28/CD3z

Overall survival
by disease burden



No. at Risk

Low burden	21	13	10	5	4	2	1
High burden	32	16	6	2	1	0	0

*** Low disease burden: <5% bone marrow blasts**

FHCRC[2]
>18 years
CD19/4-1BB/CD3z

Univariate analysis
for event-free survival

Variable	Univariate HR (95% CI)	*P* value
LDH (per 100 U/L, pre-lymphodepletion)	1.49 (1.22-1.80)	<.0001
Bridging systemic therapy[a]	5.66 (2.56-12.5)	<.0001
Platelet count (per 50,000/μL, pre-lymphodepletion)	0.57 (0.42-0.76)	.0002
Extramedullary disease (Y)	3.57 (1.66-7.65)	.001
Fludarabine added to lymphodepletion (Y)	0.30 (0.13-0.66)	.003
IL-6 (pg/mL, pre-lymphodepletion)	1.02 (1.01-1.03)	.005
Marrow blasts by flow cytometry (%)	1.01 (1.00-1.03)	.006
High-risk cytogenetics[d] (Y)	2.48 (1.12-5.50)	.03
Neutrophil count (1000/μL, pre-lymphodepletion)	0.73 (0.55-0.97)	.03
Soluble TNFRp55 (pg/mL, Day 0)	4.84 (1.07-21.8)	.04
IL-2 (pg/mL, Day 0)	3.24 (1.05-10.0)	.04
IL-8 (pg/mL, pre-lymphodepletion)	1.78 (1.00-3.15)	.05
Soluble TIM-3 (ng/mL, pre-lymphodepletion)	1.05 (1.00-1.11)	.06
Dose level ($2x10^5$ vs $2x10^6$ CAR-T cells/kg)	0.51 (0.24-1.11)	.09

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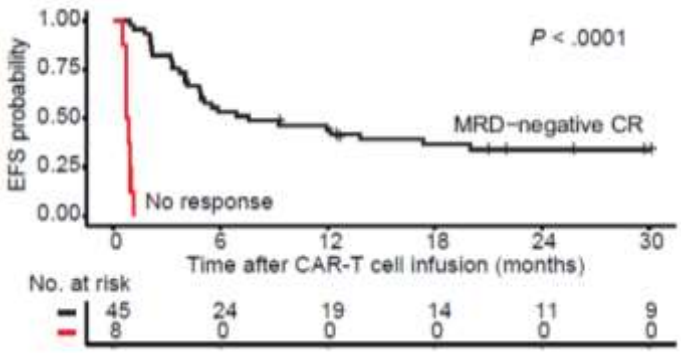
Should we transplant post-CAR-T ?

- 45 patients in MRD-negative CR, 18 bridge to HSCT (40%)
- HSCT patients were less likely to have received prior allogeneic HSCT
- HSCT (time-dependant variable) associated with better EFS in univariate analysis (HR 0.31 [95% CI 0.13-0.79], P=.014)

