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Webinar on Recent Updates in Pediatric and Adolescent Young Adult (AYA) Acute Lymphocytic Leukemia (ALL):

Focus on Middle East and LATAM Region

October 11, 2022

APTITUDE HEALTH

Global Leukemia Academy

Local Welcome

Franco Locatelli, MD, PhD

University of Rome
IRCCS Ospedale Pediatrico Bambino Gesù, Italy

APTITUDE HEALTH

Virtual Meeting

October 11, 2022

Time	Title	Speaker
12.00 PM – 12.05 PM BRT 19.00 – 19.05 GST (5 min)	Welcome and Introductions	Franco Locatelli, MD, PhD
12.05 PM – 12.15 PM BRT 19.05 – 19.15 GST (10 min)	Current Paradigm and Long-term Toxicities for Pediatric ALL • Integration of innovative immunotherapies • Role of MRD in treatment • Long-term toxicities	Franco Locatelli, MD, PhD
12.15 PM – 12.30 PM BRT 19.15 – 19.30 GST (15 min)	Bispecifics for Pediatric/AYA ALL • Review of trial results in pediatric/AYA ALL • Role of MRD in research and treatment • AYA considerations	Lia Gore, MD
12.30 PM – 12.40 PM BRT 19.30 – 19.40 GST (10 min)	CAR T Cells for Pediatric/AYA ALL • Benefits and risks of CAR Ts and bispecifics • Role of MRD in research and treatment • AYA considerations	Franco Locatelli, MD, PhD
12.40 PM – 1.00 PM BRT 19.40 – 20.00 GST (20 min)	Questions to Experts	Lia Gore, MD Franco Locatelli, MD, PhD

Global Leukemia Academy

Current Paradigm and Long-term Toxicities for Pediatric ALL

Franco Locatelli, MD, PhD

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Bambino Gesù
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UNIVERSITÀ CATTOLICA del Sacro Cuore

Current Paradigm and Long-term Toxicities for Pediatric ALL

Franco Locatelli, MD
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IRCCS Ospedale Bambino Gesù, Roma, Italy

Disclosures

Name of Company	Research Support	Employee	Consultant	Stockholder	Speaker's Bureau	Advisory Board	Other
Miltenyi					X		
Bellicum	X				X	X	
Amgen					X	X	
Jazz Pharma					X		
Medac					X		
Neovii					X	X	
Novartis					X	X	
Sanofi						X	
Sobi					X		
Gilead					X		
bluebird bio					X		
Vertex						X	

Outcome of contemporary trials involving children and adolescents with ALL

Research Group	Trial	Reference	Region	Years	Subgroup	No. of Patients	Event-free Survival†	Overall Survival†
							percent	
COG	Many trials	Hunger et al.[37]	United States, Canada, Australia, New Zealand	2000–2005	All patients B-cell ALL T-cell ALL	6994 5845 457	N/A N/A N/A	91.3 92.0 81.5
SJCRH	Total Therapy Study XV	Pui et al.[56]	United States	2000–2007	All patients B-cell ALL T-cell ALL	498 422 76	85.6 86.9 78.4	93.5 94.6 87.6
DFCI	DFCI ALL Consortium Protocol 00–01	Vrooman et al.[57]	United States, Canada	2000–2004	All patients B-cell ALL T-cell ALL	492 443 49	80.0 82.0 69.0	91.0 N/A N/A
AIEOP-BFM	AIEOP-BFM ALL 2000	Conter et al.,[49] Schrappe et al.[50]	Western Europe	2000–2006	All patients B-cell ALL T-cell ALL	4480 4016 464	80.3 80.4 75.9	91.1 91.8 80.7
MRC-NCRI	UKALL 2003	Vora et al.[58]	United Kingdom	2003–2011	All patients B-cell ALL T-cell ALL	3126 2731 388	87.2 N/A N/A	91.5 N/A N/A
DCOG	DCOG Protocol ALL-9	Veerman et al.[59]	The Netherlands	1997–2004	All patients B-cell ALL T-cell ALL	859 701 90	81 82 72	86 N/A N/A
EORTC CLG	EORTC CLG 58591	Domenech et al.[60]	Belgium, France	1998–2008	All patients	1940	82.6	89.7
NOPHO	ALL-2000	Schmiegelow et al.[61]	Denmark, Finland, Iceland, Norway, Sweden	2000–2007	All patients B-cell ALL T-cell ALL	1023 906 115	79 81 64	89 91 72

* Infants younger than 1 year of age were excluded from these studies when possible. AIEOP denotes Italian Association of Pediatric Hematology and Oncology, BFM Berlin–Frankfurt–Münster, DCOG Dutch Childhood Oncology Group, DFCI Dana–Farber Cancer Institute, EORTC CLG European Organization for Research and Treatment of Cancer–Children's Leukemia Group, MRC-NCRI Medical Research Council–National Cancer Research Institute, N/A not available, NOPHO Nordic Society of Paediatric Haematology and Oncology, SJCRH St. Jude Children's Research Hospital, and UKALL Medical Research Council Working Party on Leukaemia in Children UK National Acute Lymphoblastic Leukaemia Trial.
† Survival percentages shown are the rates at 5 years except for the rates for the AIEOP-BFM trial, which were reported at 7 years.

Hunger SP, Mullighan CG. *N Engl J Med.* 2015;373:1541-1552; Teachey DT, Pui CH. *Lancet Oncol*. 2019;20:E142-E154.

Perspectives for new trials in ALL

- Utilize novel genetic approaches
- Improve risk-stratification by wider combination of genetic factors and response (MRD)
- Avoid additional toxic agents in most patients
- Introduce novel agents under controlled conditions

MRD and genetics to guide stratification and therapy

- MRD-based choices of specific therapies
- Therapy reduction in MRD low-risk groups
- Therapy intensification in MRD high-risk groups
- Specific therapy protocols for high-risk genetic subgroups
- Interdependency of MRD and genetics

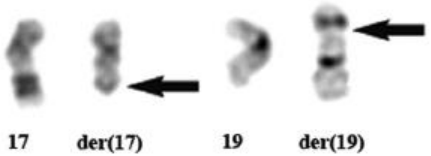
Identification of new high-risk groups and reducing relapses in high-risk patients

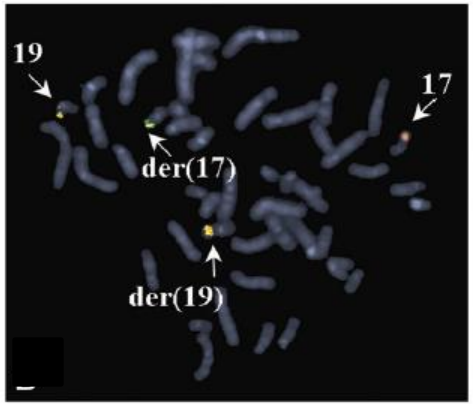
		1986	1990	1995	2000	2009	2017
High-risk criteria	PPR	■	■	■	■	■	
	noCR d33	■	■	■	■	■	■
	BCR-ABL1+		■	■	■	■	■
	MLL-AF4+			■	■	■	■
	"MRD-HR"				■	■	■
	"MRD-MRD SER"					■	■
	"FCM-MRD d15 HR"					■	■
	Hypodiploidy					■	■
	TCF3-HLF +						■
	IKZF1^{plus} and PCR-MRD at TP1 positive or inconclusive						■

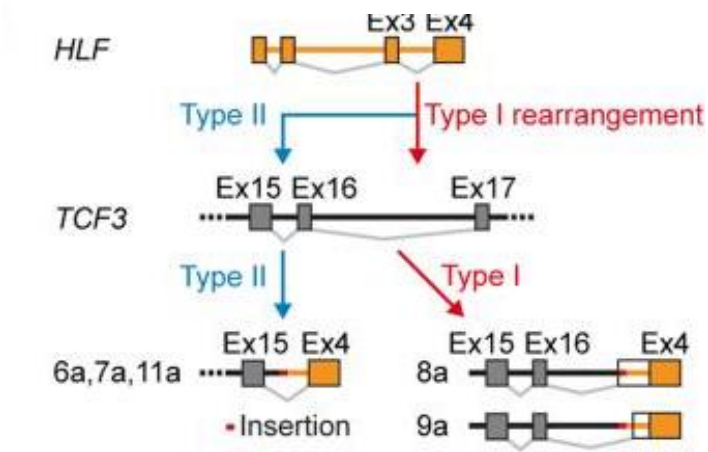
Studies ALL-BFM

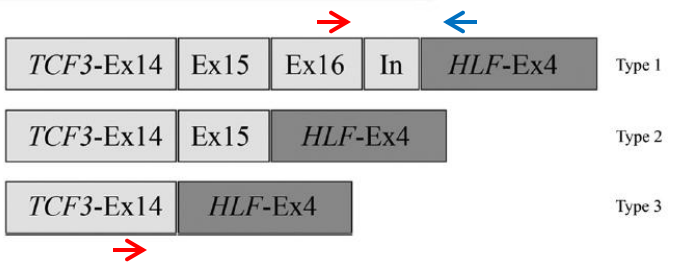
More and more patients with "intermediately unfavorable" outcome have been identified and shifted to the high-risk arm

A novel *TCF3-HLF* fusion in ALL with a t(17;19)(q22;p13)









RT-PCR

Multiplex RT-PCR (×6)

Panagopoulos I, et al. *Cancer Genet*. 2012;205:669-672.

JOURNAL OF CLINICAL ONCOLOGY

ORIGINAL REPORT

IKZF1^{plus} Defines a New Minimal Residual Disease–Dependent Very-Poor Prognostic Profile in Pediatric B-Cell Precursor Acute Lymphoblastic Leukemia

Martin Stanulla, Elif Dagdan, Marketa Zaliova, Anja Möricke, Chiara Palmi, Giovanni Cazzaniga, Cornelia Eckert, Geertruy te Kronnie, Jean-Pierre Bourquin, Beat Bornhauser, Rolf Koehler, Claus R. Bartram, Wolf-Dieter Ludwig, Kirsten Bleckmann, Stefanie Groeneveld-Krentz, Denis Schewe, Stefanie V. Junk, Laura Hinze, Norman Klein, Christian P. Kratz, Andrea Biondi, Arndt Borkhardt, Andreas Kulozik, Martina U. Muckenthaler, Giuseppe Basso, Maria Grazia Valsecchi, Shai Izraeli, Britt-Sabina Petersen, Andre Franke, Petra Dörge, Doris Steinemann, Oskar A. Haas, Renate Panzer-Grümayer, Hélène Cavé, Richard S. Houlston, Gunnar Cario, Martin Schrappe, and Martin Zimmermann, for the TRANSCALL Consortium and the International BFM Study Group

DOI: https://doi.org/10.1200/JCO.2017.74.3617

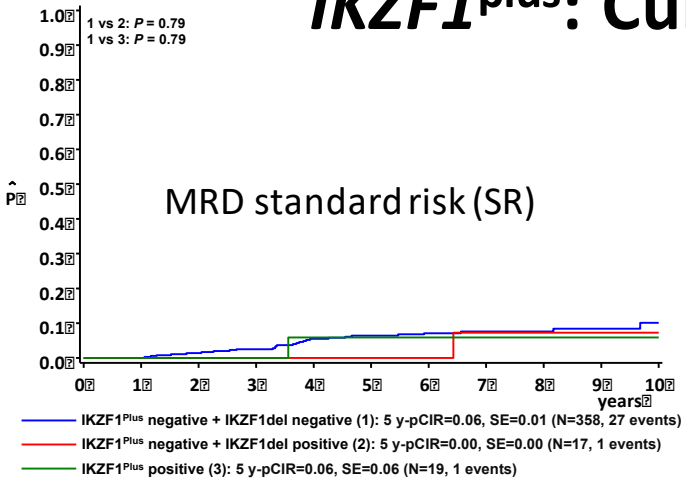
New prognostic pattern: Definition of *IKZF1*^{plus}

- Deletion of *IKZF1* and
  - *PAX5* and/or
  - *CDKN2A* and/or
  - *CDKN2B* and/or
  - *CRLF2 (PAR)* and

  - Negativity for *ERG* deletion

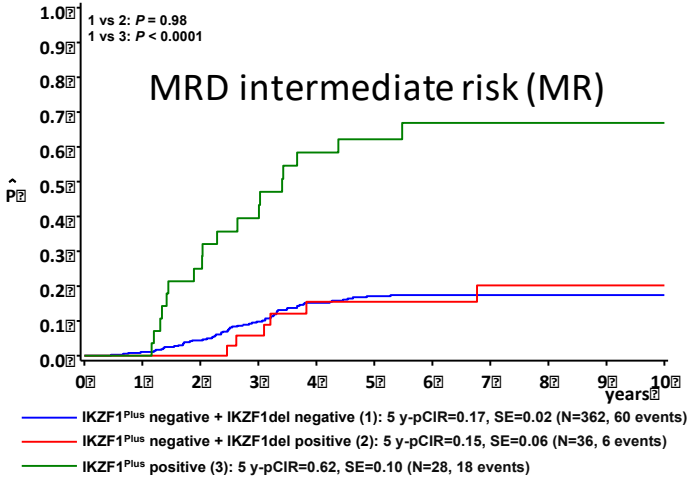
Stanulla M, et al. *J Clin Oncol.* 2018;36:1240-1249.

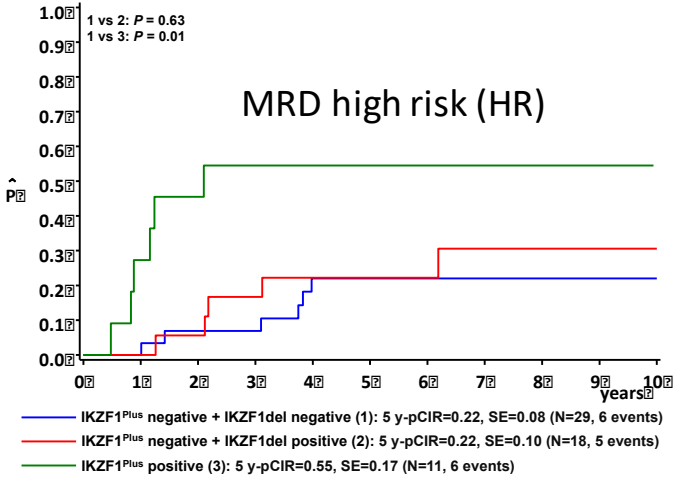
IKZF1^{plus}: Cumulative relapse incidence in MRD-based risk groups



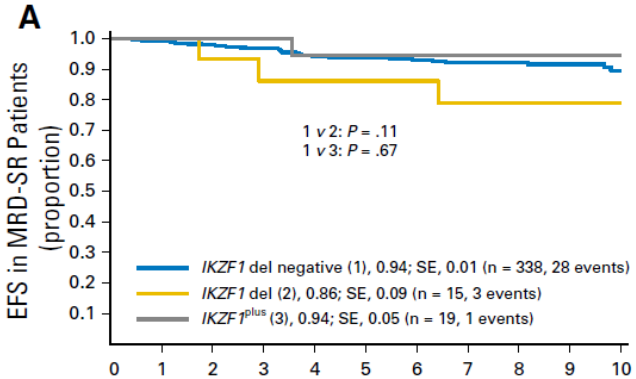
SR = 6%
MR = 62%
HR = 55%

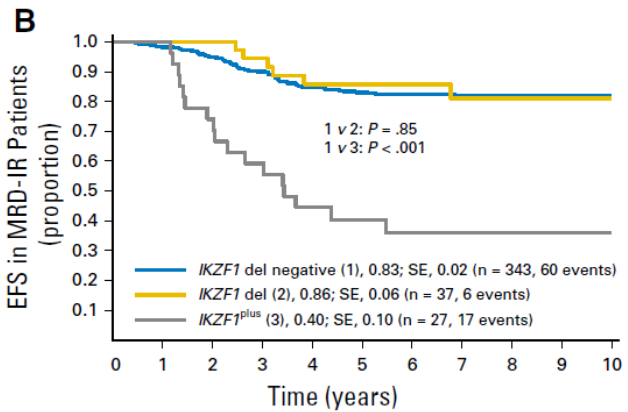
A: MRD – standard risk (MRD neg at 5w and 12w)
B: MRD – intermediate risk (MRD non-SR/HR)
C: MRD – high risk (MRD pos ≥10^{-4} at 12w)