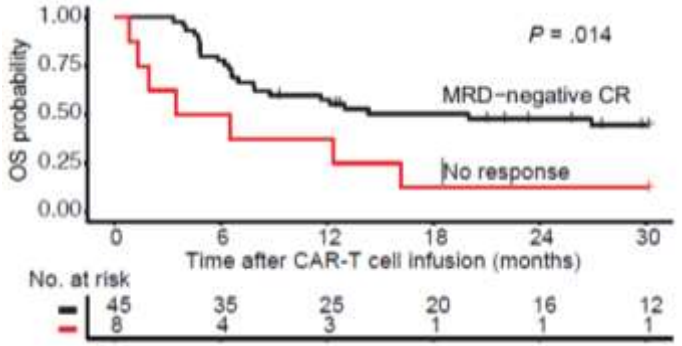
FHCRC
>18 years
CD19/4-1BB/CD3z

HSCT : pre-CAR 43%
post-CAR 40%

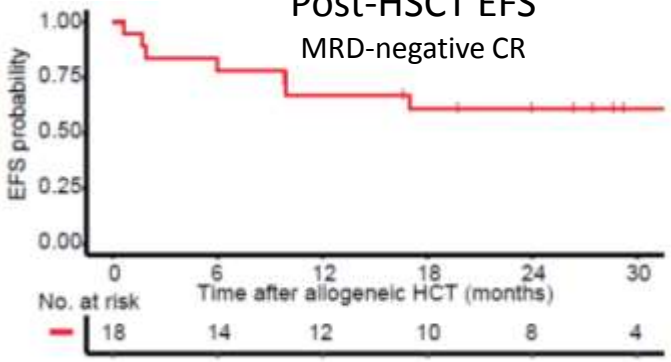
Event-free survival



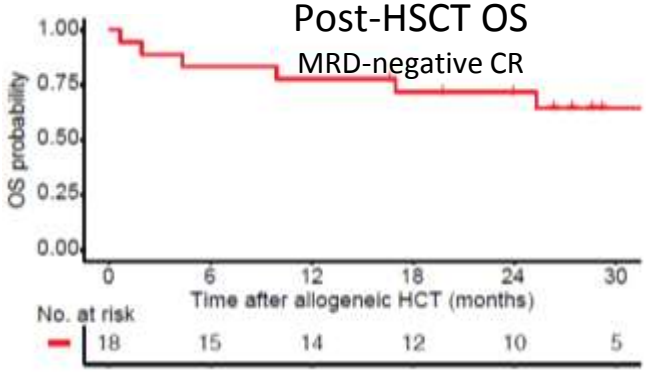
Overall survival



Post-HSCT EFS
MRD-negative CR



Post-HSCT OS
MRD-negative CR



Hay KA, et al. Blood. 2019 Apr 11;133(15):1652-1663.

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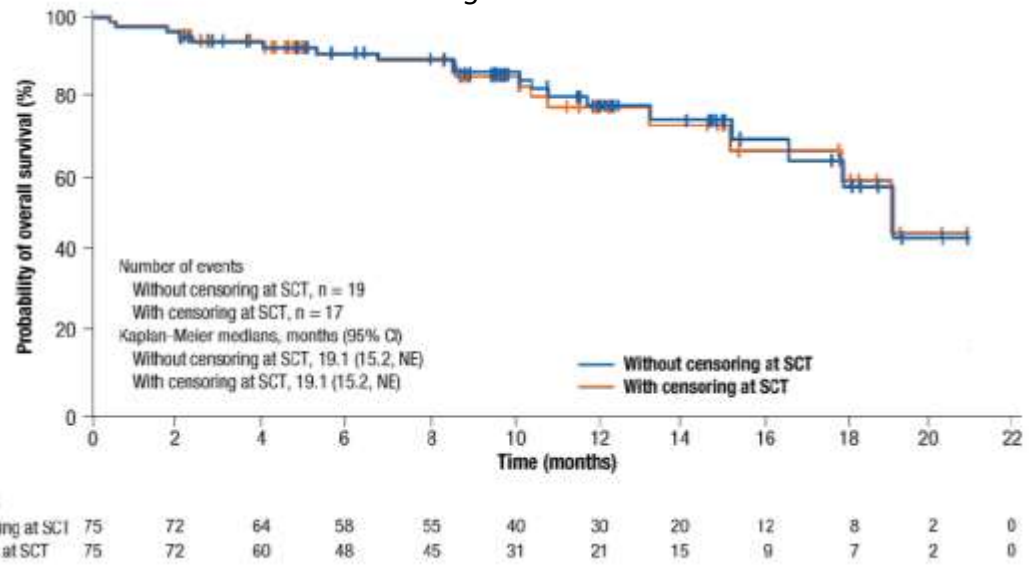
Should we transplant post-CAR-T ?