IKZF1^{plus} and MRD: Impact on EFS





A: MRD – standard risk (MRD neg at 5w and 12w)
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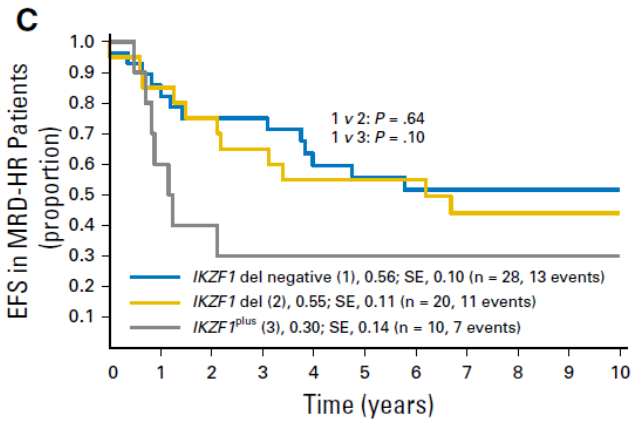
C: MRD – high risk (MRD pos ≥10^{-4} at 12w)

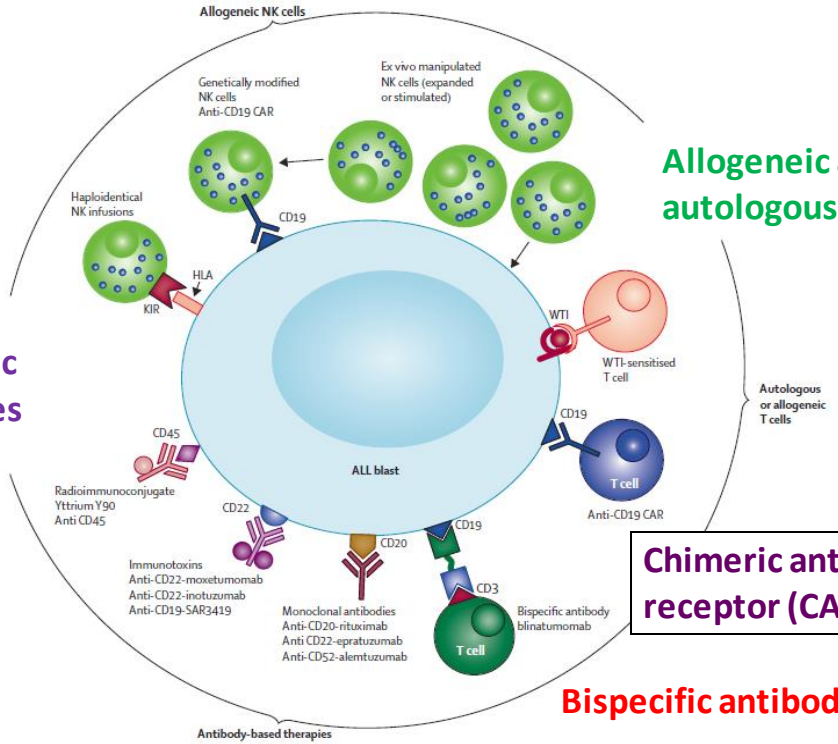


Stanulla M, et al. *J Clin Oncol.* 2018;36:1240-1249.

The essentials in pediatric ALL: Risk-stratification and frontline therapy

- Approximately 80% 5-year EFS can be achieved in unselected populations of pediatric patients
- The early treatment response – in particular through MRD detection – has been established to be the strongest prognostic factor
- Translation of novel molecular findings into improved treatment outcome is under investigation in various trials
- New molecular subgroups have been described (eg, Ph-like or *BCR/ABL*-like pB-ALL) and their prognostic role defined
- **Novel treatment approaches based on immunotherapy; evidence regarding long-term benefit is yet to be established**
- **Reduction of long-term toxicities, especially in adolescents, is a priority**

New immunologic approaches under investigation in childhood ALL



Allogeneic and autologous NK cells

Immunotoxin-specific antibodies

Chimeric antigen receptor (CAR) T cells

Bispecific antibodies/antibody constructs

Adapted from Bhojwani D, Pui CH. *Lancet Oncol.* 2013;14:e205-e217.

AIEOP-BFM ALL 2017

International collaborative treatment protocol for children and adolescents with acute lymphoblastic leukemia

Randomized phase III study conducted by the AIEOP-BFM study group

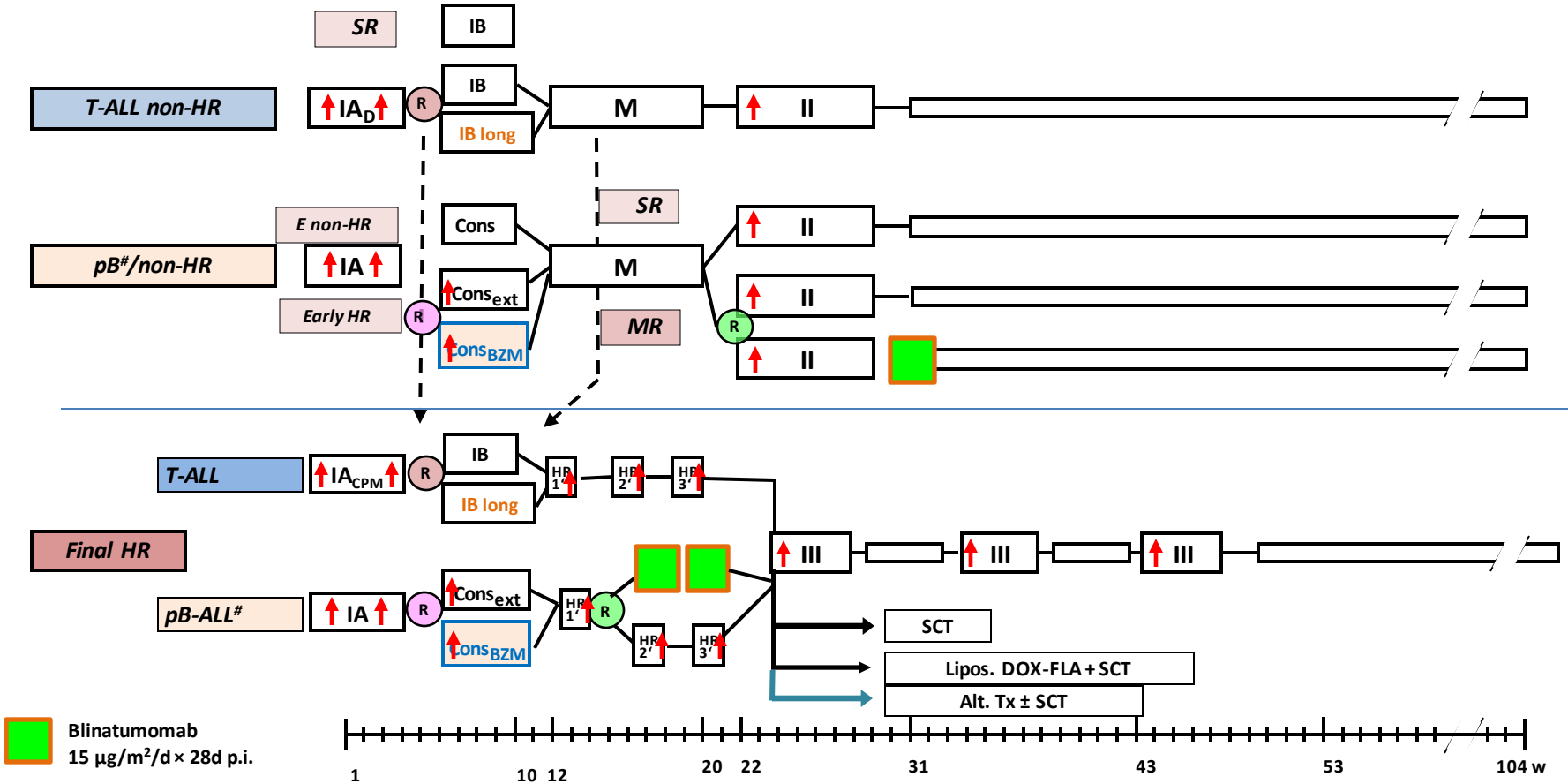
EudraCT Number: 2016-001935-12

Sponsor: Universitätsklinikum Schleswig-Holstein, Campus Kiel

New in trial AIEOP-BFM ALL 2017

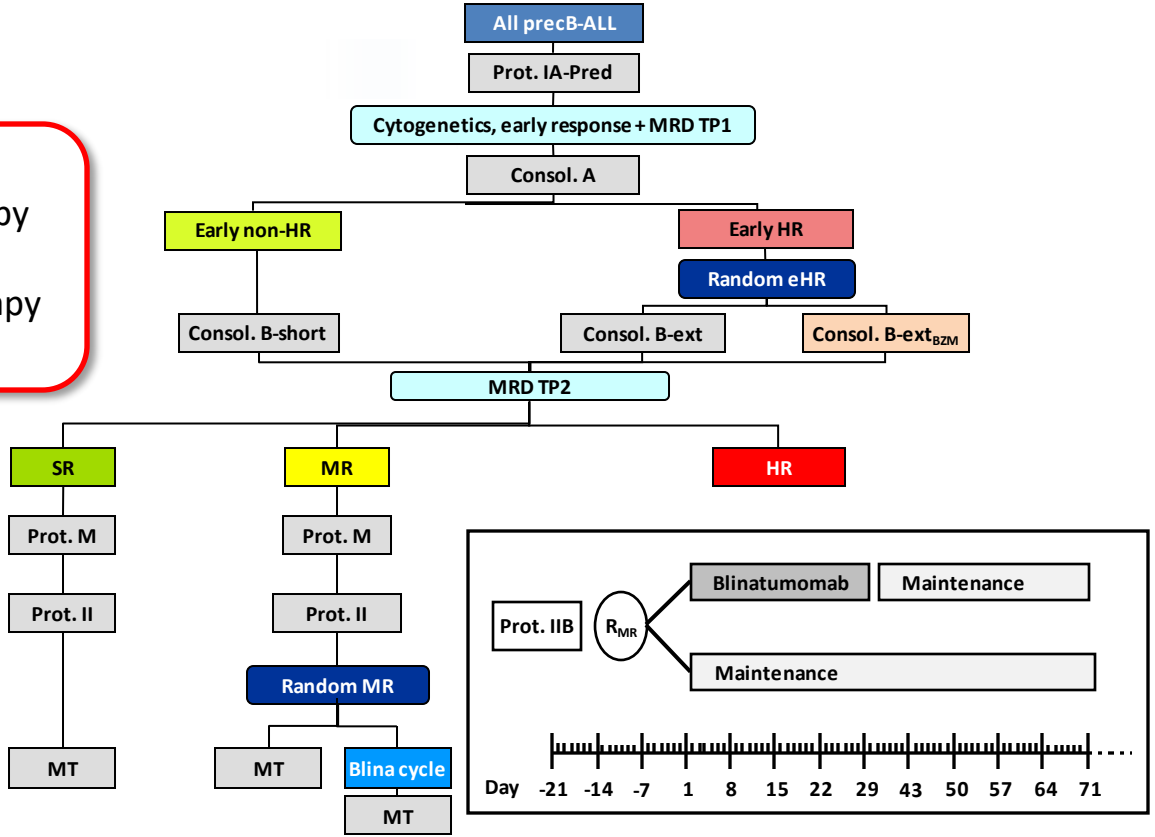
- Modified workflow and timing in genetic diagnostics
- Genetic profiles and early MRD response may be combined to characterize previously unidentified patients at high risk to relapse, eg, ***IKZF1*** ^{plus}
- **Randomized evaluation of blinatumomab in de novo ALL in all non-SR patients**
- Selective addition of novel agents in HR group
- Limitation of pCRT (only if age ≥4y, only if CNS-3, and/or if T-ALL with WBC ≥100K)
- TDM for ASP activity only in reintensification (P-II, P-III, HR-1/2/3)

AIEOP-BFM ALL 2017: Treatment overview



AIEOP-BFM ALL 2017: pB-ALL

Can pDFS of MR patients be improved by additional therapy with 1 cycle of post-reintensification immunotherapy with blinatumomab?

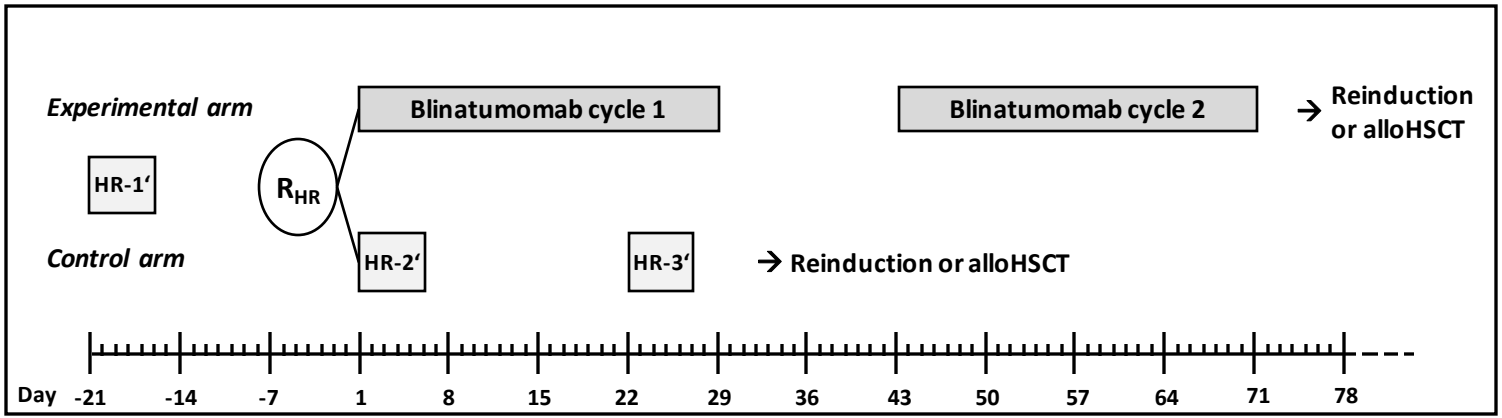


F. Locatelli, personal communication.
Trial information at https://clinicaltrials.gov/ct2/show/NCT03643276 (accessed September 2018).

AIEOP-BFM ALL 2017: pB-ALL

Approach for HR patients: Randomization HR

Can the pEFS be improved by a treatment concept including 2 cycles of post-consolidation immunotherapy with blinatumomab (15 µg/m²/d for 2 × 28 days) replacing 2 conventional highly intensive chemotherapy courses?