ELIANA[1]
3–21 years
CD19/4-1BB/CD3z

HSCT: pre-CAR 61%
post-CAR 13%

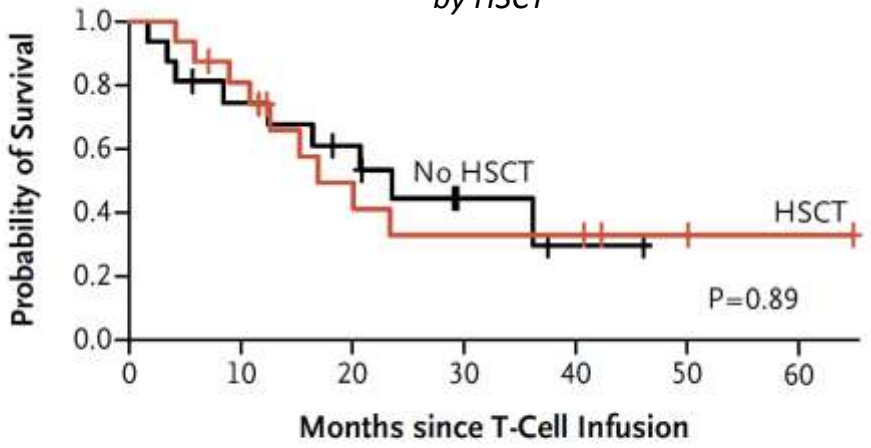
Overall survival
with censoring at HSCT



MSKCC[2]
>18 years
CD19/CD28/CD3z

HSCT: pre-CAR 36%
post-CAR 39%

Overall survival
by HSCT



No. at Risk							
No HSCT	16	11	8	3	1	0	0
HSCT	16	12	6	4	4	2	1

1. Maude SL, et al. N Engl J Med 2018;378:439–48;
2. Park JH, et al. N Engl J Med 2018;378:449–59.

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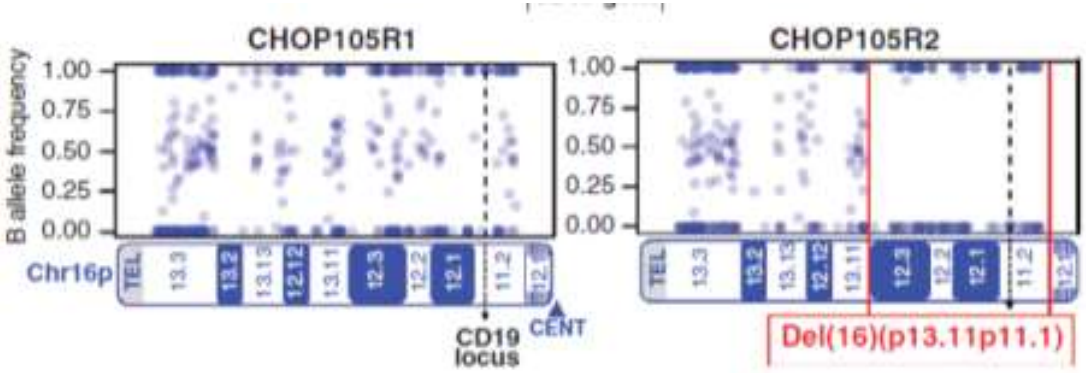
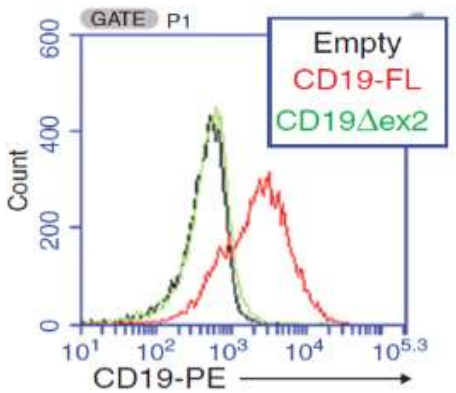
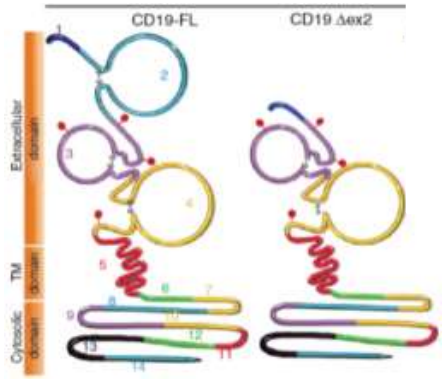
Escape mechanisms to CD19-targeted therapy

- Mutation/deletion of CD19 gene
  - Gene deletion
  - Exon 2 mutations → alternative splicing
- Lineage switch
  - ALL → AML (MLL+ disease)
- Loss of CD81 and disruption of CD19 trafficking
- Transduction of ALL blasts and antigen masking





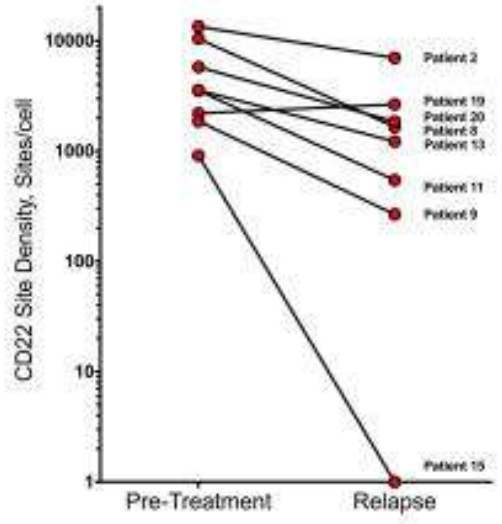


Köhnke T, et al. J Hematol Oncol 2015;8:111;
Sotillo E, et al. Cancer Discov 2015;5:1238–40;
Rayes A, et al. Pediatr Blood Cancer 2016;63:1113–5;
Ruella M, et al. Nat Med 2018;24:1499–503.