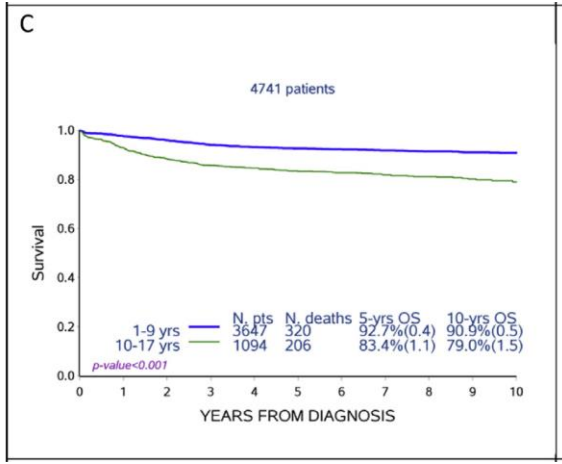
- **Expected effects by novel post-consolidation therapy in HR patients**
  - **Significant reduction of toxicity**
  - **Overcoming resistance to chemotherapy in patients with insufficient response to earlier treatment elements**

A brief focus on adolescents

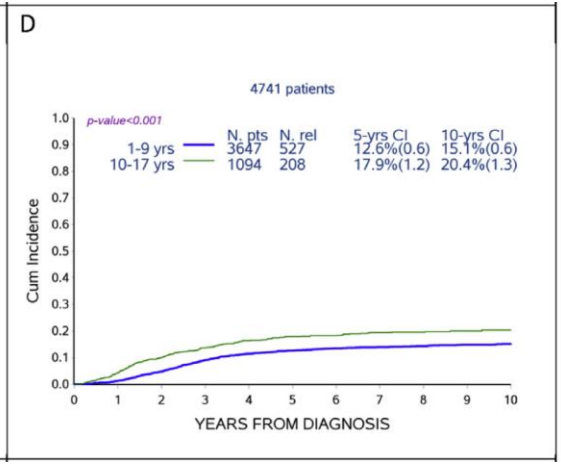
Acute and late toxicities

Outcome of adolescent patients with acute lymphoblastic leukaemia aged 10–14 years as compared with those aged 15–17 years: Long-term results of 1094 patients of the AIEOP-BFM ALL 2000 study

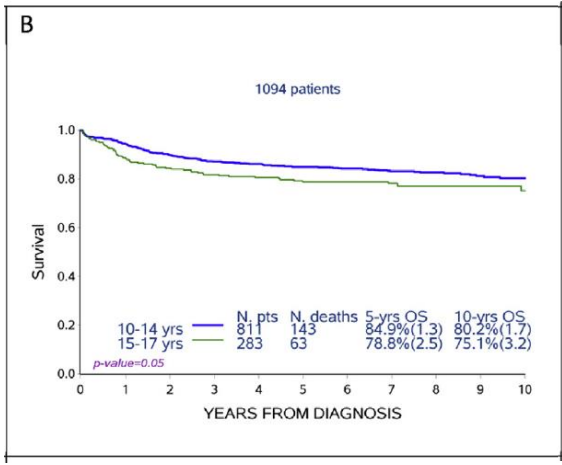
European Journal of Cancer 122 (2019) 61–71



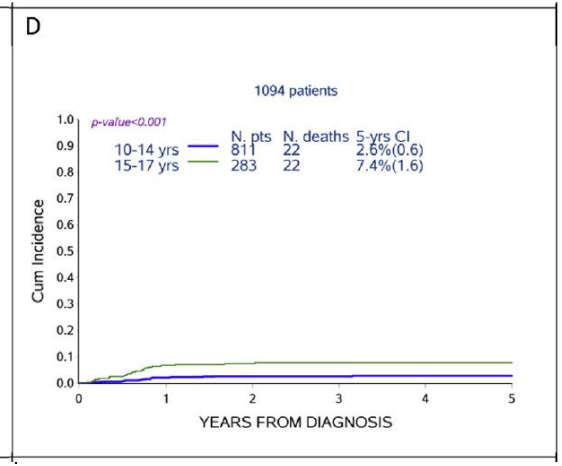
(C) OS by age



(D) Cumulative incidence of relapse (CIR) by age



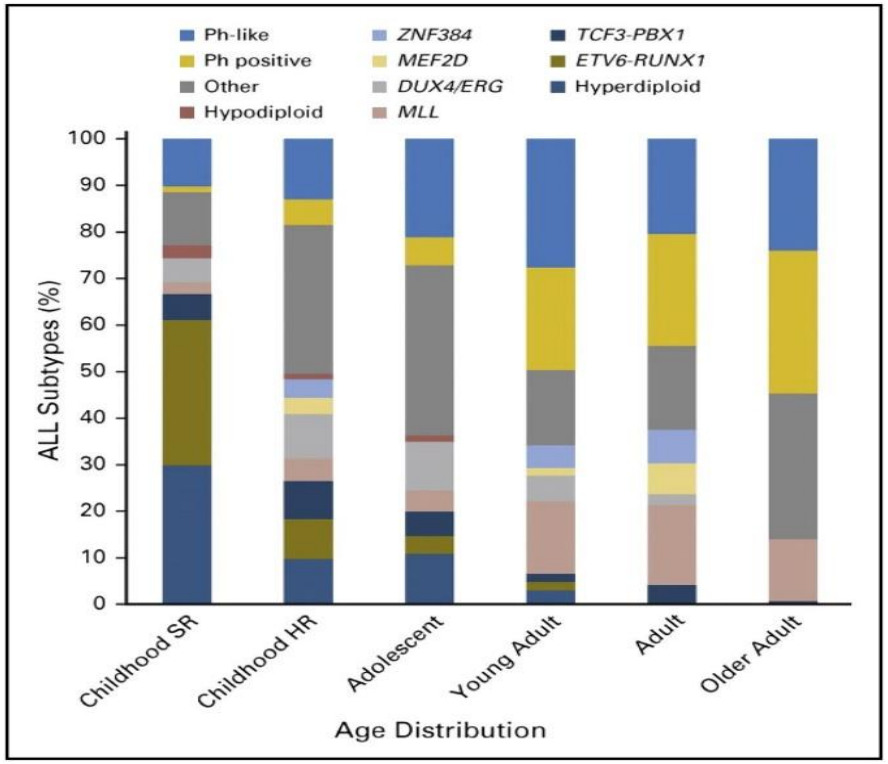
(B) Overall survival (OS) by age



(D) Cumulative incidence of death in remission as a first event by age

Acute lymphoblastic leukemia in adolescent and young adults: treat as adults or as children?

Nicolas Boissel[1,2] and André Baruchel[2,3]



Trial		Median Age	N	CR, %	Survival, %	
FRALLE93	1993-99	16	77	94	DFS	72
					EFS	67
LALA94	1994-2000	18	100	83	DFS	49
					EFS	41
CCG	1988-2001	16	196	96	EFS	63
CALGB	1988-2001	19	103	93	EFS	34
AIEOP	1996-2003	15	150	94	OS	80
GIMEMA	1996-2003	16	95	89	OS	71
DOCG	1985-99	12	47	98	DFS	71
					EFS	69
HOVON	1985-99	20	73	91	DFS	37
					EFS	34
MRC97/99	1997-2002	15-17	61	98	OS	71
					EFS	65
UKALLXII	1997-2002	15-17	67	94	OS	56
					EFS	49
NOPHO	1990-2004	13	128	96	EFS	67
FINNISH LEUKEMIA	1990-2004	19	97	97	EFS	60

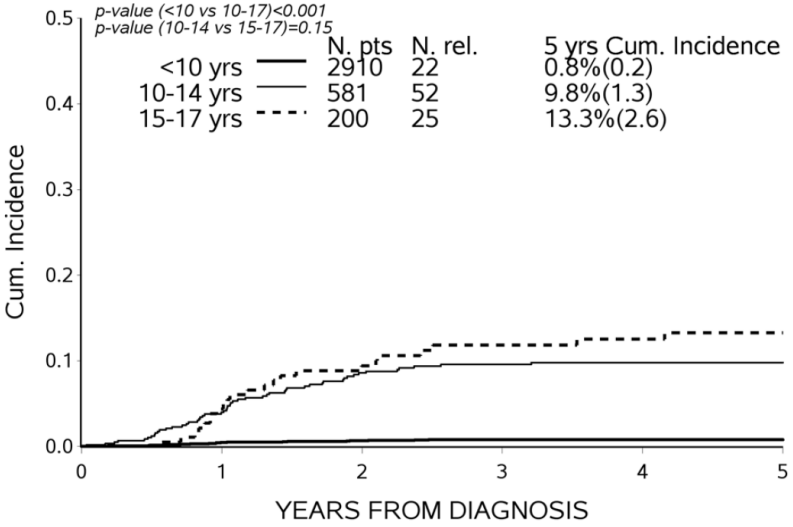
Late effects of treatment in ALL

- Second malignancies
- Osteonecrosis
- Neurocognitive sequelae
- Cardiomyopathy
- Insulin-dependent diabetes (pancreatitis)
- Chronic GvHD
- Chronic immune deficiency (CD19-directed CAR T cells)

Correspondence: Osteonecrosis in childhood acute lymphoblastic leukemia: a retrospective cohort study of the Italian Association of Pediatric Haemato-Oncology (AIEOP)

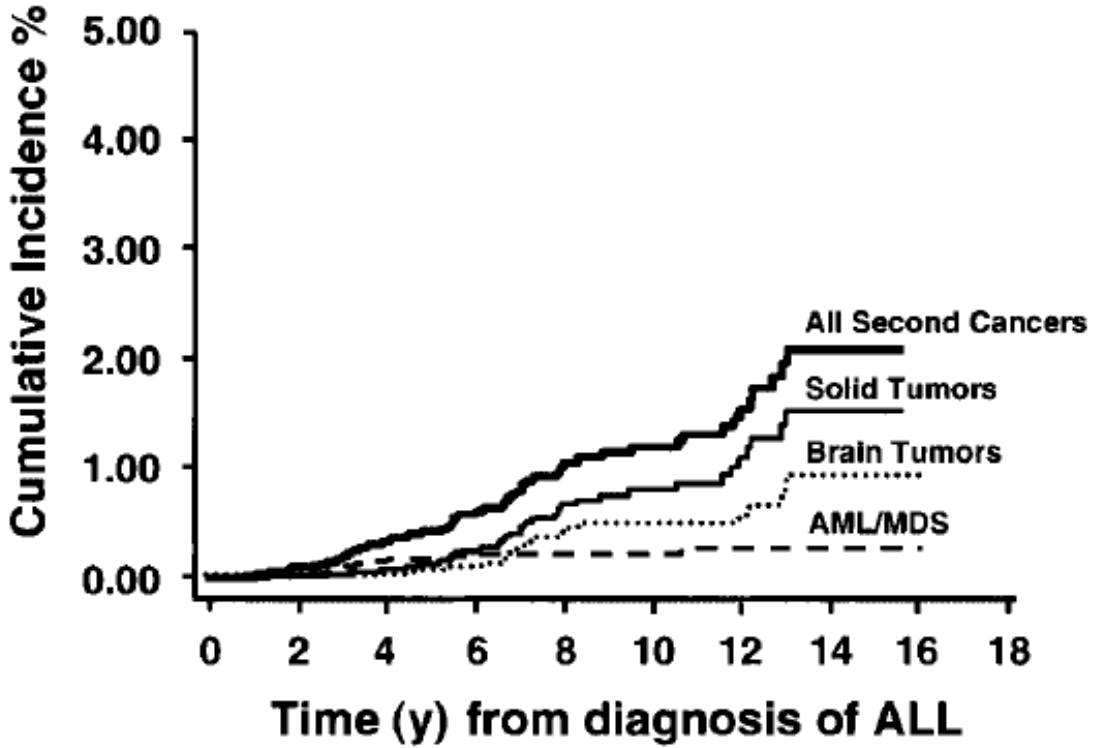
Parasole et al. *Blood Cancer Journal* (2018)8:115

a. Overall incidence in the age groups



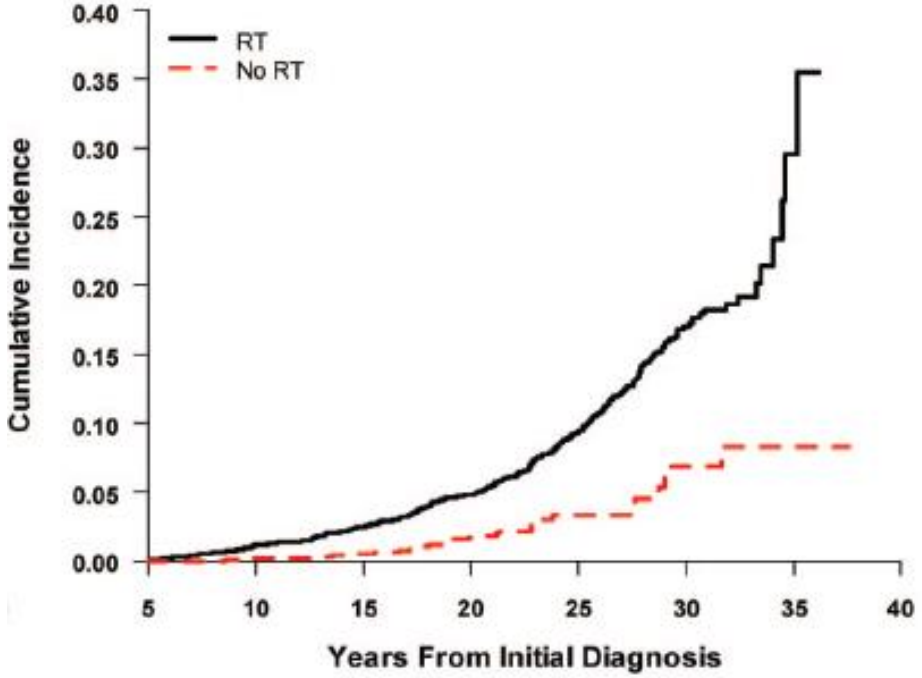
Five-year cumulative incidence of ON according to patient's age at ALL diagnosis

Cumulative incidence of second neoplasms in 8,831 children with ALL



Bhatia S, et al. *Blood*. 2002;99:4257-4264.

Second neoplasms among 5-year survivors of childhood ALL in the CCSS cohort: Role of radiotherapy



Robison LL. *Hematology Am Soc Hematol Educ Program*. 2011;2011:238-242.

Final considerations

- Treatment of childhood ALL is becoming more and more complex and sophisticated over time, integrating genetic data and MRD response in patient stratification
- The goal is that of curing more and better, sparing side effects while maintaining and even improving the high cure rate we have achieved so far
- Immunotherapy is changing the therapeutic scenario of childhood B-ALL
- Ongoing studies will define its role in newly diagnosed patients

Global Leukemia Academy

Bispecifics for Pediatric/AYA ALL

Lia Gore, MD

University of Colorado,
Anschutz Medical Campus, USA

APTITUDE HEALTH

Bispecifics in Pediatric ALL

Prof Lia Gore, MD
Chief, Pediatric Hematology/Oncology/Bone Marrow Transplant-Cellular Therapeutics
University of Colorado School of Medicine and Children's Hospital Colorado

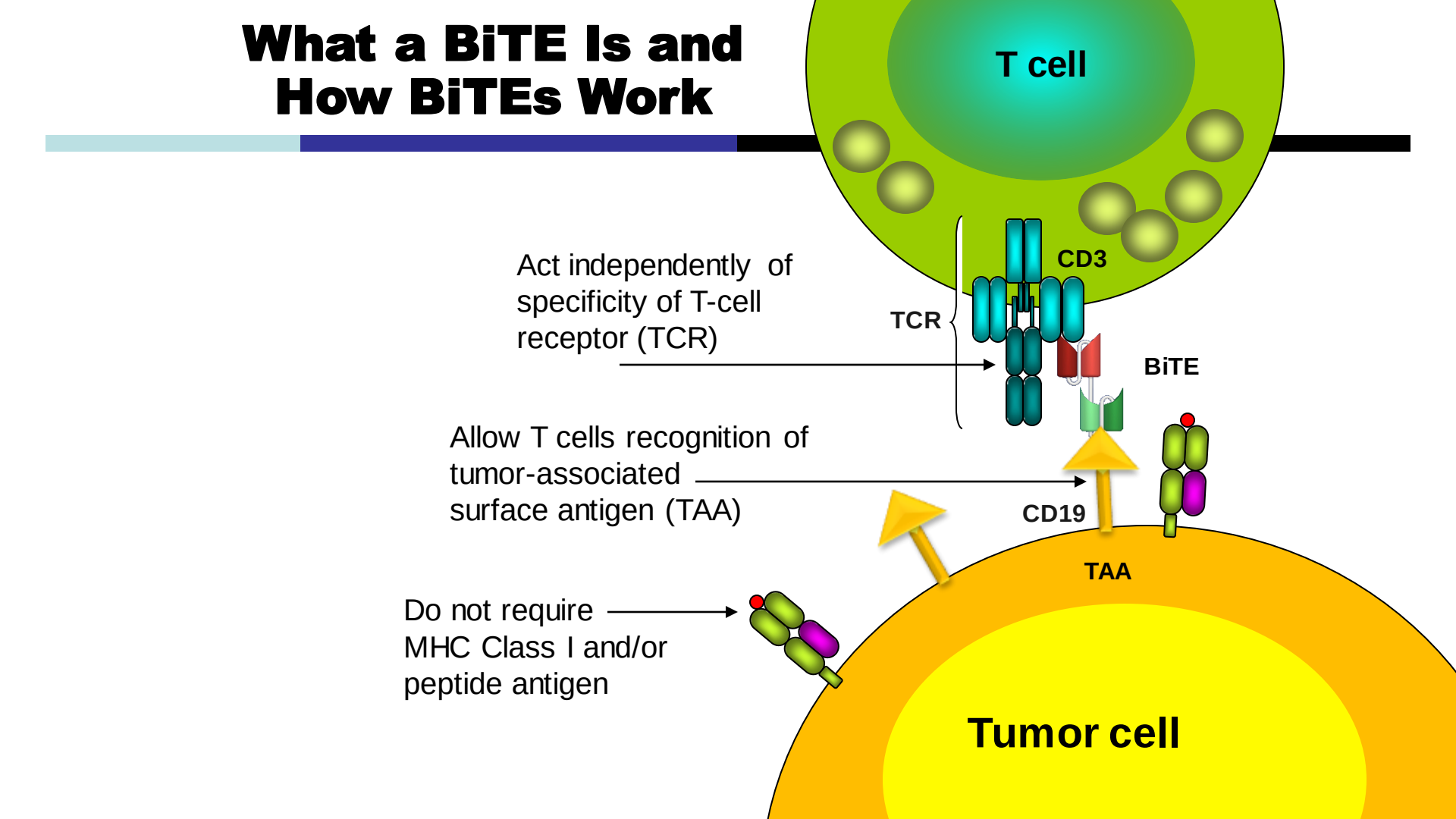
Outline of Presentation

- Definition of a “bispecific” = bispecific T-cell engager
- Mechanism of action
- Review of recent trial results in pediatric relapsed ALL
- **Future considerations**

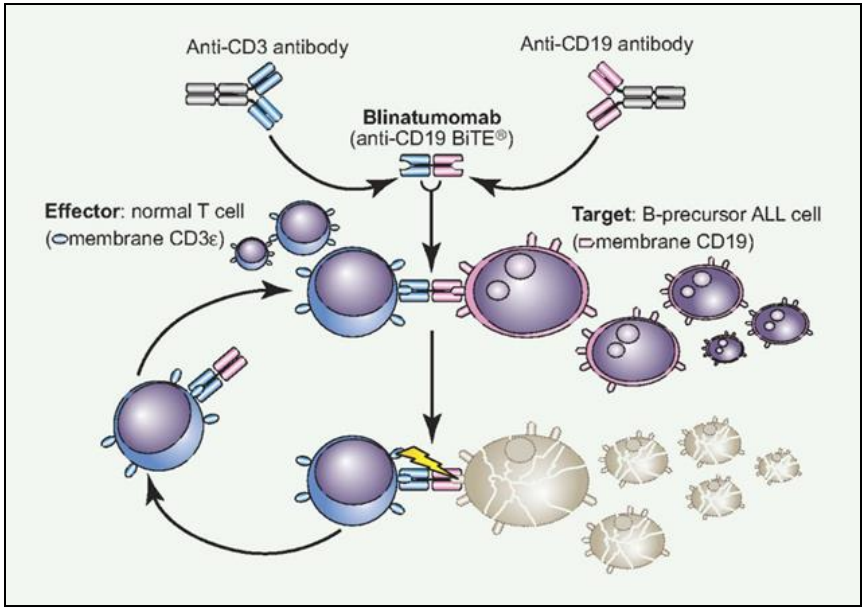
Status of Immunotherapy for ALL

- Various immunotherapy approaches are available for patients with B-ALL – primarily in use for relapsed disease
  1) Monoclonal antibodies
  2) Antibody-drug conjugates (ADCs)
  3) Bispecific T-cell engagers (BiTEs®)
  4) Cellular immunotherapies (CAR T cells, NK cells)
  5) Experimental: trispecific T-cell engagers (TriTEs), dual affinity retargeters (DARTs), and simultaneous multiple interaction T-cell engagers (SMITEs)
- Immunotherapies for T-cell disease have lagged but are expanding
- Early access to novel agents for pediatrics has been revolutionary for patients with relapsed and refractory ALL – could it be for newly diagnosed patients? Those with excess morbidity and mortality from current approaches?

What a BiTE Is and How BiTEs Work



Blinatumomab (CD19 BiTE)



Brown P. *Blood.* 2018;131:1497-1498.

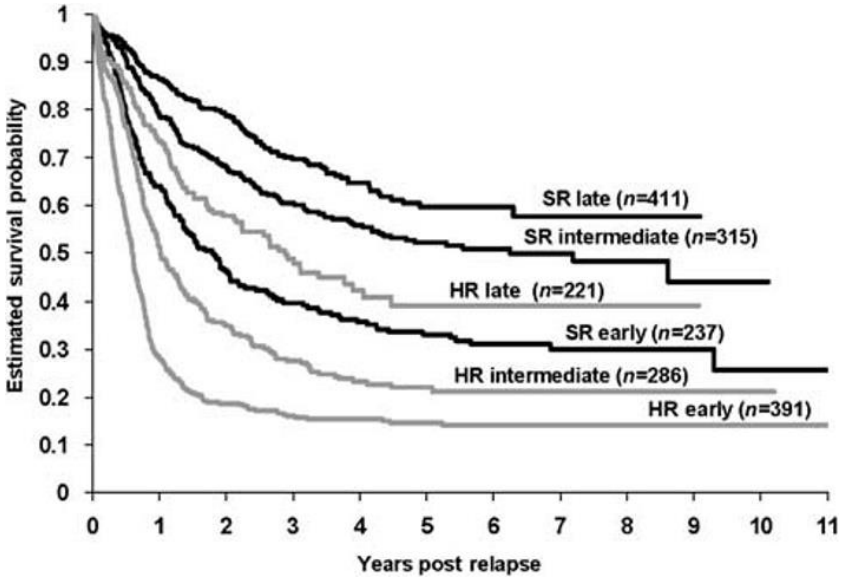
- In multiple-relapse/refractory setting (pediatrics)[1]
  - CR 35%–40%
  - MRD– CR 20%–25%
- In MRD+ setting (adults)[2]
  - 80% MRD clearance
  - 60% subsequent DFS (bridge to HSCT)

The only BiTE with wide regulatory approval for childhood B-ALL

1. von Stackelberg A, et al. *J Clin Oncol*. 2016;34:4381-4389; 2. Gokbuget N, et al. *Blood*. 2018;131:1522-1531.

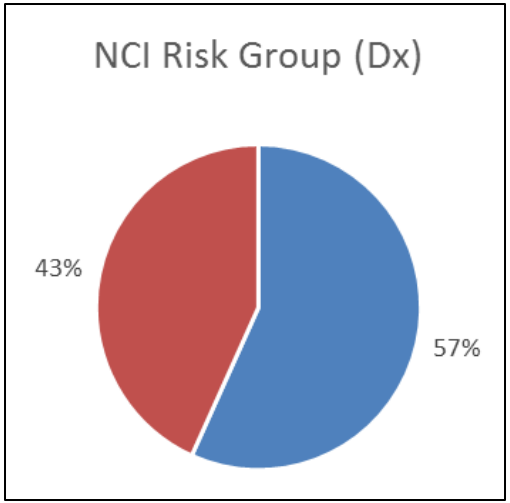
Success in Treating the Most Common Childhood Cancer

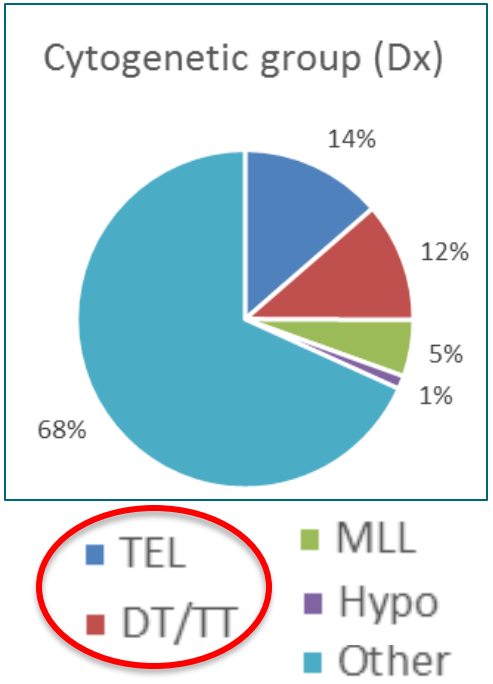
- Current regimens offer survival of 90%–99% for most patients
- Patients with some subtypes and relapsed disease do not have such hopeful outcomes



Nguyen K, et al. *Leukemia*. 2008;22:2142-2150.

Standard- and Low-Risk ALL Remain Major Contributors to Relapse

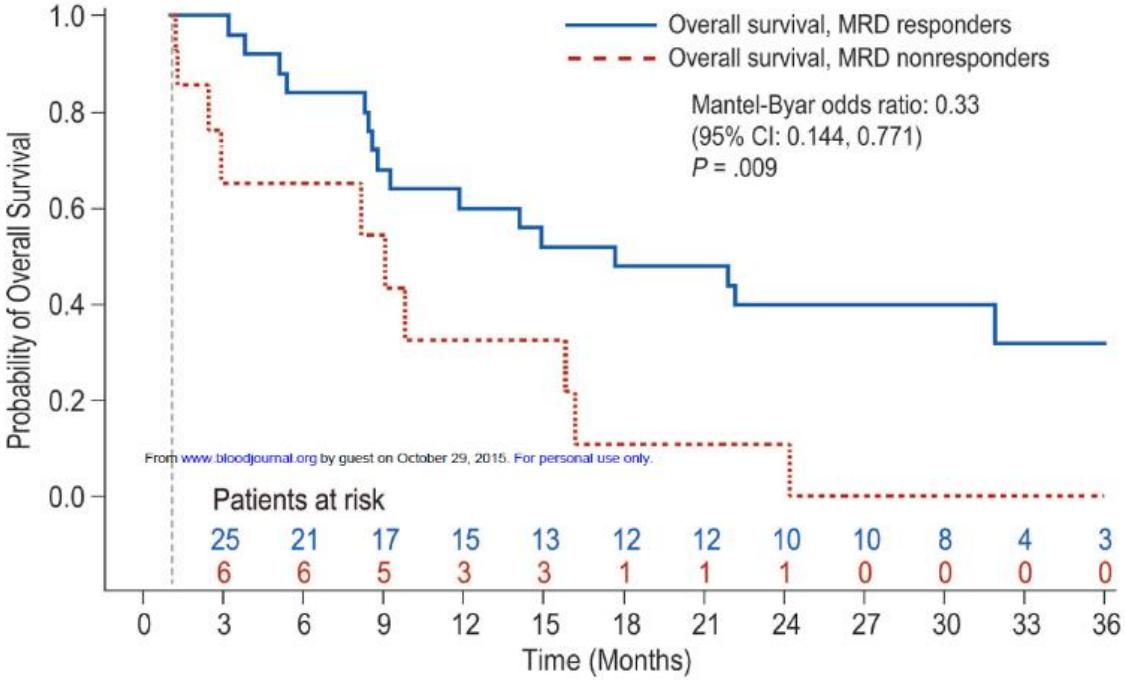




CHILDREN'S ONCOLOGY GROUP

Brown PA, et al. COG AALL1331.

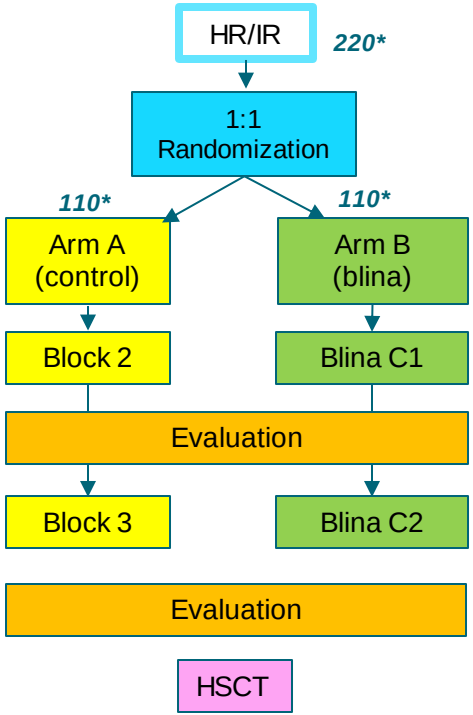
MT103-205/211: Survival With Blinatumomab Depends on MRD Response



von Stackelberg A, et al. *J Clin Oncol*. 2016;34:4381-4389.

AALL1331 Schematic

Risk Stratifications
- Risk group (HR vs IR)
- For HR
  - Site (BM vs iEM)
  - For BM: CR1 duration (<18 vs 18–36 mo)



UKALLR3, Block 2*
- VCR, DEX week 1
- ID MTX, PEG week 2
- CPM/ETOP week 3
- IT MTX or ITT

UKALLR3, Block 3*
- VCR, DEX week 1
- HD Ara-C, Erwinia weeks 1–2
- ID MTX, Erwinia week 4
- IT MTX or ITT

*UKALLR3 reference: Parker, et al. *Lancet*. 2010;376:2009-2017.

Endpoints
- Primary: DFS
- Other: OS, MRD response, ability to proceed to HSCT

Sample size n = 220 (110 per arm)
- Power 85% to detect HR = 0.58 with 1-sided α = 0.025
- Increase 2-yr DFS from 45% to 63%

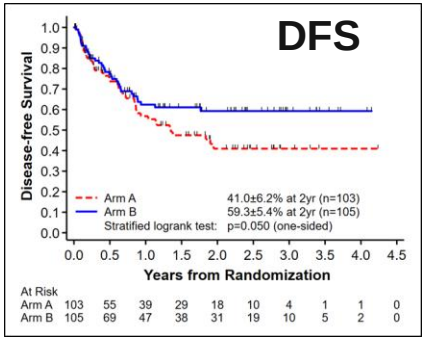
Blina C1 and Blina C2
- Blinatumomab 15 µg/m^2/day × 28 days, then 7 days off
- Dex 5 mg/m^2/dose × 1 premed (C1 only)

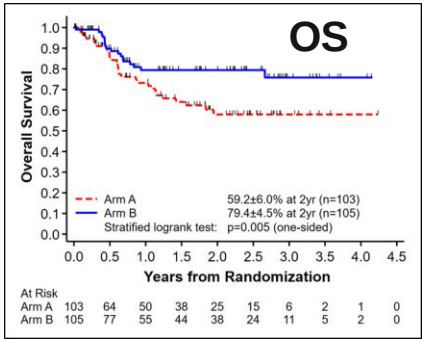
- ***First patient randomized Jan 2015***
- ***Randomization halted September 2019 (95% projected accrual)***

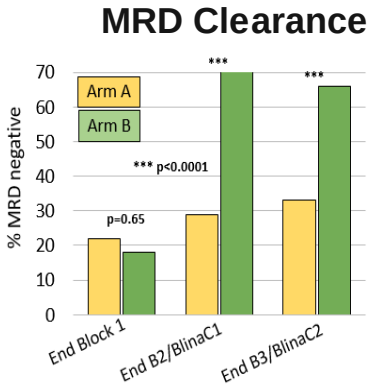
CHILDREN'S ONCOLOGY GROUP

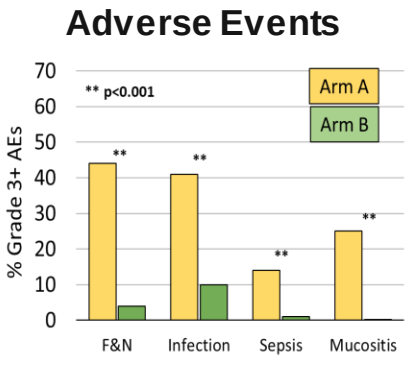
Brown PA, et al. *JAMA*. 2021;325:833-842.

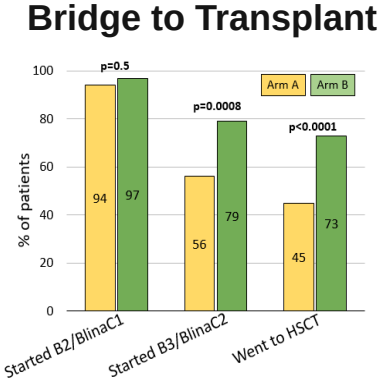
AALL1331 Established a New Standard of Care for HR/IR Relapse









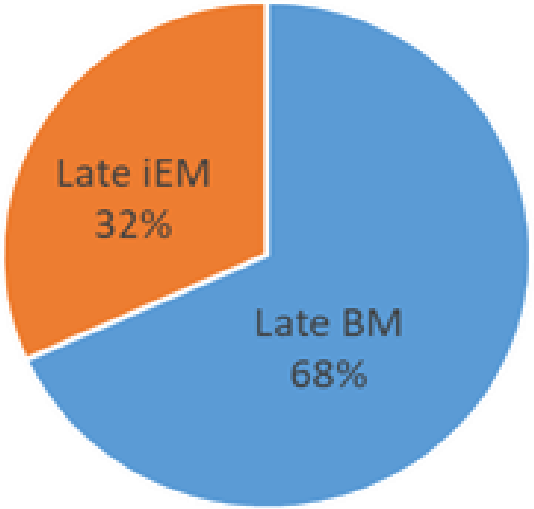


Significant contributors to the improved outcomes for Arm B (blina) vs Arm A (chemo) in HR/IR relapses may include **better MRD clearance, less toxicity, and greater ability to successfully bridge to HSCT**

CHILDREN'S ONCOLOGY GROUP

Brown PA, et al. *JAMA.* 2021;325:833-842.