CD22/4-1BB CAR-T in R/R ALL

	Population	Age (yrs)	N	CRS	Neurotox	ORR
Bethesda / NCI[1]	Ped-Ad	19 (7-30)	21	76% Grade 1-2	29% Grade 1-2	73%*
Beijing Boren Hospital[2]	Ped-Ad	10 (1-55)	34	91% Grade 1-2 (all but 1)	18% Grade 1-2	71% 4 ED, 6 failure

* At DL2/3, ≥1×10^6 CAR-T cells/kg



Relapse associated with diminished CD22 density (w/o changes in mRNA, mutation, copy number alteration)[1]

1. Fry T et al. Nat Med. 2018 Jan;24(1):20-28
2. Pan J et al. Leukemia. 2019 May 20. doi: 10.1038/s41375-019-0488-7

Options for adults with R/R B-ALL

	TOWER[1]		INO-VATE[2]		ELIANA[3,4]
Design	Phase III		Phase III		Phase II
Age	**18yrs+**		**18yrs+**		**2-21yrs***
Population	R/R Ph-negative BCP-ALL Refractory 1st early relapse (< 12 months) Untreated second+ relapse Any relapse after HSCT		R/R CD22+ BCP-ALL Refractory Due for 1st or 2nd salvage therapy Ph-positive ALL if failing 2 lines TKI		R/R BCP-ALL Refractory 2nd relapse+ 1st relapse after HSCT Ph-positive ALL if failing 2 lines TKI
	Blinatumomab	SOC†	**Inotuzumab**	SOC†	**Tisagenlecleucel**
ORR	44% (CR+CRi+CRh)	25%	81% (CR+CRi)	29%	81% (as treated) (CR+CRi)
MRD negativity	76%	48%	78%	28%	100%
Median DOR	7.3 mths	4.6 mths	4.6 mths	3.1 mths	NR[4]
Median OS	7.7 mths	4.0 mths	7.7 mths	6.6 mths	NR[4]
Safety	CRS 5%		VOD 11%		CRS 77% (Grade ≥3 46%)

Differences in populations (age, Ph+, CR1 duration…), and SOC

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*Age at diagnosis
†Different SOC regimen allowed among both studies

1. Kantarjian H, et al. N Engl J Med 2017;376:836–47;
2. Kantarjian H, et al. N Engl J Med 2016;375:740–53;
3. Maude S, et al. N Engl J Med. 2018 Feb 1;378(5):439-448;
4. Grupp SA, et al. ASH 2018, abstract 895.

First salvage therapy in adult with Ph- B-ALL

	Chemotherapy	Blinatumomab	Inotuzumab	Tisagenlecleucel
Age	18y+	18y+	18y+	≤25y
CR1 duration	• Late relapse (> 18 months)	• Early relapse	• Early relapse	• 2nd relapse • 1st relapse after SCT
Limiting prior medical history	• Allergy to ASPA • Cumulative dose of anthracycline • Polyneuropathy…	• Neurotoxicity ?	• Liver condition • Prior HSCT ?	• Neurotoxicity ?
ALL phenotype	N/A	CD19+ (90%)	CD22+ (90%)	CD19+ (90%)
Bridging chemotherapy	N/A	• Consider previous debulking	N/A	• Consider previous debulking ?
Consolidation with HSCT	• Mandatory	• Benefit of HSCT unclear	• Benefit of HSCT unclear • Risk of VOD	• Consider if : - Early Loss of B-cell aplasia - MRD+ at D28

Take home messages
R/R B-ALL in adults

1. The prognosis of relapsed/refractory adult patients remains dismal
2. The most important prognostic factor at relapse is CR1 duration
3. New immunstrategies have improved the outcome of patients
4. The choice of salvage therapy is guided by patient age, CR1 duration, number of treatment line, previous or planed HSCT, liver/neurological conditions…
5. The best way to combine these strategies has not been evaluated yet
6. Include in clinical trials !