AALL1331: Low-Risk Randomization

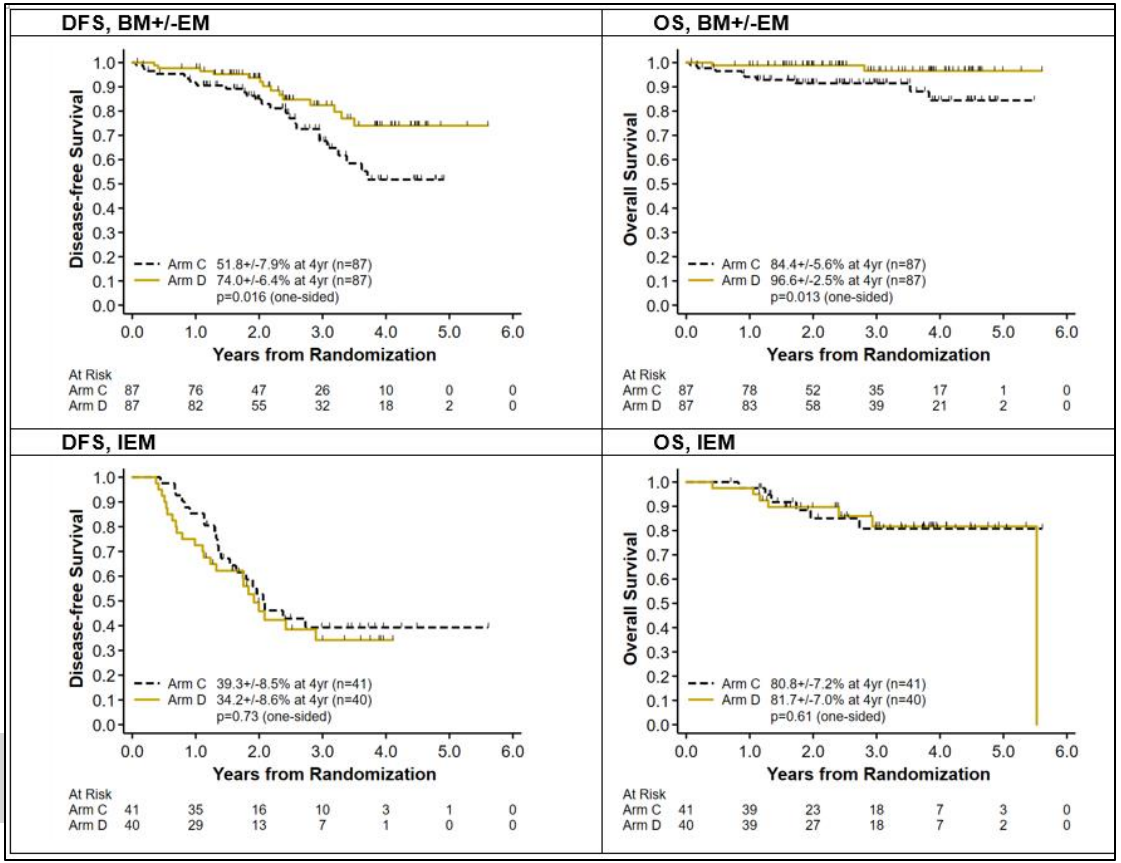


BM ± EM

IEM

DFS

OS



CHILDREN'S ONCOLOGY GROUP

Brown PA, et al. ASH 2021. Abstract LBA-1.

Toxicities of Special Interest With BiTEs and CAR T Cells Are the Same . . .

Cytokine release syndrome (CRS)

Neurologic events

- Central or peripheral
- Somnolence, neuralgia, confusion, tremor, pain, headache are most frequent
- Seizure and G-B–like syndrome

- Usually reversible with meticulous supportive care
- Nearly “required” for antileukemic response
- Difference in timing of onset, but not in severity or implications
  - Blina: starts within 24 hours; gone by 10–14 days
  - CAR T: usually within first week, typically not after fourth week

COG: Challenges for First-Relapse B-ALL

- Post-reinduction immunotherapy with blinatumomab improved outcomes, but **~40%** of patients were unable to proceed to planned post-reinduction therapy due to toxicities and/or refractory disease
- **Intent-to-treat 2-yr EFS for high-risk BM relapse: 25%**
- Goals for an effective reinduction regimen for intermediate- and high-risk relapse: ***effective bridge to transplant***
  - Avoid infectious toxicity
  - Avoid organ damage
  - MRD– prior to transplant
- Better strategies for late isolated CNS relapse
- BETTER ACCESS FOR ALL PATIENTS TO THE MOST EFFECTIVE, LEAST TOXIC THERAPY THAT HAS A SUSTAINED PROMISE OF CURE WITH HIGH QUALITY OF LIFE

CHILDREN'S ONCOLOGY GROUP

Status of Immunotherapy for ALL in Frontline

- Globally, cooperative groups are now introducing various immunotherapy constructs into frontline clinical trials

- Coordination of findings and development of future studies depend on cooperation among investigators and pharmaceutical sponsors globally
- Further implications for
  - Risk stratification and therapy plans
  - Biologic and genetic features of leukemia cells
  - Response kinetics
  - Surrogate and biomarkers of efficacy

Current/Recent Considerations With Bispecific T-Cell Engagers

- Current products all have very short half-lives, necessitating prolonged continuous infusion
  - Prolonged-half-life compounds (SQ) are in adult trials now
- Concerns over selection pressure that results in leukemic blasts developing resistance
- To date, most patients are not cured with bispecific therapies and use these as a bridge to stem cell transplant (SCT)
- Debate over role of bispecifics before and/or after SCT
  - Outcomes of patients treated with or without bispecific therapies before SCT?
  - Role of bispecific therapy after SCT for MRD?

MOC Question

For children and adolescents with first relapse of B-ALL, what regimen offers the best chance of entering CR2 in an MRD– state?

A. VXLD as reinduction chemotherapy followed by HSCT
B. VXLD + UKALL R3 consolidation chemotherapy
C. VXLD + UKALL R3 consolidation chemotherapy + carfilzomib
D. VXLD + UKALL R3 consolidation chemotherapy + blinatumomab
E. None of the above

International Cooperation Is Essential

Global Leukemia Academy

CAR T Cells for Pediatric/AYA ALL

Franco Locatelli, MD, PhD

University of Rome
IRCCS Ospedale Pediatrico Bambino Gesù, Italy

APTITUDE HEALTH

CAR T Cells for Pediatric/AYA ALL

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Università Cattolica del Sacro Cuore, Roma
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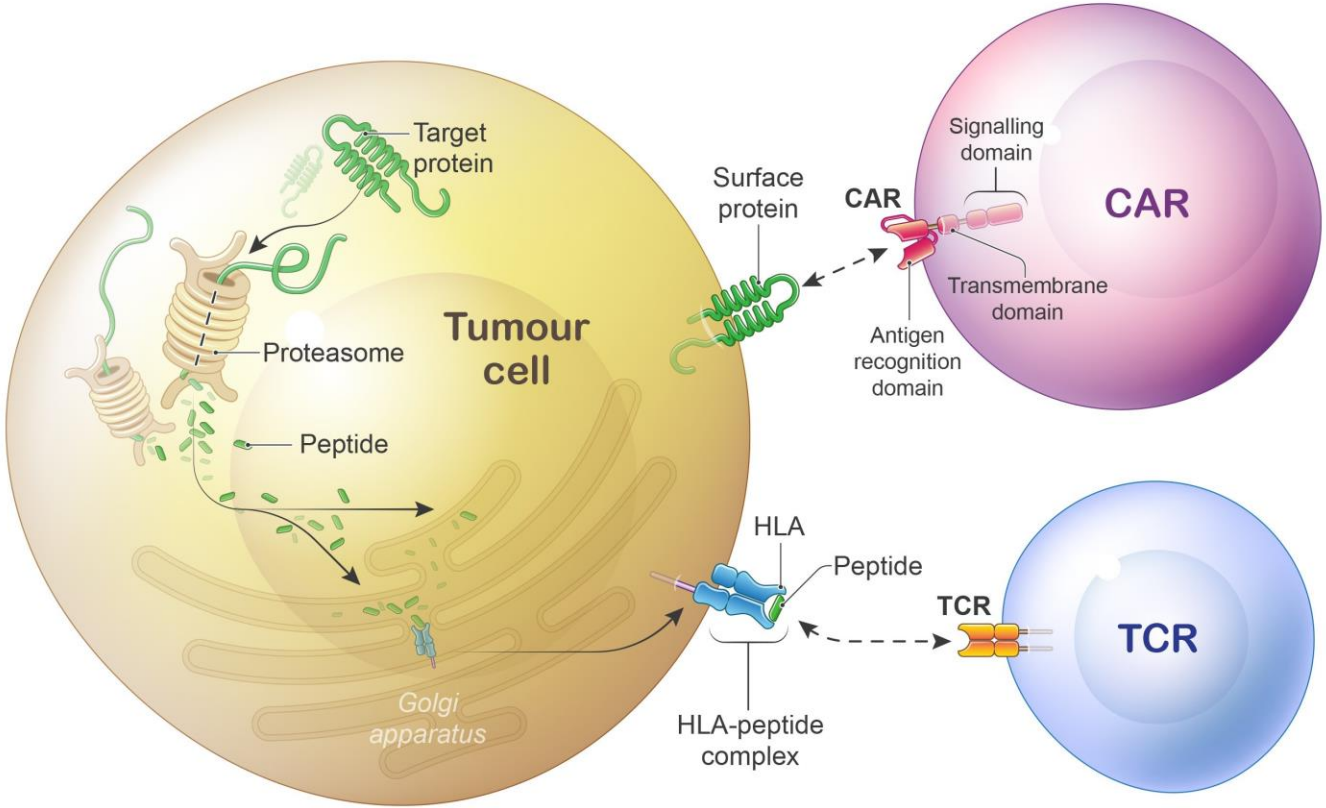
IRCCS Ospedale Bambino Gesù, Roma, Italy

Disclosures

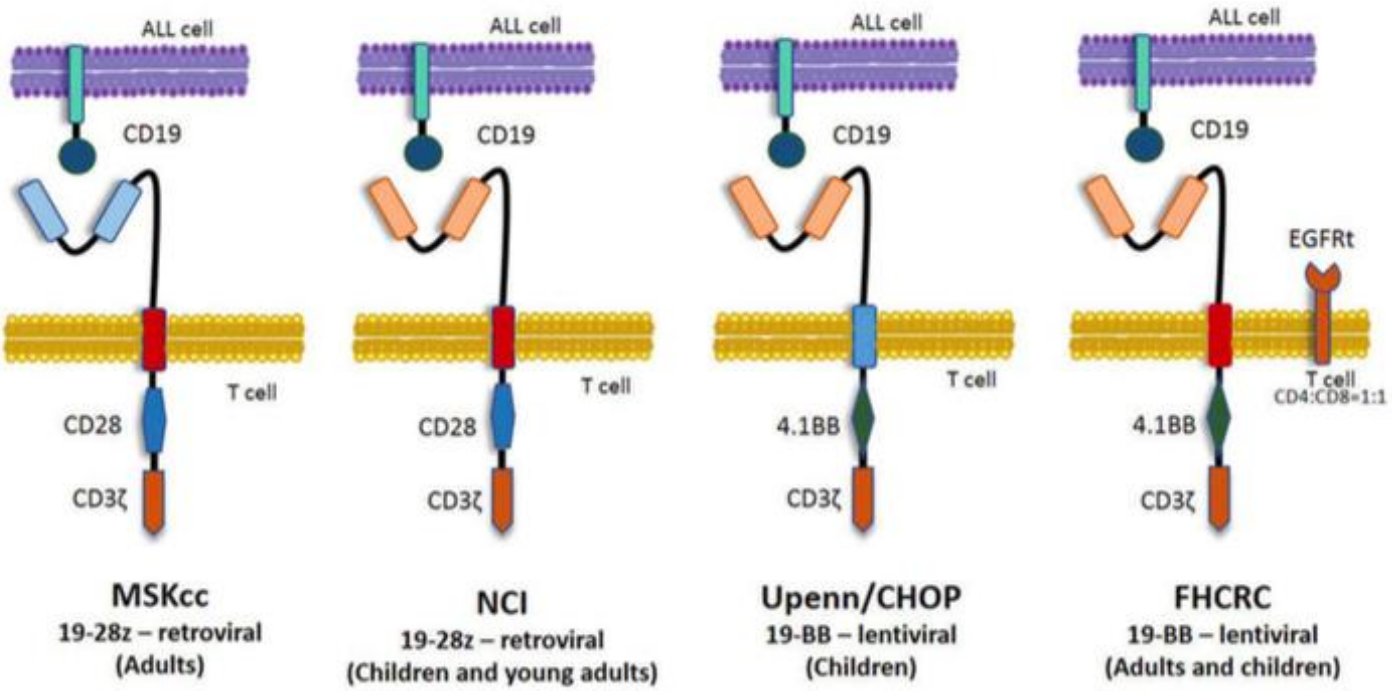
Name of Company	Research Support	Employee	Consultant	Stockholder	Speaker's Bureau	Advisory Board	Other
Miltenyi					X		
Bellicum	X				X	X	
Amgen					X	X	
Jazz Pharma					X		
Medac					X		
Neovii					X	X	
Novartis					X	X	
Sanofi						X	
Sobi					X		
Gilead					X		
bluebird bio					X		
Vertex						X	

Gene-modified T cells for treating cancer



Published constructs of second-generation CD19 CARs for ALL

CAR design is important for persistence and sustained efficacy

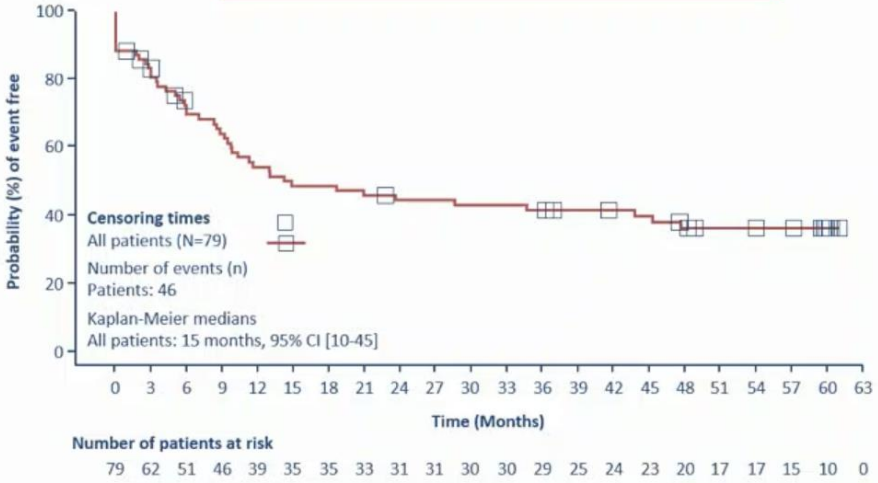


Del Bufalo F, Locatelli F, et al. *Expert Rev Clin Immunol*. 2019;15:497-509.

Median EFS was 15 Months

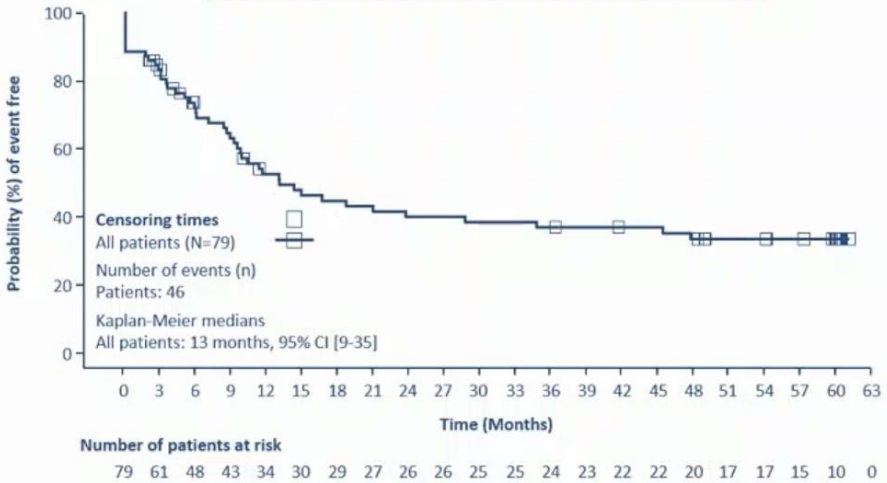
EFS Without Censoring for alloSCT

5-year EFS: 36% (95% CI, 25%-47%)



EFS With Censoring for alloSCT

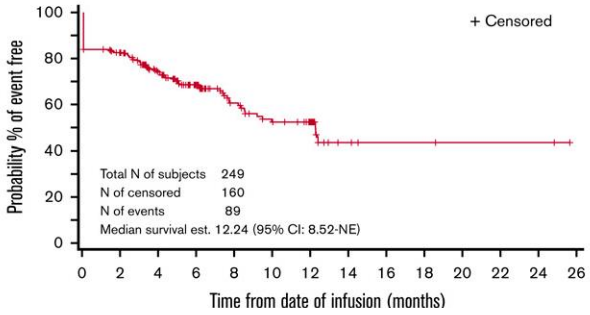
5-year EFS: 34% (95% CI, 23%-45%)

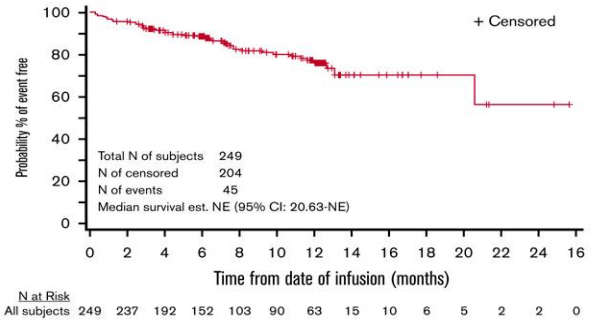


alloSCT, allogeneic stem cell transplantation; EFS, event-free survival; NE, not estimable.

Long-term outcome of CD19-CAR T cell for pediatric patients with R/R ALL

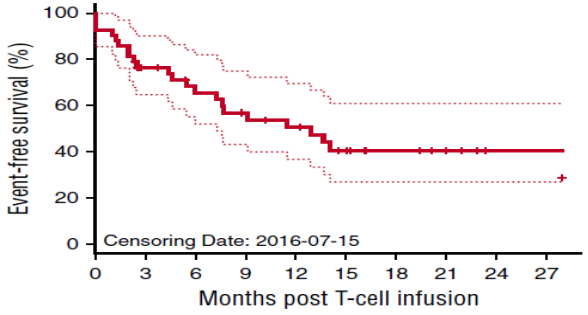
Tisagenlecleucel – real-world evidence (Novartis)

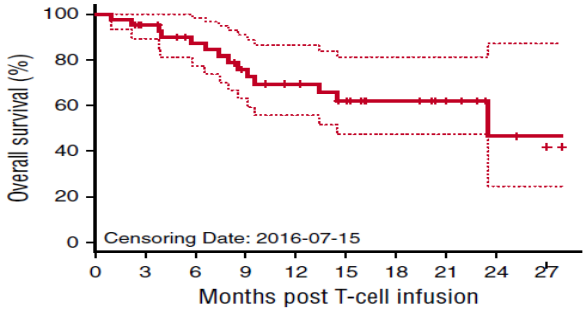




Pasquini MC, et al. *Blood Adv*. 2020;4:5414-5424.

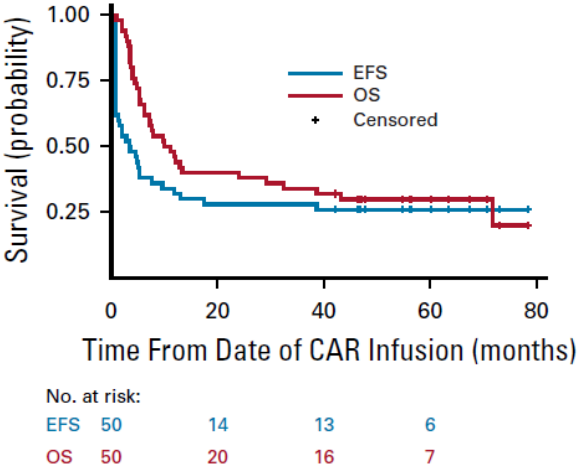
1:1 CD4:CD8 CD19CAR-T2A-EGFRt (Seattle)





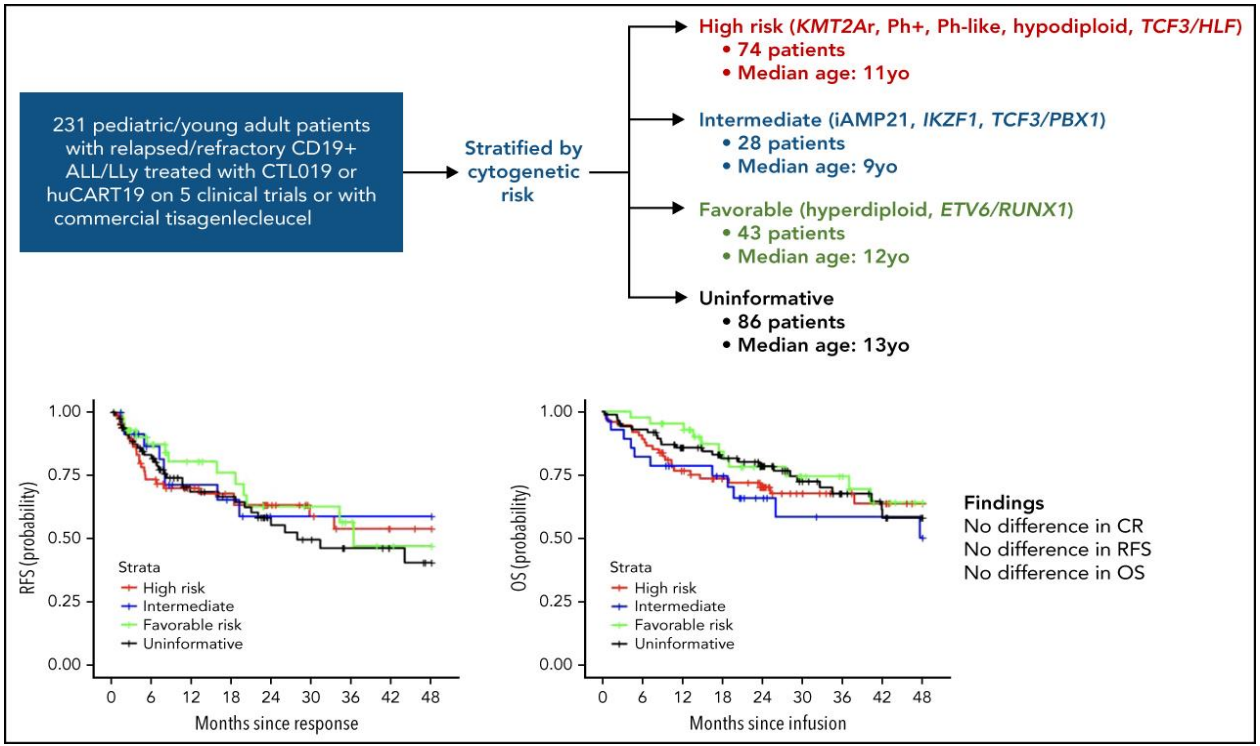
Gardner RA, et al. *Blood*. 2017;129:3322-3331.

CD19.28z-CAR T (NCI)



Shah NN, et al. *J Clin Oncol*. 2021;39:1650-1659.

Impact of high-risk cytogenetics on outcomes for children and young adults receiving CD19-directed CAR T-cell therapy



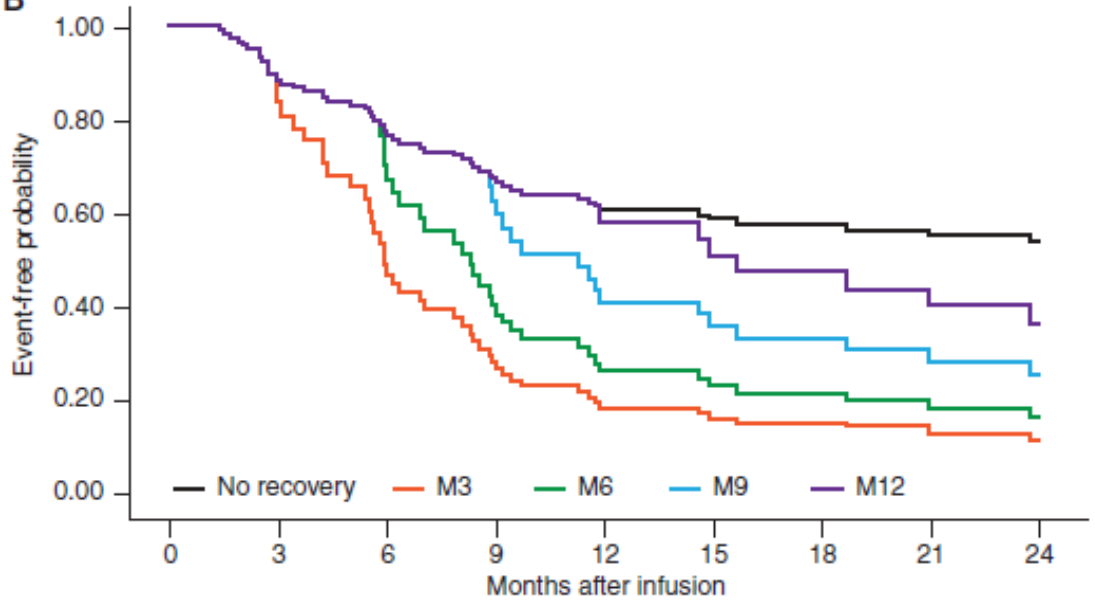
Barz Leahy A, et al. *Blood*. 2022;139:2173-2185.

B-cell aplasia and relapse after tisagenlecleucel

A

	HR (95% CI)	*P*
B-cell recovery	4.50 (2.03–9.97)	<0.001

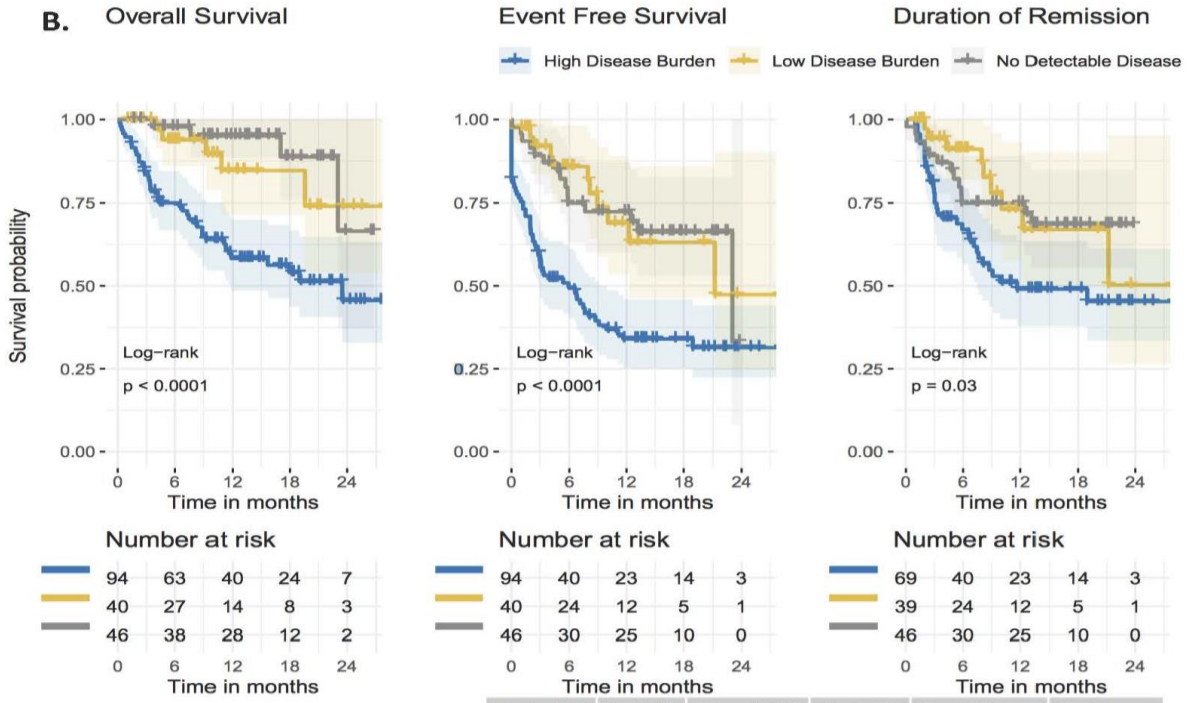
B



Cumulative risk for BCA loss within 12 months

BCA loss 6-9 mo: 3 pts
BCA loss 9-12 mo: 2 pts
→ Adjusted EFS curves based on Cox prediction model

Real-world experience with tisagenlecleucel



	6mo OS	1y OS	6mo EFS	1y EFS	6mo Drem	1y Drem
High Disease Burden	0.75	0.58	0.50	0.34	0.67	0.49
Low Disease Burden	0.94	0.85	0.86	0.69	0.91	0.73
No Detectable Disease	0.98	0.95	0.75	0.72	0.75	0.75

High disease burden
- >5% bone marrow lymphoblasts
- Peripheral blood lymphoblasts
- CNS3 status
- Non-CNS extramedullary (EM) site of disease

Schultz LM, et al. ASH 2020. Abstract 468.

CAR T cells for infant BCP-ALL

	Participants
Whole cohort (n=38)	
Age at diagnosis, months	5·2 (2·6–7·6)
Sex	
Female	17 (45%)
Male	21 (55%)
White blood cell count at diagnosis, × 10^9 cells per L	375 (130–797)
Presenting with CNS involvement	18/32 (47%)
Treated according to Interfant-06 protocol	31 (82%)
KMT2A rearrangement	29 (76%)
Refractory to one or more previous treatment lines	19 (50%)
Previous HSCT	25 (66%)
Number of previous lines of therapy not including HSCT	2 (2–3)
Previous inotuzumab	7 (18%)
Previous blinatumomab	14 (37%)
Participants who received a tisagenlecleucel infusion (n=35)	
Median age at infusion, months	17·0 (14·9–24·6)
Bone marrow disease burden before lymphodepletion	
Median (IQR)	5% (0·2–31·0)
Measurable residual disease negative	7 (20%)
0–<1%	5 (14%)
1–<5%	5 (14%)
5–<10%	2 (6%)
10–<50%	9 (26%)
50–100%	7 (20%)
CNS disease before lymphodepletion	1 (3%)

Data are median (IQR), n (%), or n/N (%). Data on race or ethnicity were not collected. HSCT=haematopoietic stem-cell transplantation. *n=34.

Table 1: **Baseline characteristics**

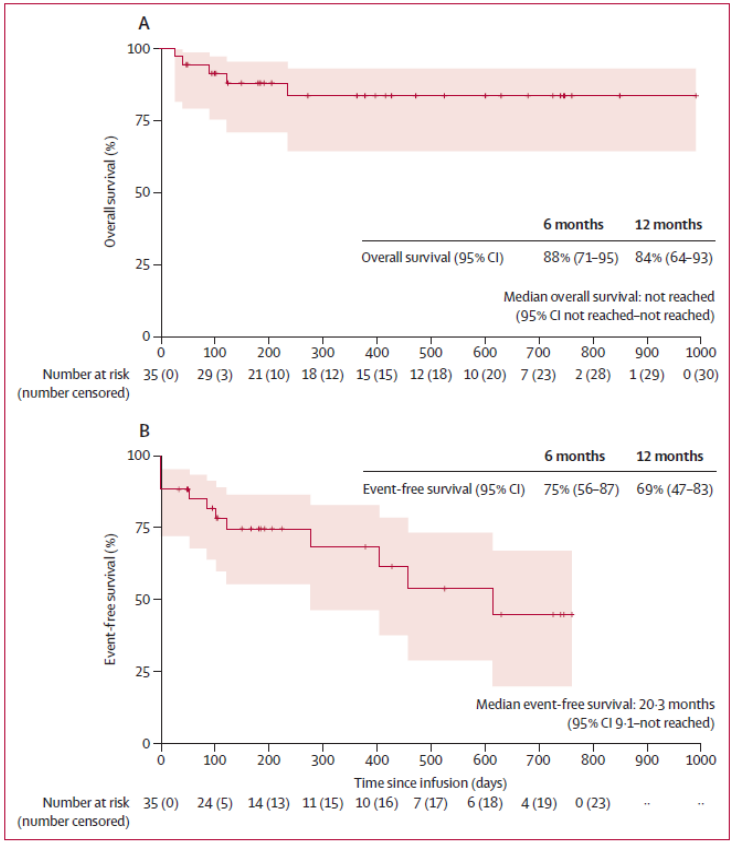
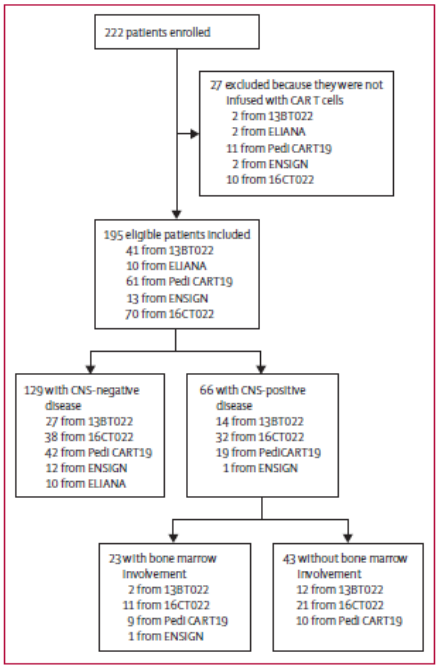


Figure 2: **Overall survival and event-free survival**

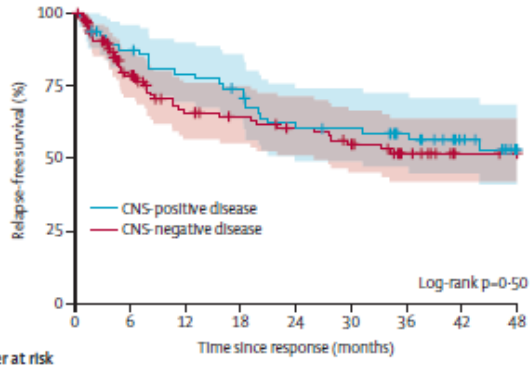
Ghorashian S, et al. *Lancet Haematol.* 2022;9:e766-e775.

CD19-targeted chimeric antigen receptor T-cell therapy for CNS relapsed or refractory acute lymphocytic leukaemia: a post-hoc analysis of pooled data from five clinical trials

Allison Barz Leahy, Haley Newman, Yimei Li, Hongyan Liu, Regina Myers, Amanda DiNofia, Joseph G Dolan, Colleen Callahan, Diane Baniewicz, Kaitlin Devine, Lisa Wray, Richard Aplenc, Carl H June, Stephan A Grupp, Susan R Rheingold, Shannon L Maude**

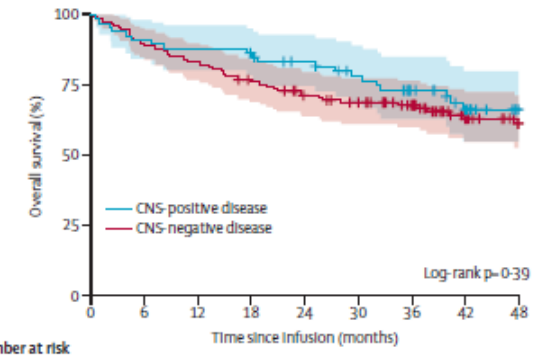


Relapse-Free Survival



Number at risk (number censored)									
CNS-negative disease	121	76	54	49	44	39	28	20	19
	(0)	(22)	(33)	(37)	(39)	(40)	(49)	(57)	(58)
CNS-positive disease	64	54	48	44	35	34	27	19	11
	(0)	(2)	(3)	(4)	(5)	(6)	(12)	(19)	(26)

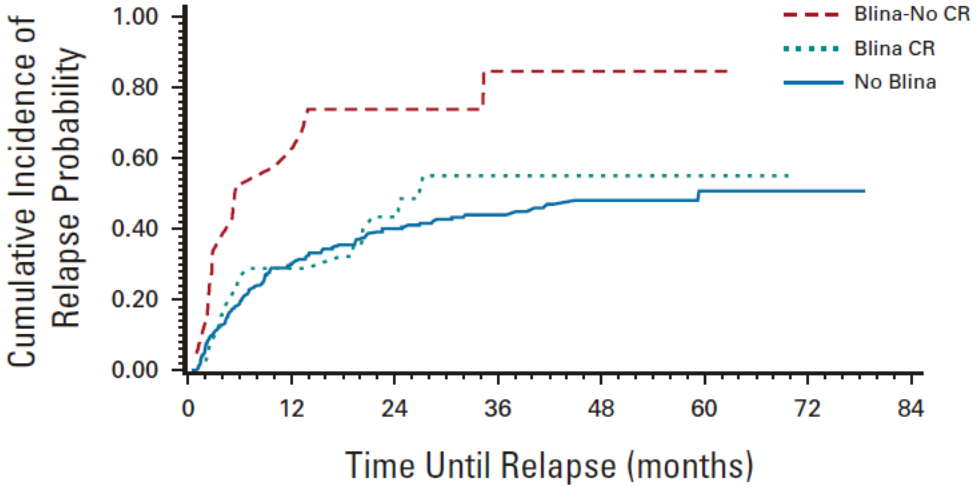
Overall Survival

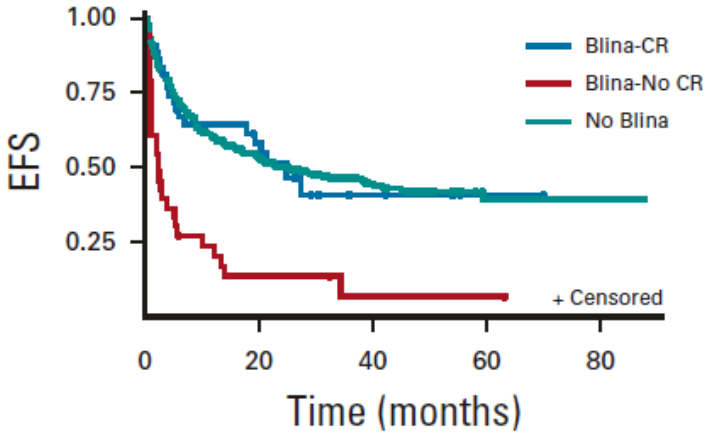


Number at risk (number censored)									
CNS-negative disease	129	116	107	96	86	80	69	46	35
	(0)	(0)	(0)	(2)	(6)	(9)	(19)	(38)	(48)
CNS-positive disease	66	60	58	56	51	45	36	28	18
	(0)	(0)	(0)	(1)	(4)	(7)	(13)	(18)	(28)

Barz Leahy A, et al. *Lancet Haematol*. 2021;8:e711-e722.

Patients who respond to blinatumomab have identical survival with “blina-naive” individuals



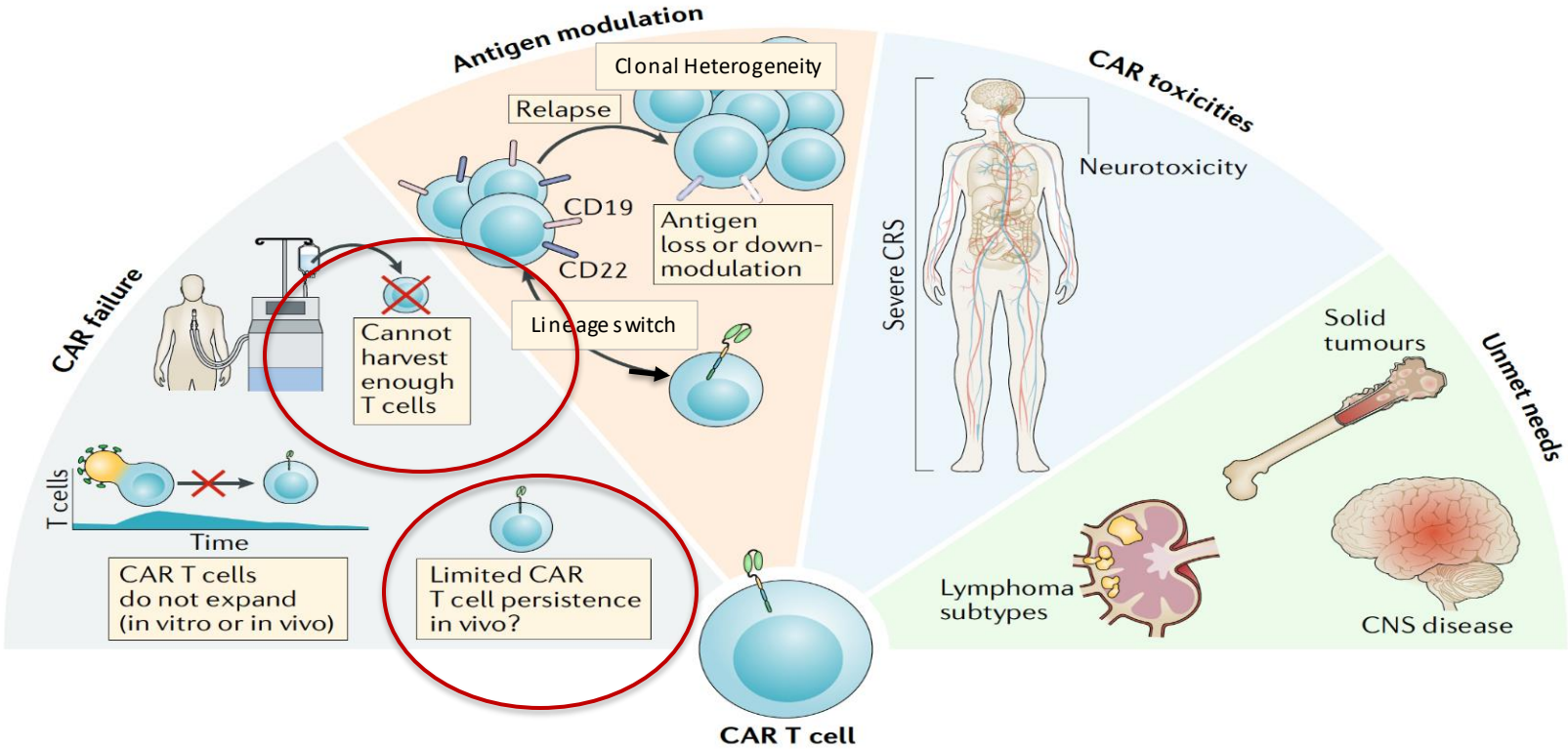


No. at risk:

Blina-CR	43	18	4	1	0
Blina-No CR	34	4	1	1	0
No Blina	343	143	48	16	1

Myers RM, et al. *J Clin Oncol*. 2022;40:932-944.

Current limitations of CAR T cells



Shah NN, Fry TJ. *Nat Rev Clin Oncol.* 2019;16:372-385.

Determinants of persistence and durability of response

B-cell/disease factors

Low CD19 antigen load

Vector integration

Genomic integration site (impact of viral vector?)

CAR T construct

Co-stimulation (CD28 vs 4.1BB)

Lymphodepletion

Flu/Cy vs other

T-cell factors

- *Fitness* of T cells

- Initial T-cell phenotype (CD4/CD8, early memory, exhaustion)

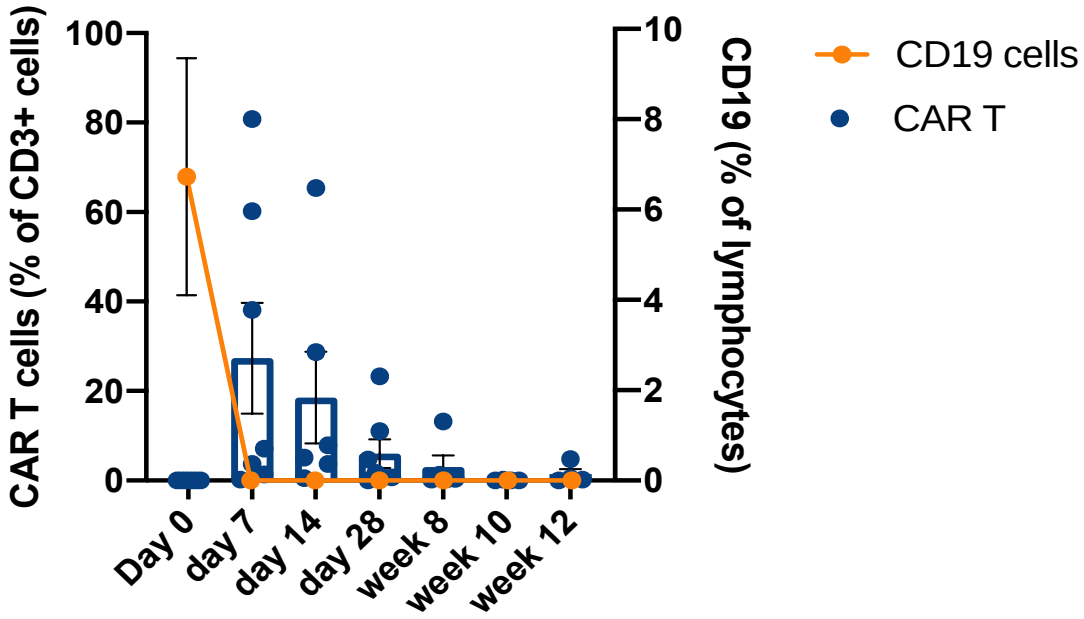
Use of healthy, allogeneic donor

Shah NN, Fry TJ. *Nat Rev Clin Oncol.* 2019;16:372-385; Gardner RA, et al. *Blood.* 2017;129:3322-3331.

Allogeneic CAR T cells: OPBG HE experience

Gender	Age, yr	Cytogenetic Anomalies	Disease Phase at Infusion	Donor and HLA Matching	CAR T Product	CAR T-Cell Dose	Disease Status at LD
F	17	iAmp21	2nd relapse, very early post-HSCT	MUD, 10/10	Retro, 2nd gen (4.1BB), cryopreserved	3×10^6 cells/kg	BM (0.3%)
M	11	TEL/AML1	4th relapse	Sibling	Lenti, 2nd gen (4.1BB), fresh	1×10^6 cells/kg	BM (0.2%) + bone and kidney
M	21	t(1;1)(q21;q22) MEF2D/BCL9	1st refractory relapse	Sibling	Retro, 2nd gen (4.1BB), cryopreserved	3×10^6 cells/kg (PRE-HSCT)	BM (12%) + bone (>10 spots) + liver
M	6	None	5th relapse (after 2 HSCTs)	Haplo	Lenti, 2nd gen (4.1BB), fresh	2×10^6 cells/kg	BM (83.7%)
M	29	KMT2A	5th relapse	Sibling	Retro, 2nd gen (4.1BB), cryopreserved	3×10^6 cells/kg	Pelvic lymph nodes + CNS
M	16	None	2nd relapse, very early post-HSCT	Sibling	Lenti, 2nd gen (4.1BB), fresh	2×10^6 cells/kg	BM (0.2%)
M	8	IKAROS+	3rd relapse, after HSCT	Sibling	Lenti, 2nd gen (4.1BB), fresh	3×10^6 cells/kg	BM (1.6%)
M	7	t(9;22)	1st refractory relapse	Sibling	Lenti, 2nd gen (4.1BB), fresh	3×10^6 cells/kg (PRE-HSCT)	BM (0.03%)
M	17	None	2nd refractory relapse	Haplo	Lenti, 2nd gen (4.1BB), fresh	3×10^6 cells/kg	BM (0.01%) + bone
M	4	47, XY (+21)	1st refractory relapse	Sibling	Lenti, 2nd gen (4.1BB), fresh	3×10^6 cells/kg	BM (0.02%)
F	25	None	4th relapse (after HSCT and autologous CD19-CAR)	Haplo	Lenti, 2nd gen (4.1BB), fresh	3×10^6 cells/kg	BM (0.03%) + mammary gland + bone

Expansion and toxicity



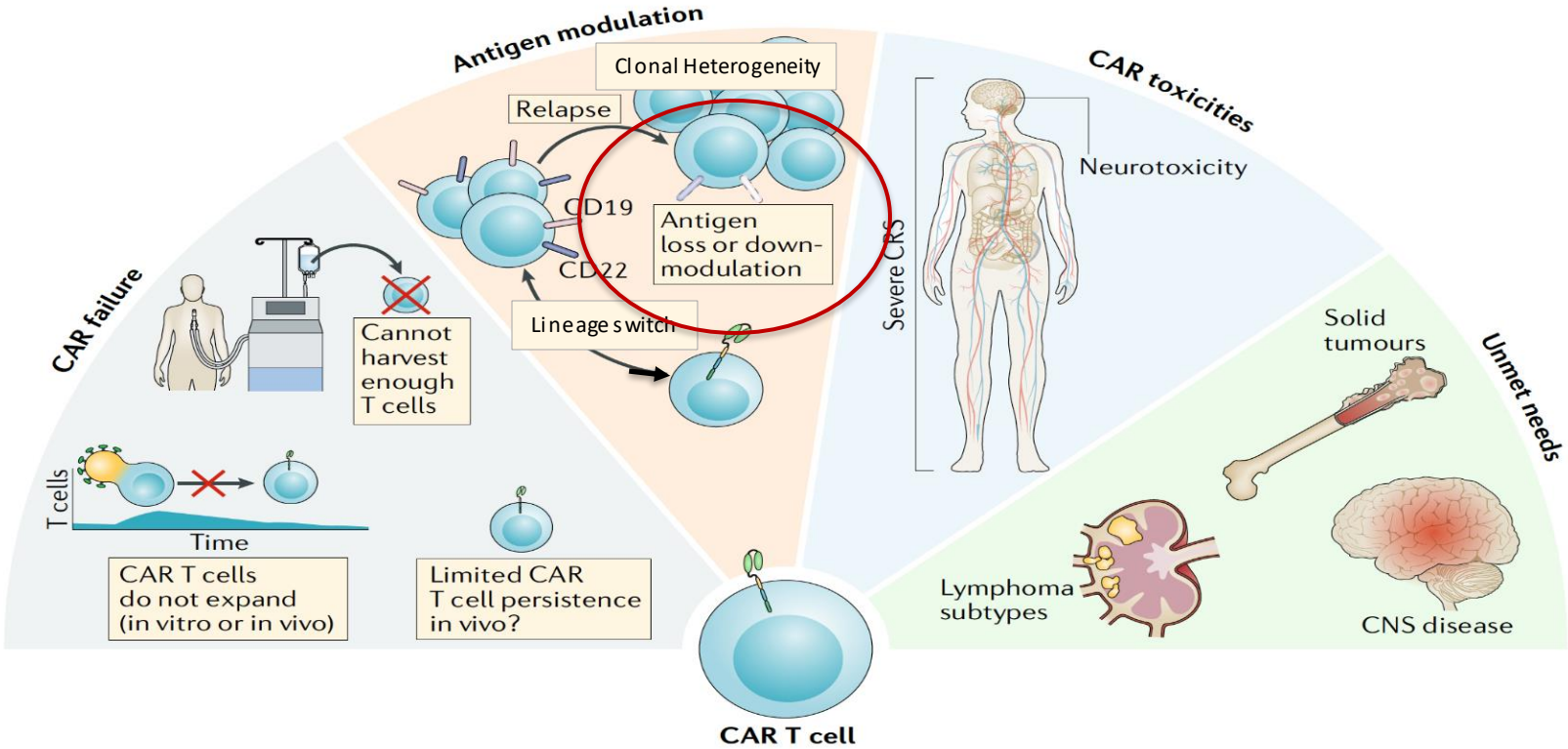
CRS	8/11
• Grade 1–2	8
• Grade 3	0
• Grade 4	0
Neutropenia	11/11
• Grade 1–2	0
• Grade 3–4	**11**
Thrombocytopenia	10/11
Anemia	10/11
B-cell aplasia	11/11
ICANS	1/11
aGVHD	**0/11**

Bambino Gesù
OSPEDALE PEDIATRICO

Outcome

Gender	Age, yr	Cytogenetic Anomalies	Disease Phase at Infusion	Donor and HLA Matching	CAR T Product	CAR T-Cell Dose	Disease Status at LD	Response at Day +28	BCA Duration	Status at Last F/U
F	17	iAmp21	2nd relapse, very early post-HSCT	MUD, 10/10	Retro, 2nd gen (4.1BB), cryopreserved	3×10^6 cells/kg	BM (0.3%)	CR (MRD neg)	Ongoing (15 m)	CD19neg relapse (14 m)
M	11	TEL/AML1	4th relapse	Sibling	Lenti, 2nd gen (4.1BB), fresh	1×10^6 cells/kg	BM (0.2%) + bone and kidney	CR (BM: MRD neg; EM: neg)	5 m (then HSCT)	Relapse post-HSCT and died
M	21	MEF2D/BCL9	1st refractory relapse	Sibling	Retro, 2nd gen (4.1BB), cryopreserved	3×10^6 cells/kg (PRE-HSCT)	BM (12%) + bone (>10 spots) + liver	BM: CR; liver: CR; bone: 3 spots	2 m (then HSCT)	**CR (MRD neg) post-HSCT (12 m)**
M	6	None	5th relapse (after 2 HSCTs)	Haplo	Lenti, 2nd gen (4.1BB), fresh	2×10^6 cells/kg	BM (83.7%)	CR (MRD neg)	Ongoing (9 m)	**CR (MRD neg) (9 m)**
M	29	KMT2A	5th relapse	Sibling	Retro, 2nd gen (4.1BB), cryopreserved	3×10^6 cells/kg	Pelvic lymph nodes + CNS	CR (MRD neg)	6 m	Relapse (7 m)
M	16	None	2nd relapse, very early post-HSCT	Sibling	Lenti, 2nd gen (4.1BB), fresh	2×10^6 cells/kg	BM (0.2%)	CR (MRD neg)	6 m	Relapse (7 m)
M	8	IKAROS+	3rd relapse, after HSCT	Sibling	Lenti, 2nd gen (4.1BB), fresh	3 × 106 cells/kg	BM (1.6%)	CR (MRD neg)	Ongoing (5m)	**CR (MRD neg) (5 m)**
M	7	t(9;22)	1st refractory relapse	Sibling	Lenti, 2nd gen (4.1BB), fresh	3×10^6 cells/kg (PRE-HSCT)	BM (0.03%)	CR (MRD neg)	Ongoing (4m)	**CR (MRD neg) (4 m)**
M	17	None	2nd refractory relapse	Haplo	Lenti, 2nd gen (4.1BB), fresh	3×10^6 cells/kg	BM (0.01%) + bone	CR (MRD neg)	Ongoing (4m)	**CR (MRD neg) (4 m)**
M	4	47, XY (+21)	1st refractory relapse	Sibling	Lenti, 2nd gen (4.1BB), fresh	3×10^6 cells/kg	BM (0.02%)	CR (MRD neg)	6 m	Relapse (3 m)
F	25	None	4th relapse (after HSCT and autologous CD19-CAR)	Haplo	Lenti, 2nd gen (4.1BB), fresh	3×10^6 cells/kg	BM (0.03%) + mammary gland + bone	CR (MRD neg)	Ongoing (3m)	**CR (MRD neg) (3 m)**

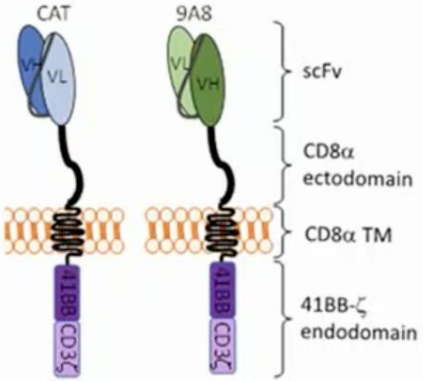
Current limitations of CAR T cells



Shah NN, Fry TJ. *Nat Rev Clin Oncol.* 2019;16:372-385.

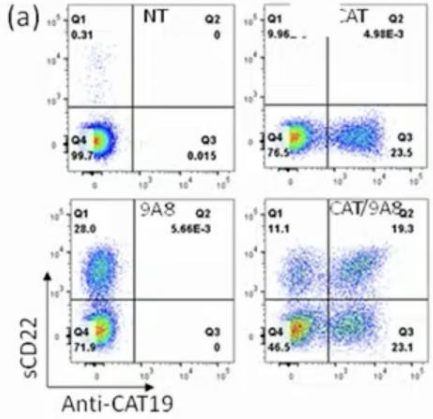
AUTO1/22 - a CD19 and CD22 dual-targeting CART

Co-transduction with two lentiviral vectors



CD22 CAR optimized for activity against low CD22 expressing leukemic cells

CAR T cell product



Three populations of CAR-T cells:

- Single positive for CD19 CAR
- Single positive for CD22 CAR
- Double positive for CD19 and CD22 CARs

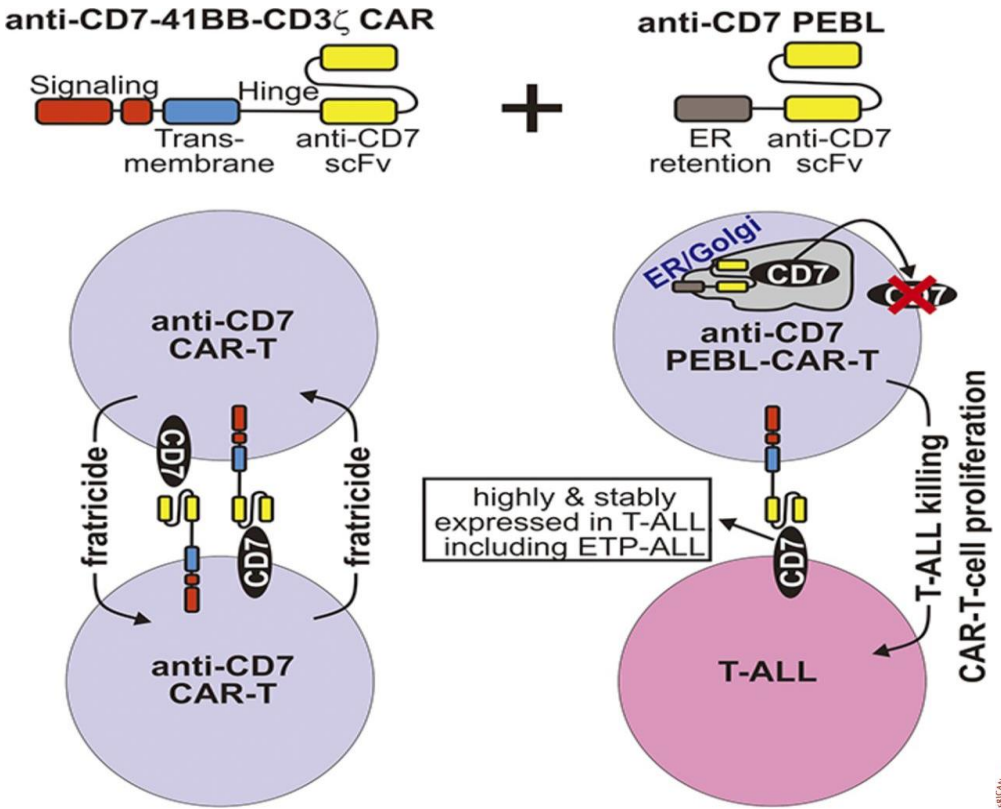
CARPALL AUTO1/22 - response

Total	N=11
Molecular MRD neg CR/Cri by d60	9 (82%)
Disease progression	2 (18%)
Events in responders	3
Emergence of molecular MRD	1
CD19+/CD22+ relapse	2

Why is CAR T-cell therapy difficult to be translated in T-ALL?

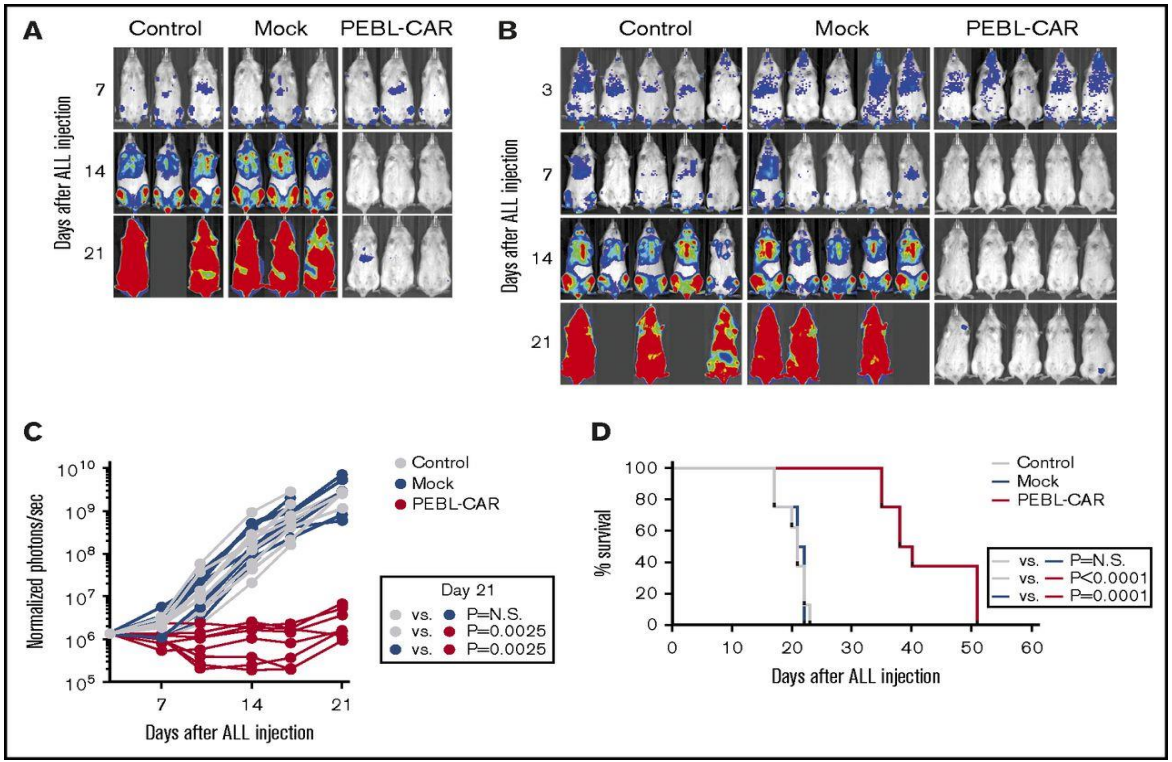
- A T-cell leukemia–specific target antigen has not yet been identified
- CAR T cells can trigger fratricide (CAR T cells killing other CAR T cells)
- Prolonged T-cell lymphopenia (CAR T cells killing normal T cells) is a life-threatening situation and, if it occurs, must be rescued in a timely manner by an allograft of hematopoietic stem cells

Blockade of CD7 expression in T cells for effective CAR targeting of T-cell malignancies



Png YT, et al. *Blood Adv*. 2017;1:2348-2360.

Blockade of CD7 expression in T cells for effective CAR targeting of T-cell malignancies



Png YT, et al. *Blood Adv*. 2017;1:2348-2360.

Take-home messages on CAR T-cell therapies

- CAR T-cell therapy has opened a new era in the treatment of childhood BCP-ALL
- Recent data indicate that CAR T cells are a suitable option in young children with *KMT2A*-rearranged ALL, as well as in patients with CNS relapses
- Novel treatment-related toxicities, mainly occurring within the first 6 weeks from treatment, have appeared
- Approaches to ameliorate CAR T-cell–associated toxicities (eg, CRS, CNS), along with improvements in manufacturing processes and cost reduction, will be essential to increase successful application to clinical practice
- Approaches to prevent/combat relapse
  - Subsequent transplant
  - Simultaneous targeting of multiple antigens
  - Humanized CAR constructs
- Promising approaches exist to translate CAR T-cell therapy to T-ALL, on the basis of strategies/targets able to avoid the fratricide

Global Leukemia Academy

Questions to Experts

Franco Locatelli, MD, PhD
Lia Gore, MD

APTITUDE HEALTH

Global Leukemia Academy

Closing

Lia Gore, MD

University of Colorado,
Anschutz Medical Campus, USA

APTITUDE HEALTH

Thank you!

- Thank you to our sponsor, expert presenters, and to you for your participation
- Please complete the **evaluation link** that will be sent to you via chat
- The meeting recording and slides presented today will be shared on the globalleukemiaacademy.com website within a few weeks
- If you have a question for any of our experts that was not answered today, you can submit it through the GLA website in our Ask the Experts section

THANK YOU!